World Scleroderma Foundation

3RD SYSTEMIC SCLEROSIS WORLD CONGRESS

ABSTRACT BOOK

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Session 1
Management and assessment of newly diagnosed SSc

S.1.2 NEW EULAR/ACR CLASSIFICATION CRITERIA FOR SYSTEMIC SCLEROSIS IN CLINICAL PRACTICE

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Background: ARA/ACR classification criteria for systemic sclerosis (SSc) developed in 1980 lack sensitivity for early and mild SSc patients. Therefore, the EULAR/ACR committee developed new classification criteria for SSc with higher sensitivity. Their applicability in clinical practice and in patients with early/mild SSc remains to be shown.
Objective: To evaluate the performance of the new classification criteria for SSc in clinical practice in a cohort of patients with early and mild disease.
Methods: Consecutive patients with a clinical diagnosis of SSc were prospectively recruited and assessed according to EUSTAR and VEDOSS recommendations. Diagnosis of SSc was based on the evaluation of two experienced experts from this tertiary scleroderma center. Patients fulfilling the old criteria were classified as "established SSc", and patients not fulfilling the old criteria were classified as early/mild SSc. Next, the new EULAR/ACR criteria were applied and patients with a total score of 9 or more were classified as definite SSc patients. The score for each patient was calculated automatically from the local database using Excel. In some patients, missing values were retrieved retrospectively from the patients' records. Baseline characteristics were statistically analyzed using Graph Pad Prism and standard descriptive statistics.
Results: The final data set for the analysis consisted of 314 patients. Two patients were excluded due to missing data on items important for classification, unavailable from the patients' records. Based on fulfillment of the old ARA/ACR criteria, 162/314 (51.6%) had established and 152/314 (48.4%) had early/mild SSc.
All 162 patients with established SSc fulfilled also the new EULAR/ACR classification criteria. Their median disease duration was 6 (IQR 3-13) years, there were 132 females/30 males, and 66 diffuse SSc/96 limited SSc patients.
The 152 patients (135 females/17 males) with early/mild SSc had disease duration 6 (2-13) years. There was 80/152 (52.6%) patients with early/mild disease who fulfilled the new EULAR/ACR classification criteria with a median score 10 (range 9-21). Remaining 72/152 (47.4%) patients, who didn't fulfill the new EULAR/ACR criteria, had a median score 6 (2-8). Most of these patients had Raynaud's phenomenon (91.1%), pathological capillaroscopy (63.8%) and SSc-autoantibodies (51.4%).
Thus, sensitivity of the new EULAR/ACR classification criteria for the overall cohort was 242/314 (77.1%) compared to 162/314 (51.6%) for the old ACR criteria.
Conclusions: In this prospective, observational cohort with early or mild SSc patients, the new EULAR/ACR classification criteria showed increased sensitivity and classified higher number of patients as definite SSc patients than the old ACR criteria.

S.1.3 2013 CLASSIFICATION CRITERIA FOR SYSTEMIC SCLEROSIS AN AMERICAN COLLEGE OF RHEUMATOLOGY/EUROPEAN LEAGUE AGAINST RHEUMATISM COLLABORATIVE INITIATIVE

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Background The 1980 classification criteria for systemic sclerosis (SSc) lack sensitivity in early SSc and limited cutaneous SSc. A joint ACR-EULAR committee was established to develop new classification criteria for SSc.
Methods Using consensus methods, 23 candidate items were arranged in a multi-criteria additive point system with a threshold to classify cases as SSc. The classification system was reduced by clustering items, and simplifying weights. The system was tested by: a) determining specificity and sensitivity in SSc cases and controls with scleroderma-like disorders; b) validating against the combined view of a group of experts on a set of cases with or without SSc.
Results Skin thickening of the fingers extending proximal to the MCPs is sufficient to be classified as SSc, if that is not present, seven additive items apply with varying weights for each: skin thickening of the fingers, finger tip lesions, telangiectasia, abnormal nailfold capillaries, interstitial lung disease or pulmonary arterial hypertension, Raynaud's phenomenon, and SSc-related autoantibodies. Sensitivity and specificity in the validation sample were 0.91 and 0.92 for the new classification criteria and 0.75 and 0.72 for the 1980 ARA classification criteria. All selected cases were classified in accordance with consensus-based expert opinion. All cases classified as SSc by the 1980 ARA criteria were classified with the new criteria, and several additional cases were now considered to be SSc.
Conclusion The ACR-EULAR classification criteria for SSc performed better than the 1980 ARA Criteria for SSc and should allow for more patients to be classified correctly as SSc.

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers***' also are not classified as having SSc.

Items	Sub-items	Weight / Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions *(only count the highest score)*	Digital Tip Ulcers	2
	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerase I [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

S.1.4 PERFORMANCE OF THE OLD 1980 ACR AND THE NEW ACR-EULAR SYSTEMIC SCLEROSIS (SSC) CLASSIFICATION CRITERIA IN PATIENTS WITH LIMITED CUTANEOUS SSC

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OBJECTIVE: To analyze the fulfillment of the old ACR1980 and the new ACR-EULAR Preliminary Classification Criteria for Systemic Sclerosis (SSc) in patients with limited cutaneous disease.
PATIENTS AND METHODS: from 1990, all patients with clinical diagnosis of SSc were included in a database containing demographic and clinical information. Patients with limited cutaneous disease were selected. The old ACR1980 and the new ACR-EULAR criteria were applied to the group. Clinical characteristics and survival were compared between patients with or without ACR1980 criteria, using Chi-Square, t test and Cox-proportion regression analysis.
RESULTS: From 404 patients, 283 (70%, 257f, 59±19y) had limited cutaneous disease. All but 4 had Raynaud, 51(18%) lung fibrosis, 34(12%) severe PAH, 280(99%) sclerodactily, 136(48%) scleroderma, 113(40%) ischaemic lesions, 113/219(52%) telangiectasia and 57/212(27%) calcinosis. Capillaroscopic changes were observed in 189/228(83%), ANA in 258(92%), ACA in 137(49%) and aScl70 in 46(16%). Only 184(65%) fulfilled ACR1980 criteria, whereas 260(92%) fulfilled the new ACR-EULAR criteria. Patients not fulfilling the old, but fulfilling the new criteria, presented more frequently PAH (p=0.05) and ACA (0.03), but less hand edema (p=0.01), joint contractures (p=0.01), calcinosis (p=0.005), GE reflux (p=0.003), lung fibrosis (p<0.0001), sclerodactily (p<0.0001), ischaemic lesions(p<0.0001), ANA (p=0.008) and aScl70 (p<0.0001). After 12±9 y of follow-up from SSc diagnosis, 63 (22%) patients died, 38 fulfilling and 25 not fulfilling ACR1980 criteria. Due to the greater prevalence of severe PAH in this group, age-adjusted mortality was higher in patients not fulfilling ACR1980 criteria (HR 0.4;95%CI 0.2-0.9;p=0.03))
CONCLUSIONS: The new ACR-EULAR criteria for the classification of SSc have much higher sensitivity than the old ACR1980 criteria for patients with limited cutaneous involvement, and allow more patients to be classified. The new criteria would help to diagnose patients with mild limited disease, not fulfilling ACR1980 criteria, but still at risk of developing severe PAH. Since PAH prognosis improves with early diagnosis, these patients might benefit from regular PAH screening, as recommended for all SSc patients.

S.1.5 EARLY ACCRUAL OF ORGAN DAMAGE IN SCLERODERMA: RATIONALE FOR DERIVATION AND VALIDATION OF A DISEASE DAMAGE INDEX IN SYSTEMIC SCLEROSIS

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Background: Unlike some other rheumatological diseases with a relapsing-remitting course, the disease course in systemic sclerosis (SSc; 'scleroderma') is often one of progressive damage in multiple organ systems. There are no validated indices to describe and quantify organ damage in SSc. Objective: We sought to (i) determine the frequency of organ damage in early disease using preliminary criteria and (ii) develop a protocol for the derivation and validation of a disease damage index (DI) in SSc (SSc-DI). Methods: Part (i) all patients enrolled in the Australian Scleroderma Cohort Study (ASCS) within two years of SSc disease onset were included. Preliminary criteria for organ damage, defined as permanent loss of organ function that prognosticates morbidity and mortality, were defined by a panel of 6 Australian experts. Frequency and accrual of organ damage at 2, 3, 4 and 5 years following onset were determined. Part (ii) an international multidisciplinary panel of 16 experts prepared a protocol for the derivation and validation of an SSc-DI. Results: Part (i) 182 patients (81% female, 54% diffuse disease) were recruited into the ASCS within 2 years of disease onset. The frequency and accrual of organ damage from years 2 to 5 are presented in Table 1 and Figure 1. Using preliminary criteria, damage was seen in all organ systems, but was most common in the skin/musculoskeletal (23.1%), respiratory (12.1%), gastrointestinal (GI; 7.1%) and genitourinary systems (31.4%) at 4 years. Part (ii) the protocol for deriving an SSc-DI is comprised of the following steps: (1) Item generation through systematic review of the literature; (2) Item reduction using a two-step Delphi exercise; (3) Nominal group discussion; (4) Item weighting using regression analysis of data in the ASCS database against the end-points of mortality, physical function and HRQoL. The newly-derived SSc-DI will be externally validated against the same end-points using data from the Canadian Scleroderma Research Group (CSRG) database ('retrospective validation'), and the INternational SYstemic sclerosis INception Cohort ('prospective validation'). Conclusion: Early accrual of organ damage in SSc forms a compelling rationale for developing a SSc-DI that may be used to systematically quantify permanent loss of organ function in this disease and may serve as an outcome measure in cohort studies and clinical trials. This SSc-DI will be derived using a combination of consensus and data-driven methodology, and externally validated to fulfill the OMERACT criteria.

Disease damage indicator	2 years n (%)	4 years n (%)
Skin / Musculoskeletal	**21 (11%)**	**42 (23.1%)**
Digital gangrene or amputation	3 (1.6%)	5 (2.7%)
Joint contractures	12 (6.6%)	31 (17.0%)
Muscle weakness	11 (6.0%)	19 (10.4%)
Gastro-intestinal	**7 (3.8%)**	**13 (7.1%)**
Esophageal stricture	2 (1.1%)	3 (1.6%)
Bowel dysmotility / pseudo-obstruction	1 (0.5%)	2 (1.1%)
Anal incontinence	4 (2.2%)	8 (4.4%)
Cardiovascular	**8 (4.4%)**	**12 (6.6%)**
Myocardial disease + either conduction defect or LV dysfunction	4 (2.2%)	5 (2.7%)
Respiratory	**9 (4.9%)**	**22 (12.1%)**
Pulmonary fibrosis + either FVC<70% or DLCO <50%	5 (2.7%)	15 (8.2%)
Pulmonary hypertension + RV dysfunction or dilatation	2 (1.1%)	6 (3.3%)
Renal		
Renal crisis ever + eGFR <60 ml/sec	**1 (0.5%)**	**1 (0.5%)**
Genitourinary		
Erectile dysfunction (men)	**6 (17.1%)**	**11 (31.4%)**

Table 1. Frequency of organ damage at 2 & 4 yrs

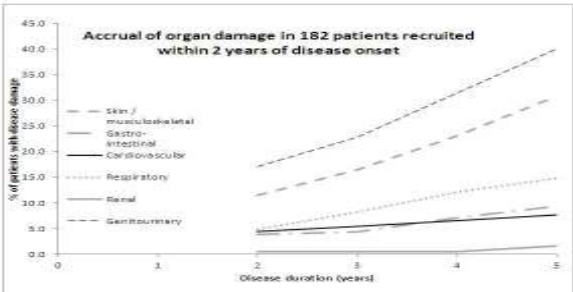

Figure 1. Accrual of organ damage in SSc in the first 2 to 5 years of disease onset

S.1.6 PERFORMANCE OF THE 2013 ACR/EULAR CLASSIFICATION CRITERIA FOR SYSTEMIC SCLEROSIS IN A SINGLE CENTER SETTING

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Background: Systemic sclerosis (SSc) is often diagnosed late in its course, when there is irreversible visceral damage, which accounts for a high morbidity and mortality rate. The 1980 American Rheumatology Association (ARA) classification criteria for SSc have a low sensitivity for early disease or the limited cutaneous subset of SSc. Recently, a new set of criteria developed by the joint effort of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) has been put forward.
Objectives: To evaluate the performance of the new classification criteria for SSc in clinical practice.
Methods: All patients diagnosed with SSc by expert opinion, who have attended our clinic between 2004-2013, were included. They were assessed according to current EUSTAR recommendations. We also included a control group of patients with primary or secondary non-sclerodermic Raynaud's phenomenon, who were assessed between 2009-2011 in the process of screening for the VEDOSS project. The 1980 ARA criteria and the 2013 ACR/EULAR criteria were applied to data from the patients' first visit and sensitivity and specificity were calculated.
Results: We included 133 expert-diagnosed SSc patients, of which 6 were excluded from the analysis because classification according to the new criteria was impossible due to incomplete data. Of the remaining 127 patients (females:males = 113:14), 49 (38.6%) presented with the diffuse subset of SSc (dcSSc). A hundred and ten patients fulfilled the 1980 ARA criteria (sensitivity: 86.6%) and 122 the 2013 ACR/EULAR criteria (sensitivity: 96.1%). All patients who fulfilled the 1980 ARA also met the 2013 ACR/EULAR criteria. Twelve patients (9.4%) fulfilled only the new set of criteria (4 with dcSSc, 7 with lcSSc, 1 with incomplete CREST syndrome). Five patients (3.9%) did not meet any set of criteria. In the control group, the 2013 ACR/EULAR criteria were fulfilled by 5 (16.1%) patients (diagnosed by expert opinion with either mixed connective tissue disease (MCTD) or with undifferentiated connective tissue disease), while the 1980 ARA criteria were met by only one patient with MCTD. The specificity of the ACR/EULAR criteria was 83.9%, while that of the 1980 ARA criteria was 96.8%.
Conclusions: The 2013 ACR/EULAR criteria have a higher sensitivity compared with the 1980 ARA criteria, being able to better detect limited or early SSc. Specificity was lower, but still acceptable. Further studies with larger cohorts and control groups are needed for these results to be validated.

S.1.7 SSC INTRINSIC SUBSET CLASSIFICATION IN PATIENTS THAT DEMONSTRATE CLINICAL IMPROVEMENT DURING TREATMENT

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Background: Gene expression analysis of skin from SSc patients has been used to identify four 'intrinsic' subsets (normal-like, limited, inflammatory and fibroproliferative).We previously reported that patients with improved skin disease during mycophenolate mofetil (MMF) were classified in the inflammatory while non-improvers were classified in the normal-like or fibroproliferative intrinsic subsets. The goals of this study are to identify clinical phenotypes of patients in intrinsic subsets and evaluate intrinsic subset classification stablity over time.

Materials and Methods: Patients with and without progressive skin disease and healthy individuals were enrolled. Standardized clinical assessments including serum autoantibody assessment, pulmonary function test, 2-dimensional echocardiography with tissue Doppler (interpreted by one research echosonographer) and high-resolution computed tomography (scored for lung disease by one chest radiologist) and skin biopsies were performed. mRSS was determined at baseline, 6-, 12-, 24-, and 36-months. Clinical response was defined as decreased mRSS>/=5.

Results: Microarray and clinical data were analyzed for 12 SSc with baseline biopsies (Registry) and 26 SSc patients with longitudinal biopsies (Study) and 12 healthy controls. 4 out of 12 Registry patients were taking MMF (2) or methotrexate (2) at baseline. 22 of 26 Study patients started MMF at baseline. SSc patients were classified as normal-like (11), limited (2), inflammatory (18), and fibroproliferative (7) intrinsic subset. 11 of 12 healthy controls were classified as normal-like. Pts in inflammatory (100% dcSSc) and fibro-proliferative (86% dcSSc) patients had higher mRSS (P=0.003) and longer SSc duration (P=0.029) compared to other subsets. Autoantibodies were not different between groups. Fibroproliferative patients had highest LV mass [86.2g/m2 (14.6), P=0.027] and lowest forced vital capacity % predicted [68 (14.5, P=0.07], while inflammatory patients had lowest tricuspid annular plane systolic excursion [1.96cm (0.37), P=0.029] (mean (SD)). 9 out of 26 (35%) patients with longitudinal biopsies changed intrinsic subset, and six (50% taking MMF) demonstrated >/=5 mRSS change. Disease duration and duration of follow-up (mean (SD)) was 53mo (35) and 27mo (10), and 75 mo (86) and 12mo (7) in patients that changed or did not change subset. Change from inflammatory to the fibroproliferative subset was most common.

Conclusions: Intrinsic subset classification of SSc patients is independent of clinical subtype. Patients in the inflammatory and fibroproliferative subsets are more likely to have heart and lung involvement. A subset of patients change from inflammatory to fibroproliferative intrinsic subset which may be due to increased disease duration, longer follow-up, treatment or combination.

Session 2
Miscellaneous and differential diagnosis of SSc

S.2.1 HOW TO DIFFERENTIATE SSC FROM SCLERODERMA- LIKE DISORDER?

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The new American College of Rheumatology/European League Against Rheumatism classification criteria will enable earlier diagnosis and, therefore, the use of newer treatment modalities for systemic sclerosis (SSc). It is therefore critical to exclude non-SSc causes for diffuse skin thickening as early as possible.
The recently described gadolinium-induced nephrogenic systemic fibrosis may mimic SSc as may other conditions which require a different treatment strategy. Recently, treatment with immunoablation and autologous stem cell transplantation has been shown to significantly benefit some patients with conditions such as scleromyxoedema and SSc. The more accurate measurement of SSc-specific autoantibodies such as topoisomerase 1, centromere and RNA polymerase has recently allowed a more precise subclassification of SSc with implications for treatment and prognosis.
Skin thickening is a nonspecific manifestation of many different processes including (rarely) early scleroderma, which is mostly symmetrical and associated with Raynaud's phenomenon, nailfold capillaroscopic changes and antinuclear antibodies. If the latter three factors are absent, then other conditions must be excluded, the commonest being eosinophilic fasciitis. Skin biopsy (looking for eosinophil infiltration, increased mucin or amyloid deposition), SSc-specific autoantibodies or paraproteins in blood and a careful medical history and system screening will exclude nonscleroderma conditions.

S.2.2 GENDER EFFECTS ON SYSTEMIC SCLEROSIS PHENOTYPE: A LONGITUDINAL EUSTAR STUDY BASED ON MORE THAN 10 000 PATIENTS

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Introduction: In agreement with other autoimmune diseases, systemic sclerosis (SSc) is associated with a sex bias (up to 8 affected women for one man). However, unlike lupus, the effects of gender on disease characteristics and outcomes are poorly known. Thus, we set out to investigate (i) gender effects on SSc phenotype and (ii) the impact of gender on disease outcomes including severe damages and mortality in a large European population.

Patients and Methods: We used the latest 2013 data extract from EUSTAR cohort. We looked at gender influence on disease onset, disease phenotype looking in particular at organ involvement, auto-antibodies, age of death and cause of death using the baseline data. For the patients with follow-up, we focused on those with at least 2 years of follow-up to estimate disease progression. Data at baseline were statistically analyzed using chi-square tests and the Student's t-test. A multivariate stepwise logistic regression analysis was also performed for all variables identified with $p < 0.10$. We applied a Bonferroni correction for multiple comparisons (adjusted probability value =0.003).

Results: 10675 SSc-patients were included (1455 males). 701/1417 (49.5%) SSc-men and 2583/9053 (28.5%) SSc-women had a diffuse cutaneous subtype (p<0.001). Mean age at onset of the disease was 46.98 (± 14.28) in males and 45.98 (± 14.34) years in female (p=0.02). In univariate analysis, a large number of characteristics were associated with male gender. In multivariate analysis, male gender was independently associated with renal crisis (OR: 5.04, CI 95% [1.98-12.84]; p=0.0007) and CK elevation (OR: 3.30 [2.10- 5.20]; p<0.0001). Conversely, they had less frequent intestinal involvement (OR: 0.41 [0.26-0.65]) and anti-centromere positivity (OR: 0.37 [0.25- 0.54]) (p<0.0001 for both comparisons). After a mean follow-up of 3.5 years, 915/1922 patients had died and 525 new onset of lung fibrosis and 39 new renal crisis were recorded. Regarding death, they occurred in 209/1098 (19%) males and 706/6715 (10.5%) females; p=0.007; HR: 1.53 CI 95% [1.29-1.83]. Mean age and disease duration at death were 60.37 and 8.46 in males and 63.96 and 12.38 years in female (p<0.01 for both comparisons). Predictors of new organ damage are under investigations.

Conclusion: Although more common in women, SSc appears strikingly more severe in males. Indeed, our results obtained through the largest worldwide database, demonstrate a higher mortality in affected men. Other outcomes are still under investigation, but our results raise the point of including male gender in the management and the decision making process.

S.2.3 EPIDEMIOLOGY OF CANCER IN SYSTEMIC SCLEROSIS. SYSTEMATIC REVIEW AND META-ANALYSIS OF CANCER INCIDENCE, PREDICTORS AND MORTALITY

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Background/Purpose: To improve our understanding of the epidemiology of cancer in systemic sclerosis (SSc) by evaluating the incidence, prevalence, relative risk of overall and site-specific malignancies in comparison with the general population, and cancer-attributable mortality.
Methods: MEDLINE, CINAHL, EMBASE and Cochrane Library (inception-May 2012) were searched. Estimates were combined using a random effects model. Consistency was evaluated using the I2statistic.
Results: 4,876 citations were searched to identify 59 articles. The average incidence of malignancy in SSc was 14 cases/1000 person-years; the prevalence ranged between 4%-22%. Cancer was the leading cause of non-SSc related deaths with a mean of 38%. Overall SIR for all-site malignancy risk was 1.85 (95% CI 1.52, 2.25; I276%).There was a greater risk of lung (SIR 4.69, 95% CI 2.84, 7.75; I293%) and haematological (SIR 2.58, CI 95% 1.75, 3.81; I20%) malignancies, including non-Hodgkin's lymphoma (SIR 2.55, 95% CI 1.40, 4.67; I20%). SSc patients were at a higher risk of leukemia (SIR 2.79, 95% CI 1.22, 6.37; I20%), liver (SIR 4.75, 95%CI 3.09, 7.31; I20%), cervical (SIR 2.28, 95% CI 1.26, 4.09; I254%) and oropharyngeal (SIR 5.0, 95% CI 2.18, 11.47; I258%) cancers. Risk factors include a-RNAP I/III positivity, male sex, and late onset SSc. Smoking and longstanding interstitial lung disease (ILD) increase the risk of lung cancer; longstanding gastroesophageal reflux disease with Barrett's esophagus and a positive family history of breast cancer, respectively, increase the risk of esophageal adenocarcinoma and breast cancer.
Conclusion: SSc patients have a two-fold increase in malignancy, and greater risk of lung and haematological malignancies that contribute significantly to mortality. Vigilance should be considered in SSc patients with a-RNAP I/III antibodies, male sex, smokers, late disease onset, a positive family history of breast cancer, long duration of ILD, Barrett's esophagus.

S.2.4 JOINT AND TENDON INVOLVEMENT PREDICT SEVERE DISEASE PROGRESSION IN SYSTEMIC SCLEROSIS: A EUSTAR PROSPECTIVE STUDY

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Objective: To determine whether inflammatory joint involvement (synovitis and tendon friction rubs) may predict the progression and severity of systemic sclerosis (SSc) in a large cohort with longitudinal follow-up.
Methods: We included patients from the EUSTAR database (MEDS online) with disease duration less than 3 years and with a follow-up of at least two years. We extracted data regarding the presence or not of synovitis (tender and swelling joints) and tendon friction rubs (rubbing sensation detected as the tendon was moved) and data related to disease progression. Skin progression was defined by a >10% worsening of the modified Rodnan skin score (mRSS). Lung progression was defined by the new onset of pulmonary fibrosis on high resolution CT scan, or the deterioration of lung volume (>10% of forced vital capacity, FVC). Cardiovascular worsening was defined for skin by new ischemic digital ulcers (DU), for lung by pre-capillary pulmonary arterial hypertension (PAH) on right heart catheterization, and for heart by the reduction of the left ventricular ejection fraction below 50% on echocardiography. Renal progression was defined by the occurrence of scleroderma renal crisis.
Results: From the 9165 patients included in the database, 1301 patients (1079 females) met our inclusion criteria (mean ± SD age of 55±15 years, mean ± SD follow-up: 4.5±2.2 years).
In univariate analysis, synovitis and tendon friction rubs were identified as predictors of skin progression (Log-rank test, p=0.0008 and p=0.0002 respectively). In multivariate analysis, after stratification for disease subset and autoantibody status, synovitis and tendon friction rubs remained predictive of skin progression (Hazard Ratio, HR: 1.69, 95% confidence interval, CI: 1.09-2.63 and 1.68, 95%CI: 1.04-2.72 respectively). No impact on lung outcomes was identified. In multivariate analysis, synovitis independently predicted cardiovascular progression both for the occurrence of new ischemic DU (HR: 1.36, 95%CI: 1.01-1.83) and left ventricular dysfunction (HR: 2.20, 95%CI: 1.06-4.57). Tendon friction rubs independently predicted in multivariate analysis scleroderma renal crisis (HR: 3.78, 95%CI: 1.01-6.19).
Conclusion: This first report of the prospective follow-up of EUSTAR patients identified for the first time the merit of inflammatory joint involvement in early SSc patients. These results obtained through the largest worldwide database support the use of these easily detected clinical findings for the risk stratification of SSc patients. These parameters might be used in the future to select high-risk patients, guide therapies and might be regarded as potential surrogate markers for severity.

Session 3
The great debate

S.3.1 THE GREAT DEBATE - "THE PLACE OF CORTICOSTEROIDS IN SSC"

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The potent anti-inflammatory effects of corticosteroid (CS) therapy find clinical application in (1) early inflammatory diffuse cutaneous SSc; (2) arthritis/tenosynovitis; (3) myositis; (4) pleuritis/pericarditis; (5) rare presentations of myocarditis; and (6) management of inflammatory manifestations of various overlap syndromes. CS therapy remains widely used although there is little hard evidence of clinical efficacy. A recent survey of > 1700 SSc patients in Germany revealed that 41.3% were receiving CS therapy with 16.1% receiving daily doses of 15 mg prednisone equivalents or more.

Adverse effects of CS are numerous and well known to rheumatologists and include fluid retention, weight gain, hypertension, diabetes mellitus, cataracts, increased risk of infection, osteopenia, avascular necrosis of bone and others. A disease-specific complication of CS is thought to be an increased risk of scleroderma renal crisis (SRC). A widely accepted case control study demonstrated an odds ratio of 4.37 for development of SRC associated with CS doses at or above the 15 mg threshold. Similar data suggested that > 30 mg per day increased risk of normotensive SRC. Prednisone exposure and dose were subsequently associated with SRC in large French and Italian series.

This clinical scenario is biologically plausible. Glucocorticoids suppress endothelial production of both prostacyclin and nitric oxide and enhance arterial contractile sensitivity to catecholamine. Bradykinin-influenced prostacyclin release is sensitive to CS while influence on arachidonic acid and COX-2 mediated effects are absent. However, CS do exert a protective effect on renal ischemia-reperfusion injury through stimulation of ERK 1/2 phosphorylation and inhibition of caspase release.

Risk factors for SRC independent of CS include a rapid rate of skin thickness progression, palpable tendon friction rubs and the presence of anti-RNA polymerase III antibody. A key question remains unanswered. Is SRC a drug-related toxicity or is the clinical setting in which the CS is employed the dominant risk factor? In a retrospective analysis of early diffuse SSc in the US study of D-penicillamine, measures of disease activity/severity were strongly associated with SRC (skin scores > 20; large joint contractures). If these features were lacking, there was no association of prednisone therapy with SRC. The highest risk of SRC was in patients with high disease activity AND corticosteroid.

Question 1: Would you use CS, and, if so, at what dose, in a 38-year-old woman with severe skin thickening (MRSS 25 after only 6 months of disease) who also has definite synovitis and inflammatory myopathy (proximal weakness, CPK 4X normal)?

Question 2: Would you use CS, and, if so, in what dose, in the following clinical scenarios? (a) a patient with progressive interstitial lung disease (FVC declined from 78% to 53% predicted with worsened extent of disease on HRCT). This patient has anti-topoisomerase 1 antibody and mild skin involvement (MRSS 12). (b) A antiU1RNP positive patient with limited cutaneous disease who presents with acute pericarditis with increased effusion unresponsive to NSAID (c) a 67 year old patient is anticentromere positive with limited cutaneous SSc. She is postmenopausal, osteoporotic and receiving PPI for reflux esophagitis. She presents with Sjogren syndrome and a rheumatoid-like arthritis.

In the absence of more robust data, we conclude that early active diffuse scleroderma has a high risk of SRC and these high risk patients are more likely to receive CS. In turn, CS appears to further increase risk of SRC in this clinical setting. Alternate strategies for control of inflammatory features should be considered. If CS remains clinically indicated, efforts should be made to limit dose and exposure

Session 4
An integrated approach to gastro-intestinal involvement

S.4.1 GI: HOW TO EVALUATE, DIAGNOSE AND TREAT UPPER AND LOWER GI INVOLVEMENT

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Raynaud's phenomenon and skin sclerosis are the most common and prominent characteristics in patients with SSc, but recent data of the EUSTAR consortium and other SSc networks show that involvement of the GI-tract is much more frequent than expected. In addition, in the registry of the German Systemic Scleroderma Network, it could be shown that higher modified Rodnan Skin Score values were significantly associated with higher frequencies of upper gastrointestinal symptoms. Main symptoms of GI involvement are meteorism, dysmotility of the esophagus, heartburn and dysphagia. In severe cases, gastrointestinal manifestations can result in lethal complications such as severe intestinal pseodoobstruction and Barrett's cancer. In contrast to the idea that limited SSc is a more benign disease entity with respect to GI symptoms, both SSc subsets are affected. In diffuse SSc, the most frequent symptoms were meteorism (80%), daytime heartburn (80%), coughing/ sore voice (80%) and stomach ache (80%), followed by nighttime heartburn (73%), diarrhea (73%), and nausea (60%). When comparing diffuse and limited SSc, the most prominent differences -with lower prevalence in limited SSc- were nighttime heartburn (-24%), daytime heartburn (-15%) stomach ache (-15%), and diarrhea (-6%). In contrast, fecal incontinence (+14%) and meteorism (+7%) were more frequently reported by patients with limited SSc. Owing to the multiple organs and compartments, questionnaires and several technical methods had to be developed to evaluate of involvement of GI tract in systemic sclerosis including the search for infra-aortic oesophageal dilatation in high resolution CT as specific sign of oesophageal involvement, oesophageal manometry, 24-hour pH monitoring, endoscopic ultrasound, oesophagogastroscopy, small bowel barium follow-through x-ray (especially for cases of intestinal pseudoobstruction), D-xylose test, jejunal cultures and H2 glucose and lactose breath test for malabsorption and bacterial overgrowth. With respect to treatment, still no evidence-based disease-modifying regimen for systemic sclerosis exists although most of the available immunsuppressants and antifibrotics have been investigated at least in small series to inhibit overall disease activity but several therapeutic approaches for the individual organs of the GI-tract have proven to be effective, including proton pump inhibitors to counteract all reflux-associated problems, prokinetic drugs such as metoclopramide and domperidone, laser photocoagulation by neodymium yttrium-aluminum garnet (YAG) and argon plasma coagulation, bipolar electrocoagulation, heater probe coagulation, and injection sclerotherapy with 5% polidocanol foe water melon stomach and many more. However, managing the various problems of SSc-related gastrointestinal disease remain amongst the most challenging in the course of the disease.

S.4.2 NEW THERAPEUTIC APPROACHES

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Although the GI system is the second most frequently involved organ system and a major determinant of quality of life amongst patients with systemic sclerosis there is little published evidence or novel approaches available to guide clinicians on the best management for these patients. This presentation will outline evolving data on novel approaches for management, as well as outlining the new UK consensus best practice pathways for the management of the Gastrointestinal manifestations of systemic sclerosis

S.4.3 MORTALITY, RECURRENCE, AND HOSPITAL COURSE OF PATIENTS WITH SYSTEMIC SCLEROSIS (SSC) RELATED ACUTE INTESTINAL PSEUDO-OBSTRUCTION

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Introduction:
Acute intestinal pseudo-obstruction is a rare gastrointestinal manifestation of SSc with little data existing as to the demographics, clinical course, outcomes and mortality of this disease.
Methods:
We undertook a retrospective chart review of patients admitted at two University Medical Centers in the city of Philadelphia over an 11.5 year period (1/2001-6/2012).Medical records were searched using ICD codes for SSc in combination with ICD codes for intestinal obstruction and fecal impaction. The medical records were then reviewed and those patients who were identified as true cases of pseudo-obstruction we collected demographic data. Continuous variables were analyzed by a student's unpaired two-tailed t test while categorical variables by the Fisher's exact test.
Results:
A total of 1,733 admissions of SSc patients to the two hospitals were identified during the time period in question. 103 admissions had ICD codes matching our search criteria and from them 64 admissions were identified as true acute intestinal pseudo-obstruction cases in 37 unique SSc patients. From these cases 73% had spontaneous resolution with conservative measures of IV hydration and bowel rest, 11% underwent surgical resection and 26% required permanent total parenteral nutrition (TPN), Hospital course was for a mean of 12+12.5 days and there was 10% mortality. In a subgroup analysis of patients who had recurrent episodes of pseudo-obstruction this was more commonly seen in women ($p=0.01$), associated with symptoms of nausea at presentation ($p=0.04$) and resulted more often to the use of prolonged TPN ($p<0.0001$). Mortality was higher in male patients ($p=0.014$) who had low hemoglobin ($p<0.00008$) and serum albumin ($p<0.001$). Patients who underwent surgery were more likely to die ($p<0.005$). A prolonged hospital stay was more often related to the use of a nasogastric tube ($p<0.05$) and a surgical resection ($p<0.05$).
Conclusion:
Acute intestinal pseudo-obstruction is a rare cause of hospitalization of SSc patients (64/1733 (3.7%) admissions). This is the largest study attempting to characterize this subpopulation of SSc patients. Based on our results most patients have spontaneous resolution with conservative measures such as bowel rest and IV hydration. Women were more likely to have recurrences and these patients were more likely to suffer from nausea symptoms at their presentation, and progressed to need permanent TPN. Mortality was higher in males especially in those patients with a low hemoglobin and serum albumin at presentation. Patients who underwent a surgical resection had a higher mortality and a more prolonged hospital stay.

S.4.4 PREVALENCE, CORRELATES AND OUTCOMES OF GASTRIC ANTRAL VASCULAR ECTASIA IN SYSTEMIC SCLEROSIS : A EUSTAR CASE-CONTROL STUDY

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Objective: To estimate the prevalence, determine the subgroups at risk and the outcomes of systemic sclerosis (SSc) patients with gastric antral vascular ectasia (GAVE).
Method: We queried the EUSTAR network for the recruitment of SSc-GAVE patients. Each case was matched for cutaneous subset and disease duration with 2 SSc controls recruited from the same centre, evaluated at the time the index case had the diagnosis of GAVE made. SSc characteristics were recorded at the time of GAVE occurrence and the last observation was collected to define the outcomes.
Results: 49 cases of SSc patients with GAVE were included (24 with diffuse cutaneous SSc) and compared to 93 SSc controls. The prevalence of GAVE was estimated at about 1% of SSc patients. By multivariate analysis, SSc-GAVE patients exhibited more frequently a diminished (<75%) DLCO value (Odds Ratio, OR : 12.8; 95% confidence interval, CI, 1.9-82.8) despite less frequent pulmonary fibrosis (OR : 0.2; 95%, CI 0.1-0.6). GAVE was also associated with the presence of anti-RNA-polymerase III antibodies (OR : 4.6; 95%CI 1.2-21.1). SSc-GAVE was associated with anemia (82%) requiring blood transfusion (45%). Therapeutic endoscopic procedures were performed in 45% of GAVE cases. After a median follow-up of 30 months (range 1-113 months), survival was similar in SSc-GAVE patients, as compared to controls but a higher number of scleroderma renal crisis occurred (12% vs. 2%. p=0.01).
Conclusion: GAVE is rare and associated with a vascular phenotype including anti-RNA-polymerase III antibodies and a high risk of renal crisis. Anemia usually requiring blood transfusions is a common complication.

Session 5
Links to inflammation, immunity and vasclular disease

S.5.1 IMMUNOLOGICAL MECHANISMS OF FIBROSIS

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Macrophages are found in close proximity with collagen-producing myofibroblasts and play key roles in the mechanisms of wound healing and fibrosis. They produce growth factors and pro-fibrotic mediators that directly activate fibroblasts, including transforming growth factor beta, insulin-like growth factor, vascular endothelial growth factor, and platelet-derived growth factor. They also regulate extracellular matrix turnover by influencing the balance of various matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases. Macrophages also regulate fibrogenesis by secreting chemokines that recruit fibroblasts and other inflammatory cells and by producing various inflammatory and anti-inflammatory cytokines. With their potential to act in both a pro- and anti-fibrotic capacity at distinct stages of the wound healing response, macrophages and the factors they express are integrated into all stages of the fibrotic process. These various and sometimes opposing functions are performed by distinct macrophage subpopulations, the identification of which is a growing focus of fibrosis research. Although collagen-secreting myofibroblasts once were thought of as the master "mediators" of fibrosis, in this presentation I will illustrate how macrophages function as the master "regulators" of fibrosis.

S.5.2 PIGMENT EPITHELIUM DERIVED FACTOR SECRETED BY SSC FIBROBLASTS INHIBITS ANGIO AND VASCULOGENESIS IN VITRO

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Background: Systemic Sclerosis (SSc) is an autoimmune disorder characterized by tissue fibrosis and defective angio/vasculogenesis. There is scanty of studies investigating the molecular mechanisms linking the two processes in SSc. Recently, a proteomic analysis of SSc dermal fibroblasts (SScFBs) secretome, identified an increased secretion of Pigment Epithelium Derived Factor (PEDF) compared to healthy fibroblasts. PEDF produced by retinal-pigmented epithelium and melanocytes (HEMs), is the major endogenous inhibitor of intraocular angiogenesis. Here we aimed to validate the increased expression of PEDF in SSc and to determine whether PEDF might play a role in SSc vasculopathy.
Methods: PEDF expression was investigated in the involved skin and FBs of 4 early diffuse SSc patients and 4 healthy controls (HC) by immunohistochemistry (IHC) and rt-PCR. Functional effects of PEDF on angio/vasculogenesis were examined by Matrigel assays and organotypic co-culture assays of HUVECs or microvascular endothelial cells (MVECs), on either primary healthy FBs (HCFBs) or SScFBs or HCFBs silenced for Caveolin-1 (Cav-1). Endothelial cells were visualized by CD31 staining. Vascular tubule number, length and junctions were analyzed by Angiosys software (TCS CellWorks).
Results: In SSc skin 52% (+/-5.9) of dermal fibroblasts were positive for PEDF vs. 13% (+/-0.68) of FBs in HC skin ($p<0.05$). Furthermore, double IHC studies indicated that PEDF positive FBs showed a decreased Cav-1 expression in both HC and SSc skin. In-vitro studies confirmed that SScFBs showed on average a 5-fold increased PEDF expression when compared to HCFBs ($p<0.0162$). Additionally, consistent with IHC studies HCFBs silenced for Caveolin-1 showed on average a 2-fold increase in PEDF mRNA levels compared to control ($p<0.0055$). Matrigel studies indicated that recombinant PEDF protein inhibited vasculogenesis, suppressing the loop number by 20% ($p<0.05$). Consistently, co-culture assays indicated that PEDF inhibited tubulogenesis, suppressing both total tubule length by 42% ($p<0.005$), number of tubules by 55% ($p<0.005$) and junctions by 73% ($p<0.001$). Importantly, co-culture assays indicated that primary SScFBs inhibited tubulogenesis on MVECs. Additionally, HCFBs silenced for Caveolin-1 inhibited HUVECs tubulogenesis, suppressing both total tubule length by 63% ($p<0.001$), number of tubules by 61% ($p<0.001$) and junctions by 88% ($p<0.001$).
Conclusion: The increased expression of PEDF in SSc may be secondary to loss of Caveolin in dermal fibroblasts and contribute to the vascular manifestation of Scleroderma. Further studies unraveling the mechanisms of the antiangiogenic effect of PEDF may shed light in understanding the molecular events linking the profibrotic phenotype and SSc vasculopathy.

S.5.3 SCLERODERMA DERMAL FIBROBLASTS OVEREXPRESS VASCULAR ENDOTHELIAL GROWTH FACTOR DUE TO AUTOCRINE TRANSFORMING GROWTH FACTOR BETA SIGNALING

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Objectives: Overexpression of vascular endothelial growth factor (VEGF) in scleroderma (SSc) skin may play a role in the pathogenesis of the disease. Our study was undertaken to evaluate whether dermal fibroblasts function as one of the sources of the increased VEGF in SSc, and to clarify its mechanism.
Methods: Protein and mRNA levels of VEGF were analyzed using immunoblotting, enzyme-linked immunosorbent assay, and real-time PCR. The DNA-binding ability of Smad3 was evaluated by DNA affinity precipitation.
Results: VEGF mRNA expression in vivo was increased in SSc skin compared to skin with other collagen diseases. Expression of VEGF protein and mRNA in cultured SSc dermal fibroblasts was constitutively and significantly upregulated. Ectopic TGF-β stimulation induced VEGF synthesis in normal fibroblasts, and TGF-β knockdown normalized the upregulated VEGF levels in SSc fibroblasts. Furthermore, Smad3 overexpression induced VEGF levels. We found that bp -532 to -521 on the VEGF promoter is a putative binding site for Smads, and that the binding activity of Smad3 to VEGF promoter was constitutively increased in SSc fibroblasts as well as in normal fibroblasts treated with exogenous TGF-β1.
Conclusions: We demonstrated that VEGF were overexpressed due to autocrine TGF-β/Smad signaling in SSc. TGF-β signaling may contribute to the pathogenesis of angiopathy as well as tissue fibrosis.

S.5.4 IL6 TRANS-SIGNALLING AND CCL2 CO-REGULATE FIBROBLAST DEPENDENT TRANS-ENDOTHELIAL MIGRATION OF MONONUCLEAR CELLS AND FIBROTIC RESPONSE IN SCLERODERMA

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Background: IL6 is a key mediator implicated in activation of extracellular matrix (ECM) in scleroderma (SSc) fibroblasts. CCL2 is a proinflammatory chemokine that is overexpressed in diffuse cutaneous systemic sclerosis (dcSSc). We explored interaction between these two mediators and their role in the recruitment of inflammatory cells and ECM production. Methods: Dermal fibroblasts were cultured from skin biopsies from healthy controls (n=4) and early stage dcSSc (n=4). Peripheral blood mononuclear cells (PBMCs) were isolated from blood samples of the latter group. Induction of CCL2 by IL6 via trans-signalling in dermal fibroblasts and the effect of SSc fibroblast-derived CCL2 on migration of PBMCs across an endothelial layer in vitro were studied using Transwell migration assays in a co-culture system. The effect of PBMC-fibroblast cross-talk on induction of ECM proteins: α -smooth muscle actin (α SMA) and Collagen type-I (Col-I) was assessed by neutralising antibodies against CCL2 or IL6 receptor and targeted ectodomain shedding inhibition using TNF-α processing inhibitor-1(TAPI-1). Results: IL6 trans-signalling increased CCL2 expression (mean ± SEM % basal expression) (33± 2.7% $p<0.03$ and 45±5.6% $p<0.04$) in control and SSc fibroblasts respectively. CCL2 expression was reduced in the presence of anti-IL6R in control fibroblasts (63±6.4%, $p<0.04$). IL6 trans-signalling increased migration of PBMCs (n=4) by 2.1 fold ($p<0.05$) and 4.5 fold ($p<0.03$) in the presence of control fibroblasts and SSc fibroblasts respectively. The migration of PBMCs was significantly reduced by the addition of neutralising antibodies against CCL2 and IL6R (44± 5.1%, $p<0.05$ and 62 ± 5.4%, $p=0.04$) respectively and both antibodies combined (44± 7.3.2%, $p<0.05$) in the presence of SSc fibroblasts. In response to IL-6 trans-signalling, there was increased expression of α SMA (53 ± 5.9%, $p<0.04$) and Col-I (70± 2.6%, $p<0.03$) at 24-hour in the presence control fibroblasts and α SMA (37± 5.9%, $p<0.03$) and Col-I (47± 3.6%, $p<0.04$) in the presence of SSc fibroblasts. TAPI-1 reduced PBMC migration in a concentration dependent manner with maximal effect at 50μM by (55± 4.1 % $p<0.04$) and TAPI-1 reduced synthesis of α SMA (27± 4.8 %, $p<0.05$) and Col-I (31± 3.6%, $p<0.03$) respectively.
Conclusions: Our data suggest that fibroblast-derived CCL2 expression is regulated by IL-6 via trans-signalling. The IL-6/CCL2 interplay regulates trans-endothelial migration of PBMCs and IL-6 trans-signalling with intramembrane shedding of IL-6R mediates the fibrotic response. Thus, CCL2/IL6 interplay may be important in SSc pathogenesis and could be targeted therapeutically.

S.5.5 THE GLOBAL MICRORNA PROFILE OF SKIN IN SYSTEMIC SCLEROSIS

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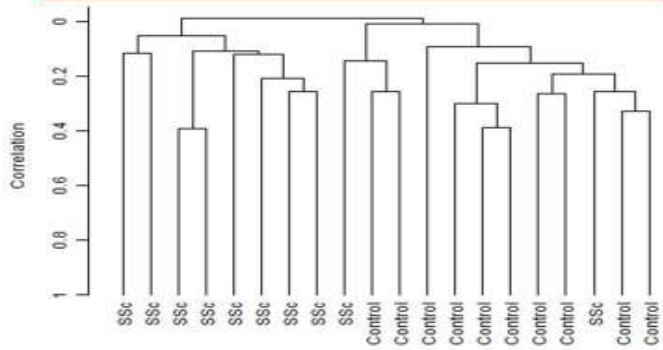
Background:
The underlying pathogenesis of systemic sclerosis (SSc) remains poorly understood contributing to limited efficacy of therapeutic options.
MicroRNAs (miRNAs) are small non-coding RNAs that play an important role in post-transcriptional gene regulation. Two families of dysregulated miRNAs, miR-21 and miR-29, have been implicated in the pathogenesis of fibrotic diseases and replicated in SSc. These studies focused on a miRNA of interest and global skin miRNA profiling in SSc has not been reported.
Recent advances in quantitative polymerase chain reaction (qPCR) allow simultaneous measurement of hundreds of miRNAs. The objective of this study was to use this technology to identify the unbiased, global miRNA profiling of SSc skin and evaluate their potential role in its pathogenesis.
Methods:
We investigated the miRNA profile in SSc skin compared to unaffected controls using multiplex qPCR platform. We obtained forearm skin samples (3 mm punch biopsy) from 10 patients with early SSc (<5 yrs, on no immunosuppression) and 10 age-, gender- and ethnicity matched controls. Total RNA was isolated using Qiagen miRNAeasy mini kit and examined by Exiqon LNA-enhanced (locked nucleic acid) miRNA qPCR. Levels of 752 miRNAs were determined. Unsupervised hierarchical clustering analysis was performed. Patient and control sample miRNA levels were compared and differences with a $p<0.01$, false discovery rate (FDR) <10% and fold change >2 were considered statistically significant.
Results:
The unsupervised hierarchical clustering analysis showed that the miRNA skin profile almost perfectly separated SSc patients and controls. Only one patient clustered along with controls (Figure 1). Comparison of patient to control samples revealed 26 miRNAs that were differentially expressed. Eighteen of these (69%) were part of the largest known human miRNA cluster (miR-379/miR-656) located on chromosome 14q32.3. Three miRNAs were encoded in a cluster on chromosome X (Xq26.3). We confirmed the previously reported up-regulation of miR21-5p in SSc.
Conclusions:
To our knowledge, this is the first global, unbiased examination of miRNAs in SSc skin. The miRNA profile almost perfectly separated SSc patients and controls. We observed 26 dysregulated miRNAs, most of them coming from two clusters, one of them located in chromosome X. This finding might have important biological implications considering the female predilection of SSc. Dysregulation of these miRNA clusters have not been reported in SSc and other autoimmune diseases. The results of our study link miRNA to the pathogenesis of SSc and could have important ramifications for future drug and biomarker development.

Figure 1: Unsupervised clustering of miR profiles observed in patient and control skin samples



S.5.6 THE PRESENCE OF A COLD TEMPERATURE SENSOR IN THE VASCULAR ENDOTHELIUM: ENHANCED EXPRESSION IN SSC SKIN AND ENDOTHELIAL CELLS DYSFUNCTION AFTER ACTIVATION

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Background: Cold exposure results in severe vasospasm and reperfusion vascular injury in SSc. The mechanisms responsible for enhanced cold sensitivity in SSc are poorly understood. Transient Receptor Potential Melastatin 8 (TRPM8) is a known cold sensing cation channel receptor. To date, TRPM8 expression has not been characterized in microvascular endothelial cells (MVEC). In this study we thought to investigate TRPM8 expression in normal and SSc MVEC and skin. We also investigated the effects of TRPM8 activation on MVEC gene expression.
Methods: MVEC were isolated from involved SSc skin and from matched healthy control subjects. The expression of TRPM8 was determined by RT-PCR, immunohistochemistry and by western blot analysis. TRPM8 activation was triggered by the addition of the agonist menthol or by exposure to cold temperature (18C°). The intracellular calcium concentration was determined by Ca2+ microfluorometry. The expression levels of TRPM8 in SSc-MVEC and SSc skin biopsies and the effects of TRPM8 activation on MVEC mRNA expression of ET1, NOS3 and PTGIS were determined by real time PCR.
Results: TRPM8 gene and protein expression in MVEC were confirmed by RT-PCR, Western blotting and immunohistochemistry. MVEC intracellular calcium ([Ca2+]i) influx into the cells in response to the addition of TRPM8 agonist menthol are demonstrated by Ca2+ microfluorometry studies. The activation of TRPM8 in MVEC by cold temperature or by menthol significantly increased the expression of ET1 (2.4 folds ± 0.21) and decreased NOS3 (62% ± 5.1 reduction) and PTGIS (61% ± 4.8) expression levels. These effects were reversed by the addition of the TRPM8 antagonist capsazepine. TRPM8 mRNA expression levels were significantly increased in SSc-MVEC (2.6 fold ± 0.22 vs. control MVEC) and SSc-skin biopsies (5.5 fold ± 2.3 vs. control skin biopsies).
Conclusions: The study demonstrates that human MVEC express functional TRPM8 and that there is increased expression of TRPM8 in SSc skin and in SSc-MVEC. TRPM8 may be involved in cold-induced vascular dysfunction through increase ET1, and decrease the NOS3 and PTGIS mRNA expression. The increased expression levels of TRPM8 in SSc-MVECs and SSc skin may mediate the known enhanced cold sensitivity in SSc. These results suggest that the blockade of TRPM8 activation could be an effective therapeutic strategy in SSc vasculopathy.

Session 7
Treatment and DMARDS in SSc

S.7.1 HOW TO TREAT RAPIDLY PROGRESSIVE SSC

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Systemic sclerosis (scleroderma; SSc) has a high mortality and morbidity but varies widely in rate of disease progression, reflecting clinical heterogeneity and disease subset. The most rapidly progressive cases are usually those with diffuse skin involvement and typically the maximum rate of progression is within the first 3 to 5 years of disease onset. The rate of change in skin scleroiss score can be assessed and has been associated with increased risk of major complications including cardiac involvement, lung fibrosis or scleroderma renal crisis. In many cases progression occurs over the first few months of disease and is associated with swelling and skin thickening affecting the distal limbs, pruritis over the proximal skin and the presence of tendon friction rubs on clinical examination. This constellation of signs is recognised to put a patient at high risk of scleroderma renal crisis and vigilant observation and patient education is important to minimise the delay in diagnosing this treatable complication that previously had very high mortality. Elevated ESR, platelet count and CRP are also recognised as markers of disease activity and poor outcome. In addition to skin progression there is risk of lung fibrosis and serious cardiac involvement with systolic impairment and cardiac arrhythmias. Thus treatment for SSc at this stage should include supportive management of manifestations such as Raynaud's phenomenon and reflux oesophagitis and investigation for major organ based pathology,. Severe skin disease or presence of cardiac or lung fibrosis my require treatment with intravenous cyclophosphamide followed by maintenance immunosuppression with mycophenolate mofetil or methotrexate although less severe cases may be treated initially with these oral drugs, reserving cyclophosphamide for more severe or refractory patients. Finally, there are emerging data supporting the potential value of HSCT in this group. The challenge is case selection as the ASTIS trial suggests a potential treatment related mortality of up to 10% although long term survival sand disease burden may be significantly improved. Cases with cardiac involvement, pulmonary hypertension and smokers may be especially at risk of TRM and are probably not suitable cases for this treatment despite their poor overall prognosis with standard therapy. Autoantibody reactivity may be especially helpful in identifying cases of rapidly progressive diffuse SSc as the anti-RNA polymerase III and anti-U3RNP positive patients are more often in this group and ANA patterns can eb defined early in the disease. This is important considering the emphasis on early diagnosis that will identify milder cases of SSc and so predictors of rapid progression are especially valuable.

Session 8
Mechanism of fibrosis

S.8.2 SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 3 (STAT3) REGULATES TRANSFORMING GROWTH FACTOR-BETA INDUCED FIBROSIS IN SYSTEMIC SCLEROSIS

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Background: Systemic sclerosis (SSc) is an autoimmune disease characterized by uncontrolled activation of fibroblasts resulting in excessive accumulation of collagen. TGFβ is considered as a crucial participant in the pathogenesis of SSc. Signal transducer and activator of transcription 3 (STAT3) is a transcription factor modulating the expression of targeted genes. STAT3 is activated by phosphorylation by several receptors tyrosine kinases, particularly by Janus kinase 2 (JAK2). The aim of this study was to evaluate the role of STAT3 in TGFβ signaling and its potential as a novel anti-fibrotic target.
Methods: Activation of STAT3 in human skin and murine models was analyzed by IF staining for STAT3 and phosphorylated STAT3 (pSTAT3). Specific inhibitors of JAK2 and STAT3 and knockdown strategies were used to study the STAT3 signaling in vitro and in vivo. The potential anti-fibrotic effect of STAT3 inhibition was evaluated in two mouse models of SSc: bleomycin-induced fibrosis and fibrosis induced by overexpression of a constitutively active TGFβ receptor type I (TBR).
Results: Increased activation of STAT3 signaling with accumulation of pSTAT3 was observed in the skin of SSc patients and in murine models of SSc. Stimulation with TGFβ increased the expression of STAT3 protein and induced nuclear accumulation of pSTAT3 in human fibroblasts. Inhibition of JAK2 by selective inhibitor TG101209 abrogated the TGFβ induced activation of STAT3 as well as nuclear accumulation of pSTAT3, demonstrating that TGFβ activates STAT3 in a JAK2 dependent manner. Inactivation of STAT3 with the selective STAT3 inhibitor S3I-201 significantly abrogated the TGFβ induced activation of human fibroblasts by reduction of Col1a1 (-71 %, p=0.0095) and Col1a2 (-35 %, p=0.0095) mRNA levels, collagen release (-56 %, p=0.05) and myofibroblast differentiation. The same results were observed when STAT3 was inactivated by conditional knockout in murine fibroblasts. In the model of bleomycin induced fibrosis, treatment with S3I-201 decreased dermal thickening by 33 % (p=0.0009), hydroxyproline content (HP) by 51 % (p=0.001) and myofibroblast counts by 55 % (p=0.0009). Anti-fibrotic effects with reduced dermal thickening, decreased HP content and reduced myofibroblast differentiation were also observed in TBR induced fibrosis.
Conclusion: We demonstrate for the first time the role of STAT3 in SSc. We showed that STAT3 serves as a downstream mediator of TGFβ. Inhibition of STAT3 prevented fibroblast activation and demonstrated potent anti-fibrotic effect in two different preclinical models of SSc. Our findings may have direct translational implications as several STAT3 inhibitors are currently in clinical trails.

S.8.3 INVESTIGATING THE ROLE OF MYOCARDIN RELATED TRANSCRIPTION FACTOR (MRTF) IN SYSTEMIC SCLEROSIS (SSC)

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MRTF-A is a 120kDa transcription factor widely expressed and normally sequestered in the cytosol by binding to G actin. Following actin polymerisation downstream of Rho signalling, MRTF-A is released and functions as a signalling molecule partnering serum response factor, influencing gene transcription via CARG elements. Genes expressing CARG like elements induced by MRTF-A/SRF include CTGF and type I collagen. The MRTF-A/SRF axis is highly relevant to SSc.

MRTF-A signal transduction was studied in healthy control and SSc fibroblasts. The MRTF-A/SRF small molecule inhibitor CCG1423 was used to block MRTF-A in vitro. SSc fibrotic responses were modelled by collagen gel contraction, CTGF, and type I collagen expression. MRTF-A signalling was assayed by Western blotting of nuclear and cytoplasmic extracts. Wound healing and fibrosis was studied in an MRTF-A knockout mouse and wild type. Immunochemistry looking for nuclear localisation of MRTF-A was used to determine presence of active signalling in SSc involved skin and healthy control.

SSc fibroblasts showed enhanced nuclear localisation of MRTF-A at 8 hours following exposure to TGFβ (4ng/ml) not seen in control fibroblasts. Immunochemistry of SSc skin biopsy revealed enhanced nuclear localisation in dermal fibroblast like cells, keratinocytes within the epidermis, as well as in perivascular cells. Following excisional wounding MRTF-A mice wounds failed to close normally and increased in size during days 1-7, wound area decreasing by day 11. When compared to wild type, MRTF-A knockout wounds were enlarged at day 7 (wild type area 6mm2, knockout area 12.4 mm2, $p<0.03$), and at day 11 (wild type area 0.42 mm2, knockout area 3.4 mm2, $p<0.01$). Day 11 wounds were extracted and found to exhibit abnormal histology,showing reduced scar formation, and altered vasculogenesis. Small blood vessels within the granulation tissue were dilated, and exhibited extravasation of red blood cells. Gel contraction by wild type fibroblasts was enhanced by TGFβ and blocked by CCG1423 1μM (basal conditions mean gel mass =0.176g, TGFβ treated = 0.118g, TGFβ+CCG1423 =0.238g, $p<0.002$). Dermal fibroblasts from MRTF-A knockout mice showed reduced basal gel contraction, and impaired response to TGFβ, (basal conditions mean gel mass =-0.349g, TGFβ treated =0.259g, TGFβ+CCG1423 =0.313g ($p<0.05$ basal vs wild type). Studies of belomycin induced skin fibrosis in MRTF-A -/- mice are ongoing.

MRTF-A signalling is abnormal in SSc involved skin. MRTF-A knockout mice fail to contract wounds adequately and show reduced scar formation, as well as abnormal vasculogenesis. CCG1423 and derivatives may be potential anti-fibrotics and of benefit in SSc.

S.8.4 EPHRIN B2 IS OVEREXPRESSED IN HUMAN SCLERODERMA SKIN AND MEDIATES FIBROBLAST TO MYOFIBROBLAST DIFFERENTIATION, AND INDUCES FIBROSIS IN MICE

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Ephrin B2 is a member of ephrin family belonging to the largest sub-family of membranous receptor protein-tyrosine kinases. The role of ephrin B2 in the pathophysiology of scleroderma (SSc) disease is largely unknown. In the present study we explored the potential of ephrin B2 in mediating fibroblast-myofibroblast differentiation and fibrosis associated with the pathophysiology of SSc disease.

Our immunohistochemistry, Real-Time PCR and western blot analysis show that Ephrin B2 expression was elevated in SSc skin compared to normal human skin. Further, ELISA results showed enhanced ephrin B2 production in SSc skin fibroblasts compared to fibroblasts isolated from healthy donors. In addition, the expression of ephrin B2 receptor, ephB4, is elevated in SSc skin compared to normal human skin. Interestingly, we identified that in vitro treatment of normal human skin fibroblasts with recombinant ephrin B2 is able to transform fibroblasts into myofibroblastic cells exhibiting all typical myofibroblastic-characteristics including increased stress fibre formation, increased cell spreading and focal adhesions, increased activation of focal adhesion kinase (FAK, a critical mediator of fibroblast to myofibroblast differentiation) and increased expression of alpha-smooth muscle actin (alpha-SMA) expressing myofibroblasts. In addition, treatment with the recombinant ephrin B2 is able to enhance fibroblast functions including increased rate of fibroblast migration and adhesion to fibronectin in both normal and SSc skin fibroblasts.

Mice were then injected subcutaneously with recombinant mouse ephrin B2/Fc (100ug/Kg/mouse) daily for two weeks and degree of fibrosis was determined. Mice treated with recombinant mouse ephrin B2/Fc exhibited significant skin fibrosis associated with enhanced collagen deposition, dermal thickness, hydroxyproline content, alpha-SMA-expressing myofibroblasts and increased expression of p-FAK, type I collagen and CTGF. We then generated fibroblast-specific ephrin B2 knockout mice (KO) mice in which Cre is under the control of a fibroblast-specific regulatory sequence from the pro-alpha-2(I) collagen gene to achieve ephrin B2 inactivation specifically in the fibroblasts. Wild type mice and ephrin B2 mice were subjected to bleomycin-induced skin and lung fibrosis. Results showed that all ephrin B2 KO mice showed significant protection from bleomycin-induced skin and lung fibrosis associated with significant reduction in dermal thickness, skin fibrosis, lung fibrosis, collagen synthesis, alpha-SMA expression and phosphorylation of FAK.

Our study, for the first time, provides compelling evidence that ephrin B2 is a key mediator of fibroblast to myofibroblast differentiation and targeting ephrin B2 could open up new potential therapeutic avenues to counteract fibrotic and adhesive signalling associated with SSc and related diseases.

S.8.5 EXPERIMENTAL RENAL INJURY IN A TGFBETA DEPENDENT MOUSE MODEL OF SCLERODERMA

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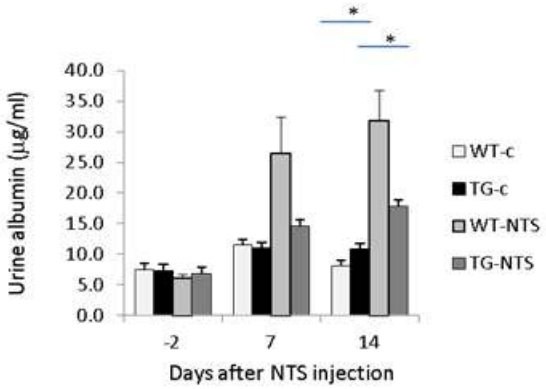
Purpose: Accelerated hypertension and rapidly progressive renal dysfunction are hallmarks of scleroderma renal crisis, a predominantly vascular and fibrotic condition without major inflammatory features compared with other autoimmune rheumatic diseases. No current animal model of scleroderma (SSc) develops this complication. The TβRIIδk-fib transgenic mouse model of SSc constitutively develops hypertension and large vessel adventitial fibrosis without renal disease. The response to long-term elevation of blood pressure or an inflammatory renal insult has not been studied. We have therefore explored the link between altered TGFβ bioactivity, vasospasm and inflammatory stress on the systemic vascular endothelium using NO synthase inhibition and the nephrotoxic nephritis model in this strain.

Methods: Histological assessment of cardiac and renal architecture, immunostaining for microvessel density and inflammatory cells and assessment of microalbuminuria by ELISA were performed on adult transgenic (TG) animals following treatment with either L-NAME or a single dose of nephrotoxic serum with pre-immunisation. Biochemical analysis of the TGFβ signalling pathway was performed assessing RNA and protein using whole organ isolates, and by immunostaining of tissue sections. Results were compared to appropriate TG and WT control groups.

Results: Increased cardiac mass and cardiac collagen measured by qPCR and Sircol® assay in TG and WT treated groups demonstrated that L-NAME treatment successfully induced hypertensive stress in this strain. Whole kidney lysates from L-NAME treated TG animals showed upregulated expression of Col1a1 (TG untreated copy number 3937±315, TG treated 6319±48, $p<0.05$) and Pai-1 (TG untreated 410±57, TG treated 740±74, $p<0.05$), and glomerulosclerosis was present on sirius red staining in the TG treated group, suggesting that these animals exhibited an enhanced renal fibrotic response when compared to WT treated animals. No other structural vascular changes were identified. In contrast, by day 14, TG animals had developed significantly less proteinuria following treatment with nephrotoxic serum (NTS) when compared with WT littermates. Examination of PAS stained samples showed glomerular damage in both WT and TG animals treated with NTS, with increased severity and number of damaged glomeruli in WT treated mice compared with TG.



Conclusions: This mouse model of scleroderma demonstrates exaggerated fibrotic response to hypertensive injury and is relatively resistant to experimental glomerulonephritis. This is likely to be a consequence of increased tissue levels of TGFβ. Both of these processes may underpin the unique vascular pathology seen in scleroderma renal crisis, this mouse strain provides a platform for further studies of renal injury in scleroderma.

S.8.6 DIRECT THROMBIN INHIBITOR DABIGATRAN ETEXILATE PROTECTS ALVEOLAR EPITHELIAL CELLS FROM APOPTOSIS IN A BLEOMYCIN MODEL OF SCLERODERMA-ASSOCIATED INTERSTITIAL LUNG DISEASE

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Background/Aims: Apoptosis of alveolar epithelial cells (AEC) is an important early event implicated in the pathogenesis of scleroderma-associated interstitial lung disease (SSc-ILD). However, the mechanisms underlying AEC apoptosis remain obscure. We previously demonstrated that the direct thrombin inhibitor dabigatran etexilate has marked anti-inflammatory and anti-fibrotic effects in vitro and in vivo in a bleomycin murine model of SSc-ILD. The aim of this study was to investigate the effects of dabigatran etexilate on apoptosis of AEC.

Materials and Methods: Lung injury was induced in 6-8 week old female C57BL/6 mice by a single intratracheal (IT) instillation of bleomycin. Dabigatran etexilate was given as supplemented chow beginning on day one following bleomycin instillation. Mice were euthanized one, two, and three weeks after IT bleomycin instillation and lung tissue, isolated AEC, bronchoalveolar lavage fluid (BALF), and plasma were investigated. Apoptosis was measured by ELISA and in situ cell death detection assay. Caspase-3, CCAAT enhancer-binding homologous protein (CHOP), immunoglobulin-binding protein (BiP), and activating transcription factor 4 (ATF4) were studied by immunoblotting and immunofluorescent staining. Reactive oxygen species (ROS) were measured by flow cytometry. The level of active thrombin in BALF was routinely monitored using thrombin substrate N-Benzoyl-Phe-Val-Arg-p-nitroanilide (Sigma) by a spectrophotometric method.

Results: In control mice receiving IT saline alone or IT saline plus dabigatran etexilate, alveolar structures were composed mostly of elongated type 1 AEC with few cuboidal type 2 AEC expressing surfactant protein C (SPC). Alveoli of bleomycin-treated mice were characterized by presence of multiple AEC type 2 cells similarl to what we have observed in alveoli of SSc-ILD patients. Lung tissue isolated 7 and 14 days after bleomycin treatment exhibited extensive apoptosis of AEC confirmed by TUNEL and caspase-3 positive staining. SPC-positive AEC were characterized by the presence of ROS and ER stress markers (BiP, ATF4, and CHOP). In contrast, significantly less apoptosis, lower amounts of ROS, and reduced ER stress markers were observed in bleomycin treated mice receiving dabigatran etexilate. Primary AEC cells isolated one and two weeks after bleomycin instillation continued to express high amounts of CHOP and caspase-3, which were not detectable by Western blotting in cells isolated from control mice. By contrast, significantly lower expression of CHOP and caspase-3 was detected in bleomycin treated mice receiving dabigatran etexilate.

Conclusions: We conclude that dabigatran etexilate reduces apoptosis of AEC by blocking reactive oxygen species and by decreasing endoplasmic reticulum stress in these cells.

S.8.7 STIMULATION OF THE SOLUBLE GUANYLATE CYCLASE (SGC) INHIBITS DERMAL FIBROSIS BY BLOCKING NON-CANONICAL TGF-BETA-SIGNALING

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Background: The soluble guanylate cyclase (sGC) converts GTP to cGMP to regulate vascular tone and homeostasis. The sGC stimulator riociguat has recently demonstrated high efficacy and excellent tolerability in phase 3 clinical trials for pulmonary arterial hypertension (PAH) and chronic thrombembolic pulmonary hypertension (CTPH). In the current project, we investigated a novel anti-fibrotic role of the sGC in systemic sclerosis (SSc).

Methods: Normal and SSc fibroblasts as well as sGC-knockout fibroblasts were treated with the sGC stimulator BAY41-2272 (lead compound of riociguat) or the stable cGMP analogue 8-Bromo-cGMP and stimulated with TGFβ. Crosstalk between sGC signaling and TGFβ signaling was studied by levels of phosphorylated SMAD2 and 3 (IF, WB), SMAD-reporter activity and target gene expression. In vivo, we investigated the anti-fibrotic activity and the tolerability of sGC stimulation in bleomycin-induced skin fibrosis, tight skin-1 mice, and mice challenged with an adenovirus expressing a constitutively active TGFβ receptor I (TBR model).

Summary of the results: When assessing the anti-fibrotic activity of the sGC, we observed that sGC stimulation by BAY41-2272 inhibited TGFβ-dependent fibroblast activation and collagen release from SSc and healthy fibroblasts in a dose dependent manner. In addition, sGC stimulation was effective in preventing the development of skin fibrosis and reversing established skin fibrosis in the bleomycin model and in tight skin-1 mice. sGC stimulation was well-tolerated and did not have significant effects on systemic blood pressure and heart rate as indicated by telemetry studies. Mechanistically, sGC knockout fibroblasts confirmed that the sGC is essential for the anti-fibrotic effects of BAY41-2272. Furthermore, we observed that 8-Bromo-cGMP mimicked the effects of BAY41-2272 and reduced TGFβ-dependent collagen release. Nuclear p-SMAD2 and 3 levels, SMAD-reporter activity, and transcription of classical TGFβ target genes remained unchanged upon sGC stimulation, suggesting that the anti-fibrotic sGC activity is independent of canonical TGFβ-signaling. In TGFβ-driven experimental fibrosis (TBR model), sGC stimulation inhibited TGFβ-driven fibroblast activation and collagen release, but did not change p-SMAD2 and 3 levels and TGFβ target gene expression, confirming that non-canonical TGFβ cascades mediate the anti-fibrotic sGC activity.

Conclusions: We identified a novel anti-fibrotic role of the sGC. sGC activity increases cGMP levels, blocks non-canonical TGFβ signaling and inhibits fibrosis in various model systems of SSc. Since sGC stimulators have shown excellent efficacy and tolerability in phase 3 clinical trials for PAH and CTPH, they may be further developed for the simultaneous treatment of fibrosis and vascular disease in SSc.

Session 10
Cardiovascular involvement

S.10.1 CONDUCTION AND RHYTHM DEFECTS IN SCLERODERMA

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Signs or symptoms of arrhythmias or conduction defects are frequently reported in patients with systemic sclerosis. These rhythm disorders may have several origins (i.e. related to primary heart involvement, pericardial disease, valvular regurgitation, pulmonary arterial hypertension...) and may negatively affect the overall prognosis of these patients. It is important to identify patients at high risk for cardiac arrhythmias thanks to a complete cardiologic evaluation, find out the underlying heart disease including SSc related myocardial involvement; in addition, some therapeutics options in SSc patients may differ from that are recommended on other population

S.10.2 IMPROVEMENT OF DIGITAL ULCERATIVE DISEASE IN PATIENTS WITH SYSTEMIC SCLEROSIS IS ASSOCIATED WITH BETTER FUNCTIONAL PROGNOSIS

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Background/Objective: Ischemic digital ulcers (DU) represent a major complication of systemic sclerosis (SSc) leading to hand disability. We investigated the impact of controlling the ulcerative disease on hand disability and quality of life after one year in SSc patients treated with bosentan.

Methods: ECLIPSE is a 2-year prospective, observational study. Patients with SSc who experienced at least one DU in previous year and received bosentan were included between October 2009 and March 2011. Demographical and clinical data were collected at inclusion and at 1 year, as well as disability scores (Cochin hand function scale (CHFS), health assessment questionnaire disability index (HAQ-DI)), pain score (Visual Analog Scale), and quality of life (SF-36). A controlled ulcerative disease was defined by the absence of new ulcer between inclusion and one-year follow-up. Data are presented as means ± standard deviations.

Results: Follow-up data were available at one year for 120 patients out of the 190 included patients. Patients' characteristics were similar to those of the overall cohort. Mean ages at inclusion and SSc diagnosis were 54±15 and 44±15 years, respectively. SSc was diffuse in 42% of the cases. At inclusion, patients had been receiving bosentan for 15.6±22.1 months. During the one-year follow-up, 46 (38%) patients experienced a new DU and the incidence of the event was 0.6 event/patient-year [95% confidence interval: 0.44-0.81]. Nevertheless, the proportion of patients with DU decreased from 61% to 22% and the number of DU per patient decreased from 1.4±1.8 to 0.6±1.6 ($p < 0.0001$). This diminution was associated with a significant decrease in disability scores from 29.4±20.1 to 25.0±20.2 ($p = 0.005$) on the CHFS and from 0.96±0.68 to 0.88±0.73 ($p = 0.04$) for the HAQ-DI; the pain score decreased from 4.3±3.1 to 2.9±2.8 ($p < 0.0001$). Improvements in the physical and mental components of the SF-36 were non-significant except for bodily pain ($p = 0.04$) and mental health ($p = 0.01$).

Patients with a controlled ulcerative disease ($n = 58$) significantly improved CHFS ($p = 0.04$), HAQ-DI ($p = 0.04$), and physical component of the SF-36 ($p = 0.05$) compared with patients with an uncontrolled disease ($n = 62$).

During the one-year follow-up, 21 (17%) patients discontinued bosentan for an adverse event including 5 patients presenting elevated aminotransferases.

Conclusion: In patients with SSc receiving bosentan, a controlled ulcerative disease is associated with a significant attenuation of disability.

S.10.3 PREDICTION OF CARDIAC AND VASCULAR EVENTS IN SYSTEMIC SCLEROSIS: INPUT FROM ENDOTHELIN-1 TYPE A RECEPTOR ANTIBODIES

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Objective: Cardiac and peripheral microvascular alterations are key features of systemic sclerosis (SSc). We have previously reported that angiogenic markers can predict cardiovascular outcomes in SSc (1). In parallel, a cross-sectional study reported an association between severe cardiovascular complications and functional antibodies against angiotensin II type 1 receptor (AT1R) and Endothelin-1 type A receptor (ETAR) (2). Therefore, our aim was to investigate the respective merit of all these markers in a prospective cohort.
Methods: serum levels of anti-AT1R and anti-ETAR autoantibodies, placenta growth factor (PlGF) and soluble vascular adhesion molecule (sVCAM) were measured with sandwich ELISA in a prospective cohort of 75 SSc patients. Circulating endothelial progenitor cells (EPCs) were quantified in peripheral blood by flow cytometry after cell sorting (1). The occurrence of at least one cardiac/vascular event was assessed during a planed 3-year follow-up by a composite index defined by the occurrence of at least one of the following event: a) one or more new ischemic digital ulcer (DU), b) pre-capillary pulmonary hypertension (PH) confirmed by right heart catheterization, c) left ventricular (LV) dysfunction, defined by a LV ejection fraction (EF)<50%, d) scleroderma renal crisis (SRC) (1).
Results: The mean±SD age of SSc patients (64 women) was 55±12 year old and the mean±SD disease duration was 9±8 years at baseline. Twenty-eight patients developed at least one cardiac/vascular event (DU in 18, PH in 5, LV dysfunction in 4 and SRC in a single patient). By univariate analysis, high baseline serum levels of anti-ETAR were predictive of the occurrence of cardiac/vascular events (p=0.002), together with low EPC counts (p=0.003) and increased levels of PlGF (p=0.0005) and sVCAM (p=0.009). No predictive value of anti-AT1R antibodies was identified. Multivariate analysis confirmed high serum levels of anti-ETAR antibodies (hazard ratio, HR: 3.71, 95% confidence interval, CI 1.44-9.52, p=0.03) and PlGF (HR: 5.22, 95%CI 1.96-15.87, p=0.01) as independent predictors of further development of cardiac/vascular events. The combination of high serum levels of anti-ETAR antibodies and PlGF was highly predictive of cardiac and vascular events occurrence during follow-up (HR 7.27 95%CI 2.49-23.51, p=0.0002).
Conclusion: This study identifies for the first time anti-ETAR antibodies as an independent predictor of cardiac and vascular events in SSc. This functional antibody, together with other angiogenic markers and in particular PlGF, may serve as biomarkers to improve cardiovascular risk stratification and therefore allow earlier therapeutic intervention.
References: (1) Avouac et al, Ann Rheum Dis 2012; (2) Riemekasten et al, Ann Rheum Dis 2011

Session 11
Interstitial lung disease

S.11.1 SSC-ILD: WHO TO TREAT AND HOW TO TREAT?

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Pulmonary disease is the leading cause of hospitalizations and mortality in patients with systemic sclerosis (SSc). Approximately 70-80% of patients with SSc have evidence of ILD. The majority of these patients remain relatively stable with respect to their SSc-ILD. However, in patients who have active ILD, significant loss in the lung physiology occurs early after the onset of SSc and close monitoring is warranted. This presentation will discuss the management of ILD in SSc with a focus on whom to treat, how long to treat and what pharmacological therapies to use.

S.11.2 PROGRESSIVE DETERIORATION OF PATIENTS WITH SCLERODERMA WITH PULMONARY INVOLVEMENT: 11-YEAR OUTCOMES FROM THE SCLERODERMA LUNG STUDY (SLS1)

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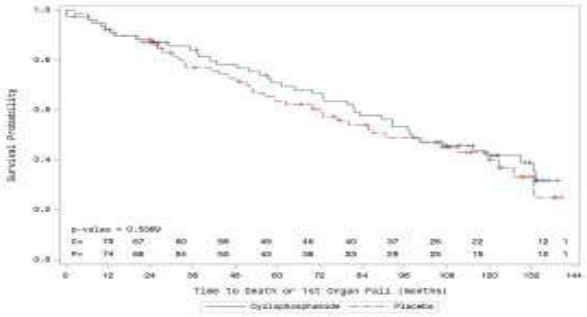
Background: SLS1 was a 13 site pivotal clinical trial showing benefit in lung function, skin thickening and quality of life measures after a 1-year course of oral cyclophosphamide (CY) (Tashkin, et al NEJM 2006). From 2000 to 2004, 158 subjects with diffuse or limited scleroderma, active alveolitis and an FVC of 45-85% predicted were randomized to CY or placebo. At year two (one year off study drug), benefits dissipated and follow-up was discontinued.
Objectives: To determine late outcomes in this well defined scleroderma population.
Methods: Protocol and telephone interview scripts were IRB approved at SLS sites. Staff searched two public death registries for all subjects. Data included dates of organ failure (oxygen use, cardiac ablation or pacing, lung, cardiac, kidney or stem cell transplant, dialysis or TPN), cancer development, and employment and Eastern Oncology Group (ECOG) performance status. Kaplan Meier (KM) estimates were censored at death or date last known alive.
Results: Of 158 study participants, 40 survive without organ failure, 18 survive with organ failure, 66 are deceased, 2 have no available data and 32 (20%) were unreachable, not in death registries, and dates recorded for last known alive. Organ failure developed in 33 subjects (14 CY and 19 placebo) with 31 experiencing lung failure. Seven CY and six placebo recipients developed cancer. Physical performance was significantly impaired in 28 (48%) of the 58 survivors: 5 were fully active; 26 were ambulatory but restricted in strenuous activity; 21 were ambulatory and capable of self care but unable to carry out work activities; and 7 were capable of only limited self care. Twenty-eight (48%) of survivors reported they were unemployed due to health reasons. Twenty-two (14%) of the 158 subjects are known to be alive and free of organ failure or significant physical impairment. In Table 1, times to 50% survival are presented by baseline characteristics. Decreased DLCO, decreased FVC and increased Rodnan scores at randomization were associated with significantly shorter durations of organ failure-free survival. Figure 1 depicts the 11-year KM probability of organ failure-free survival by treatment.
Conclusions: The SLS1 cohort showed progressive mortality, organ failure and physical impairment in both treatment arms. At the time of data collection, only 14% were known to be alive and free of significant physical impairment or organ failure. A 1-year course of CY did not provide long-term benefit and better treatments are needed for scleroderma lung disease.

Table 1. Long-term Outcomes in the Scleroderma Lung Study

Factor at Randomization	Number of Subjects	Time (Months) to 50% Survival (95% CI) Death	Survival Free of Organ Failure
Treatment			
Cyclophosphamide	79	115 (92, NA)	98 (79, 132)
Placebo	79	NA* (105, NA)	90 (62, 122)
Patient Age (yrs)			
<40	42	138 (86, NA)	92 (81, NA)
>=40	115	126 (100, NA)	97 (72, 122)
Disease Extent			
Diffuse	94	119 (89, NA)	90 (70, 115)
Limited	64	138 (106, NA)	126 (79, 132)
Disease Duration (yrs)			
<3	85	126 (79, NA)	89 (58, 132)
>=3	71	128 (97, NA)	105 (81, 128)
Smoking History			
No	96	133 (115, NA)	97 (81, 128)
Yes	58	138 (70, NA)	98 (57, 132)
Rodnan Skin Score			
<16	94	138 (126, NA)	126 (85, 133)
>=16	64	97 (64, NA)	77 (51, 100.0)
DLCO (% predicted)			
<45	75	97 (77, 138)	79 (52, 90)
>=45	83	NA* (119, NA)	132 (111, NA)
FVC (% predicted)			
<65	53	83 (52, NA)	52 (40, 81)
>=65	105	133 (115, NA)	115 (92, NA)

NA* indicates that the survival probability is >50% at all available time-points.



S.11.3 SURVIVAL AFTER LUNG TRANSPLANTATION IN SYSTEMIC SCLEROSIS. A SYSTEMATIC REVIEW

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Background/Purpose: Lung transplantation is a life-saving option for systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH) and interstitial lung disease (SSc-ILD) patients. Yet, there is risk of post-transplantation mortality. The objective of this study was to evaluate survival of SSc patients post-lung transplantation. We secondarily evaluated SSc lung transplant recipient characteristics, and compared post-lung transplantation survival of SSc patients to non-SSc patients (idiopathic PAH, and ILD).

Methods: A systematic review of MEDLINE, EMBASE, Cochrane Central Registry of Controlled Trials and CINAHL (all inception to 2012) was performed to identify studies evaluating post-lung transplant survival in SSc compared to non-SSc patients. Two reviewers independently abstracted study and survival data using a standardized form.

Results: 226 citations were screened to identify 7 observational studies reporting SSc patients who underwent single lung, double lung, or heart-lung transplantation. Mean age at transplantations ranged 46-53 years. SSc post-transplantation survival ranged 69%-91% at 30-days, 69%-85% at 6-months, 59%-93% at 1-year, 49%-80% at 2-years, and 46%-79% at 3-years. ILD post-transplant survival was 80% at 30-days, 80%-90% at 6-months, 59%-83% at 2-years, and 69% at 3-years. IPAH post transplant survival was 79% at 30-days, 79%-90% at 6-months, and 74%-90% at 1-year. The reporting of overlapping cohorts potentially including the same patients precluded meta-analysis. Causes of death in SSc patients, when reported, included graft failure (n=6), infection (n=8), cardiac events (n=3), hemorrhagic stroke (n=1), respiratory failure (n=3), malignancy (n=2), pulmonary hypertension (n=1), complications of bronchiolitis obliterans syndrome (BOS) (n=1), anesthetic complication (n=1), and scleroderma renal crisis (n=1). There were no reports of recurrence of SSc in the lung allograft.

Conclusion: SSc survival post-lung transplantation is very good, and improving with time. The short-term and intermediate-term survival post-lung transplantation are similar to IPAH and ILD patients requiring lung transplantation. Future researchers should delineate the access process for lung transplantation and report the occurrence of acute rejection, infection, bronchiolitis obliterans syndrome, renal dysfunction and dialysis, gastroparesis, and need for tube feeding.

S.11.4 GENETIC MARKERS OF SUSCEPTIBILITY AND INTERSTITIAL LUNG DISEASE IN SYSTEMIC SCLEROSIS PATIENTS: AN IMMUNOCHIP STUDY

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Objectives: We analyzed 186 known autoimmune risk loci finemapped in the Immunochip custom array with the aim to identify novel SSc risk loci shared with other autoimmune diseases and to narrow down previously SSc associated loci. Moreover, we intended to establish firm genetic markers for interstitial lung disease in SSc patients.

Methods: We genotyped 1,959 SSc cases and 3,582 controls of European ancestry from the United States and Spain using the Immunochip custom array. Classical HLA alleles, amino acid residues and SNPs imputation were performed and a fitting model for the association in the HLA region was defined using conditional logistic regression analyses. In addition, eight SNPs were chosen for replication in 4,017 SSc cases and 5,935 controls from 6 additional populations of European ancestry, reaching a combined population of 5,876 SSc cases and 9,517 controls. Furthermore, a pulmonary involvement case-case analysis was performed considering the interstitial lung disease (ILD) status of the SSc patients (determined using HRCT). For this phenotype-specific analysis, Immunochip genotype data were available for 589 ILD+ SSc patients and 1,333 ILD- SSc patients from 4 European cohorts.
Pooled analysis of the discovery populations with the replication cohorts was performed using the inverse variance method under a fixed effects model. Significance threshold was established at the genome-wide level ($p < 5x10-8$).

Results: We identified a model comprising 6 polymorphic amino acidic positions and 7 SNPs that explained the observed significant associations in the HLA region. Moreover, we identified 3 novel SSc risk loci showing genome-wide level associations. These novel loci included: DNASE1L3, SCHIP1 | IL12A and ATG5. Remarkably, the association of the rs35677470 functional missense variant in the DNASE1L3 locus with the ACA+ subset of patients is the most significant non-HLA association with SSc revealed to date ($p = 2.70x10-32$ OR=2.00). In addition, we further refined the area of association for the STAT4, IRF5/TNPO3 loci and related an observed peak of association in the PXK gene to the novel DNASE1L3 locus. Seven SNPs showed suggestive p-values in the ILD+ versus ILD- patient analysis and a replication step comprising 497 ILD+ and 853 ILD- patients is in progress.

Conclusions: This study provided a comprehensive insight into the association of the HLA region with SSc, identified 3 new SSc susceptibility loci and proposed new candidates for SSc-related ILD.

Session 12
Pulmonary Arterial Hypertension

S.12.1 PAH: HOW TO MAKE THE RIGHT DIAGNOSIS AT THE RIGHT TIME

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With the availability of effective targeted therapies for pulmonary arterial hypertension associated with systemic sclerosis (SSc-PAH), the detection of early stages of SSc-PAH has become a major task for the treating physicians. The most frequent diagnostic measures used in clinical practice to detect suspected PAH are lung function tests with DLCO and transthoracic echocardiography. However, while in advanced stages echocardiography might be a useful tool to suspect PAH, accumulating data show that standard echocardiography as a single measure is insufficient to detect PAH in early or even preclinical stages. These findings have let to different initiatives trying to establish recommendations and screening algorithms for the early detection of SSc-PAH. Recommendations were based on different consensus methods such as Delphi exercises and the RAND/University of California, Los Angeles consensus methodology. Evidence-based data were derived from multicenter studies with multivariate regression analysis and resulted in prediction scores such as the DETECT-score for PAH and the Cochin Risk prediction score for PH. These and other recommendations and prediction scores will be presented and their use in clinical practice will be discussed in this presentation. Most importantly, right heart catheterization remains the gold standard for the diagnosis of PAH

S.12.2 CHARACTERISTICS OF SYSTEMIC SCLEROSIS PATIENTS WITH PULMONARY HYPERTENSION AND A PULMONARY CAPILLARY WEDGE PRESSURE >15 IN THE PHAROS REGISTRY

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Background Systemic sclerosis (SSc) commonly leads to pulmonary hypertension (PH), which may be associated with left heart disease and an elevated pulmonary capillary wedge pressure (PCWP). Patients in this PH subgroup may have mean pulmonary artery pressures (mPAP) in proportion to their elevated PCWP (pulmonary venous hypertension, "PVH") or higher than expected given their PCWP ("out-of-proportion PH"). It is not known what causes this difference in patients with SSc.
Methods Baseline characteristics from 48 patients in the PHAROS registry who had a PCWP>15 on right heart catheterization (RHC) were retrospectively analyzed. Characteristics of those who died before 2 years of follow-up (n=10) were compared to those who were alive at 2 years (n=20). Patients were divided into 2 groups based on their initial RHC diastolic pressure gradient (DPG=diastolic PAP minus PCWP): PVH (DPG<5mmHg) or out-of-proportion PH (DPG>5mmHg). Comparisons were made between groups using unpaired t-tests or Chi square. Kaplan-Meier analysis compared survival and time to first hospitalization.
Results: At baseline, the mPAP was 36.8±11.8 mmHg and the PCWP was 19.4±3.3mmHg. Univariate factors associated with death prior to 2 years are shown in the table. In multivariate analysis, the only independent factors associated with death prior to 2 years were lower 6MWD (p=0.01) and higher PCWP (p= 0.01). The out-of-proportion PH group (n=26) had higher baseline mPAP (42.7±13.0 vs. 29.7±3.7mmHg, p<0.0001), DPG (12.7±8.6 vs. 2.9±1.5mmHg, p<0.0001), and pulmonary vascular resistance (376±235 vs. 204±101 dynes/sec/cm5, p=0.003) compared to the PVH group (n=22). Although there was no difference in baseline immunosuppression use overall, mycophenolate (MMF) use was less common in the out-of-proportion PH group (8% vs. 37%, OR 0.15, p=0.027). There were no differences between the PVH and the out-of-proportion PH groups in age, sex, disease duration, pulmonary function, SSc subtype, or 6MWD (all p>0.05). There was no difference in 3-year survival between the 2 subgroups (PVH: 1-year=95%, 3-year=61%; out-of-proportion PH: 1-year=85%, 3-year=63%, p=0.73). There was a trend towards shorter time to first hospitalization in the out-of-proportion PH group (p=0.13).
Conclusion: In patients with SSc-PH and a PCWP>15, lower 6MWD and higher PCWP were independently associated with an increased risk for death within 2 years. In SSc patients with a PCWP>15, those with out-of-proportion PH were less likely to be on MMF compared to those with PVH. The relationship between MMF and PH in SSc needs further investigation, as MMF's anti-fibrotic effects may theoretically decrease pulmonary artery remodeling in these patients.

Table Baseline characteristics in patients dying prior to 2 years of follow up compared to those who survived for more than 2 years

Parameter	Death within 2 years	Survival > 2 years	p value
Age (years)	58.3±15.5	54.1±12.3	0.68
Sex (% female)	56%	85%	0.16
SSc disease duration (years)	8.9±6.8	8.2±8.4	0.83
Scleroderma type (%)			
Limited	40%	55%	0.71
Diffuse	50%	35%	
NYHA functional class			
I/II	30%	73%	p=0.05
III/IV	70%	27%	
Immunosuppressant use at baseline (% yes)	20%	44%	0.40
6-minute walk distance (meters)	186±96	366±107	p=0.002
Borg Dyspnea Score	5.7±3.2	2.7±2.0	p=0.03
Mean pulmonary artery pressure (mmHg)	40.0±9.8	32.7±9.1	p=0.05
Pulmonary capillary wedge pressure (mmHg)	22.9±4.3	18.6±2.4	p=0.001

S.12.3 RECOMMENDATIONS FOR SCREENING AND DETECTION OF CONNECTIVE-TISSUE DISEASE ASSOCIATED PULMONARY ARTERIAL HYPERTENSION

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Background: Pulmonary arterial hypertension (PAH) affects up to 15% of patients with connective tissue diseases (CTD) and is one of the leading causes of mortality in systemic sclerosis (SSc) and mixed connective tissue disease (MCTD). Previous recommendations were developed as part of larger efforts in PAH and did not provide detailed recommendations in CTD-PAH.

Objectives: To develop recommendations for screening and early detection of CTD-PAH using rigorous data-driven and consensus-building methodology.

Methods: We performed a systematic review for the screening and diagnosis of PAH in CTD by searching available databases. Using the RAND/UCLA methodology, we developed case scenarios followed by 2 stages of voting—first one was voted anonymously by 10 international experts on 1 (inappropriate) -9 (appropriate) scale and 2nd voting after face-to-face meeting.

Results: The key recommendations include:

1. All patients with SSc should be screened for PAH.
2. MCTD or other CTD's with scleroderma features (referred hereon as scleroderma-spectrum disorders) should be screened similar to patients with SSc.
3. Screening of asymptomatic patients is not recommended for MCTD or other CTD patients without features of scleroderma.
4. RHC is mandatory for diagnosis of PAH.
5. Acute vasodilator testing is not required as part of the evaluation of PAH in patients with SSc, SSc-spectrum disorders, or other CTDs.
6. Initial screening evaluation in patients with SSc and scleroderma-spectrum disorders include pulmonary function test (PFT) including diffusion capacity carbon monoxide (DLCO), Transthoracic echocardiogram (TTE), NT- Pro BNP, and DETECT algorithm if DLCO% < 60% and >3 years disease duration.
7. In SSc and SSc-spectrum disorders, TTE and PFT should be performed on an annual basis or TTE, PFT, and NT-Pro BNP if new signs or symptoms develop.

Recommendations for RHC for SSc and scleroderma-spectrum disorders

Non-invasive test	Threshold for RHC	Signs or symptoms* required for RHC
TTE	TR velocity of 2.5-2.8 m/s	Yes
	TR velocity of >2.8 m/s	No
	Right atrial (RA major dimension >53 mm) or right ventricular enlargement (Mid cavity RV dimension > 35 mm), irrespective of TR velocity	No
FFTs	FVC/DLCO ratio > 1.6 &/or DLCO <60%**	Yes
	FVC/DLCO ratio >1.6 &/or DLCO<60% & NT-Pro BNP >2 times upper limit of normal**	No
Composite measure	Meets DETECT algorithm in patients with DLCO< 60% & disease duration> 3 years	No

* Symptoms: dyspnea on rest or exercise, fatigue, pre-syncope/ syncope, chest pain, palpitations, dizziness, lightheadedness. Signs: Loud pulmonic sound, peripheral edema ** TTE without overt systolic dysfunction, greater than grade I diastolic dysfunction or greater than mild mitral or aortic valve disease or evidence of PH

Conclusions: We provide consensus-based and evidence-driven recommendations for screening and early detection of CTD-PAH. It is our hope that these recommendations will lead to early detection of CTD-PAH and ultimately improve patient outcomes.

S.12.4 A COMPARISON OF THE PREDICTIVE ACCURACY OF THREE SCREENING MODELS (DETECT V. ESC/ERS V. ASIG) FOR PULMONARY ARTERIAL HYPERTENSION IN SYSTEMIC SCLEROSIS

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Background and Aim: There is evidence that screening for Pulmonary Arterial Hypertension (PAH) in systemic sclerosis (SSc) improves outcomes. We compared the predictive accuracy of two recently published SSc-PAH screening algorithms (DETECT 2013 and Australian Scleroderma Interest Group - ASIG 2012) with the commonly used European Society of Cardiology / Respiratory Society (ESC/ERS 2009) guidelines.
Method: We included 71 consecutive SSc patients with suspected PAH undergoing RHC. We excluded patients with FVC<40%. The three screening models were applied to each patient as follows: a positive screen in DETECT was a score of 300+ in 'step 1' (FVC/DLCO%, telangiectasia, anti-centromere antibody, NT-proBNP, urate, ECG right axis deviation) together with a score of 35+ in 'step 2' (step 1 points, RA area, tricuspid regurgitant velocity [TRV]) calculated using a nomogram; a positive screen in the ASIG algorithm was DLCOCORR <70% and FVC/DLCOCORR>=1.8, or NT-proBNP>=210 pg/ml; a positive screen in the ESC/ERS guidelines was TRV >3.4 m/s, or TRV >2.8-<=3.4 and symptoms, or TRV <=2.8 m/s and symptoms and additional suggestive echo variables. PAH was defined as mPAP>25 and PCWP<=15 mmHg on RHC. For each model, contingency table analysis was used to determine sensitivity, specificity, positive (PPV) and negative predictive values (NPV) for PAH. These test properties were also evaluated in an 'alternate scenario analysis' where the prevalence of PAH was set at 10%.
Results: RHC revealed PAH in 27 (38%) patients, while 10 patients had WHO group 2 and 3 PH and were excluded from further analyses. TR jet was undetectable in 3 patients to whom the ESC/ERS guidelines could not be applied; none had PAH on RHC. Test properties of the three models are summarized in Table 1. Both DETECT and ASIG algorithms performed equally well with sensitivity and NPV of 100%. However, the ESC/ERS guidelines had NPV of only 90%, missing one case of PAH. All three models lacked specificity, ranging from 29% to 47.1%. With PAH prevalence set at 10%, the NPV of the models was unchanged, but the PPV dropped (Table 1).
Conclusion: In this cohort, the DETECT and ASIG algorithms out-perform the ESC/ERS guidelines, detecting all patients with PAH. The specificity of all models is low, as may be expected in a screening test. The ESC/ERS guidelines have limitations in the absence of a TR jet. Ultimately, the choice of SSc-PAH screening algorithm will depend on cost and ease of application.

Table 1. Comparison of the performance of DETECT v. ESC/ERS v. ASIG screening models for SSc-PAH

				PAH prevalence set at 10%		
	DETECT n=61	**ESC/ERS** n=58	**ASIG** n=61	**DETECT** n=61	**ESC/ERS** n=58	**ASIG** n=61
Sensitivity (95% CI)	100% (87.2-100)	96.3% (81-99.9)	100% (87.2-100)	100% (54.1-100)	96.3% (54.1-100)	100% (54.1-100)
Specificity (95% CI)	35.3% (19.7-53.5)	29.0% (19.7-53.5)	47.1% (29.8-64.9)	35.3% (23.8-50.4)	29.0% (12.5-36.8)	47.1% (35.4-62.9)
PPV (95% CI)	55.1% (40.2-69.3)	54.2% (39.2-68.6)	60% (44.3-74.3)	14.7% (5.6-29.2)	13.1% (4.9-26.3)	17.4% (6.8-34.5)
NPV (95% CI)	100% (63.1-100)	90.0% (55.5-99.7)	100% (79.4-100)	100% (83.2-100)	99.7% (73.5-100)	100% (87.2-100)

S.12.5 CLINICAL SUBTYPE AND AUTOANTIBODIES BOTH HELP PREDICT PULMONARY ARTERIAL HYPERTENSION, BUT AUTOANTIBODIES ARE STRONGER PREDICTORS OF DEVELOPING SECONDARY PULMONARY HYPERTENSION

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PURPOSE: Our objective was to assess whether clinical subtype (limited versus diffuse skin) or antibody is a stronger predictor of pulmonary hypertension (PH) development.
METHODS: From our prospectively enrolled institutional SSc databank we performed a cross-sectional study of SSc patients seen between 1.1.2000 and 31.12.2009. PH was defined as a mean pulmonary artery pressure (PAP) > 25 mmHg on right heart catheterization (RHC) or echocardiogram with PAP > 45 and diagnosed by a cardiologist. PH was classified as pulmonary arterial hypertension (PAH), or "secondary" PH from heart (PH-heart) or interstitial lung disease (PH-ILD). Patients with PH not related to SSc were excluded. Antibody testing was performed for nine SSc-antibodies by immunofluorescence, immunodiffusion and immunoprecipitation. Separate logistic regression models were created to perofrmed whether antibody or clinical subtype were predictors of PAH and secondary-PH (PH-heart + PH-ILD). To answer this targeted question age at initial visit, gender, clinic subtype and antibody were included in the models using a cut-off of $p < 0.10$. Interactions were assessed.
RESULTS: 13 patients were excluded. Of the 1,152 SSc patients included, 80% were female, 91% Caucasian, the mean age at first visit was 51 ± 13 years, and 56% had limited SSc. 97% had complete antibody testing. 197 (17%) had PH. There were 113 (10%) with PAH, 23 (2%) with PH-heart and 61(5%) with PH-ILD. 81% were RHC confirmed. Antibody distribution was 20% anti-centromere (ACA), 18% anti-Scl70, 24% anti-RNA polymerase III, 6% anti-U1RNP, 8% anti-Th/To, 4% anti-PM/Scl, 3% anti-U3RNP, 2% anti-U11/U12 RNP, 1% anti-Ku and 11% with other antibodies on immunoprecipitation. The final model for PAH is shown in Table 1 and for secondary-PH in Table 2. As testing for Th/To and U3RNP are not readily available, and these are grouped in published literature as a "positive nucleolar ANA", they were combined. On final multivariable analysis age, limited skin, and Th/To or U3RNP (positive nucleolar ANA) were predictors of PAH, with clinical subtype and these antibodies having similar odds ratios.
For secondary-PH increasing age, male gender, and anti-U11/12 positivityincreased the risk, while ACA-positivity decreased the risk. Limited skin disease was a weaker predictor for secondary-PH, and was excluded from the multivariable model when stricter criteria ($p < 0.05$) were used.
CONCLUSIONS: Both clinical subtype and Th/To or U3RNP antibodies are important, nearly equivalent predictors of PAH. However, age, gender and antibodies were clearly stronger predictors of risk for developing secondary-PH then clinical subtype.

Table 1: Multivariable Predictors of PAH

		Odds Ratio (95% Confidence Interval)	p-value
Age (years) at initial visit			< 0.0001
	< 35	----	
	35-44	0.88 (0.37 – 2.10)	
	45-54	1.07 (0.48 – 2.42)	
	55-64	2.11 (0.94 – 4.73)	
	>65	3.64 (1.64 – 8.07)	
Limited cutaneous involvement		2.74 (1.67 – 4.48)	< 0.0001
Th/To or U3RNP positive (nucleolar ANA)		2.66 (1.61 – 4.41)	< 0.0001

Table 2: Multivariable Predictors of Secondary PH

		Odds Ratio (95% Confidence Interval)	p-value
Age (years) at initial visit			0.03
	< 35	----	
	35-44	1.23 (0.43 – 3.59)	
	45-54	1.95 (0.72 – 5.29)	
	55-64	2.70 (0.98 – 7.43)	
	>65	3.53 (1.25 – 9.97)	
Male		2.18 (1.32 – 3.59)	< 0.002
Anti-U11/U12 RNP positive		1.51 (0.93 – 2.45)	0.02
ACA		0.27 (0.11 – 0.67)	0.004
Limited cutaneous involvement		3.12 (1.17 – 8.34)	0.09

S.12.6 PROGNOSTIC VALUE OF NT-PROBNP IN SYSTEMIC SCLEROSIS PATIENTS WITHOUT PULMONARY HYPERTENSION

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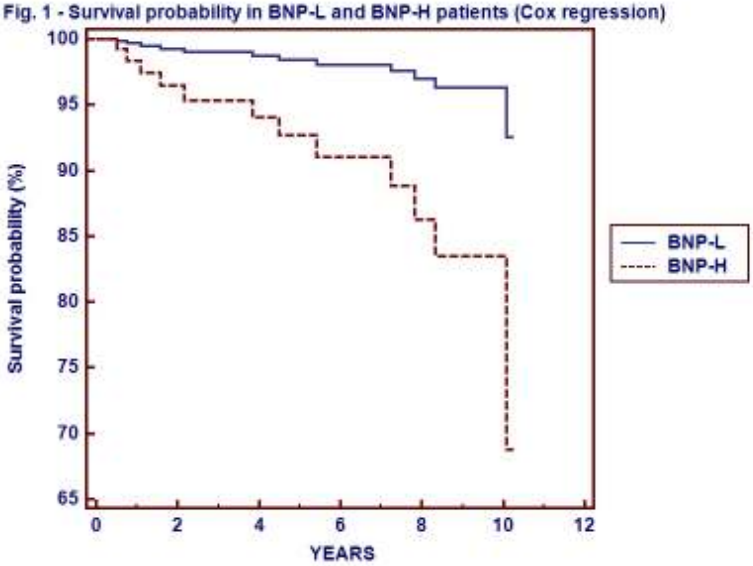
BACKGROUND: NT-proBNP has a recognized role as a diagnostic and prognostic marker in systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH) (1). However, NT-proBNP levels are known to increase in a number of pathologic conditions potentially affecting the prognosis SSc patients (2).
AIM OF The STUDY: to assess the prognostic value of raised NT-proBNP in SSc patients without PAH.
MATERIALS AND METHODS: 92 (88 F 4 M) SSc patients (limited 78, diffuse 14) were analyzed. Patients with right heart cath-confirmed PAH, severe valvular heart disease or LV systolic disfunction (EF < 55%) were excluded from the study, with inclusion of patients with borderline PAPs at cardiac echo but cath mean pulmonary arterial pressure < 25 mmHg. The patients were divided in two groups according to NT-proBNP levels <=400 pg/mL (BNP-L, N=74) or > 400 pg/mL (BNP-H, N=18). Baseline variables were compared by analysis of variance or chi-square statistics. Survival analysis was performed by Cox proportional- hazard regression.
RESULTS: Mean age at entry was 57.58 ± 13.27 yrs. Mean echo pulmonary arterial pressure was 30.55±7.66 mmHg. Average NT-proBNP levels were 261.63 pg/mL (range 5 – 3129). Mean age (67.7±8.75 vs. 55.12±13.06, p=0.000), PAPs (36.86±5.91 vs. 28.91±6.47, p=0.000), the prevalence of diffuse SSc (33.3% vs 10.8%, p=0.027), clinically significant interstitial lung involvement (55.6% vs. 20.3%, p=0.006), mRSS (13.71±11.47 vs 4.50±6.23) and the percentage of patients with active digital ulcers (50.0% vs. 18.9%, p=0.010) were significantly higher in BNP-H patients. BNP-H patients had lower mean DLCO (61.30±19.58 vs 76.17±18.63, p=0.025), walked a significantly shorter distance at 6MWT (259.45±142.11 vs. 368.15±107.58, p=0.005), and showed lower mean hemoglobin levels (11.78±1.29 vs 12.75±1.30, p=0.007). Mean serum creatinine and VAS scores (RP, Dyspnea, GI involvement) were not different between the 2 groups (p > 0.05). During follow-up (mean FU time 7.50±2.49 yrs) 12 patients died, 8 in the BNP-H group and 4 in the BNP-L group. In Cox analysis, only NT-proBNP levels and ILD presence were included in the regression model. Survival probability was significantly lower in BNP-H patients (p=0.0025).

Fig. 1 - Survival probability in BNP-L and BNP-H patients (Cox regression)



CONCLUSION: high levels of NT-proBNP are associated with increased mortality in SSc patients even in the absence of overt pulmonary arterial hypertension. Our findings lend further support to the inclusion of NT-proBNP dosage in the periodic screening algorithms of SSc patients.

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Special Lecture

DESSCIPHER, A JUMP IN THE FUTURE

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DeSScipher aims at improving clinical practice in the management of SSc for which no orphan drug is available. Over a three-year period, building upon the expertise of a multidisciplinary experienced consortium combining clinicians, physicians, biostatisticians, biologists and chemists, DeSScipher will provide a systemic approach to SSc. This approach isbased on five observational trials including different dimensions of the SSc disease: from early detection to severe complications, from child to adult patients, different organ levels (lung, heart) and integrates all generated outputs at the complexe level of the SSc disease. This project is comparing the outcomes of different preventive measures and treatments in terms of efficacy of off-label drugs and of adverse events from the early phase to severe phases of the SSc-associated diseases. DeSScipher will define appropriate outcome measures (OM) in SSc management. It includes several key experts - experienced in working together - from the EUSTAR consortium with more than 150 expert centres and 9000 well controlled and documented patients. Consequently, it is the aim of the DeSScipher project to improve clinical practice in the management of SScoccuring in adults but also in children by relying on the activities of the EUSTAR consortium. The concept of DeSScipher is using the EUSTAR long-term databank MEDSonline (Minimal Essential Data Set), the EUSTAR biobank and a preliminary diagnostic tool VEDOSS and to analyse and extend these data to shed light on specific molecular, genetic and functional details of SSc pathophysiology ranging from the early inflammatory phase to alterations of the vascular architecture to the clinically overt fibrosis of the connective tissues of the skin and internal organs. To facilitate the approach of DeSScipher, five observational trials are running to cover the disease evolution phases from early diagnosis such as digital ulcers and hand arthritis to the associated morbidity-driving pathologies such as interstitial lung disease, pulmonary hypertension or left heart disease. For this purpose, DeSScipher compares different scenarios: preventative measures and/or treatments to define appropriate primary and secondary outcome measures in order to evaluate the effectiveness as well as the adverse effects of the off-label candidate drugs and orphan drugs. For that purpose, the MEDSonline database as the biggest database in the field of an orphan rheumatic disease and the EUSTAR biobank have also been made available for and implemented by DeSScipher. DeSScipher will also serve as prototype approach for all other orphan diseases in the field of rheumatology and clinical immunology with similar problems in recruiting and documenting patients for testing novel drugs and establishing validated general international recommendations. Interested to contribute ? Visit the booth at the 3rd WSC or our website www.desscipher.eu or mail desscipher@med.uni-giessen.de
Funded by the 7FP of the EU and - in part - by EUSTAR/EULAR

Poster Tours – Clinical
Poster Tour 1: Raynaud & Ulcers

PS01 DECREASE OF BRACHIAL ARTERY ENDOTHELIAL-DEPENDENT FLOW-MEDIATED DILATION CHARACTERIZES VERY EARLY SYSTEMIC SCLEROSIS (VEDOSS) PATIENTS.

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Background: Endothelial dysfunction is a key feature of systemic sclerosis (SSc) preceding and potentially contributing via tissue ischemia to the widespread fibrosis characteristic of this condition. Multiple studies have revealed an increased prevalence of large-vessel disease in patients with SSc. Recently new preliminary criteria for very early diagnosis of systemic sclerosis (VEDOSS) have been proposed. The aim of this study was to investigate the endothelial dysfunction through brachial artery endothelial-dependent flow-mediated dilation (FMD) in patients with Raynaud's phenomenon (RP).
Methods: 42 consecutive patients with RP were enrolled. Patients were divided into 3 study cohorts: patients with primary RP with normal capillaroscopic findings and without any autoantibodies (n=10), VEDOSS patients (n=8) and defined SSc patients(n=24), respectively. Ten gender and age matched healthy individuals were enrolled as control group. Demographic, clinical and immunological parameters have been collected at the beginning of the study. 11 out of 24 (45.8%) SSc patients presented history of ulcers. Ultrasound assessment of FMD was performed in all RP subjects and in healthy subjects to evaluate endothelial dysfunction. VEGF, VEGF-RII, IL-6 and IL-6R plasma were determined through ELISA.
Results:
FMD was significantly reduced in patients with SSc compared to healthy subjects and compared with primary RP patients(SSc:6.9±6.3% vs HS:18.6±7.0% and RP:10.2±5.2%;p<0.0001 and p=0.024 respectively). The impairment of FMD was comparable in VEDOSS patients and in SSc patients, but interestingly also the VEDOSS patients presented a significant reduction of FMD when compared with healthy controls and primary RP controls(VEDOSS:5.1±3.6% vs HS:18.6±7.0% and RP:10.2±5.2%;p<0.0001 and p=0.04 respectively]. IL6 levels were significantly higher in patients with SSC compared to healthy controls, primary RP and VEDOSS patients (SSC:3.8±4.6% vs HS:2.0±3.0%, RP: 0.9±0.4% and VEDOSS:1.8±1.3%; p=0.03, p<0.0001 and p=0.02 respectively). VEGF plasma level was increased in SSc patients compared to healthy controls (SSC:26.6±38pg/ml vs HS:13.8±25.9pg/ml;p=0.05). Considering the clinical features of SSc patients no differences in cytokines levels and in FMD emerged. IL6 plasma levels directly correlate with skin score value in SSc patients (R=0.41;p=0.03).
Conclusions: An impairment of FMD was present in patients with RP, in particular in SSc and VEDOSS patients, suggesting a contemporary impairment of microvascular and macrovascular compartments in these patients. The deeper FMD impairment that characterized either SSc and VEDOSS patients, suggests that the endothelial dysfunction is already established since the early phases of the disease. However, the increased circulating levels of IL6 found in SSc patients, suggests its possible inflammatory action on endothelial dysfuction inducing SSc organ damage.

PS02 DIAGNOSTIC STANDARDS FOR CHILDREN WITH RAYNAUD'S PHENOMENON

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Background: Raynaud's phenomenon (RP) can be the first symptom of a connective tissue disease in children, in particular juvenile systemic scleroderma (JSSC) or systemic lupus erythematosis (SLE). However, the prevalence of RP in healthy school children has been shown to be as high as 15%[1]. There are currently no guidelines or agreed management strategies amongst Paediatric Rheumatologists on how to differentiate primary from secondary RP or how often patients require evaluation.
Objectives: To develop consensus standards for good clinical practice for children with RP.
Methods: A consensus meeting was organized in the frame of the PRES scleroderma working group. A nominal group technique was used. 75% consensus was defined as agreement.
Results: The following agreements were reached:
1. All patients with RP should be screened with an ANA test.
2. All ANA positive patients should be screened for scleroderma-specific antibodies (e.g. anti-SCL 70 and anti-centromere antibodies).
3. All patients with RP should be investigated by capillaroscopy. Capillaroscopy will be classified into 'normal', 'aspecific changes' or 'scleroderma pattern'.
4. All patients who have additional symptoms pointing to a definite connective tissue disease should be evaluated according to disease specific guidelines.
5. ANA-negative and capillaroscopy-negative patients should be followed-up at least every 6 months.
6. ANA positive patients without disease-specific antibodies and with negative capillaroscopy findings should be followed-up at least every 6 months.
7. ANA and disease-specific antibody positive patients should have organ specific evaluation according to symptoms, examination and relevant to that particular disease e.g. patients who are ANA and Scl-70 positive may need organ specific evaluation for JSSC as per the Juvenile systemic sclerosis inception cohort protocol (www.juvenile- scleroderma.com).
8. ANA-positive patients, who have no disease specific antibody but have positive capillaroscopy results, should be followed-up at least every 3 months.
9. ANA-negative patients with positive capillaroscopy result should be followed-up at least every 6 months.
10. The group could not reach an agreement regarding treatment, due to a lack of data for the paediatric age group. The group agreed that implementation of adult recommendations for paediatric care might be reasonable, but robust paediatric trials are needed.
Conclusions: The group made a suggestion for a standard of good clinical practice for RP in children. Our aim is that this will facilitate a large multicentre prospective follow-up study of children with RP.
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PS03 ANTI-ENDOTHELIAL CELL ANTIBODIES AS BIOMARKER OF SEVERE VASCULAR MANIFESTATIONS IN SYSTEMIC SCLEROSIS

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BACKGROUND: Systemic sclerosis (SSc) is a connective tissue disease of unknown etiology characterized by vasculopathy. Vascular injury occurs early in the course of disease, and previous studies suggest a primary role of anti-endothelial cell antibodies (AECA). The aim of the present study was to assess the association between AECA and the occurrence of severe vascular events in SSc patients.

METHODS: Fifty-eight SSc patients with severe vascular manifestations (19 with digital ulcers and amputation, 36 with symptomatic pulmonary arterial hypertension and 3 with scleroderma renal crisis), 62 SSc patients without severe vascular manifestations (20 with diffuse cutaneous SSc, 22 with limited cutaneous SSc and 20 with SSc sine scleroderma) and 60 healthy controls were included in this study. Sera were examined for the presence of IgG-AECA, using a cellular enzyme-linked immunosorbent assay (Cyto-ELISA). Human umbilical vein endothelial cells (HUVEC) were used as antigenic substrate for Cyto-ELISA.

RESULTS: Serum IgG-AECA levels in SSc patients with severe vascular manifestations ($p = 0.0001$) as well as in those without these manifestations ($p = 0.038$) were significantly higher than in the control group. Subgroup analysis showed that only patients with digital ulcers and amputation ($p = 0.001$) and those with symptomatic pulmonary arterial hypertension ($p = 0.019$) had significantly higher levels of AECA compared to controls. The frequency of IgG-AECA was significantly higher (29%) in patients with major vascular events (47% in patients with digital ulcers and amputation, 22% in patients with symptomatic pulmonary arterial hypertension and 0% in patients with scleroderma renal crisis) than in patients without these events (13%) (20% in patients with diffuse cutaneous SSc, 14% in patients with limited cutaneous SSc and 5% in patients with SSc sine scleroderma) ($p = 0.041$). Thirty-eight percent of patients with digital ulcers had these antibodies, versus 6% of those without digital ulcers ($p = 0.022$).

CONCLUSION: The strong association of IgG-AECA with major vascular events introduces these antibodies as an important serological biomarker for vascular disease severity in systemic sclerosis.

PS04 NAILFOLD VIDEOCAPILLAROSCOPY AND OTHER PREDICTIVE FACTORS ASSOCIATED WITH NEW DIGITAL ULCERS IN SYSTEMIC SCLEROSIS: RESULTS FROM THE CAP STUDY

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Background: Digital ulcers (DU) are painful, disabling and affect almost 50% of systemic sclerosis (SSc) patients. Nailfold videocapillaroscopy (NVC) non-invasively assesses SSc-related micro-angiopathy and may be useful in predicting DU (1–4).

Objective: To identify NVC variables and other factors which predict the occurrence of new DU in SSc patients.

Methods: International, prospective, cohort study in SSc patients, with two strata: DU-history and No-DU-history at enrollment. The No-DU-history patients had to be diagnosed within the last two years. Eligibility was not restricted by medication use. Baseline clinical characteristics including locally evaluated, standardized NVC (fingers II-V) were collected. Patients were followed up to 6 months for new DU. Univariable and Multivariable Logistic Regression (ULR and MLR) was performed to assess statistical significance (Wald Chi-square) of variables and their discriminatory ability (receiver operating characteristic area under the curve (ROC AUC). Internal model validation was performed by bootstrap method.

Results: Of the 623 patients enrolled (14 countries, 59 centers), 591 had data on DU-outcome [new DU (Cases) or no new DU (Non-cases)]. 468 (79%) patients had a DU history, of whom 103 (22%) developed new DU. 123 (21%) patients had no DU history, of whom 5 (4%) developed new DU. The present analysis focuses on the DU-history stratum (mean age 54.0 years, 79.5% females, 59.8% with limited cutaneous SSc).
Three baseline variables were selected in the final prognostic model: i) Mean number of capillaries/millimeter (middle finger, dominant hand) of 3.8 (95%CL 3.5, 4.2) in Cases and 4.7 (4.5, 4.9) in Non-cases (Wald $p<0.001$; ROC AUC=0.614 [95%CL 0.553, 0.674]); ii) Mean number of DU 1.8 (95%CL 1.2, 2.4) in Cases and 0.6 (0.4, 0.7) in Non-cases (Wald $p<0.001$, ROC AUC=0.678 [95%CL 0.622, 0.734]); iii) Critical digital ischemia present in 14.6% of Cases and in 3.3% of Non-cases (Wald $p<0.001$; ROC AUC=0.556 [95%CL 0.521, 0.592]); The prognostic model had a ROC AUC of 0.738 (95%CL 0.681, 0.795). Bootstrap results were consistent with the final model.

Conclusions: NVC imaging and assessment are feasible in international multicenter studies. The model for DU prediction in SSc patients with a history of DU uses number of capillaries (middle finger, dominant hand), current number of DU, and current critical digital ischemia. The model may add to the available tools for the early detection of SSc patients at high risk of developing new DU.

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4 Smith Ann Rheum Dis 2012;71:1636

PS05 MICRORNA-34A AND MICRORNA-155 IN RAYNAUD PHENOMENON: POSSIBLE EPIGENETIC BIOMARKERS OF ENDOTHELIAL DYSFUNCTION IN SYSTEMIC SCLEROSIS.

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Aim of the study. MicroRNAs(miRs) are a novel class of post-transcriptional regulators implicated in the pathogenesis of distinct human pathologies. MiR-34a and miR-155 were found to be related to endothelial senescence and inflammation. The aim of this study was to investigate the expression of miR-34a and miR-155 in peripheral blood mononuclear cells(PBMCs) in Systemic sclerosis(SSc).
Methods. Twenty-seven consecutive patients with Raynaud phenomenon(RP) were enrolled in this exploratory study. Patients were divided into 3 study cohorts: patients with primary RP (n=8), early SSc patients(eSSc) (n=9) fulfilling the proposed Very Early Diagnosis Of Systemic Sclerosis (VEDOSS) criteria and definite SSc patients (n=10) respectively. Gender and age matched healthy individuals (n=7) were enrolled as a control group. Demographic, clinical and immunological parameters have been collected at the beginning of the study. Expression of miR-34a and miR-155 was evaluated by qPCR on PBMCs. To identify miR-34a HumanTargetScan cross-referenced was employed. Identified targets were verified by qPCR. VEGF, VEGF-RII, IL-6 and IL-6R plasma levels were determined through ELISA.
Results. MiR-155 is overexpressed either in PBMCs of SSc (p=0.04) and eSSc (p=0.0002) compared to healthy controls. MiR-34a expression is increased only in SSc compared to healthy controls (p=0.013). Patients with primary RP did not differ for miR-155 and miR-34a expression from healthy controls (p>0.05). Anti-Scl70+SSc patients have significantly higher expression of miR-34a in PBMCs compared to anti-centromere+SSc patients (p=0.04). Furthermore, SSc patients with active and/or previous digital ulcers have significantly higher miR-34a expression compared to patients without ulcers (p=0.01). Finally the expression of miR-34a directly correlated with skin score value (R=0.52, p=0.032) in both SSc and eSSc patients and with IL-6 plasma levels (R=0.42, p=0.01). IL-6 receptor (IL6-R) was selected as target of miR-34a. IL6-R gene expression was significantly higher in eSSc patients compared to SSc (p=0.02). VEGF plasma levels were significantly higher in SSc patients compared to healthy control(p=0.01) as well as IL-6 plasma levels (p=0.02).
Conclusions. The increased expression of miR-34a and miR-155 in PBMCs differentiates SSc patients from RP patients. The overexpression of miR-155 was already found in eSSc, suggesting a possible endothelium impairment since the early phases of the disease. The increased expression of miR-34a in PBMCs of SSc patients, together with the down regulation of its target gene, IL6-R, characterize the subsequent vascular impairment and specific organ involvement associated to increased IL-6 circulating levels. Therefore miRNAs expression analysis could be an useful tool to differentiate between primary and SSc associated RP.

PS06 PHOSPHODIESTERASE-5 INHIBITORS FOR THE TREATMENT OF SECONDARY RAYNAUD'S PHENOMENON: SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED TRIALS

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Introduction. Recent controlled trials have assessed the efficacy of phosphodiesterase-5 (PDE-5) inhibitors in secondary Raynaud's Phenomenon (RP). However, the conclusions are conflicting and whether these drugs are effective remains unclear. The objective of this systematic review and meta-analysis was to determine the efficacy of PDE-5 inhibitors on the Raynaud's Condition score (RCS), the frequency and the duration of attacks.
Methods. A systematic review of articles was performed (sources included Medline, Embase, Web of Science, the Cochrane Central Register of Controlled Trials). Only double-blind, randomized, controlled trials (RCTs) were included. Study selection was done independently by 2 authors using predefined data fields, including study quality indicators. The PRISMA statement guidelines were followed.
Results. Six RCTs were included (1 with sildenafil, 1 with modified-release sildenafil, 3 with tadalafil and 1 with vardenafil). PDE-5 inhibitors significantly decrease mean RCS by -0.46 [-0.74;-0.17] ($p=0.002$), the daily frequency of ischaemic attacks by -0.49 [-0.71;-0.28] ($p<0.0001$), and daily duration of RP attacks by -14.62 [-20.25;-9] min ($p<0.0001$).
Conclusion. This meta-analysis shows that PDE-5 inhibitors significantly improve RCS, frequency and duration of RP attacks as compared with placebo in secondary RP. However, this effect is moderate and seems to be comparable to that of CCBs.

Poster Tours – Clinical
Poster Tour 2: Raynaud &Ulcers

PS07 CHARACTERIZATION OF LOWER LIMB CUTANEOUS ULCERS IN SYSTEMIC SCLEROSIS: THE ANALYSIS OF 554 LESIONS

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Cutaneous ulcers represent one of the most frequent complications in course of systemic sclerosis (SSc). The upper limb ulcers have been evaluated and characterized extensively, but there are only few studies on the lower limb ulcers.
Aim: The aim of the study was to assess prevalence, features and pathogenesis of the lower limb ulcers in course of SSc.
Materials and Methods: Sixty consecutive SSc patients with lower limb cutaneous lesions were enrolled. All patients performed accurate health examination and evaluation of cutaneous lesions, routine blood tests, videocapillaroscopy and arterial and venous lower limb Color Doppler Ultrasonography. Arteriography was performed in patients with occlusive peripheral arterial disease diagnosed at Ultrasonography.
Results: In the lower limbs, 554 different types of lesions were observed. The mean time to healing was 157.5 ± 192 days (median 90 days): the lesions recurred in 25.5% of cases.
Lesions were classified in hyperkeratosis, ulcers and gangrenes. Three hundred forty one (61.6%) hyperkeratoses, 208 (37.5%) ulcers and 5 (0.9%) gangrenes were observed. Ulcers were subsequently divided in: pure ulcers, ulcers secondary to hyperkeratosis and ulcers secondary to calcinosis. One hundred sixty two (77.8%) pure ulcers, 32 (11.1%) ulcers secondary to hyperkeratosis and 32 (11.1%) of ulcers secondary to calcinosis were observed.
Pure ulcers were divided in pure microvascular ulcers 66 (40.7%), venous 58 (35.8%), macrovascular 10 (6.2%) and mixed ulcers 28 (17.3%). Distribution of arterial, venous and lymphatic pathology is shown in table 1.Time to healing of the lower limb ulcers correlated inversely to the frequency of medications (p< 0,000), as expected. The presence of infection was associated to a significantly longer time to healing (p<0,003).Time to healing correlated also to duration of Raynaud phenomenon (p<0,04) and to duration of SSc (p<0,000).
Rate of recurrence correlated to Raynaud phenomenon (p<0,000) and disease duration (0,000).
Risk of amputation was associated with presence of critical peripheral arterial disease (p<0.05), with duration of Raynaud phenomenon (p<0.000) and with disease duration (p<0.000).
Conclusions: Our data indicate that lower limb lesions have often a multifactorial pathogenesis in SSc. This is the first study that characterized extensively a large number of lower limb cutaneous lesions in SSc. The comprehension of characteristics and pathogenesis of these lesions is essential for their correct management.

Peripheral arterial disease (haemodinaminacally significant)	17 (28.3%)
Critical peripheral arterial disease	6 (10%)
Monckeberg medial sclerosis	4 (0.7%)
Venous insufficiency/Post-phlebitic syndrome	18 (30%)
Lymphoedema	13 (21.7%)

PS08 CLINICAL FEATURES AND CHARACTERISTICS OF PATIENTS WITH DIGITAL ULCERS (DU) IN SYSTEMIC SCLEROSIS (SSC) IN THE CZECH REPUBLIC: DATA FROM THE DUO REGISTRY.

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Objectives. The aim was to describe disease characteristics of SSc patients with DU and their treatment in the Czech Republic at the time of enrolment.
Methods. In participating centres all patients with current or a history of SSc/DU who have given written consent in accordance with the Czech regulations are enrolled. Here we report on the demographics and treatment of these patients.
Results. Czech patients (n=81) enrolled in the DUO Registry from April 2008 to March 2013, were mostly female (n, %, 71, 87.7%). The disease of the patients was classified as limited SSc in 56.8%, as diffuse SSc in 28.4% and as overlap SSc/mixed connective tissue disease 13.6%. The proportion of patients with at least one ongoing DU at enrolment was 67.9%. DU associated interventions on fingers that were done in the past included upper limb sympathectomy (21%), debridement (23.5%) and surgical amputation (13.6%). Complications that were experienced in the past were mainly gangrene (29.6%), soft tissue infection requiring systemic antibiotics (19.8%), and rarely osteomyelitis (6.2%). At enrolment in the registry, analgesics and anti-inflammatories were administered to 84% of the patients, whereas prostacyclines only to 16%, and endothelin receptor antagonists (ERA) only to 6.2%. Among the topical treatments used (24.7%), topical antibiotics were the most (17.3%), followed by non-adhering dressing (8.6 %). Dry dressing was applied only in 3.7% and hydrocolloids in 2.5%.
Discussion. Considering disease subsets, in the Czech Republic overlap SSc/mixed CTD were more frequent but diffuse subset occurred much less frequent compared to the whole DUO population, were the diffuse subset was 40% (3). The proportion of patients with at least one ongoing DU was higher than in Germany but lower than in France, UK and Italy. Sympathectomy, debridement, and surgical amputation were performed much more often compared to Germany, France, UK and Italy. When evaluating complications, gangrene was more frequent in Czech patients compared to the four countries. Occurrence of soft tissue infection requiring antibiotics was similar only with the Italian population. Treatment with ERA is comparable only with the UK cohort.
Conclusions. The data from the Czech part of the DUO Registry reflect certain national specificities and approaches to the management of SSc patients. The observed differences in other EU countries in patients and disease characteristics, and in management modalities may be also due to selection biases. These findings draw attention to the need for a more harmonised European approach in establishing better management of SSc/DU patients.

PS09 PREDICTORS OF DIGITAL ULCERS IN PATIENTS WITH SECONDARY RAYNAUD PHENOMENON: CORRELATION BETWEEN CLINICAL AND HEMODYNAMIC FEATURES, CAPILLAROSCOPY, ENDOTHELIUM DYSFUNCTION AND ANGIOGENESIS BIOMARKERS.

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Background/Purpose: Digital Ulcers (DU) are a major disabling complication of Systemic Sclerosis (SSc) interfering with personal and professional life of our patients. The aim of our study was to analyze functional dysfunction of endothelium, capillaroscopy and angiogenesis biomarkers inpatients with SSc, with or without peripheral microvascular complications, in order to try to predict the development of digital ulcers in these patients.
Methods: This is a prospective study of a cohort of patients attending our Raynaud´sClinic (n108). Demographic and epidemiological data, autoimmuneserological screening, inflammatory protein screening, Flow mediated dilation(FMD) and end diastolic volume (EDV), capillaroscopy, Endothelin-1(ET-1), ADMA, VEGF andEndoglin were analyzed and compared to a control group (n31). Statistical calculations were performed using SPSS (v 20.0). Comparison and distribution between groups were performedusing Kruskal-Wallis test. The Mann-Witney test was used to compare continuous variables wit nominal variables. A p value 0.05 was considered significant.
Results: Flow mediated dilation (FMD) was reduced in patients with digital ulcers. The brachial artery diameter at 60 s after cuff deflation had statistical differences (P0.001) between SSc patients with digital ulcers compared to SSc patients without DU or primaryRaynaud phenomenon(RP). End diastolic volume was significantly different between groups (P0.001) suggesting an increase in peripheral resistance in patients with DU. FMD was more reduced in patients with late pattern(Cutolos classification) in capillaroscopy and a statistical differences (P0.001) between early and late pattern (P 0.007) was found. Endothelin-1 and ADMA were increased in patients with DU (P0.001) which might explain an excessive vasoconstrictor tone in these patients in association with occlusion of distal digital circulation (avascular areas in capillaroscopy) leading to the reducedFMD in patients with DU. VEGF was increased in SSc patients without DU, we found no difference with primary RP (P0.168). A statistical differences (P0.002) between patients with DU and SSc patients with no DU or with primary RP was found in VEGF. Endoglin was increased in patients with DU (p0,001). Patients with Cutolos late pattern in capillaroscopy had a increase in the angiostatic biomarker endoglin in comparison with the other groupsp <0,005).
Conclusion: In our cohort, we identified patients at risk of developing DUs: Ssc 70 positive, decreased FMD and low EDV, late pattern of Cutolos classification, increased ET-1, ADMA and endoglin and a reduced VEGF.Microvascular lesions and an increase in the peripheral resistance associated to endothelial dysfunction and a impaired angiogenesis with an imbalance in favor of increased angiostatic biomarkers may be behind the underlingmechanism of DU.

PS10 IONTOPHORESIS OF TREPROSTINIL AS A TREATMENT OF ISCHEMIC DIGITAL ULCERS IN SYSTEMIC SCLEROSIS: A PROOF-OF-CONCEPT STUDY

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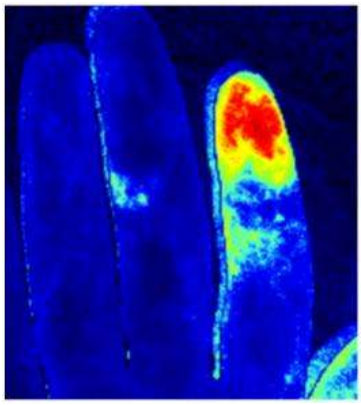
Objectives. Ischemic digital ulcers (DUs) are a complication of systemic sclerosis (SSc). Intravenous prostanoids are the only approved treatment for active DUs but they induce dose limiting side effects. Iontophoresis is a non-invasive drug delivery method that could be an alternative to i.v. treatment. Our primary objective was to evaluate the effect of treprostinil iontophoresis on digital skin blood flow in patients with SSc. First we performed pharmacokinetic and incremental dose studies in healthy subjects.
Methods. Three consecutive studies were conducted: first, twelve healthy volunteers received treprostinil and placebo by iontophoresis on the forearm. Intra-dermal and plasma drug concentrations were assessed over 8h. Then, a placebo-controlled, double-blind incremental dose study assessed the safety and the effect of treprostinil on the digital skin blood flow of 22 healthy subjects. The highest dose was then compared with placebo in a double-blind study including 12 SSc patients.
Results. The pharmacokinetic study showed that peak dermal concentration was reached at 2h, while the drug was undetected in the plasma. On the finger pad, skin blood flow was higher with treprostinil than at the placebo site with a single dose of 240 mC/cm² in healthy subjects (AUC0-4h were 29703±23460 and 18426±18365%BL.min, respectively; P=0.006) as well as in SSc patients (AUC0-4h were 47826±43941 and 30000±27543%BL.min, respectively; P=0.023) (Figure). The procedure was safe.
Conclusions. Digital iontophoresis of treprostinil was feasible and well tolerated. It increased skin perfusion in healthy participants and in patients, suggesting that iontophoresis of treprostinil could be tested as a treatment for SSc-related DUs.



PS11 EVALUATION OF THE EFFICACY OF SILDENAFIL ON TIME TO HEALING IN PATIENTS WITH SCLERODERMA AND ISCHAEMIC DIGITAL ULCERS (SEDUCE): PATIENTS' CHARACTERISTICS AT BASELINE.

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Background/Objective: Intravenous iloprost is usually considered in the treatment of ischaemic digital ulcers (DUs) in patients with systemic sclerosis (SSc) despite low evidence on DUs healing in a recent meta-analysis (1). Three small RCTs comparing various PDE-5 inhibitors to placebo suggested DUs healing (2-4), but this was not the primary endpoint.

Methods: SEDUCE was a randomized, placebo controlled, parallel groups study conducted in SSc patients with active fingers ischaemic DUs at inclusion. The aim of SEDUCE was to evaluate the efficacy of a 12-week period with sildenafil 20mg TID or a placebo on time to DUs healing. Patient's characteristics, history of SSc and history of digital ulcerative disease including complications and treatments were collected at baseline.
Results: 84 patients (64 females, age 49.4±13.7 years) were randomized in the study. Phenotypes were diffuse cutaneous SSc in 40 (40.8%), limited cutaneous SSc in 36 (43.4%) and limited SSc in 7 (8.4%). Modified Rodnan skin score was 13.1±8.5. All patients had a history of Raynaud phenomenon (RP) and first non-RP ScS symptom occurred 10.1±7.5 years before baseline. 34 patients had interstitial lung disease (extensive in 8), 4 had history of renal crisis, and 2 had pulmonary hypertension. DLco was 59.0±17.7%. Ischaemic DUs disease evolved for 7.4±6.2 years with a mean number of 2.4±1.8 DUs at baseline. This was the first DUs episode for 8 patients (9.6%) but 51 (61.4%) had a history of 5 or more DUs episodes. 73.5% have had a DUs episode within the 12 previous months. Sympathectomy was noticed in the history in 7 patients and 9 patients have had amputation (self-amputation in 8 and surgical amputation in 2). 49 patients had a history of intravenous iloprost for DUs (15 during the 6 previous months). 39 patients ever had endothelin receptors antagonists that were on-going in 27 (32.5%) at entry in the study. The last randomized patient finished the study in August 2013. The results of the study are expected for the first trimester of 2014.
Conclusion: Patients included in the SEDUCE study had severe active DUs.

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PS12 LASER SPECKLE CONTRAST ANALYSIS TECHNIQUE FOR THE FOLLOW-UP OF DIGITAL ULCERS IN SYSTEMIC SCLEROSIS PATIENTS.

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Background. The decrease of blood perfusion and the risk of digital ulcers are typical aspects of systemic sclerosis (SSc) (1,2). The care of digital ulcers includes both local and systemic treatments (3).
Objective. The aim of this study was to monitor the evolution of digital ulcers with laser speckle contrast analysis (LASCA) technique, in SSc patients treated for ten days with advanced local medications.
Methods. We enrolled five SSc patients with digital ulcers of recent onset (mean age 61±5 years, mean disease duration 7±5 years). At the beginning of the observation (T0) blood perfusion (BP) was evaluated in all patients at the level of the dorsal and palmar surface of whole hand with LASCA (4). Different regions of interest (ROI) were created at the level of fingertip, periungual and ulcer regions. The perfusion was measured in perfusion units (PU) (4). All patients were treated with local dressing, that are elastic and appropriate also for small lesions and curved surfaces. Before applying the dressing the ulcer was cleaned to remove fibrin, to promote granulation of and to prevent the penetration of bacteria into the tissue. The dressing was replaced every 2 days. The patients continued their systemic therapy with acetylsalicylic acid, proton pump inhibitor and anti-hypertensive drugs. After 10 days of treatment (T1) LASCA was repeated, with the same modalities reported above.
Results. A statistically significant increase of BP was observed between T0 and T1 in the ROIs created at the level of the ulcer area (T0 42.54 PU, T1 58.91 PU, respectively, p=0.04), while no statistically significant diffenence of BP was observed between T0 and T1 at fingertips and periungual levels. We also observed a positive correlation between BP at the level of the fingertip and BP at the level of the ulcer area at both T0 (r=0.92, p=0.03) and T1 (r=0.87, p=0.05). During treatment the ulcers improved and the necrotic tissue was gradually replaced by granulation tissue.
Conclusions. This is the first study evaluating the evolution of blood perfusion at the level of digital ulcers with the LASCA technique. LASCA gives a quantifiable and objective evaluation of perfusion of the ulcer area during treatment.
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Poster Tours – Clinical
Poster Tour 3: Pulmonary/Interstitial Lung Disease

PS13 PULMONARY FIBROSIS INDUCED BY BLEOMYCIN IS DRIVEN BY HIGH COLLAGEN V AND TGF-<BETA> SYNTHESIS

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Background: Fibrosing lung diseases are a serious problem to health and are highly ranked among chronic degenerative diseases due to its morbidity. Our group has already observed an important participation of collagen V (COLV) in different types of pulmonary fibrosis, such as systemic sclerosis and idiopathic pulmonary fibrosis. In this context, the better characterization, not only of this extracellular matrix (ECM) component but also of the others ECM components in the experimental models is necessary to identify their interactions. The aim of this study was to evaluate the participation of COLV fibers and TGFβ- in experimental model of pulmonary fibrosis induced by bleomycin (BLM).Methods :For induction of pulmonary fibrosis, groups of male mice C57Bl/6 (n=5-6), aged 4 to 6 weeks-old with 20-25g, were administered by intratracheal route with bleomycin (BLM) (0.1U/mouse). Sterile saline was used as control. For analysis, mice were sacrificed 14 (early stage) and 21 (late stage) days after induction of pulmonary fibrosis. Lungs were removed for routine histology, immunohistochemistry and histomorphometry. All experimental procedures were performed according to the guidelines of the Ethical Committee of the Faculty of Medicine of University of São Paulo (FMUSP), São Paulo, Brazil (process code 372/11). Results: A significant higher amount of COLV was found in late stage of BLM when compared to control group (9.74±0.67 vs. 5.14±1.08; $p<0.001$) and between early and late stages (2.27±0.67 vs. 9.74±0.67; $p<0.001$). An increase in TGF-β expression was observed in early stage of pulmonary fibrosis when compared to control (22.28±1.05 vs. 1.42±0.49; $p<0.001$) and also between late stage versus controls (34.86±2.32 vs. 1.42±0.49; $p<0.001$). A significant difference between the early and late stages of pulmonary fibrosis was observed as well (22.28±1.04 vs. 34.86±2.32, $p<0.001$). Higher amounts of COLI and COLIII were observed in early (41.56±8.38; 32.09±4.81; respectively, $p<0.05$) and late stage in BLM (15.26±1.57; 21.69±3.05; respectively, $p<0.05$) when compared with control group. In addition, higher amounts were observed in total collagen evaluated by 4-hidroxyproline in BLM group when compared to control (33.09 ±5.76, early stage; 42.06±1.55, late stage; $p<0.0003$). Conclusion:The higher amounts of COLV and TGF-β that we observed in the last stage of pulmonary injury produced by BLM probably are important components that contribute to the maintenance of the remodeling process evolution. These data suggest that strategies aimed at preventing the effect of this ECM component may have a greater impact in patients with pulmonary fibrosis.
Financial Support: FAPESP, CNPq

PS14 DISTORTED LUNG FRAMEWORK IS RELATED TO IL-17+ CELLS IMMUNOEXPRESSION IN SYSTEMIC SCLEROSIS

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Background: Although the role of immune dysfunction in the pathogenesis of systemic sclerosis (SSc) is generally accepted, the exact pathways that cause immune dysfunction in SSc remain to be elucidated. Alterations in cellular immunity have been typified by aberrant T cells biology in tissues as well as in the peripheral blood of SSc patients. Investigators have documented an increased number of IL-17+ cells in peripheral blood, in bronchoalveolar lavage and in skin tissue of patients with SSc. More recently, IL-17+ cells have been associated to collagen overexpression in fibroblast of patients with scleroderma. Objectives: Considering that the prognosis of SSc is associated to lung compromising, the aim of this study was to evaluate the expression of IL-17+ cells in the pulmonary fibrosis process of these patients. Patients and methods: Lung biopsies were obtained from 14 female patients with SSc (age range 26–56 y, mean 44.1 y): 9 patients had limited SSc, and 5 patients had diffuse SSc according to the American College of Rheumatology criteria. Control samples were collected from necropsies of 6 individuals without pulmonary pathology. The study was approved by the local ethical committee (CAPPesq 0960/08). The samples were fixed in formalin and then embedded in paraffin. The collagen I, III and V deposit in pulmonary interstitium was evaluated by immunofluorescence and quantified by image analysis using the software Image-Pro Plus 6.0. IL17+ cells were immunostained by immunohistochemistry with diaminobendine substrate system and evaluated by the point counting method. Results: Alveolar septa was 4.7-fold greater in SSc when compared to controls. There was no difference in thickened alveolar septa and collagen content between limited and diffuse SSc. However, in both SSc forms, collagen I was higher expressed than collagen III and V (44.49±0.93% vs. 39.75±2.75%, p=0.011; 44.49±0.93% vs. 40.62±0.702%, p=0.002). The amount of IL-17+ cells in the pulmonary interstitium was higher in SSc patients when compared to controls (3.455±0.36% vs. 1.72±0.19%, p=0.01). Limited and diffuse SSc presented the same amounts of IL-17+ cells. Conclusions: Distorted lung framework found in SSc is associated to IL-17+ cells immunoexpression, thus suggesting that this cytokine is involved in altered pathway of SSc pulmonary fibrosis and may represent a promissory immune therapeutic target.

Financial support: FAPESP, Federico Foundation

PS15 DOES MYCOPHENOLATE MOFETIL (MMF) HAVE AN EFFECT ON PULMONARY HEMODYNAMICS? OBSERVATIONS FROM THE PULMONARY HYPERTENSION ASSESSMENT AND RECOGNITION OF OUTCOMES IN SCLERODERMA (PHAROS) COHORT

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Background: Systemic sclerosis (SSc) related pulmonary hypertension (PH) carries a high mortality; with SSc pulmonary arterial hypertension (PAH) having a 4x higher mortality then idiopathic PAH. It is unknown whether immunosuppressant (IS) drugs, particularly mycophenoloate mofetil (MMF), have any effect on vascular remodeling in SSc PH since it has not been formally studied. This analysis looks at the possible effects of MMF in SSc patients who have developed PH.

Methods: PHAROS is a prospective registry designed to provide substantive data to recognize aspects of PH unique to SSc. Patients were stratified by history of MMF or No IS use (no MMF or other immunosuppressant drugs) at the time of the diagnosis of PH by right heart catheterization (RHC). Calculations are derived from non-parametric analyses using Mann-Whitney and Fisher's Exact as applicable followed by regression analyses.

Results: There were 39 SSc patients who had received MMF (mean duration 0.92 years) and 203 patients receiving No IS prior to diagnosis of PH. Patients treated with MMF when compared to the No IS group, were more likely to be younger, have diffuse SSc and have shorter disease duration. Patients treated with MMF had a significantly lower mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) with no difference in pulmonary capillary wedge pressure (PCWP) (Table 1). However, stratified analyses between diffuse and limited SSc patients on MMF revealed no significant differences in mPAP, PVR, PCWP nor in FVC, TLC, FEV/FVC nor DLCO (Table 2). In the group as a whole, MMF (p=0.046) and SSc subtype (p=0.01) were the only independent determinants of mPAP when adjusted for differences in age, FVC and disease duration.

Conclusions: Patients treated with MMF compared to the No IS group had lower mPAP and PVR at time of the diagnosis of PH with no difference between groups in PCWP. Differences in mPAP between groups were not explained by differences in age, FVC, or disease duration. These data suggest that MMF could potentially play a role in pulmonary artery remodeling and modifying the severity of PH. These findings warrant prospective controlled investigations of MMF in SSc PH.

Table 1. Comparison between SSc patients on No IS medications and MMF at time of first RHC. Continuous variables are reported as median, interquartile range; categorical values are proportional.

	No IS	MMF	p Value
n	203	39	
Age	60 (52,68)	54 (47,62)	*0.0149
Sex (% female)	84%	65%	0.6481
N (%) Limited SSc	144 (71%)	14 (35%)	*< 0.0001
Time from 1st SSc Symptom (years)	11.2 (5.3,21.0)	4.9 (3.0,10.3)	*0.0004
mPAP	33 (28,44)	29 (25,35)	*0.0016
PVR	335 (242,492)	222 (162,344)	*0.0006
PCWP	11 (8,14)	11 (9,15)	0.7034
FVC	78.1 (64,88)	68.9 (48,84)	*0.0298
TLC	76.5 (66,95)	62.8 (47,80)	*0.0032
FEV/FVC	81 (75,87)	87 (81,95)	*0.0048
DLCO	37.5 (30,50)	26.3 (20,39)	0.0609
FVC:DLCO	1.84 (1.6,2.4)	1.85 (1.4,2.5)	0.6908
6MWD	330.3 (238,428)	386.2 (343,475)	*0.0298

Table 2. Comparison of patients on MMF by limited and diffuse subtypes.

	lcSSc on MMF	dcSSc on MMF	p Value
n	14	23	
Age	57.5 (50,63.8)	51 (40,63)	0.2185
Sex (% female)	64%	67%	1.0
Time from 1st SSc Symptom (years)	8.4 (6.8,15.3)	4.1 (2.8,8.8)	*0.0176
Duration of MMF prior to RHC	0.47 (0.18,1.6)	0.55 (0.15,1.2)	0.9694
mRSS	3 (2,5)	18 (7,28)	*< 0.0001
PH Meds at Time of RHC	36%	85%	0.1014
mPAP	29 (26,36)	29.0 (25,33)	0.7507
PVR	234 (140,466)	222 (166,340)	0.7485
PCWP	11.5 (9.8,16.5)	11.0 (9,15)	0.7621
FVC	75.5 (57.2,90.0)	61.7 (48.5,76.2)	0.1039
TLC	68.9 (54.7,46.0)	60.3 (46.8,77.9)	0.1898
FEV/FVC	84.5 (79.0,88.5)	87.0 (81.8,95)	0.5181
DLCO	36.2 (31.4,40.2)	32.5 (25.2,38.4)	0.2862
FVC:DLCO	2.04 (1.4,2.6)	1.73 (1.2,2.3)	0.5168
6MWD	417.1 (362,502)	388.8 (241,484)	0.3384

PS16 DEVELOPMENT OF A COMPOSITE OUTCOME MEASURE FOR SYSTEMIC SCLEROSIS-RELATED INTERSTITIAL LUNG DISEASE

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Background: While clinical trials in SSc-ILD have traditionally used FVC as the primary outcome, combining individual outcomes may lead to a more comprehensive measure of treatment response and minimize the risk of type 1 error that can occur when multiple tests are performed on several individual outcomes. The purpose of the present study was to develop a composite outcome measure to assess treatment response in patients with SSc-ILD.

Methods: Using data from the SLS-I study comparing cyclophosphamide treatment versus placebo in 158 patients with SSc-ILD, we entered the following outcome variables into a multivariate regression model to determine which variables had a significant treatment effect at 12 months: change in FVC, TLC, Quantitative lung fibrosis (QLF) by HRCT and mRSS; and the Transitional dyspnea index (TDI). We subsequently combined the variables with significant treatment effects ($p<0.05$) in a principal component analysis to assess the difference between treatment groups.

Results: Of the 158 patients, 77 had complete outcome data and were included in this analysis. The multivariate model demonstrated significant treatment effects for the following outcome variables (estimate [SE]; p-value): change in FVC (4.4 [1.7]; $p=0.01$), change in QLF (-12.5 [3.8]; $p=0.002$), TDI (3.5 [0.8]; $p<0.0001$). Combining these 3 outcome variables, the first principal component explained 62% of the total variation in these variables. The regression model with the first principal component for these 3 variables as the composite outcome demonstrated a significant treatment effect favoring cyclophosphamide ($R2=0.3;\beta=0.91$; $p<0.0001$). When we combined only change in QLF and TDI, the first principal component explained 70% of the total variation in these outcome variables. The regression model using the first principal component for these 2 variables as the composite outcome also demonstrated a significant treatment effect favoring cyclophosphamide ($R2=0.3;\beta=0.95$; $p<0.0001$).

Conclusion: The composite outcome comprised of change in FVC, change in QLF, and TDI, demonstrated a significant treatment effect favoring cyclophosphamide for the treatment of SSc-ILD. Eliminating change in FVC from the composite outcome did not change the overall treatment effect. Both composite outcome measures demonstrated a more significant treatment effect than using FVC alone as the outcome measure. These findings suggest that combining a patient-reported outcome with a structural outcome into a single measure may serve as a more robust measure of treatment response compared with change in FVC or QLF alone. This model requires validation using another dataset.

PS17 LUNG ULTRASOUND FOR DETECTING INTERSTITIAL LUNG DISEASE IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Objective
To determine whether LUS is a reliable tool for the detection of ILD in patients with SSc compared to the gold-standard, high-resolution computed tomography (HRCT).

Patients and Methods
Consecutive patients diagnosed with SSc (ACR 1980), whom as part of their clinical evaluation had undergone a HRCT for the past three months and did not have clinical signs of right heart failure and active pulmonary infection were studied.

A blind operator of clinical and tomographic medical history of patients achieved the LUS for the detection of B-lines with the method described by Gargani et. al. using a 3.5 MHz convex transducer. The sum of artifacts found in anterolateral and posterior chest results in a score that measures the degree of interstitial lung involvement. A study of more than 10 B-lines was taken as positive.

It was considered that HRCT was positive for ILD when had at least ground-glass opacity, lung fibrosis or honeycombing. The HRCT's were also objectively evaluated by an expert using the scoring proposed by Warrick et. al. (0 to 30).

Results
A total of 34 patients were included, with a mean age of 51 years and a disease duration of 6 years on average. The 55% of the patients were limited disease and the 45% diffuse.

There was a statistically significant difference in the number of B-lines among patients with or without ILD on HRCT (113,04 ± 81,05 vs 11,90 ± 9,33; p <0,0001).

A statistically significant positive linear correlation was found between the number of B-lines and the Warrick score (r 0,5569, p <0,0006). Also a significant negative correlation between LUS score and forced vital capacity was found (r -0.5509, p <0.0070).

The correlation between LUS and HRCT for individual patients was 85%, with a sensitivity of 100% (NPV 100%) and specificity of 50% (PPV 82.76%). A ROC curve analysis demonstrated the analytical relationship between the number of B-lines and the presence of ILD at HRCT (AUC 0.994, 95% CI 0.885 to 1.000, P <0.0001). A total number of B-lines >22 had a sensitivity of 100% and a specificity of 90%.

Conclusions
Lung ultrasonography is a valid method for the detection of ILD in SSc. Its high sensitivity and negative predictive value make it a powerful screening tool in these patients. However, its main limitation is the lack of specificity because B-lines may also be detected in cardiogenic pulmonary edema and parenchymal infectious sequelae

PS18 INTERSTITIAL LUNG DISEASE IN SYSTEMIC SCLEROSIS: CLINICAL PRESENTATION AND COURSE DIFFERENCES BETWEEN PM/SCL AND SCL-70 ANTIBODIES

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Objectives: To describe the characteristics of patients with Interstitial Lung Disease related to Systemic Sclerosis (ILD-SSc), with positive anti-PM/Scl antibody compared to a group with anti-Scl-70.

Methods: Sixty-three Spanish patients with ILD-SSc were selected in a retrospective observational study. ILD diagnosis was based in high-resolution computed tomography (HRCT), 14 had positivity for anti-PM/Scl antibody and 49 for anti-Scl-70. Clinical assessments, including pulmonary function test, were collected. Non-parametric tests and Kaplan-Meier curves were performed for statistical analysis.

Results: There were significant differences between anti-PM/Scl and anti-Scl-70 patients attending the first non-Raynaud phenomenon symptom at onset of SSc. Arthritis and puffy hands were the first symptoms in 57.1% of anti-PM/Scl patients ($p<0.001$), whereas the thickening of skin was in the 55.1% of anti-Scl-70 group ($p<0.001$). Diffuse subset was higher in anti-Scl-70 antibody (69.4% vs. 7.1%, $p<0.001$). There were no differences in age at ILD diagnosis nor the basal HRCT or forced vital capacity (FVC). Scl-70 patients had more peripheral vascular disease (100% vs. 78.6%, $p=0.009$) and gastrointestinal involvement (57.1% vs 88.9%, $p<0.001$). Inflammatory myopathy was associated to PM/Scl antibody (71.4% vs 6.1%, $p<0.001$). Regarding the lung course, the time of follow-up since ILD diagnosis was similar in both groups. Any grade of dyspnea was less commonly presented in anti-PM/Scl patients (50.0 vs 73.4%, $p=0.03$). An increment of 1.1% in FVC% predicted was documented in the PM/Scl group, while in the anti-Scl-70 group a decrease of 10.9% was observed ($p=0.004$). PM/Scl patients had less percentage of significant worsening in FVC% (15.4% vs. 52.4%, $p=0.01$), with higher proportion of a significant improvement in FVC% than Scl-70 group (30.8% vs. 7.1%, $p=0.01$). Severe restrictive pattern (FVC < 50%) during follow-up was less frequently documented in PM/Scl patients (7.7% vs 42.9%, $p=0.02$). The progression-free survival (PFS) which endpoint was defined as death or a decline greater than 10% in FVC%, was higher in anti-PM/Scl patients after 10 years from diagnosis of ILD (76% vs 29%, $p=0.04$)

Conclusions: We have found that PM/Scl antibody is related to more inflammatory myopathy and less peripheral vascular disease and gastrointestinal involvement. The anti-PM/Scl patients had a stabilization of FVC during follow-up. Even a third part had an improvement higher than 10% in FVC. This group presented less severe restrictive pattern, and a better progression-free survival. Results in our study have shown similar outcomes to the previously published, which highlights that ILD-SSc has a different behaviour depending on the immunologic profile.

PS19 LONG TERM FOLLOW-UP AFTER INTRAVENOUS CYCLOPHOSPHAMIDE PULSE THERAPY FOR SCLERODERMA INTERSTITIAL LUNG DISEASE: RESULTS OF A SINGLE CENTER EXPERIENCE

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Objectives: To analyze pulmonary function tests (FVC, DLCO), pulmonary artery pressure (PAP, ECHO-Doppler), and skin thickening (modified Rodnan' skin score, mRSS) at years 1,4,7 of follow-up after IV cyclophosphamide (CYC) treatment for active scleroderma interstitial lung disease (SSc-ILD: ground glass and/or pulmonary fibrosis on chest HRCT and reduction in FVC and/or DLCO for more than 10% during 2 consecutive visits).

Results: Among 230 SSc patients at our EUSTAR site, 42 had an active ILD. 28 patients started CYC before year 2007 and 17- before 2004). Age, disease duration, follow-up, and cumulative CYC doses were (mean +/- SD) 50.7 +/- 12.7 years, 16.3 +/- 17.9 months, 6.5 +/- 6 years, 8.96 +/- 3.8 G. Eight patients died (6 -due to SSc). Three patients developed complications: 2-pneumonia, 1-hepatitis B reactivation and Kaposi sarcoma, 1-premature menopause. During the first year FVC remained stable, DLCO and mRSS declined significantly. Main changes in FVC, DLCO, and mRSS were observed in first 4 years after CYC treatment with mild additional reduction in the follows years. PAP elevation was more prominent between 4th and 7th years. Mean annual changes (in %) in FVC, DLCO, mRSS, and PAP during 0-4 years and 4-7 years were: FVC 3.2 and 0.4 ($p<0.004$), DLCO 4.6 and 0.9 ($p<0.001$), and mRSS 1.8 and 0.2 ($p<0.002$). Among presenting features (cough, dyspnea, lung crepitus, acute phase reactants, autoantibodies) only elevated CK correlated with FVC, DLCO and PAP ($p=0.04$, $p=0.026$, $p=0.028$) changes. Cumulative doses of CYC higher than 6G had no additional effects on changes in variables. Highest annual reduction in FVC and DLCO during first 4 years correlated with mortality ($p=0.022$).

Conclusions: In SSc-ILD CYC infusions stabilized FVC during the 1st year but did not prevent further FVC and DLCO reduction as well as PAP elevation. CYC rapidly and significantly improved mRSS. Cumulative doses of CYC above 6G had not additional influence on FVC, DLCO, and mRSS reduction. Elevation of PAP became significant between 4th and 7th years of follow-up. CYC may be an effective induction therapy for SSc-ILD especially regarding lung volumes. The effect of CYC was lost in next years of follow-up. In the light of possible side effects it is a need for maintenance therapy with alternative DMARD after stabilization of pulmonary function tests with CYC. High annual rated of FVC and DLCO reduction might be an indication for more aggressive treatment early in the course of SSc-ILD.

Poster Tours – Clinical
Poster Tour 4: Pulmonary Arterial Hypertension

PS20 PULMONARY ARTERIAL HYPERTENSION (PAH) IN A CONTEMPORARY DRUG REGISTRY: RESULTS OF THE VOLT STUDY WITH AN EMPHASIS ON PAH ASSOCIATED WITH CONNECTIVE TISSUE DISEASE (CTD).

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VOLT (VOL-ibris Tracking) was an observational, multicenter registry, collecting safety information on the endothelin receptor antagonist ambrisentan (AMB) use in clinical practice.
Methods: The primary objective was to assess the overall safety profile of ambrisentan in clinical practice. The study was powered to detect a doubling of aminotransferase elevation >3x the upper limit of normal (ULN), from 1.5% to 3% per annum. Information on adverse events (AEs), AMB exposure and reasons for stopping, use of other PAH medications, functional class, hospitalisations and death was also collected.
Results: Demographics are shown in Table 1. The population was in line with PAH populations seen in registries and similar between the overall population and the CTD subgroup. Cumulative overall exposure was 2188 patient years, with a mean of 2.2 years/patient in the overall population, and 2.0 years/patient in the CTD-population. Exposure-adjusted rate of aminotransferase elevations >3xULN (ALT and/or AST, highest value given) was in line with the assumed background rate, and similar between the overall population (2% (95% CI: 1.5%,2.7%) and the CTD population (2.8% (95% CI: 1.5%,4.8%). The most common AEs reported (>10%) were oedema (24%), dyspnoea (15%), anaemia (12%) and heart failure (12%), and was similar in the CTD population (though 10% of CTD patients also experienced pneumonia). Hospitalisations and death occurred in 30% and 22% respectively of the overall population, and 26% and 27% respectively of the CTD-population.
Conclusions: The population recruited is consistent with a real life PAH population. The results suggest that the safety profile of ambrisentan in clinical practice is similar to that seen in randomised clinical trials, and that ambrisentan in CTD-PAH has a similar safety profile to the overall population.

Table 1: Baseline Demographics

Characteristic	Overall Population (n=998)	CTD population (n=238)
Mean Age	59.5	62.3
Female	667 (67%)	207 (87%)
Race:		
White/Caucasian	849 (85%)	207 (87%)
Missing	113 (11%)	22 (9%)
Other	36 (4%)	9 (4%)
Years since PAH diagnosis	2.9 years	2.4 years
Diagnosis of PAH	Idiopathic PAH 446 (45%) Heritable PAH 8 (<1%) PAH associated with underlying diseases 418 (42%) Missing 126 (13%)	Limited Systemic Sclerosis (CREST) 124 (52%) Systemic Lupus Erythematosus 26 (11%) Mixed CTD 18 (8%) Missing 70 (29%)
Baseline Functional Class	N=990	N= 235
I	22 (2%)	5 (2%)
II	258 (26%)	65 (28%)
III	642 (65%)	148 (63%)
IV	68 (7%)	17 (7%)

PS21 AUTOANTIBODY PROFILE IN SYSTEMIC SCLEROSIS ASSOCIATED PULMONARY HYPERTENSION

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Objectives. Pulmonary hypertension (PH) is a severe complication of systemic sclerosis (SSc), affecting around 10% of patients. A recent meta-analysis showed an overall 3-year survival of 52%(1). The impact of autoantibody on clinical phenotype of PH-SSc patients is not completely established. This study aimed to describe and compare the type of PH and hemodynamic characteristics between different profiles of autoantibody in SSc patients.
Methods. Five hundred and forty tree patients diagnosed with PH on right heart catheterisation (mean pulmonary arterial pressure mPAP >= 25mmHg) between 1998 and 2012 were retrieved from our local database. Anti-nuclear antibody (ANA) profiles (n=457) were retrieved from clinical immunology records (missing data in 86 patients).
Results. The distribution of ANA among SSc-PH patients was as follows: anticentromere antibody (ACA) 39%, anti-topoisomerase I (ATA) 12%, anti-RNA polymerase III (ARA) 6%, anti-U1RNP 6%, anti-U3RNP 5%, anti-PM/Scl 3%, anti-Th/To 3%. Seven percent of patients had multiples specificities or anti-dsDNA or anti-Ro/SSa alone. Fifteen percent were ANA positive in immunofluorescence and ENA (extractable nuclear antigen) negative. Five percent were ANA negative. Types of PH in patients with different ANA are presented in Figure 1. In PAH-SSc patients (n=308), significant differences were found between ANA groups for: age at PAH diagnosis (p<0.001), mPAP (p=0.025), FVC (p<0.001) and DLCO (p<0.001). Patients with ACA, ATA, ENA negative and ANA negative had the highest means of age at PAH diagnosis; patients with anti-U3RNP and anti-PM/Scl had the lowest. Patients with ACA had a higher FVC than ATA and ENA negative patients (p<0.05). Patients with ATA and ENA negative had the lowest DLCO. There was a trend for lower mPAP in ATA than in ANA negative patients (p=0.091). No other significant difference in hemodynamic characteristics was found between PAH-SSc patients.
Conclusion. PAH was the cause of PH in more than half of patients with ACA, anti-U3RNP anti-Th/To, ENA negative and ANA negative. In PAH-SSc, there were differences in age at PH diagnosis and pulmonary function tests between ANA groups. However, no difference was found in hemodynamic characteristics.

References:
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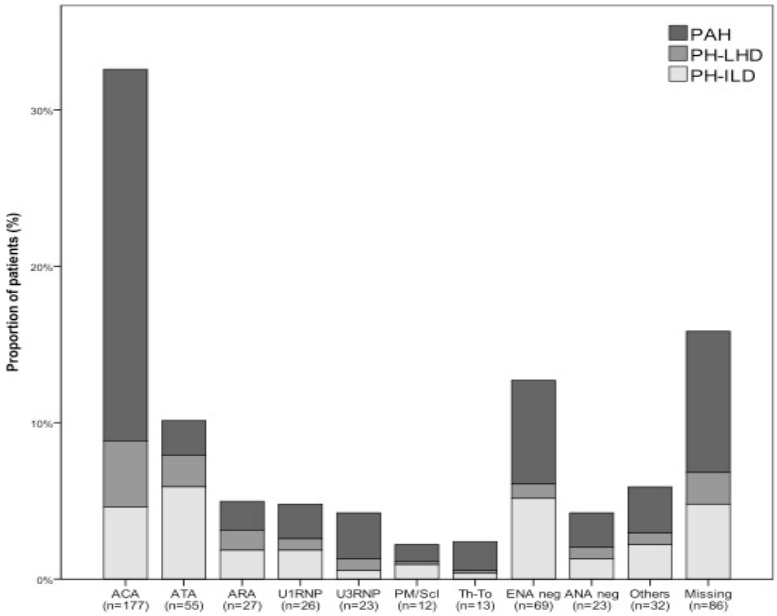

PS22 RELEVANCE OF THE 6-MINUTE WALKING TEST IN ASSESSING THE SEVERITY OF PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH SYSTEMIC SCLEROSIS, WITHOUT INTERSTITIAL LUNG DISEASE

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Introduction

In patients with idiopathic pulmonary arterial hypertension, 6-minute walking test (6MWT) correlates well with hemodynamic parameters and is a robust prognosis factor. In PAH associated with systemic sclerosis (SSc-PAH) however, data are more scarce and still a matter of debate. Various comorbidities caused by the underlying systemic disease may be confounding factors. Moreover, no study has evaluated the correlation between the 6MWT and the hemodynamics (i.e. the gold standard test to assess the severity of PAH) in this population yet. Our study aimed to assess whether there is a correlation between the 6MWT and the hemodynamic parameters measured during the right heart catheterization (RHC), in SSc-PAH patients without interstitial lung disease (ILD).

Methods

We included 75 patients with SSc-PAH and without ILD on chest HRCT, prospectively enrolled in the French PAH Network. Several data were collected at baseline regarding the clinical status (age, sex, BMI, NYHA class), the 6WMT (total distance, HR and deltaHR,SaO2 and deltaSaO2, Borg score), the RHC (mRAP, mPAP, sPAP, dPAP, CO, CI, PVR, TPR, systolic stroke volume), the PFT (FEV1, FVC, TLC, DLCO/VA, PaO2, PaCO2) and the TTE. The correlation of the 6MWT total distance with each hemodynamic parameter, but also with other data, was studied by linear regression.

Results

Univariate analysis showed a statistically significant correlation between the 6MWT total distance (expressed in meters and in percentage of normal value) and all the RHC hemodynamic parameters, especially the mPAP (R^2=0.10, p=0.0045), CI (R^2=0.20, p<0,0001) and PVR (R^2=0.18, p=0,0001). A similar correlation was also found between 6WMT total distance (when expressed in percentage of normal value) and the NYHA class, FEV1 and FVC.

In multivariate analysis, the 6WMT total distance (expressed in meters) was significantly and independently correlated with the CI, dPAP, FVC, age and NYHA classes 3 and 4. Those 5 parameters accounted for 46% of the 6MWT total distance, the CI explaining the majority of the distance (R^2=0,24).

Discussion

To our knowledge, this study is the first to prove a correlation between the 6MWT total distance and the hemodynamic parameters of PAH severity, in SSc-PAH patients without ILD. It further establishes the relevance of this test in assessing the severity of the PAH in this population.

Conclusion

Although potentially confounding comorbities are frequent, the 6MWT remains a relevant way to assess the severity of the PAH in SSc patients without ILD. However, other factors are probably involved in the 6MWT total distance, since the studied parameters accounted for only half of it.

PS23 COST SAVINGS WITH A BIOMARKER-BASED SCREENING ALGORITHM FOR PULMONARY ARTERIAL HYPERTENSION IN SYSTEMIC SCLEROSIS

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Background and aim: Most screening models for pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc) use transthoracic echocardiography (TTE) as a 'first tier' test. TTE is costly, requires expertise, and is limited by the absence of a TR jet and inestimable sPAP in up to 30% of patients. We have recently derived and validated a novel screening algorithm for SSc-PAH, based on serum NT-proBNP measurement combined with pulmonary function testing (PFT), which is highly sensitive and easy to use. In this study, our objective was to compare the accuracy and cost of SSc-PAH screening using this new algorithm (ASIGnew), with an existing TTE-based algorithm (ASIGold).

Methods: We included consecutive patients enrolled into the Australian Scleroderma Cohort Study who had undergone their first screening for pulmonary arterial hypertension using TTE and PFT between 2007 and 2012, and in whom serum had been collected for NT-proBNP measurement using the Elecsys immunoassay, at the time of screening or right heart catheterization (RHC). The existing Australian Scleroderma Interest Group SSc-PAH screening algorithm (ASIGold) recommends RHC for patients with sPAP >=40 mmHg on TTE or DLCO <=50% with FVC >85% predicted on PFT. In ASIGnew, patients screen positive if either DLCO <70% and FVC/DLCO >=1.8 on PFT, or NT-proBNP level is >=210 pg/ml. All patients who screen positive then undergo TTE followed by RHC. PAH was defined based on RHC as mPAP >25mmHg at rest and PCWP <15mmHg. The cost of the tests was obtained from the Australian medical benefits schedule. We compared ASIGold and ASIGnew in terms of (i) the number of TTE and RHC required to diagnose one case of PAH and (ii) the total cost of screening, and the cost of diagnosing one case of PAH.

Results: The results of the application of the algorithms to 643 patients are presented in Table 1. ASIGold missed 1 case of PAH detected by ASIGnew. ASIGnew resulted in 64% fewer TTE and 10% fewer RHC. ASIGnew resulted in a cost saving of $88,084 for the 'first' PAH screen in this cohort of 643 patients. This is a cost saving of $1,011.50 per case of PAH diagnosed.

Conclusion: Our biomarker-based SSc-PAH screening algorithm has better accuracy that the existing algorithm, reduces the number of TTE and RHC required, reduces the overall costs of screening, and reduces the cost of diagnosing each case of PAH.

	$ASIG_{OLD}$	$ASIG_{NEW}$
Total number of patients	643	643
Number (%) screen+	256 (40%)	231 (36%)
% screen+ with PAH on RHC	45%	50%
TTE required	643	231
RHC required	256	231
NNS to get one screen+	2.50	2.78
Number of RHC to diagnose one case PAH	2.20	2.00
NNS to diagnose one case of PAH	5.50	5.56
Total cost of screening and diagnosis	$851,917	$727,833
Cost of diagnosis of one case of PAH	$7,311.70	$6,300.20

Table 1. $ASIG_{OLD}$ and $ASIG_{NEW}$ algorithms applied to 643 consecutive patients with SSc. NNS=number needed to screen. All costs are in Australian Dollars.

PS24 VALUE OF SYSTOLIC PULMONARY ARTERIAL PRESSURE AS A PROGNOSTIC FACTOR OF DEATH IN SYSTEMIC SCLEROSIS EUSTAR POPULATION

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Objective To assess the prognostic value of systolic pulmonary artery pressure (sPAP) estimated by echocardiography in the multinational EULAR Scleroderma Trial and Research (EUSTAR) cohort.
Methods Data of patients with echocardiography documented between January 1st 2005 to December 2011 31st were extracted from the EUSTAR database. Stepwise-forward multivariable statistical Cox PH analysis was used to examine the independent effect on survival of selected variables.
Results Based on our selection criteria, 1476 patients were included in the analysis. 87% of patients were females, mean age was 56.3±13.5 years and 31% had diffuse systemic sclerosis (SSc). Mean duration of follow-up was 2.0±1.2 years (median 1.9 years). Taking index sPAP < 30 mmHg as reference, hazard ratio for death were 1.67 [95%CI 0.92-2.96] if index sPAP was between 30-36 mmHg, 2.37 [1.14-4.93] for sPAP between 36-40 mmHg, 3.72 [1.61-8.60] for sPAP between 40-50 mmHg and 9.75 [4.98-19.09] if sPAP was > 50 mmHg. In a multivariable Cox model, sPAP and DLCo were independently associated with the risk of death (HR=1.833; 95%CI=[1.035-3.247] and HR=0.973; 95%CI=[0.955-0.991] respectively).
Conclusion An estimate sPAP above 36 mmHg at baseline echocardiography was significantly and independently associated with a reduced survival, regardless the presence or not of pulmonary hypertension based on right heart catheterization.

PS25 ABERRANT BMP SIGNALLING MAY CONTRIBUTE TO PULMONARY COMPLICATIONS IN A TGF DEPENDENT MURINE MODEL OF SCLERODERMA.

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Background
Patients with pulmonary arterial hypertension associated with scleroderma (PAH-SSc) have a poorer prognosis compared to those with idiopathic (iPAH) or heritable (hPAH) forms of the disease, but the mechanisms that contribute to the development of PAH-SSc remain unclear. BMPRII mutations with concomitant effects on BMP signalling are an established cause of hPAH and some iPAH but these are not present in PAH-SSc.
Method
We investigated BMP signalling in the lung in the TRIIk-fib model of PAH-SSc in which TGF signalling is upregulated. The TRIIk-fib mouse develops a structural pulmonary vasculopathy with smooth muscle hypertrophy and raised right ventricular pressures. Experiments were performed on whole lung isolates and explant cultured fibroblasts (n=6) from the TRIIk-fib mouse and compared with wildtype littermate controls. Structural and biochemical analysis of components of the TGF superfamily and downstream signalling pathway was investigated by Western blot and immunohistochemistry and confirmed using qPCR measurement. Migration assays investigated the effects of PDGF-BB on lung fibroblasts from TRIIk-fib and WT controls (n=3). Confirmatory biochemical and functional studies on scleroderma fibroblasts were also performed.
Results
The TRIIk-fib model has increased levels of pSmad 2/3, indicative of enhanced TGF signalling. Consistent with an imbalance in the TGF/BMP axis we observed a significant reduction in BMPRII protein expression in the TRIIk-fib model, both in whole lung isolates ($p<0.05$), and explant cultured fibroblasts ($p<0.05$). A reduction of BMPRII was also observed in explant cultured lung fibroblasts from SSc patients compared to healthy controls. Murine fibroblasts exhibited a blunted response to BMP ligands ($p<0.05$). TRIIk-fib lung fibroblasts and SSc fibroblasts also exhibited enhanced migratory response compared controls ($p<0.05$).
Conclusion
In hPAH 70% of patients possess mutations in the BMPRII gene, which leads to a reduction in functional cell surface associated receptor. Here we demonstrate the TRIIk-fib transgenic murine model of PAH-SSc exhibits reduced expression of BMPRII as a reciprocal response to increased TGF signalling, with associated downstream signalling alterations independent of mutations in the BMPRII. We also show a similar trend in clinical material with a reduction of BMPRII in SSc fibroblasts and whole lung histology. Interestingly TRIIk-fib and SSc fibroblasts exhibit a heightened migratory response to PDGF-BB. Collectively our data suggests loss of BMPRII expression by non-genetic means may contribute to the development of PH in the TRIIk-fib mouse model by promoting an imbalance in the TGF/BMP axis and a similar mechanism may contribute to PAH in scleroderma.

PS26 CHARACTERISATION OF LATE-OUTGROWTH ENDOTHELIAL PROGENITOR CELLS FROM SYSTEMIC SCLEROSIS PATIENTS

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Introduction
Vascular complications associated with systemic sclerosis (SSc) including pulmonary arterial hypertension (PAH-SSc), result from endothelial damage and loss of barrier function. The causes of endothelial dysfunction are unclear, but the integrity of the endothelium is likely to be significantly diminished in SSc. Endothelial progenitor cells (EPCs) derived from peripheral blood mononuclear cells (PBMCs) express endothelial and haematopoietic markers. It is thought they home to sites of vascular injury and differentiate into endothelial cells and restore the barrier. In SSc patients circulating levels of EPCs are reduced. This study aimed to: (i) develop a robust method to isolate and grow healthy control (HC) and SSc EPCs from PBMCs. (ii) Compare the cellular functions of EPCs to mature endothelial cells.

Methods
Peripheral blood was taken from HC (n=10) and SSc donors (n=10). EPCs were cultured from PBMCs, and EPC colonies grown to passage 4. EPCs and human pulmonary artery endothelial cells (hPAECs) were seeded into transwell inserts and grown to confluence. Cells were incubated with TNFa (10ng/ml), and their capacity to form biological barriers and support immune cell influx was assessed using FITC-albumin (0.5mg/ml) and neutrophil transmigration. We further assessed the responses of EPCs to TNFa stimulation by ELISA to quantify pro-inflammatory cytokine release.

Results
We demonstrate that EPCs form biological barriers with similar capabilities as mature hPAECs in vitro. TNFa significantly enhanced permeability of EPCs ($P<0.05$) and hPAECs ($P<0.05$) monolayers. Consistent with EPCs possessing similar cellular activities as mature endothelial cells, TNFa stimulated neutrophil transmigration in monolayers of EPCs ($P<0.05$) and hPAECs ($P<0.05$) and enhanced the secretion of IL-8 in both EPCs ($P<0.01$) and hPAECs ($P<0.05$). We sought to determine the frequency of EPC colony formation from PBMCs and found no significant difference in the capacity to form EPC colonies in HC and SSc patient PBMCs.

Discussion
We have developed a robust method for isolating EPCs from PBMCs. We have demonstrated that endothelial progenitors can maintain an endothelial barrier consistent with that observed by mature hPAECs in vitro. We have established that EPCs respond to TNFa in a similar manner to mature PAECs, secreting pro-inflammatory cytokines such as IL-8 and supporting neutrophil transmigration. We have shown no significant difference in the capacity of PBMCs from SSc patients to form EPC colonies compared to healthy control donors. The biological function and importance of EPCs from SSc patients in vasculopathy, restoration and maintenance of the endothelial barrier function remains unclear.

PS27 AUTOANTIBODIES TARGETING ANGIOTENSIN TYPE 1 AND ENDOTHELIN TYPE A RECEPTORS AS BIOMARKERS AND MEDIATORS OF SYSTEMIC SCLEROSIS ASSOCIATED PULMONARY ARTERIAL HYPERTENSION

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Objective: Systemic sclerosis (SSc) associated pulmonary arterial hypertension (PAH) portends worse outcome than other forms of PAH. Vasoconstrictive and vascular remodeling actions of Endothelin-1 (ET-1) and Angiotensin II (Ang II) via endothelin receptor type A (ETAR) and angiotensin receptor type-1 (AT1R) are implicated in PAH pathogenesis in general. We hypothesized that autoantibodies (Abs) targeting and activating AT1R and ETAR may contribute to SSc-PAH pathogenesis and tested their functional and biomarker relevance.

Methods and Results: Anti-AT1R and -ETAR Abs detected by ELISA were significantly higher and more prevalent in patients with SSc-PAH (n = 81) and connective tissue disease(CTD)-associated PAH (CTD-PAH; n = 110) as compared to other forms of PAH/PH (n = 106). High anti-AT1R and anti-ETAR Abs predicted development of SSc-PAH and SSc–PAH-related mortality in a prospective analysis. Both autoantibodiesAbs increased endothelial cytosolic Ca2+ concentrations in isolated perfused rat lungs which could be blocked by respective specific receptor antagonists. Stimulation of third to fourth-generation intralobar pulmonary rat artery ring segments in a small vessel myograph with anti-AT1R and anti-ETAR Abs increased vasoconstrictive responses to Ang II and ET-1 and implicated cross-talk between both pathways demonstrated by reciprocal blockade with respective antagonists. Transfer of SSc-IgG containing both autoantibodies into healthy C57Bl/6J mice lead to more abundant vascular and epithelial alpha smooth muscle actin expression and inflammatory pulmonary arteriopathy.

Conclusions: Anti-AT1R and ETAR Abs discriminate SSc-PAH/CTD-PAH from other forms of PH and serve as predictive and prognostic biomarker of SSc-PAH. Both antibodies contribute to SSc-PAH via increased vascular endothelial reactivity and induction of pulmonary arteriopathy.

Poster Tours – Clinical
Poster Tour 5: Cardiac

PS28 SUBCLINICAL BIVENTRICULAR SYSTOLIC FUNCTION IS IMPAIRED IN PATIENTS WITH SYSTEMIC SCLEROSIS: A SPECKLE TRACKING-BASED ECHOCARDIOGRAPHIC STUDY

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Background/Purpose : Myocardial involvement is associated with poor prognosis in patients with systemic sclerosis (SSc). In the present study we aimed to evaluate subclinical left ventricular (LV) and right ventricular (RV) systolic dysfunction in SSc patients without any cardiovascular disease, by using a strain imaging method, "speckle tracking echocardiography" (STE).
Methods : Thirty-six SSc patients were screened, 7 patients were excluded because of ischemic heart disease. We studied 29 patients with SSc (diffuse/ limited: 15/14) and 20 age and sex-matched healthy controls(HC), without any cardiac disease and with preserved LV-EF. Conventional echocardiography and STE-based strain imaging were performed to assess biventricular deformation analyse. Association with anti-Scl 70 was sought in patients with SSc.
Results: In SSc patients (Female/Male: 25/4) the mean age was 47.7 years. Anti Scl-70 was positive in 13 (44.8%) patients. Left ventricular conventional echocardiographic measurements (LV end diastolic diameter, LV end systolic diameter and LV EF) were similar between SSc and HC. Regarding RV conventional parameters, right atrium was significantly enlarged, tricuspidal annular plane systolic excursion (TAPSE) was decreased and systolic pulmonary artery pressure was increased in SSc compared to HC ($p<0.001$). Both LV and RV longitudinal peak systolic strain/ strain rate were significantly impaired in SSc, demonstrating subclinical LV and RV systolic dysfunction ($p<0.001$) (table).
We obtained significant positive correlation between TAPSE and RV longitudinal peak systolic strain/strain rate ($r=0.744$ and $r=0.706$, respectively, $p=0.0001$). Systolic PAB was negatively correlated with both LV and RV longitudinal peak systolic strain/strain rate (LV: $r=-0.552$ and $r= -0.637$, respectively, $p<0.001$ and RV: $r=-0.547$ and $r=-0.638$, respectively, $p=0.001$). Anti Scl -70 positive patients had impaired LV longitudinal peak systolic strain and strain rate values, compared to the others, however the difference did not reach statistical significance (13.01±1.26 % to 13.04±1.90 %, $p=0.96$ for strain; 0.30±0.06 1/s to 0.31±0.15 1/s, $p=0.79$ for strain rate).
Conclusion : SSc is associated with myocardial systolic dysfunction. Deformation analysis by STE-based strain imaging is a novel promising modality allowing for detailed measurement of early deterioration in biventricular systolic function in patients with SSc.

Table. Conventional echocardiography and Speckle tracking echocardiography (STE) results of SSc patients and healthy controls.

	SSc	HC	p value
Right atrium (cm)	3.71±0.30	3.43±0.20	0.004
TAPSE (cm)	2.01±0.41	2.82±0.54	0.0001
Systolic PAB (mmHg)	34.13±8.96	22.07±3.87	0.0001
LV longitudinal peak systolic strain (%)	13.3±1.51	18.87±3.78	0.0001
LV strain rate (1/s)	0.31±0.11	1.77±0.54	0.0001
RV longitudinal peak systolic strain (%)	11.83±1.93	14.19±2.29	0.001
RV strain rate (1/s)	0.30±0.18	2.66±0.4	0.0001

Values were presented as mean ±SD. TAPSE;tricuspidal annular plane systolic excursion, PAB;pulmonary artery pressure, LV; left ventricle, RV; right ventricle

PS29 IMPAIRED FUNCTIONAL CAPACITY IN PATIENTS WITH SYSTEMIC SCLEROSIS IS RELATED TO RIGHT VENTRICLE DYSFUNCTION

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Objective: Systemic sclerosis (SSc) is characterised by cardiovascular manifestations, which may affect patient's clinical symptoms. The study was designed to assess whether the impaired exercise tolerance in patients with SSc without overt cardiopulmonary complications is related to the left ventricle (LV) or right ventricle (RV) dysfunction and vascular remodeling.

Methods: Forty seven patients (F/M 36/11; age 51.7±9.9) with diagnosed SSc and clinical symptoms of the heart dysfunction (NYHA I/II) were enrolled into the study. In all the patients, pulmonary arterial hypertension (PAH), pulmonary fibrosis, left ventricle (LV) systolic dysfunction and valvular heart diseases were excluded. The following tests were performed: echocardiography, ultrasound vascular indexes: flow mediated dilatation, nitroglycerin mediated dilatation and arterial tonometry parameters: pulse wave velocity, pulse pressure and augmentation index. The above indexes were related to the 6 minute walk test (6MWT) results.

Results: The 6MWT mean value was 440.0±72m. The LV diastolic dysfunction parameters did not correlate with 6MWT. The RV systolic dysfunction (fraction area change<32%), decreased tricuspid annular plane systolic excursion (TAPSE < 20mm) or low peak systolic velocity of lateral tricuspid annulus (TDI: RV S' <20cm/s) were found in 1 (2%), 5 (11 %), 43 (92%) patients, respectively. The 6MWT values correlated with TAPSE (r=0.318, p=0.030, Fig. 1) and TDI: RV S' (r= -0.295, p=0.048). There were no significant correlations between ultrasound and arterial tonometry parameters and 6MWT values.

Conclusion: After exclusion of typical causes of low exercise capacity in SSc, the shortened 6MWT distance observed in this group seems to be related to the RV systolic impairment, which supports application of regular echocardiographic screening for early detection of the heart involvement in SSc patients.

PS30 MMP12 CONTRIBUTES TO HEART AND SKIN FIBROSIS IN ANGIOTENSIN II MODEL

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Background: MMP12 is a macrophage-secreted elastase that is highly elevated in the serum and tissue of SSc patients. Angiotensin II (AngII), a vasoconstrictive peptide, is a well-known inducer of heart and skin fibrosis. The goal of this study was to characterize the extent of vascular injury and to investigate the contribution of MMP12 in the AngII model of skin and heart fibrosis.

Methods: AngII was administered continuously over 14 days by subcutaneous osmotic pump in C57Bl and MMP12KO mice. Collagen content measurements were performed by Picrosirius Red (heart) and Gomori's Trichrome (skin) staining and hydroxyproline assays. Apoptosis was evaluated by IHC staining of cleaved Caspase-3. Analysis of injured endothelial cells was performed by IHC staining of vWF, THBS1 and MMP12. Protein levels of vWF, THBS1 and MMP12 in human dermal microvascular endothelial cells (HDMECs) in response to AngII were evaluated by Western blot. The activation of perivascular cells was performed by IHC and immunofluorescence staining of aSMA, NG2, PDGFRβ, CD45 and Collagen I.

Results: Cleaved Caspase-3 staining showed moderately increased apoptosis in heart and skin of AngII treated mice. Immunostaining in the heart and skin of AngII treated mice showed increased expression of vascular injury markers: vWF, THBS1 and MMP12. Protein levels of vWF, THBS1 and MMP12 were also increased in AngII treated HDMECs. PDGFRβ-positive cells colocalized with vessels only in control mice, but were greatly increased in numbers in the heart and skin of AngII mice. Furthermore, in the heart Collagen I producing cells were also positive for PDGFRβ and NG2, while in the skin, in addition to PDGFRβ and NG2 expression, were also positive for aSMA. Additionally, there was an increased number of fibrocytes (CD45/aSMA and CD45/NG2 cells) in the skin, but not in the heart, of AngII treated mice. MMP12KO mice infused with AngII showed markedly reduced expression of vascular injury markers and reduced number of PDGFRβ positive cells. Histological examination showed reduced perivascular collagen deposition in the heart and decreased collagen deposition in the skin of AngII treated MMP12KO mice. Moreover, total hydroxyproline content was reduced in the skin of MMP12KO mice infused with AngII.

Conclusions: These observations demonstrate that persistent injury to endothelial cells in AngII model may lead to activation of peri-endothelial cells resulting in fibrosis. Moreover, this study suggests that MMP12 is a key mediator of vascular injury and fibrosis in AngII model and may represent a therapeutic target in SSc.

PS31 RELATIONSHIP BETWEEN INTERLEUKIN-6 AND CARDIAC INVOLVEMENT IN SYSTEMIC SCLEROSIS

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Objectives. To explore the relationship between IL-6 levels and echocardiographic abnormalities, arrhythmia and heart rate variability, parameters of 6-minute walk test (6MWT), and NT-proBNP levels in SSc patients.
Methods. This case-control study included 31 SSc patients with preserved left ventricular ejection fraction (LVEF) and no concomitant disease, and 32 matched healthy controls.
All subjects underwent clinical examination, serological analysis, and echocardiographic assessment including pulsed-wave tissue Doppler imaging to evaluate cardiac function. They also underwent 24-hour Holter monitoring analysed for arrhythmia and heart rate variability (HRV) in the time domains, and 6MWT to evaluate exercise capacity.
Results. The level of IL-6 was significantly increased in patients with SSc (3.2 vs 2.2 pg/ml, P<0.001). SSc patients had significantly lower values of LV systolic (7.7 vs9.25 cm/s, P<0.001) and early diastolic (8.7 vs 10.3 cm/s, P=0.014) myocardial velocities and higher E/e' (9.04 vs 7.37, P=0.001) ratio, although there was no between-group difference according to LVEF (68 vs 65%, P=0.248). On evaluating right ventricle, there was no significant between-group difference in systolic tricuspid annular velocity (13 vs13.9 cm/s, P=0.105), but the peak early diastolic velocity was significantly lower (11.7 vs 13.6 cm/s, P=0.044) and E/e' significantly higher (4.3 vs 3.38, P=0.008) in SSc patients. Number of ventricular ectopic beats, prevalence of supraventricular tachycardia (SVT) episodes were increased in the patients with SSc compared to controls (P=0.046; P=0.027). In SSc patients, HRV analysis showed significantly lower values of SDNN (standard deviation of all NN intervals) (P=0.047). 6MWT distance was shorter in SSc as compared with healthy controls (P=0.004). IL-6 level showed correlation with LV mean e' (r=-0.57; P=0.001) and E/e' (r=0.55; P=0.001), aortic stenosis (r=0.49; p=0.003), prevalence of SVT(r=0.50; P=0.004), NT-proBNP (r=0.52; P=0.003), and disease activity according EUSTAR score (r=0.79; P<0.001).
Conclusion. Depressed cardiac function is common, even in asymptomatic patients with SSc. IL-6 level is increased in patients with SSc and significantly correlates with LV diastolic dysfunction, prevalence of aortic stenosis and supraventricular tachycardia episodes, NT-proBNP, and EUSTAR score. These results support the role of IL-6 in the development of cardiac disease in SSc patients.

Key words: systemic sclerosis, cardiac involvement, interleukin-6, tissue Doppler echocardiography, arrhythmia, heart rate variability, 6-minute walk test.

PS32 EXTENSION OF CARDIAC DAMAGE THROUGH THE DELAYED ENHANCEMENT OF CARDIAC MAGNETIC RESONANCE: PREDICTIVE VALUE OF A COMBINED APPROACH BASED ON CLINICAL AND LABORATORY FINDINGS, EKG-HOLTER AND CARDIAC MR

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Background: Cardiac involvement is a relevant prognostic determinant in Systemic Sclerosis(SSc), but the diagnosis is often delayed due to the lack of a specific diagnostic algorithm. Recently our group demonstrated the presence of histological myocarditis in patients with SSc and cardiac symptoms.
Methods: Forty SSc-patients with symptoms of cardiac involvement(dyspnea, palpitation) and/or signs of cardiac failure and elevation of cardiac enzymes underwent EKG-holter and cardiac magnetic resonance(CMR). Median follow-up was 24±0.2 months.
Results: Major EKG-holter modifications were present in 32.5% of patients. Twenty-two(55%) patients presented CMR-abnormalities. CMR study demonstrated T2 hyperintensity in 3 patients while none of the patients presented early gadolinium enhancement and 21(52.5%) patients presented late gadolinium enhancement(LGE). We identified 3 different patterns of distribution of LGE: subepicardial, midwall and subedocardial. Twelve patients presented a single pattern of distribution, while 7 patients(35.0%) presented more than one: 60.0% of patients presented a midwall distribution of LGE, 31.6% of patients presented a subepicardial LGE with a linear distribution pattern and 21.0% presented a subendocardial LGE distribution. Nineteen(47.5%) patients showed hypokinetic area and only one patient an akinetic area. The mean EF of left ventricle was 61.7±10.8%, and of right ventricle was 58.1±10.3%. Hypokinetic and akinetic area corresponded with the LGE area in all but one patient. 92.3% of patients with EKG-holter abnormalities showed CMR modifications suggestive of myocardial involvement, with respect to 37% of patients without EKG-holter abnormalities but with CMR modifications($p<0.001$). Patients with major abnormalities on EKG-holter presented a higher number of involved myocardial segments on CMR(3.7±2.3) with respect to the patients without EKG-abnormalities(0.9±1.4)($p=0.012$).
After a mean follow-up of 24±0.2 months, 4 patients(10%) died for arrhythmias or heart failure and 2 died for sepsis after a scleroderma renal crisis.
The 4 patients, who died at follow-up for cardiac complication, had severe dyspnea, elevated cardiac enzymes, myositis, major EKG-holter abnormalities, reduction of EF and LGE on CMR at baseline;75% of patients who died had a subendocardial distribution pattern of LGE on CMR.
Conclusions: These data confirm that SSc cardiac involvement is associated with a bad prognosis, expecially in patients with EKG-holter abnormalities and CMR modifications. The study of distribution of LGE and of hypo and akinetic areas on CMR is a useful tool to characterize the extension of myocardial damage, but probably only a combined approach, based on clinical presentation, laboratory parameters, EKG-holter examination and histological findings can identify patients with a poor outcome related to heart involvement in SSc.

PS33 KEY ROLE OF CARDIAC BIOMARKERS IN THE ASSESSMENT OF SYSTEMIC SCLEROSIS: CONTRIBUTION OF HIGH SENSITIVITY CARDIAC TROPONIN

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Objective: Microangiopathy is a cardinal feature of systemic sclerosis (SSc), which plays a critical role in the development of primary myocardial involvement and pulmonary hypertension, two major causes of death in SSc. Our aim was to measure plasma concentrations of two cardiac biomarkers, high sensitive Cardiac troponin T (HS-cTnT), a marker of myocyte necrosis and/or ischemia, and N-terminal fragment of pro-BNP (NT-proBNP), a marker of cardiac strain, in two large cohorts of SSc patients and controls.
Methods: 161 SSc patients (aged 57±17 years, 135 women corresponding to 84%) were included and were compared to 213 healthy controls (aged 55±11, 170 women-80).
Results: Among the SSc cohort, mean disease duration was of 9±8 years, 65 patients (40%) had the diffuse cutaneous subset. HS-cTnT and NT-proBNP plasma levels were significantly increased in SSc patients versus controls (p=0.0001 and p<0.0001 respectively). SSc patients were more likely to have above the cut-off value concentrations of HS-cTnT (>14 ng/L) and NT-proBNP than controls (30/161 patients (19%) with HS-cTnT >14 ng/l vs. 4/213 controls (2%), p<0.0001; 17/161 patients (11%) with increased NT-proBNP levels vs. 8/213 controls (4%), p=0.02). Similar results were observed in the subgroup of patients free of any cardiovascular risk factors.
Associated factors with HS-cTnT levels >14 ng/L were diabetes mellitus (p=0.01), hypertension (p=0.04), pulmonary arterial hypertension (PAH) (p=0.02), diffuse cutaneous subset (p=0.03), ESR >28 mm (p=0.001) and previous treatment with prednisone (p=0.03). Logistic regression analysis confirmed diabetes mellitus, ESR >28 mm and the diffuse cutaneous subset as factors independently associated with HS-cTnT >14 ng/L.
Increased NT-proBNP concentrations were only associated with the presence of PAH (p=0.0001). The strength of the association between PAH and elevation of both HS-cTnT and NT-proBNP (p<0.0001) was more important than between PAH and NT-proBNP alone.
Conclusion: Plasma levels of HS-cTnT and NT-proBNP are increased in SSc patients. Associated factors with increased cardiac markers include the diffuse cutaneous subset and increased ESR, which are all markers disease activity. Given the prognostic significance of these biomarkers, they might be helpful to select the patients that justify further examinations in case of suspicion of cardiac complication.

PS34 THE ROLE OF INFLAMMATORY PROGENITORS IN MYOCARDIAL FIBROGENESIS IN THE INFLAMMATORY DILATED CARDIOMYOPATHY

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Background: Heart-specific inflammation– myocarditis is a common cause of pathological tissue remodelling and heart failure with the phenotype of inflammatory dilated cardiomyopathy (iDCM). During the last years there was a shift in SSc-related death causes, indicating iDCM as a major cause of death in these patients. Despite the high unmet clinical need, so far little is known about the etiology of iDCM and the mechanisms leading to heart dysfunction in SSc patients.

Objective: The mouse model of experimental autoimmune myocarditis (EAM) mimics human iDCM. We used this model to study mechanistic aspects of the progression from acute cardiac inflammation into iDCM.

Methods: Alpha-myosin heavy chain peptide/complete Freund's adjuvant immunization was used to induce EAM in wild-type and Nitric oxide synthase 2-deficient (Nos2-/-) BALB/c mice. Chimeric mice, reconstituted with enhanced green fluorescence protein (EGFP)+ bone marrow were used to track the fate of inflammatory cells. Inflammatory CD133+ progenitors were isolated from inflamed hearts, cultured in vitro and injected intracardially at different stages of EAM. In vitro inflammatory CD133+ progenitors were differentiated into myofibroblasts with TGF-b, and into macrophages with Macrophage-Colony Stimulating Factor (M-CSF).

Results: Myocarditis peaked 21 days after immunization and numbers of cardiac pathological myofibroblasts progressively increased on follow-up. In chimeric mice >60% of cardiac myofibroblasts were EGFP+ 46 days after immunization, indicating their bone marrow origin. At day 21 cardiac infiltrates contained about 30% of inflammatory CD133+ progenitors and only small subset expressed macrophage-specific antigen F4/80. CD133+, but not CD133- cells, isolated from acutely inflamed hearts represented the cellular source of cardiac myofibroblasts at late stage of EAM. Mechanistically, in vitro myofibroblast differentiation of inflammatory CD133+ progenitors depended on TGF-b-mediated phosphorylation of Smad proteins and activation of Wnt signalling. Anti-TGF-b antibody treatment prevented myocardial fibrosis in immunized mice, and inhibited myofibroblast differentiation of inflammatory CD133+ cells. CD133+/F4/80hi cells show impaired myofibrogenic potential compared to CD133+/F4/80- cells. M-CSF treatment of wild-type but not Nos2-/- mice with EAM markedly increased CD133+/F4/80hi cells in the myocardium, and CD133+ progenitors isolated from M-CSF-treated wild-type mice failed to differentiate into myofibroblasts. Accordingly, M-CSF prevented post-inflammatory fibrosis and left ventricular dysfunction in wild-type but not in Nos2-/- mice.

Conclusions: Active and NOS2-dependent induction of macrophage lineage differentiation abrogates TGF-b-mediated myofibrogenic differentiation potential of heart-infiltrating inflammatory CD133+ progenitors. Thus, modulating the in vivo differentiation fate of specific progenitors might become a novel approach for the treatment of iDCM.

Poster Tours – Clinical
Poster Tour 6: Outcomes, quality of life, psychological & social

PS35 AN INTERNATIONAL COLLABORATION TO CONDUCT LARGE-SCALE TRIALS OF NON-PHARMACOLOGICAL INTERVENTIONS IN SCLERODERMA: THE SCLERODERMA PATIENT-CENTERED INTERVENTION NETWORK (SPIN)

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Background. Psychosocial and rehabilitation interventions are increasingly used to attenuate disability and improve health-related quality of life (HRQL) in chronic diseases, but are typically not available for patients with rare diseases such as scleroderma (systemic sclerosis, SSc). Conducting rigorous, adequately-powered trials of these interventions for patients with rare diseases is difficult, and there are no adequately powered RCTs published for any educational, psychological or rehabilitation interventions for people living with SSc. The Scleroderma Patient-centered Intervention Network (SPIN) is an international collaboration of patient organizations, clinicians, and researchers. The aim of SPIN is to develop a research infrastructure to test accessible, low-cost self-guided online interventions to reduce disability and improve HRQL for people living with scleroderma. Once tested, effective interventions will be made accessible through patient organizations partnering with SPIN.

Methods. SPIN utilizes a novel research design, the cohort multiple RCT (cmRCT) design to collect longitudinal data related to problems experienced by people living with SSc and as a framework for developing, evaluating, and delivering psychosocial and rehabilitation interventions. In the cmRCT design, patients consent to participate in a cohort for ongoing data collection. The aim is to recruit 1,500-2,000 patients from centers across the world within a period of 5 years (2013-2018). Currently, over 20 centers from Canada, US, France, UK, the Netherlands, Australia and Mexico are involved in the SPIN Cohort. Eligible participants are persons >=18 years of age with a diagnosis of systemic sclerosis. In addition to baseline medical data, participants will complete patient-reported outcome measures every 3 months. Upon enrolment in the cohort, patients will consent to be contacted in the future to participate in intervention research and to allow their data to be used for comparison purposes for interventions tested with other cohort participants. Once interventions are developed, patients from the cohort will be randomly selected and offered interventions as part of pragmatic RCTs. Outcomes from patients offered interventions will be compared to outcomes from trial-eligible patients who are not offered the interventions.

Discussion. The use of the cmRCT design, the development of self-guided online interventions, and partnerships with patient organizations will allow SPIN to develop, rigorously test, and effectively disseminate psychosocial and rehabilitation interventions for people with scleroderma on an ongoing basis.

PS36 EARLY MORTALITY IN AUSTRALIAN AND CANADIAN SCLERODERMA PATIENTS: RATIONALE FOR ESTABLISHING A MULTI-NATIONAL INCEPTION COHORT OF PATIENTS WITH SYSTEMIC SCLEROSIS

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Background and aim: Studies of 'prevalent' cohorts wherein most patients have longstanding disease at recruitment, may underestimate mortality in systemic sclerosis (SSc) due to survivor bias. The aim of this study was to quantify mortality in Australian and Canadian patients with SSc and to compare patients with prevalent and incident disease.

Methods: In each of the Australian and Canadian cohorts, we quantified mortality as 1) Standardised Mortality Ratio (SMR); 2) Years of Life Lost (YLL), based on Australian Bureau of Statistics and Statistics Canada data for the general population; and 3) Percentage survival in the first decade of disease in a) the whole 'prevalent' cohort and b) in a subset of patients recruited within 5 years of onset of the first non-Raynaud manifestation (the 'incident' cohort). We determined a single primary cause of death (SSc or non-SSc related) and all other SSc organ involvement that contributed to death, using a 'harmonised' death case report form.

Results: In the Australian cohort of 1279 patients, 55.7% of 97 deaths recorded between 2007 and 2012 were SSc related; the most common cause of SSc-related death was heart-lung disease (40/52 deaths; 24 PAH, 7 ILD, 9 PAH and ILD). Malignancy, atherosclerotic vascular disease and sepsis (21, 8 and 5/43 deaths, respectively) were the most common non-SSc related causes. Regardless of the primary cause, SSc organ involvement contributed to death in 60% of cases. In multivariable regression, predictors of mortality were male sex, older age at disease onset and presence of PAH. In the 'incident' Australian cohort of 333 patients, there were 24 deaths during follow-up, with PAH and ILD accounting for all early SSc-related deaths. In the prevalent (n=1308) and incident (n=338) Canadian cohorts, the findings were very similar, with 59.7% of 150 deaths in the prevalent cohort between 2005 and 2012 being SSc related; once again the most common cause of SSc-related death was heart-lung disease. As seen in Table 1, SMR and YLL were higher, and % survival was lower in the incident cohorts compared with the respective prevalent cohorts.

Conclusion: Mortality in Canadian and Australian SSc patients is similar, and substantial. Our results suggest that prevalent cohorts underestimate mortality in SSc by failing to capture early deaths, particularly in diffuse disease. Collectively, these findings provide a compelling rationale for establishing a large multi-national inception cohort of patients with SSc to more accurately quantify early mortality in this disease.

	Australian Patients 2007-2012		**Canadian Patients 2005-2012**	
	'Prevalent' cohort n=1279	'Incident' cohort n=333	'Prevalent' cohort n=1308	'Incident' cohort n=338
Number of deaths	97	24	150	53
SMR (95% CI)				
Women	6.4 (4.9-7.8)	5.7 (2.3-9.0)	4.1 (3.3-4.8)	5.3 (3.7-7.0)
Men	8.8 (5.1-12.6)	16.0 (7.3-24.7)	6.6 (4.4-8.9)	8.4 (3.9-13.0)
Overall	**6.8 (5.6-7.9)**	**8.7 (5.6-11.8)**	**4.5 (3.9-5.1)**	**5.9 (4.5-7.2)**
YLL (years)				
Women	**15.9**	**18.1**	**19.3**	**20.7**
Men	**12.9**	**15.0**	**16.3**	**19.3**
% survival in first decade of disease				
Diffuse disease	**95%**	**70%**	**94%**	**70%**
Limited disease	**99%**	**95%**	**97%**	**85%**

Table 1. A comparison of measures of mortality in Australian and Canadian 'prevalent' and 'incident' cohorts

PS37 IMPACT OF AUTOANTIBODY PROFILE ON SURVIVAL IN SYSTEMIC SCLEROSIS

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Introduction: Although autoantibodies have been demonstrated to associate strongly with organ complications in systemic sclerosis (SSc), their association with survival remains unclear.

Methods: Autoantibody specificities were determined by the hospital Immunology laboratory in 649 consecutive SSc patients, followed for up to 15 years.

Results: The cohort had 84% female and 41% dcSSc patients. The most frequently observed antibody was anti-centromere antibody (ACA), found in 25.3% of the patients. Anti-topoisomerase I (ATA) was present in 23%, anti-RNA polymerase antibody (ARA) in 10.5% and anti-U3RNP in 4.6% of the aptients. More infrequently seen antibodies included anti-U1RNP in 5.9%, anti-PmScl in 3.7%, anti-Th/To in 0.6%, anti-Ku in 0.8%, anti-Jo1 in 0.9% and anti-Ro antibodies in 4.8%. Of the cohort, 3.4% were ANA negative and 3.4% had other rarer antibodies. Of the 118 (18.2%) patients who had unspecified anti-nuclear antibodies (ANA), 78% were tested for extractable nuclear antigen (ENA) reactivities and were negative. Of those, 66.4% had fine speckled, 27.4% had nucleolar and 35% had homogenous pattern.

Univariable Cox regression analysis revealed that the only SSc-specific antibody that demonstrated significant association with survival was ACA (HR 0.68, p=0.022). Nevertheless, when correcting for subset, the association disappeared, suggesting that the better survival among ACA positive patients is due to the predominantly limited skin involvement in this group.

On the other hand, unspecified ANA positivity significantly increased the risk of death (HR 1.89, p<0.001) and this was independent of subset. Analysis of each pattern separately demonstrated that this is mainly a results of the increased risk of death seen in patients with unspecified ANA with homogenous (HR 1.74, p=0.018) and fine speckled pattern (HR 1.47, p=0.049). KM survival at the end of follow-up was similar in patients with SSc-specific autoantibodies (67% in ARA, 59% in ACA, 55% in ATA and 53% in U3RNP positive patients) while demonstrating significant reduction in those with non-specified ANAs (34%).
We grouped together patients with unspecified ANAs and those with known antibody specificities, associated with the same pattern. Analysis of associations with disease outcome showed no difference in survival between patients with and without the three most frequently observed patterns.

Conclusions: While SSc-specific antibodies do not predict survival, unspecified ANAs may be associated with worse outcome. Pooling autoantibodies together showed no significant increase in mortality related to immunofluorescent pattern, which suggests that a potentially unidentified autoantibody may be associated with worse survival in SSc patients.

PS38 DEVELOPING AN INTERVENTION FOR BODY IMAGE DISTRESS IN SYSTEMIC SCLEROSIS: AN UPDATE FROM THE SCLERODERMA PATIENT-CENTERED INTERVENTION NETWORK (SPIN)

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Background. Appearance changes are common in systemic sclerosis. These changes often affect visible and socially relevant body parts, and can be difficult to conceal. Commonly affected parts of the body include face, mouth, and hands, and can include telangiectasias, calcinosis, hyper-/hypo-pigmentation of the skin, narrowing of the mouth and nose, digital ulcers, and hand contractures. Currently available medical treatments do little to ameliorate these changes. Research on systemic sclerosis has found that patients rate disease-related changes in appearance as one of the most significant stressors associated with scleroderma, and some patients experience significant body image distress. Body image concerns have been associated with depression, low self-esteem, anxiety, and social impairments, including problems in sexual functioning. However, to date there are no interventions available to address body image concerns in systemic sclerosis.

Objective. To develop and evaluate a web-based, patient-centered intervention designed to address body image distress in systemic sclerosis.

Methods. The Scleroderma Patient-centered Intervention Network (SPIN) is an international consortium of researchers, clinicians, patients, and patient advocates. The SPIN Body Image Distress Working Group brings together representatives from all of these groups to develop an online intervention for body image distress in systemic sclerosis. To date, the Working Group has reviewed the relevant research and clinical literature on body image distress in systemic sclerosis and has examined existing programs designed for other populations. Qualitative interviews have been conducted with patients and patient advocates in order to gain insights into body image concerns, and to obtain recommendations for program design and content.

Results. The online intervention addresses both personal and social aspects of body image concerns. Cognitive-Behavioral Therapy and Acceptance and Commitment Therapy approaches are incorporated. There is also an educational component that addresses body changes associated with scleroderma and how to cope with these changes across cognitive, emotional, and interpersonal levels.

Conclusion. This body image intervention for systemic sclerosis is a novel development that will fill a major gap in quality-of-life interventions available to patients with systemic sclerosis. The web-based design of the intervention makes it easily accessible to a wider range of patients than would otherwise have access to such a programme. A planned evaluation of the programme via a cohort multiple randomized controlled trial will be implemented to assess the intervention's efficacy.

PS39 IMPACT OF MALE SEX ON SURVIVAL IN SYSTEMIC SCLEROSIS

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Background/Purpose: Systemic sclerosis (SSc) has a female predominance with a female-to-male ratio of 3:1. Sex differences have been seen in many autoimmune diseases; however, little is understood about the effect of sex on SSc disease manifestations and survival. The objectives of this study were to evaluate differences in survival and disease manifestatons between males and females with SSc.
Methods: We conducted a retrospective cohort study of patients from the Toronto Scleroderma Program who fulfilled the American College of Rheumatology (ACR) classification criteria for SSc and were >16 years of age. We evaluated differences in age of onset, disease manifestations, serology, and survival between males and females.
Results: 907 patients (745 females, 162 males) were included. Males more frequently had diffuse SSc than women (45% versus 31%, p = 0.007). Men were more likely to have renal crisis (10% versus 7%), abnormal nail fold capillaries (30% versus 25%), digital ulcers (35% versus 32%), esophageal dysmotility (89% versus 85%), telangiectasia (81% versus 77%), and interstitial lung disease (42% versus 32%). Females more frequently had anticentromere antibodies (19% versus 9%), pulmonary arterial hypertension (38% versus 33%), and Raynaud's phenomenon (96% versus 94%). There were 186 deaths (37 males, 149 females). Males had increased mortality compared to females (Hazard Ratio (HR) 1.56, p=0.02). The median survival time was 17.3 years for males and 24.7 years for females. After adjusting for differences in SSc subtype, serology and presence of interstitial lung disease, men still had increased mortality compared to females (HR 1.64, p = 0.009).
Conclusion: Males with SSc have an increased burden of disease and decreased survival compared to females with SSc.

PS40 APPEARANCE DISSATISFACTION, SOCIAL DISCOMFORT, AND HELPLESSNESS IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Background: Systemic sclerosis (SSc) has been related to marked appearance change (AC), particularly on the face, mouth, and hands. AC has previously been shown to have both personal (i.e., body image) and interpersonal (i.e., social relationships) components for patients with SSc. Because SSc-related disfigurement can be unpredictable and uncontrollable, AC may be associated with feelings of helplessness among patients with SSc.

Objective: The present study examined the relationship between satisfaction with appearance and helplessness in patients with SSc.

Methods: A sample of patients (N = 178) from the UCLA Quality of Life (QOL) Study completed the Brief Satisfaction With Appearance Scale (Brief-SWAP) and the Arthritis Helplessness Index (AHI, modified for scleroderma). The Brief-SWAP yields two subscales evaluating Dissatisfaction with Appearance and appearance-related Social Discomfort, in which higher scores indicate greater dissatisfaction or discomfort. The AHI yields two subscales of Helplessness (e.g., My scleroderma is controlling my life) and Internality (e.g., If I do all the right things, I can successfully manage my scleroderma), in which higher scores indicate greater helplessness/less control. In two separate models, hierarchical linear regressions examined the relationship of the Brief-SWAP subscales to each of the AHI subscales. Both models controlled for disease severity, as measured by the modified Rodnan skin score, and age. Age was considered in both models as a moderator of the relationship of Brief-SWAP subscales to AHI subscales.

Results: A significant main effect ($p < .001$) was found for appearance-related social discomfort as it relates to AHI Helplessness, such that greater social discomfort due to SSc-related AC was associated with greater feelings of helplessness. Dissatisfaction with appearance was not significantly ($p > .05$) associated with helplessness. In the model predicting AHI Internality, neither social discomfort nor subjective dissatisfaction with appearance demonstrated significant main effects ($ps > .05$) after controlling for disease severity and age. No significant interaction effects were found ($p > .05$).

Conclusions: These findings suggest that appearance-related social distress is associated with greater feelings of helplessness among SSc patients, while dissatisfaction with appearance is not. Although data analyzed here were cross-sectional, findings suggest that social challenges associated with scleroderma-related appearance changes may contribute to a sense of helplessness in patients. Given the extent of AC among SSc patients, this is an area that deserves greater study in order to increase understanding of the spectrum of outcomes associated with body disfigurement.

PS41 PREDICTION OF WORSENING OF SKIN FIBROSIS IN PATIENTS WITH DIFFUSE SYSTEMIC SCLEROSIS USING THE EULAR SCLERODERMA TRIALS AND RESEARCH (EUSTAR) REGISTRY AND VALIDATION IN A SECOND COHORT

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Objectives
To identify predictors for progressive skin fibrosis in patients with diffuse cutaneous SSc (dcSSc) to enable 1) clinical risk-stratification and 2) improved cohort enrichment in trials with skin fibrosis as the primary endpoint.

Methods
Observational prospective study using the EUSTAR database: Worsening of skin fibrosis was defined as increase in MRSS >5 points and >/=25% from the 1st to the 2nd visit. Inclusion criteria: dcSSc, ACR criteria fulfilled, MRSS>/=7 at 1st visit, valid data for MRSS at 2nd visit, period in between visits 12±2 months. In the univariate analysis, patients with progressive skin fibrosis were compared to non-progressive patients. Predictive markers with p<0.2 were included in the multivariate logistic regression analysis. For validation, a second cohort with new patients was extracted from the EUSTAR database 11 months after the first data extraction.

Results
Out of 637 patients, 9.7% had progressive skin disease. Patients with a lower MRSS (</=22/51) at baseline visit and shorter disease duration (</=15 months) developed significantly more often progressive skin fibrosis. Univariate analysis suggested the following prediction parameters: joint synovitis (p=0.009), disease duration (p=0.023), MRSS at baseline (p=0.015), and the interaction between disease duration and sex (p=0.02), respectively between disease duration and CK elevation (p=0.047).
In the multivariate analysis, different prediction models with varying combinations of the previously identified predictors were compared. The model with the highest prediction success rate (n=8/18, 44.4%) including joint synovitis, female sex, short disease duration, low MRSS at baseline, and the interaction of female sex and short disease duration, showed an area under the ROC curve of 0.73 (95% CI=0.66-0.79, p<0.0001) with an overall accuracy of 89.9% (98.1% for no progression, 14.3% for progression).
Other models with broader inclusion criteria revealed lower prediction success rates (e.g. 23.8% (n=20/84) for a model including low MRSS at baseline and short disease duration), but would simplify the recruiting process.
In the EUSTAR validation cohort, out of 188 patients, 6.4% had progressive skin disease. In the multivariate analysis, essentially the findings from the original cohort were confirmed. Interestingly, among the prediction markers, a low MRSS at baseline (</=22/51) had a particularly high impact in all prediction models (range OR 5.394–10.463).

Conclusion
These data from a large EUSTAR cohort analysis including a 2nd internal verification cohort demonstrated that the identified criteria allow the enrichment of clinical trials for dcSSc patients with progressive skin fibrosis by up to 4.5-fold which will have an important impact on the future clinical study design in SSc.

Poster Tours – Clinical
Poster Tour 7: Imaging

PS42 MRI INFLAMMATORY LESIONS OF THE HAND COULD BE PREDICTORS OF DIGITAL ULCERS, DISEASE ACTIVITY AND LOWER FUNCTIONAL CAPACITY IN SYSTEMIC SCLEROSIS

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Background: Joint involvement is frequent finding and correlate with poor life quality in systemic sclerosis (SSc). MRI is useful method for detecting and quantification of inflammatory lesions of the hand (bone oedema, erosions, synovitis and tenosynovitis) in systemic sclerosis patients.
Objective: The aim of the study was to investigate association of clinical features, laboratory tests and probability for the occurrence of inflammatory changes on the hand in systemic sclerosis.
Method:102 patients with systemic sclerosis were investigated (mean age 53y). Contrast enhanced, low field MRI of the wrist and MCP2-5 joints was performed to all the patients. MRI inflammatory changes (bone oedema, erosions , synovitis and tenosynovitis) were assessed and scored by OMERACT RAMRIS scoring system. Different clinical features (age, sex, SSc subtype, disease duration (date of first non Raynaud symptom), Raynaud phenomenon, articular or periarticular pain, joint swelling and contractures, digital ulceration, HAQ, acroosteolysis (by standard PA radiographs of hand and wrist), pulmonary fibrosis (by CT and pulmonary function tests), pulmonary arterial hypertension (pulmonary arterial pressure higher than 30mmHg at rest on Doppler echocardiography) and laboratory tests (antinuclear antibodies, anti topoisomerase antibodies, anti centromere antibodies, RF, CRP,Creatine phosphokinase) and disease activity (by Valentini index) were carried out.
Results:By multiple logistic regression analysis taking into account all clinical and laboratory variable, we found that MRI inflammatory lesions of the hand were associated and probability for the occurrence of inflammatory changes was higher for the SSc patients with digital ulcers (OR=4.687;95%IP: 1,002-22,256; p<0,05), HAQ>1,5 (OR=8,226;95%IP: 1,740-38,896; p<0,01) and disease activity (OR=3,132; 95%IP: 1,027-9,551; p<0,05).
Conclusion: Inflammatory findings (bone oedema, erosions, synovitis ant tenosynovitis) on the hand by MRI in SSc could be predictors for digital ulcers, active disease and impaired functional capacity in systemic sclerosis .Regular monitoring of clinical features and organ involvement are essential in all the patients with systemic sclerosis, especially those with proven inflammatory changes on MRI of the hand.

Characteristics	OR	95% CI for OR		p
Age	1,024	0,982	1,069	0,271
Disease duration	1,061	0,963	1,168	0,233
Female	0,953	0,100	9,128	0,967
Disease duration >5 y	1,143	0,372	3,511	0,816
Diffuse SSc	0,745	0,215	2,578	0,642
Raynaud phenomenon	0,000	0,000	-	0,999
Digital ulcers	4,687	1,002	22,256	0,049
HAQ > 1,5	8,226	1,740	38,896	0,008
Distal phalange resorption	3,488	0,727	16,732	0,118
Muscle weakness	1,049	0,110	10,048	0,967
DLCO < 75%	1,971	0,566	6,867	0,286
FVC < 75%	1,130	0,277	4,616	0,864
sPAP>30mmHg	5,224	0,641	42,563	0,122
Positive ANA	1,099	0,309	3,904	0,884
Positive anti topo-I Ac	4,000	0,485	32,984	0,198
Positive ACA	0,447	0,143	1,398	0,166
↑ Creatine phosphokinase	-	0,000	-	0,999
Positive CRP	2,656	0,549	12,841	0,224
Positive RF	-	0,000	-	0,999
Active disease	3,132	1,027	9,551	0,045

PS43 EVALUATION OF BLOOD PERFUSION IN DIFFERENT SKIN AREAS OF SYSTEMIC SCLEROSIS PATIENTS BY LASER SPECKLE CONTRAST ANALYSIS AND CORRELATIONS WITH NAILFOLD MICROANGIOPATHY EXTENT.

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Objective. This study aimed at investigating by laser speckle contrast analysis (LASCA) blood perfusion (BP) at different skin sites in systemic sclerosis (SSc) patients, looking for any correlation with the extent of the nailfold capillary damage.
Methods. Sixty-eight SSc patients (mean disease duration 7±6 years) and 68 healthy subjects (CNT) matched for age and sex were enrolled. BP was assessed by LASCA in the facial and dorsal/palmar regions of the hand in both SSc patients and CNT. Different regions of interest (ROI) were created on their hands: fingertips, periungual areas, dorsum and palm of both hands as well as their face: forehead, tip of nose, zygomas and perioral regions. The average BP was scored as perfusion units (PU) (1). Videocapillaroscopy (NVC) was used to detect the proper pattern of nailfold microangiopathy (early, active or late) (2).
Results. SSc patients had a statistically significant lower median BP than CNT at the level of fingertip (86 and 189 PU, respectively, $p<0.0001$), periungual (69 and 140 PU, respectively, $p<0.0001$) and palm areas (78 and 111 PU, respectively, $p<0.0001$). Whereas, both groups had similar BP values at dorsum of hands, whole face, and different ROIs of the face. There was a statistically significant correlation between BP of the fingertips and BP of the periungual areas in both SSc patients and CNT ($p<0.0001$). A statistically significant correlation was also observed in both groups between palm and fingertip areas ($p<0.0001$), dorsum and periungual areas ($p=0.0003$ and $p=0.05$, respectively), dorsum and palm ($p=0.0008$ and $p=0.0001$, respectively). The median BP gradient between fingertips and palm was lower in SSc patients than in CNT (11 and 67 PU, respectively, $p<0.0001$), as was the gradient between the dorsum and periungual areas (25 and 69 PU, respectively, $p=0.0009$). A significant progressive decrease of BP was observed in SSc patients with progressive pattern of nailfold microangiopathy (early, active, and late) at the level of fingertip ($p=0.004$), periungual ($p=0.007$) and palm areas ($p=0.02$).
Conclusions. This study shows that LASCA detects significant differences in BP at the level of fingertips, periungual areas, and palm of hands in SSc patients versus CNT. Furthermore a statistically significant correlation was observed between nailfold microangiopathy extent and BP at the level of fingertips, periungual areas, and palm of hands in SSc patients.
References.
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PS44 CORRELATION BETWEEN BLOOD PERFUSION AND DERMAL THICKNESS IN DIFFERENT SKIN AREAS OF SYSTEMIC SCLEROSIS PATIENTS.

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Objective. The aim of this study was to identify possible correlations between peripheral blood perfusion (BP) and dermal thickness (DT) in three different areas of skin (periungual, dorsum of hand and zygoma), in SSc patients.
Methods. Sixty-three SSc patients (mean age 64±11SD years) were enrolled. BP was analysed by laser speckle contrast analysis (LASCA) at the level of dorsal region of hands and face in SSc patients (1). Different regions of interest (ROI) were created at level of periungual areas of the 3rd finger bilaterally, dorsum of both hands and zygomas, and the average BP was scored as perfusion units (PU). Both high frequency ultrasound (US) and modified Rodnan skin score (mRss) were used to evaluate average DT at the level of dorsum of 3rd finger, hand and zygoma bilaterally (2). US and LASCA were also performed in 63 age and sex matched healthy subjects (CNT).
Results. A negative correlation was observed between BP and both ultrasound-DT ($p=0.0005$) and mRss ($p=0.007$) in SSc patients at the level of fingers. No statistically significant correlation was found between BP and both ultrasound-DT and mRss at level of dorsum of hand and zygomas in SSc patients. In CNT no statistically significant correlation was detected between BP and ultrasound-DT at the level of fingers, dorsum of hands or zygomas. SSc patients showed a statistically significant lower BP at level of periungual areas when compared with healthy subjects ($p<0.0001$). No statistically significant difference in BP values was observed between SSc and CNT at the level of dorsum of hand and zygomas. SSc patients showed a statistically significant higher ultrasound-DT at the level of periungual areas, dorsum of hands and zygomas than CNT ($p<0.0001$, for all). A statistically significant positive correlation was observed between ultrasound-DT and mRss in SSc patients at level of the three areas (periungual $p<0.0001$; dorsum of hand $p=0.03$; zygoma $p=0.0001$).
Conclusions. This study demonstrates a relationship between periungual BP evaluated by LASCA and finger DT evaluated by both US and mRss in SSc patients. SSc patients have a statistically significant higher DT at level of dorsum of finger, hand or zygoma than healthy subjects. There is a significant positive correlation between US and mRss in the assessment of DT.

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PS45 STABILISATION OF MICROCIRCULATION IN EARLY SYSTEMIC SCLEROSIS PATIENTS WITH DIFFUSE SKIN INVOLVEMENT FOLLOWING RITUXIMAB TREATMENT.

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Background. Systemic sclerosis (SSc) is a multisystemic autoimmune disease characterized by fibrosis of the skin and internal organs, generalized microvasculopathy and antibody response against various cellular antigens. In between others, our group recently reported stabilisation of internal organ involvement during 2-year follow-up in an open pilot study of a 2-treatment course (month 0/6) of rituximab (RTX) in patients with early diffuse SSc (dcSSc). As SSc is characterized by progressive microangiopathy over time it may be worthwhile to investigate whether treatment with RTX could also stabilize microangiopathy in dcSSc.
Aim. This study assesses microangiopathic evolution by nailfold videocapillarocopic (NVC) analysis after two treatment course (month 0/6) with rituximab in early dcSSc patients.
Methods. Twelve months follow-up (open-label study) of six consecutive patients with early dcSSc. Patients received an infusion of two times 1000 mg RTX at month 0 and 6, together with 100 mg methylprednisolone. Low-dose prednisolone (no higher than 10 mg/day) was allowed, provided that patients were taking a stable dose at least 12 weeks before inclusion. All disease-modifying antirheumatic drugs (except methotrexate) were stopped 12 weeks before screening. Patients were on a stable dose methotrexate (10-25 mg/week) as background therapy since at least 12 weeks. Capillaroscopic assessment, clinical read outs (modified Rodnan skin score, mRSS; lung function and echocardiography) and disease activity score (DAS) were performed at 0, 3, 6 and 12 months.
Results. There was a clinical significant change in skin score with a mean (SD) mRSS of 24.8 (5.95) at baseline and 10.2 (1.17) at month 12 (Mixed Model Analyses, MMA, p<0.001) and a significant decrease in DAS, with a mean of 4.2 (1.69) at baseline and 0.6 (0.74) at month 12 (MMA p<0.001). Indices of internal organ involvement remained stable (table 1). Semi-quantitatively scored NVC parameters remained stable showing no progression of the microvascular damage during follow-up: mean score (SD) of capillary loss at baseline/12 months: 2.170 (0.408)/1.830 (0.408) (MMA p=0.341), mean score (SD) of giants at baseline/12 months: 0.670 (0.516)/1.17 (0.408) (MMA p=0.093), mean score of haemorrhages at baseline/12 months: 0.670 (0.516)/1.00 (0.000) (MMA p=0.529) and mean score of neoangiogenesis at baseline/12 months: 0.830 (0.408)/0.830 (0.753) (MMA p=0.383) (table 2).
Conclusions. This is the first open pilot study to show that two immunosuppressive treatment courses with RTX may not only have potential efficacy for skin and stabilisation of internal organ involvement but also additional stabilisation of microangiopathic parameters in early dcSSc.

Table 1. Changes in clinical parameters in patients with early and severe Diffuse cutaneous Systemic Sclerosis (DcSSc) treated with Rituximab (N=6)

Variable	Statistic	0M	3M *	P-Value*	6M	P-value*	12M	P-value*	P-value MMA 12M
mRSS	Mean, SD	24.8 (5.95)	18.6 (8.68)	0.026	13.8 (5.19)	<0.001	10.2 (1.17)	<0.001	<0.001
	Median (Q1;Q3)	25.0 (19.3;30.0)	15.0 (12.3;26.0)		13.5 (8.8;19.0)		10.0 (9.0;11.3)		
	Min, max	(17.0;35.0)	(11.0;35.0)		(9.0;26.0)		(9.0;12.0)		
DLCO (% of normal)	Mean, SD	70.2 (12.98)	61.0 (12.21)	0.187	60.7 (11.98)	0.219	69.8 (18.13)	0.771	0.802
	Median (Q1;Q3)	68.0 (59.8;85.0)	61.0 (51.0;71.0)		67.0 (57.3;73.3)		69.5 (59.0;88.8)		
	Min, max	(53.0;87.0)	(44.0;78.0)		(43.0;91.0)		(38.0;93.0)		
FVC (% of normal)	Mean, SD	99.7 (13.77)	94.4 (11.08)	0.250	108.3 (17.74)	0.028	101.2 (13.87)	0.646	0.781
	Median (Q1;Q3)	99.0 (88.8;113.3)	97.0 (84.0;103.3)		108.5 (86.0;116.0)		101.5 (91.0;111.5)		
	Min, max	(79.0;117.0)	(77.0;103.0)		(74.0;125.0)		(76;113)		
TLC (% of normal)	Mean, SD	87.3 (9.49)	83.0 (8.52)	0.070	88.7 (15.74)	0.749	94.3 (14.4)	0.602	0.181
	Median (Q1;Q3)	87.0 (78.0;94.8)	81.0 (76.5;93.5)		85.0 (79.3;101.8)		94.0 (87.8;104.5)		
	Min, max	(78.0;102.0)	(74.0;99.0)		(67.0;112.0)		(74.0;108.0)		
FEV (% of normal)	Mean, SD	93.3 (16.15)	91.0 (12.02)	0.447	98.8 (12.20)	0.796	97.3 (11.74)	0.677	0.088
	Median (Q1;Q3)	90.0 (83.5;104.2)	97.0 (78.5;101.5)		95.0 (79.8;101.0)		98.0 (87.5;107.0)		
	Min, max	(92.0;119.0)	(77.0;105.0)		(74.0;107.0)		(80;113)		
DAS	Mean, SD	4.2 (1.69)	1.8 (1.15)	<0.001	1.1 (0.38)	<0.001	0.6 (0.74)	<0.001	<0.001
	Median (Q1;Q3)	3.8 (3.8;5.5)	2.0 (0.75;2.75)		1.0 (0.5;1.6)		0.3 (0.0;0.88)		
	Min, max	(2.0;7.0)	(0.0;3.0)		(0.5;2.0)		(0.0;2.0)		
sPAP (mmHg)	Mean, SD	30.3 (2.67)*	30.4 (6.19)	0.781	33.0 (8.59)*	0.754	30.4 (4.49)*	0.450	0.601
	Median (Q1;Q3)	31.0 (27.8;33.0)*	28.0 (25.5;36.5)		32.0 (25.5;41.0)*		29.0 (26.5;33.0)*		
	Min, max	(27.0;33.0)*	(23.0;39.0)		(23.0;44.0)*		(25.0;37.0)*		
LVEF (% of normal)	Mean, SD	58.5 (8.19)*	67.8 (7.82)	0.094	59.7 (4.93)	0.850	63.5 (5.72)	0.259	0.238
	Median (Q1;Q3)	57.5 (51.5;62.8)*	69.0 (58.0;73.0)		59.0 (55.0;63.3)		64.0 (58.8;68.0)		
	Min,max	(46.0;69.0)*	(55.0;78.0)		(53.0;67.0)		(55.0;69.0)		

*Significance of all values versus baseline; *N=2; *N=4; MMA=Mixed Model Analysis; mRSS: modified Rodnan skin score; DLCO: diffusion capacity for carbon monoxide; FVC: forced vital capacity; TLC: total lung capacity; FEV: forced expiratory volume; DAS: disease activity score; sPAP: systolic pulmonary artery pressure; LVEF: left ventricular ejection fraction.

Tabel 2. Microangiopathic evolution (semi-quantitative scores) in patients with early DcSSc treated with rituximab (N=6)

Cap Variable	Statistic	0M	3M *	P-value*	6M	P-value*	12M	P-value*	P-value MMA
SQ Capillary loss	Mean, SD	2.17 (0.408)	2.20 (0.447)	0.113	2.17 (0.753)	1.000	1.83 (0.408)	0.147	0.341
	Median	2.0 (2.0;2.25)	2.0 (2.0;2.50)		2.0 (1.75;3.00)		2.0 (1.75;2.00)		
	Min, max	2.0;3.0	2.0;3.0		1.0;3.0		1.0;2.0		
SQ Giants	Mean, SD	0.67 (0.516)	1.00 (0.000)	0.172	1.00 (0.000)	0.000	1.17 (0.408)	0.014	0.093
	Median	1.00 (0.00;1.00)	1.00 (0.00;1.00)		1.00 (0.00;1.00)		1.00 (1.00;1.25)		
	Min, max	0.00;1.00	1.00;1.00		1.00;1.00		1.00;2.00		
SQ Haemorrhages	Mean, SD	0.67 (0.516)	0.80 (0.447)	0.500	0.83 (0.408)	0.405	1.00 (0.000)	0.154	0.529
	Median	1.00 (0.00;1.00)	1.00 (0.50;1.00)		1.00 (0.75;1.00)		1.00 (1.00;1.00)		
	Min, max	0.00;1.00	0.00;1.00		0.00;1.00		1.00;1.00		
SQ Neoangiogenesis	Mean, SD	0.83 (0.408)	1.20 (0.998)	0.132	1.00 (0.632)	0.171	0.83 (0.753)	1.000	0.383
	Median	1.00 (0.75;1.00)	1.00 (0.50;2.00)		1.00 (0.75;1.25)		1.00 (0.00;1.25)		
	Min, max	0.00;1.00	0.00;3.00		0.00;2.00		0.00;2.00		

*P-value versus Baseline; SQ: semi-quantitative; *N=4

PS46 ASSESSMENT OF SKIN BLOOD FLOW AND STRUCTURE IN LOCALISED SCLERODERMA USING NON-INVASIVE IMAGING

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Background: Localised scleroderma (morphoea) often occurs in patients with no other symptoms of a connective tissue diease such as systemic sclerosis (SSc). Extensive morphoea can cause major morbidity, disability and disfigurement and its pathophysiology is poorly understood. Studying morphoea enhances knowedge of the structure and function of areas of skin affected by scleroderma, isolated as they are from the other disease processes associated with SSc; this consequently enables a better understanding of the pathogenesis of scleroderma in general. The aim of this study was to investigate, with non-invasive imaging, the relationship between perfusion and the localised abnormalities of skin structure which characterise morphoea.

Methods: 32 patients with morphoea underwent imaging at affected and unaffected sites. The skin was imaged with high frequency ultrasound (HFUS) and optical coherence tomography (OCT) to determine thickness. Perfusion was imaged directly with dual wavelength (red [deeper] and green [superficial]) laser Doppler imaging (LDI), and indirectly with thermography.

Results: Epidermal and dermal thickness was decreased at affected compared to unaffected sites; however, only differences in epidermal thickness ($p=0.03$ [HFUS] and $p=0.005$ [OCT]) were significant for active plaques, and only one of the epidermal thickness measurements ($p=0.11$ [HFUS] and $p= 0.004$ [OCT]) was significant for inactive plaques. Deeper perfusion was higher within plaques than at unaffected sites ($p<0.001$ for red LDI, $p<0.0001$ for thermography) but superficial perfusion (green LDI) was similar between sites. An inverse association was found between epidermal thickness and superficial perfusion (HFUS and green LDI) but no association was found for deeper perfusion (HFUS and thermography).

Conclusions: This is the first study of morphoea to look for associations between HFUS, OCT and LDI and thermography. The study confirms loss of epidermal thickness and an increase in deeper perfusion in morphea plaques. Changes in soft tissue thickness are not confined to epidermis and dermis but occur also in underlying tissue (evidenced by red LDI results). The relationship between perfusion and the loss of subcutaneous tissue requires further investigation to fully understand the pathogenesis of morphea plaques.

PS47 VIRTUAL TOUCH IMAGING AND QUANTIFICATIONTM: IS IT POSSIBLE TO DISTINGUISH "UNAFFECTED" SKIN IN SCLERODERMA PATIENTS FROM HEALTHY SKIN?

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Background/Purpose: Skin involvement is a fundamental clinical feature in systemic sclerosis (SSc), often considered the primary outcome in clinical trials. Nonetheless, it remains orphan of a sensitive and reliable quantitative assessment technique. Virtual Touch Imaging and Quantification (VTIQ) is a new elastography imaging method that provides qualitative and quantitative information about absolute skin stiffness.
The purpose of this study was to compare absolute skin stiffness values of clinically unaffected scleroderma skin and the skin of healthy controls (HC), using VTIQ.

Method: Absolute skin stiffness was measured on the basis of shear-wave velocity (expressed in meters per second), using a VTIQ, at 16 of the 17 anatomical sites of the modified Rodnan skin score (mRSS) (anterior chest, abdomen, upperarms, forearms, fingers, hands, thighs, legs and feet bilaterally). Twenty-six patients (13 limited SSc, 13 diffuse SSc), and 17 age- and gender-matched HC were included.
Higher shear-wave velocity values represent harder tissues. mRSS was established at each anatomical site by an assessor blinded to the VTIQ findings. For the purpose of this study we only included, for SSc patients, anatomical sites with clinically unaffected skin (local mRSS = 0). Comparison between groups was performed through Mann-Whitney test, p values <0.05 were considered significant.

Results: Absolute skin stiffness measurements were higher in all SSc "unaffected" areas than in the HC, reaching statistical significance in eight out of 16 measurements sites (See table 1).

Conclusion: VTIQ adds sensitivity to the assessment of skin stiffness in SSc. What appears to be "normal" skin in SSc may be already pathologic, as shown by increased sheer-wave velocity. VTIQ may help in the identification of patients in an early phase of the disease and assist in the evaluation of novel therapies.

Table 1 – Shear wave velocities values (m/s) in SSc patients and controls.

	Patients	n (*)	Controls	Differences between patients and controls (p value)
Anterior chest	2,8 (0,7)	17*	2,3 (0,7)	0,05
Abdomen	2,5 (0,4)	21	2,0 (0,8)	0,016
Upperarm left	2,7 (0,5)	19	2,3 (0,4)	0,004
Upperarm right	2,4 (0,4)	18	2,2 (0,5)	NS
Forearm left	2,5 (0,3)	14	2,1 (0,4)	0,008
Forearm right	2,5 (0,4)	13	2,3 (0,3)	NS
Hand left	2,8 (0,4)	7	2,2 (0,5)	NS
Hand right	2,7 (0,4)	7	2,2 (1,1)	0,011
Phalanx left	2,7 (0,4)	1	2,3 (0,4)	-
Phalanx right	3,1 (0,8)	3	2,2 (0,4)	-
Thigh left	2,3 (0,6)	23	2,1 (0,3)	NS
Thigh right	2,4 (0,4)	23	2,1 (0,2)	0,004
Leg left	3,1 (1,0)	19	2,4 (0,4)	0,012
Leg right	2,6 (0,5)	18	2,5 (0,5)	NS
Foot right	2,9 (0,7)	14	2,2 (0,3)	0,003
Foot left	2,6 (0,6)	15	2,3 (0,4)	NS

Shear wave velocities values (m/s) are shown as mean (standard deviation). p<0.05 was considered statistically significant. NS, not significant; n (*): Number of sites from 26 SSc patients with local mRSS = 0. *Of the 17 patients with mRSS=0, 16 had a limited SSc, and one had a diffuse SSc.

PS48 IMAGING OF SCLERODERMA WITH OPTICAL COHERENCE TOMOGRAPHY

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Background: Systemic scleroderma (SSc) is a connective tissue disease with abnormalities in vascular, immunological and fibrotic pathways. The vasculopathy is characterized by fibrointimal proliferation of small vessels and vasospastic episodes that may lead to tissue ischaemia and over time morphological skin changes characterized by skin fibrosis. Optical Coherence Tomography (OCT) provides a non-invasive, easily applicable optical imaging method for assessment of skin. In several clinical studies using OCT scanning, it has been demonstrated a potential tool for non-invasive assessment of non-melanoma skin cancer. Scleroderma is characteristic in OCT scans due to the homogeneous appearance of dermis due to fibrosis. This poster demonstrates the characteristic OCT morphology of scleroderma and other skin conditions with fibrosis.
Methods: Skin morphology and scar formation were studied using VivoSight OCT scanner (Michelson Diagnostics Ltd., UK). The system's 10 micron axial resolution is complemented by 7.5 micron lateral resolution throughout a 2 mm depth range in tissue. OCT is an optical analogue of ultrasound imaging, the images produced are similar to b-mode ultrasound images, showing a vertical section of the tissue but with a resolution better than a typical high-frequency ultrasound system.
Results: The normal skin in OCT scans clearly demonstrates the well-known layering of the skin. This architectural pattern is, however, in striking contrast to the OCT images obtained from scleroderma skin and other similar skin conditions as keloids. In scleroderma a disarray of the normal layering of the skin was demonstrated. The OCT images displayed no difference between the two types of scleroderma (morphea and systemic scleroderma). However, in contrast to keloid tissue the scleroderma images displayed a more cohesive appearance indicating a difference in density of collagen or other dermal structures. The poster will display multiple OCT images.

Conclusion: In scleroderma novel anti-fibrosing agents and other treatment options are emerging and non-invasive monitoring of dermal collagen morphology is warranted during treatment trials. An OCT study from 2013 has demonstrated a good correlation between OCT images of systemic scleroderma skin and the modified Rodnan skin score and further OCT studies of scleroderma is ongoing.

Poster Tours – Clinical
Poster Tour 8: Therapy/Miscellaneous

PS49 TOWARDS PERSONALIZED MEDICINE: MOLECULAR DIAGNOSTICS FOR SYSTEMIC SCLEROSIS- UTILIZING GENE EXPRESSION PROFILING TO GUIDE PATIENT MANAGEMENT

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Systemic sclerosis (SSc) is a devastating autoimmune disease of unidentified etiology. To date, almost every efficacy trial in SSc has failed. However, multiple SSc clinical trials have shown efficacy for subsets of patients for unknown reasons. Gene expression analysis has elucidated a fundamental factor underlying these challenges: SSc is a heterogeneous disease and the molecular pathways underlying the disease differ among subsets of patients. Clinically similar patients, all diagnosed with SSc, may have different deregulated pathways underlying their particular disease. While cutaneous fibrosis, internal organ involvement, vascular abnormalities and autoantibody formation are common across subtypes, prognosis and response to therapy vary with gene expression subtypes. This is critical to both the treatment of individual patients and the clinical development of novel therapies.

Gene expression profiling and molecular classification of SSc patients can reveal actionable molecular information to inform treatment decisions. This approach is now standard for other diseases, e.g. stratification of breast cancer patients, 25-30% of whom overexpress HER2, which drives tumor growth. Administering Herceptin, which targets HER2, to a global population of breast cancer patients would be detrimental (due to side effects), ineffective (due to non-responders), and uneconomical. But the ability to molecularly classify patients has rapidly transformed care for this and other disease states.

We have developed a microarray-based test (ScleroType™) that distinguishes the natural subtypes of SSc. Knowledge of the pathological factors that drive disease enables the precise selection of drugs that specifically target the patient's deregulated pathway, and the precise selection of patients that are able to respond to a specific drug under development while delivering real-time quantitative feedback as to whether a drug is working in that patient. In an investigator-initiated clinical trial of mycophenolate mofetil (MMF), nearly all SSc patients who demonstrated clinical improvement (assessed by skin score) belong to the inflammatory gene expression subset. In contrast, in trials for imatinib mesylate, patients who demonstrated improvement expressed a fibroproliferative gene expression signature. Work with other established and experimental drugs is ongoing.

Celdara Medical provides detailed molecular profiling for SSc as a service, in a highly automated and controlled CLIA-certified environment. We are receiving reimbursement for this test from leading American insurance companies. Physicians, drug developers, and of course, patients will benefit from the fundamental knowledge about a specific patient's disease that is provided by molecular subtyping. Here we present the state of the art as well as future directions being undertaken in our labs.

PS50 ANTI IL-6 RECEPTOR ANTAGONIST FOR THE TREATMENT OF DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS

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Background: Systemic sclerosis (SSc) is an autoimmune connective tissue disorder of unknown etiology that is characterized by fibrosis of the skin and internal organs. Few reports have hypothesized that interleukin-6 (IL-6) is involved in the pathogenesis of SSc. Tocilizumab is an IL-6 receptor antagonist used primarily for the treatment of rheumatoid arthritis. Currently there is growing evidence for the benefit of Tocilizumab in other systemic autoimmune diseases, including SSc.

Objective: To examine the effects of Tocilizumab treatment on patients with severe diffuse cutaneous SSc (dcSSc) in whom conventional treatments for SSc have failed.

Methods: Three dcSSc patients were administered Tocilizumab at a dose of 8 mg/kg body weight once every 4 weeks. All patients had severe dcSSc with cutaneous and systemic involvement, and an immense negative impact on their quality of life. Clinical and biological assessments were performed before and after 4 to 14 infusions of Tocilizumab.

Results: All three patients showed disease improvement with Tocilizumab treatment. Patients' blood works normalized or improved substantially. Rodnan skin score and swollen and tender joint counts decreased. The two patients who suffered from lung involvement showed improved respiratory function tests. All three patients had improved ADL (activities of daily living) scores with Tocilizumab treatment. However, Tocilizumab treatment had no effect on the patients' Raynaud's phenomenon, digital ulcers or gastro-intestinal reflux. Tocilizumab was well tolerated by all three patients.

Conclusion: All three cases of dcSSc reported showed improvement under treatment with Tocilizumab. Tocilizumab may be beneficial for the treatment of resistant SSc. Tocilizumab should be considered as treatment in cases of sever SSc where conventional treatment has failed, or alternatively for patients with contraindications for conventional treatment.

PS51 SAFETY AND EFFICACY OF COMBINED B CELL-DEPLETION THERAPY WITH RITUXIMAB AND CYCLOPHOSPHAMIDE IN SYSTEMIC SCLEROSIS.

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Introduction: Systemic sclerosis (SSc) is a multisystemic autoimmune disease characterized by fibrosis of skin and internal organs, generalized microvasculopathy, and antibody response against various cellular antigens. There is growing evidence that B cells play a key role in the pathogenesis of Systemic Sclerosis (SSc)1. Cyclophosphamide is the most widely used and studied treatment for early and severe SSc-ILD2. Furthermore there are preliminary studies on the efficacy of Rituximab in SSc skin involvement3. However there are no data about combined B cell-depletion therapy with Rituximab and Cyclophosphamide.

Objective: Clinical assessment of combined B cell-depletion therapy with Rituximab and Cyclophoshamide in SSc.

Materials and Methods: Patient 1: 48-year-old women, affected by lcSSc with rapidly progressive skin involvement, polyarthritis and mild lung involvement; anti-Scl70 negative, anti-RP11 positive; basal Modified Rodnan Skin score 17. Patient 2: 44-year-old man, with recent onset lcSSc characterized by severe rapidly progressive skin involvement, oesophageal and joint involvement; anti-Scl70 negative, anti-RP11 positive; basal Modified Rodnan Skin score 27.

Both patients received Rituximab 1 gm on days 1 and 15 plus Cyclophosphamide 500 mg every two weeks for six months. Patients were retreated after nine months with Rituximab (1 gm x 2). Patients were evaluated every three months, with total follow-up of 12 months.

Results: Both patients showed a decrease in Modified Rodnan Skin score. In patient 1, who presented a less severe cutaneous involvement, skin involvement improved dramatically. In both patients there was an improvement of joint involvement; patient 1 doesn't need DMARDS therapy while patient 2 started Methotrexate three months after retreatment with Rituximab. There was also an improvement of quality of life evaluated by SF-36 Questionnaire, in particular in the items concerning physical functioning, role-physical and bodily pain. The combined therapy Rituximab plus Cyclophosphamide was well tolerated; no patient showed neutropenia. Patient 2 presented cutaneous herpes zoster reactivation 8 months after the beginning of the protocol.

Conclusions: Combined B cell-depletion therapy with Rituximab and Cyclophosphamide in SSc represents an effective and acceptable choice in selected patients with progressive SSc.

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	Pt. 1			Pt.2		
	0	+ 6 M	+12 M	0	+ 6 M	+ 12 M
Tender J	4	0	0	7	0	2
MRSS	17	15	7	27	21	20
SF 36 FP	10	-	65	10	-	45
SF 36 RP	0	-	50	0	-	25
SF 36 BP	30	-	84	0	-	30
SF 36 GH	20	-	37	10	-	35
SF 36 VT	15	-	50	10	-	15
SF 36 SF	37	-	75	25	-	12
SF 36 RE	100	-	100	0	-	33
SF 36 MH	52	-	80	8	-	24

PS52 5-YEAR FOLLOW UP OF ABATACEPT THERAPY FOR SYSTEMIC SCLEROSIS WITH CHRONIC ARTHRITIS.

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Objective: To assess long term safety and effectiveness of abatacept therapy for systemic sclerosis with chronic arthritis.
Case report. We describe the case of a 76 years old female patient with chronic arthritis anti-CCP and RF positive, though non-erosive, from 2003, refractory to several treatments (failed methotrexate, leflunomide, etanercept, rituximab). She received abatacept 10 mg/kg/month, from december 2008 in association with methotrexate 15 mg weekly. Systemic sclerosis was diagnosed in 1995 and caractherized by limited skin involvement, Raynaud's phenomenon, teleangiectasia, calcinosis, disphagia without documented esophageal dilatation (CREST syndrome). Before starting abatacept the polyarthritis was active with DAS28 5.1. At baseline, antinuclear-centromere antibodies were positive 1:1280. A mild reduction of TLCO (63%) without interstitial lung disease and with normal pulmonary arterial pressure by echocardiography (20 mmHg) were reported.
After the first year of treatment, abatacept induced a significant reduction in swollen and tender joint count, improvement in DAS28 with a EULAR good response (DAS28 1.74). Then we observed a slight increase in DAS28 compatible with a moderate response from december 2011 up to date. No radiological erosion was detected at hands and feet.
Skin involvement remained stable, no digital ulcer occurred. Pulmonary and cardiologic assessment were made every year: mild reduction of TLCO persisted until month 48, then a slight decrease was reported at month 56 (TLCO 49%) without clinical variations and with a mild but non significant increase of pulmonary arterial pressure (32 mmHg) that remained in normal range. No decrease in FVC and TLC was detected. Neither deterioration of esophageal dysmothility nor symptoms of gastrointestinal involvement were reported. Renal function remained in normal range (serum creatinine 1 mg/dl).
Abatacept was well tolerated during 56 months and treatment is still ongoing.
Conclusions. Abatacept proved to be a good treatment also in the long term for systemic sclerosis associated to chronic arthritis. In agreement with previous studies 1 further controlled investigation is worthwhile.

1 Elhai M, Meunier M, Mattucci-Cernic M et al. Outcomes of patients with systemic sclerosis-associated polyarthritis and myopathy treated with tocilizumab or abatacept: a EUSTAR observational study. Ann Rheum Dis 2013; 72: 1217-1220.

PS53 WHAT ARE SYSTEMIC SCLEROSIS-RELATED CALCINOSES MADE OF AND CAN WE DISSOLVE THEM?

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Background and aim: Approximately 25- 40% of patients with systemic sclerosis will develop calcinosis, with the knees, elbows and fingertips being commonly affected.1 There is limited information in the literature on the composition of calcinotic lumps,2,3 although what is available (mostly X-ray diffraction data, microscopy and thermal analyses) suggests that they consist of B carbonated apatite. The aim of this research was to unite all of these methods and more to provide a complete image of the structure and composition of calcinoses associated with systemic sclerosis with a view to identifying compounds which are able to break them down.
Methods: Micro-computed tomography (XCT), thermal (TGA), powder x-ray diffraction (PXRD), elemental, electron microscopy (SEM) and infra-red (IR) analyses were carried out to determine the elemental composition and internal structure of the deposits. The calcinotic deposits had either extruded spontaneously or were surgically removed. For dissolution studies, samples were covered with a solution of the desired reagent and sonicated. The amount of calcium taken up by the solution was measured by elemental analysis.
Results: Hydroxyapatite (Ca10(PO4)6(OH)2) was the main component of the four samples examined. The presence of carbonate was confirmed by IR and TGA studies. The internal composition of these deposits was probed by SEM and XCT, which show that the samples have very different structures, despite having similar elemental compositions. This is shown in figure 1a, where the sample on the right is visibly more porous than that on the left. The dissolution screening indicated that picolinic and citric acid and selected aminocarboxylate calcium chelators were most effective at breaking down or dissolving the deposits.
Conclusion: Calcinotic deposits were found to consist of hydroxyapatite with a carbonated component. A greater understanding of the composition of these structures could lead to a better understanding of their formation, potential prevention and improved treatment. Citric and picolinic acids and aminocarboxylate compounds were identified as potential compounds for treating calcinosis.

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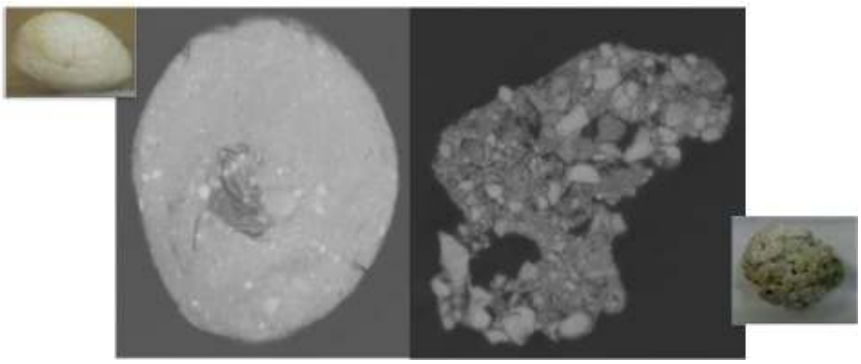

PS54 ANTICENTROMERE ANTIBODY, DISEASE DURATION AND HISTORY OF SURGICAL DEBRIDEMENTS PREDICT CALCINOSIS IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Background

Calcinosis (subcutaneous deposits of calcium occurring predominantly over pressure points), is a characteristic feature of systemic sclerosis (SSc), occurring in 20-40% of patients. Our aim was to examine clinical and serological associates of SSc-related calcinosis, and whether it is possible to build a model to predict presence of calcinosis.

Methods
This was a retrospective cohort study of patients with SSc attending a tertiary referral centre. Clinical and demographic features were reviewed. The variables examined were: age, gender, disease subtype, duration of SSc, previous intravenous prostanoid infusions, surgical debridement and/or amputation, autoantibody status (anticentromere and antitopoisomerase), pulmonary fibrosis and pulmonary hypertension. Logistic regression was used to investigate associations between demographic and clinical factors and the odds of clinical calcinosis. Variables of interest were then combined in a multiple regression model to obtain adjusted odds ratios and confidence intervals.

Results
A total of 317 patients (86% female, median age 60 years, range 24-91) were included. Ninety-four (30%) had clinically apparent calcinosis. Age distribution, and gender, were similar in those with and without calcinosis. Although a number of predictors suggested themselves during exploratory analysis of the data, only surgical debridements (history of debridements in 30.9% of those with and 8.6% without calcinosis), anticentromere status (positive in 54.3% with and 31.8% without calcinosis) and disease duration (17.0 years with and 10.7 years without calcinosis) remained significant after adjusting for other variables. Therefore a patient who had had debridements was more likely to have calcinosis compared to one who had not (OR [95% CI]: 3.39 [1.61 to 7.13]). Similarly, a patient with anticentromere positivity was more likely to have calcinosis (OR [95% CI]: 2.28 [1.24 to 4.21]). The odds of having calcinosis increased with disease duration (OR [95% CI]: 1.08 [1.04 to 1.11]): the odds of having calcinosis increased by 8% (CI, 4 to 11%) for each year since diagnosis. The specificity of the model was high (correctly classifying a patient who did not have calcinosis 91% of the time), but the sensitivity was relatively low, correctly classifying a patient who did have calcinosis only 35% of the time.
Conclusions
In a cohort of patients with SSc attending a tertiary centre, history of surgical debridement, positive anticentromere antibody and disease duration were predictors of calcinosis. However, the low sensitivity of a multiple regression model suggests there are other important predictors of calcinosis that have not been accounted for in this analysis.

PS55 ANTI-CARBAMYLATED PROTEIN ANTIBODIES ARE PRESENT IN SYSTEMIC SCLEROSIS

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BACKGROUND

Anti-CarP antibodies, a newly discovered autoantibody system in rheumatoid arthritis (RA), are present in patients with arthralgia and their presence predicts the development of RA independent from anti–CCP antibodies (1).

Protein carbamylation, promoted by uremia and inflammation (2), is linked to vascular dysfunction and activation of mesangial cell with consequent collagen deposition and fibrosis (3,4,5). Thus we investigated for the presence of anti-CarP antibodies in patients with systemic sclerosis (SSc), where vascular damage is relevant.

PATIENTS AND METHODS

We enrolled 48 patients with SSc. The mean age was 59,3 years (range 22–80 years), mean disease duration 116,3 months (range 3–360 months). Twenty-three patients (47,9%) had a diffuse form of the disease and 25 (52%) a limited one.

We found pulmonary fibrosis in 25 (52%) SSc patients, gastrointestinal symptoms in 24 (50%), pulmonary hypertension in 14 (29%), cardiac involvement in 9 (18,75 %).

Twenty-eight (58,3%) patients had an articular involvement.

Detection of Anti-CarP antibodies were performed by ELISA according to Shi J et al. while rheumatoid factor (RF) was measured by nephelometry.

RESULTS

Eight patients (16,6%) were positive for anti-CarP antibodies, 14 (29%) had RF. In the SSc group of patients anti-CarP positivity was significantly higher than in the control group: 8 (16,6%) patients versus 1 (2%) control (311 UI, range 57–1762, versus 135 UI, range 39–749; $p < 0,001$).

We found a significant correlation of anti-CarP antibody serum levels with RF ($p < 0,03$). Almost all the anti-CarP antibody positive patients had articular involvement (7/8 patients, 86%), but it didn't gain a statistical significance. No significant correlation was found with any other clinical and laboratory data.

CONCLUSIONS

Anti-CarP antibodies are present in patients with SSc and correlates with RF positivity.

Further investigations on a major number of cases are needed to assess the role, if any for these new autoantibodies in this disease.

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Poster Tours – Clinical
Poster Tour 9: Musculoskeletal system & rehabilitation

PS56 THE DEVELOPMENT OF A MODIFIED HAND MOBILITY IN SCLERODERMA TEST AND ITS POTENTIAL AS AN OUTCOME MEASURE IN SYSTEMIC SCLEROSIS

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Objective. To develop the hand mobility in scleroderma (HAMIS) test to a modified HAMIS (mHAMIS) to make the test more feasible and to evaluate its psychometric properties in early systemic sclerosis (SSc) and during long-term follow-up.
Methods. This retrospective study is based on 266 patients previously examined using the original HAMIS. It comprises a cross-sectional part to develop the mHAMIS test, and a longitudinal design, to evaluate the psychometric properties of mHAMIS. Data were stratified into three groups with different disease durations: 1) 0 – 3 years, 2) 3.1 – 5 years, and 3) 5.1 – 9 years after disease onset. Sixty-four patients were assessed in the first group and were included in the longitudinal study. Disease parameters were: skin involvement using disease subset and the modified Rodnan skin score, digital lesions and serum cartilage oligomeric matrix protein (COMP).
Results. Cronbach's alpha with item reduction was calculated separately for each group. Based on these analyses, a mHAMIS test consisting of finger flexion, finger extension, finger abduction and dorsal extension was created. The internal consistency of mHAMIS was: 0.78, 0.83 and 0.73 in the three groups. In the whole study group, mHAMIS showed a significant correlation with hand skin score (rs: 0.44), and was able to discriminate limited cutaneous SSc from diffuse cutaneous SSc (p=0.001). Longitudinal values of the mHAMIS, the hand skin score and serum COMP were closely paralleled, and the change in mHAMIS score between baseline and the first follow-up examination was significantly correlated with the change in hand skin score (rs=.44; p=0.001) and the change in serum COMP (rs=.68; p=0.001).
Conclusions The mHAMIS involves 4 easily measurable items, and has the potential to be a relevant measure of outcome in the evaluation of the consequences of fibrotic skin involvement in SSc.

PS57 ANALYSIS OF PATIENTS WITH SYSTEMIC SCLEROSIS AND RHEUMATOID ARTHRITIS OVERLAP SYNDROME.

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INTRODUCTION
Joint involvement is a common clinical feature in patients with systemic sclerosis (SSc), however, a true overlap with rheumatoid arthritis (RA) is rarer.
PURPOSE
The aim of the present work was to investigate prevalence, clinical and therapeutic approach as well as the serological profile of a series of SSc-RA patients.
PATIENTS AND METHODS
Of the 439 patients with SSc evaluated at our clinic, we retrospectively identified those who have an overlap syndrome and then we analyzed the main epidemiological, clinical and serological features of patients with SSc-RA.
RESULTS
We identified 68 patients with overlap syndrome, including 18 with RA. Table 1 shows the main features of the patients with SSc-RA compared with those without RA.
There were no significant differences between the two groups in the prevalence of diffuse cutaneous SSc (26.3% in SSc-RA versus 28%), in the organ involvement (heart, lung and esophagus) and in the prevalence of digital ulcers.
The prevalence of anticentromere antibody (ACA) was lower in overlap SSc-RA (22.3% vs 47%, p 0.06). SSc patients with RA developed arthralgia prior to Raynaud's phenomenon at a significantly higher incidence than those without (72% versus 25%, p <0.001).
In 60% of the patients the diagnosis of RA was subsequent to SSc onset, in 20% the diagnosis antedated SSc and in 20% was made in the same year. Eight of the 12 patients (75%) had erosive arthritis.
Rheumatoid factor (FR) and anti-citrullinated protein antibodies (ACPA) were more significantly higher in patients with SSc-RA (55.5% vs. 10.7%, p <0.001; 27.2% vs. 0.45%, p <0.001, respectively).
SSc-RA overlap syndrome subjects were compared with a group of patients with RA alone matched for age, sex and disease duration. Between the two groups there were no significant differences in the therapeutic approach (use of biological drugs and total dose of glucocorticoids). In boths groups the most used DMARDs were Methotrexate, Hydroxychloroquine and Leflunomide.
DISCUSSION
The data of our study confirm those present in the literature. RA is one of the most common overlap disease in SSc patients (4,1%). RA doesn't seem to have a significant impact on the disease features of SSc. Furthermore SSc-RA patients seem to have a disease profile similar to RA subjects without SSc, as the therapeutic approach shows no difference.

Table 1: Epidemiological features of SSc-RA as compared to SSc non RA subjects

	SSc with RA N 18	SSc without RA N 421	p
male:female	1:17	1:11	NS
Age, years (mean ± ds)	64,12 ± 10,99	59,25 ± 14,23	NS
Age at onset of SSc, years (mean ± ds)	52,31 ± 13,66	49,88 ± 14,77	NS
Age at onset of RA, years (mean ± ds)	54,47 ± 13,37	-	
Duration of SSc, years (mean ± ds)	10,81 ± 9,74	10,14 ± 9,2	NS
Duration of RA, years (mean ± ds)	7,80 ± 10,72	-	

PS58 ANTI-CCP ANTIBODIES AND RHEUMATOID FACTOR IN SYSTEMIC SCLEROSIS – PREVALENCE AND USEFULNESS

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Introduction: It is known that a-CCP antibodies and rheumatoid factor (RF) are the main tools to diagnose rheumatoid arthritis (RA). In systemic sclerosis (SSc), arthralgia are common manifestation but arthritis occurs rather rare. According to literature a-CCP antibodies and RF may be present in SSc, particularly with joint involvement.
The aim: The aim of the study was to assess the prevalence and usefulness of a-CCP antibodies and RF IgM in two groups of patients (pts) with SSc (limited cutaneous - lcSSc and diffuse cutaneous – dcSSc).
Material and Methods: The study was performed in 126 (99-female and 27-male) consecutive SSc patients treated in Department of Rheumatology, fulfilled the ACR classification criteria of SSc (57 diffuse SSc-dcSSc and 69 limited SSc –lcSSc). The mean age 53.5+/-13.11 years (range 18-81). The mean disease duration 6.27+/-6.02 years (range 0.1-23). A-CCP antibodies and RF in IgM class were determined using a ELISA commercial test. The different clinical and serological features of SSc was determined.
Result: According to our observation: 107/126 (80%) SSc pts had joint manifestations (arthralgia or arthritis), 38/126 (30%) SSc pts had arthritis and 8/126 (6.6%) had overlap syndrome (SSc- RA). The mean disease activity score28 (DAS 28) in group with SSc-RA was 4.46 +/-1.29. A-CCP antibodies was found in 10 of 89 (11.2 %) SSc pts and RF IgM in 59 of 89(66%) pts. In group with joint involvement the a-CCP was present in 9 of 78 (11%) pts and RF in 54 of 77 (70%) pts. 1 of 10 (10%) pts had positive a-CCP antibodies and 4 of 13 (31%) pts had positive RF in SSc group without joint manifestations. In group with arthritis a-CCP antibodies was present 7 of 31 (22.6%) and RF was present in 20 of 28 (71%) pts. The significant higher titers of a-CCP antibodies ($p=0.007$), RF IgM ($p=0.038$), erythrocyte sedimentation rate (ESR) ($p=0.019$) and CRP ($p=0.032$) were observed in SSc group with arthritis compare to group without arthritis. Significant correlation was found between the group of SSc pts with arthritis and presence of a-CCP antibodies ($p=0.013$, $\varphi=0.263$) and between the group of SSc pts with arthralgia and presence of RF IgM ($p=0.025$, $\varphi= 0.238$). No relationship was observed with arthritis and presence of RF IgM in SSc group.
Conclusions:
1. The prevalence of rheumatoid factor is common in systemic sclerosis.
2. In systemic sclerosis rheumatoid factor correlate with arthralgia and a-CCP antibodies correlate with arthritis.

PS59 EFFECTS OF PRESSURE RELIEVING INSOLES FOR FOOT PROBLEMS IN PEOPLE WITH SSC: THE PISCES RANDOMIZED CONTROLLED TRIAL

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BACKGROUND

Foot problems associated with systemic sclerosis (SSc; scleroderma) are common and disabling.
The objective of this randomized controlled trial was to evaluate whether foot pain and foot-related health status in SSc can be improved through the provision of a simple pressure-relieving and insulating insole.

METHODS

A multicentre RCT conducted in four UK participating centres. A total of 141 consenting patients with confirmed SSc and plantar foot pain were randomised to receive either a commercially available pressure-relieving thermally insulating insole or a sham insole. Randomisation on a 1:1 basis was performed centrally.
The primary end point was a reduction in pain measured using the 100mm pain subscale of the Foot Function Index, after 12 weeks of intervention. Sample size was determined a priori based on a requirement to detect a 15mm difference (SD 25.7, alpha =0.05 and power =90%).
In a subset of 49 patients at the lead centre, plantar pressure measures (maximum mean pressure at heel and forefoot, with and without insoles in situ) were also obtained.

RESULTS

One hundred and thirty patients provided valid data for the primary endpoint. In both groups there was a systematic improvement in FFI pain subscale scores from baseline to 12 weeks (Active group -13.1mm, 95%CI -18.66 to-7.55 ; Sham group -10.7, 95%CI -16.17 to -5.28). An ANCOVA model adjusting for centre, gender and baseline FFI score confirmed no difference in effect between the intervention and sham groups (difference=-2.4, 95%CI -7.70 to 2.94, p=0.3778). Compared to a shoe-only baseline measure, the pressure was lowered in the heel region by use of the active insole (median difference (range) -24kPa (-75,22)) compared to the sham -4.6kPa ((-23,10), (p<0.01)), but in the forefoot the difference between insole types was not significant; pressure change -17.2 kPa (-61,19) for the active insoles and -10.8kPa (-39,0) for sham insoles (p=0.31).

CONCLUSIONS

The study compared a simple therapeutic insole with a sham device and found that over 12 weeks both produced a clinically worthwhile improvement in patient reported foot pain but with no difference between intervention arms. The active device produced a significantly greater reduction in pressure than the sham at the heel although not at the forefoot. This exploratory analysis suggests therefore, that despite careful selection the sham device introduced some unintended physical effect. The difficulty with employing a true sham as a control in physical intervention trials such as this may suggest the need for a zero intervention arm for similar studies in future.

PS60 HAND DISABILITY IN PATIENTS WITH SYSTEMIC SCLEROSIS: THE ROLE OF AN INDIVIDUALIZED REHABILITATION PROGRAM

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INTRODUCTION

Hand is often the first site of clinical manifestation of systemic sclerosis (SSc) and its function can be compromised not only by skin thickening but also by vascular injury and local tissue, joint and tendon inflammation. Patients may experience loss of joint mobility that interferes with everyday activities and can cause severe disability. The aim of the present study was to evaluate the results of an individualized hand rehabilitation program in 27 patients with SSc.

PATIENTS AND METHOD

Twenty-seven consecutive patients (herefrom defined as cases) with a diagnosis of SSc made according to the criteria of LeRoy, who attended our outpatient or daycare clinic (Trento) were enrolled. The main demographic and clinical characteristics of the 27 cases are shown in Table 1. Twenty-five controls were recruited from another Rheumatology Unit (Modena). There was no significative difference in the demographic and clinical characteristics between cases and controls. The case group underwent a rehabilitation program consisting of 19 individual sessions of 45 minutes, every day for the first week and then two days a week for the subsequent 7 weeks. Each session included a combination of finger and wrist stretching and strengthening exercises, massages and occupational therapy. The outcomes considered were the Health Assessment Questionnaire (HAQ), the Hand Anatomic Index (HAI) and the Hand Mobility in Scleroderma (HAMIS) test. Both cases and controls underwent evaluation by the same examiner at baseline (T0) and after two months (T2); the cases were also evaluate at 12 months (T12). Non-parametric test were used for all the statistical analysis, for more clarity data in tables were expressed as mean and standard deviation. The level of statistical significance was set at $P < 0.05$.

RESULTS

At baseline there was no significant difference in HAQ, HAI and HAMIS between cases and controls. We found that at baseline HAQ of both cases and controls correlate significantly with hand function parameters: HAI dx (r= -0.43, P= 0.001), HAI sx (r= -0.40, P= 0.003), and HAMIS (r= 0.58, P=< 0.001). In the case group the rehabilitation program was associated with a significant improvement of both HAQ and hand function outcomes at 2 months. At 12 months only HAMIS remained significantly improved (Table 2).

DISCUSSION

Our study shows that in SSc patients hand function correlates with HAQ and that an individualized rehabilitation program can improve both parameters. The benefit was only partially mainteined at twelve months, therefore it could be useful to repeat the program at least yearly.

Table 1. Main demographic and clinical characteristics of cases (n=27)

Age*, yrs		63.9 (12.4)
Female, n (%)		23 (85.2)
Disease duration*, yrs		6.7 (2.4)
Disease subset	lcSSc, n (%)	16 (59.3)
	dcSSc, n (%)	11 (40.7)
Autoantibodies	ANA, n (%)	8 (29.6)
	ACA, n (%)	8 (29.6)
	Anti-Scl70, n (%)	11 (40.7)
TSS*		7.7 (4.2)
Ulcers, n (%)		11 (40.7)
ILD, n (%)		16 (59.3)
DLCO*, %		65.4 (19.6)
PAH, n (%)		2 (7.4)

*Continuous data are espressed as mean (standard deviation)
lcSSc= limited cutaneous Systemic sclerosis; dcSSc= diffuse cutaneous Systemic sclerosis; ACA = anticentromere antibodies; Anti-Scl70 = anti-Scl70 antibodies; TSS = modified Rodnan total skin score; DLCO= diffusing capacity for carbon monoxide, % predicted; PAH= pulmonary artery hypertension

Table 2. Variations of measured parameters in cases treated with a rehabilitative program and controls

	Mean (stardard deviation)			*p**	
	T0	T2	T12	T0-T1	T0-T12
Cases (n=27)					
HAQ*	0.88 (0.76)	0.72 (0.65)	0.85 (0.83)	0.014	ns
HAI dx	3.10 (1.05)	3.43 (1.04)	3.26 (1.21)	<0.001	ns
HAI sx	3.48 (1.05)	3.85 (0.99)	3.58 (1.07)	<0.001	ns
HAMIS	10.11 (9.53)	7.78 (9.28)	7.56 (8.66)	<0.001	<0.001
Controls (n=25)					
HAQ	0.73 (0.85)	0.74 (0.84)	-	ns	-
HAI dx	3.44 (1.31)	3.43 (1.33)	-	ns	-
HAI sx	3.64 (1.19)	3.58 (1.10)	-	ns	-
HAMIS	9.16 (10.10)	9.28 (10.28)	-	ns	-

*Wilcoxon signed rank test
T0= baseline; T2= two months; T12= twelve months
HAQ= Health Assessment Questionnaire; HAI= Hand Anatomic Index; HAMIS: Hand Mobility in Scleroderma
ns: not significant

PS61 SYSTEMIC SCLEROSIS-RELATED SYNOVITIS: IMAGING FEATURES AND HISTOLOGICAL EXAMINATION OF THE SYNOVIAL TISSUE

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Previous studies have shown an increased prevalence of synovitis and tenosynovitis in systemic sclerosis (SSc) as detected by musculo-skeletal ultrasound (US) or magnetic resonance imaging (MRI). The histological correlate of synovitis detected by imaging is not yet known as synovial biopsies were not available in these studies.

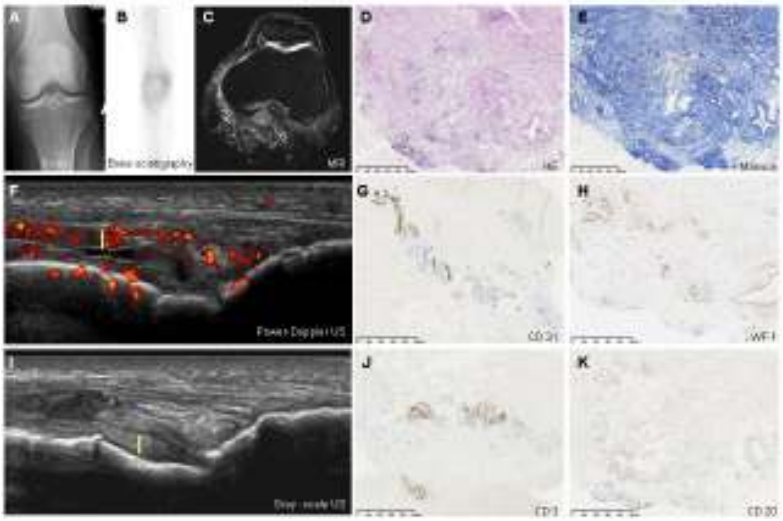
We aimed to assess the inflammatory and non-inflammatory lesions in synovial biopsies in patients suffering from SSc-related arthritis.

Seven synovial biopsies from 4 SSc patients (2 diffuse and 2 limited SSc) were obtained. Three patients had paired synovial biopsy before and after immunsupressor treatment shift and one patient had a single biopsy before starting immunosupressor therapy. Five knee biopsies and two wrists biopsies were analyzed by immunohistochemistry (IC). Imaging studies (MRI, US and/or arthroscopy) were performed prior to biopsies.

Disease duration from the Raynaud phenomena to the first synovial biopsy was 1-14 years. All patients had oligoarthritis at the time of the first biopsy. Imaging studies confirmed the presence of synovitis with increased synovial thickness and areas with hypervascularisation. In addition, in one patient, intra-articular calcifications were observed. Microscopic examination of the synovium revealed increased thickness and altered global architecture with marked angiogenesis, inflammatory cell infiltrates, increased collagen deposition and extracellular deposits. The increased thickness of the synovium was due both to increased deposition of collagen and infiltrates of inflammatory cells. These changes paralleled those observed by imaging and correlate with the duration of arthritis. IC revealed an increased density of T lymphocytes and macrophages with low density of B-cells and plasmocytes. Peri-vascular T-cell infiltrates and T-cells aggregates around inflammatory nodules were present, the latter being associated with marked deposits of non-collagen, amorphous material. Angiogenesis consisted mainly in increased density of immature vessels as detected by WT1 immunostaining. Arteriolar onion-skin like lesions were present in biopsies from more severe patients. At the time of the second biopsy, persistent arthritis was noted despite changes in immunupressor therapy. Paired synovial biopsies confirmed the persistency of abnormal synovial findings.

The histological correlate of joint involvement is shown to be synovitis in which the synovium is invaded by an inflammatory lymphocytic infiltrate, macrophages and immature vessels. Both inflammatory and non-inflammatory changes are present in the synovium from SSc patients including increased vascularity, collagen deposition and fibrosis. This pattern is distinct from that described in lupus arthritis, rheumatoid arthritis, psoriatic arthritis and osteoarthritis.

Imaging studies and immunohistochemistry characterization of the synovial biopsy in a 43 years old patient suffering from bilateral knee arthritis related to diffuse SSc



Poster Tours – Clinical
Poster Tour 10: Upper and Lower Gastrointestinal/nutrition

PS62 EVALUATION OF THE PATIENT-REPORTED OUTCOMES MEASUREMENT INFORMATION SYSTEM (PROMIS®) GASTROINTESTINAL (GI) SYMPTOMS MEASURES IN SYSTEMIC SCLEROSIS (SSC)

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Introduction: The National Institutes of Health PROMIS® roadmap initiative is a cooperative research program designed to develop, evaluate, and standardize item banks to measure patient-reported outcomes (PROs) across different medical conditions as well as the US population (www.nihpromis.org). As part of the National Institutes of Health PROMIS® roadmap initiative, we developed GI Symptoms measures that assess 8 domains: Gastroesophageal reflux (13 items), disrupted swallowing (7 items), diarrhea (5 items), bowel incontinence/soilage (4 items), nausea and vomiting (4 items), constipation (9 items), belly pain (6 items), and gas/bloat/flatulence (12 items). All scales are calibrated using a two-parameter IRT graded response model and scored on a T-score metric with a mean of 50 and SD of 10 in the U.S. general population. This paper evaluates the construct validity of the GI measures in patients with SSc.

Methods: 165 patients with SSc were administered the PROMIS GI Symptoms measures and UCLA SCTC GIT 2.0 instrument. GIT 2.0 has 5 symptom scales: reflux, distention/ bloating, diarrhea, constipation, and fecal incontinence. Product-moment correlations of the PROMIS GI measures with the GIT 2.0 symptoms scales were used to evaluate construct validity. In a subset of patients (N=37), both instruments were administered at 2 time points. F-statistics was calculated from one-way ANOVAs to assess responsiveness to change

Results:

Patients with SSc GI involvement had scale scores 0.2-0.7 SD worse than US population. Hypothesized correlations were larger than other scales and in the right direction (Table). F-statistics were greater for 6 of 8 PROMIS scales (range 0.45 for belly pain to 3.21 for reflux scale) vs. GIT 2.0 except for diarrhea scale (0.67 vs. 0.98 for GIT 2.0) and constipation scale (1.37 vs. 1.79 for GIT 2.0).

Conclusion: PROMIS GI Symptoms scales are significantly correlated with the hypothesized GIT 2.0 scales and 6 of 8 scales showed greater responsiveness to change than the GIT 2.0.

Table: Product-moment correlations between PROMIS GI Symptoms scales and UCLA SCTC GIT scales

	Reflux *	Distention / bloating	Diarrhea	Constipation	Fecal incontinence
Reflux	**0.77**	0.44	0.13	0.25	-0.03
Disrupted swallowing	**0.61**	0.39	0.16	0.21	0.13
Nausea and vomiting	**0.66**	0.44	0.20	0.22	0.18
Belly pain	0.45	0.49	0.23	0.34	0.04
Gas/bloat/flatulence	0.48	**0.73**	0.30	0.29	0.10
Diarrhea	0.25	0.25	**0.65**	0.02	0.54
Constipation	0.37	0.32	0.05	**0.76**	-0.01
Fecal incontinence	0.12	0.11	0.43	-0.16	**0.87**

*GIT 2.0 Reflux scale asks about reflux, dysphagia to solid foods, and nausea/ vomiting.

PS63 UPPER GASTROINTESTINAL BLEEDING PREDICTS HIGHER MORTALITY IN SYSTEMIC SCLEROSIS PATIENTS

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Background: The gastrointestinal tract is involved in nearly all patients with systemic sclerosis (SSc) and is a source of great morbidity and even mortality.
Aim: To assess whether there is correlation between upper gastrointestinal (UGI) endoscopy findings and mortality in SSc patients.
Methods:The records of 256 SSc patients seen in our rheumathologic clinic between the years 2003-2013 were reviewed. 140 patients who had at least one detailed endoscopic report and at least 6 months follow-up were included in the study. Patients data included demographic details, type of SSc, disease duration, modified Rodnan skin score (mRSS).
Endoscopic findings that were included in the analysis were esophagitis, ulcerations, tumors, gastric antral vascular ectasia (GAVE), gastric erosions, submucosal hemorrhages and lumen bleeding. The statistical methods used included descriptive statistics, T test, Spearman's correlation and multiple logistic regression analysis.
Results: Forty seven patients (16 diffuse SSc) had evidence of GAVE or antral erosions and hemorrhage. The mortality rate in this group, during the follow up was 37%, compared to 25% in the group of 93 (39 diffuse) SSc patients without endoscopic evidence of GAVE or UGI bleeding (p=0.009). There were no statistical differences between the groups regarding age (mean (SD) 55(13)years versus 55(14) years. The mRSS was higher in the group with UGI bleeding (mean (SD) 8(7) versus 5.6(4), but it did not reach statistical significance. The disease duration was shorter (mean (SD) 6.5(5.8) years versus 10.5(6.5)) – $P<0.05$.
Esophagitis was found in 90% of patients. All patients were under PPI treatment.
Conclusions: A diagnosis of GAVE or UGI bleeding on endoscopy was associated with higher mortality, in our cohort. Shorter disease duration might be correlated with more aggressive course

PS64 NUTRITIONAL SUPPORT IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Systemic sclerosis (SSc) is a multisystem autoimmune disease which involves gastrointestinal tract in about 90% of cases. It may contribute to nutritional deterioration.

Objective: To assess whether the application of a nutritional support protocol (1) to these patients could improve their nutritional status.

Methods: Unicentric prospective study, performed on an outpatient basis, in a county hospital. "Malnutrition universal screening tool" (MUST) was used to screen risk for malnutrition. Weight, height, energy and protein requirements, macronutrient intake and nutritional biochemical parameters were evaluated. Nutritional intervention was performed in patients at risk for malnutrition (MUST above 1) every three months until 1 year.

Results: Of the 72 patients, 9 (12.5%) were at risk for malnutrition. Iron deficiency anemia (18.35%) and vitamin D deficiency (54%) were the most frequently observed nutritional deficits.

Data (mean ± DS) (n=9)	Baseline	12 months
Weight (kg)	51.5±8.5	54.3±9.1
BMI (kg/m²)	21.0±2.5	22.0±3.2
Energy intake (Kcal)	1487±203	1870±175
Protein intake (g)	67±12	75±19
Carbohydrates (%)	39.9±7.18	43.7±4.3
Proteins (%)	18.2±1.7	16.2±2.8
Fats (%)	40.5±6.2	39.9±2.5
Fiber (g)	15.4±6.9	24.3±14.8
Hemoglobin (12-16 g/dl)	11.73±1.39	12.55±1.33
Vitamin D (>30ng/ml)	21.5± 8.87	27.3±1.78
Albumin (35-52 g/dl)	38.7±2.03	40±2.82
Ferritin (30-400 ng/ml)	59.5±37.7	52±39.5

Conclusions: Dietary intervention was able to improve body weight and food intake. Hemoglobin values and vitamin D deficiency improved with iron and vitamin D supplements.

(1) Reumatol Clin 2012; 8: 135–140.

PS65 VASCULAR EVENTS ARE RISK FACTORS FOR ANAL INCONTINENCE IN SYSTEMIC SCLEROSIS: A STUDY ON MORPHOLOGY AND FUNCTIONAL PROPERTIES AS MEASURED BY ANAL ENDOSONOGRAPHY AND MANOMETRY

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Objectives: The aim of the study was to study the anal sphincter morphology, anal sphincter pressure and the rectoanal inhibitory reflex in patients with systemic sclerosis (SSc) complicated by anal incontinence (AI) and to investigate possible risk factors for AI in SSc.
Methods: 19 SSc patients with severe AI were investigated using anal endosonography, anal manometry, and rectal manovolumetry. To determine risk factors for AI, data concerning disease characteristics for each SSc patient with AI were compared to 5 SSc patients without AI.
Results: Mean (SD) internal sphincter thickness was 1.3 (0.46) mm in patients with AI which was thinner ($p<0.001$) than reference data from healthy individuals whose internal sphincter measured 2.2 (0.45) mm whereas external sphincter thickness did not differ. Mean (SD) resting pressure in AI patients was lower than reference data from healthy individuals (60 (22) vs 94 (29) mmHg, $p<0.002$), whereas squeeze pressure did not differ. Centromeric antibodies, and features of vascular disease, ie presence of pulmonary arterial hypertension, digital ulcers, pitting scars or the need for Iloprost infusions were associated with AI, whereas fibrotic manifestations, ie modified Rodnan skin score, the diffuse cutaneous SSc subset or low vital capacity were not.
Conclusions: SSc patients with AI have a thin internal anal sphincter and a low resting pressure. Risk factors for AI among SSc patients are centromeric antibodies and vascular disease which supports the hypothesis that gastrointestinal involvement in SSc is in part a vascular manifestation of the disease.

PS66 FAECAL LEVELS OF CALPROTECTIN IN SYSTEMIC SCLEROSIS ARE STABLE OVER TIME AND ARE HIGHER COMPARED TO PRIMARY SJÖGREN'S SYNDROME AND RHEUMATOID ARTHRITIS

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INTRODUCTION
Faecal calprotectin (FC) has been proposed to be a biomarker of gastrointestinal (GI) disease in systemic sclerosis (SSc). The purpose of this study was to extend cross-sectional observations and prospectively assess the variability of FC over time in SSc patients. We also aimed to examine FC in relation to immunosuppressive therapy. Finally we wanted to analyse FC in other rheumatic diseases to evaluate the specificity of FC for SSc GI disease.
METHODS
FC was measured in consecutive patients with SSc, primary Sjögren's syndrome (pSS), rheumatoid arthritis (RA) and in healthy hospital workers. The intraindividual variability of FC in SSc was assessed with intra class correlation (ICC) and κ statistics. Associations between FC and objective markers of GI disease and immunosuppressive medication were investigated.
RESULTS
FC was associated with micronutrient deficiency and GI pathology as assessed by cineradiography confirming our previous results. FC showed only a limited intra-individual variation in SSc, ICC=0.69 (95% CI: 0.57-0.78) and κ=0.64 (95% CI: 0.56-0.73). Generalised immunosuppression did not have any significant impact on FC. FC was significantly higher in SSc patients compared to patients with pSS or RA as well as compared to healthy subjects.
CONCLUSIONS
FC is a promising non-invasive biomarker for GI disease in SSc. In view of stable levels over time, FC could be a useful marker when novel, more specific drugs targeting the GI tract in SSc will be introduced.

PS67 GASTROINTESTINAL MUCOSAL ABNORMALITIES USING VIDEOCAPSULE ENDOSCOPY IN SYSTEMIC SCLEROSIS

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Objective: The aims of this prospective study were to: 1) determine both prevalence and characteristics of gastrointestinal mucosal abnormalities in unselected patients with SSc, using videocapsule endoscopy; and 2) evaluate whether the presence of gastrointestinal mucosal abnormalities is associated with clinical digestive manifestations, findings of gastric mucosal damage on gastroscopy, esophageal motor impairment as well as extra-digestive manifestations of SSc.
Methods: 50 consecutive patients with SSc underwent videocapsule endoscopy. All SSc patients also completed questionnaires for digestive symptoms.
Results: The prevalence of gastrointestinal mucosal abnormalities was 52% in our SSc patients. Vascular mucosal lesions were predominant, including: 1) watermelon stomach (n=9), 3 of these latter patients exhibited antral gastritis on gastroscopy 2) gastric and/or small intestinal telangiectasia (n=7); and 3) gastric and/or small intestinal angiodysplasia (n=10). We observed a marked correlation between gastrointestinal vascular mucosal lesions and: 1) the presence of anti-centromere antibody (p=0.01); and 2) the absence of anti-Scl 70 antibody (p=0.007).
Conclusion: Our study underscores the usefulness of videocapsule endoscopy in identifying gastrointestinal mucosal abnormalities in 52% of our patients with patients. Moreover, our series highlights that gastrointestinal vascular lesions were predominant in our patients, occurring at early stage of SSc (< 3 years). Interestingly, our findings underline that videocapsule endoscopy should be performed to disclose the presence of small intestinal vascular lesions (telangiectasia, angiodysplasia) in: 1) SSc patients with normal gastroscopy; and 2) persistently anemic watermelon stomach patients with SSc in whom, after appropriate endoscopic treatment, gastroscopy shows only mild remanence of antral vascular ectasia.

PS68 ASSESSMENT OF VALIDITY OF GASTROINTESTINAL MORPHOLOGY PROCEDURES AND BACTERIAL OVERGROWTH TESTS USED IN SYSTEMIC SCLEROSIS, BASED ON OMERACT CRITERIA

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Background: The gastrointestinal tract (GI) is involved in nearly all patients with systemic sclerosis (SSc) and is a source of significant morbidity and mortality. There is no single objective measure to assess the extent and severity of GI involvement in SSc patients. The evaluation of the regional morphology and motility and absorptive/ secretory functions of the GI tract by dedicated tests, provides a systematic approach to the assessment of GI involvement in SSC Only validated measures enable scientific research of the disease outcome and the effect of therapeutic interventions.
Objectives To assess the validity of the morphology and bacterial overgrowth measures used to examine the GI tract in SSc, using the OMERACT criteria.
Methods: We performed a systematic literature search for published data on GI involvement in SSc, using the PubMed database for English-written articles and the Cochrane library from 1966 through the end of 2012. The keywords used were “systemic sclerosis” (SSc) and “scleroderma “and they were combined with text words such as esophagus, stomach, small bowel, colon, anorectal, malabsorption, bacterial overgrowth and procedures used for morphology and bacterial overgrowth assessment (eg endoscopy, breath test, ultrasound, lactulose test, xylose test, barium studies, mucosal biopsy), randomized controlled studies (RCT), clinical studies. Articles obtained from these searches were reviewed for additional references. Case reports or case series of less than 8 patients, articles with non separable data for SSc patients and reviews were excluded. The validity of the tests was evaluated according to the OMERACT principles.
Results: The search identified 468 titles or abstracts. Only 58 articles which answered the inclusion criteria and demonstrated at least one type of validation, were included. Of the 21 morphology, malabsorption and bacterial overgrowth tests examined only 5 tests (gastroscopy, UGI barium studies, mucosal biopsy, hydrogen and methane breath tests and 72 hours fecal fat test) are fully validated. There are a number of partially validated measures, including small bowel follow-through, colonoscopy, endoluminal MRI, endoanal US, jejunal cultures, xylose and lactulose tests.
Conclusions: Technologic advance lead to the introduction of new tests in GI assessment with better spatial and temporal resolution. However only a minority of morphology, malabsorption and bacterial overgrowth tests are partial or fully validated in SSc, conforming OMERACT principles. Proper validation in SSC of the modalities reviewed will provide valuable tools to improve our understanding of SSC and to be used as outcome measures in interventional studies.

Poster Tours – Clinical
Poster Tour 11: Pregnancy & sexual problems

PS69 SEXUAL DYSFUNCTION: THE PHYSICAL AND PSYCHOLOGICAL BURDEN ON WOMEN IN SYSTEMIC SCLEROSIS

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Background: Systemic Sclerosis (SSc) is a multisystem connective tissue disease associated with significant mortality predominantly as a consequence of cardiopulmonary complications but it is also associated with significant comorbidities including sexual dysfunction. The aims of this study were to evaluate the prevalence of the problem amongst women with SSc from a major single-centre in UK, the impact of SSc on sexual relationship and difficulties faced.

Method: 100 women with limited (lcSSc) or diffuse (dcSSc) scleroderma were invited to complete a validated Female Sexual Function Index(FSFI) questionnaire that examined six major domains: desire, orgasm, arousal, lubrication, satisfaction and pain. The questionnaire was broadened to evaluate the psychological effects of sexual difficulties in interpersonal relationships including health professionals.

Results: 50% responded to the questionnaire of which 52% had diffuse disease subset with mean age (±SD, years) 56 ±1.41. Mean disease duration is similar for both disease subsets with (mean ±SD, years) 12 ±2.8. 54% of the patients developed sexual difficulties after their diagnosis and the mean duration from SSc diagnosis to first sexual complaint was (mean, ±SD, years) 4.0 ±5.8. 84% of the patients reported significant sexual problems in the overall FSFI domains. 60% of the affected women revealed that their sexual complications had inflicted strain in their relationships leading to reduction of activities shared, emotional and financial changes.Some patients even reported breakdown in relationship as a consequence of sexual dysfunction. 46% of the subjects were able to discuss their sexual concerns with their partners, whilst 30% chose not to as they wish to keep these issues to themselves or felt embarrassed to discuss about their difficulties.Among the 32 (64%) women who discussed the problems with their partners, 56% found it to be helpful. 76% of the subjects reported that they had never been asked about sexual health by health professionals. However 52% revealed that they would have discussed their sexual problems if they were concerned. Interestingly 72% of these women admitted to not raising any concern about their sexual problems.

Conclusion: Our study showed that sexual dysfunction is common among women with SSc and presents a major burden for them and their partners physically and psychologically. It is often neglected by the patients and not openly discussed with partners and health professionals. Multidisciplinary teams treating scleroderma patients should be aware of and actively enquire about sexual health as it is a subject worth exploring so that patients' quality of life can be improved.

PS70 IN WOMEN WITH SYSTEMIC SCLEROSIS, SEXUAL FUNCTION IS AFFECTED BY DISEASE-RELATED AND PSYCHOLOGICAL CONCERNS

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Objective:
In Systemic Sclerosis (SSc) patients, sexual function is somewhat impaired. Our aim is to evaluate sexual function in women with SSc in comparison to controls and to investigate the association with socio-demographic and disease characteristics, physical and psychological variables.
Methods:
46 women with SSc (age: 56.1 ± 12.4 years; 29 with lSSc, 17 with dSSc) and 46 healthy women (age: 52.0 ± 9.0 years) were assessed for socio-demographic characteristics, gynecological anamnesis and administered with Female Sexual Function Index (FSFI), Short Form-36 (SF36), Health Assessment Questionnaire (HAQ), Hospital Anxiety and Depression Scale (HADS), Rosenberg Self-Esteem Scale (RSES), Coping Orientation to Problems Experienced-New Italian Version (COPE-NIV), Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F).
Patients were also assessed for disease duration and subset, Female Sexual Function in SSc (FSFS), Hand Mobility In Scleroderma Test (HAMIS), Cochin Hand Functional Disability Scale (CHFDS), Mouth Handicap in Systemic Sclerosis Scale (MHISS), Disability Sexual and Body Esteem Scale (PDSBE); fist closure, hand opening and mouth opening.
Results:
in SSc patients, only FSFI desire subscale score was significantly lower (p=0.035) versus controls. FSFI scores were not different in dSSc versus lSSc patients (P=NS).
Total FSFI score, similar to controls, by bivariate analysis was negatively correlated with age (p=0.014), HADS-d (p<0.001), FACIT-F (p=0.044), COPE-NIV Avoidance Strategies subscale (p=0.012); and positively related with PDSBE (p<0.001), SF-36 summary mental index (p=0.006) scales. FSFI total score was also negatively correlated to HAQ (p=0.022), total MHISS (p=0.038) and HAMIS (p=0.037) scores.
At multivariate analysis, in SSc, the factors independently associated with FSFI were vaginal dryness (B=-0.72; p<0.001), PDSBE (B=0.42; p=0.001) and HADS depression scale (B=-0.23; p=0.035). Together, these variables explained 70% of the variance in total FSFI.
At multivariate analysis in healthy participants, the factors independently associated with FSFI were age (B=-0.47; p=0.001), FACIT-F (B=-0.36; p=0.006), physical problems PP subscale of SF-36 (B=0.29;p=0.02) and COPE-NIV transcendental orientation scale (B=-0.24;p=0.037), together, explaining 44% of the variance in total FSFI.
Conclusion:
In SSc, sexual function, although not different from controls, is influenced by specific disease-related and psychological concerns, different from variables affecting sexual function in healthy controls. Thus, it should be included in patients evaluation and assessed in daily practice.

PS71 SEXUAL DYSFUNCTION IS ASSOCIATED WITH ANXIETY AND HIGHER BODY MASS INDEX IN WOMEN WITH SYSTEMIC SCLEROSIS

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Introduction:
Impaired sexual function and limited sexual activity appear to be common among women with chronic illnesses, including Systemic Sclerosis (SSc). Physical and psychological consequences of the disease may be severe and their potential impact in the patient's sexual function is often neglected.

Objective:
To evaluate sexual function in patients with SSc and its relationship with biological and psychological aspects of the disease experience.

Methods:
A total of 36 SSc women were assessed. A standardized questionnaire was used to register demographic parameters, current therapies and clinical manifestations of SSc. Sexual function was assessed by self report using of the Female Sexual Function Index (FSFI), which evaluates 6 different sexual domains referring to the previous 4 weeks: Desire, Arousal, Lubrication, Orgasm, Satisfaction and Pain. An individual score was calculated for each sexual domain and an FSFI total score (sum of the weighted individual scores) was obtained for each patient. A cut-off value of 22.5 was used to classify patients as having sexual dysfunction or not (Brook Levis et al). Psychological, Functional and Quality of Life aspects were evaluated through the Hospital Anxiety and Depression Scale (HADS), Health Assessment Questionnaire (HAQ) and Short Form 36 (SF-36), respectively.
Statistical analysis was performed through SPSS. Comparison between groups was assessed through Mann-Whytney test or Chi 2 test, as adequate. p values <0.05 were considered significant in all statistical analyses.

Results:
A total of 36 SSc women were included. Mean age was 58.8±11.1 years (mean ± SD) and 80.6% presented the limited disease subtype. 91.7% had a partner and 55.6% were sexually active. Among the sexually active patients, 55% had sexual dysfunction (FSFI total score < 22.5). Desire was the most affected domain (mean Desire score of 1.691±0.647 and 3.467±0.88, in patients with and without sexual dysfunction, respectively). Mean Body Mass Index (BMI) was significantly higher in women with sexual dysfunction (28.04±4.626 vs 23.23±2.473; p=0.016). Higher anxiety levels were present in patients with sexual dysfunction (mean HADS-anxiety subscale of 10.73±2.054 vs 8.56±2.128; p=0.031,), although depression levels (HADS-depression subscale), functional disability (HAQ) and quality of life (SF-36) were similar in both groups. No differences were observed in sexual function according to SSc disease subtype.

Conclusion:
The majority of the sexually active SSc women suffered of sexual dysfunction and this was related with higher anxiety and BMI levels, which poses additional questions in the treatment of these patients. Further research to investigate sexual dysfunction among these patients is needed.

PS72 THE VASCULAR HYPOTHESIS OF FEMALE AND MALE SEXUAL DYSFUNCTION

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To investigate the clitoral blood flow in systemic sclerosis (SSc) women and the flow inside cavernous arteries in SSc men. Doppler indices [peak systolic velocity (PSV), end diastolic velocity (EDV), the resistive index (RI), pulsatile (PI) indices and S/D (systolic/diastolic) ratio] were measured using an Aplio Ultrasound System SSA-790 (Tokio, Japan) equipped with convex 7.5 MHz probe. In SSc women Doppler indices of clitoral artery were measured at baseline, conversely in SSc men Doppler indices of cavernous arteries were measured at the peno-scrotal junction before and after pharmacostimulation with 20 mcg prostaglandin E1. Nailfold videocapillaroscopy (NVC) was performed by an optical probe videocapillaroscopy equipped with magnification 200 x contact lens and connected to image analysis software (Pinnacle Studio Version 8, Pinnacle Systems, Mountain View, California). The nailfold (distal row) of the second, third, fourth and fifth finger was examined in each patient.

Twenty women [median age 37 (25-45) years] and 20 men [median age 44 (21-58) years] fulfilling the American College of Rheumatology preliminary criteria for the classification of SSc were enrolled. The Female Sexual Function Index (FSFI) and International Index of Erectile Function-5 (IIEF-5) were used to assess sexual function in women and men, respectively. FSFI was reduced in 6 (30%) of 20 SSc women and IIEF-5 was reduced in 16 (80%) of 20 SSc men.

Eight women have an early capillaroscopic pattern, 6 have an active capillaroscopic pattern and 6 have a late capillaroscopic pattern. No significant differences of PSV and EDV were observed in the three capillaroscopic patterns. Conversely, PI, RI and S/D ratio were significantly different in the three capillaroscopic patterns. PI ($p<0,01$), RI ($p<0,001$) and S/D ratio ($p<0,01$) increased with progression of capillaroscopic damage.

Also in SSc men Doppler indices of cavernous arteries were different in three capilaroscopic groups. PSV ($p<0,001$) decreased and EDV ($p<0,001$) increased with progression of capillaroscopic damage. No significant differences of RI ($p>0,05$) were observed in three capillaroscopic groups.

We can conclude that artery inflow of clitoral and cavernous arteries is reduced in the vast majority of SSc women and men. The artery inflow decreased with progression of capillaroscopic damage.

PS73 IMPRESS 2 (INTERNATIONAL MULTICENTRIC PROSPECTIVE STUDY ON PREGNANCY IN SYSTEMIC SCLEROSIS). PROSPECTIVE, CASE-CONTROL STUDY OF PREGNANCY IN SYSTEMIC SCLEROSIS

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Background: Systemic Sclerosis (SSc) has its usual onset in the mid-forties, but it's not unusual to find SSc women wanting a child, especially nowadays where a great number of women delay pregnancy. Data on pregnancy in SSc are limited. We recently published a large retrospective study: IMPRESS (Italian Multicentric study on PREgnancy in Systemic Sclerosis), partially supported by Italian patients associations, that studied 99 SSc women and their 109 pregnancies, admitted in 25 Italian centers within the years 2000-2011, compared with a general obstetric population (GOP). In SSc women preterm deliveries (25% vs. 12%) and severe preterm deliveries (<34 weeks) (10% vs. 5%), intrauterine growth restriction (IUGR, 6% vs. 1%) and very-low-birth-weight babies (5% vs. 1%) were significantly more frequent than in the GOP. Multivariable analysis found that corticosteroid use was associated with preterm deliveries, while folic acid and anti-Scl70+ was protective. The disease remained stable in most SSc patients, but there were four cases of progression within one year from delivery.
Aim of the study: to plan a new fully prospective study: IMPRESS 2 (International Multicentric PRospective Study on PREgnancy in Systemic Sclerosis).
Patients and methods: we're planning a fully prospective, case-control study of 3 groups of people, enrolled at an International level: 1. 100 pregnant SSc patients, 2. 200 non-pregnant matched SSc women, 3. 200 healthy pregnant women. Their children will be studied at birth and at 1 and 3 years of age. IMPRESS 2 study will prospectively investigate disease activity of SSc during and after pregnancy, pregnancy complications and outcome in patients with SSc, children outcome at 1 and possibly 3 years, and the modern incidence of renal crisis, severe cardiac involvement and pulmonary hypertension in women with SSc, both pregnant and non-pregnant. Several ethical committees of the participating centres have approved the study, and enrolment is started: 14 pregnancies worldwide are currently ongoing.
Expected results and Conclusion: IMPRESS 2 will answer to the following important questions. 1. are complications of SSc more frequent during pregnancy than in the non-pregnant state? 2. Which is the current incidence of renal crisis, cardiac involvement, and pulmonary hypertension in scleroderma women, both pregnant and non-pregnant? 3. Is folic acid use protective for prematurity? 4. Are some autoantibodies protective for prematurity? 5.Which is the impact of prematurity on children development? Which is their IQ at 3 years? These data will be extremely important for counseling fertile SSc women contemplating a pregnancy.

Poster Tours – Clinical
Poster Tour 12: Therapy

PS74 ALLOGENIC SKIN GRAFTING FOR SYSTEMIC SCLEROSIS ULCERS: PRELIMINARY DATA OF AN ITALIAN COHORT

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Backgroud: Systemic sclerosis (SSc) is a systemic autoimmune disease of unknown etiology. Digital ulcers are common in patients with SSc with a prevalence around 30% while nondigital ulcers in are estimated at 4%. Both ulcers can cause severe pain and morbidity. Reconstructive surgery for hard-to-heal ulcers can be performed using preserved cadaver skin (allograft). This technique has been used both in burns and in chronic leg wounds by reducing pain, accelerating healing and minimizing scarring. The aim of this study was to assess the effect of allograft in a cohort of SSc patients with chronic ulcers.
Methods: From January 2006 to December 2012 consecutive SSc subjects affected by chronic ulcer (refractory to conventional treatment) referred to our vascular surgery department to perform allogenic skin grafting were enrolled. Data were retrospectively retrieved from clinical charts. Diagnosis of SSc was established using ACR criteria (1980). The primary outcome was to assess effectiveness in terms of pain reduction, evaluated using a visual analogue scale (VAS)and tolerability (rate of infection).
Results: A total of 43 SSc patients (5 male, 38 female) were treated using allogenic skin grafting. The mean age at the time of intervention was 60.8 years (min 39 – max 83). The ulcers were localized in the following areas: 34 lower extremities (10 digital), 8 upper extremities (3 digital), 1 both upper and lower digital ulcers. The mean ulcer duration was 27 months (min 2, max 140). Other risk factors for ulcers development recorded was:venous insufficiency (13 patients), arterial hypertension (17 patients), diabetes (3 patients), hypercholesterolemia (5 patients), obesity (1 patient).
The VAS for pain reduced by 84%: before the mean VAS value was 7.55 (min 4 – max 10) and immediately after the procedure was 1.18 (min 0 – max 5) – $p<0.001$.
No serious side effects was recorded after the procedure. All patients healed completely, but 37 % had an ulcer recurrence in the same location during the subsequent year. No patient presented an infection in the grafting area during the first 4 weeks after the surgery.
Conclusion:The use of allogenic skin grafting may be a safe and effective treatment for SSc chronic ulcers. This procedure seems to favour wound healing and significantly reduces pain as compared to conservative dressing. Further studies and randomized controlled trials are needed to identify prognostic factors of response to allografts and to help the selection of patients most suitable for the procedure.

PS75 AUTOLOGOUS FAT TRANSFER FOR DIGITAL ULCERS TREATMENT IN SYSTEMIC SCLEROSIS

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Objective: Digital ulcers (DUs) occur in up to 50% of patients with Systemic Sclerosis (SSc). DUs are painful, recurring and lead to functional disability. Management of DUs includes pharmacologic and local therapy: the healing is slow and the ulcer can become infected or evolve to gangrene. Autologous fat grafting (AFG) is a technique used in reconstructive surgery to promote repair of soft tissues. We used AFG to treat DUs refractory to conventional treatment to enhance healing.
Methods: We treated 9 SSc patients with 16 DUs. All were treated with iv Iloprost: 8 patients with CCB (calcium channel blocker), 7 with low dose aspirin, 2 with sildenafil and 4 with bosentan to prevent recurrence. The purified fat tissue was injected on the border of larger ulcers or at the finger base of smaller DUs. The AFG was done from 2 to 8 months since the ulcer onset.
Results: No improvement was observed in 3 pts. The outcome was positive with complete healing in 10 DUs and size reduction > 50% in 2, in 8 to 12 weeks. In all but three patients the pain improved allowing a reduction of analgesics.
Conclusions: The AFG was able to hasten ulcer healing and to reduce pain and the need of pharmacological therapy in the majority of the cases. The lack of efficacy on healing and pain was observed when the ulcers were long-lasting and with concurrent atherosclerotic macroangiopathy, especially those located on legs. Furthermore in a single patient the AFG was effective on the digital ulcer whereas the outcome of the ulcer of the heel was very poor.

PS76 LUNG TRANSPLANTATION IN SISTEMIC SCLEROSIS: EXPERIENCE IN A SPANISH CENTER

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Objectives:
To describe the clinical features, evolution, complications and survival of patients with Systemic Sclerosis (SSc) who received lung transplantation.

Methods:
Six patients with SSc that underwent lung transplantation between May 2005 and July 2012 were included. Data were obtained from review of medical records and databases. Follow-up was continued until July 2013.

Results:
All patients were caucasian. Four (66%) were women with a mean age of 45 ± 8 years at the transplantation moment. Distribution by SSc subset according to the Le Roy and Medsger's criteria was: 4 limited and 2 diffuse. All patients had Raynaud's phenomenon and mild to moderate esophageal involvement; 5 musculoskeletal and heart involvement; 3 digital ulcers and pulmonary arterial hypertension (PAH).
Lung transplantation was carried out due to: interstitial lung disease (ILD) in 3 patients, ILD associated to PAH in 2, and 1 to PAH. Five lung transplants were bilateral and one unilateral. Initial complications were: gastroparesia in 3 patients, diaphragmatic palsy in 1, and acute cellular rejection in 2. Two individuals showed no early complications. Late complications were: bronchial stenosis in 2 patients, bronchiolitis obliterans syndrome in 2, and restrictive allograft syndrome in 1. All patients were immunosupressed with tacrolimus, mycophenolate mofetil and corticosteroids.
Median survival was 83% at one year and 80% at two years. Deaths were due to respiratory infections in two patients (39 and 54 months after transplantation) and lung adenocarcinoma in one (7 months after transplantation).

Conclusions:
Lung transplantation is an effective treatment for advanced ILD and/or PAH associated to SSc patients. Bilateral lung transplantation was the most common procedure. In our series, infectious complications were the leading cause of death. Mortality at one and two years was similar to that described in the literature for other lung transplantation indications. More studies are needed to assess long term effectiveness of this treatment.

PS77 LONG TERM EFFICACY OF PERIORAL AUTOLOGOUS FAT TRANSPLANTATION ON SCLERODERMA SKIN FIBROSIS: A CONTROLLED STUDY VERSUS HYALURONIC ACID FILLER.

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Autologous fat tissue grafting (AFTG) has been successfully used in the treatment of different sclerotic conditions, including scleroderma.
We evaluated in patients with SSc who complained of a reduced mouth opening, the long-term efficacy, safety and durability of AFTG of the lips in improving mouth opening in comparison with hyaluronic acid (HA) filler. We also investigated whether these procedures may induce some changes in the microvascular architecture and dermal structure of the treated skin area.
Materials and Methods. We studied 25 patients with dcSSc, (median age 35+15 yrs, disease duration 11+8years): 15 were treated by topical perioral AFTG according to Coleman technique and 10 by HA filler. Baseline and after treatment (at months 3, 6, and 12) mouth opening changes were assessed by measuring inter-incisal distance and oral perimeter, skin hardness was tested by digital durometer. Pre- and post-treatment modifications of microvascular architecture were assessed by counting capillaries in the inferior lip videocapillaroscopy (VC) images. Similarly, histological sections of perioral skin biopsy were examined at baseline and 3 months to evaluate dermo-epidermic junction (DEJ), the collagen content (by Masson's Trichrome staining) and microvessel density (MVD) (by anti-CD34/CD31staining).
Results. 3 months after treatment both the inter-incisal distance and oral perimeter significantly increased ($p < 0.001$), and durometer scores were significantly decreased in comparison to the baseline evaluation ($p=0.03$). At the same time, a significant skin neovascularization became evident, both considering the VC images ($p < 0.001$) and MVD scores in IH sections ($p < 0.0001$). Finally, some skin histological aspects also improved, as shown by the significant changes in DEJ flattening scores ($p < 0.0001$) and collagen content with less abnormal and denser collagen bundles. At 6 and 12 months, despite the disappearance of filling effect, both the functional improvement in mouth opening and the increased number of capillaries were maintained. No effect either on the mouth opening, VC images and skin histological aspects was observed in SSc patients treated by HA filler.
Conclusions. The present study shows that, in patients with SSc, AFTG can improve mouth opening, induce a neovascularization, and partially restore the skin structure. All these effects were confirmed in the long-term observation. The lack of functional and biological effects in the control group treated by HA filler, suggests that the observed therapeutic effect of lipostructure may be specifically ascribed to the on site transplantation of fat tissue. Our study may open new perspectives for the local and general therapeutic approach to SSc.

PS78 NEW FAT-DERIVED PRODUCTS FOR TREATING INDUCED-SKIN LESIONS OF SCLERODERMA IN NUDE MICE

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Scleroderma is an auto-immune disease characterized by an excessive fibrosis of the skin. We previously validated a murine model of scleroderma and showed an antifibrotic and a proangiogenic effect of fat microinjection (MF). Fat is harvested with a 14 gauge , 2mm cannula and reinjection is performed with a 21 gauge cannula. In addition to the MF, we purify the stromal vascular fraction (SVF) of adipose tissue and platelet-rich plasma (PRP) from blood. We evaluated and compared the efficacy of MF, SVF, PRP, and mixtures of these products: MF + SVF and MF + PRP, in the murine model of skin-induced lesions of scleroderma. This project was divided in three parts: Induction of skin sclerosis in nude mice by daily subcutaneous injections of bleomycin (BLM) during 4 weeks. Preparation and subcutaneous injections of the different cell therapy products of human origine. Skin biopsies 8 weeks post-injections. 66 nude mice were used. Fat was harvested from the abdomen, to obtain MF and SVF, peripheral whole-blood was taken ta prepare PRP. We injected 0.5 cc of the different cell therapy products containing respectively: 131,000 cells injected/mouse for the SVF and 0.64 million of platelets injected/mouse for PRP derived products. BLM skin-induced lesions were checked by histological analyses in control mice. BLM-treatment induced a 21.74% increase of the dermis thickness, a 40.28% increase of the epidermis thickness i.e. a 23.74% increase of the total skin thickness. Time didn't affect skin-induced lesions of scleroderma and injections of the control solutions (chloride sodium or ringer lactate) didn't reverse skin sclerosis. This work has demonstrated the effectiveness of these different biotherapies on skin-induced lesions of scleroderma. MF, MF + SVF and MF + PRP completely reversed while SVF and PRP partially corrected skin sclerosis. A 13.7% decrease of the dermis thickness was observed with SVF, and a 20.7% decrease was observed with the PRP. Products containing MF were still present 8 weeks post-injections, suggested the long-term potential effects of the MF. The number of visible vessels observed in the deep dermis was significantly increased in SVF or MF + SVF conditions, compared to others, showing the expecting SVF proangiogenic effects. We highlighted the interest of mixtures MF + SVF and MF + PRP compared to the MF, SVF and PRP separately for their regenerative and proangiogenic properties. These effects on the sclerotic skin should have potential clinical applications in the treatment of the SSC human disease.

PS79 THE USE OF ADIPOSE-DERIVED REGENERATIVE CELLS (ADRCS) IN THE TREATMENT OF SCLERODERMA OF THE HANDS: A PROSPECTIVE TRIAL

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INTRODUCTION
Hand disease in Systemic Sclerosis can be complicated by acrocyanosis, digital ischemia, ulcers and digital retraction which lead to functional disability, pain, and a significant impairment of the quality of life. Currents treatments are modestly effective. The safety, feasibility, functional and trophic effects of the injection of stromal vascular fraction (SVF) from adipose tissue in the fingers of patients with SSc were evaluated.
PATIENTS AND METHODS
12 patients with scleroderma who had undergone many treatment failures and expected an improvement of their hand disability were included, after consent and verification of the inclusion / non-inclusion criteria. All had a Cochin hand function disability Scale > 20/90. The trial was granted a favorable opinion by the Ethical Committee and the French Health Products Safety (ANSM).
120 grams of fat were harvested from the abdominal region by liposuction under local anesthesia and immediately supported by the cell treatment unit. 5 ml of FVS were extracted with the Celution ® 800/CRS (Cytori Therapeutics, Inc, USA) medical device. 1 ml was reinjected in the fingers under neuroleptic analgesia, using a 25-gauge cannula (0.5 mm), in the lateral areas of the proximal interphalangeal regions in the long fingers and in the metacarpophalangeal region in the thumbs. The injection was performed 2 hours after harvesting and quantification of the cell product. The average dose of cells injected per finger was 3.7 106. Clinical monitoring was programmed at one, seven, twenty-one days, two and six months.
RESULTS
Mean age was 54.5 ± 10.3 years, 7 patients had a cutaneous limited scleroderma and 12 had Raynaud's syndrome which appeared at 14.3 ± 7.7 years (range 5-34) before. Duration of scleroderma was 9.9 ± 7 years (range 2-24). Rodnan score was 14 ± 9.7 (range 3-32). The ulnar and radial arteries were patent by Doppler ultrasound. No infectious or ischemic complications were observed. No serious adverse events were reported. Results from several tests showed a significant improvement (p<0,001): Cochin hand functional disability scale; pain in hands evaluated with the visual analogic pain scale. Raynaud's syndrome; SSc-HAQ. Hand mobility test (HAMIS) and Rodnan score focused on hand were improved.
CONCLUSION This study demonstrates the feasibility and tolerability of injecting autologous FVS in the fingers. An improvement was observed in hand functions, the intensity of pain in the fingers, Raynaud's syndrome and quality of life.

PS80 NO CORRELATION OF CD4+ LYMPHOPENIA AND CLINICAL RESPONSE TO AUTOLOGOUS STEM CELL TRANSPLANTATION FOR SYSTEMIC SCLEROSIS

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Background: Autologous stem cell transplantation (aSCT) for systemic sclerosis (Ssc) has recently been proven effective. Nevertheless there are patients who respond to therapy very impressively and sustained and others who do not or relapse. Purpose of this study was to evaluate a possible correlation of long lasting lymphopenia and response to treatment.

Methods: CD4+ lymphocytes of 32 (20 male and 12 female) patients who underwent aSCT in Tuebingen were evaluated. Our treatment regimen consists of cyclophosphamide (CYC) + granulocyte stimulating factor (GCSF) for mobilization; CD34+ selection and CYC + antithymocyteglobuline (ATG) or CYC + ATG + thiotepa (n=6) for conditioning (n=26). Response to treatment was defined as improvement of modified rodnan skinscore (mRSS) >25%. As a relapse we counted patients with any worsening in thoracal CT scan or >25% in mRSS. CD4+ lymphocytes were counted using immunophenotyping by fluorescence activated cell sorting.

Results: Twenty-seven (84%) of the patients responded to treatment whereas 5 patients (15%) showed no improvement. Six patients (19%) relapsed and 21 (66%) achieved an ongoing treatment success. We found a long lasting lymphopenia in most of the patients but no correlation between sustained response and lymphopenia, even more those patients with good response recovered rather earlier.

Conclusion: CD4+ lymphopenia is not the key mechanism underlying the ongoing response to aSCT for patients with Ssc.

PS81 INTEREST OF MICRO REINJECTION OF AUTOLOGOUS ADIPOSE TISSUE IN THE FACE OF PATIENTS WITH SYSTEMIC SCLEROSIS

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Orofacial manifestations of systemic sclerosis (SSc), found in over 90% of cases, are responsible for functional disability and significant aesthetic discomfort. The score Mouth Handicap in Systemic Sclerosis (MHISS) assesses specifically disability involving the mouth and the face. It explains for over 36% of the total disability related to SSc.
SSc presents with a wide range of orofacial manifestations including perioral skin fibrosis, perioral wrinkles, limited mouth opening, sicca syndrome and temporo-mandibular pain syndrome.
In the absence of standard treatment, we propose an open study analyzing the functional and aesthetic effects of micro reinjection of autologous fat in the face of SSc patients.
Adipose tissue has been used for more than one century for its volumizing and trophic properties. Indeed, it contains stromal vascular fraction rich in multipotent mesenchymal stem cells called Adipose-Derived Stem Cells (ADSCs).
MATERIAL and METHODS
This prospective single-center opened pilot study includes 13 patients with SSc according to the American College of Rheumatology criteria and the Leroy & Medsger criteria for SSc. All patients wish for a therapeutic care of their face. They present a MHISS score greater than 20 and a mouth opening less than 55 millimeters. They have no anticoagulant medication or daily corticosteroid greater than 20mg per day, their BMI exceed 17. Micro fat grafting is a minimally invasive procedure performed under local anesthesia. Fat tissue is harvested using a 14 gauge or 2mm cannula. Then it is refined as described by SR Coleman. 10 to 25cc of this product is transferred through a 21 gauge or 0.8mm cannula in four points of the face.
Patients are assessed at baseline, three and six months after surgery.
RESULTS
The expected outcome is improvement of the MHISS score at least 5 points over 48.
The results of secondary endpoints will evaluate clinical data (Health Assessment Questionnaire adapted to scleroderma, painful facial syndrome, sicca syndrome, Rodnan score for the face, tolerance) and paraclinical aspects (cutometry data and 3D photography).
CONCLUSION
The injection of autologous adipose tissue has shown efficacy in the treatment of limited forms of scleroderma . This study aims to evaluate the effectiveness of this non-invasive procedure in treatment of orofacial manifestations in SSc. It could offer a safe and non-invasive way to improve patients' quality of life.

PS82 HUMAN ADIPOSE-DERIVED STROMAL CELLS FOR CELL-BASED THERAPIES IN THE TREATMENT OF COUTANEOUS MANIFESTATIONS IN PATIENTS AFFECTED BY SYSTEMIC SCLEROSIS (SSC)

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The present study was designed to evaluate the clinical outcome of cell-based therapy with cultured adipose derived stromal cells (ASCs) for the treatment of cutaneous manifestations in patients affected by systemic sclerosis (SSc). ASCs have an extraordinary developmental plasticity, including the ability to undergo multilineage differentiation and self-renewal. Moreover, ASCs can be easily harvested from small volumes of liposuction aspirate, showing great in vitro viability and proliferation rate. Here we isolated, characterized, and expanded ASCs, assessing both their mesenchymal origin and their capability to differentiate towards the adipogenic, osteogenic, and chondrogenic lineage. We developed an effective method for ASCs transplantation into sclerodermic patients by means of a hyaluronic acid (HA) solution, which allowed us to achieve precise structural modifications. ASCs were isolated from subcutaneous adipose tissue of six sclerodermic patients and cultured in a chemical-defined medium before autologous transplantation to restore skin sequelae. The results indicated that transplantation of a combination of ASCs in HA solution determined a significant improvement in tightening of the skin without complications such as anechoic areas, fat necrosis, or infections, thus suggesting that ASCs are a potentially valuable source of cells for to improve dermal repair in rare diseases such as SSc and generally in skin disorders.

Poster Tours – Basic
Poster Tour 13: Pathogenesis

PS83 ANGIOTENSIN RECEPTOR TYPE 1 AND ENDOTHELIN RECEPTOR TYPE A ON IMMUNE CELLSMEDIATE MIGRATION AND THE EXPRESSION OF IL-8 AND CCL18 WHEN STIMULATED BY AUTOANTIBODIES FROM SYSTEMIC SCLEROSIS PATIENTS

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Background: Agonistic autoantibodies against the angiotensin II receptor type 1 (AT1R) and the endothelin receptor type A (ETAR) have been identified in patients suffering from systemic sclerosis (SSc). Here we examined the expression of AT1R and ETAR in human immune cells and pathological effects mediated through these receptors by corresponding autoantibodies (Aabs).
Methods: AT1R and ETAR protein expression on peripheral blood mononuclear cells (PBMCs) from healthy individuals and SSc patients was analyzed using flow cytometry, and mRNA expression was examined by real-time PCR in PBMCs from healthy donors. In addition, PBMCs from healthy donors were stimulated in vitro with affinity-purified immunoglobulin G (IgG) fractions from SSc patients positive for AT1R- and ETAR-Aabs, and with IgG from healthy donors serving as control. Alterations in chemotactic motility and cytokine secretion were analyzed using chemotaxis assays and ELISA, respectively. Results were correlated with characteristics/clinical findings of the IgG donors.
Results: Both AT1R and ETAR were expressed on human peripheral lymphocytes and monocytes. Protein expression of both receptors was decreased in SSc patients when compared to healthy donors and correlated negatively with disease duration. In addition, IgG fractions of SSc patients induced T cell migration in an anti-AT1R and anti-ETAR Aab level-dependent manner. Moreover, IgG of SSc patients was capable of stimulating PBMCs to produce more IL-8 and CCL18 than IgG of healthy donors. All effects could be significantly abrogated by the application of selective AT1R and ETAR antagonists. Statistical analysis revealed a negative correlation between SSc IgG-induced IL-8 concentrations and disease duration, between SSc IgG-induced CCL18 concentrations and time since onset of lung fibrosis as well as an association of CCL18 concentrations with vascular complications of the corresponding SSc IgG donors.
Conclusion: We demonstrated the expression of both, AT1R and ETAR, on human peripheral T cells, B cells and monocytes, and found a decreased receptor expression on cells from SSc patients suggesting downregulation due to chronic activation. The inflammatory and profibrotic effects upon Aab stimulation in vitro, and their associations with clinical findings indicate a role for autoantibody-mediated activation of immune cells mediated through the AT1R and ETAR in the pathogenesis or even the onset of the disease.

PS84 ANTI-AT1R AND ANTI-ETAR AUTOANTIBODIES FROM PATIENTS WITH SSCANDTHEIRAGONISTIC EFFECTS

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Background: Functional autoantibodies to angiotensin II type 1 receptor (AT1R) and endothelin 1 type A receptor (ETAR) are found in elevated levels in systemic sclerosis (SSc) and show association to increased risk of SSc-related manifestations and reduced cumulative survival. Biologic effects of these autoantibodies (anti-AT1R and anti-ETAR autoantibodies) have been demonstrated in vitro. Here, the functional effects were studied in vivo using animal models.
Objectives: To analyse functional effects of anti-AT1R and anti-ETAR autoantibodies in vivo using animal models.
Methods: Healthy C57Bl/6J mice were subjected to passive transfer treatment either with anti-AT1R and anti-ETAR autoantibody-positive IgG of SSc patients or with IgG of healthy donors as control. Experiments were performed with short term IgG transfer over seven days and with long term transfer over three months. Bronchoalveolar lavage fluid (BALF) was performed at the end of experiments and the cellular composition was analysed by microscopic differentiation in a blinded fashion. Lung architecture was visualized by staining with Hematoxylin and Eosin (H&E) of paraffin embedded sections and assessed by light microscopy. Plasma of treated mice was analysed for cytokines and chemokines using a bead array system (BioPlex®).
Results: Mice treated with anti-AT1R and anti-ETAR autoantibody-positive IgG of SSc patients (SSc-IgG group) showed distinct differences compared to mice that were treated with IgG of healthy donors (NC-IgG group). Cellular composition of the BALF revealed an increase of neutrophils in the BALF of the SSc-IgG group compared to the control NC-IgG group in the short and long term transfer. In the plasma elevated levels of the murine chemokine KC (functional homologue to human interleukin-8) were found in the short term transfer. Long term transfer resulted alteration of lung architecture featuring increased immune cell infiltrates showed by H&E staining of lung sections of SSc-IgG group compared to NC-IgG group.
Conclusions: Our findings demonstrate the potential to induce features of SSc pathogenesis in animal models in vivo by autoantibody positive IgG of SSc patients. Previous in vitro studies indicate direct receptor activation by anti-AT1R and anti-ETAR autoantibody-positive SSc-IgG and activation of the angiotensin and endothelin receptors by these autoantibodies could account in part for in vivo effects seen here. Therefore, receptor inactivation studies will be performed to assess a deeper knowledge of anti-AT1R and anti-ETAR autoantibody-mediated effects in vivo which could help to improve our current understanding of SSc pathogenesis.

PS85 SYSTEMIC SCLEROSIS SERA AFFECT ANGIOGENESIS, WOUND HEALING CAPACITY ANDMIGRATION OF DERMAL BLOOD MICROVASCULAR ENDOTHELIAL CELLS: THERAPEUTIC IMPLICATIONS OF CYCLOPHOSPHAMIDE

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Objective: Systemic sclerosis (SSc) is a complex connective tissue disease characterized by extensive fibrosis and vascular abnormalities. Dermal capillaries are progressively reduced in number with consequent chronic tissue hypoxia insufficiently compensated by angiogenesis. In SSc, clinical studies reported that cyclophosphamide (CYC) treatment may improve nailfold capillary damage. In the present study, we evaluated the effects of sera from naïve or CYC-treated SSc patients on the in vitro capacity of human adult dermal blood microvascular endothelial cells (B-MVECs) to perform angiogenesis, and to migrate and proliferate in response to injury.

Methods: Dermal B-MVECs were challenged with sera from SSc patients (n=21; n=13 limited SSc (lSSc), n=8 diffuse SSc (dSSc)), naïve (n=8) or under CYC treatment (n=13), and healthy controls. Angiogenesis was evaluated after 24 hours of cell seeding on Geltrex (reduced growth factor basement membrane matrix) in EBM containing 2% fetal bovine serum and 10% control or SSc serum. The number of branching points was quantified. Wound healing assay was performed on confluent cells grown in 12-well plates and evaluated at 24 hours after wounding. Chemotaxis was assessed by using the Boyden chamber assay.

Results: Angiogenesis was significantly reduced upon challenge with sera from naïve SSc patients compared with healthy controls ($p<0.005$). Moreover, angiogenesis was significantly lower in the presence of naïve dSSc sera compared with naïve lSSc sera ($p=0.02$). Upon challenging of B-MVECs with sera from CYC-treated SSc patients, the angiogenic capacity was comparable to that of cells treated with healthy sera. Wound healing capacity was significantly decreased upon challenge with sera from both naïve and CYC-treated SSc patients compared with healthy controls (both $p<0.005$), with no difference between naïve and CYC-treated SSc sera. The Boyden chamber assay gave similar findings with significantly lower migration of B-MVECs in the presence either of naïve SSc or CYC-treated SSc sera compared with healthy sera (both $p<0.001$). Furthermore, both wound healing capacity and chemotaxis were significantly reduced upon challenge with naïve dSSc sera compared with naïve lSSc sera ($p<0.001$).

Conclusions: Naïve SSc sera have significant inhibitory effects on angiogenesis, wound healing capacity and chemotaxis of dermal B-MVECs. Challenge with CYC-treated SSc sera effectively maintained B-MVEC angiogenesis on Geltrex at levels comparable to those of healthy control sera. Conversely, it was not able to specifically restore B-MVEC wound healing capacity and migration. Therefore, in SSc CYC treatment might foster angiogenesis mainly through the normalization of the endothelial cell invasive capacity and cell-matrix interactions.

PS86 FROM MICROVASCULATURE TO FIBROBLAST: CONTRIBUTION OF ANTI-ENDOTHELIAL CELL ANTIBODIES (AECA) IN SYSTEMIC SCLEROSIS

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Systemic Sclerosis (SSc) is an autoimmune disease characterized by skin and internal organ fibrosis, caused by microvascular dysfunction. In the last years, the hypothesis that anti-endothelial cell antibodies (AECA) could play a key role in microvascular damage seems to be always more convincing. Some of these AECA are capable of causing antibody-dependent cellular apoptosis and of stimulating the microvasculature in the release of pro-inflammatory and pro-fibrotic cytokines at the same time. In the present study, AECA contribution in the development of microvasculature damage was evaluated by stimulating human-microvascular-endothelial-cells (MVECs) with SSc sera (with and without AECA), and with sera from healthy donors. The conditioned MVECs culture media were then added to control (CTR), not affected-skin (NA) and affected-skin (SSc) fibroblast cultures respectively. The presence of AECA contributed to MVECs over-release of endothelin-1 (ET-1) in the culture medium and finally to cell apoptosis. Fibroblast (CTR, NA and SSc) proliferation resulted increased after treatment with AECA-positive conditioned media compared to AECA-negative and control conditioned media. Moreover, both AECA-positive (in major contribution) and AECA-negative conditioned media were responsible of alpha-smooth-muscle-actin (αSMA) over-expression in fibroblasts compared to control conditioned media. Moreover, fibroblast type-I-collagen synthesis chanced in presence of AECA. Finally, the synthesis of fibroblast transforming-growth-factor-beta (TGF-β) was statistically higher in AECA-positive conditioned media compared to AECA-negative and control conditioned media. These findings support the concept that AECA may mediate the crosstalk between endothelial damage and dermal-fibroblast activation in SSc.

PS87 CIRCULATING ANGIOGENIC FACTORS IN SSC PATIENTS – ASSOCIATION WITH CLINICALMANIFESTATIONS

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Background: The involvement of the small arteries and capillaries, causing SSc vasculopathy belongs to the pathological background of systemic sclerosis (SSc). Recent studies have shown elevated levels of angiogenic molecules in plasma from SSc patients, which may reflect the dysregulation of the endothelium function during the disease [1]. Scleroderma interstitial lung disease (ILD) is bound up with VEGF deficiency [2]. Other data suggest increased serum levels of VEGF in SSc patients with higher pulmonary blood pressure [3].
Objectives: To evaluate the serum concentrations of angiogenic factors and the relationships among them. To assess the relations of angiogenic cytokines with organ involvement in patients with SSc.
Methods: Serum levels of VEGF, fibroblast growth factor 2 (FGF-2), angiopoietn-1 (Ang-1), angiopoietin-2 (Ang-2) and endostatin were assessed by ELISA in a group of 27 patients with SSc and 25 healthy controls. Some basic diagnostic procedures including laboratory tests, HRCT, echocardiography, capillaroscopy were performed to assess organ involvement due to SSc.
Results: A total of 27 SSc patients (19 women, 8 men) with a mean age of 53.7±12.0 years were enrolled in the study. Mean disease duration was 6.3±6.3 months. The levels of VEGF (53.3vs39.3;$p<0.01$), Ang-2 (8.3 vs 3.4) and endostatin (177.2vs126.0) were significantly higher in SSc patients than in the healthy population ($p<0.0001$). No differences between FGF-2 and Ang-1 concentrations among SSc patients and the control group were noted. A significant increase of Ang-2 was revealed in a subgroup of patients with limited SSc (lSSc) (13.5±8.9 vs 7.3±4.4; $p<0.05$). Elevated concentrations of endostatin were observed in SSc patients with confirmed arterial pulmonary hypertension (243.8±120.3 vs 158.8±48.5;$p=0.007$). No correlations of other features of organ involvement (capllaroscopic changes, digital ulcers, interstitial lung disease) and angiogenic factors were noted.
Conclusions: Angiogenic profile observed in our study showed a domination of angiostatic factors including Ang-2 and endostatin. Our results confirm earlier data suggesting that elevated levels of angiogenic factors reflect a pro-inflammatory state in SSc endothelium and may contribute to the development of clinical symptoms of the disease.

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PS88 CIRCULATING ENDOTHELIAL MICROPARTICLES REFLECT MICROVASCULAR IMPAIRMENT IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Objective: Vascular injury is believed to play an essential role in the development of systemic sclerosis (SSc). However, the pathogenesis of SSc-related microangiopathy is not well understood. In addition, reliable assessment of endothelial state in vivo in SSc patients still remains a challenge. Endothelial microparticles (EMPs) are considered markers of the endothelial state.
Purpose: We aimed to assess possible relationships between circulating EMPs and clinical features including microvascular impairment in patients with SSc.
Methods: Forty seven patients fulfilling the ACR classification criteria for SSc and 27 age- and sex-matched healthy controls were included into the study. Clinical evaluation of patients was obtained, including nailfold capillaroscopy. Based on the capillaroscopic findings patients were classified into 3 groups showing an early, active or late pattern, according to the criteria proposed by Cutolo et al [Rheumatol 2004; 43: 719]. EMPs were identified with flow cytometry after staining platelet-poor plasma with combinations of fluorescent cell-specific monoclonal antibodies (anti-CD31, -51, -42b, -62E and AnnexinV). The following types of EMPs were evaluated: total EMPs (CD31+/CD42b-), activated EMPs (CD62E+/AnnV-,) and apoptotic EMPs (CD62E+/AnnV+ or CD51+).
Results: All types of EMPs were significantly elevated in SSc patients as compared with healthy controls. The concentrations of total EMPs tended to be lower in SSc patients with digital ulcers as compared with those without digital ulcers ($p=0.09$).
The mean concentration of total EMPs in SSc patients with late pattern in capillaroscopy was significantly lower as compared with SSc patients with early capillarscopic pattern ($p<0.05$), and tended to be lower as compared with SSc patients with active pattern ($p=0.1$). There were no significant differences in the levels of total EMPs between SSc patients with early and those with active patterns in capillaroscopy ($p>0.05$). Moreover, total EMPs and activated EMPs showed opposite correlations with the number of ramified capillaries ($R=-0.40$ and $R=0.37$, respectively, $p<0.05$ for both).
No other statistically significant associations or correlations could be found between the concentrations of total EMPs or any of EMPs' subpopulations and other clinical or immunological parameters including disease subtype, disease duration, the presence of interstitial lung disease, severity of skin or lung involvement, the presence of specific autoantibodies (ACA or anti-Scl70) or ESR values.
Conclusions: Our results suggest that quantity and phenotype of circulating EMPs might reflect microvascular changes in SSc. Further studies are required to reveal the role of EMPs in the development of microangiopathy in SSc.

PS89 IGG SUBCLASSES OF AUTOANTIBODIES DIRECTED AGAINST THE ANGIOTENSIN RECEPTOR TYPE 1 AND THE ENDOTHELIN RECEPTOR TYPE A AND THEIR CLINICAL RELEVANCE

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Background: IgG4-related diseases are often characterized by a generalized inflammatory fibrosis which is also present in patients suffering from systemic sclerosis (SSc). Recent findings indicate the importance of autoantibodies (Aabs) against the angiotensin II type-1 receptor (AT1R) and the endothelin type-A receptor (ETAR) in the pathogenesis of SSc. Therefore, we analysed the levels of anti-AT1R/ETAR IgG sublasses in patients with SSc to determine a possible role of IgG subclasses as markers for disease manifestations in SSc.

Material and Methods: Sera from 91 SSc patients, 59 patients suffering from systemic lupus erythematosus (SLE), and 199 healthy donors were analysed for the levels of anti-AT1R and anti-ETAR Aabs as well as for the different anti-AT1R and anti-ETAR IgG subclasses by ELISA. The results were associated with clinical manifestations using Mann-Whitney test and correlated with the time since onset of disease manifestations by Spearman correlation test.

Results: IgG3 followed by IgG1 was found to show highest anti-AT1R/ETAR Aab levels in all analyzed groups, in which SSc patients as well as SLE patients had higher IgG1 and IgG3 anti-AT1R/ETAR Aab levels as compared to healthy donors. Comparing SLE and SSc patients IgG1 and IgG3 showed a bit higher anti-AT1R/ETAR Aab levels in SLE.
Within the SSc group patients with diffuse SSc had the higher anti-AT1R/ETAR IgG3 levels as compared to those with limited disease or overlap forms.
Correlation analysis with SSc-related clinical manifestations revealed that levels of anti- AT1R/ETAR IgG3 negatively correlated with time since onset of Raynaud's phenomenon, and with time since first detection of PAH. Of note, there were negative correlations between levels of anti-AT1R/ETAR IgG3 levels and diffusion capacity for carbon monoxide (DLCO) as well as between anti-AT1R/ETAR-IgG3 levels and forced vital capacity (FVC) values ($p = 0.02/0.07$ and $p = 0.01/0.03$, respectively).

Conclusion: Interestingly, not IgG4 but IgG3 showed highest anti-AT1R/ETAR Aab levels when compared to other IgG subclasses. However, in SSc patients, anti-AT1R/ETAR IgG3 levels are strongly correlated to certain disease manifestations, whereby high anti-AT1R/ETAR IgG3 levels are associated with low DLCO and FVC indicating deterioration of lung function. According to these findings high anti-AT1R/ETAR IgG3 levels could predict for lung function deterioration and represent a new marker for SSc complications.

PS90 DECREASED EXPRESSION OF NEUROPILIN-1 IN SYSTEMIC SCLEROSIS: POTENTIAL CONTRIBUTION TO IMPAIRED ANGIOGENESIS

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Objectives: In SSc vascular involvement is a primary event characterized by vascular tone dysfunction and increased circulating levels of vascular endothelial growth factor (VEGF). Neuropilin-1 (NRP1) is a receptor for both class-3 semaphorin (sema) family of axon guidance molecules and VEGF. NRP1 is required for optimal VEGF/VEGFR-2 signaling, and NRP1-deficient mice exhibit vascular defects including disorganized blood vessels, lack of normal branching and missing capillary networks. Sema3a controls physiological and pathological angiogenesis. In the present study, we investigated the possible involvement of sema3a/NRP1 axis in SSc.
Methods: Soluble NRP1 (sNRP1) and sema3a levels were measured by quantitative colorimetric sandwich ELISA in serum samples from SSc patients (n=49) and age- and sex-matched healthy controls (n=39). Patients were classified according to nailfold videocapillaroscopy (NVC) patterns (early, active and late). NRP1 and sema3a protein expression was evaluated by immunofluorescence and western blot in skin biopsies from SSc patients (n=10) and healthy controls (n=8). NRP1 expression was also evaluated in human dermal microvascular endothelial cells from SSc patients (SSc-MVECs) and healthy controls (H-MVECs) at basal level, and in H-MVECs after stimulation for 24 hours with recombinant human VEGF165 (10 ng/ml), SSc sera (n=3) and healthy sera (n=3).
Results: Circulating sNRP1 levels were significantly reduced in SSc patients (median 0.22 ng/ml) compared with healthy controls (median 0.69 ng/ml) ($p=0.005$). In particular, sNRP1 levels were significantly lower in either SSc patients with active or late NVC patterns than in controls (both $p<0.05$). Moreover, sNRP1 levels were significantly decreased in SSc patients with digital ulcers compared both with patients without digital ulcers ($p=0.009$) and controls ($p=0.001$). No significant differences in sema3a levels were detected between patients and controls. NRP1 expression was decreased in clinically affected skin biopsies from SSc patients compared with healthy skin, especially in dermal endothelial cells and stromal cells. H-MVECs showed higher NRP1 protein expression compared with SSc-MVECs. Stimulation with recombinant VEGF165 strongly upregulated NRP1 expression in H-MVECs. NRP1 expression in H-MVECs increased after treatment with healthy sera compared with basal condition, while it decreased after challenging with SSc sera (both $p<0.005$ vs basal H-MVECs). Sema3a expression was not different in skin biopsies from SSc patients compared with controls.
Conclusions: NRP1 expression is significantly decreased in SSc, and lower sNRP1 levels correlate with the severity of nailfold capillary modifications and presence of digital ulcers. NRP1 might play a role in the vascular damage and in the impairment of the angiogenic process in SSc.

PS91 INVOLVEMENT OF PLEXIND1/SEMAPHORIN 3E PATHWAY ON THE DYSREGULATION OF VASCULAR TONE CONTROL IN SSC PATIENTS

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Objective: The main hallmark of SSc is vasculopathy characterised by dysregulation of angiogenesis and vascular tone leading to loss of capillaries. The vascular and nervous system have several anatomic similarities that extend to level of the molecular mechanisms. Emerging evidence suggests that proteins involved in transmitting axonal guidance cues, including class III semaphorin families, also play a critical role in blood vessel guidance during physiological and pathological vessel development. Sema3E acts through its receptor plexin-D1 to control endothelial cell positioning and patterning of the developing vasculature. Sema3E is a natural antiangiogenic molecule that causes filopodial retraction in endothelial cells inhibiting cell adhesion by disrupting integrin-mediated adhesive structures. The aim of the present study was to investigate if plexin-D1/Sema3E axis could be involved in dysregulated vascular tone control (RF) characteristic of SSc.
Methods: Sema3E levels were measured by quantitative colorimetric sandwich ELISA in serum samples from 45 subjects with primary Raynaud's phenomenon (PRF) without ANA, Scl70, ACA positivity, 48 SSc patients and 48 age- and sex-matched healthy controls. Patients were classified according to nailfold videocapillaroscopy (NVC) patterns (early, active and late). Sema3E levels were expressed as median and range and compared by Mann-Whitney U test. Differences were considered significant for p values less than 0.05. Western blot was used to evaluate plexin-D1/Sema3E axis in human dermal microvascular endothelial cells from healthy subjects (H-MVECs) at basal condition and after stimulation with recombinant human VEGF165 (10 ng/ml), lcSSc sera (n=3) and healthy sera (n=3) for 24h.
Results: Sema3E sera levels were significantly higher both in PRF subjects (median 0.54 ng/ml) and SSc patients (median 0.67 ng/ml) respect to healthy controls (median 0.19 ng/ml) (both $p<0.001$). In particular, sema3E levels were significantly higher in SSc patients with early NVC pattern both respect to active/late pattern and PRF (both $p<0.05$). Moreover, sema3E levels were significantly increased in SSc patients without ulcers compared with patients with digital ulcers ($p=0.018$). H-MVECs stimulated with SSc sera showed higher levels of the activated plexin-D1 form and sema3E protein expression in respect to basal H-MVECs and healthy sera. No differences were found in plexin-D1/Sema3E axis after challenging with VEGF.
Conclusions: Circulating sema3E is significantly increased both in PRF and SSc. Higher sema3E levels are increased in the early stages of SSc without digital ulcers. Our findings suggest that plexin-D1/Sema3E axis might have a role in the dysregulation of vascular tone control.

PS92 DECREASED EXPRESSION OF THE ENDOTHELIAL CELL-DERIVED FACTOR EGFL7 CONTRIBUTES TO IMPAIRED ANGIOGENESIS AND VASCULOGENESIS IN SYSTEMIC SCLEROSIS

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Objective: Microvascular damage and defective angiogenesis and vasculogenesis play a major role in the pathogenesis of systemic sclerosis (SSc). Epidermal growth factor-like domain 7 (EGFL7) is a proangiogenic molecule predominantly expressed and secreted by endothelial cells and their progenitors which controls vascular development and integrity. In the present study, we investigated the possible involvement of EGFL7 in SSc.
Methods: Serum EGFL7 levels from 60 patients with SSc and 35 age- and sex-matched healthy volunteers were examined by colorimetric sandwich enzyme-linked immunosorbent assay. The expression of EGFL7 in forearm skin biopsies (n=16 SSc, n=10 controls), cultured dermal microvascular endothelial cells (MVECs) (n=3 SSc, n=3 controls) and late-outgrowth peripheral blood endothelial progenitor cell (EPC)-derived endothelial cells (n=15 SSc, n=8 controls) was investigated by immunofluorescence and Western blotting. Anti-CD31/pan-endothelial cell marker antibodies were used in double immunofluorescence experiments to specifically investigate endothelial EGFL7 expression in skin sections.
Results: Serum EGFL7 levels were detectable in 68.6% of healthy controls and 45% of SSc cases ($p<0.05$). Circulating levels of EGFL7 were significantly decreased in SSc patients compared with healthy controls ($p=0.01$). Serum levels of EGFL7 were significantly lower both in limited cutaneous SSc and diffuse cutaneous SSc patients than in controls ($p=0.02$ and $p=0.04$, respectively). In SSc, decreased serum EGFL7 levels were significantly correlated with the severity of nailfold capillary abnormalities. Patients with most severe capillary changes and digital ulcers had serum EGFL7 levels significantly lower than healthy controls ($p=0.006$ and $p=0.002$, respectively), while the EGFL7 levels did not differ significantly between controls and SSc patients with less capillary damage and lack of digital ulcers. Endothelial EGFL7 expression was strongly downregulated or even almost completely undetectable in SSc affected dermis compared with controls ($p<0.001$). In cultured SSc dermal MVECs and late-outgrowth peripheral blood EPC-derived endothelial cells, EGFL7 was significantly downregulated compared with cells obtained from healthy subjects ($p<0.01$ and $p<0.001$, respectively).
Conclusions: Our findings suggest that the loss of EGFL7 expression in endothelial cells and their progenitors might play a role in the development and progression of peripheral microvascular damage and defective vascular repair process characteristic of SSc.

PS93 NAILFOLD CAPILLAROSCOPIC ASSESSMENT AND VASCULAR BIOMARKERS IN SYSTEMIC SCLEROSIS: LOW CD40L LEVELS IN PATIENTS WITH LATE SCLERODERMA PATTERNS

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Objectives: To determine the relationship between vascular biomarkers reflecting the vascular injury and neoangiogenesis with capillaroscopic changes in systemic sclerosis (SSc).
Methods: Seventy-two SSc patients (66 female) fulfilling Leroy and Medsger classification criteria were evaluated, including clinical findings nailfold videocapillaroscopy (NVC) was performed qualitatively (early, active and late scleroderma patterns) in all patients (Cutolo M, et al. J Rheumatol 2000). Serum samples of patients were collected for flow-cytometric analysis of CD40L, tPA, MCP-1, sE-selectin, IL-8, IL-6, VEGF, sP-selectin, TGF-β1 ve VCAM levels (Bender MedSystems, Vienna, Austria) at the same time with NVC. Results were compared with Pearson chi-square / Fischer's, Mann Withney U ve Kruskal Wallis tests.
Results: The mean age of the patients was 44.9 and disease duration from the appearance of Raynaud's and non-Raynaud symptoms were 5.8±5.9 and 3.2±2.4 years. Of the patients 23(%32) had diffuse and 49(%68)limited cutaneous involvement, 15(%21) were anti-centromere(+) and 34(%47) were anti-Scl70(+). When we compared with healthy subjects; tPA (p=0.02), MCP-1 (p=0.001), sE-selectin (p=0.008) and TGF-β1 (p=0.001) levels were significantly higher, sP-selectin (p=0.011) ve IL-8 (p=0.001) levels were lower in SSc patients. SSc patients grouped according to NVC patterns as 'early'(n=10), 'active'(n=37) and 'late'(n=25). Between groups according to NVC patterns, only sCD40L(pg/ml) levels were significantly lower in the 'late' group (p=0.043), higher in patients with limitted cutaneus involvement (p=0.01) and smoking history (n=32,%44) (p=0.033). The other markers were similar between NVC groups.
Conclusions: There was lower sCD40L serum levels in patients with late NVC patterns, although the levels were similar to healthy controls in patients with early, active NVC pattern.CD40L may be a key molecule in the early/active phase of vascular involvement. Higher concentrations of sCD40L in patients with limited cutaneous disease and smoking history might be related to its role in vascular pathology. NVC is a useful method for investigating the vascular pathogenesis in SSc.

PS94 DIAGNOSTIC TARGETS REVEALED BY HIGH-RESOLUTION PROTEIN PROFILING OF HUMAN PLASMA MICROPARTICLES

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Background: Microparticles (MP) are small membranous vesicles shed from cells undergoing apoptosis or activation. They are found in the circulation and they carry information about cellular origin and events which lead to their formation. In addition, they may reflect disease processes in the body.

Methods: MPs were obtained from 1 mL platelet poor citrate plasma by repeated ultracentrifugation (five times 20.000 x g, 30 min at room temperature). Proteins present in the MP preparations were identified and quantified followed by data-analysis using MaxQuant for protein ID and label-free quantitation. In this study, MPs from a cohort of 38 uniformly collected samples from patients with systemic sclerosis (SSc) and 25 healthy controls (HC) were analyzed.

Results: Altogether more than 530 unique proteins were identified. Univariate statistics, hierarchical clustering, and principal components analysis were applied to analyze the protein intensity to search for disease classifiers. Thirty proteins showed highly significant differences between SSc and HCs ($p<0.05$ after Benjamini-Hochberg correction for multiple hypothesis testing). Among these, TGF-beta was found increased ($p = 0.003$) and several mitochondrial proteins were reduced ($p= 0.003$). The protein concentration of MPs from SSc patients was correlated with soluble markers of vascular activation analysed regarding association with SSc subgroups or specific organ manifestations in SSc patients.

Conclusion: MPs in the circulation are a valuable reservoir of information on disease states. The data from the present study of SSc patients show that both highly specific and sensitive diagnostic novel target molecules and markers associated with disease severity may be present in the MP protein profiles.

Poster Tours - Basic
Poster Tour 14: Pathogenesis

PS95 S100A4 SERUM LEVELS CORRELATE WITH SKIN FIBROSIS, LUNG INVOLVEMENT AND DISEASE ACTIVITY IN SYSTEMIC SCLEROSIS

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Background: In our previous study we demonstrated that S100A4 is overexpressed in scleroderma (SSc) skin, fibroblasts and preclinical models of SSc in a TGF-beta dependent manner. We showed that S100A4 is a new regulator of TGF-beta signalling and its inhibition prevents the stimulatory effects of TGF-beta. Inactivation of S100A4 prevented dermal fibrosis induced by bleomycin and in Tsk-1 mice.
Objectives: To evaluate S100A4 in sera of SSc patients and characterize its potential association with SSc-related features.
Methods: A total of 33 patients (29 females; mean age 52.8; disease duration 4.2 years; dcSSc/lcSSc = 8/25) who met the ACR classification criteria for SSc and 20 healthy individuals matched by age and sex were included in this study. Serum S100A4 levels were measured using ELISA (CycLex Co., Ltd., Nagano, Japan). CRP, ANA and ENA complex were evaluated. SSc-related manifestations were obtained from the Czech Registry Database of SSc patients. Skin changes were assessed using the modified Rodnan skin score (mRSS) and EUSTAR SSc activity score was determined. Data are presented as mean ± SEM.
Results: S100A4 serum levels were significantly increased in SSc patients compared with healthy controls (119.2±23.4 vs. 43.9±3.3ng/ml, p=0.011). Patients with diffuse cutaneous SSc had significantly higher levels of serum S100A4 compared with patients with limited cutaneous SSc or healthy controls (201.8±53.1 vs. 92.7±24.0ng/ml, p=0.017 and 201.8±53.1 vs. 43.9±3.3ng/ml, p=0.001, respectively). Levels of S100A4 positively correlated with mRSS (r=0.556, p=0.001). Furthermore, S100A4 levels negatively correlated with forced vital capacity (FVC) and saturation of peripheral oxygen (SPO2) (r=- 0.362, p=0.038 and r=-0.414, p=0.029, respectively). Of particular interest, S100A4 levels positively correlated with EUSTAR SSc activity score (r=0.750, p=0.0001). However, only correlations between S100A4 and mRSS, and S100A4 and EUSTAR SSc activity score were approved at corrected level of statistical significance after Bonferroni's correction (p<0.01). The presence of autoantibodies (ANA, anti-centromere, anti-Scl70), pathological capillaroscopic pattern (early, active or late), and presence of the main individual clinical symptoms of SSc did not significantly affect levels of serum S100A4.
Conclusions: We demonstrate that S100A4 serum levels are significantly increased in SSc patients compared with healthy controls. Higher levels of S100A4 are associated with dcSSc subset, skin involvement, deteriorated parameters of lung involvement and higher disease activity. These data support our previous findings on the role of S100A4 as a regulator of TGF-beta induced fibroblast activation and dermal fibrosis in SSc.

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PS96 SECRETED FRIZZLED-RELATED PROTEIN 4 CAN BE INDUCED BY TRANSFORMING GROWTH FACTOR-BETA, IS REGULATED BY CAVEOLIN-1 AND CAN INDUCE NON-CANONICAL WNT SIGNALING IN FIBROBLASTS

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Background: Systemic Sclerosis (SSc) is a heterogeneous disease characterized by autoimmune activation, fibroproliferative vasculopathy, and tissue fibrosis of skin and multiple internal organs. Several studies have indicated that both caevolin-1 (CAV-1) and WNT/β-catenin signaling play important roles in the pathogenesis of tissue fibrosis. Indeed, CAV-1 is downregulated by 40% in SSc skin compared to healthy controls and, intriguingly, tissue expression studies with SSc skin biopsies show both upregulation of canonical WNT ligands1,2 and consistent upregulation of Frizzled-Related Protein 4 (SFRP4), a putative WNT antagonist, at both mRNA at protein level3,4.

Methods: Immortalized primary healthy (HC) and SSc fibroblasts were cultured in 10% DMEM and starved in 0.5% DMEM for 24hrs prior to stimulation with recombinant TGFβ (10ng/ml), Wnt-5a (100ng/ml) and/or SFRP4 (100-1000ng/ml). Gene expression was quantified by SYBRgreen RT-PCR and by western blot. CAV-1 siRNA was transfected at a final concentration 10nM. Canonical WNT signaling was assessed by TOPflash TCF/LEF reporter activity. ELISA was used to measure both the levels of Phospho-c-Jun from whole cell lysates.

Results: In SSc fibroblasts, the basal expression of SFRP4 is increased at both protein level and also by 264% at mRNA level compared to HC [p<0.001]. TGFβ stimulation upregulated SFRP4 mRNA by 170% [P<0.01] at 48hrs and by 348% [P<0.01] at 72hrs. TGFβ also induced a time-dependent increase of both SFRP4 and α-SMA protein expression, while reducing CAV-1. siRNA-mediated silencing of CAV-1 was sufficient to induce a time-dependent increase in SFRP4 protein expression. Wnt-3a induced a 600% increase in TOPFlash activity, co-treatment with SFRP4 decreased this activity by 283%. In contrast, SFRP4 induced a 260% increase [p<0.001] in c-JUN phosphorylation at 10min in both HC and SSc fibroblasts. This was similar to non-canonical Wnt-5a stimulation. Interestingly, basal c-Jun phosphorylation was increased by 180% [P<0.005] in SSc compared to HC fibroblasts. However, SFRP4 treatment did not affect collagen or α-SMA protein levels within a dose range of 100-1000ng/ml.

Conclusions: Indeed, the increased expression of SFRP4 observed in SSc may be a direct consequence of CAV-1 downregulation by TGFβ in tissue fibroblasts. Given the non-canonical WNT activity of SFRP4, a TGFβ primed microenvironment may be responsible for shaping the phenotype of both fibroblasts and neighboring cells, through aberrant WNT pathway activation. Investigation of the mechanisms linking CAV-1 expression and SFRP4 function will improve our understanding of the pathogenetic role aberrant WNT activation plays in SSc.

PS97 TARGETING IL-6 BY BOTH PASSIVE OR ACTIVE IMMUNIZATION STRATEGIES PREVENTS INFLAMMATION-DRIVEN SKIN FIBROSIS

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Objective: Interleukin 6 (IL-6) is a pleiotropic cytokine involved in inflammatory and autoimmune processes. Preliminary data have suggested that IL-6 might contribute to systemic sclerosis (SSc). Our aim was to compare the efficacy of both passive and active immunization against IL6 to reduce skin fibrosis in complementary mouse models of scleroderma.
Methods: We first evaluated the monoclonal IL-6R antibody MR16-1 in the mouse model of bleomycin-induced dermal fibrosis, reflecting early and inflammatory stages of SSc. Six-week-old DBA/2 mice received in parallel subcutaneous injections bleomycin (0,5 mg/ml) and intraperitoneal (ip.) injection of MR16-1 or control antibody at a dose of 2 mg at day 0 followed by one ip. injection of 1 mg at day 7 and 14. Then, we assessed the merit of MR-16 in the tight skin (Tsk-1) mice, an inflammation-independent mouse model of skin fibrosis. Tsk-1 mice received a first ip. injection of 2 mg of MR16-1 or control antibody at the age of 5 weeks followed by one ip. injection of 1 mg once a week for 5 weeks. Thereafter, because of the drawbacks of anti-cytokine monoclonal antibodies, we developed an innovative strategy using active immunization against a small peptide derived from murine IL-6, which was performed in the mouse model of bleomycin-induced dermal fibrosis.
Results: Passive immunization with MR16-1 exerted antifibrotic effects in the mouse model of bleomycin-induced dermal fibrosis: dermal thickness, hydroxyproline content and myofibroblast counts were reduced by 25±4% (P=0.02), 30±6% (P=0.007) and 45±7% (P=0.005) respectively, compared to mice receiving control antibody. MR16-1 demonstrated no efficacy in Tsk-1 mice. Mice immunized against the mIS200 peptide derived from murine IL-6 exhibited in the bleomycin mouse model similar antifibrotic effects as passive immunization. We observed a significant reduction of dermal thickness by 20±3% (P=0.02), hydroxyproline content by 25±4% (P=0.005) and myofibroblast counts by 41±9% (P=0.01), compared to the group immunized against the carrier protein alone.
Conclusion: We demonstrated that passive and active immunization targeting IL-6 had similar antifibrotic properties in a mouse model of inflammation-driven dermal fibrosis. Translation to human disease is now required, and targeting early and inflammatory stages of SSc sounds the most appropriate. This strategy is currently under investigation in a phase-3 clinical trial assessing the efficacy of tocilizumab to improve skin involvement in patients with early diffuse SSc. Our results also highlight the relevance of active immunotherapy that might be an avenue for IL6 axis in immunotherapy in a near future.

PS98 ENDOTHELIN-1 MEDIATES DOWNSTREAM PROFIBROTIC EFFECTS BY TRANSFORMING GROWTH FACTOR-BETA 1 IN SYSTEMIC SCLEROSIS SKIN FIBROBLASTS

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Background: Systemic sclerosis (SSc) is an autoimmune connective tissue disorder characterized by excess collagen deposition, vascular changes and production of autoantibodies that affect multiple organs. Transforming growth factor β1 (TGF-β1), which promotes collagen synthesis, extracellular matrix (ECM) remodeling and myofibroblast differentiation, is thought to play a key role in the pathogenesis of SSc. The vasoconstrictive peptide endothelin-1 (ET-1) is known to be a potent fibrotic factor similar to TGF-β1. ET-1 binds to two distinct subtypes of G protein coupled receptors, ET receptor A (ETRA) and ET receptor B (ETRB). The fibrotic functions of each ET receptor remain unclear partially because ET receptor distribution and expression differ according to the disease, affected organ and cell type. Our study aimed to examine the ET-1-mediated effects of TGF-β1 on the fibrogenic phenotype of SSc skin fibroblasts using a single and/or dual ET receptor antagonist.

Methods: Human SSc skin fibroblasts (SSc fibroblasts) were obtained from SSc patients. Recombinant TGF-β1, recombinant ET-1, SIS3 as an inhibitor of Smad3 phosphorylation, BQ123 as a single ETRA antagonist, BQ788 as a single ETRB antagonist and bosentan as a dual ETRA/ETRB receptor antagonist were used in this study. The SSc fibroblasts were incubated with TGF-β1 in the presence of SIS3. In addition, the effects of BQ123, BQ788 and bosentan were explored. Expression of ET-1, CTGF and type I collagen was evaluated using ELISA and real-time RT-PCR. ETRA and ETRB expression were assessed using immunohistochemistry and fluorescence activated cell sorting (FACS) analysis.
Results: Both ETRA and ETRB were expressed in SSc fibroblasts. TGF-β1 increased ET-1 mRNA and protein expression, and this increase in ET-1 was suppressed by SIS3. Upregulation of COL1A1 and CTGF by TGF-β1 was reduced by an ETRA or ETRB antagonist, and a dual ETRA/ETRB antagonist had an additive inhibitory effect.

Conclusions: TGF-β1 produced ET-1 through Smad3 phosphorylation, and a dual ETRA/ETRB antagonist decreased COL1A1 and CTGF mRNA levels in fibroblasts. These findings suggest that both ETRA and ETRB signaling are associated with a fibrotic phenotype in SSc skin fibroblasts and that dual ETRA/ETRB might be a novel therapeutic target for SSc skin fibrosis.

PS99 THE ROLE OF MCSF AND ENDOTHELIN 1 IN FIBROCYTE DIFFERENTIATION

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Introduction: Systemic sclerosis (SSc) is a complex autoimmune fibrotic disease, characterised by elevated deposition of extracellular matrix (ECM) proteins, including collagen type I. The disease is heterogeneous; organs commonly affected by fibrosis are the skin, kidney, lung and heart. Vascular complications include pulmonary arterial hypertension (PAH), occuring in 12-40% of patients.
CD14+ monocytes are a functionally heterogeneous cell type able to differentiate into a number of cell phenotypes including macrophages and fibrocytes. In culture fibrocytes adopt a spindle shape, co-express haematopoietic - CD45RO and 25F9, along with mesenchymal markers including aSMA and collagen type I. Fibrocytes amplify the inflammatory/immune response through distinct mechanisms, including antigen presentation, cytokine and chemokine secretion, and the production of MMPs. We and others have shown fibrocyte differentiation is enhanced by fibrogenic cytokines. Here we seek to understand the mechanism by which SSc fibrocytes influence the local microenvironment of the tissue.
Methods: CD14+ peripheral blood mononuclear cells (PBMCs) were isolated from SSc patient and healthy control blood. PBMCs were cultured in the presence of macrophage colony stimulating factor (MCSF; n>10) and/or endothelin-1 (ET-1; n>10); after 14 days of culture number of fibrocytes was assessed. The effect of pharmacological inhibitors including ETRA and ETRB antagonism on fibrocyte differentiation (n=6 SSc and control) was investigated. Secreted factors in culture media from SSc and control fibrocytes were assessed by ELISA (n=6), and the effects of conditioned media explored in 3D-collagen gel
Results: MCSF and ET-1 significantly induced fibrocyte differentiation, in combination differentiation was significantly augmented ($P<0.05$) in comparison to mono-treatment. SSc fibrocytes more readily differentiated from CD14+ PBMCs than healthy control donors in response to MCSF ($P<0.05$), ET-1 ($P<0.05$) as well as MCSF with ET-1 in combination ($P<0.01$). ETRA and ETRB antagonists, BQ123 and BQ788 (respectively), and Bosentan (a dual ETR antagonist) inhibited MCSF induced fibrocyte differentiation in a concentration dependant manner. Furthermore SSc fibrocytes secreted significantly more CTGF than control fibrocytes ($P<0.05$) cultured with MCSF. Consistent with fibrocytes acting in a paracrine manner, conditioned media from SSc fibrocytes promoted fibroblast gel contraction by control cells ($P<0.05$).
Discussion: Here we show CD14+ SSc PBMCs more readily differentiate into fibrocytes and that activation via the ETRA/B is essential for ET-1 and MCSF induced fibrocyte differentiation. Suggesting MCSF acts indirectly via ET-1 release; possibly resulting in a positive feedback loop. Our data suggests fibrocytes may contribute to the development of a pro-fibrotic environment through influencing tissue resident fibroblasts in a paracrine manner.

PS100 SIMVASTATIN MODULATES AORTIC INTIMA/MEDIA THICKNESS IN AN ANIMAL MODEL OF SYSTEMIC SCLEROSIS

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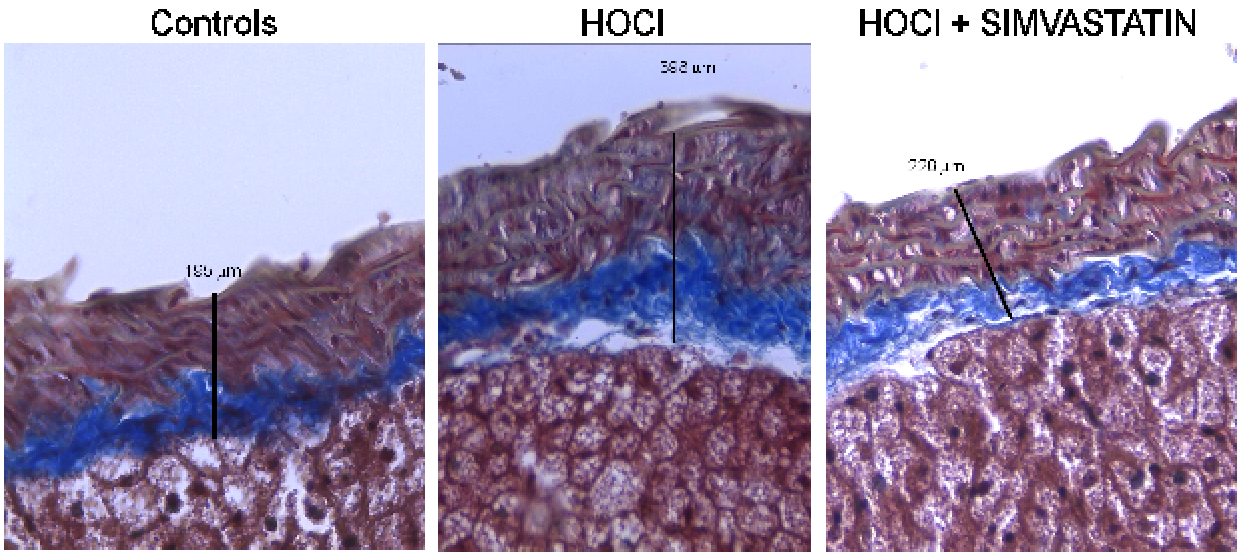
Background/Purpose: Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by vasculopathy and organ fibrosis. Although many previous studies highlighted microvascular alterations in SSc, a growing body of evidence exists for structural and functional abnormalities in the macrovascular circulation. Recent reports shows that in SSc patients macrovasculopathy occurs preferentially at the forearm and aorta.
Aim of the study was therefore to evaluate the effect of simvastatin administration on aortic intima-media (IM) thickness and ratio in a murine model of systemic sclerosis

Methods: SSc-like illness was induced in BALB/c mice by daily subcutaneous injections of HOCl as an oxidant stress for 6 weeks. Mice (n=24) were randomized in three arms to treatment w11ith either HOCl (n=10), HOCl plus simvastatin (n=9); or vehicle alone (n=5). Simvastatin treatment was initiated 30 minutes after HOCl subcutaneous injection (40 mg/kg) continuing daily for the 6 weeks. Thoracic aorta was evaluated by histological methods. IM thickness and ratio were measured for statistical analysis.

Results: In HOCl treated mice aortic IM thickness was significantly higher than controls, showing an increase of 104% ($p<0.0001$). Treatment with simvastatin diminished this increase by 92% ($p<0.0001$). Simvastatin treated animals had a significantly thinner intima layer (-9%, $p<0.0001$) and media layer (-197%, $p<0.0001$) compared to HOCl group. IM ratio was also decreased in HOCl treated mice compared to controls (0.75 vs 1.74, $p<0.0001$) and significantly increased by simvastatin administration (1.61 vs 0.75, $p<0.0001$).

Conclusion: Administration of simvastatin moderates the increase of IM thickness in this animal model of SSc. Further analysis on IM ratio suggests that aortic media layer is thickened in HOCl treated animals and this increase can be prevented by simvastatin.



PS101 SUSCEPTIBILITY OR RESISTANCE TO EXPERIMENTAL LUNG FIBROSIS IS PREDICTEDBYRESIDENT LUNG FIBROBLAST GENE EXPRESSION SIGNATURE

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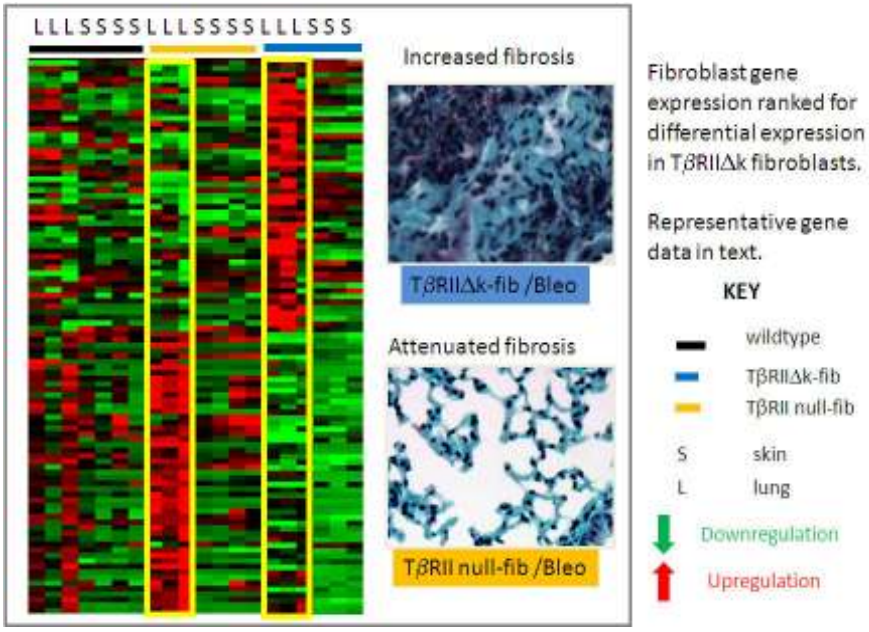
Background: In scleroderma (SSc), lung fibrosis is linked to epithelial damage and dysregulated repair mechanisms. Resident lung fibroblasts may affect multiple cell types including epithelium, endothelium, smooth muscle cells and fibrocytes. We have used two complementary transgenic mouse strains with altered TGFβ signalling to better understand the regulatory role of resident lung fibroblasts in defining susceptibility to fibrosis.
Methods: The TβRIIδk-fib mouse model of SSc, in which TGFβ signalling is upregulated in fibroblasts, is susceptible to fibrotic lung injury whereas the TβRII-null-fib strain, in which TβRII is conditionally knocked out in fibroblasts, is resistant to bleomycin-induced lung fibrosis. We have used an illumina® microarray platform to profile lung or skin fibroblasts from these two strains and identified a cohort of genes that determine susceptibility or resistance to experimental lung fibrosis, comparing to a control group using whole lung from TβRIIδk-fib animals and wildtype littermates (n=3) on the same microarray platform. Technical validation of data and additional quantitation of gene expression was performed using quantitative RT-PCR assays with replicate samples.
Results: The TβRIIδk-fib lung fibroblast gene expression signature includes key genes that are implicated as pathogenic drivers of fibrosis and inflammation and potential biomarkers in SSc. Conversely, many of these genes are downregulated in TβRII-null-fib mice, including BMP4 (fold reduction in TβRII-null-fib 31.8, $p<0.02$; fold upregulation in TβRIIδk-fib compared with WT 2.01, $p<0.6$); elastin (TβRII-null-fib 17.8, $p<0.14$; TβRIIδk-fib 1.86, $p<0.09$); CCL2 (TβRII-null-fib 56.8, $p<0.09$; TβRIIδk-fib 1.72, $p<0.03$)and MMP13 (TβRII-null-fib 13.2, $p<0.08$; TβRIIδk-fib 3.6, $p<0.4$).



CTGF (CCN2) was strongly upregulated in TβRIIδk-fib lung fibroblasts, but showed less downregulation than other genes in the TβRII-null-fib, probably reflecting multiple pathways of activation. No signature of overexpression was present in the whole lung analysis suggesting that fibroblast-specific differences in gene expression determine altered fibrotic response.

Conclusion: These data define a cohort of genes differentially expressed in fibroblasts that associate strongly with susceptibility or resistance to experimental lung fibrosis. These transcripts include many that are important in tissue repair and that have previously been shown to be over expressed in SSc skin samples. They suggest that the same resident fibroblast gene expression signature may govern fibrosis in both lung and skin.

PS102 EXCESSIVE FIBROSIS AND PULMONARY VASCULAR REMODELING IN FRA-1 TRANSGENIC MICE

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Introduction: Excessive fibrosis and microvasculopathy are typical pathogenic processes of systemic sclerosis (SSc). It has been reported that mice overexpressing Fra-2, which is a component of a transcription factor AP-1, spontaneously develop vascular remodeling with obliteration of pulmonary small arteries as well as generalized fibrosis found predominantly in the lung. We accidentally found that mice transgenic for another AP-1 component Fra-1 (Fra-1-TG mice) died early due to cardiopulmonary insufficiency. Detailed histologic findings in the lung and skin of this mouse strain were evaluated.

Methods: We examined 8 pairs of Fra-1-TG and wild-type mice (age between 5-16 weeks). In Fra-1-TG mice, murine fra-1 gene was overexpressed ubiquitously under the control of the major histocompatibility complex class I antigen H2Kb promoter. Paraffin-embedded tissue sections were subjected to Hematoxylin and Eosin, Masson-Trichrome, and Elastica-van Gieson staining. Expression of CD31 and α-smooth muscle actin (SMA) was further evaluated by immunohistochemistry. Right ventricular overload was evaluated by transthoracic echocardiography with Doppler technique and the ratio of the right to left ventricle size (RV/LV ratio) by postmortem examinations.

Results: Fra-1-TG mice died at a median age of 14 weeks with signs of cardiopulmonary insufficiency. At age of 5 weeks, diffuse thickening of alveolar walls was apparent with infiltration of mononuclear inflammatory cells in perivascular area and in alveolar walls..Subsequently, active deposition of extracellular matrix (ECM) progressed serially and uniformly, leading to diffuse fibrosis in the parenchyma. The Fra-1-TG mice also developed excessive ECM deposition in the dermis with loss of subcutaneous fat tissue. .In terms of pulmonary vasculature, intimal and medial thickening in small-to-medium-sized pulmonary arteries were already present at the age of 5 weeks. These changes progressed with age and resulted in concentric laminar fibrosis, resulting in narrowing of the vascular lumen. Neo-muscularization of small arterioles was also detected after age of 10 weeks. At 16 weeks, Fra-1-TG mice represented pulmonary hypertension confirmed by typical echocardiographic findings of tricuspid regurgitation and an increased RV/LV ratio. These histologic and functional changes were not found in wild-type mice.

Conclusions: Fra-1-TG mice spontaneously developed excessive fibrosis in the lung and skin as well as pulmonary vascular remodeling, characteristic of patients with SSc. Mice overexpressing Fra-1 and Fra-2 exhibit the similar fibrotic/vasculopathic phenotype, indicating involvement of the AP-1 pathway in pathogenesis of SSc.

Poster Tours - Basic
Poster Tour 15: Pathogenesis

PS103 INCREASED FREQUENCY OF INTERLEUKIN-2 PRODUCTION BY TH17 LYMPHOCYTES IN PERIPHERAL BLOOD OF SYSTEMIC SCLEROSIS PATIENTS

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Background/Purpose. The pathogenesis of systemic sclerosis (SSc) is largely unknown, although proinflammatory cytokines are considered to play a central role. We hypothesized that Th17 cell populations and cytokine expression may be altered in SSc.
Our purpose was to investigate the pattern of expression of proinflammatory cytokines by peripheral blood (PB) IL-17+ T cell populations in SSc and to explore clinical associations.

Methods. This study included 41 SSc patients and 20 age- and sex-matched healthy controls (HC). All SSc patients fulfilled the American College of Rheumatology Criteria for the classification of SSc and were classified according to LeRoy et al. as having limited cutaneous SSc (lSSc, n=29) or diffuse cutaneous SSc (dSSc, n=12). Clinical evaluation included disease duration, modified Rodnan skin score (mRSS), digital necrosis and target organs' involvement. The autoantibody profile was collected from medical records.
Each participant was submitted to a blood sample collection, which was processed in order to separately analyze the intracellular expression of IL-2, TNF-α,and IFN-γ in Th17 cells.
Data was statistically analyzed using the SPSS® version 20.0. Mann-Whitney test was used to evaluate differences between groups. Correlations between continuous variables were assessed by Spearman's correlation coefficient. P values < 0.05 were considered statistically significant.

Results. The mean age was 56.1±11.8 and 52.0±9.9 years for SSc patients and HC respectively. Females represented 78% of the SSc group and 80% of the HC. The patients had a mean mRSS of 11.32±7.76 and mean disease duration of 9.5±8.5 years.
The frequency of PB Th17 cells was not statistically different in SSc patients when compared to HC, neither between lSSc, dSSc and HC. A difference between lSSc, dSSc and HC regarding the frequency of IL-2-producing Th17 cells was found. We also found differences between lSSc and HC regarding the frequency of TNF-α-producing Th17 cells. There were no differences between groups regarding the frequency of IFN-γ expression among Th17 cells. We also have negative findings regarding disease duration and internal organs' involvement. The frequency of IL-2-producing Th17 cells showed a positive correlation with mRSS (p=0.002).

Conclusion. IL-2-producing Th17 cells frequency is higher in SSc than in HC. The frequency of IL-2-producing Th17 cells was correlated with the extension of skin involvement. These findings support the hypothesis that IL-2 produced by Th17 cells may be involved in the pathological process of SSc, regardless of the disease subset.

PS104 ROLE OF IL-13-PRODUCING CD8+ T CELLS IN THE PATHOGENESIS OF SYSTEMIC SCLEROSIS

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T lymphocytes play an important role in systemic sclerosis (SSc), a connective tissue disease characterized by inflammation, fibrosis and vascular damage. Its most characteristic feature is cutaneous fibrosis that is attributable to excessive deposition of collagen and other connective tissue components by activated dermal fibroblasts. Although the pathogenesis is still unclear, this fibroblast activation is believed to result from their interaction with immune mediators, such as T cell-derived cytokines, and other growth factors. We recently found that dysregulated production of the profibrotic cytokine IL-13 by peripheral blood effector CD8+ T cells correlates with more severe forms of cutaneous SSc and is associated with defects in the molecular control of IL-13 production, such as the aberrant expression of the transcription factor GATA-3. Here we report our most recent results. Firstly, we found that CD8+ T-cell supernatants from SSc patients induce collagen production by normal skin fibroblasts and that this is inhibited by the addition of an anti-IL-13 antibody. Secondly, we established that increased numbers of CD8+ T cells expressing skin homing receptors and producing IL-13 are found in the peripheral blood of SSc patients compared to normal controls. Thirdly, we demonstrated that high numbers of CD8+IL-13+ T cells are present in the sclerotic skin of SSc, particularly in the early stages of the disease. Furthermore, we found that CD8+ T cells in the skin lesions of SSc patients express markers of cytotoxicity, such as Granzyme B, and are therefore potentially cytotoxic. We conclude that IL-13-producing CD8+ T cells are directly implicated in driving the pathogenesis of SSc. These new insights into disease pathogenesis suggest novel therapeutic targets that may be exploited for the treatment of SSc.

PS105 TOLL LIKE RECEPTOR 3: A CROSSROAD IN SCLERODERMA ETIOPATHOGENESIS

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Background: Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by excessive deposition of extracellular matrix (ECM) components, immune activation and neoangiogenesis. The pathogenesis of scleroderma is still poorly elucidated; however, an increasing burden of evidence suggests (Toll-like Receptor) TLR3 involvement. In SSc fibroblasts, polyinosinic-polycytidylic acid [poly(I:C)], the TLR3 synthetic agonist, was indeed shown to induce type I (interferon) IFN and transforming growth factor-β modulated genes and to be the only TLR ligand up-regulating endothelin-1 expression via IFN-γ. Furthermore, stimulation of lung fibroblasts with poly(I:C) induced myofibroblast differentiation, and ECM production via TGF-β and NF-κB. In fibroblast-like synoviocytes, TLR3 activation enhanced the expression of metalloproteinases and proangiogenic molecules. In our working hypothesis, nucleic acid-containing immune complexes (ICs) isolated from scleroderma patients bearing different autoantibody antigenic specificities might activate TLR3, thus inducing several mediators involved in SSc pathogenesis.

Aim: to characterize the role of TLR3 as potential mediator in the initiator phase of scleroderma.

Methods: fibroblasts were isolated from skin biopsies obtained from healthy donors and cultured in adequate conditions up to the eight passage. ICs were purified using polyethylene glycol precipitation from sera of healthy controls and scleroderma patients carrying different autoantibody specificities (antibodies against centromere proteins, DNA topoisomerase I, RNA polymerase and Th/T0). Fibroblasts were transiently silenced for TLR3 using a specific small interfering RNA (siRNA); silencing was confirmed by RT-PCR and Western Blotting. TLR3-silenced and un-silenced cells were incubated with ICs of different sources or TLR agonists (poly(I:C) and LPS). Levels of TLR3 mRNA expression in different experimental conditions were analyzed by RT-PCR. Adhesion molecule (ICAM-1) expression was evaluated by cell-ELISA; interleukin (IL)-6 and IL-8 secretion in the supernatants was measured by commercial ELISA assays.

Results: Both mRNA and protein TLR3 levels were significantly reduced by specific silencing. The maximal up-regulation of TLR3 mRNA expression was observed at a poly(I:C) concentration of 1 µg/ml. ICAM-1 expression was significantly increased in cells treated with both TLR agonists and ICs from SSc patients but not healthy controls. Similarly, IL-6 and IL-8 secretion was elevated in the same experimental conditions. TLR3 specific silencing significantly affected ICAM-1, IL-6 and IL-8 levels.

Conclusions: Our data suggest that TLR3 activation by ICs isolated from SSc patients leads to fibroblast activation, with upregulation of adhesion molecule expression and pro-inflammatory interleukin secretion.
Further work is needed to better investigate TLR role as a potential mediator in SSc.

PS106 ENHANCED IL-8 PRODUCTION BY MONOCYTES IN SYSTEMIC SCLEROSIS PATIENTS WITH PULMONARY FIBROSIS

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Background/Purpose. Substantial evidence supports the implication of immune-activated cells, cytokines and chemokines in the pathogenesis of systemic sclerosis (SSc). In fact, interleukin 6 (IL-6) and IL-8 play a crucial role in immunity and fibrosis, both key aspects of SSc. Recent evidence, suggests that an increase of activated circulating monocytes (Mo) on peripheral blood of SSc patients have a potential role on SSc pathogenesis. This could be the source of macrophages that accumulate in injured areas and are active producers of fibrosis-inducing cytokines.
Our purpose was to investigate the pattern of expression of IL-6 and IL-8 cytokines by peripheral blood Mo and to explore clinical associations.

Methods. This study included 43 SSc patients and 20 healthy controls (HC). All SSc patients fulfilled the American College of Rheumatology Criteria for the classification of SSc (limited cutaneous SSc (lSSc, n=30) or diffuse cutaneous SSc (dSSc, n=13), according to LeRoy et al.). A further subdivision was made, based upon the duration of disease, as early- (n=11) and late-stage (n=32), and these groups were individually compared with HC. A clinical evaluation was performed and registered.
Each participant was submitted to a blood sample collection, which was processed according to a protocol, designed to separately analyze the intracellular expression of IL-6 and IL-8 in Mo cells.
Data was statistically analyzed using the SPSS® version 20.0 for windows. Mann-Whitney U-test was used to evaluate differences between groups. Correlations between continuous variables were assessed by Spearman's correlation coefficient. P values < 0.05 were considered statistically significant.

Results. The mean age was 56.7±12.3 and 52.0±10.0 years for SSc patients and HC respectively. Females represented 79% of SSc and 80% of the control group. The mean disease duration was 9.4±8.3 years and the mean mRSS was 12.0±8.1.
The frequency of circulating IL-6 and IL-8-producing Mo cells was not statistically different between SSc patients and HC.
The percentage of IL-8-producing Mo cells was significantly higher in patients with pulmonary fibrosis (p=0.009). No statistically significant differences were observed between early and late-stage SSc, concerning IL-6 and IL-8 expression among Mo. There were no significant association between disease subset, history of digital necrosis or mRSS and the frequency of IL-6 and IL-8 expression among Mo cells.

Conclusion. IL-8-producing Mo cells frequency is higher in SSc patients with pulmonary fibrosis. These findings support the hypothesis that IL-8 produced by these cellular type may be involved in the pathological process of SSc, regardless of the disease subset.

PS107 MOLECULAR ASPECTS OF IL-13 UP-REGULATION BY CD8+ T CELLS FROM SSC PATIENTS

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Systemic sclerosis (SSc) has the highest fatality rate among connective tissue diseases and is characterized by vascular damage, inflammation and fibrosis. T cells are important in pathogenesis and produce cytokines that contribute to the induction of fibrosis. We found previously that dysregulated production of the profibrotic cytokine IL-13 by effector CD8+ T cells is associated with more severe skin thickening in SSc, and defects in the molecular control of IL-13 production. We observed that total and naïve CD8+ T cells from the blood of SSc patients present an increased expression of the Th2-specific transcription factor GATA-3, and this is associated with augmented IL-13 production and specific clinical manifestations. Furthermore, silencing of GATA-3 with specific siRNA blocks IL-13 production in CD8+ T cells, demonstrating a causal relationship between GATA-3 and IL-13. GATA-3 is also highly expressed by CD8+ T cells in the sclerotic lesions of SSc patients, where it may be associated with the overproduction of IL-13. GATA-3 function is controlled at different levels, including by interactions with other nuclear proteins expressed in T cells. The Th1-specific nuclear factor T-bet induces IFN-γ production and inhibits Th2 cytokines, including IL-13, by antagonizing GATA-3 expression and/or function. Here we show that peripheral blood CD8+ T cells from SSc patients while expressing higher levels of IL-13 and GATA-3, still maintain similar levels of IFN-γ and T-bet compared to controls. Moreover, we found that the interaction between T-bet and GATA-3 in SSc CD8+ T cells is weaker compared to normal controls, which allowed more GATA-3 to bind to the IL-13 promoter and induce its expression. We conclude that increased IL-13 expression by SSc CD8+ T cells results, at least in part, from reduced down-regulation of GATA-3 by T-bet. Thus, our data provide new insights into SSc pathogenesis and will enable establishment of highly relevant biomarkers of immune dysfunction in patients with SSc that can be used as novel therapeutic targets for this currently incurable disease.

PS108 EXPRESSION OF THE TRANSCRIPTION FACTOR FORKHEAD BOX E3 (FOXE3) IN PERIPHERAL BLOOD MONONUCLEAR CELLS OF PATIENTS WITH SYSTEMIC SCLEROSIS

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Introduction: The process of epithelial (or endothelial)-mesenchymal transition (EMT) is at the basis of generation of renal and pulmonary fibrosis, and, in systemic sclerosis (SSc), has been regarded as one of the possible mechanism for accumulation of lymphocyte/monocyte-derived fibrocytes or myofibroblasts, which contribute to tissue fibrosis. Forkhead box E3 (FOXE3) is a transcription factor involved in EMT of lens epithelial cells (LEC). Its expression progressively decreases with the migration of LEC from the anterior to the equatorial region. FOXE3 expression cessation marks initiation of fiber differentiation. No data are available on FOXE3 expression in sites other than LEC. Therefore, in this study, we investigate FOXE3-expression in peripheral blood mononuclear cells (PBMC) of SSc patients, to eventually explore its potential role in the generation of lymphocyte/monocyte-derived fibrocytes or myofibroblasts, hence of tissue fibrosis.

Material and methods. PBMC were isolated from heparinized peripheral blood of 10 patients with SSc and 7 healthy blood donors (HBD) by Ficoll-Hypaque density gradient centrifugation. Lymphocyte subsets (CD2+, CD19+) and monocytes (CD14+) were isolated by positive selection using microbeads. CD2+ cells (5x105 cells/ml) were stimulated with TGF-β (1µg/ml) and IL-6 (10 ng/ml) for 7 days. Total RNA was extracted and semi-quantitative PCR was performed to assess FOXE3 gene expression. The levels of FOXE-3 mRNA were quantified by normalizing its expression against that of GAPDH. Expression was measured as mean relative expression level (MREL). Variation of expression was measured as mean fold change (MFC).

Results: FOXE3 was expressed in CD2+, CD19+ and CD14+ cells from SSc patients and HBD. Specifically, expression level of SSc was similar to that of HBD in both CD19+ (MREL, SSc= 0.02; HBD= 0.08) and CD14+ (MREL SSc= 0.52; HBD=0.61) cells, while in CD2+ cells, the expression in HBD was higher (MREL=0.58) than in SSc patients (MRE 0.22). FOXE3 expression markedly increased following TGF-β stimulation in CD2+ cells from all HBD (MFC=1.43) and 5 SSc patients (MFC 1.94), whereas it decreased in CD2+ cells from the remaining 5 SSc patients (MFC = 0.71). IL-6 stimulation had no significant effect on FOXE-3 expression in CD2+ cells from both SSc patients and HBD.

Conclusion: This study has shown, for the first time, the FOXE3 expression in PBMC of SSc patients, and an heterogeneity in the expression level changes in SSc CD2+ cells following stimulation with TGF-β but not IL-6. Whether this heterogeneity parallels that of clinical manifestations remains to be determined.

PS109 ANTIBODIES ANTI-RO/SSA IN SYSTEMIC SCLEROSIS

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Antibodies to Ro are reported in systemic sclerosis (SSc), with a variable frequency from 3% to 11% when detected by immunoprecipitation assays and from 12% to 37% with ELISA or line immunoassay. Anti-Ro detected by ELISA have been associated with sicca, polymyositis and, more rarely, interstitial lung disease (ILD).
Methods: we studied the immunological repertoire of 444 patients affected by SSc, diagnosed using ACR and Le Roy criteria. Antinuclear antibodies have been detected by indirect immunofluorescence on HEp-2 cells. Antibodies to ENA were determined by counterimmunoelectrophoresis, using a rabbit thymus and spleen extracts as substrate.
Results: anti-Ro antibodies were found in 23 cases (5.1%), as isolated antibody in 11 patients (48%), while associated to anti-topoisomerase I, anti-U1RNP and anti-La in 6, 2 and 4 cases, respectively.
Anti-Ro+SSc showed a high female to male ratio (22:1), mean age at onset of 44 years (SD: 12) and a limited cutaneous SSc in 13 cases (56%). Digital ulcers and SSc active capillaroscopy pattern were found in 43.5% of cases. Calcinosis and joint anchilosis were rarely detected. By contrast 16 patients (69%) showed arthralgias with arthritis in 22%. Organ complications were diagnosed in high number of cases: esophageal involvement was diagnosed in 69% of patients, ILD in 52%, pulmonary hypertension in 17.4% of cases. Sicca symptoms were found in 17 patients (74%). Myositis, renal crisis were diagnosed only in one patient, each. Three patients died during follow-up, due to renal crisis, lung cancer and heart attack.
Comparing 23 anti-Ro+SSc with a sample of 100 anti-Ro negative SSc, we found that anti-Ro+ SSc showed a lower age at disease onset (44 vs 57.7 years, $p<0.005$), a lower rate of calcinosis (4% vs 32%, p:0.03) and a higher frequency of hypergammaglobulinemia (54% vs 16%, $p<0.005$, OR: 6.2, CI: 2-19).
When compared with 252 ACA+SSc, anti-Ro+SSc showed a higher rate of diffuse cutaneous type (43% vs 1%, $p<0.005$), a lower age at disease onset (44 vs 51.9 years, p: 0.013), higher rate of mortality (13% vs 3.6%), a significant higher rate of ILD (52% vs 8%, $p<0.005$, OR: 15.2, CI: 5-45) and a higher rate of pulmonary hypertension (17% vs 5.5%, p: 0.05). No significant difference was found with 125 anti-topoisomerase I+ patients.
Conclusions: anti-Ro antibodies are rarely found in SSc, usually associated with sicca, lung involvement and articular symptoms. Compared with ACA+SSc, they showed a more frequent pulmonary complications and earlier disease onset.

PS110 MEMORY (CD27+) B CELL IMPAIRMENT IS A CHARACTERISTIC FEATURE OF PATIENTS WITH SYSTEMIC SCLEROSIS AND PULMONARY FIBROSIS

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INTRODUCTION: B cells are likely to be involved in the pathogenesis of systemic sclerosis (SSc). Yet, the phenotypic and functional features of memory (CD27+) and naïve (CD27-) B cell sub-populations expressing the stimulatory CD19 or the inhibitory CD22 molecule have not been studied in detail.
AIM: The aim of the present study was to properly characterize the heterogeneous B cell subsets expressing CD19, CD22, and CD27 by flow cytometric analysis.
METHODS: A total of 31 individuals were studied, including 14 SSc, 5 Sjögren's syndrome, 5 psoriatic arthritis patients and 7 normal controls (NCs). Peripheral blood mononuclear cells (PBMCs) were isolated using standard Ficoll-Hypaque procedures and the expression of CD19, CD22 and CD27 on B cells was examined by flow cytometry.
RESULTS: CD19 mean fluorescence intensity (MFI) expression was significantly higher in naïve or memory B cells of untreated SSc patients, compared to treated SSc patients or controls (pathological or normal)($p<0.05$). Memory B cells expressing CD19 or CD22 were significantly decreased in SSc patients compared to NC ($p<0.05$). Similar findings but to a lesser extent were also found in pathological controls. CD27–CD19+ (naïve B cells) were more frequent in SSc patients compared to controls (<0.01). The memory CD19+/naïve CD19+ and the memory CD22+/naïve CD22+ ratios were lower in SSc patients compared to controls. Significant loss of CD27+ expressing CD19+ and CD22+ B cells was a characteristic feature of SSc patients with lung involvement compared to SSc patients without lung involvement (pulmonary fibrosis) ($p<0.01$).
CONCLUSIONS: Our data demonstrate that patients with SSc, and in particular those with lung fibrosis, are characterized by a significant loss of memory B cells.

PS111 IRF8 GENE CONTRIBUTES TO DISEASE SUSCEPTIBILITY AND INTERACTS WITH NF-KB BY MODULATING INTERFERON SIGNATURE IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Introduction. Systemic Sclerosis (SSc) is a polygenic autoimmune disease (AID) characterized by fibroblast dysregulation. It shares some genetic bases with other AIDs, as evidenced by autoimmune gene pleiotropism. Fibroblast dysregulation can be also observed in Primary Biliary Cirrhosis (PBC), another polygenic AID, which can be associated with SSc in the so called Reynold's Syndrome.

Objective. The present study was undertaken to investigate whether single nucleotide polymorphisms (SNPs) identified by a large GWAS in PBC might contribute to SSc susceptibility by a cross-disease approach.

Methods. Sixteen PBC susceptibility SNPs were genotyped in a total of 1,616 SSc patients and 3,621 healthy controls all of whom were of European Caucasian origin.

Results. We observed an association between PLCL2 rs1372072 (OR=1.23 [95% CI 1.12-1.33] Padj=7.22x10-5, NF-kB rs7665090 OR=1.16 [95% CI 1.06-1.25], Padj=0.01, and IRF8 rs11117432, OR=0.75 [95% CI 0.67-0.86], Padj=2.50x10-4 with SSc susceptibility. We subsequently queried associations according to the main subtypes and found that rs1372072 and rs11117432 were associated with the limited cutaneous subgroup (Padj=0.001 and Padj=0.003, respectively) and that rs7665090 was conversely associated with the diffuse cutaneous subset (Padj=0.007). We then looked for genotype – phenotype correlations by measuring mRNA expression of PBMC, obtained from patients (n=39) and controls (n=24), and observed that the IRF8 protective allele was associated with decreased IFIT1 expression reflecting type 1 interferon signature. We investigated gene interactions between the 3 associated SNPs that revealed an epistatic interaction between NF-kB and IRF8 SNP (OR=0.56 [95% CI 0.00-0.74], P=4x10-4). Interestingly, we observed that the effects of IRF8 and NF-kB were only observed in patients carrying the susceptibility allele from both genes.

Conclusion. By a cross disease approach querying pleiotropic genes, we identified 2 new susceptibility genes for SSc and confirmed IRF8 locus. We also identified functional effects of IRF8 variant affecting interferon signature and that an interaction between IRF8 and NF-kB genes might play a role in SSc susceptibility.

Poster Session

PS112 ACTIVATION OF LIVER X RECEPTORS INHIBITS EXPERIMENTAL FIBROSIS BY INTERFERING WITH INTERLEUKIN-6 RELEASE FROM MACROPHAGES

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Background. Liver X receptors (LXRs) are orphan nuclear receptors with emerging roles in metabolic and autoimmune diseases. Here, we investigated the role of LXRs in experimental skin fibrosis and evaluated their potential as anti-fibrotic targets for systemic sclerosis (SSc) and other fibrotic diseases.

Methods. We studied the role of LXRs in bleomycin-induced skin fibrosis and in tight skin-1 (Tsk-1) mice, reflecting different subtypes of fibrotic disease. To dissect the role of both LXR isoforms in fibrosis, we generated LXRα- and LXRβ-knockout mice as well as LXR-α/β-double-knockout mice. To establish the mode of action of the anti-fibrotic effects of LXRs, we investigated the effects of LXRs on fibroblasts and macrophages.

Summary of the results. LXR activation by the LXR agonist T0901317 had potent anti-fibrotic effects in both bleomycin-induced skin fibrosis and Tsk-1 mice as assessed by skin thickness, hydroxyproline content, and the number of myofibroblasts. The anti-fibrotic activity of LXRs was particularly prominent in the inflammatory bleomycin-model in which LXR activation reduced skin thickening in a dose-dependent manner by up to 64%, the hydroxyproline content by up to 91% and the number of myofibroblasts by up to 91%.

LXRα-, β- and LXRα/β-knockout mice showed a similar response to bleomycin challenge as wildtype animals. In line with these results, low levels of the LXR target gene ABCA-1 in the skin of bleomycin-challenged and control mice suggested a weak baseline activation of the anti-fibrotic LXR signaling, which, however, could be specifically activated by T0901317. The specificity of T0901317 on LXRs was again reflected by the LXRα/β-knockout mice in which the LXR agonist lacked anti-fibrotic activity.

Of note, fibroblasts were not the direct targets of the anti-fibrotic effects of LXRs. By contrast, LXR activation inhibited macrophage infiltration in fibrotic tissue and decreased the release of the pro-fibrotic cytokine interleukin-6 from macrophages, resulting in reduced fibroblast activation and collagen release.

Conclusions. We identified LXRs as novel therapeutic targets for SSc and other fibrotic diseases, a yet unknown aspect of these nuclear receptors. Our data suggest that LXR activation might be particularly effective in patients with inflammatory disease subtypes. Activation of LXR interfered with the release of interleukin-6 from macrophages and, thus, inhibited fibroblast activation and collagen release.

PS113 CORRELATION BETWEEN SHORTER DISEASE DURATION IN SYSTEMIC SCLEROSIS (SSC) AND ANTI-COLLAGEN TYPE V

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Introduction: Collagen type V is a highly immunogenic molecule with preserved globular and telopeptide domains found inside heterotypic fibrils in the skin mixed with collagen types I and III. Experimental studies have shown that rabbit's immunization with human type V collagen triggers epitope spreading with activation of Th2 lymphocytes, increased release of cytokines, augmented B lymphocytes activation and production of high titers of anti-type V collagen. There is an animal model of SSc where rabbits immunized with collagen type V developed a disease similar to human disease, with vasculopathy and tissue fibrosis. Studies in humans also have shown that type V collagen is overexpressed in the skin of patients within early stages of SSc. Objective: To correlate the prevalence of anti-type V collagen with different clinical manifestations of SSc, disease duration and severity. Patients and Methods: 81 female patients who fulfilled the ACR criteria for SSc: 18 patients with early SSc, 27 patients with diffuse SSc and 36 patients with limited SSc. The control group was 19 healthy patients age matched to patients with early SSc. The anti-type V collagen analysis was performed by ELISA. Results: The mean age of Early SSc group and control group was (45.2 and 44.9 respectively). The defined SSc group (limited and diffuse), the average age was 55.6 years, (p=0.001). The prevalence of anti-type V collagen in early SSC, defined SSc and control groups was respectively 33%, 17% and 5% (p=0,07). The prevalence of Anti-type V collagen in early SSc group was significantly higher than in the control group (p=0,042). There was a correlation between shorter disease duration and positivity of anti-type V collagen (p=0.009). Conclusion: The titers of Anti-type V collagen in human were increased in early stages of SSc. Our research suggests the importance of this protein mainly in the pathogenesis of SSc in early phases of the disease in humans, as has been previously described in a rabbit animal model by Teodoro et al. We could speculate from this finding that type V collagen could be an interesting therapeutic target and an additional diagnostic tool mainly in early stages of SSc. Further longitudinal studies with a larger number of patients are needed to validate our findings.

PS114 SYSTEMIC SCLEROSIS AND OCCUPATIONAL EXPOSURE: A CASE CONTROL STUDY OF 100 PATIENTS AND 300 CONTROLS

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Objective: This case control study assessed: the relationship of systemic sclerosis (SSc) related to occupational exposure, the risk of SSc related to occupational exposure in male and female patients.
Methods: From 2005 to 2008, 100 patients with a definite diagnosis of SSc were included in the study; 3 age, gender, and smoking habits matched controls were selected for each patient. A committee of experts evaluated blindly occupational exposure to crystalline silica, white spirit, organic solvents, ketones, welding fumes, epoxy resins, pesticides; an occupational exposure score was calculated for all subjects.
Results: Increased ORs for SSc was found for: crystalline silica ($p<0.0001$), white spirit ($p<0.0001$), aromatic solvents ($p=0.0002$), chlorinated solvents ($p=0.014$), trichlorethylene ($p=0.044$), ketones ($p=0.002$) and welding fumes ($p=0.021$). Elevated risk associated with high final cumulative score in SSc was observed for: crystalline silica, white spirit, chlorinated solvents, trichlorethylene, aromatic solvents, any type of solvents, ketones and welding fumes. A marked association between SSc and occupational exposure was further found for: 1) crystalline silica, chlorinated solvents, trichloroethylene, white spirit, ketones and welding fumes in male patients; and 2) white spirit, aromatic solvents, any type of solvent and ketones in female patients
Conclusion The results show the impact of occupational risk factors in the development of SSc for: crystalline silica, white spirit, aromatic solvents, chlorinated solvents, trichlorethylene, ketones and welding fumes. The risk associated with high cumulative exposure was markedly increased in SSc. Finally, our series shows that the association of SSc and occupational exposure was variable according to gender.

PS115 A GENOME-WIDE ASSOCIATION STUDY FOLLOW-UP SUGGESTS A POSSIBLE ROLE FOR PPARG IN SYSTEMIC SCLEROSIS SUSCEPTIBILITY

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Introduction: A recent genome-wide association study (GWAS) comprising a French cohort of systemic sclerosis (SSc) reported several non-HLA single-nucleotide polymorphisms (SNPs) showing a nominal association in the discovery phase. We aimed to perform a follow up strategy in order to identify previously overlooked susceptibility variants.
Methods: Sixty six non-HLA GWAS-genotyped SNPs showing a P-value < 10-4 in the discovery phase of the French SSc GWAS were analyzed in the first step of this study performing a meta-analysis which combined data from the two published SSc GWASs. A total of 2,921 SSc patients and 6,963 healthy controls were included in this first phase. Two SNPs, PPARG rs310746 and CHRNA9 rs6832151, were selected for genotyping in the replication cohort (1,068 SSc patients and 6,762 healthy controls) according to the results of the first step. Genotyping was performed using TaqMan SNP genotyping assays.
Results: In the first step of our study, we found nominal associations for both PPARG rs310746 (PMH = 1.90 x 10-6, OR= 1.28) and CHRNA9 rs6832151 (PMH = 4.30 x 10-6, OR= 1.17) genetic variants with SSc. In the replication phase, we observed a trend of association for PPARG rs310746 (P-value = 0.066, OR= 1.17). The combined overall Mantel-Haenszel meta-analysis of all the cohorts included in the present study revealed that PPARG rs310746 remained associated with SSc with a nominal non-genome wide significant P-value (PMH = 5.00 x 10-7, OR= 1.25). No evidence of association was observed for CHRNA9 rs6832151 either in the replication phase or in the overall pooled-analysis.
Conclusion: Our results suggest a role of PPARG gene in the development of SSc.

PS116 PREVALENCE OF ANTI-RNA POLYMERASE III ANTIBODIES IN SYSTEMIC SCLEROSIS: NEW DATA FROM A FRENCH COHORT, SYSTEMATIC REVIEW AND META-ANALYSIS

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Objectives. Studies assessing the prevalence of anti-RNA polymerase III antibodies (ARA) in systemic sclerosis (SSc) have yielded a wide range of results. We described a new SSc cohort tested for ARA and performed a systematic review and meta-analysis to assess the worldwide prevalence of ARA and potential factors of variability.

Methods. Seropositivity for ARA was evaluated in a French cohort of SSc patients. A systematic review of the literature was carried out in PubMed and EmBase. Meta-analysis was performed using available data on prevalence, clinical characteristics of SSc patients and assays used for ARA testing.

Results. One hundred and thirty-three French SSc patients were tested for ARA, leading to a local prevalence of 6-9%. Thirty studies representing a total population of 8437 SSc patients were included in the meta-analysis. The prevalence of ARA was highly variable ranging from 0 to 41%. The overall pooled prevalence of ARA was 11% (95% confidence interval [95% CI]: 8-14) but heterogeneity was high among studies (I^2 93%, $p<0.0001$). Geographical factors such as continents and countries partially explained this heterogeneity and correlated with the prevalence. No other baseline SSc characteristics significantly correlated with the prevalence.

Conclusion. Our new cohort and meta-analysis of the literature confirmed that ARA prevalence in SSc is variable between centers with a pooled prevalence of 11% (95% CI: 8-14). Geographical factors were significantly associated with prevalence, underlying the probable implication of genetic background and environmental factors. The heterogeneity among studies remained largely unexplained.

PS117 SEMAPHORIN 3A AS A POSSIBLE IMMUNOREGULATOR IN SYSTEMIC SCLEROSIS

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Background: Semaphorin 3A (sema 3A), is now recognized as a potent immuno-regulator during all stages of the immune response, early initiation as well as late phases of inflammatory processes. Sema 3A expression has been recognized on T regulatory cells as a suppressive marker, contributing to the regulatory properties of these cells. Defective expression of sema 3A in CD4+ T cells derived from rheumatoid arthritis (RA) patients has been reported. T reg cells in Ssc were reported to be reduced in amount and function. The expression of semaphorin 3A hasn't been evaluated in systemic sclerosis (SSc) thus far.
Aim: To measure expression of semaphorin 3A in serum and on regulatory T-cells cells in Ssc patients and normal controls and correlate it with demographic, clinical and laboratory parameters in SSc.
Methods: SSc patients were evaluated for demographics, clinical manifestations, routine laboratory results, serum autoantibodies, semaphorin 3A serum levels (measured by commercial ELISA kit) and expression on regulatory T cells CD 4+ CD 25+ (by flow cytometry), nailfold capillaroscopy patterns, pulmonary function tests, echocardiograms, high resolution lung CT scans, modified Rodnan skin score (mRSS), Medsger disease severity scale and Valentini activity index.
Results: 27 SSc patients were evaluated and compared with healthy controls. 10 SSc patients had diffuse disease with lung fibrosis and 17 had limited cutaneous disease. Sema 3A concentration in SSc was lower than healthy controls both as measured by ELISA 14.4±5.6 ng/ml vs. 27.1±8.4 ng/ml ($p < 0.001$) and by flow cytometry on regulatory T cells 61.7 ±15.7 % vs. 88.7±3.6 % ($p < 0.001$). Sema 3A levels negatively correlated with the disease duration B = -0.4, p value=0.036 but not with disease severity.
Conclusions: This is the first study to demonstrate low serum levels of sema 3A in SSc patients. The reduced expression of sema 3A has specifically been demonstrated on regulatory T cells and was found to worsen with disease duration. These findings are in line with previous studies that described T-reg deficit in SSc which is related to disease duration. Low level of sema 3A, a regulator of autoimmune activity, may play a role in the pathogenesis of SSc. Further studies are needed to further understand this novel relationship.

PS118 INFLUENCE OF ALPHA 2 DO COLLAGEN V OVEREXPRESSION IN PHYSIOPHATOLOGY OF FIBROSIS SYSTEMIC SCLEROSIS PATIENTS

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BACKGROUND: Systemic sclerosis (SSc) is disease of unknown etiology its pathophysiology is thought to be based on vascular alterations as well as immunological and fibrotic processes. Collagen V assembles into diverse molecular forms and α1(V)(2)α2(V) controls fibrillogenesis. We have recently demonstrated increased mRNA α2(V) expression in early SSc correlated with disease activity (Autoimmun Rev, 11(11):827-35, 2012). We evaluate if the α1(V)(2) and α2(V)-containing fibrils leads to ultrastructural modifications at dermis and in fibroblasts culture of skin biopsy and related the different subtypes with the fibrosis.
METHODS: Biopsies from 5 early-SSc female patients (ACR criteria), with <2 years of diagnosis and treatment naive and 5 samples of normal skin from healthy individuals were studied. All biopsies were submitted for electron microscopy, immunofluorescence to identify α1(V)(2) and α2(V) and were quantified by image analysis. Dermal fibroblasts were cultivated in coverslips in a mono-layer (cell 10-9) util 100% confluence for three dimensional reconstruction. From fibroblasts, COLV chains were identified by SDS / PAGE and immunoblotting, COL5A1 and COL5A2 expression and were detected by PCRq and sequencing of COL5A1 and COL5A2 chains cDNA was performed.
RESULTS: Ultrastructural level by transmission electron microscopy results showed a dense packing of collagen in epidermal–dermal interface, characteristic marks of extracellular matrix alterations, including highly dense packing of collagen and vascular basement membrane thickening was frequently seen in superficial derm 3D-reconstruction revealed that α1(V)(2) and α2(V) exhibited dense fluorescence around dermal fibroblasts, along the small vessels and capillaries walls. The α1(V)(2) in fibroblasts displayed a granular intracytoplasmic and perinuclear pattern with higher intensity in SSc compared to controls. In contrast, a dense filamentous protrusion around the nucleus and pericellular pattern was found for α1(V)(2) in dermal fibroblasts from SSc patients. Morphometric analysis revealed that the expression of α2(V) was significantly higher than controls ($p > 0.05$ and $p = 0.001$, respectively) and was observed increased α2(V) expression when compared to α1(V)(2), but in the epidermal–dermal, near the basement membrane of papillary dermis, the α1(V)(2) expression was absent. Immunoblot confirming the increased production of this chain. The COLVA1/COLVA2 gene indicate that in dermal fibroblasts from SSc patients was higher than that observed in normal fibroblasts ($p<0.05$), but no difference was found in polymorphic genes COL5A1 and COL5A2.
CONCLUSION: We conclude that overexpression of α2(V) and absence of chains α1(V)(2) alters the skin histoarchitecture, contributed by the disarrangement and thickness mainly in the early stage and may be related with cutaneous severity.

PS119 SERUM FREE LIGHT CHAINS OF IMMUNOGLOBULINS ARE ASSOCIATED WITH DISEASE ACTIVITY IN SYSTEMIC SCLEROSIS : A PROSPECTIVE AND CONTROLLED STUDY

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Introduction: There is a free light chains excess production over immunoglobulin heavy-chain synthesis by B lymphocytes. Serum free light chains (SFLC) are high in monoclonal gammopathy and can serve as a diagnosis tool for myeloma. Recent studies have suggested that SFLC could be interesting biomarkers for diagnosis and disease activity assessment in autoimmne diseases like Sjögren syndrome, lupus or rheumatoid arthritis. There are no data in systemic sclerosis (SSc).
Patients and Methods: 134 patients with SSc were prospectively enrolled. Following data were gathered: age at diagnosis, SSc subtypes, visceral involvement, biological manifestations including rheumatoid factor and beta2 microglobulin, SSc activity score and association with other autoimmune diseases. SFLC were assessed by Combylite ® (The Binding Site, Birmingham, RU). SFLC were also assessed in a control group of 401 blood donnors who were matched for age and sex.
Results : Mean and median SFLC values were significantly higher in SSc than in controls (median : 19.99 mg/L, mean 24.03 mg/L vs median 15.43 mg/L, mean 17.50 mg/L, respectively, $p<0.05$). In univariate analysis, there was a significant correlation between SFLC and the modified Rodnan score, past or current digital ulcers, systolic pulmonary arterial pressure, DLCO and EUSTAR as well as Medsger scores. SFLC were also correlated with erythrocyte sedimentation rate, CRP and IgG, IgA, IgM levels. While there was a correlation with the presence of a subjective sicca syndrome, we did not find a significant association with the presence of another autoimmune disease.
Conclusion: Our study is the first to assess SFLC in SSc. We show that SFLC are higher in SSc than in controls. Moreover SFLC is significantly correlate with activity and severity of the disease. Our results add an additional line of evidence that B cells activation plays probably a role in the pathophysiology of SSc.

PS120 COLLAGEN CROSS LINKING ENZYMES LOXL2 AND PLOD2 SHOW NO ASSOCIATION WITH SYSTEMIC SCLEROSIS

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Background: Scleroderma or systemic sclerosis (SSc) is a rare complex disease. The exact aetiology of SSc is not fully understood however genetic factors have shown to play a role in disease pathogenesis. SSc has shown evidence of dysregulation of the vascular and immune systems, with end point fibrosis. To date, a number of candidate gene studies and Genome-wide association studies (GWAS) have shown the replication of a number of key immunological loci. Here we genotyped polymorphisms across two collagen cross linking enzymes LOXL2 (Lysyl oxidase-line protein 2) and PLOD2 (Pro-collagen-lysine, 2-oxoglutrate 5-dioxygenase 2) to ascertain a potential pathological role in SSc.

Methods: 728 SSc cases and 260 healthy controls were genotyped for polymorphisms in LOXL2 and PLOD2 as part of a larger genotyping study. All patients and controls were of Caucasian decent and were categorised according to three mutually exclusive autoantibody status: anti-topoisomerase1 (ATA), anticentromere (ACA) and antiRNA-polymerase (ARA). Patients were further classified into sub-phenotypes according to major organ involvement; pulmonary hypertension, pulmonary fibrosis and renal crisis. All genotyping was performed by the KASP system (allele specific PCR, KBioscience, UK). All genotype data and sub-phenotype analysis was performed using PLINK.

Results: Our cohort consisted of 274 (38%) patients with lung fibrosis, 112 (15%) with pulmonary hypertension and 63 (9%) with renal crisis. 255 (35%) patients were positive for ACA, 155 (21%) patients were positive for ATA, and 140 (19%) patients were positive for ARA. The SSc cases and the healthy controls were genotyped and all SNPs and individuals passed quality control checks for Hardy-Weinberg equilibrium (p=0.05) and missingness (p=0.1). A case-control and sub-phenotype analysis were performed using PLINK, of which no association was found in any individual SNP or haplotype in either loci.

Conclusions: Here we show two loci LOXL2 and PLOD2 which show potential functional contribution to SSc pathogenesis, but which to not demonstrate a genetic association. As our study cohort was small we were hindered by the low numbers of each phenotype and therefore may lack statistical power, however our cohort is clearly defined and we would expect to find an association if present. Our data suggests it is unlikely SNPs in LOXL2 and PLOD2 contribute to the genetics of SSc pathogenesis however replication of these polymorphisms would confirm our findings. Although no genetic association was found, these loci may still contribute to the functional pathways of disease manifestations and warrant further investigation

PS121 VITAMIN D ANTIBODIES IN SYSTEMIC SCLEROSIS PATIENTS: ANTIBODIES PRESENCE AND CLINICAL AND LABORATORY CORRELATIONS

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Background: Vitamin D is a pivotal factor not only in disorders that involve calcium metabolism, such as osteoporosis and osteomalacia as well as an immunomodulatory effect as noted in several autoimmune conditions in diseases.
Very low levels of vitamin D were also demonstrated in systemic sclerosis (SSC) patients. Patients with vitamin D deficiency showed longer and more severe disease. Furthermore, an inverse relationship was found between skin involvement and vitamin D serum concentrations. Associations were found Between Systemic Sclerosis pattern of disease and Scleroderma-Specific Autoantibodies. Novel research demonstrated the presence and importance of anti-vitaminD antibodies in SLE, this motivated our research team to seek for similar antibodies among scleroderma patients.
Materials and methods:Our study population was comprised of 55 scleroderma patients and 41 donors from our hospital staff served as the control group. Levels of IgG & IgM autoantibodies against Vitamin D2 and D3 were compare the between scalroderma patients & controls. Furthermore, Scleroderma patients were assessed for disease severity and Auto-antibodies profile was taken.
Results: we found significant differences in the levels of Anti vit D2 antibodies between Scalaroderma & control:
- IgG D2 was found lower among Sclaroderma group as compared to controls (0.27±0.26 vs. 0.34±0.29, p=0.026, Mann Whitney test)
- IgM D2 is higher among Sclaroderma group as compared to controls (0.48±0.22 vs. 0.39±0.33, p=0.013, Mann Whitney test).
However, we found no significant differences in the levels of Anti vit D3 antibodies between Scalaroderma & control. Furthermore, no correlation was found to other auto-antibodies or disease severity or sub-organ damage.
Conclusions: To our knowledge this is the first time these novel anti-vitamin D antibodies are studied in scleroderma patients. Furthermore, it is the first time a correlation to vitamin D2 subgroup is identified. Further research and evaluation regarding the role, pathophysiological significance and therapeutic potential is required.

PS122 A LOSS OF TELOCYTES ACCOMPANIES FIBROSIS OF MULTIPLE ORGANS IN SYSTEMIC SCLEROSIS

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Objective: Telocytes are a distinct population of stromal (interstitial) cells recently identified in a variety of tissues and organs. By their extremely long cytoplasmic processes telocytes form a three-dimensional network that functions as a scaffold to define the correct organization of tissues/organs during pre-natal life or their repair/renewal in post-natal life. According to their specific locations within different organs, telocytes may participate in intercellular signaling, either by cell-to-cell contacts or by secreting paracrine signaling molecules, immune surveillance, neurotransmission, and tissue regeneration by forming tandem cell structures with stem cell niches. Recently, we have shown that telocytes display severe ultrastructural damages suggestive of ischaemia-induced cell degeneration and are progressively lost from the clinically affected skin of systemic sclerosis (SSc) patients. On this basis, in the present study we investigated the presence and distribution of telocytes in the internal organs of SSc patients.

Methods: Archival paraffin-embedded samples of gastric wall, myocardium and lung were obtained from SSc patients and controls. Tissue sections were stained with Masson's trichrome to detect fibrosis. Telocyte distribution was investigated on sections subjected to CD34 immunostaining and haematoxylin counterstain. CD34/CD31 double immunofluorescence was performed to unequivocally differentiate telocytes (CD34-positive/CD31-negative) from vascular endothelial cells (CD34-positive/CD31-positive).

Results: The histopathological examination of Masson's trichrome-stained sections showed the typical fibrotic changes of SSc. A generalized fibrosis affected all SSc gastric wall layers, with most severe changes in the muscularis mucosae, submucosa and muscularis propria. Few telocytes entrapped in the fibrotic extracellular matrix were found in the muscularis mucosae and submucosa. In the muscularis propria, the network of telocytes was discontinuous or even almost completely absent around smooth muscle bundles and cells, and around ganglia and nerve strands at the myenteric plexus. Wide areas of fibrosis, hypertrophy of myocardial fibers and macrophage infiltration were observed in SSc myocardium. Telocytes disappeared from these fibrotic areas. Lung sections from SSc patients displayed the typical features of non-specific interstitial pneumonia with both diffuse cellular inflammation and collagen deposition. Few or no telocytes could be observed in the thickened alveolar septa and in the interstitial space around terminal bronchioles.

Conclusions: In SSc, the loss of telocytes does not occur only in the skin, but it is a widespread process affecting also the internal organs targeted by the fibrotic process. Since telocytes are believed to be key players in the regulation of tissue/organ homeostasis, our data suggest that telocyte loss may have important pathophysiological implications in SSc.

PS123 INCREASED FREQUENCY OF TH1 AND TC1 LYMPHOCYTES PRODUCING TUMOR NECROSIS FACTOR ALPHA IN PERIPHERAL BLOOD OF LATE-STAGE SYSTEMIC SCLEROSIS

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Background/Purpose. Substantial evidence supports the implication of immune-activated cells, cytokines and chemokines in the pathogenesis of systemic sclerosis (SSc). The frequency of T cells expressing activation markers is increased in the peripheral blood (PB) of SSc patients. Proinflammatory cytokines, such as IL-2, TNF-α and IFN-γ, seem to be mostly involved in immune responses at early stages of the disease. However, discrepancies exist between the results of several studies.
We undertook the present study to investigate the pattern of expression of proinflammatory cytokines by PB Th1 and Tc1 populations and to explore associations with disease duration.

Methods. Forty SSc patients and 18 healthy controls (HC) were included. All SSc patients fulfilled the American College of Rheumatology Criteria for the classification of SSc (limited cutaneous SSc (lSSc, n=29) or diffuse cutaneous SSc (dSSc, n=11), according to LeRoy et al.). A further subdivision was made, based upon the duration of disease, as early- (n=11) and late-stage (n=30), and these groups were individually compared with HC. A thorough clinical evaluation was performed and registered.
All patients signed an informed consent and provided a PB sample, which was processed to separately analyze the intracellular expression of IL-2, TNF-α and IFN-γ in Th1 and Tc1 cell populations.
Data was statistically analyzed using the SPSS® version 20.0. Mann-Whitney and Kruskal-Wallis tests were used to evaluate differences between groups. Correlations between continuous variables were assessed by Spearman's correlation coefficient. P values < 0.05 were considered statistically significant.

Results. The mean age was 56.0±11.9 and 51.7±9.9 years for SSc patients and HC respectively. Females represented 77.5% of SSc and 83.3% of the control group. The mean disease duration was 9.6±+8.55 years and the mean mRSS was 11.60±7.65.
The frequency of Th1 and Tc1 circulating cells was not statistically different between SSc patients and HC. The percentage of Th1 and Tc1 cells producing TNF-α was significantly higher in late-stage than in early-stage SSc (p=0.034 and p=0.005, respectively). The percentage of Tc1 cells producing IFN-γ was significantly lower in early-stage than in late-stage SSc (p=0.017). No statistically significant differences were observed between early and late-stage SSc, concerning IL-2 expression among Th1 and Tc1 cells and IFN-γ expression among Th1 cells.

Conclusion. The frequency of TNF-α-producing Tc1 cells was higher in late-stage SSc. The potential pathogenic relevance of these observations justifies further investigation, concerning the profile of proinflammatory cytokines and their potential involvement in different stages of the disease.

PS124 HELICOBACTER PYLORI AS A TRIGGER OF SYSTEMIC SCLEROSIS: IMMUNOLOGICAL ASPECTS

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INTRODUCTION: Helicobacter pylori infection has been considered a potential trigger of systemic sclerosis (SSc), possibly via a mechanism of molecular mimicry involving H. pylori heat shock 60 kDa (hsp60) and SSc-related autoantigens.
AIM: The aim of the study was to investigate the fine specificity of antigen-specific immune responses against the immunodominant H. pylori antigens in patients with SSc, and compare it with that seen in other rheumatic diseases. We also assessed the role of microbial/self molecular mimicry in the induction of H. pylori-related SSc autoantibody reactivity.
METHODS: A total of 56 H.pylori-infected individuals were studied including 19 SSc patients, 23 patients with other rheumatic diseases (Sjögren's syndrome, n=16, psoriatic arthritis, n=7) and 14 normal controls. Antibody reactivity to individual H. pylori antigens was assessed by immunobloting and line dot assays (EUROIMMUN, Germany). Autoantibody reactivity was investigated using ELISA (INOVA) and line dot assays (EUROIMMUN). Inhibition studies were performed using recombinant hsp60 or purified H. pylori extracts (EUROIMMUN). To assess the role of microbial/self molecular mimicry, serum samples from H. pylori –infected SSc pre-incubated with purified hsp60 or H. pylori antigenic extracts in order to see if they loose their autoantibody reactivity against Scl-70, centromere or other SSc-related autoantigens
RESULTS: Antibody reactivities to H. pylori antigens such as hsp60, VacA, CagA, BabA2, omp6, HomD, HomB, PRX, hopK, TonB, TPX, NapA, TsaA, UreA, UreB, UreG, FabG, HP0175, HP0318 did not differ between SSc patients and controls (pathological or healthy). Pre-incubation of serum samples from SSc patients with H. pylori extracts abolished reactivity to H. pylori antigens (60-95%) but did not alter reactivity to SSc-autoantigens, such as Scl-70 or centromere autoantibodies (less than 7% inhibition).
CONCLUSIONS: The fine specificity of antibody responses to H. pylori antigens in patients with SSc does not differ from other autoimmune rheumatic diseases. Molecular mimicry and immunological cross-reactivity involving H. pylori and SSc autoantigens does not appear to play a role in the induction of humoral autoimmune responses in SSc.

PS125 ROLE OF ANGIOSTATIN AND ENDOSTATIN IS SYSTEMIC SCLEROSIS

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Systemic Sclerosis (SSc) is a connective tissue disease characterized by vascular injury and widespread fibrosis involving the skin and various internal organs, which results from an unbalance between proangiogenic and antiangiogenic factors. Angiostatin and endostatin are proteolytic fragments of different extracellular proteins known for having antiangiogenic activity.

The aim of this study was to determine the concentrations of circulating endostatin and angiostatin in patients with SSc and to assess a relationship between these concentrations and disease subtypes (Pre-scleroderma, limited SSc - lcSSc, and diffuse SSc – dcSSc), evolution phase (early, intermediate and late), different organ involvement (according to Medsger score) and nailfold capillaroscopic changes.

Sixty-one consecutive patients were selected from a 190-patients-population with SSc, at the Clinical Immunology Unit of a portuguese hospital, with later exclusion of four patients. Forty-seven patients fulfilled the American College of Rheumatology criteria for SSc while the remaining ten were classified as Pre-scleroderma patients.

Endostatin ($p<0,001$) and angiostatin ($p=0,005$) were found to be significantly higher in patients with SSc than in healthy controls. Also, it was shown that angiostatin levels were elevated in dcSSc ($p=0,025$) and lcSSc ($p=0,014$), while endostatin was increased in all SSc subtypes - Pre-scleroderma, lcSSc and dcSSc ($p<0,001$). Likewise, analysis according to evolution phase found that endostatin was elevated in all stages ($p<0,001$) while angiostatin was only significantly higher in intermediate ($p=0,037$) and late phase of disease ($p=0,015$). Moreover, it was shown that endostatin was increased in lcSSc, with or without CREST syndrome ($p<0,001$), and angiostatin was exclusively elevated in lcSSc patients with CREST ($p=0,023$). Analysis of endostatin and angiostatin concentrations in various stages of organ involvement and of nailfold capillaroscopic changes found no significant differences.

These results are in consonance with the ones found in previous studies, which also concluded that endostatin and angiostatin concentrations were elevated in SSc patients, although contradictory results were reported in regard to endostatin. Additionally, we recognised the important role that endostatin might play as an early marker of disease and that angiostatin becomes increasingly relevant as disease advances. At last, finding increased concentrations of angiostatin only in CREST patients made us wonder – could there be different pathogenic mechanisms in limited SSc?

PS126 ROLE OF CD8+ LYMPHOCYTES IN SYSTEMIC SCLEROSIS

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Introduction: Scleroderma (SSc) is a rare and heterogeneous disease involving the connective tissue and microvasculature but its complete pathogenesis remains unclear. The interrelationship between the vascular endothelium and cells of the immune system, highlighting the role of T lymphocytes, seems to be an important component. In fact, in early phases of SSc, before fibrosis occurs, the affected tissues exhibit mononuclear inflammatory infiltrate composed of macrophages, mast cells and lymphocytes, especially of T-cells. Most studies to date concerning the role of T lymphocytes in the pathogenesis of SSc have focused on CD4+ T cells and evidence regarding the role CD8+ T-cells is scarce and contradictory.

Objectives and methods: The present study aimed to analyze the changes of T lymphocytes in the peripheral blood of patients with SSc and its relation to the subtype (LeRoy criteria), stage of the disease, different organ involvement (Medsger score) and nailfold capillaroscopic changes. Sixty-one consecutive patients were selected from a 190 patients with SSc, at the Clinical Immunology Unit of a university Portuguese hospital, with later exclusion of four patients. Blood samples were analyzed by flow cytometry for T-cell subsets (CD4, CD8) and T-cell activation markers (HLA-DR, CD45RO) and compared with healthy controls.

Results: Fifty-five out of the 57 patients studied were women (97%); 10 patients presented pre-scleroderma, 34 limited (lSSc) and 13 the diffuse (dSSc) subtypes. Patients with limited and diffuse subtypes were classified in early (eSSc 7 patients), intermediate (iSSc 10 patients) and late (laSSc 30 patients) disease, according to Medsger classification. There was a statistically significant reduction in the number of total lymphocytes and T-cells in SSc patients comparing to healthy controls. Both CD4+ and CD8+ T-cells were lower in patients comparing to controls, but differences were statistically significant only for CD8+ T-cells. CD8+ T-cells were decreased both in limited and diffuse subtypes, as in all stages of disease. Regarding cellular activation there was a decrease in the number of CD8+CD45RO+, but not of CD8+HLA-DR+, comparing to healthy controls. CD8+CD45RO+ was also decreased in limited and diffuse subtypes as in early and intermediate stages of the disease. No relation of CD8+ to organ involvement or nailfold capillaroscopic was found.

Discussion and conclusion: Our study indicates that T cells may play a relevant role in the pathogenesis of scleroderma especially concerning the CD8+ T-cells and the disease subtype, in the initial phases.

PS127 PROPYLTHIOURACIL ATTENUATES AORTIC VASCULOPATHY IN AN ANIMAL MODEL OF SYSTEMIC SCLEROSIS

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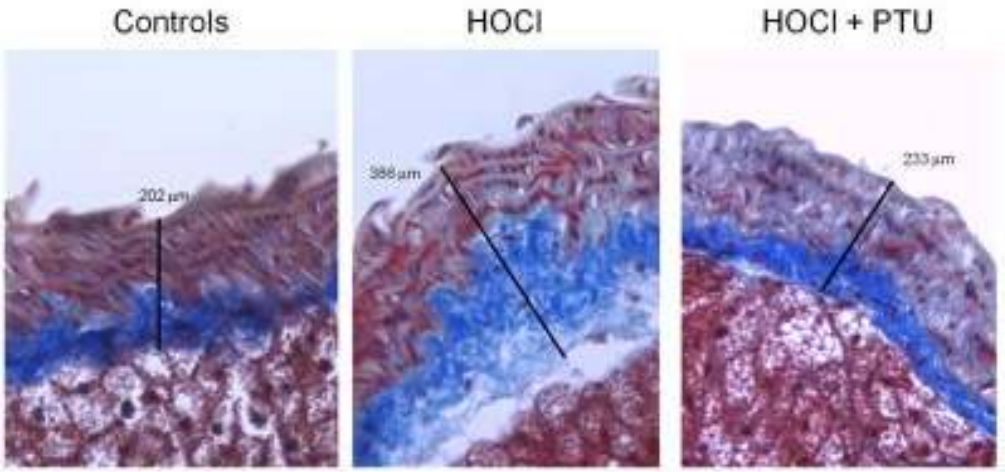
Background/Purpose: Systemic sclerosis (SSc) is a generalized connective tissue disorder of unknown etiology characterized by thickening and fibrosis of the skin and distinctive visceral involvement associated with vascular damage. Traditionally, the vasculopathy of SSc has been considered mainly to affect small arteries and capillaries but there is recent evidence showing that SSc is also associated with large vessel disease. Increased aortic augmentation index and pulse wave velocity in comparison to age and sex matched healthy controls indicate large-vessel involvement in patients with SSc. A second , and as yet poorly accounted for, endocrine feature of scleroderma is its overlap with thyroid abnormalities. Recent experimental data suggest that propylthiouracil (PTU) abrogates the development of cutaneous and pulmonary fibrosis in SSc murine model and reduces the development of plexiform lesions in an animal model of primary pulmonary hypertension. The aim of the study is therefore to evaluate the effect of propylthiouracil administration on intima-media (IM) thickness and ratio in a murine model of systemic sclerosis.

Methods: Chronic oxidant stress SSc was induced in BALB/c mice by daily subcutaneous injections of HOCl for 6 weeks, characterized in detail as the Cochin chronic oxidant stress model of SSc . Mice (n=25) were randomized in three arms: treatment with either propylthiouracil plus HOCl (n=10), HOCl (n=10), or vehicle alone (n=5). Propylthiouracil treatment (12 mg/kg) was initiated 30 minutes after HOCl subcutaneous injection and continued daily for the 6 weeks. Thoracic aorta was evaluated by histological methods. IM thickness and ratio were measured for statistical analysis.

Results: HOCl injections induced an increase in aortic IM thickness when compared to controls by 101% ($p<0.0001$). In mice treated with HOCl and PTU there was a 84% reduction of IM thickness ($p<0.0001$). PTU treated animals had a significantly thinner intima layer (-13%, $p<0.0001$) and media layer (-198%, $p<0.0001$) compared to HOCl group. IM ratio was also decreased in HOCl treated mice compared to controls (0.72 vs 1.76, $p<0.0001$) and significantly increased by PTU administration (1.62 vs 0.72, $p<0.0001$).
Conclusion: Our data suggest that PTU, probably through its antioxidant direct effect or indirectly through thyroid function inhibition , substantially moderates the increase of aortic thickness found in HOCl treated animals reducing collagen deposition in media layer and aortic fibrotic changes.



PS128 THE RELATIONSHIP BETWEEN NAILFOLD CAPILLAROSCOPIC ASSESSMENT AND TELANGIECTASIA SCORE WITH SEVERITY OF PERIPHERAL VASCULAR INVOLVEMENT IN SYSTEMIC SCLEROSIS

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Objectives: To determine the association of nailfold video-capillaroscopy (NVC) findings and telangiectasia score with digital ulcer (DU) history and severity of peripheral vascular involvement(PVI) in Systemic Sclerosis(SSc).

Methods: Fifty-nine SSc patients fulfilling Leroy and Medsger criteria were evaluated including Telangiectasia Score(TS) (Shah AA,et al. J Rheumatol 2010), Modifiye Rodnan Skin Score(MRSS), Valentine Activity Scale(VAS) and Medsger Severity Scale(SS). Qualitative (early,active and late patterns) (Cutolo M,et al. J Rheumatol 2000) and semiquantitative assessments [capillary number(CN), irregularly enlarged capillaries(IEC), giant capillaries, capillary ramifications, microhaemorrhages, capillary array disorganisation and microangiopathy evolution score(MES)] (Sulli A,et al. Ann Rheum Dis 2008) was performed by NVC.

Results: The mean age of patients was 45.6 and 91,5% were females. The mean duration of Raynaud's, non-Raynaud symptoms, skin involvement (year) were 6.1±6.5, 3.1±2.0, 3.0±2.0 respectively. Of the patients 20(34%) had diffuse, 35(59%) had limited cutaneous involvement and 4(7%) had sine-scleroderma;13(22%) were anti-centromere(+) and 29(49%) were anti-Scl70(+). DU history (DU+) was present in 27(46%) and telangiectases were present in 34(58%). When we compare DU+ and DU- groups, the mean CN was 2.0±0.5 vs 1.4±0.7 ($p<0.001$), IEC was 1.8±0.6 vs 1.4±0.7 ($p<0.05$), MES was 2.5±1.5 vs 1.8±1.0 ($p<0.05$); early pattern was in 1 vs 9, active pattern was in 14 vs 16, late pattern was in 12 vs 7 patients. Current PVI was grouped as severe (SS;2-4) (n=16) or non-severe (SS;0-1) (n=43). The frequency of severe PVI was 22% in females(12/54) and 80% in males(4/5). When we compare severe and non-severe groups, the mean CN was 2.1±0.4 vs 1.5±0.7 ($p<0.001$), MES was 2.8±1.6 vs 1.8±1.1 ($p<0.05$); early pattern was in 0 vs 10, active pattern was in 9 vs 21, late pattern was in 7 vs 12 patients. The mean TS was 2.7±4.6 vs 1.9±2.1 in DU+ and DU- groups, 3.0±5.5 vs 2.0±2.4 in severe and non-severe groups. The mean values of TS, MRSS, VAS, SS were similar between groups.

Conclusions: DU history and severe PVI in SSc was associated with capillary loss and microangiopathy. 'Early' NVC pattern was very rare in patients with DU history and was not found in patients with severe PVI. Males had severe PVI more frequent than females. Telangiectasia scores were not significantly different in patients with digital ulcer history or severe PVI. NVC may be a helpful method in the assessment of SSc patients with PVI, warranting prospective studies.

Table-1: DU History, Current Severity of Peripheral Vascular Involvement and NVC Pattern

		NVC Pattern			
		Early	Active	Late	Total(n)
DU history -		9	16	7	32
DU history +		1	14	12	27
PVI	Non-Severe	10	21	12	43
	Severe	0	9	7	16

PS129 EFFICACY OF BOSENTAN IN THE TREATMENT OF RAYNAUD'S PHENOMENON: ANALYSIS OF THREE COHORTS OF PATIENTS

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Systemic sclerosis (SSc) is a chronic autoimmune inflammatory pathogenic disease of the connective tissue, characterized by progressive fibrosis thickening of skin and internal organs. The first vascular event is Raynaud's phenomenon (RP).
In our study we evaluated the efficacy of the endothelin receptor antagonist, bosentan, in patients with Raynaud's Phenomenon secondary to Systemic Sclerosis in treatment with prostanoids (Iloprost), with Bosentan or with both drugs.
We evaluated a sample of 78 patients with SSc divided in 3 groups. Group ILO: 25 patients in treatment with ACE inhibitors and prostanoids; Group BOS: 31 patients treated with Bosentan 125mg bid, never undergone prostanoid therapy (For personal reasons or specific controindications); and Group BOS+ILO: 22 Patients in treatment with ACE inhibitors, prostanoids and Bosentan 125mg bid. All Patients were aged between 46 and 69 years (mean 57.3 ± SD 11.70), with SSc according to ACR criteria. Follow up was performed every 4 weeks for 12 months and each patient kept a diary where reported: :
- Onset data of Raynaud's Phenomenon
- Duration: minutes
- Raynaud's Condition Score (RCS): Limitation of daily activity on a scale of 1 to 10 (meaning 10 as a total inability to do the activity)
- Pain VAS (1-10): 1 meaning the least pain and 10 as the maximum pain
- Number of daily attacks
- Ulcers onset (date)

Short Form 36 items Health Survey (SF-36) was performed every 12 weeks.
Results. The reduction of RP attacks at week 48 from the baseline was statistically significant in group BOS and BOS+ILO (respectively delta-2.1 p=0.007, delta-2.5 p=0.009). There was decrease of duration in RP attacks in all groups and the Raynaud's Condition Score showed a statistically significant improvement (δ-1.5 p=0.007, δ-3.7 p=0.002, δ-2.7 p=0.007), while VAS Pain showed an improvement in Group BOS and BOS+ILO (δ-2.5 p=0,003, δ-1.6 p=0.0007) at the 48th week. SF-36 showed improvements, in particular physical activity showed an improvement only in patients of group BOS+ILO (p=0.003), while the mental health showed same results in patients of Group BOS and BOS+ILO (p=0.004). Six patients of Group ILO and only one patient of Group BOS showed the onset of new digital ulcers, while none of the patients of Group BOS+ILO has presented a new digital ulcer.
Conclusion. Bosentan seems to be effective and may be a valid alternative for the treatment of severe Raynaud's Phenomenon for patients where prostanoids therapy is contraindicated or refused, moreover seems to have a synergic effect with prostanoids treatment.

PS130 CORRELATIONS BETWEEN PERIPHERAL MICROVASCULAR DISEASE SEVERITY AND VITAMIN D SERUM LEVELS IN SYSTEMIC SCLEROSIS PATIENTS

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Background. Low 25-hydroxy-vitamin D [25(OH)D3]) serum concentrations correlate with disease activity in several autoimmune connective tissue diseases (CTD), such as rheumatoid arthritis, systemic lupus erythematosus, and undifferentiated connective tissue disease (1). Systemic sclerosis (SSc) is an autoimmune CTD characterized by a progressive sequence of microvascular, immune-response and fibrotic alterations in several organs.
Objective. The aim of the study was to assess possible associations between 25(OH)D3 serum levels and both microvascular damage severity and clinical features in SSc patients.
Methods. 120 SSc patients were enrolled (mean age 66±11SD years; 84% female; mean disease duration calculated from onset of Raynaud's phenomenon 13±12 years), 58 from the Academic Division of Clinical Rheumatology, University of Genova, Italy and 62 from the Department of Rheumatology, Ghent University Hospital, Belgium. All patients were evaluated by nailfold videocapillaroscopy (NVC) to classify and to score the severity of the microangiopathy (identification of early, active and late NVC patterns, and calculation of microangiopathy evolution score [MES]), as previously reported (2,3). 25(OH)D3 serum levels were evaluated by radioimmunoassay: vitamin D concentrations were classified as normal (>30 ng/ml), insufficient (30 <25(OH)D3 <10 ng/ml) or deficient (<10 ng/ml) (4). Clinical features of the disease were assessed using Medsger's severity scale (score 0-4) (5). Statistical analysis was performed by nonparametric tests.
Results. 25(OH)D3 was found insufficient or deficient in 61% and 26% of SSc patients, respectively. 25(OH)D3 resulted significantly lower in patients with "late" NVC pattern of microangiopathy in comparison with either "active" or "early" patterns (17±12 vs 18±13 vs 20±7, $p<0.005$). Negative statistically significant correlations were found between 25(OH)D3 concentrations and both MES ($r=-0.49$, $p<0.003$) and peripheral vascular disease according to Medsger scale ($r=-0.24$, $p<0.01$). There was no significant relationship between serum 25(OH)D3 and other clinical features of SSc, including skin, lung, gastrointestinal, renal, heart and joint involvement, assessed using the Medsger's severity scale. No statistical significant differences were found between skin subsets or gender.
Conclusion. This study demonstrates a negative correlation between 25(OH)D3 serum concentrations and progressive severity of peripheral microvascular/vascular clinical involvement in SSc patients.

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PS131 SCLERODERMA DIGITAL ULCER HEALING: BENEFICIAL ROLE OF BOSENTAN AND OPPONENT ROLE OF SKIN DIGITAL FIBROSIS

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AIM OF STUDY: The most recent guidelines for the management of digital ulcers (DU) in systemic sclerosis (SSc) indicate the use of iloprost to induce wound healing and bosentan to prevent the onset of new DU. The aim of our study was to evaluate whether the combination treatment may overcome the effect of the individual drugs.

MATERIALS AND METHODS: From 2009 to 2012, we recruited 34 patients (31 F/3 M, mean age 43.8 years) with SSc according to the 1988 LeRoy criteria and with DU persistent despite intravenous iloprost at least 6 months. The population enrolled was selected, relative to the skin fibrosis digital, for its complete absence or its presence with modified Rodnan skin score (mRSS).

Patients were subjected for 6 months combination therapy with iloprost (1 infusion per month, for 6 hours/day) and bosentan (62.5 mg bid 1 month and 125 mg bid the remaining 5 months).

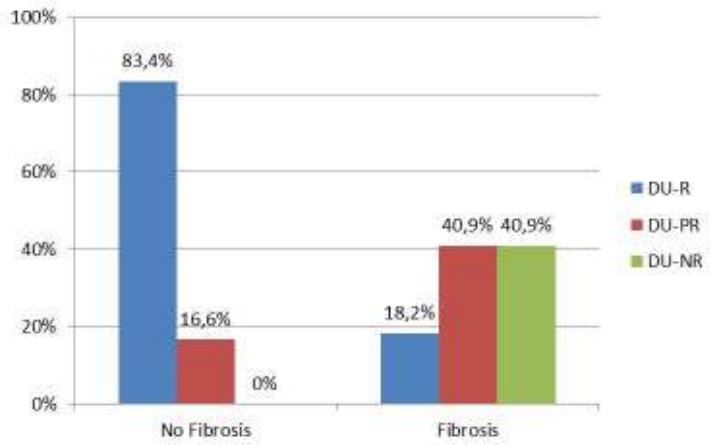
RESULTS: Patients had initially 69 DU (58 hands and 11 toes). After 6 months of treatment with iloprost and bosentan 34 (50%) DU were healed (R), 18 (32.4%) were in remission (PR), 17 (17.6%) did not respond (NR) and no new UD was recorded (0%).

With regard to the hands, 34 DU were R (58.7%), 15 were PR and 9 were NR. The number of DU went from 58 to 24 (PR + NR) (p =0.004). The mean of DU went from 1.7 to 0.7 (p =0.00003).

The 11 patients with skin fibrosis (Rodnan skin score grade 3) had initially 22 DU and at the end of study only 4 R (18%), 9 PR and 9 NR (NR + PR 82%).

The 23 patients with Rodnan skin score grade 1, 36 DU had at the beginning of the study, at the end of treatment 30 R (83.4%), 6 PR and or NR (16.6%).

By comparing the results of the populations respectively with and without digital fibrosis: DU-R were 83.4% vs. 18,2% (P = .024), DU-PR were 16.6% vs. 40.9% (P =0.00004), DU-NR were 0% vs. 40.9% (P =0.0001).



CONCLUSIONS: Overall, 58.7% of digital ulcers treated with both iloprost and bosentan healed completely. In particular, patients with mRSS grade 1 showed a recovery of 83.4% compared to 18% of patients with mRSS grade 3.

We conclude that the association iloprost more bosentan proves more effective than iloprost alone in determining the healing of DU and that the skin fibrosis strongly influences the healing process of DU.

PS132 DEVELOPMENT OF A MOUSE MODEL OF SCLERODERMA-RELATED SKIN ULCER

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Introduction. Digital ulcers are a major complication of systemic sclerosis (SSc). They are painful, cause functional impairment, and have a negative impact on the quality of life. The treatment of digital ulcers is challenging, and therapeutic options are currently limited. The development of animal models of SSc-related ulcers would help to screen drugs with potential benefit. However, to our knowledge, such models do not exist. The objective of this work is to develop a mouse model of cutaneous ulcer on fibrotic skin that mimics human disease.

Methods. The study involved four groups of BALB/c mice (n=8 in each group). Dermal fibrosis was induced in 2 groups by daily intradermal injection of HOCl, during 6 weeks. Wounds were made with biopsy punch of different diameters (2, 3 and 4-mm). Two groups were subsequently equipped with silicone rings centered and fixed around the wound to assess the impact of wound contraction (phenomenon observed in rodents) on the healing process. Groups were set up as follows:

- Group 1: healthy skin, 3 pairs of 2, 3 and 4-mm wounds
- Group 2: fibrotic skin (HOCl), 3 wounds (2, 3 and 4-mm diameter)
- Group 3: healthy skin, 4-mm wound with silicone ring
- Group 4: fibrotic skin, 4-mm wound with silicone ring

Daily assessment of wound healing was performed by taking pictures analyzed with image processing software (ImageJ). Repeated-measure ANOVAs were performed to compare the impact of diameter, fibrosis, and silicone ring on time to 90% healing. Intra-individual reproducibility of the lesions was assessed in healthy mice (group 1) and expressed as within-subject coefficient of variation (CV).

Results. The time to 90% healing for 4-mm wounds was 157±5 and 204±12 hours in groups 1 and 2, respectively (P=0.001). There was no significant difference for 2 and 3-mm wounds. Reproducibility was better for 4-mm wounds (CV=13.5%) than for smaller wounds (CVs>20%). The silicone ring further increased time to 90% healing in groups 3 and 4, with a significant interaction between time and group (p=0.03).

Conclusion. Standardized skin lesion using a 4-mm biopsy punch and splinted with a silicone ring on the back of HOCl mice provides a potentially interesting model of SSc-related ulcer. This model could be useful to assess the effect of drugs on wound healing.

PS133 CORRELATIONS BETWEEN VIRTUAL TOUCH IMAGING AND QUANTIFICATION ABSOLUTE SKIN STIFFNESS, NAILFOLD CAPILLAROSCOPY PATTERN AND DIGITAL ULCERS IN SYSTEMIC SCLEROSIS PATIENTS

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Background/Purpose: Microvascular damage as assessed by nailfold capillaroscopy is one of the best evaluable predictors of the systemic sclerosis (SSc) development and progression. The modified Rodnan skin score (mRSS) is employed to clinically evaluate the severity of skin involvement in SSc. However, this method lacks sensitivity to slight alterations in skin stiffness, and has high intraobserver and interobserver variability.
Recent studies have suggested that shear-wave elastography, namely Virtual Touch Imaging and Quantification (VTIQTM), may increase the sensitivity and validity of skin involvement evaluation in SSc.
The aim of this study was to explore possible associations between finger skin stiffness and different patterns of nailfold capillaroscopy and digital ulcers (DUs) in SSc patients.
Methods: The study included twenty-six consecutive SSc patients (23 females and 3 males, mean age 55.3 ±12.1 SD years), according to the ACR criteria for SSc, or the le Roy´s criteria for classification of early SSc. A complete medical history and clinical examination were carried out for all the patients. All patients were evaluated by nailfold capillaroscopy and classified into three major patterns "early", "active", and "late" pattern, as previously reported (1). Both mRSS and VTIQTM absolute skin stiffness were determined at the dorsum of the middle phalanx of the third finger bilaterally.
An ACUSON S3000™ (Siemens) ultrasound system equipped with a 9 MHz probe was used for VTIQTM. The significance of differences between groups was calculated with Mann–Whitney test or Kruskal-Wallis test, as appropriate. p values < 0.05 were considered statistically significant.
Results: The skin was statistically significant stiffer at the level of the dorsum of the middle phalanx of the third right finger (p=0.027) and left finger (p=0.025), in the group with DUs (See table 1).
No differences in finger absolute skin stiffness were found in association with the different capillaroscopy patterns (See table 2).
Conclusions: Measurements of skin stiffness by VTIQTM may improve the objective evaluation of skin stiffness in SSc patients and add a new dimension to the assessment of DUs. Further studies are warranted to validate and refine this non-invasive method to evaluate skin involvement in SSc clinical practice.
Table 1- Clinical findings in 26 SSc patients.
Table 2 – Shear-wave velocity values (m/s) according nailfold capillaroscopy pattern in 26 SSc patients.

Table 1- Clinical findings in 26 SSc patients.

	Digital ulcers		Differences between the groups (p value)
	Yes (n= 11)	No (n= 15)	
Age (years)	52.6 (11.4)	57.3 (12.6)	–
RP duration (years)	16.9 (10.2)	13.3 (8.8)	–
SSc duration (years)	14.1 (9.3)	11.3 (8.3)	–
mRSS, at the left finger	2.4 (0.8)	1.3 (1.3)	–
mRSS, at the right finger	2.4 (0.8)	1.4 (0.8)	–
SWV, at the right finger	5.3 (2.6)	3.4 (1.5)	0.027
SWV, at the left finger	5.4 (2.2)	3.6 (1.7)	0.025

RP, Raynaud's phenomenon; SWV, shear-wave velocity in m/s.
Results are shown in mean (SD).

Table 2 – Shear-wave velocity values (m/s) according nailfold capillaroscopy pattern in 26 SSc patients.

	Early n=4	Active n=6	Late n=9	Nonspecific n=7	Differences between the groups (p value)
SWV, at the right finger	3.7 (0.8)	3.1 (0.9)	3.7 (2.0)	6.0 (3.0)	NS
SWV, at the left finger	4.0 (1.7)	3.0 (1.0)	4.2 (2.2)	5.9 (2.4)	NS

SWV, shear-wave velocity in m/s.
Results are shown in mean (SD).

PS134 GINKGO BILOBA REDUCES THE DURATION AND SEVERITY OF RAYNAUD'S ATTACKS OF PATIENTS WITH SYSTEMIC SCLEROSIS

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Introduction: Systemic sclerosis (SSc) is a connective tissue disease with unknown etiology which causes remarkable morbidity and mortality. Raynaud's phenomenon (RP) is a complication of SSc leading to ischemia of extremities and digital gangrenes. Treatment of RP is a clinical problem and often remains inefficient. Ginkgo biloba is derived from the leaf of the Maidenhair tree. Its' extract is leaded to improve tissue circulation; this study was designed to evaluate the efficacy of ginkgo biloba in the treatment of RP in systemic sclerosis.
Materials and Methods: A total of Seventeen patients with SSc and RP were received either Ginkgo biloba pills (40 mg three times per day) or placebo for 3 months in a randomized, double blind, controlled trial. A two-week assessment period before treatment was done during which patients were asked to record the frequency, duration, and severity [using 10-point Raynaud's Condition Score (RCS)] of attacks in a diary form before intervention. They continued to record the same data in their diary forms after intervention and were visited at the end of each month.
Results: The mean duration of attacks and the RCS were significantly decreased in Ginkgo group compared with the baseline ($P<0.05$), whilst no significant reduction was observed in the mean number of attacks ($P=0.147$). In the placebo group no significant reduction was shown in the mean duration or number of attacks, and RCS.
Conclusion: Ginkgo biloba reduces the duration and severity of Raynaud's attacks of patients with systemic sclerosis.

Keyword: Ginkgo biloba, Raynaud's phenomenon, Scleroderma, Systemic sclerosis

PS135 BLOOD FLOW IN THE HANDS OF A PREDEFINED HOMOGENEOUS SYSTEMIC SCLEROSIS POPULATION: THE PRESENCE OF DIGITAL ULCERS AND THE IMPROVEMENT WITH BOSENTAN

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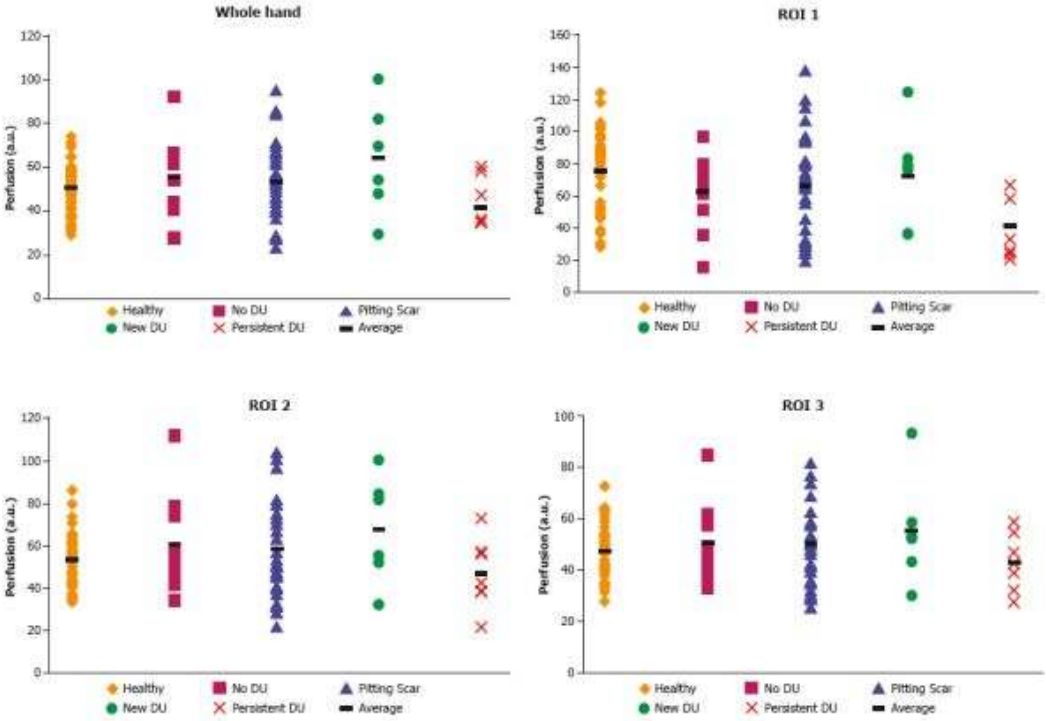
Background: Digital ulcers (DU) are complications of systemic sclerosis (SSc) and arise as a result of ischaemia due to vasculopathy of the digital arteries. Rosato et al have shown that blood perfusion in the hands can assessed in SSc patients using the non-invasive technique of laser Doppler perfusion imaging. Using this technique they demonstrated that patients with SSc had a significantly reduced blood flow in the hands of up to 50% compared with healthy subjects. In addition, they found that SSc patients, who had pulmonary arterial hypertension (PAH) and were treated with bosentan, had improved blood flow in the hands over time. However, as patients with active DU were excluded from their study they were unable to relate blood flow to the presence of DU.
This is the first study to examine the relationship between blood flow in the hands of SSc patients and the presence of digital ulcers (DU). Additionally, the effect of bosentan on blood flow in the hand was assessed in a subset of patients who had reduced blood flow relative to healthy subjects.
Methods: Adult patients with SSc and a recent history of DU and healthy subjects were included. Patients were classified into 4 subgroups: no current DU or pitting scars; pitting scars only; new DU; or persistent DU. The hand was categorised into three regions of interest (ROI) and blood flow was measured by laser Doppler perfusion imaging at baseline, 4 and 12 weeks. Patients who had a reduction in blood flow of more than 50% relative to healthy control subjects in ROI 1 on baseline, in at least one of the hands, were treated with bosentan for 12 weeks.
Results: Fifty-two SSc patients and 51 healthy subjects and were included in the analysis. There was no significant difference in blood flow in the hand across the patient subgroups at baseline (shown in figure 1). Sixteen SSc patients had a reduction of blood flow of at least 50% versus healthy subjects and received bosentan. Bosentan significantly ($p<0.05$) increased the blood flow in the whole hand after 12 weeks compared with baseline.
Conclusion: No relationship was found between blood flow in the hands of SSc patients and presence of DU. After 12 weeks of bosentan treatment the blood flow had increased in the SSc patients but had not normalised to that of healthy subjects.

Figure 1. Typical examples of hands as categorised by perfusion status



PS136 ACUPRESSURE FOR THE TREATMENT OF RAYNAUD'S PHENOMENON: A PILOT RANDOMIZED CONTROLLED TRIAL

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Background/Purpose: Raynaud's phenomenon (RP) affects approximately 10% of the US population. The high cost, lack of efficacy, and side effects of conventional medical therapies necessitates the need for complementary or alternative options.
Methods: A pilot single-center RCT of vasodilation acupressure, relaxation acupressure vs. RP education obtained from the Raynaud's Association (control). Patients with either primary (N = 15) or secondary (N = 8) RP were randomized from January through April by block randomization to the 3 groups for an 8 week period. Patients randomized to acupressure were instructed on how to self-perform at home by a single investigator and a DVD was provided with instructions. The primary endpoint was a decrease in the severity, frequency and duration of RP. All patients kept a daily Raynaud's diary, (recording the number and duration of attacks, pain, tingling and numbness on a 0-100 scale), and daily Raynaud's condition score. At baseline and 8 weeks, EndoPAT was performed to determine endothelial function, and serum was collected for biomarker analysis (VEGF, tPA, sE-Selectin, BFGF, VCAM-1, ICAM). Data analysis was conducted using the last observation carried forward and paired statistical analyses were used to assess difference.
Results: 23 patients were randomized and 7 discontinued prematurely (5 patients withdrew due to time restraints, 1 each for unrelated medical problems and lost to follow-up). Since there was no statistical difference between acupressure groups, they were combined and compared to the education group. 78% of patients were female, 96% were Caucasian, the mean age was 49.8 (SD=16) yrs; 5/16 patients in the acupressure group had secondary RP and 1/7 in the control group had secondary RP.. There was no statistical difference in the baseline characteristics between the acupressure groups vs. the control group. At the end of study, there were no statistical differences between the acupressure vs. education groups. However, there were trends in the patient reported severity of RP favoring acupressure groups (Table). In addition there were no significant differences in EndoPAT measurements or serum markers of vasculopathy. Sensitivity analysis using the completers showed similar results.

Table: Change from week 1 compared to week 8*

Variable	Group A+B	Control	P value
No of attacks Mean (SD)	N: 12 -8.3 (8.0)	N: 6 -7.2 (12.8)	1.0
Pain Mean (SD)	N: 12 -13.6 (30.1)	N: 6 9.6 (27.6)	0.12
Tingling Mean (SD)	N: 12 -5.3 (13.9)	N: 6 -1.2 (7.5)	0.84
Numbness Mean (SD)	N: 12 -10.5 (37.0)	N: 6 1.1 (22.1)	0.80
Average duration of attacks Mean (SD)	N:12 -0.2 (18.7)	N: 6 0.8 (11.2)	0.08
RCS average for difficulty Mean (SD)	N:12 -2.0 (2.4)	N: 5 -0.6 (2.9)	0.72
RCS average for pain Mean (SD)	N:12 1.4 (2.0)	N: 5 0.4 (3.0)	0.63
Endopat Mean (SD)	N: 14 0.1 (0.4)	N: 7 0.2 (0.8)	0.55
Patient VAS Mean (SD)	N: 16 -1.6 (2.2)	N: 7 -0.7 (2.0)	0.39
MD VAS Mean (SD)	N: 16 -2.1 (2.0)	N: 7 -1.9 (1.3)	1.0

*Using LOCF

Conclusion: Our pilot RCT showed that acupressure groups showed trends in improvement in symptoms associated with RP. However, there were no differences in the endothelial function and serum markers of vasculopathy. The parameters used to evaluate patients with RP have marked variability and supports the need for a composite measure to be developed for RP trials.

PS137 COMPARISON OF POSTOCCLUSIVE HYPEREMIA IN SYSTEMIC SCLEROSIS AND PRIMARY RAYNAUD'S PHENOMENON

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Cutanous postocclusive reactive hyperemia (PORH) is mediated by sensory nerves and endothelial derived hyperpolarizing factors. Such a response is abnormal in the finger pad of patients with systemic sclerosis (SSc). However, the regional variation of the response remains undetermined. The primary objective of this study was to compare the PORH on several locations of the dorsum of the hand of patients with SSc, matched primary Raynaud phenomenon (PRP) and controls.
Methods. Fifteen patients with SSc, 15 sex and age-matched patients with PRP, and 15 matched healthy controls underwent a post occlusive hyperemia test following a 5 min ischemia, recorded using laser speckle contrast imaging (LSCI).
Results. PORH was abnormal in terms of peak and area under the curve on all fingers in patients with PRP and SSc compared with controls, excepted the thumb where PORH was normal. In contrast, the kinetic of the response was altered only in patients with SSc.
Conclusions. PORH is abnormal in terms of amplitude in all finger excepted the thumb in patients with PRP and SSc, whereas altered kinetic of the response is a specificity of SSc.

PS138 NAILFOLD VIDEOCAPILLAROSCOPY AND SERUM VEGF AS BIOMARKERS OF SEVERITY IN SYSTEMIC SCLEROSIS?

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INTRODUCTION. Nailfold videocapillaroscopy (NVC) identifies the microvascular hallmarks of systemic sclerosis (SSc) for diagnosis and monitoring the progression and severity of SSc. The vascular endothelial growth factor (VEGF) is the principal mediator of angiogenesis and high levels are found in serum and skin of SSc patients with diffuse disease, late NVC patterns, or long-term disease. The aim of our study is to investigate NVC findings and serum VEGF levels in different subsets of SSc patients with variable internal organ involvement, disease activity and severity.

PATIENTS AND METHODS. Newly diagnosed SSc patients (n=44) fulfilling the ACR criteria were consecutively enrolled at our center in 2001-2012. Twenty healthy subjects were used as controls. NVC images of right and left II-V fingers, clinical, immunologic, clinimetric, and instrumental evaluations and serum samples for VEGF determination by ELISA commercial kit were used for analyses (statistical significance $p<0.05$).

RESULTS. The number of NVC giant capillaries was significantly lower in SSc with DLCO< 50% ($p=0.03$) and gastrointestinal involvement ($p=0.02$), while avascular areas negatively correlated with Valentini-Medsger severity index ($p=0.016$, r= - 0,38) and were significantly lower in ACA (+) SSc patients ($p=0.02$). Neoangiogenesis was less frequent in SSc with signs of early disease ($p=0.045$) and without gastrointestinal involvement ($p=0.045$). The mean capillary density was significantly higher in ACA (+) SSc ($p=0.02$) than in other patients. No correlation was observed between CSURI index and the presence or number of skin ulcers. CSURI<2,94 was significantly less frequent in ACA (+) patients (OR 0.15 (95% CI 0.03-0.84). SSc with early NVC pattern had significantly shorter disease duration ($p=0.02$),higher DLCO ($p=0.04$) and FVC ($p=0.049$) than SSc patients with late NVC pattern. The early NVC pattern was significantly more frequent in ACA (+) SSc patients (OR 30; IC95% 4-22).VEGF level in SSc sera was significantly higher compared to healthy controls [0.49Units (0.02-3.2) vs. 0.36Units (0.11-0.73), $p<0.05$], it was inversely correlated to DLCO ($p<0.05$, r -0.4) and directly to ground glass and interstitial score at HRCT ($p<0.05$, r +0.4). No association was identified between VEGF levels and gastro-esophageal involvement, pulmonary arterial hypertension, early-active-late capillaroscopy pattern, CSURI score, capillary density, number of giant capillaries, avascular and neoangiogenesis areas, and digital ulcers.

CONCLUSIONS. Our data confirm the importance of NVC for the diagnosis of SSc and also for prediction of disease severity and organ involvement since the SSc onset. Of note, serum VEGF levels play an additional role as biomarker of SSc pulmonary interstitial involvement.

PS139 SCLERODERMA AND DIGITALS ULCERS TREATMENT ACCESS

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BACKGROUND: Scleroderma (SD) is an Infrequent disease. The incidence is 2.3 to 22.8 cases per 1 million populations per year and the prevalence is 50-300 cases per 1 million populations over the word. Argentina lacks Epidemiological data but it is estimated between 40.000-42.000 cases of scleroderma. This study shows that more than 50 % of the patients with SSC had digital ulcers (DU). From July 2011 to August 2013 167 patients with SD and UD have been included in the study (contact by phone and web) Most of them had varying degrees of loss of function of the hand and access to treatments dependent on the health coverage.

OBJECTIVE: Understand the buying process to access to the specific medication for patients with SD and UD in Argentina during the period July 2011 to August 2013.

METHOD: Analyzed 167 patients with active digital ulcers in scleroderma, which were contacted by phone and web with AADEYR, to receive information about health coverage.

RESULTS: In a sample of 167 patients, 68% had medical coverage through a private system and social work (National Provincial Trade and prepaid), corresponding to the remaining 32% had access to medicines by the Public Health System. In the case of the private system is excluded patients with certified disabilities to achieve 100% coverage, otherwise, had a refund ranging from 40% to 70% of the drug cost. However, 80% of patients in the private sector and the state, with or without certificate of disability also experienced some delays in access to medicines for two months or more, depending on the type of health coverage.

CONCLUSIONS: The hetereogenicity of the health coverage and the administrative bureaucracy that characterizes Argentina's health system goes against the efficient use of resources and achievement of acceptable levels of equity. While the Certificate of disability allows 100% refund, no guarantees quick access to prescribed medications. Most patients ignore the possibility of obtaining this certificate and how to proceed. Therefore it becomes essential to inform to patients population about their rights to access the health system thereby ensuring adherence to drug treatments.

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PS140 DIGITAL ULCERS IN SYSTEMIC SCLEROSIS

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Objectives: To assess the prevalence of digital ulcers in systemic sclerosis (SSc) and their association with clinical and serological features.
Patients and methods: One hundred fifty (150) patients attending the rheumatology department at Ben Aknoun Hospital, as part of a prospective study and fulfilling the ACR and/or Leroy and Medsger criteria for systemic sclerosis were evaluated. The analysis of results was performed by the Epidata analysis. Data were expressed as the median and range or mean ± standard deviation (SD) and 95% confidence interval (95% CI), when appropriate. The statistical significance for the various associations was calculated using the Khi 2 test. The difference was significant when p value < 0.05.
Results: 139 women and 11 men with a median age of 45.12±13.59 years and a disease duration (first non-Raynaud symptom) of 9.7 years. 42 patients had a diffuse scleroderma, 108 patients had a limited scleroderma. 93 (62%) patients had digital ulcers.
Digital ulcers were associated with the extent of skin involvement (p 0.0008), interstitial lung disease (p 0.003), telangiectasia (p 0.001) and anti topoisomerase I antibodies (p 0.0005). The Disability Index of the Health Assessment Questionnaire (HAQ-DI) and the Cochin Hand Function Scale (CFHS) score were higher in the patients with digital ulcers (p 0.003).
Conclusion: Digital ulcers are frequent. They are disabling and associated with a severe disease.

PS141 EPIDEMIOLOGICAL STUDY FOR THE EARLY DETECTION OF SYSTEMIC SCLEROSIS IN PATIENTS WITH RAYNAUD PHENOMENON

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Raynaud phenomenon (RP) may precede to the diagnosis of systemic sclerosis (SSc) by years. The purpose of this study was to evaluate patients with RP for the early diagnosis of SS and other connective tissue diseases (CTD). Methods This study was developed under conditions of routine clinical practice in two stages*. Stage I inclusion and screening; Stage II prospective 24-month follow-up. The study population included patients from 17 primary care units. Results 158 patients, 130 women and 28 men, with a mean age of 47±17 years were evaluated. The mean age of women was 45 ± 16 years and the mean age of men was 53 ± 19 years. Mean time of evolution of RP was 93 months. A presumptive diagnosis of the RP was made by consultation with the rheumatologist and the definitive diagnosis was achieved by blood test results and capillaroscopy pattern. The presumptive diagnosis of Primary Raynaud Phenomenon (PRP) was given to 44.30% (n=70) patients and the presumptive diagnosis of Secondary Raynaud Phenomenon (SRP) to 48.10% (n=76) patients. The definitive diagnosis of PRP was given to 37.3% (n=59) patients and the definitive diagnosis of SRP to 55.1% (n=87) patients. Of all patients with a presumptive diagnosis of PRP, 84.3% (59) had definitive diagnosis whereas 15.7% (n=11) changed to definitive diagnosis of SRP. The definitive diagnosis of SRP was distributed as follows: 1.4% (n=1) early SS, 1.4% (n=1) paraneoplasic RP, 10.0% (n=7) undifferentiated CTD, 1.4% (n=1) mixed CTD and 1.4% (n=1) cervical rib. All patients with definite diagnosis of PRP had ANA negative. All patients with SS and 95% of patients with early SS had ANA positive. Ninety-six percent of patients with early SS had centromere positive. Ninety percent of patients with PRP showed a normal pattern in the nailfold capillaroscopy and 10% showed a nonspecific pattern. The total of 21 patients with diagnosis of SS and 93% (n=13) patients with early SS showed a characteristic SS capillaroscopy pattern. Ninety-five percent (n=73) of patients with negative ANA showed a normal capillaroscopy pattern and 97% (n = 30) of patients with positive ANA and anti-centromere showed a characteristic SS capillaroscopy pattern. Conclusions This study showed significantly more patients with secondary vs primary RP. There was a good agreement between the presumptive diagnosis and the definitive diagnosis. The most common diagnoses associated with SRP are SS (13%), followed by early-SS (9%) and lupus (8%).* partially supported by an unrestricted Atelion grant

PS142 EVOLUTION OF PATIENTS WITH SCLERODERMA AND SEVERE DISTAL ISCHEMIC EVENTS AFTER STOPPING TREATMENT WITH BOSENTAN

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Objectives. Bosentan is effective in preventing recurrence of digital ulcers (DU) due to scleroderma and is proposed for treating distal ischemic phenomena in diseases such as scleroderma or thromboangiitis obliterans. However, duration of treatment is not established. Our aim was to evaluate the outcome of patients with previous or active acral ischemic lesions after discontinuation of bosentan.
Material and method. A multidisciplinary hospital committee evaluated the indication for maintaining bosentan as a treatment and secondary prevention of severe acral ischemic lesions (DU, acral ulcers and digital ischemia) in a series of patients with scleroderma and other immune-mediated diseases. Patients in whom bosentan was stopped were monitored per protocol in a consultation specialized in the treatment of these diseases.
Results. Treatment was stopped in 10 patients: 9 with scleroderma (8 diffuse and one sine scleroderma) and 1 with unspecified systemic vasculitis with underlying hypercoagulable state. Mean time of treatment with bosentan before interruption was 71.4 months (range 15-108). Baseline treatment after discontinuation of bosentan: pentoxifylline (9), calcium channel blockers (7) aspirin (6), misoprostol (2), enalapril (2), tadalafil (1) fluoxetine (1), simvastatin (1) and anticoagulants (1). Four patients (40%) had acral ischemic lesions at the time of interruption: two had DU (mean number 2) and 3 had leg ulcers. After bosentan cessation, 7 patients (70%) had acral ischemic lesions (persistence or worsening of previous lesions and development de novo), 6 of them (60%) required at least one hospital admission for intensive treatment with intravenous iloprost (mean time to iloprost 3.1 months). Reintroduction of bosentan was authorized in 5 patients (50%), an average of 4.6 months after cessation. At restart, 4 patients had DU (mean number 6'7), 3 had ulcers in the legs and/or feet and 1 had digital ischemia; after a mean follow-up of 7.4 months, all of them improved (mean number of DU 1.2), with complete healing in 2 cases (40%). After a mean follow up of 8 months, 2/5 patients who remained without bosentan (40%) had acral ischemic lesions, consisting of DU in both cases (mean number 2), and multiple feet ulcers in one of them (worsening of previous).
Conclusions. Discontinuation of bosentan in patients with scleroderma and severe previous or active acral ischemic phenomena was associated with a high rate of recurrent lesions, which were extensive in most cases.

PS143 BOSENTAN TREATMENT OF DIGITAL ULCERS RELATED TO SYSTEMIC SCLEROSIS

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Microangiopathy is the main histopathologic feature that is early detectable in the course of SSc and digital ulcers are a major complication which influences the personal and professional life of patient. DU is painful, heals slowly,is difficult to treat and often require hospital based treatment. Bosentan has recently been proved to be efficacious for the prevention of new digital ulcers. Over the last 10 years controlled trials have shown clear benefits in the use of prostanoids. Objectives: to assess the variation of digital ulcers number in SSc patients receiving a combined therapy with prostanoids (Iloprost) and endothelin receptor antagonist (Bosentan) Methods: Data were collected retrospectively from patients with DU, with and without pulmonary arterial hypertension, who were initiating bosentan and prostanoid's therapy in 2004 (8 patients), in 2005 (6 patients), in 2006 (4 patients), in 2007 (10 patients),in 2008 (10 patients) and followed until December 2012. Relevant measures included number of DU, occurrence of new DU, overall DU clinical status: improved, stabilized, and worsened. We explored associations of disease subset, antibody profile, organ involvement, season, time interval after onset of Raynaud's phenomenon with development of DU and we describe potential risk factors for DU. Results 38 patients (29 F and 7 M) with SSc and DU were included. PAH was also present in 7 patients (18,4%). At the start of combined therapy (bosentan + iloprost), the median number of DU was 3.0. More Digital Ulcers were present at the end of the cold season from February to May (p 0,036). 32 patients (84,2%) improved, in these patients digital ulcers healed within an observational period of 2,80 months (min 1,max 6 months), 3 patients (7,8%) stabilized, 3 patients (7,8%) had soft tissue infection requiring antibiotics, followed by gangrene and finally by surgical amputation. At 24° month of combined therapy 24 patients (63,1%) did not develop any new DU, after the follow-ups at December 2012: 3 patients were died for PAH, only 2 pts (7,2%) had active digital ulcers and only Diffuse SSc, SCL-70 and lung fibrosis are significantly associated with DU.

PS144 FUNCTIONAL VASCULAR ABNORMALITIES IN SYSTEMIC SCLEROSIS (SSC) MIGHT BE USEFUL FOR DISEASE SUB SETTING:A LASER SPECKLE CONTRAST STUDY

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Vascular involvement is a key feature of Systemic sclerosis (SSc) and involves both the micro and macrovasculature. Vascular changes are central in the disease's pathogenesis and the assessment of vascular involvement has a prognostic value, therefore vascular assessment has a pivotal significance, both for research and clinical purpose. A non invasive technique to monitor cutaneous vascular function is the response to a physiological challenge using laser speckle contrast imaging. The aim of our study was to evaluate occlusive hyperemia test in 51 consecutive SSc patients as compared to 30 healthy subjects and 22 primary Raynaud's patients (PRP) (LeRoy and Medsger).

SSc patients were divided in limited cutaneous (lc-SSc=6), diffuse cutaneous SSc (dc-SSc=29) and very early SSc (16), according to authoritative sources.Cutaneous blood flow was measured using a high frame rate LSkI (Pericam PSI system, Perimed, Jarfalla). The occlusive/ischemic test was performed by inflating for 4 minutes a cuff placed on the left arm to 30 mm Hg above the systolic pressure. The recovery time (time needed to recover the basal flux after occlusion in seconds), the peak flux (hyperemic peak reached after occlusion) and the area under the hyperemic curve were recorded.

Correlation between clinical data and laser measurements were performed by non parametric tests and contingency tables for cathegorical variables (Stat-View, SAS). In view of the high number of comparisons involved, only p values equal or below 0,01 were considered significant. A statistical significant difference in peak flow was outlined between PRP subjects and healthy subjects (475 vs 255 %) and between PRP subjects and SSc patients (475 vs 231%) (p>0,0001). Furthermore, the area under the post-ischemic hyperemic curve (AUC), was statistically higher in PRP as compared to SSc (156 vs 69 p = 0,0023). Within SSc subjects, a statistical significant difference was detected in the hyperemic peak flow between very early SSc and established SSc (432 vs 139% p = 0,0003). A statistical significant difference in the area under the curve was outlined also between early and late pattern at capillaroscopy (129 vs 44 p=0,0043). Moreover a correlation between capillary density and AUC was unveiled (rho=0,49, p = 0,0005).

These data show a different pattern of vascular involvement in early SSc as compared to established disease that mirror capillaroscopic changes. In this context, functional features of early and established disease seem to be the physiologic counterpart of abnormalities detected by capillaroscopy. Functional abnormalities might be useful for disease sub-setting.

PS145 NAILFOLD CAPILLAROSCOPY BY DIGITAL USB-MICROSCOPE: AN INEXPENSIVE AND EASY METHOD FOR IDENTIFYING SCLERODERMA PATTERN

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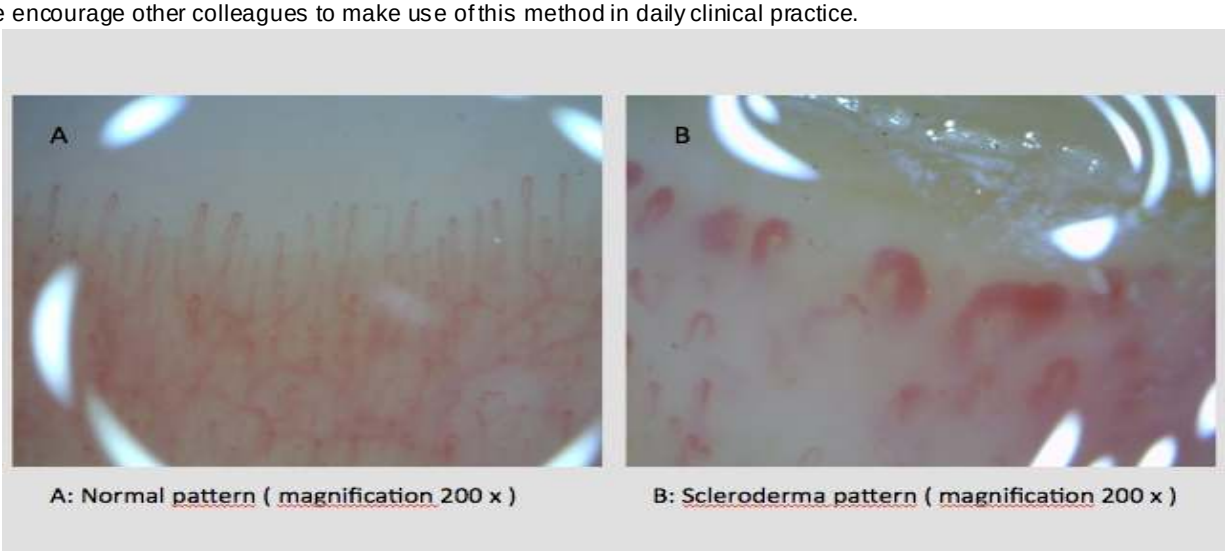
Background: Nailfold capillaroscopy (NFC) is a well established method for identifying microvasculopathy in scleroderma patients [1,2]. NFC has gained an important role as a tool to differentiate between primary and secondary Raynaud phenomenon (RP). The classification criteria for systemic sclerosis (SSc) are currently under revision, and NFC may become crucial for the early diagnosis of SSc [3].
Videocapillaroscopy is the current gold standard for screening patients with possible scleroderma pattern [1,4].
The digital USB-microscope is similar to the Videocapillaroscope. The price is less than 1500 $, software included.
The aim of our project was to identify scleroderma-pattern in patients formerly classified as Undifferentiated connective tissue disease (UCTD) by using a digital USB-microscope.
Method: Our rheumatology outpatient clinic in Southern Norway serves a population of 300 000. We reviewed the electronical medical records from 2003 to 2013 of all adult patients initially diagnosed as UCTD (n=228).
Patients who had been re-diagnosed with other diseases were excluded (n=110).
UCTD-patients without anti-centromer/anti-SCL-70 and RP were also excluded (n=75).
Eventually we classified 3 subgroups for NFC investigation (n=43):
1. Patients who already had been re-diagnosed as CREST or SSc (n=11).
2. UCTD-Patients with positive anti-centromer/anti-SCL-70 antibodies and RP (n=18).
3. UCTD-Patients with positive anti-centromer/anti-SCL-70 antibodies, without RP (n=14).
A digital USB-microscope (Dino-Lite AM-413HNT) with high magnification (200x) was used.
This small handheld device, with an inbuilt camera is connected to a computer with an USB-port.
As standard we evaluated capillary density, capillary architecture, number of giant capillaries, microhemorrhages and signs of neoangiogenesis.
We registered the specific scleroderma pattern (i.e. early-active-late)[4].
All investigations were performed by one investigator (HB).
Time spent per patient (8 fingers): 10-15 min.
Results: Our final studygroup contained 43 patients.
In the first subgroup, scleroderma-pattern was identified in 11/11 patients (100%).
In the second subgroup, scleroderma pattern was identified in 13/18 patients (72.2%) and registered as early:5, active:5, late:3, respectively.
As expected, scleroderma pattern was not identified in any of the 14 patients in the third subgroup.
Conclusion: Nailfold capillaroscopy by digital USB-microscope camera is a simple, fast to perform and inexpensive method.
The pictures are provided with a good resolution and are easy to interpret.
We find this method suitable for identifying vasculopathy in assessing patients diagnosed with UCTD.
Our findings support recent reports [5], though further investigations are needed.
We encourage other colleagues to make use of this method in daily clinical practice.



A: Normal pattern (magnification 200 x) B: Scleroderma pattern (magnification 200 x)

PS146 MICROCIRCULATORY EFFECTS OF ILOPROST ON NEW DIGITAL ULCERS IN PATIENTS WITHSYSTEMIC SCLEROSIS

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Vascular involvement plays a decisive role in SSc pathogenesis; it is responsible of some important clinical manifestations of the disease; more frequently Raynaud's phenomenon and digital ulcers (DU) with a deep impact on patients' quality of life.Nailfold capillary microscopy is an important non-invasive tool for clinicians studying microvascular abnormalities in SSc. Objectives: the aim of the study was to evaluate the effects of iloprost, by nail fold capillaroscopy, on the microvascular damage of SSc patients with new digital ulcers. Methods: we included in the study 14 (12 F-2 M) unselected consecutive pts with SSc admitted in our unit during 2012 for new digital ulcers. They had mean age 51.2 years (range 13-84), disease duration 12.2 years ± 7.5 (range 1-24). All met the preliminary American College oh Rheumatology classification criteria for SSc. And according skin cutaneous subsets: 10 pts with Limited cutaneous SSc,, 4 with Diffuse cutaneous SSc. Nail fold capillaroscopy was performed using a Videocap 3.0 (DS Medica) with magnification 200x at study baseline (T0) and every 3 months (T1) and 6 months (T2).All the patients were treated with intravenous iloprost (40 µg/ day) in cycles of 5 consecutive days and one intravenous infusion every 14 days. Results Active digital ulcers healed in all 14 patients within an observational period of 2,80 months (min 1,max 6 months).At baseline (T0) the late NVC pattern was present in 3 pts (21,5)%),the active pattern in 8 pts (57%) and the early pattern in 3 pts(21,5%).At the end of the follow-up (T2) the number of capillaries/mm was higher than To (7,83±0,38 vs 6,71±0,52 mm)) 1 pts shifted from the late to the active pattern. At T1 we observed a statistically significant progressive increase of capillaries /mm and progressive increase of capillary ramifications Conclusion these results suggest a reduced progression of the microvascular damage together with larger extent of reactive neo-angiogenesis.

PS147 SURGICAL TREATMENT OF SCLERODERMA – RE-THINKING THE ROLE AND TIMING OF PERIPHERAL SYMPATHECTOMY IN THE HAND

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While a multitude of therapeutic options exist for ischemic ulcers in scleroderma, peripheral sympathectomy surgery is frequently offered late in the disease process. The purpose of the present study was to critically analyze the results of peripheral sympathectomy in patients with a confirmed diagnosis of scleroderma.

A retrospective analysis of all scleroderma patients who underwent peripheral sympathectomy between January 1, 2003 and December 31, 2012 at Stanford University Medical Center was performed. These patients underwent stripping of the adventitia to the radial and ulnar arteries in the wrist, the radial artery in the dorsal hand, and the superfical arch and common digital arteries in the hand. Vascular bypass was performed as indicated. Parameters included patient age, gender, length of follow-up, presence of preoperative pain and/or digital ulceration, number of digits affected, duration of symptoms prior to surgical intervention, number and type of surgical procedures after peripheral sympathectomy, rate of symptomatic (pain) improvement, rate of ulcer healing, and rate of postoperative complications.

A total of 15 patients (one male and 14 females) with a mean age of 49.5 years (range, 33 to 68 years) were included in the study. Peripheral sympathectomy was performed in all patients (23 hands). Pain improvement/resolution was seen in 21/23 hands (91.3 percent). Digital ulcers healed in all patients with only 2 patients (2 hands; 12.5 percent) requiring surgical intervention for ulcer recurrence. Minor complications were seen in 6 hands (26.1 percent); none of which required surgical intervention.

Peripheral sympathectomy is a well-tolerated procedure in scleroderma patients and is associated with a favorable outcome with predictable pain relief and ulcer healing in the majority of patients. The notion to offer peripheral sympathectomy only after failed conservative treatment should be re-considered, as early surgical intervention may not only improve symptoms such as pain but may also delay the deleterious soft tissue findings seen in scleroderma by improving perfusion to the hands.

PS148 INTRAVENOUS ILOPROST TREATMENT SIDE EFFECT PROFILE IN PATIENTS WITH DIGITALULCERS DUE TO SYSTEMIC SCLEROSIS

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OBJECTIVES: Digital ulcers due to systemic sclerosis is an important cause of morbidity . This condition is treated with intravenous iloprost .But with this treatment side effects are commonly seen. In this study we wanted to report side effects occurring during iloprost use in our clinic.

METHODS: 29 patients (7 Male/ 22 Female) with ischemic digital ulcer due to systemic sclerosis are included in the study. All of the patients are given intravenous iloprost. Side effects occurring during the treatment are recorded in their patients files. Data is evaluated retrospectively.

RESULTS:Mean age of patients who received treatment is 43,9 ± 12,9 years. Nausea is observed in 4 patients (13.7%) , vomiting in 3 patients(10.3%), headache in 6 patients (20.6%) , and hypotension in 4 patients (13.7%). Two patients' treatments are stopped because of the side effects. In one patient the side effect was serious vomiting and in the second one it was hypotension and headache that required the treatment to be stopped.

CONCLUSION: Although side effects of intravenous iloprost treatment in patients with digital ulcers due to systemic sclerosis is very common, most of the patients continued their treatment

PS149 DEVELOPMENT OF A NEW SCORING SYSTEM TO ASSESS DIGITAL ULCERS IN PATIENTS SUFFERING FROM SYSTEMIC SCLEROSIS

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Introduction: Digital ulcers are a common complication in patients suffering from systemic sclerosis. Whereas pain and impairment of the hand function can be judged using standardized questionnaires, no validated tool exists to assess the severity of the digital ulcers. The aim of our study is the development of a new scoring system to assess the severity of digital ulcers in patients suffering from systemic sclerosis.
Methods: In an interdisciplinary collaboration between dermatologists and rheumatologists, we developed a scoring system to assess the severity of digital ulcers in standardised manner. The assessment includes several clinical features (medical history, current therapy, fingertip rewarming time, photographic assessment) and the localization and extension of digital ulcers. Size and depth of digital ulcers were assigned to a defined value. Altogether the sum of the parameters results in a final score.
Results: Initially 10 patients (8 female, 2 male, mean age 54 years) with systemic sclerosis suffering from digital ulcers were assessed with an exploratory score. The average number of digital ulcers was 3 per patient with a mean digital ulcer score of 4.1. The mean completing time for the score was 7 minutes.
Conclusion: The data show that it is possible to develop a digital ulcer score which considers clinical patient data supporting an improved measurement of the severity of digital ulcers. Feasibility needs consideration, therefore the assessment of the ulcers and the calculation of the score requires a system which is fast and easy to perform in a standardised manner.

PS150 QUANTITATIVE ANALYSIS OF NAILFOLD CAPILLARY MORPHOLOGY AND CORRELATION WITH RAYNAUD'S PHENOMENON IN PATIENTS WITH FIBROMYALGIA

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Background: Nailfold capillaroscopy (NFC) has been used to examine morphological and functional changes of microcirculation in connective tissue diseases. It has been demonstrated that NFC patterns reflect the abnormal microvascular dynamics that may play a role in fibromyalgia syndrome (FM).
Objectives: The aim of this study was to determine the NFC pattern in FM and its association with clinical features as like raynoul's phenomenon of FM.
Methods: Sixty four patients with FM and 31 age and sex-matched healthy controls were included for this study. Nailfold capillary patterns were quantitatively analyzed using computerized NFC. Other NFC parameters consisted of capillary number within central 3 mm, deletion score, apical limb width, capillary width, and capillary dimension. Capillary dimension was determined by calculating the number of pixel with Adobe Photoshop. Clinical parameters included tender point count, fibromyalgia Impact Questionnaire (FIQ), arthralgia, headache, raynaud's phenomenon as like numbness or coldness sensation, irritable bowel syndrome, dry eye, and dry mouth.
Results: FM patients had lower capillary number but higher deletion score than health controls on NFC (21.8±2.9 versus 17.3±1.7, $p < 0.05$, 0.7±0.6 versus 2.2±0.9, $p < 0.05$, respectively). Both apical limb width and capillary width were also significantly decreased in FM patients (3.7±0.6 versus 1.1±0.2, 7.5±1.4 versus 5.4±0.5, respectively), indicating that FM patients have the abnormality of decrease in digital capillary diameter as well as capillary density. Interestingly, there was no difference in the capillary dimension on Adobe Photoshop between the two groups, which suggests that length or tortuosity of capillaries in FM patients is increased to compensate diminished microcirculation. Physical function by FIQ showed a weak negative correlation with capillary dimension ($r = -0.248$, $p = 0.048$). However, no association was found between NFC pattern and other clinical parameter.
Conclusion: Using computer-based quantitative system, we identified that FM patients had an altered capillary density and diameter in the digits. Diminished microcirculation on NFC may explain FM symptoms such as peripheral coldness, and might cause the hormonal and biochemical abnormalities in FM pathogenesis.

Key words: Nailfold Capillaroscopy, Fibromyalgia

PS151 OBSERVATION PATIENTS WITH RAYNAULD SYNDROM IN SLOVAK POPULATION INCLUDE CAPILLAROSCOPY FINDINGS, USING CAPILLAROSCOPY FOR SEARCHING PATIENT WITH EARLY STAGE OF SCLERODERMA

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Introduction: Systemic sclerosis (SSc) is a connective tissue disease characterized by excessive collagen deposition and by vascular hyperactivity and obliteration of microvasculopathy. Raynaud phenomenom appears years before other scleroderma patterns. The capillaroscopy findings and their changes could help us to define the diagnosis of scleroderma in early stages or decide of therapy. The modified Scleroderma Health Assessment Questionnaire (SHAQ) could be important to monitoring activity of disease.
Methods: We evaluate 97 patients with systemic sclerosis, 80,4 % of patients with limited SSc (lSSc), 10,3 % of patients with CREST syndrome, 7,2 % of patients with diffuse SSc (dSSc) and 2,1 % of patient with overlap syndrome with SSc. We monitoring skin score by mRodnan, presence of organ involvement, presence of antibodies include Scl70 and anticentromeric antibodies. We observed HAQ-DI and SHAQ and capillaroscopy examination.
We apply capillaroscopy to 97 patients with SSc and 25 pat. with only episodic Raynaud phenomenon too.
Results: In observation patients with dSSc has higher frequency of pulmonary hypertension (28.6 % vs. 12.8 % in lSSc patients and vs. 10 % in CREST), lung involvement control by DLCO – 85.7 7% in dSSc vs. to 67.1 % in lSSc, although fibrosis detected by CT was similar. Activity score was higher in patients with dSSc (4,41), vs 2,33 in patients with lSSc. Skin score modifying by Rodnan was higher than 14 in 87.5 % in patients with dSSc, to 16.7 % in patients with lSSc and 40 % in patients with CREST. SHAQ score was a little bit higher in patients with dSSc (1,6) and CREST (1.67) to lSSc (1.43).
In all patients with SSc we find picture of SSc in different stages. In 7 patients with episode of Raynaud phenomenon only during winter we found early SSc changes (in number of capillaries, dilatation, megacapillary and some haemorhagies).
Conclusion: Monitoring clinical findings, organ involvement is important in patients with SSc, for therapy and prognosis. Observation of skin score, activity score, HAQ-DI and SHAQ score could help to control of activity and prognosis of patients with SSc. Capillaroscopy findings could help us to define stage of scleroderma and to find early stages of disease.

PS152 COMPUTERIZED NAIL-FOLD VIDEO CAPILLAROSCOPY AND SYSTEMIC SLEROSIS

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Introduction: The computerized nail-fold video capillaroscopy (CNVC) is the gold standard in the exploration of Raynaud phenomenon (RP). It permits to determine with a tall sensitiveness a large specificity systemic sclerosis (SSc) not yet identified showing morphological abnormalities of capillaries and rheological disorders. CNVC aimed diagnostic is a non-invasive examination that must be realized not in all unexplained RP but also in all unidentified arthromyalgias, unexplained pulmonary hypertension (PH), undetermined vasculitic leg ulcers, Interstitial lung diseases, aperistaltic esophagus etc ….

Aims : To review the mains manifestations justifying the CNVC and to appreciate its rentability in the SSc diagnosis.

Patients and Methods : We have studied through 200 requests for CNVC the main symptoms which have oriented the physician to SSc suspicion (arthralgia, myalgia, scleroderma, RP… etc)

Results : A 200 requests retrospectively analyzed. Most requests are established to determinate the character organic or not of RP (80%). The other requests (associated or isolated) are digital ulcers (10), digital ischemia (5), familial story of SSc (2), unexplained pulmonary hypertension (5), sever malabsorption syndrome (3), kidney failure (4), primary biliary cirrhosis (5), pruritus (5), syndrome erectile dysfunction (2) and young woman myocardial infraction (1). The common motivations associated are arthralgia (15), myalgias(5), dental alterations (4), muscle weakness (10), erosive esophagitis (5), sever reflux esophagi is (10), dysphagia (14), leg ulcers (1) and morphea (2). The CVNC oriented to the SSc diagnosis in 70% showed typical aspect (mega capillaries, hemorrhage, or rarefaction of capillaries) and was more performed in cutaneous and musculoskeletal symptoms. Nerveless we have identified some cases of SSc thought gastrointestinal (5), ischemic heart disease (1) and PH (1) requests.

Conclusion : CVNC is a no invasive examination, which must be realized not only in all unexplained RP but also- as reported in this work- in arthomyalgias and any others symptoms suggesting SSc We recommend to extend this exploration in each item recognized as potential symptom in SSc. The rentability of CVNC is operator dependant and the multidisciplinary confrontation improve its rentability

PS153 TREATMENT OF DIGITAL ULCERS IN SYSTEMIC SCLEROSIS: REVIEW OF ELEVEN PATIENTS FROM A SINGLE CENTER AND DISCUSSION ON OUTCOME

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BACKGROUND: In systemic sclerosis (SSc), digital ulcers (DU) are debilitating and recurrent complications. Treatment is not dissociable from that of Raynaud's phenomenon (RF), expressing the same microvascular disfunction at different stages.
OBJECTIVES: Clinical characterization of a population of SSc patients with DU, its treatment, complications and outcome.
METHODS: Retrospective analysis of a cohort of 48 SSc patients, follow-up 1999 to 2013. Clinical data were obtained from patient files and disease registries.
RESULTS: DU were detected in 11 patients: four males and 7 females, mean age of 62,4 years (49-79 years). Ten patients had limited type SSc (three had calcinosis) and one had diffuse type scleroderma. Anticentromere autoantibodies (ACA) were positive in 8 patients, anti-Scl-70 antibodies in one patient and antiphospholipid antibodies (APLA) in one. All 11 patients were treated with calcium channel blockers (CCB) for RF. Healing of DU was made with intravenous prostanoid in ten, repeated infusions were required for healing in four patients and for persistent RF in five. Ten patients were treated with bosentan, one patient with APLA experienced recurrence of DU but no digital loss. Alteration of liver function tests (LFT) was present in three patients: one patient with a history of alcohol intake, and two with previous exposure to methotrexate. Antiaggregant therapy was prescribed in ten patients and oral anticoagulants in two patients. Two patients had digital loss and two other patients healed with scars. Patients with digital loss were late presenters. The only patient that required hospitalization for diagnosis presented with pulmonary arterial hypertension (PAH), DU and digital loss; PAH normalized after treatment with bosentan. Five patients required hospitalization for treatment of DU. Two patients are dead: one with massive digestive bleeding; the other of liver failure, he had a history of alcohol intake. One patient is lost to follow-up. Three patients are still professionally active.
CONCLUSIONS: DU in SSc are markers of damage and prognosis, with increased morbidity (hand disability, reduced quality of life) and mortality. Treatment comprises detection of complications, promotion of healing and preventing recurrence. Evidence supports recommendations on standard of care. Intravenous prostanoids and CCB are effective and have the highest level of evidence. Bosentan is recommended to prevent recurrence of DU, improving outcome. In this small series, patients with worse outcomes had longer follow-up and late diagnosis, already with end-organ damage. More recent patients have better results even at older ages, mirroring earlier referral and improved bundles of care.

PS154 EFFECT OF SARPOGRELATE FOR RAYNAUD'S PHENOMENON SECONDARY TO SYSTEMIC SCLEROSIS

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Microangiopathy is one of the primary pathological manifestations of systemic sclerosis (SSc). Raynoud phenomenon (RP) is the most popular clinical sign from initial to chronic phase of SSc. In RP vasospasm and intimal proliferation occur, resulting in a fixed blood vessel deficit. There are many drugs which have been used for RP and reported their efficacy. However, it is insufficient for the treatment of RP, because there are also a number of patients who are intractable to these medications. Sarpogrelate hydrochloride, a selective 5-HT2A receptor antagonist, has various functional mechanisms, such as the inhibitory effects of platelet aggregation, vasoconstriction, form cell formation and vascular smooth muscle cell proliferation. In this study, we evaluated the efficacy of sarpogrelate hydrochloride for the secondary RP in SSc patients. Sarpogrelate hydrochloride statistically improved 10-point Raynaud's Condition Score (3.0 vs. 1.6, p=0.00151) and the coldness of the fingers (49.2 vs. 29.4, p=0.00007) compared to baseline data prior to administration. Then, there were no differences in the pain of fingers, sense of numbness evaluated with VAS and HAQ disability index, respectively.

PS155 CURRENT APPROACH TO DIGITAL ULCERS IN SYSTEMIC SCLEROSIS

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Digital ulcers (DUs) are among the most frequent recurrent vascular complications in patients with systemic sclerosis (SSc). Ischemia in the context of SSc-related vasculopathy is the main pathogenetic mechanism for the development of fingertip DUs. Epidermal thinning, mechanical friction and inflammation contribute for appearance of DUs over bony prominences and in the regions of calcinosis. For successful outcome of treatment of DUs a combination of vasodilators e. g., calcium channel blockers (CCBs), intravenous prostanoid, phosphodiesterase inhibitors, endothelin receptor antagonists and antiplatelet drugs should be administered. In addition local antiseptic care should be provided. In some cases analgetics and antibiotics are required. Impaired hand function and quality of life are major consequences of DUs. In a part of the cases infection of soft tissue or osteomyelitis develop or digit amputation may be indicated. The therapeutic efficacy of CCBs, intravenous prostanoids and endothelin receptor blockers for the treatment of RP and DUs in SSc is proved in randomized clinical trials. The other above mentioned medications such as antiplatelet drugs, antibiotics and local treatment as well as combination therapies are also recommended in these case and are used in the leading scleroderma centers as complex approach is necessary for successful outcome.

PS156 BOSENTAN FOR DIGITAL ULCERS IN PATIENTS WITH SYSTEMIC SCLEROSIS: SINGLECENTER EXPERIENCE

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Background: Systemic sclerosis (SSc), characterized by cutaneous and visceral fibrosis with diffuse vascular pathology, is a complex autoimmune disease and may be complicated by digital ulcers (DU) in up to 50% of cases. Leading to pain, superposed chronic infections, autoamputation, and eventually impairment in hand function, these ulcers pose not only medical problems but psychological and social concerns also become apparent. Although the etiopathogenesis of the disease is not clear, increased endothelin-1 (ET-1) activity is thought to be involved in the pathogenesis of the vascular component. Bosentan, a dual ET-1 antagonist, by binding to ET-A and B receptors, competitively inhibit ET-1 and proved to be an effective treatment option in preventing new DUs in 2 large, multicenter, placebo-controlled studies and in treating current DUs in relatively small series. It also has beneficial effects on micro- and macrovascular hemodynamics and severity of digital fibrosis documented by improvement in venous occlusion plethysmography, flow mediated dilation and modified Rodnan skin score, respectively. Controversies exist in its use in Raynaud's phenomenon secondary to SSc.
Aim:We conducted a retrospective study to investigate the effect of bosentan on DU prevention and healing.
Methods: Between the years 2010-2013, in Ankara University Department of Rheumatology, a total of 26 patients who were diagnosed as SSc, having DUs and using bosentan were included in the study. Diagnosis of SSc was based on subcomittee for scleroderma 1980 criteria of American Rheumatism Association (ARA) and patients were classified as limited or diffuse cutaneous SSc according to LeRoy's classification. Frequencies (%) for categoric variables and means (± standard deviations) for continuous variables were used in descriptive statistics. Health Assesment Questionnaire - Disability Index (HAQ-DI) scores for SSc were used for functional assesment.
Results:4(15,4%) of patients were male and 22(84,6%) were female. Mean age was 49,46(±14,79). Mean disease duration was 8,98(±8,7) years and mean duration of DUs was 2.85(±2.8) years. All patients were given bosentan for a mean of 14(±10,3) months. 8(30.8%) patients were classified as limited and 18(69.2%) as diffuse cutaneous SSc. Under bosentan treatment 7(26.9%) patients had new DUs and all of these patients had diffuse cutaneous SSc. Overall response rate, designated as no new DUs was 73,1%. 12(46.2%) patients needed additional i.v. iloprost under bosentan treatment.
Conclusion: The major limitation of this study was the absence of a control group and a relatively small number of patients. Also the number of DUs was not measured, limiting the ability to see whether a reduction in the number of new DUs did ocur under bosentan treatment, which was the primary end point in RAPIDS-2 trial. In this trial there were no difference in bosentan and placebo arms in terms of development of new DUs and also no difference in two arms in DU healing was found although some smaller series indicate. As a result, bosentan, by inhibiting endothelin-1 in endothelium and subendothelial smooth muscle has a favorable effect on micro- and macrovascular hemodynamics resulting in a decrease in development of new DUs and on fibrosis, which also may be aggravated by endothelin-1. Further preclinical studies shedding light on etiopathogenesis of SSc and larger clinical trials are needed for more definitive treatment strategies.

PS157 MINIMAL CLINICALLY IMPORTANT INVESTIGATIONS IN SYSTEMIC SCLEROSIS

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Objective: The aim of this study was to examine the minimally clinically important investigations for starting immunosuppression in patients with SSc.
Methods: The baseline visits of SSc patients referred to an academically day patient clinic for a two-day health care program between 2009 and 2012 were recorded. This annual program compromised visits to health care professionals and laboratory investigation, HRCT-thorax, lung function, Cardiopulmonary Exercise Test (CPET), echocardiography, ECG, SSc Health Assessment Questionnaire (SHAQ) and Short Form-36 (SF-36). After 2 weeks a multidisciplinary consultation resulted in a change of treatment if appropriate. The change of treatment was divided in start with immunosuppression versus no start with immunosuppression for the analysis. Logistic regression analysis was used to determine the relationship between start and no start with immunosuppression as dependent variable and clinical parameters as independent variables.
Results: Two hundred twenty-six patients participated in the day care program for at least one visit. Their mean age was 54 years, 82% of the patients were female and 73 patients had a diffuse cutaneous SSc. Fourteen patients had a previous autologous haemopoietic stem cell transplantation and were excluded for the logistic regression analysis. Forty-six patients started with immunosuppression after visiting the day patient clinic.
Multivariate regression analysis showed that shorter disease duration, higher MRSS, anticentromere negativity, alveolitis and lower VO2 max of predicted were significantly associated with the start of immunosuppression.
Conclusion: Autoantibodies, MRSS, HRCT-thorax and CPET are minimally clinical important investigations that are advocated in clinical evaluation.

PS158 COMBINED PULMONARY FIBROSIS AND EMPHYSEMA (CPFE) IN SYSTEMIC SCLEROSIS

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Background: Combined pulmonary fibrosis and emphysema (CPFE) is a recently described syndrome, in which emphysema in upper lung zones coexist with pulmonary fibrosis in lower lobes in the same individual. These patients have a characteristic lung function profile, with unexpected subnormal dynamic and static lung volumes, contrasting with a significant reduction of carbon monoxide diffusing capacity (DLCO) and exercise hypoxemia. CPFE has recently been described in association with connective tissue disease

Objectives: The aim of this study was to describe the recently individualized syndrome of CPFE in a population of patients with systemic sclerosis (SSc).

Methods: In this multicenter case-control study, we retrospectively investigated data from patients with SSc who also had CPFE. The demographic characteristics of the patients, the results of pulmonary function testing, and treatment, and the outcomes of the patients were analyzed. For each patient with CPFE and SSc, two patients with SSc and pulmonary fibrosis without emphysema were included.

Results: 31 SSc patients with CPFE were identified and paired with 62 controls exhibiting only pulmonary interstitial lung disease. In the Cochin hospital cohort, CPFE prevalence was 3.5% of SSc patients, and 8.2 % of those with interstitial lung disease. CPFE patients with SSc were more likely to be male (77% vs 16%, $p<0.0001$), smokers (84% vs 37%, $p<0.0001$), and to have a limited SSc (52 vs 21% $p< 0.01$) than control SSc patients. At diagnosis, pulmonary function testing revealed a marked decrease in DLCO (39% vs 50% of theoretical value, $p<0.0001$) in CPFE patients compared to controls, despite similar lung volumes (total lung capacity 78 vs 80%, forced vital capacity 77% vs 78%). Autoantibody profiles did not differ significantly between SSc patients with or without CFPE. Over follow up, CPFE patients with SSc more frequently developed pulmonary hypertension (52 vs 10%, $p<0.0001$), had more frequent unscheduled hospitalisation (45% vs 11%, $p<0.01$) and showed decreased survival ($p<0.02$ by Log rank test analysis) as compared to those with SSc without CFPE.

Conclusion: CPFE is a distinct pulmonary manifestation within the spectrum of lung diseases occurring in patients with SSc. SSc patients with CPFE more frequently develop pulmonary hypertension and show increased morbidity and decreased survival as compared to those with pulmonary fibrosis without emphysema.

PS159 DYNAMICS OF DISEASE SEVERITY INDEX AND ESCSG ACTIVITY INDEX IN SSC-ASSOCIATED ILD DURING LONG-TERM FOLLOW UP

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Background: The course of SSc-ILD is not well estimated in prospective long-term study
Objectives: to evaluate alterations total index severity of disease and EScSG activity index in patients with SSc–ILD during 5-year follow up.
Methods: it was a prospective longitudinal study involving 77 pts (4 were men) with SSc-ILD. The mean age was 46±13 years. The mean time between two evaluations was 58,9±12 months. Pts. were divided into 3 groups based on the dynamics of ILD by HRCT: 1 group – pts with improvement of ILD (n=16), 2 –pts without any dynamic of ILD (N=39); 3 – pts with progressive of ILD (n=22). We examined the total severity index of disease (scores of organ systems are combined in one score) and Europen Scleroderma Study Group (EScSG) activity index at baseline (point 1, P1) and through the 5 years (point 2 (P2) in all pts.
Results: the mean scores of EScSG activity index in all pts and in the groups 1,2 were normal and haven't got any changes, however increased in group 3 (2,4±1,52 vs 3,25±1,97) in follow-up (p>0,05) respectively. We found a statistically significant difference the mean scores of EScSG activity index between the group 3 and groups 1, 2 in the P2 (p=0,004 and p=0,03 respectively). The mean score of total severity index in all pts and in the groups 1,2 didn't change and were: 6,5±2,5 vs 6,9±2,3; 5,75±3,1 vs 5,5±2; 6,7±2,3 vs 6,3±2,1 but increased in group 3 (6,7±2,7 vs 8,1±2,3) (p>0,05) in P1 and P2 respectively. Total severity index in group 3 was significantly higher than in group 1 (p=0,002) in P2.The mean score of EScSG index correlated with total severity index in the P1 and P2 as all pts as in the group1 and 2 (0, 57 and 0,53; 0,51 and 0,37; 0,67 and 0,71 (p<0,05) respectively). However we didn't find any correlation between them in the group 3 (0,64 and 0,18 p>0,05) in follow-up.
Conclusion: after five-years follow up the EScSG activity index and total severity index of disease in pts with progressive of ILD were higher than in pts without progression of ILD.

PS160 THE PREVALENCE AND CLINICAL RELEVANCE OF INTERSTITIAL LUNG DISEASE ON THE HIGH-RESOLUTION COMPUTED TOMOGRAPHY (HRCT) IN EARLY SYSTEMIC SCLEROSIS PATIENTS

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Purpose: To determine the prevalence of interstitial lung disease (ILD) in early SSc patients and to compare the clinical differences between those SSc patients with and without ILD.

Methods: 103 SSc patients from an inception SSc cohort of newly diagnosed SSc (disease duration from NRP to study entry were within 36 months) seen at the Rheumatology clinic, Chiang Mai University Hospital from January 2010 to June 2013 were identified. 83 (80.6%) had HRCT performed within 3 months of the study entry were included. Data abstracted include baseline clinical characteristics, laboratory investigations and HRCT findings. The HRCTs were read by one experienced chest radiologist. Comparing between patients with and without ILD were made using Chi-square test, Fisher's exact test, Student's t test and Mann-Whitney U test, as appropriate.

Results: Of the 83, mean (SD) age was 52.8 years (7.8), and median disease duration was 8 months (8-36). Median (range) duration from HRCT performed to study entry was 0 month (0-3). 47 (56.6%) were female and 63 (75.9%) were classified as diffuse cutaneous SSc (DcSSc). There were patients with dyspnea, cough, NYHA class II, GERD symptoms, and positive anti Scl-70 of 43.4%, 24.1%, 62.6%, 37.3%, and 80.7% respectively. Mean (SD) values were: Modified Rodnan's skin score [MRSS] 20.5 (11.0), Hb 12.5 (1.7), Cr 0.9 (0.3), % LVEF 67.6 (8.8), estimated systolic pulmonary artery pressure [sPAP] 31.9 (9.6). Median (range) values were: ESR 33 (1-116), CK 236 (32-3521). Current medications were: 38.6% low dose prednisolone, 27.7% colchicine, 24.1% chloroquine, 19.3% cyclophosphamide, 12% methotrexate, and 7.2% azathioprine.
62 (74.7%) were classified as having ILD determined by HRCT including 49 (59%) NSIP and 13 (15.7%) UIP. 7 (8.4%) had sPAP >=45 mmHg determined by echocardiography. There were no significant differences between early SSc patients with and without ILD with respect to age, gender, disease duration, cough, NYHA class, GERD, MRSS, ESR, CK and positive anti Scl-70. However, early SSc with ILD had higher proportion of DcSSc (82.2 % vs. 57.7%, p=0.02), dyspnea (51.6% vs. 19%, p=0.009), and less methotrexate used (6% vs. 28% p=0.014).

Conclusions: ILD is a common finding in our early SSc populations which is more prevalent in DcSSc patients with dyspnea. However, more than half of ILD patients were asymptomatic. Therefore, baseline HRCT of chest should be performed in SSc patients as early as possible to determine and promptly treat lung complication.

PS161 PROGNOSTIC FACTORS OF FUNCTIONNAL OUTCOME IN SYSTEMIC SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG DISEASE

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Introduction
Interstitial lung disease (ILD) is a frequent complication of systemic sclerosis (SSc). It is one of the first causes of mortality in this disease. ILD screening is mandatory at the initial evaluation and a close follow-up is necessary. However, the outcome and the factors influencing the evolution of ILD are still a matter of debate in SSc.
Patients and Methods.
We retrospectively collected all pulmonary function tests (PFT) performed in 75 SSc patients with ILD with a mean follow up of 5 years and a median number of 5 PFT. FVC and DLCO evolution was modelled using a linear mixed model with random coefficients. Clinical, biological and HRCT data at baseline were collected. HRCT were analyzed using the Wells score and the Goh staging system.
Results.
Seventy five SSc patients (57 females ; 23 diffuse cutaneous SSc) with ILD (18 extensive forms according to Goh) were included. The linear mixed model with random coefficients showed that DLCO significantly decreased of 1.45±0.34%/yr while FVC remained stable. Multivariate analysis, patients with NYHA III/IV dyspnea, age<50yrs and/or less than 50% of ground glass opacities had a lower initial FVC. CRP>10 mg/L was the sole significant and independent parameter associated with a higher decrease in FVC over time. For DLCO, presence or past history of digital ulcer, grade 1 ILD and initial DLCO>70% were significantly associated with a higher decrease of DLCO over time. SSc subtypes and ILD extension had no influence on the FVC and DLCO outcomes.
Conclusion.
Modeling PFT outcome in SSc-associated ILD is interesting to find prognostic factors. Initial CRP, refelecting IL-6 production, appears as an important prognostic factor for FVC evolution overtime. Conversely, SSc subtypes and ILD extension were nor prognostic factor for PFT evolution in our study.

PS162 INTERSTITIAL LUNG DISEASE IN SOUTH AFRICANS WITH SYSTEMIC SCLEROSIS

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Background: Interstitial lung disease (ILD) is one of the leading causes of death in systemic sclerosis (SSc). It has been poorly characterized in SSc patients in Sub-Saharan Africa. The aim of the study was to describe the associations of ILD in SSc patients with baseline demographic, clinical and laboratory features.

Methods: A retrospective review of case records, from 1992 until 2012, of patients with SSc attending a tertiary Connective Tissue Diseases Clinic. SSc ILD was defined based on features of ILD on high-resolution computed tomography (groundglass opacification, reticulonodular opacities, honeycombing, consolidation, or traction bronchiectasis) with/without restrictive pulmonary function tests. Comparisons between ILD and non-ILD groups at presentation were performed using Fisher's exact test, and Student's t-test where appropriate. A p value <0.05 was considered significant.

Results: Of 151 patients evaluated, 60 (40%) had ILD. The female:male ratio was 9:1 in the non-ILD group and 5:1 in the ILD group (p=0.222). The majority of patients were Black in both groups (>85%). The mean (SD) age at diagnosis was 42.7 (12.1) years and 45.0 (13.4) years for patients with ILD and non-ILD, respectively (p=0.142). Univariate analysis is displayed in the table below.

Variable	ILD (n=60)	Non-ILD (n=91)	p-value
Mean duration (range)	6.13 years *(0-20)*	3.95 years *(0-20)*	0.009
Diffuse:limited disease	6:1	1.2:1	<0.0001
Gold mining history (%)	5 *(8.3)*	1 *(1.1)*	0.037
Cough (%)	21 *(35.0)*	15 *(16.5)*	0.005
Dyspnoea (%)	27 *(45.0)*	24 *(26.4)*	0.009
Bibasal crackles (%)	28 *(46.7)*	10 *(11.0)*	<0.001
Positive ANA (%)	57 *(95.0)*	77 *(83.5)*	0.039
Scl-70 antibodies (%)	13 *(22.8)*	12 *(15.6)*	0.002
Anti-centromere antibodies (ACA) (%)	0 *(0.0)*	10 *(13.0)*	0.002
Nucleolar ANA pattern (%)	13 *(22.8)*	28 *(36.4)*	0.002

On multivariate analysis the independent predictors of ILD were: disease duration (p=0.007); diffuse disease (p<0.0001); gold mining history (p=0.026); dyspnoea (p=0.01); and bibasal crackles (p<0.001).

Conclusion: ILD in South African SSc patients is common. There should be a high index of suspicion for ILD in SSc patients presenting with a gold mining history, dyspnoea, cough and bibasal crackles. Disease process appears to be driven by the diffuse subtype and anti-Scl-70 antibodies. Limited subtype, ACA and nucleolar anti-nuclear antibody (ANA) patterns may have a protective effect.

PS163 COMPARISON OF INTERSTITIAL LUNG DISEASE CT INDEXES AND PULMONARY FUNCTION VALUES IN SISTEMIC SCLEROSIS PATIENTS

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Background: Pulmonary fibrosis is the main death cause in systemic sclerosis (SSc). Lung involvement is assessed with spirometry (which evaluates pulmonary function) and chest Computed Tomography (CT) scan (that identifies interstitial fibrosis). FVC < 70 % and DLco < 75 % are considered pulmonary functional values associated with a remarkable interstitial lung disease (ILD) and, therefore, they are adverse prognostical indicators. Both qualitative and semiquantitative radiologic ILD assessment have a considerable interobserver variability. To overcome this problem quantitative scores (called CT indexes) correlating with ILD extent detectable on chest CT have been proposed.
The aims of this work are to find: a) whether there is a correlation between pulmonary functional tests and CT indexes , b) which CT indexes have the best performance in discriminating patients with a pulmonary function indicative of an extensive ILD.

Methods: Chest TC and spirometry of 90 SSc patients (31 from Parma, 30 from Turin, 29 from Piacenza) meeting ACR criteria were performed. Digital Imaging and COmmunications in Medicine (DICOM) images of chest CT were processed with OsiriX (a free and user-friendly DICOM-viewer) in order to obtain patients' CT indexes. The Spearman rank test was used to verify the correlations between CT indexes and spirometrical measures. CT indexes discriminative ability was verified using ROC analysis. A p-value < 0.05 was considered statistically significant.

Results: Whole lung kurtosis (tKurt) is the best FVC correlating CT index (rho = 0,623; p < 0,0001). Parenchymal lung skewness (nSkew) is the best CT index correlating with DLco (rho = -0,582; p < 0,0001). ROC analysis showed that tKurt = 6,32 can discriminate very well patients with FVC < 70% (sensibility 80,0%, specificity 74,3%). Similarly nSkew = 2,2 distiguishes subjects with DLco < 75% (sensibility 85,7%, specificity 52,2%).

Conclusions: Spirometry and CT indexes correlations are consistent with literature. The identification of CT index values corresponding to spirometric cutoff indicative of a considerable limitation of lung function makes TC ILD quantification useful in establishing SSc patients prognosis. Obtaining CT indexes with a free and user-friendly software can contribute to widespread in clinical practice this new SSc ILD assessment.

PS164 SYSTEMIC SCLEROSIS INTERSTITIAL LUNG DISEASE EVALUATION: COMPARISON BETWEEN SEMIQUANTITATIVE AND QUANTITATIVE CT ASSESSMENTS

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Background: The pulmonary fibrosis extent in sistemic sclerosis (SSc) patients has a crucial prognostic value. The gold standard to detect an interstitial lung disease (ILD) is the chest Computed Tomography (CT). ILD can be estimated through semiquantitative radiological scores and quantitative methods. The first ones are time consuming and they have a considerable inter / intra-observer variability. Quantitative scores are based on the detection of the parameters of the distribution of lung attenuation (also called CT indexes) which can be obtained only by using expensive and not so much user-friendly softwares.
The main aim of this work is to investigate whether a DICOM-viewer open-source software (OsiriX) can obtain CT indexes correlating with a semiquantitative score performed by an experienced radiologist. Secondary objectives are: to evaluate the discriminative ability of CT indexes in identifying patients with severe pulmonary involvement (according to radiologist's opinion), and to establish which method (quantitative vs semi-quantitative) takes more time.

Methods: ILD detectable on chest CT of 32 patients with SSc was assessed with a radiological semiquantitative score. The same CTs were blindly processed by a rheumatologist using OsiriX to obtain the distribution parameters of lung attenuation. The semiquantitative score and the CT indexes were correlated through the Spearman rank test, the discriminative ability of CT indexes was verified using ROC curves and the Student t test was used to verify if there was a difference between the execution times of the two ILD assessment methods.

Findings: The majority of CT indexes obtained showed a statistically significant correlation of moderate degree ($0,41 < r < 0,6$) with the semiquantitative assessment (p-value < 0.05). The lung attenuation distribution parameter with the best discriminative ability was the standard deviation of attenuation values belonging to the part of the lung without any radiological evidence of fibrosis - nSdev (AUC = 0.976, 95% CI 0.843 to 1.000, p-value <0.0001). The best nSdev cut-off value that identifies patients with severe pulmonary involvement was 113.2 HU. Semiquantitative assessment was more time consuming than the quantitative method (291 vs. 102, p-value $< 0,0001$).

Interpretation: CT indexes correlating with a radiological semiquantitative ILD assessment can be obtained in a short time with OsiriX. Moreover there is a cutoff of one the CT indexes (nSdev) that can discriminate very well patients with a unfavorable prognostic pulmonary involvement.

PS165 ENHANCED ACTIVATION OF TGFBETA-RELATED SIGNALING MOLECULES IN MONOCYTES FROM HEALTHY AFRICAN AMERICANS AND SSC ILD PATIENTS

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Background. We reported recently that healthy AA monocytes share abnormalities with Scleroderma-associated Interstitial Lung Disease (SSc ILD) monocytes including low caveolin-1 levels. Because the level of TGFbeta is higher in the blood of healthy AA than in healthy C and because TGFbeta treatment decreases caveolin-1 levels in healthy C monocytes, here we have determined whether TGFbeta signaling is activated in SSc ILD and healthy AA monocytes, and is regulated by caveolin-1.
Methods. The study was approved by the university's IRB for Human Subject Research. Monocytes were isolated from the blood of SSc ILD patients and healthy donors by negative selection. The caveolin-1 scaffolding domain (CSD) peptide was used to restore caveolin-1 function to cells deficient in caveolin-1. SSc ILD patients fulfilled the ACR criteria for the classification of systemic sclerosis. Monocyte migration was assayed in Multiwell Chemotaxis Chambers using cells treated with CSD or control peptide. Smad2/3, pSmad2/3, ERK, pERK, and caveolin-1 levels were determined by Western blotting and immunostaining.
Results. We observed that ERK activation is enhanced in SSc ILD monocytes and in healthy AA monocytes compared to healthy C monocytes, while other MAP kinases (JNK and p38) are activated only in SSc monocytes. pSmad2/3 and total Smad2/3 were expressed at very high levels in SSc monocytes, but were expressed only at low levels in both AA and C monocytes. CSD treatment inhibited ERK activation in AA and SSc and Smad2/3 activation in SSc monocytes. Treatment of healthy C monocytes with TGFbeta upregulated pERK and pSmad2/3. This effect of TGFbeta was also reversed by restoring caveolin activity with CSD. We previously demonstrated that monocyte migration is enhanced in healthy AA monocytes and SSc monocytes and that this enhancement is reversed by CSD. Here we show that TGFbeta treatment increases the migration of both healthy C and healthy AA monocytes by a similar ratio (about 2.5-fold) ($p < 0.001$), so the enhanced migration of AA monocytes compared to C monocytes was maintained following TGFbeta treatment. Treatment with CSD inhibited migration by > 50%, demonstrating that the enhanced migration of TGFbeta-induced healthy AA monocytes is due to their relative lack of caveolin-1. TGFbetaRI was also upregulated in AA and SSc monocytes and its expression was also inhibited by CSD.
Conclusion. Our results demonstrate that high serum TGFbeta and low caveolin-1 levels in monocytes may play a role in the predisposition of the AA population to SSc ILD via enhanced TGFbeta signaling and the resultant effects on monocyte migration.

PS166 CLINICAL CHARACTERISTICS OF SYSTEMIC SCLEROSIS PATIENTS WITH INTERSTITIAL LUNG DISEASE WHO DO NOT REQUIRE IMMUNOSUPPRESSIVE TREATMENT

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Background: Systemic sclerosis (SSc) is a connective tissue disease characterized by thickening of the skin and internal organs. Interstitial lung disease (ILD) is one of the major causes of death in this disease. Certain subset of ILD patients can be closely observed without potentially harmful immunosuppressive treatment. However, clinical characteristics of these patients are not clearly defined.

Method: A total of 151 SSc patients who were cared at Seoul National University Hospital between 1978 and 2013 were enrolled in this study. All of the patients were diagnosed as SSc according to the preliminary criteria of SSc by American College of Rheumatology and were diagnosed as having ILD based on chest computed tomography or radiography. Detailed data on clinical characteristics, treatment and its outcome were obtained by reviewing medical records. After calculating survival outcome of the patients, characteristics of the patients who did not require immunosuppressive treatment were defined.

Result: The mean (± S.D) age at diagnosis of SSc was 48.7 (±12.9) years with 88.7% of female predominance. ILD was diagnosed at the time of SSc in most of the patients. Among 151 patients, 72 (47.1%) required an immunosuppressive treatment which includes 45 cyclophosphamide, 8 azathioprine, 16 glucocorticoids and 3 others. During a total of 1,743 person-years of follow-up, 40 patients died (0.02 death/person-year). Mean survival time after diagnosis of SSc was 25.4 years (95% confidence interval (CI), 22.2-28.6) and that of SSc patients who received immunosuppressive treatment was 19.6 years (95% CI, 16.4-22.8). Interestingly, 52.9% of patients with ILD showed stable lung function without significant mortality (mean survival time, 30.0 years with 95% CI of 26.2-33.9). The clinical characteristics of these patients included near normal values of pulmonary function test (functional vital capacity, 79.5 ± 16.7%; DLCO, 66.3 ± 20.5%), no evidence of pulmonary arterial hypertension measured by echocardiography and no evidence of gastrointestinal involvement.

Conclusion: Certain subset of SSc patients with ILD may be treated without immunosuppressive treatment. Our results suggest a way to avoid potentially harmful immunosuppressive treatment in SSc patients with ILD.

PS167 ELEVATED SERUM LEVELS OF TUMOR-ASSOCIATED ANTIGENS IN SYSTEMIC SCLEROSIS: CORRELATION WITH LUNG FIBROSIS

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Background. Some tumor-associated antigens (TAAs) are expressed, apart from cancer cells, on the surface of inflammatory cells. The production of some TAAs may also be increased in some autoimmune diseases including systemic sclerosis (SSc).
Objectives. To assess serum carcinoembryonic antigen (CEA), CA-15.3, CA 125 and CA-19.9 levels in SSc patients, and to identify any possible associations with scleroderma lung involvement.
Methods. Eighty-two SSc patients (70 females and 12 males), mean age 64±13 years (range 34-91), disease duration 6±5 years (range 1-27), were consecutively studied. None of the patients had any malignancies prior and at the time of the study. All patients underwent to high-resolution scan (HRCT) and pulmonary function tests (PFTs); CEA, CA 19.9, CA 15.3 and CA125 serum levels were determined by electrochemiluminescence immunoassays; the normal upper limit determined by the manufacturer, were as follows: CEA < 2.5 ng/ml, CA19.9 <33 U/ml, CA 15.3 < 46.5 U/ml, CA125 < 21 U/ml.
Results. CEA was elevated in 28 (32%) of SSc patients, CA 19.9 in 7 patients (9%), CA 15.3 in 28 patients (36%), CA 125 in 6 patients (8%). Lung fibrosis, as detected HRCT was significantly associated with CEA ($p<0.0003$, $r=0.4$), CA15.3 ($p<0.001$, $r=0.4$), and CA125 values ($p<0.01$, $r=0.3$), while no association was seen for CA 19.9. Reduced forced vital capacity (FVC) was significantly associated only with CA 15.3 ($p=0.0001$), and reduced diffusion lung capacity for carbon monoxide (DLCO) only with CEA ($p=0.04$). There was an inverse correlation between CA 15.3, FVC and DLCO ($r= -0.52$ and $r= -0.44$, respectively).
Conclusions. The production of some TAAs may be elevated in SSc patients without any evidence of pulmonary or abdominal tumor; CEA, CA15.3, and CA125 may have a negative prognostic role, being associated with lung fibrosis as documented by HRCT and PFTs. Further studies on higher number of patients are warranted in order to identify a complementary biomarker for lung involvement in SSc among TAAs, or alternatively a surrogate biomarker with prognostic significance.

PS168 RESIDUAL VOLUME: A CANDIDATE AS EARLY MARKER OF INTERSTITIAL LUNG DISEASE INSYSTEMIC SCLEROSIS PATIENTS?

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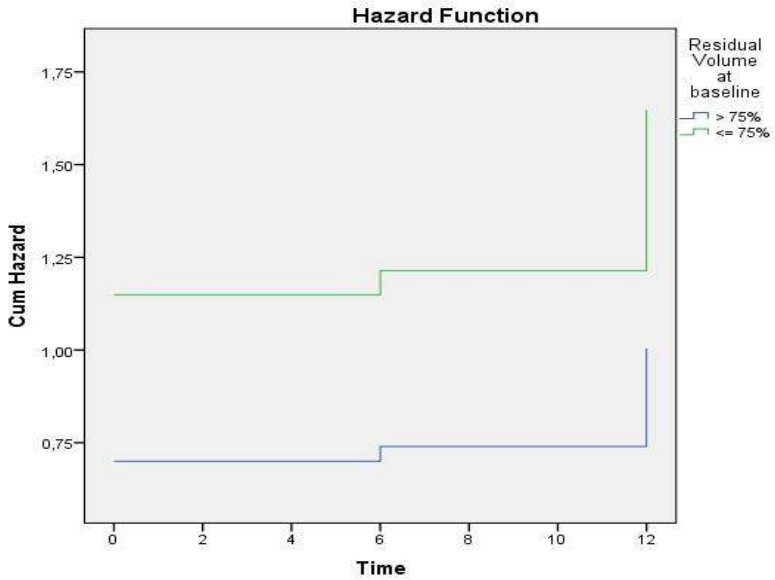
BACKGROUND: Interstitial lung disease (ILD) affects 40% of systemic sclerosis (SSc) patients. In clinical trials and in clinical practice, pulmonary function test (PFT) and high resolution chest tomography (HRCT) are useful to assess the lung disease. Although a variety of PFT parameters have been used to study ILD in SSc, only the forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) have been validated as an outcome measures in clinical trials. The changes of the residual volume (RV), in SSc patients, have never been evaluated.
OBJECTIVES: To assess RV predictive value for the presence of ILD-SSc and to investigate possible RV changes over 1 years of follow-up time, in SSc patients.
METHOD: 70 consecutive SSc patients (age 59,7 ys ± 4,5; disease duration: 8,4 ys ± 1,2; males: (n=) 7; females: (n=) 63) were enrolled; all patients underwent clinical examinations and PFT (RV, DLCO, TLC, FVC), every 6 months for 1 year, and HRCT at baseline and after 12 months. 31 patients had ILD at baseline. The results are expressed as means ± 1 standard deviation. Differences between baseline and follow-up parameters were evaluated by ANOVA for repeated measures. The hazard ratio were calculated by Cox regression.
RESULTS: RV significantly decreases in 12 months (baseline: 95,84% ± 5,8; a 6 months: 87,84% ± 4,07; 12 months: 82,48% ± 4,5; p=0,013). We want underscore that DLCO, FVC, TLC tend to decrease in 12 month but no significantly. We subdivided patients with ILD and patients without and we found that: RV differed significantly (p=0,04) between SSc patients with ILD (baseline: 89,2% ± 9,7; 6 months: 81,67% ± 6,47; 12 months: 79,8% ± 5,1) and SSc patients without ILD (baseline: 109% ±8,05; 6 months: 100,7% ± 6,1; 12 months: 92,2% ± 9,9). PFT parameters (DLCO, TLC, RV) values lower than 75%, did not represent a risk to develop ILD at 12 months (Fig.1).
CONLUSION: Although we cannot demonstrate that RV has a predictive value for ILD; its faster decrease than DLCO, FVC, TLC can make RV a candidate as early markers of ILD development. A larger cohort of SSc patients and a longer follow-up may unravel this issue.



PS169 A NEW METHOD TO EVALUATE THE EXTENT OF PULMONARY FIBROSIS IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Introduction: Pulmonary fibrosis is a major cause of severe morbidity and mortality in systemic sclerosis (SSc). With high resolution computer tomography (HRCT) fibrotic lesions have been reported in up to 80 % of the patients, but only a minority of these will develop severe respiratory dysfunction. Patients with fibrosis on HRCT are often categorized into one group when risk factors and SSc disease characteristics are described. The aim of this study was to evaluate the extent of pulmonary fibrosis detectable on HRCT.

Methods: From a database consisting of 137 SSc-patients from Stockholm County, we investigated all patients categorized as having pulmonary fibrosis (signs of pulmonary fibrosis on one or more HRCT). A rheumatologist (ER) and a radiologist (SN) examined the first HRCTs performed in these patients. Three slices, located just above the diaphragm, at the carina junction and the slice located intermediate between these two locations, on each side were examined for signs of honeycombing.
Table 1 scoring system:

0	No signs of pulmonary fibrosis	0%
1	Honeycombing involving <5% of the pulmonary parenchyma	2,5%
2a	Honeycombing involving 5-15%	10%
2b	Honeycombing involving 15-25%	20%
3	Honeycombing involving 25-49%	37,5%
4	Honeycombing involving 50-75%	62,5%
5	Honeycombing involving >75%	87,5%

Each score represents a fixed percentage. Scores were summarized and divided by six (number of examined slices) to obtain an average fibrosis score (AFS).
Results: 56 patients (41%) were categorized as having pulmonary fibrosis. Of these 7 patients had no signs of pulmonary fibrosis on the first HRCT, 34 patients had <15% AFS and 12 patients had >15% AFS .
Autoantibody profile differed between patients with vs. patients without fibrosis. Patients with pulmonary fibrosis had anti topoisomerase 1 (ATA) ($p<0.001$) and anti Sjögren Syndrome antigen A (SSA) antibodies ($p=0.05$) more frequently, but were less often anticentromere (ACA) antibody positive ($p<0.001$).
ATA were more common in patients with >15% AFS vs. patients with <15% AFS (75% vs 46%, $p<0.01$) and no patients with >15% AFS was ACA postive. There were no differences regarding age, gender, smoking habits, diffuse/limited skin involvement or reflux between patients with or without fibrosis or between patients with >15% vs. <15% AFS
Conclusion: Among SSc patietns with pulmonary fibrosis, the majority (78%) had a mild fibrosis with a limited engagement of the lung parenchyma. Our results highlight the need for a scoring system to evaluate the extent of pulmonary fibrosis in SSc

PS170 POSSIBLE ASSOCIATION OF AMBRISENTAN WITH DETERIORATION OF CONNECTIVE TISSUEDISEASES-ASSOCIATED INTERSTITIAL LUNG DISEASE

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BACKGROUND. Previous study has shown that the use of ambrisentan increased risk of respiratory hospitalization when treating idiopathic pulmonary fibrosis (IPF) (Ann Intern Med, 2013; 158: 641).
AIM. To investigate the effect of ambrisentan use on interstitial lung disease (ILD) associated with connective tissue diseases (CTD) (CTD-ILD).
METHOD. We retrospectively searched CTD patients treated with ambrisentan in our institute since 2010 when the medication was approved in Japan. Among 17 patients treated with ambrisentan, 11 CTD patients (65%) had ILD. Clinical findings including pulmonary function test before and after the treatment were evaluated.
RESULTS. The 11 patients (91% were female) consisted of 5 with diffuse cutaneous systemic sclerosis (SSc), 2 with limited cutaneous SSc, 2 with overlap syndrome with SSc and systemic lupus erythematosus, 1 with primary Sjögren syndrome, and 1 with polymyositis. The mean age at initial presentation (SD) and the mean follow-up period (SD) were 57 (15) year-old and 157 (316) months, respectively. Ambrisentan was initiated at the mean age (SD) of 60 (15). The mean value (SD) of % functional vital capacity (FVC), KL-6, and NT-pro BNP were 78 (19) %, 1221 (944) U/ml, and 218 (297) pg/ml, respectively. Phosphodiesterase type 5 inhibitor (in 7 patients, 64%), beraprost (in 5, 45%), tacrolimus (in 2, 18%), cyclosporine (in 1, 9%), and prednisolone (in 8, 73%) were included as concomitant medications. After the treatment with ambrisentan, progressive dyspnea developed in 6 patients (55%). Ambrisentan was discontinued in 2 patients (18%) according to the recommendation regarding IPF. Additional 3 patients (27%) shortly withdrew from ambrisentan because each patient developed abdominal distension, dizziness, and edema, respectively. Among 7 patients treated with ambrisentan for more than 6 months, pulmonary function test was consecutively available in all patients except one with severe respiratory failure. Among the 6 patients, a worsening of % FVC with more than 10% and 5% was seen in 3 (50%) and 1 (17%) patient, respectively, and the deterioration of CTD-ILD with ground-glass opacities was seen in 3 patients by chest CT during the treatment with ambrisentan. An improvement of % FVC by nearly 10% was noted in one patient after the cessation of ambrisentan.
CONCLUSION. The result showed potential association of ambrisentan with the deterioration of CTD-ILD. The possibility could not be denied that it was just a natural course of the disease. Further analysis with a larger population is needed to clarify its association.

PS171 LL-37: IS IT A NEW MARKER FOR INTERSTITIAL LUNG DISEASE (ILD) IN SYSTEMIC SCLEROSIS (SSC)?

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AIM OF THE STUDY: fibrosis of the skin and visceral organs is the hallmark of SSc and ILD is the leading cause of SSc related morbidity and mortality. LL-37 peptide is the only cathelicidin of the human antimicrobial peptide family. LL-37 has important antimicrobial effects and has also immunomodulatory activity. Furthermore recent data defined its anti-fibrotic effects on dermal fibroblasts and anti-apoptotic effects on SSc dermal fibroblasts. The aim of the study was to investigate the possible association between SSc related ILD and circulating levels of LL-37.
MATERIALS AND METHODS: 86 participants were divided into 3 groups: SSc patients with pulmonary involvement (n=30), SSc patients without pulmonary involvement (n=28) and controls (n=28). The pulmonary involvement was defined as SSc related ILD appearance on HRCT scans like ground-glass, reticular and honeycomb pattern. For the measurement of the LL-37 (Hycult Biotech) levels from blood samples of the patients ELISA has been used. Three groups were compared with each other based on median values.
RESULTS: LL-37 concentrations were remarkably lower in SSc patients with ILD as compared to SSc patients without ILD (1,3575 ng/ml vs 4,6175 ng/ml, p=0,035) and control subjects (1,3575 ng/ml vs 5,5300 ng/ml, p=0,009). In SSc patients without pulmonary involvement, LL-37 serum levels were similar to the control group (p=0,812).
CONCLUSIONS: Significantly lower levels of LL-37 were observed in patients with SSc-ILD. Our results suggest that reduction of the levels of the peptide may be associated to the development of ILD. It remains to be tested in larger SSc cohorts if the circulating levels of LL-37 might be used as an indirect marker of ILD.

PS172 COMPARISON OF BAL AND SERUM CYTOKINES AND PREDICTIVE VALUE OF SERUM CYTOKINES IN SYSTEMIC SCLEROSIS PATIENTS

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Objective: To identify a specific pattern of BAL and serum cytokines in patients with systemic sclerosis (SSc) and pulmonary involvement and to investigate their association with survival.
Methods: BAL cytokines (IL-6, IL-7, IL-8, IL-10, CCL2, CCL4, TGF-β, TNF-α) were measured in 24 SSc patients with interstitial lung diseases (ILD), the same cytokines were measured in serum by bioplex analysis in 153 SSc patients fulfilling the ACR criteria, including the 24 SSc-ILD patients. Pulmonary involvement was documented and patients were followed up for a mean period of 66.2 months.
Results: SSc patients with pulmonary involvement had different BAL and serum cytokine patterns and BAL cytokines were mostly comparable or higher (IL-7, IL-8, TNF-α) than serum cytokines; there was some correlation of BAL and serum cytokines (serum IL-8 with BAL IL-8 and TNF-α, serum TGF-β with BAL IL-7, CCL2 and TNF-α). BAL cytokines IL-8 and CCL2 were increased in patients with ILD and pulmonary hypertension (PH-ILD) compared to patients with ILD only. Of the serum cytokines, IL-6 was significantly increased in patients with ILD and PH-ILD compared to SSc patients without pulmonary involvement. Levels of CCL2 were lower in patients with PAH and PH-ILD than in patients without pulmonary involvement and CCL4 was lower in patients with ILD. The serum cytokine IL-6 could predict survival in patients with SSc, all patients with pulmonary involvement, pulmonary hypertension and SSc-ILD patients. In addition, IL-8 was identified as a novel predictive marker for survival in a SSc-ILD cohort.
Conclusion: In conclusion, the analysis of both BAL and serum cytokines implicates a role as biomarkers for distinct but different cytokines in both compartments. Our findings extend earlier work on the association of serum cytokines with clinical manifestations and survival. IL-6 and IL-8 may be interesting targets for therapeutic trials.

PS173 B LYMPHOCYTE DEPLETION IN SYSTEMIC SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG DISEASE AFTER TREATMENT WITH STANDARD AND LOW DOSES OF RITUXIMAB

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Background. There is increasing data suggesting potential beneficial effects of rituximab (RTX) in systemic sclerosis, but the adequate RTX dosage in systemic sclerosis-associated interstitial lung disease (SS-ILD) have not yet been clearly defined. The extend of B-cell depletion in pts treated with different doses of RTX is not investigated.
Objectives: to evaluate the peripheral blood B lymphocyte depletion in SS-ILD after therapy with different doses of RTX
Material methods: RTX was added to the ongoing treatment with corticosteroids of 30 pts (28 female), median age 47 years, range 17-71. The median disease duration before RTX treatment was 7 years (range 0.9-18) and the median post-treatment follow-up time was 12 months (range 6-34). Twenty pts was administered an infusion of 1g RTM 2 times, 8 pts – 500 mg 2 times and 2 pts - 500 mg once. B cell depletion was analyzed by flow cytometry.
Results. B-cell depletion was induced effectively in all pts at baseline. At Month 12 B cells in the peripheral blood were still depleted (0-0,005õ109/l) in 18 (60%) pts, reduced to (0,006-0, 05 õ109/l) in 11 (37%) pts and in one pts B lymphocyte recovery was shown. At the end of the study pts receiving 2 g RTM had lower B lymphocytes level (0,006± 0, 01; median 0, 0007) than pts receiving 1 g (0, 02 ± 0, 06, median 0,004), but differences were not significant. Mean dose of RTM in completely depleted pts did not differ from incompletely depleted ones (1, 4 ± 0, 6 g è 1, 27± 0, 5 g accordingly). Twelve months after therapy 25 (83, 3%) pts improved significantly ("good result" of treatment) and 4 (13, 4%) pts had "moderate effect". One (3, 3%) pts (showed recovery of B-cells) was stable for 11 month but then developed the flare. Twenty two pts received immunosuppressants before RTM treatment and 9 - after.
Conclusion: low dose 1 g RTX is comparable with typical RTX dosing 2 g with respect to B-cell depletion and the good effect on clinical outcome in patients with SS-IPL. This observation suggests that different therapeutic strategies could be taken into consideration.

PS174 SMALL ANIMAL MRI FOR NON-INVASIVE LONGITUDINAL FOLLOW UP OF PULMONARY FIBROSIS IN MICE

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Background: Pulmonary fibrosis, either idiopathic or secondary to diseases such as systemic sclerosis, is a devastating and life threatening disorder for which effective treatment is still lacking. The bleomycin-induced pulmonary fibrosis model is well-characterized and the most widely used mouse model. The resulting fibrosis is routinely quantified by end-stage histological assessments, lacking the ability to follow-up on disease progression and potential therapeutic effects in the individual animal. At present, imaging tools for the evaluation of lung disease with good temporal and spatial resolution in vivo are limited.
Objectives: To optimize and evaluate lung MRI protocols to visualize disease onset and progression in the bleomycin-induced model of lung fibrosis. We compared prospectively and retrospectively gated MRI sequences and validated our results with established CT imaging of lung fibrosis and histochemical techniques.
Methods: Male C57Bl/6 mice were intratracheally instilled with bleomycin (0.05U in 50 µl of PBS) or sham. The mice were scanned with MRI and CT at baseline and weekly until 3 weeks after instillation. After the last imaging time point, mice were sacrificed, ex vivo CT data were acquired and the lungs were isolated for histological analysis and collagen quantification. MRI images were acquired at 9.4T (Bruker Biospin, 20 cm) in combination with a 7.5cm quadrature coil, using the following sequences: (1) a respiratory triggered RARE sequence, (2) a respiratory triggered ultra short echo (UTE) sequence and (3) a retrospectively gated FLASH sequence IntraGate. For reconstruction, 70% of the respiration and ECG period was used. MRI data were quantified using ImageJ.
Results: The prospectively gated UTE and RARE protocols as well as retrospectively gated IntraGate-FLASH imaging were able to visualize an increase of hyperintense focal spots over time, corresponding to progression of lung fibrosis as corroborated by lung CT images. Quantification of the mean lung signal intensity shows an increase over time, which was confirmed by the decrease in aerated lung volume quantified from the CT data and by histology. Conclusions: The evaluated MRI protocols were all able to non-invasively visualize and quantify lung disease progression. Moreover, the IntraGate-FLASH protocol does not need setup of respiratory triggering for lung imaging, making it an easy to use and efficient alternative to more conventional sequences. Where CT provides poor soft tissue contrast, MRI has the potential to provide contrast differences between vasculature, fibrotic areas and inflammation, without concerns for radiotoxicity when scanning repetitively.

PS175 PULMONARY INVOLVEMENT IN SSC PATIENTS – A SINGLE CENTRE EXPERIENCE

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Background: Interstitial lung disease (ILD) is the most frequent pulmonary complication and it is a major cause of death in systemic sclerosis (SSc). SSc-ILD has two patterns: the non-specific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP).
Objective: To assess the computer tomographic (CT) patterns of lung disease in patients with systemic sclerosis interstitial lung disease (SSc-ILD) and the association with clinical, immunological parameters and the presence of pulmonary arterial hypertension (PAH).
Methods: This is a retrospective study of 42 SSc patients who have been evaluated by high resolution computer tomography (HRCT) in our clinic. The patients underwent physical examination, evaluation of skin involvement, 6-minute walk test (6MWT), echocardiographic assessment, immunological assessment and pulmonary assessment by HRCT and/or diffusion capacity for carbon monoxide (DLCO). Clinical data obtained by review of the medical records were classified according to current criteria.
Results: All the patients evaluated by HRCT were symptomatic or/and had a modified DLCO. From 42 patients evaluated by HRCT 33 (78,57%) patients had ILD pattern. Of those with ILD, 27% (24 of 33 subjects) had a nonspecific interstitial pneumonia (NSIP) pattern and 73% (9 of 33 subjects) had the usual interstitial pneumonia (UIP) pattern. There were 4 males: 2 with UIP pattern and 2 with NSIP pattern, and 29 women: 7 with UIP pattern and 12 with NSIP pattern. Eighteen of 33 (55%) subjects had limited skin involvement, 14 of 33 (42%) had diffuse skin involvement and one patient had scleroderma sine scleroderma. The skin involvement, the presence of dyspnea or the 6MWT showed poor association with the HRCT pattern (p>0,05). Antinuclear antibodies (ANA) were positive in high titer in both NSIP and UIP pattern with poor association. On echocardiographic evaluation the group with UIP pattern had a higher percent (33%) of patients with probably PAH (PAPs>50 mmHg) then the group with NSIP pattern (4%) (p=0,05). In the UIP group 44,4% of patients had diastolic dysfunction compared with 16,7% the NSIP group (p>0,05).
Conclusions: In our group the UIP pattern was more frequent then in other reports. Women were more likely to have the NSIP pattern. The group with UIP pattern had a higher percent of patients with PAPs>50 mmHg and with diastolic dysfunction. These findings may suggest that the presence of UIP pattern can be associated with PAH and diastolic dysfunction.

PS176 USE OF IMMUNOSUPPRESSANTS IN SSC PATIENTS WITH INTERSTITIAL LUNG DISEASE – RESULTS OF THE DESSCIPHER PROJECT OF THE EUSTAR GROUP

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Background: Interstitial lung disease (ILD) represents one of the most frequent causes of death in systemic sclerosis (SSc) patients. Yet, there are no approved drugs for treatment of SSc-ILD, consensus is rare and data facilitating a treatment algorithm for everyday practice are lacking. We describes the current treatment strategies in a large European cohort of patients with SSc-ILD.
Methods: Scleroderma Trial and Research (EUSTAR) data base was searched focussing on ILD and immunosuppression.
Results: We identified 3 272/10 507 patients fulfilling ACR/ACR-EULAR criteria with additional signs of ILD and at least one report on immunosuppression. Diffuse SSc was present in 45.7% and limited SSc in 47.9% with a mean age of 55.3 years and mean disease duration of 8.4 years.
Mean age was 55.3 years, with 83.1% females and a mean SSc disease duration of 8.4 years. Mean mRSS was 11.1±9.0, skin involvement was in 45.7% of the diffuse and in 47.9% of the limited SSc subtype, and 6.3% had sclerodactily only.
2,307 (70.5%) patients had at least one episode of immunosuppressive therapy. The 965 (29.5%) patients with ILD symptoms but without ever use of immunosuppressants were on average 5.1 years older, had a 2.9 years longer disease duration, more often limited skin involvement, higher DLCO and FVC1 values.
Most frequently used immunosuppressants were prednisolone (pred) (59.7%), cyclophosphamide (cyc) (17.4%), azathioprine (aza) (14.7%), methotrexate (mtx) (14.2%), mycophenolate mofetil (mmf) (11.1%), less frequently used were D-penicillamine (dpa) (2.7%), rituximab (2.3%), tumor necrosis factor inhibitors (0.7%), and imatinib (0.5%). With regard to highest treatment intensity ever received, similar proportions of patients got monotherapies (34.5%) and combinations of two drugs (32.2%), while triple therapy was comparably rare with 3.4%. Combinations of more than 3 immunosupressive drugs were exceptions (n=12 patients).
When ranking individual treatment regimen, most frequently was pred mono therapy (31.2%), and combinations with pred/cyc (11.5%), pred/aza (9.3%), pred/mtx (8.4%), and pred/mmf (6.7%). Similarly frequent were monotherapies with aza (4.3%), mtx (4.2%), cyc (4.1%) or mmf (3.5%). Double combination of pred+rit or pred+dpa received both 1% of the patients. Triple combinations in 112 patients were pred/mtx/aza, pred/cyc/aza and pred/cyc/mtx.

Conclusion: Use of immunosuppressants is frequent in SSc-ILD patients showing a wide variety of single and combined substances. Prospective studies are necessary to define indications and outcomes. The EU-funded international DeSScipher research project was initiated to achieve this goal, comprising 5 prospective observational trials addressing the most frequent medical problems in SSc patients.

PS177 ALPHA2 (V) CHAIN AND COLVA2 INDUCES THE FIBRILLOGENESIS PROCESS IN DISTORTEDLUNG FRAMEWORK OF SYSTEMIC SCLEROSIS

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Background/Purpose: Fibrosis is a process associated with several diseases such as systemic sclerosis (SSc) and may involve some vital organs such as the lungs. Among the types of collagens involved in SSc, collagen V (COLV) can be highlighted considering its immunological aspects. It is known that mutations in COLV gene are involved in vascular diseases and that its unusual increase is correlated with the pathogenesis of SSc. Considering these characteristics, the aim of this study was to evaluate if the changes in total COLV mRNA expression, previously described in the literature, may be a reflex of the abnormal expression between its chains (COLVα 1 and COLVα 2) in the lungs of patients with SSc. Methods/Patients: Expression of α1(V)(2)α2(V) and α1(V) and α2(V) molecular isoforms of COLV and tridimensional reconstruction (3D) were evaluated in 10 patients with SSc without pulmonary hypertension that underwent surgical lung biopsy and 6 controls of normal individuals who died from trauma. The SSc diagnoses were established according to the American College of Rheumatology and the work was approved by the Ethics Committee (CAPPesq 0960/08). The amount of α1(V)(2)α2(V) and α1(V) andα 2(V) in lung biopsies was evaluated by immunofluorescence and quantified through the image analysis software (Image Pro-Plus 6.0). COLVA1 and COLVA2 gene expression analysis was made by qRT-PCR Real Time. Results: The α2(V) immunostaining showed distorted and strongly thickened fibers in lung with irregular bundles of α2(V) distributed in parallel and perpendicular arrangements. These distributions resulted in a dense network around of the vessels in SSc patients compared with thin fibers pattern from the healthy controls. In contrast, α1(V) expression was lower interstitial compartment of the lung when compared with respective controls. Histomorphometric analysis of SSc lung demonstrated increased expression of the α2(V) in thickened alveolar septa, compared to controls (6,020 ± 2,291, $p< 0.01$) as well as the molecular profile demonstrated increased COLVA2 gene expression in SSc lung (19,75 ± 3,187, $p=0.001$). Interestingly, α2(V) expression was 70% more frequent than α1(V) molecular isoform in SSc lung. Conclusion:The overexpression of α2(V) chain and COLVA2 gene may drive the fibrillogenesis process in distorted lung framework from SSc patients, reinforcing the participation of COLV in this disease.

PS178 EFFICACY AND SAFETY OF INTRAVENOUS CYCLOPHOSPHAMIDE IN SCLERODERMA LUNGDISEASE OF ELDERLY

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Background. The efficacy of cyclophosphamide for scleroderma lung disease has been demonstrated in several randomized controlled trials. Infection is most concerning adverse event of the therapy, especially in elderly patients.
Objectives. The aim of this study was to evaluate the efficacy and safety of intravenous cyclophosphamide for interstitial lung disease (ILD) in elderly patients with scleroderma.
Method. We performed a retrospective study of scleroderma patients with ILD who were at least 70 years old and treated with intravenous cyclophosphamide. Patients' data, including pulmonary function test, six-minute walk test and adverse events regarding cyclophosphamide therapy, was collected.
Results. Four patients, all female and diffuse type, were included. Mean age, follow-up period and cumulative CYC dose were 75 years, 15.7 months and 3.31g. At the end of the follow-up period, FVC, DLCO and six-minute walk test improved: 62.3% and 77.6% (P=NS); 52.4% and 60.3% (P=NS); 421.4m and 543.7m (P=NS). There were any adverse events except for mild thrombocytopenia.
Conclusion. Intravenous cyclophosphamide is a highly effective therapy for ILD with few adverse events in elderly patients.

PS179 PULMONARY ARTERIAL HYPERTENSION, CLASSIFICATION CRITERIA

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OBJECTIVE: To analyze the fulfillment of the old ACR1980 and the new ACR-EULAR Preliminary Classification Criteria for Systemic Sclerosis (SSc) in patients with severe pulmonary arterial hypertension (PAH) associated to SSc.

PATIENTS AND METHODS: from 1990, all patients with clinical diagnosis of SSc were included in a database containing demographic and clinical information. Severe PAH patients, defined by mean pulmonary arterial pressure (mPAP) >40mmHg in right heart cathetherization, in the absence of lung fibrosis and left cardiac dysfunction, were selected. The old ACR1980 and the new ACR-EULAR criteria were applied to the group. Clinical characteristics, hemodynamics and survival were compared between patients with or without ACR1980 criteria, using Chi-Square, t test and Kaplan-Meyer analysis.

RESULTS: From 404 patients, 36 (9%, 2m/34f, age 56±16y) had severe PAH as defined. Time from Raynaud onset to HAP diagnosis was 16±11y. Two had diffuse and 34 limited cutaneous disease. ANA were positive in 34 (94%), ACA in 26(72%) and aRNP in 4 (11%). None had aScl70. Mean mPAP was 55±11mHg, wedge pressure 10±3mmHg, and pulmonary arteriolar resistance (PAR) 13±7UW. Only 19(52%) fulfilled the old ACR1980 criteria, but all patients fulfilled the new ACR-EULAR criteria. From the 17 patients not fulfilling the old ACR criteria, all presented Raynaud, 16(94%) sclerodactily, 8(47%) finger edema, 13(76%) telangiectasia, 4/15(27%) calcinosis and 13/14(93%) low DLCO. One patient had renal crisis. Capillaroscopy was abnormal in 15/16(96%), ANA was positive in 14(82%), ACA in 11/16(69%) and aRNP in 2/16(13%). Only proximal scleroderma, ischaemic lessions and calcinosis ($p<0.0001$ for all) were more frequent in patients fulfilling the old ACR1980 criteria than in those fulfilling only the new ACR-EULAR criteria. Hemodynamics were similar in both groups. Median survival was also similar. After 6±6 years of follow-up, 13 patients fulfilling and 12 not fulfilling the old ACR1980 criteria had died.

CONCLUSIONS: The new ACR-EULAR criteria for the classification of SSc have an excellent performance in patients with SSc-associated severe PAH. Since nearly half of this group of patients do not fulfill the old ACR1980 criteria, and present only with minor signs of the disease before developing HAP, our study points out: 1) the need to apply the new criteria to all patients with Raynaud and SSc suspicion in clinical practice; and 2) as SSc-HAP has better prognosis if diagnosed and treated early, it seems mandatory to screen all SSc patients, even those with very mild limited disease, to detect HAP as early as possible.

PS180 EPOPROSTENOL RESCUE THERAPY IN SYSTEMIC SCLEROSIS-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION AND IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION

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Background/Purpose: Epoprostenol has been demonstrated to improve hemodynamics, functional class, and six-minute walk distance (6MWD) in systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH) and idiopathic PAH (IPAH) patients. In contemporary practice, it is usually reserved for patients who have failed treatment with endothelin receptor antagonists and/or phosphodiesterase-5 inhibitors. The effect of epoprostenol rescue therapy on survival has not been evaluated. The objective of this study was to evaluate the role of intravenous epoprostenol as rescue therapy in the SSc-PAH and IPAH patients.
Methods: Patients attending the University Health Network Pulmonary Hypertension Program between 1998 and 2012 were included if they had a diagnosis of SSc-PAH and IPAH based on a mean pulmonary artery pressure (mPAP) of > 25 mmHg and a pulmonary capillary wedge pressure of <15 mmHg on cardiac catheterization, and had been treated with intravenous epoprostenol after treatment with endothelin receptor antagonists and/or phosphodiesterase-5 inhibitors for PAH. The primary outcome was survival. Survival was defined as the time from initiation of epoprostenol to death from any cause. Patients were censored as of May 1, 2012. Survival was evaluated using Kaplan Meier curves.
Results: 1140 patients were reviewed to identify 36 patients with SSc-PAH and 24 patients with IPAH treated with epoprostenol after failure with oral pulmonary hypertension specific therapies. 83% of SScPAH and 75% of IPAH patients were female. The mean (standard deviation) PAH duration prior to initiation of epoprostenol was 3.3 (5.7) years for SScPAH, and 2.1 (2.1) years for IPAH patients. Median 1-, 2-, 3-, 4-, 5-year survival for SSc patients was 85.7%, 60.7%, 53.6%, 46.1%, 42.3%; and for IPAH patients was 83.3%, 70.8%, 65.8%, 59.2%, 59.2%. There was no significant difference in survival between the SScPAH and IPAH patients treated with epoprostenol (p=0.13).
Conclusion: Our findings demonstrate desirable long-term survival and support the use of epoprostenol as rescue therapy for SSc-PAH and IPAH patients.

PS181 SEX DISPARITIES IN SURVIVAL OF SYSTEMIC SCLEROSIS-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION AND IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION PATIENTS

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Background/Purpose: Systemic sclerosis (SSc) associated pulmonary arterial hypertension (PAH) and idiopathic PAH (IPAH) are conditions with poor survival. There is evidence to suggest that sex affects survival. The primary objective of this study was to evaluate the effect of sex on survival in SSc-PAH and IPAH. We secondarily evaluated the effect of sex on disease onset, time to diagnosis, disease progression and treatment.
Methods: Patients were included if they attended the Toronto Scleroderma Program or the University Health Network Pulmonary Hypertension Program; had a diagnosis of SSc-PAH or IPAH defined as a mean pulmonary artery pressure >25mmHg and age > 16 years. Sex was defined as self-reported biological and physiological characteristics at birth (male, female). The primary outcome was the time from diagnosis to death from all causes. Secondary outcomes were sex differences in age of diagnosis, disease duration and SSc manifestations. Cox proportional hazards model were used to evaluate survival.
Results: 52 male and 267 female SScPAH; and 47 male and 107 female IPAH patients were identified. Male SSc patients had a shorter mean (standard deviation) time from SSc diagnosis to PAH diagnosis (5.6 (8.7)) versus (8.4 (9.6)), p=0.047), increased frequency of renal crisis (19% versus 9%, p= 0.04), interstitial lung disease (67% versus 49%, p=0.02), and digital ulcers (29% versus 19%, p<0.001). Male IPAH patients had a higher frequency of diabetes (30% versus 12%). Despite adjusting for these differences, male SScPAH patients have decreased 1-, 2-, 3-, and 5-year survival (82.6%, 70.6%, 60.8%, 48.2%) compared to females (84.4%, 73.4%, 64.2%, 52.8%). Similarly, male IPAH patients have decreased 1-, 2-, 3-, and 5-year survival (93.4%, 87.9%, 84.8%, 77.7%) compared to females (94.5%, 91.0%, 88.7%, 83.2%).
Conclusion: Sex disparities appear to exist in survival of SSc-PAH and IPAH patients. Further investigation is needed to evaluate this disparity, mechanisms for disparity, and the role of a targeted screening and treatment approach.

PS182 PROGNOSIS OF SYSTEMIC SCLEROSIS (SSC) PATIENTS WITH PULMONARY HYPERTENSION

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Statement of Purpose
Pulmonary hypertension (PH) is a major poor prognostic factor in patients with connective tissue disease. In particular, patients with SSc accompanied by PH have an extremely lower survival rate than SSc patients without PH. Survival rate of SSc patient 24 months after development of PH is less than 50%. Recent progress of treatment strategy for PH has dramatically changed by vasodilators which improve hemodynamics of pulmonary circulation. In this study, we investigated the prognosis of SSc patients with PH in our hospital.
Methods
This is a retrospective cohort study of 324 SSc patients that is treated in our hospital between May 1992 and December 2012. SSc patients were divided into two groups (SSc with PH or without PH), and the survival rate was compared between these two group using the Kaplan-Meier method. In addition, the causes of death in these patients were analyzed using univariate analysis to extract the influencing factors. Survival of SSc patients with PH was compared between1992 to 2005 and 2006 to 2012. Survival of SSc patients with PH was also compared between the difference of with or without presence of interstitial pneumonia (ILD).
Results
The prognosis of SSc patients who develop PH was found to be poor than SSc patients without PH. There was no significant difference in the survival rate, observed between SSc patients with PH associated with ILD and those with pulmonary arterial hypertension (PAH). Poor prognostic factor for survival in SSc patients were found diffuse type, finger ulcer, complicated by PH, treatment with prednisolone (PSL) and intravenous cyclophosphamide (IVCY) pulse Therapy. The survival rate of SSc with PH patients for one year, significantly improved after 2005, which was 50% and became 80% after 2006. Treatment by prostaglandin analogue (PGI2), endothelin receptor antagonist and PDE-5 inhibitor dramatically improved the survival of SSc with PH. On the other hand, PSL and IVCY therapy reduced their survival rate. Presence of disease-specific autoantibodies did not affect their survival rate.
Conclusion
Pulmonary vasodilators such as PGI2, endothelin receptor antagonist and PDE-5 inhibitor, dramatically improved survival of SSc with PH. It should be noted that immunosuppressant PSL and IVCY reduced the survival of SSc with PH. Our study suggests that pulmonary vasodilators should be used but not immunosuppressive therapy towards SSc patients with PH.

PS183 SURVIVAL IN SSC-PAH BY SERUM AUTOANTIBODY STATUS

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Background/Purpose: Previous studies have shown that anticentromere (AC) and isolated nucleolar (NUC) antibodies are the most common autoantibodies in patients with systemic sclerosis (SSc) and World Health Organization (WHO) group 1 PAH. The goal of the present study was to determine the association between serum autoantibodies and survival in patients with newly diagnosed PAH who are enrolled in the PHAROS (Pulmonary Hypertension and Recognition of Outcomes in Scleroderma) Registry.

Methods: We evaluated patients from the multi-center, prospective, observational PHAROS registry who had definite PAH diagnosed by right-heart catheterization (RHC) (mean pulmonary artery pressure (mPAP) ? 25mmHg and pulmonary capillary wedge pressure (PCWP) ? 15mmHg) within 6 months of enrollment. Medical history, laboratory (including serum autoantibodies), pulmonary function test, echocardiogram, 6-minute walk distance, and RHC data were collected at baseline and biannually or as clinically indicated. Mortality data were collected from participating centers' electronic medical records and/or the Social Security Death Index. Kaplan-Meier estimates for survival were determined for 6 different autoantibody groups. Multivariable Cox regression analyses were performed to assess risk of death by hazard ratios (HR) in each autoantibody group, controlling for age, sex, SSc disease duration (defined as duration since first Raynaud symptom), forced vital capacity (FVC) % predicted, and skin score.

Results: 163 PHAROS subjects met WHO group 1 PAH criteria and had serum autoantibody information available (7 missing autoantibody data, 7 with negative autoantibody test). More than half had either AC or NUC; 61 (37%) subjects had AC, 39 (24%) NUC, 28 (17%) had other, 11 (7%) Scl70, 9 (6%) RNA polymerase III (RNApol), 8 (5%) U1RNP autoantibodies. The mean SSc disease duration at PAH diagnosis was longest for AC (19.3±13.4y) and shorter for NUC patients (12.2±9.8, compared to AC p=0.02). Thirty-five (21%) subjects died over a mean follow-up time of 2.4+1.7 (median 2.0, range 0-7.2) years. 1-, 2-, 3-, and 5-year survival across all antibody groups was 93%, 86%, 76%, and 63%; 1-year survival estimates were 92% for AC; 91% for NUC; 76% for Scl70; 100% for U1RNP; 88% for other. No patients with RNApol or negative autoantibodies died over the follow-up period. For all autoantibody groups, unadjusted and adjusted HR revealed no statistically significant association between risk of death and autoantibody positivity.

Conclusion: Anticentromere and NUC autoantibodies are prevalent in SSc patients with PAH. PAH may be a late complication in AC patients, but may occur earlier in SSc patients with other autoantibodies. There does not appear to be a significant association between SSc antibody type and survival in patients with PAH.

Table 1: Clinical characteristics for World Health Organization group 1 (PAH)

Mean (SD) or as indicated	Overall N=170 (100%)	Nucleolar N=39 (23%)	Anticentromere N=61 (36%)	Scl-70 N=11 (6%)	RNA pol III N=9 (5%)	U1RNP N=8 (5%)	Other N=28 (16%)	Negative N=7 (4%)	p-value*
Age (y)	60.1(10.8)	55.7(10.5)	62.9(9.1)	57.0(7.8)	61.7(11.8)	49.1(13.0)	62.2(11.9)	61.1(6.2)	.001
Sex, n (% female)	145(85)	32(82)	57(93)	9(82)	6(67)	6(75)	24(86)	6(86)	.34
Race, n (% Caucasian)	137(81)	26(67)	51(84)	8(73)	7(78)	7(88)	24(86)	7(100)	.16
SSc Disease duration: (y)									
From Raynaud onset	15.0(12.1)	12.2(9.8)	19.3(13.4)	8.8(10.2)	10.6(9.2)	11.7(10.6)	13.8(12.5)	10.5(4.1)	.018
From non-Raynaud onset	10.8(9.3)	7.6(6.1)	13.5(11.2)	8.4(10.2)	10.5(8.9)	10.2(9.5)	9.6(9.0)	11.2(3.8)	.13
SSc subtype: n (%)									
lcSSc	124(73)	28(72)	59(97)	5(45)	2(22)	5(63)	15(54)	3(43)	<0.0001
dcSSc	41(24)	11(28)	2(3)	6(55)	7(78)	1(13)	10(36)	4(57)	
Unclassified	5(3)	0(0)	0(0)	0(0)	0(0)	2(25)	3(11)	0(0)	
mRSS	8.40(8.826)	10.34(11.83)	5.76(4.79)	13.91(10.94)	18.11(13.72)	8.13(7.51)	7.24(6.62)	7.8(6.38)	.0008
6MWD (m)	340.2(125.3)	358.1(125.3)	312.5(121.0)	338.1(159.4)	314.4(104.6)	323.8(203.9)	363(111.9)	239.3(70.7)	.38
Echocardiogram									
SPAP (mmHg)	60.77(21.17)	62.11(22.78)	61.70(20.80)	55.11(17.04)	57.43(13.03)	68(30.39)	57.95(20.77)	48.25(11.32)	.71
Heart catheterization									
mPAP (mmHg)	37.21(10.44)	38.59(11.38)	37.80(10.40)	33.27(10.1)	32.44(5.48)	42.38(9.99)	35.21(8.95)	31.43(7.07)	.13
PCWP (mmHg)	10.00(3.30)	10.33(3.56)	9.93(3.410)	11.27(2.61)	11.33(3.50)	8.625(2.39)	9.3(2.9)	10.29(3.88)	.41
Pulmonary function tests									
FVC % Predicted	80.1(22.5)	75.9(38.0)	85.4(15.0)	75.1(10.2)	69.9(12.8)	80.8(24.6)	76.6(14.5)	87.5 (16.2)	.27
DLCO % Predicted	42.3(17.0)	41.6(18.4)	44.4(17.0)	37.6(11.4)	33.5(11.7)	50.3(27.6)	41.4(15.0)	52.8(23.5)	.27
Survival Rate, %									0.75***
1-year	93%	94%	94%	89%	100%	100%	92%	100%	
2-year	87%	88%	89%	63%	100%	100%	88%	100%	
3-year	76%	74%	72%	63%	100%	86%	79%	100%	
5-year	66%	74%	54%	63%	100%	57%	79%	50%	

*Comparing among antibody groups

*** Testing equality of survival curves over antibody groups

PS184 THE SIGNIFICANCE OF A 'NORMAL DLCO' IN SCLERODERMA (PHAROS) COHORT

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Background: The Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) is a prospective longitudinal study of patients at risk of developing pulmonary arterial hypertension (PAH) and those who have definite pulmonary hypertension (PH). Pulmonary function tests (PFT), which capture the diffusion capacity (DLCO), are obtained in the routine care on SSc patients in this cohort. The purpose of this study was to describe the significance of a normal DLCO identified on PFT in PHAROS.
Methods: Entry criteria into PHAROS for SSc patients at high risk for PAH included: DLCO <55% predicted, a forced vital capacity (FVC) %/DLCO% ratio >1.6 or an estimated pulmonary arterial systolic pressure (PASP) on echocardiogram > 35mmHg. PAH is defined by a mean pulmonary artery pressure (mPAP) greater than or equal to 25 mmHg, a pulmonary capillary wedge pressure (PCWP), left atrial pressure, or left ventricular end-diastolic pressure less than or equal to 15 mmHg, and a pulmonary vascular resistance (PVR) greater than 3 Wood units. Patients complete are seen yearly for physical examination, PFT, echocardiogram, 6 minute walk, and clinical outcomes. We used Fisher's exact to examine associations between two categorical variables and unpaired t-test for continuous variables. Significance was assigned at $p< 0.05$.
Results: In this SSc patient population with PAH (n=166), DLCO of > 60% at time of RHC (n=17) versus <60% (n=133). The significant PFT data in this group with normal DLCO versus < 60%, includes a FVC that was lower, (91% vs 79% predicted, $p<0.05$) and mean DLCO that was higher 76.9% vs. 37.5% predicted ($p<0.0001$). RHC parameters not differ significantly between those with normal DLCO and those with DLCO < 60%.
Of the 17 patients with DLCO initially > 60%: 5 patients showed a DLCO < 50% predicted on repeat PFT; 7 had very mild PAH with a PVR < 300, which for 2 on repeat RHC was non progressive; 2 had repeat RHCs that showed significant diastolic dysfunction. Only 3 of these 17 patients had significant PAH with 'normal' DLCO, but also had increased PVR, and increased basic natriuretic peptide (BNP). None of the 166 patients died. There were no significant differences in demographics (age, sex, race, disease duration, SSc subtype, or antibody status).
Conclusions: Normal DLCO in PAH in SSc is very uncommon and rarely is severe. If it severe other clinical identifiers such as increased BNP, or RHC parameters such as increased PVR were present.

PS185 UTILITY OF B-TYPE NATRIURETIC PEPTIDES IN THE ASSESSMENT OF PATIENTS WITH SYSTEMIC SCLEROSIS-ASSOCIATED PULMONARY HYPERTENSION IN THE PHAROS REGISTRY

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Purpose: Elevations of B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) have been associated with worse outcomes in patients with pulmonary arterial hypertension (PAH). Elevated NT-proBNP has been integrated into novel PAH screening algorithms for patients with systemic sclerosis (SSc). We sought to assess the prognostic utility of natriuretic peptide levels in SSc patients at high risk for or with incident pulmonary hypertension (PH).

Methods: PHAROS is a multicenter prospective cohort of SSc patients at high risk for PAH (pre-PAH) or with definite PH diagnosed by right heart catheterization (RHC) within 6 months of enrollment. Criteria for pre-PAH include any one of the following: diffusing capacity (DLCO) <55% predicted, forced vital capacity/DLCO ratio >1.6, or pulmonary artery systolic pressure on echocardiogram >40 mmHg. Patients with definite PH have a resting mean pulmonary artery pressure >25 mmHg. A pulmonary capillary wedge pressure <15 mmHg was used to differentiate Group I (PAH) from Group II (PH related to left heart disease). Those with moderate or severe interstitial lung disease on chest imaging and FVC <60% predicted were included in Group III (PH related to hypoxemia).

Results: 205 definite PH (135 Group I, 35 Groups II, 35 Group III) and 187 pre-PAH patients had natriuretic peptide levels available. Mean BNP and NT-proBNP levels were significantly higher in the definite PH compared with the pre-PAH patients (471.7±892.3 vs. 103.8±300.4 pg/mL and 1490.8±2506.1 vs. 125.0±189.8 pg/mL, p<.0001). Group III patients had the lowest BNP and NT-proBNP levels, but there was no significant difference between Groups I and II. In both the definite PH and Group I patients, NT-proBNP had stronger correlations with hemodynamic parameters than BNP (Table). The sensitivity and specificity of BNP>100 and NT-proBNP>210 for a diagnosis of Group I PAH was 55% vs. 68% (p=.19) and 72% vs. 81% (p=.07), respectively. 14 pre-PAH patients developed definite PH (10 Group I PAH) during a mean follow-up time of 3.7±1.4 years. BNP>100 and NT-proBNP>210 were not predictive of the development of PH or PAH, however, patients who developed PAH had a trend toward higher baseline NT-proBNP, but not BNP, levels compared with those who did not (149.4±64.7 vs. 125.7±197.7, p=.06). In the definite PH group, 33 deaths occurred (17 Group I PAH). Neither BNP nor NT-proBNP was predictive of death.

Conclusions: NT-proBNP may be a better biomarker than BNP for early identification and monitoring of PAH in SSc patients, but confirmation of our results is necessary.

Table. Correlations Between Natriuretic Peptide Levels and Baseline Hemodynamics in Patients with Incident Systemic Sclerosis Associated Pulmonary Hypertension

A. Groups I, II, and III Pulmonary Hypertension

	Mean±SD (N)	r=Correlation with BNP	P-value	r=Correlation with NT-proBNP	P-value
BNP, pg/mL	471.7±892.3 (341)	1	NA	NA	NA
NT-proBNP, pg/mL	1490.8±2506.1 (64)	NA	NA	1	NA
Mean pulmonary artery pressure, mmHg	38.1±11.1 (166)	0.43	<0.0001	0.53	<0.0001
Pulmonary vascular resistance	510.2±385.5 (162)	0.36	0.0001	0.53	<0.0001
Cardiac output, L/min	5.04±1.7 (163)	-0.28	0.0027	-0.53	<0.0001

B. Group I Pulmonary Arterial Hypertension

	Mean±SD (N)	r=Correlation with BNP	P-value	r=Correlation with NT-proBNP	P-value
BNP, pg/mL	460.7±897.6 (95)	1	NA	NA	NA
NT-proBNP, pg/mL	1861.8±2694.9 (40)	NA	NA	1	NA
Mean pulmonary artery pressure, mmHg	39.6±11.1 (106)	0.32	0.006	0.53	0.001
Pulmonary vascular resistance	584.8±419.3 (104)	0.36	0.002	0.56	0.0008
Cardiac output, L/min	4.86±1.6 (105)	-0.23	0.06	-0.62	0.0001

PS186 THE DIFFERENCES, WHICH SEEM TO BE A PATHOPHYSIOLOGY OF PULMONARY HYPERTENSION, OF CAROTID DOPPLER AND ECHOCARDIOGRAPHIC FINDINGS IN EACH CONNECTIVE TISSUE DISEASE

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Background: The pathophysiology of pulmonary hypertension (PH) in systemic sclerosis (SSC) and systemic lupus erythematosus (SLE) is regarded as pulmonary artery stenosis by endothelial, adventitial and smooth muscle dysfunction. This pathophysiology can increase the stiffness of other arteries as well as pulmonary artery. However, studies about the difference of pathophysiology of PH in each connective tissue disease (CTD) have been rare. The aims of this study were 1) to compare carotid Doppler and echocardiographic findings in patients with SSC and SLE, and 2) to assess the relationship between these findings and right ventricular systolic pressure (RVSP).

Methods: This is a prospectively observational study. We enrolled 46 patients from Dec. 2012 to Jun. 2013.The inclusion criteria were 1) All SSC patients, 2) SLE with exertional dyspnea. We evaluated comprehensive echocardiography and carotid Doppler. Possible PH was defined if the RVSP was more than 37mmHg. Unlike PH was defined if the RVSP was less than 37mmHg.

Results: The mean value of common carotid artery (CCA) intima-media thickness (IMT) in SSC (0.61 [0.57-0.78] mm) was significantly thicker than in SLE (0.55 [0.49-0.63]; p=0.016).

7 out of 23 SSC patients and 6 out of 23 SLE patients had possible PH. The ratio of early diastolic transmitral filling velocity to early diastolic septal mitral annular velocity (E/SE') (21.9 [17.0-30.5]) in possible PH and SLE group was significantly higher than in unlike PH and SLE group (9.7 [7.6-12.9]) ($p<0.001$). Ejection fraction (EF) (56.3 [48.5-64.8] %) and early diastolic septal mitral annular velocity (SE') (5.0 [3.8-5.9]) in possible PH and SLE group were significantly lower than in unlike PH and SLE group (68.1 [64.8-72.4], p=0.003; 9.0 [6.2-10.6], p=0.001).

There was significant inverse correlation between SE' and RVSP ($r = -0.633$, $p = 0.001$), correlation between E/SE' and RVSP ($r = 0.864$, $p < 0.001$) and inverse correlation between EF and RVSP ($r = -0.646$, $p = 0.001$) in SLE group. But, the correlations between SE', E/SE', EF and RVSP in SSC group were not observed. The correlation between the mean value of CCA IMT and RVSP in SLE was observed ($r = 0.416$, $p = 0.048$). In multivariate regression analysis, in dependent predictor of increasing RVSP was only E/SE' in SLE ($r2 = 0.874$, $\beta = 0.971$, 95% CI = 0.422-1.520, $p = 0.002$).

Conclusion: Arterial stiffness in SSC was higher than in SLE. Diastolic dysfunction seems to be an important cause of PH in SLE.

PS187 SURVIVAL AT PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITHSYSTEMIC SCLEROSIS: SINGLE EXPERT CENTRE EXPERIENCE

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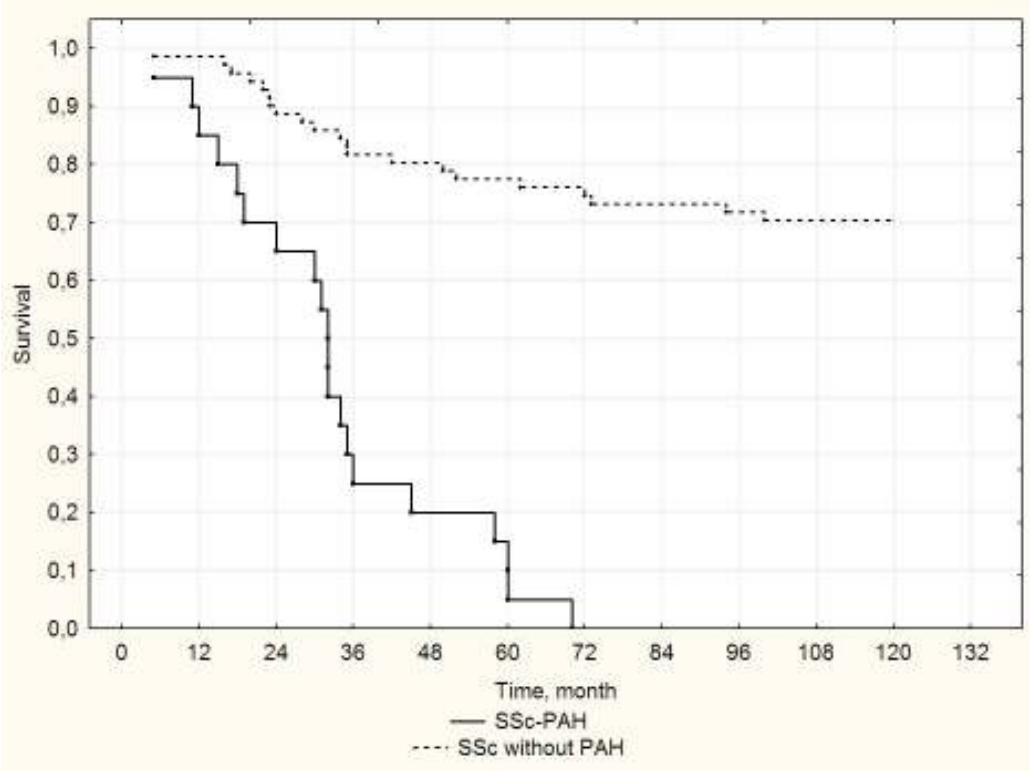
OBJECTIVES:
To measure survival in patients with systemic sclerosis associated pulmonary arterial hypertension (SSc-PAH) in natural history.
METHODS:
Twenty two patients with SSc-PAH and 100 SSc patients without PAH were included in the period between 1998 and 2008 year when the PAH specific therapy in Russia were not available. Patients were given basic treatment (diuretics, digoxin, oxygen and warfarin). Survival was measured from the date of diagnosis of pulmonary hypertension by cardiac catheterization.
RESULTS:
The 1-, 3-, and 5-year Kaplan-Meier survival rates were 85, 25 and 5%, respectively in the SSc-PAH group and 99, 85 and 75% in the SSc patients without PAH. The median survival SSc-PAH patients after diagnosis PAH by cardiac catheterization were 30 month. The hazard ratio for total mortality in the SSc-PAH group was 6.8 [95% confidence interval (CI) 2.1–16.7] compared to SSc without PAH ($p < 0.001$).
CONCLUSION:
SSc-PAH patients had a higher risk of death than SSc patients without PAH. The data obtained are comparable with results obtained previously; indicate the nature of a fatal disease in the absence of specific PAH therapy.



PS188 ECHOCARDIOGRAPHIC ALTERATIONS IN A SERIES OF PATIENTS WITH SYSTEMIC SYSTEMIC SCLEROSIS

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Aims: To describe the prevalence and types of echocardiographic abnormalities in a cohort of patients with scleroderma.
Material and method: A descriptive study based on the assessment of echocardiograms performed on a cohort of patients diagnosed with sistemic sclerosis and followed up in a specialized unit in systemic autoimmune diseases at an Andalusian (Spain) third level hospital. Most echocardiograms were performed as part of the screening program of pulmonary arterial hypertension that is being carried out in our unit.
Results: 149 patients (pts) were assessed. Echocardiograpic alterations were detected in 112 pts (75.1%): 1) Tricuspid insufficiency in 75 (50.3%, mild in 86.6%), and was associated with high systolic pulmonary pressure in 43 pts (57.3%) and with dilated right cardiac chambers in 11 pts (14.7%). 2) Left ventricular (LV) hypertrophy in 40 (26.8%): mild in 36 (90%) and moderate en 4 (10%). 3) Diastolic dysfunction in 36 (24.2%), light in all but 1. 4) Aortic valvulopathy en 22 (14.8%) with insufficiency in 18 (12.1%): mild in 16 (88.9%) and moderate in 2 (11.1%) and stenosis in 4 (2.7%mild in all of them). 5) Mitral valvulopathy in 19 pts (12.7%) with insufficiency in 18 (12.1%): mild in 15 (83.3%) and moderate in en 3 (16.7%); stenosis in 1 (0.6%). 6) Pericardial effusion in 9 (6%), mild in 8 (88.9%) and moderate in 1. 7) Other alterations: left atrial dilations en 15 pts (10.1%), left ventricle diastolic dysfunction in 1 (0.7%).
Discussion: Cardiac involvement is a serious manifestation of scleroderma is associated with decreased survival. The frequency of subclinical involvement depends on the methods used for its detection and echocardiography, along with clinical assessment, remains the tool of choice for early diagnosis.
Conclusions: 1) By systematic echocardiographic study, we found a very high prevalence of alterations among patients with scleroderma. 2) Valvular dysfunction, especially tricuspid, with or without underlying elevation in pulmonary artery pressure, was the most frequent abnormality found. 3) A high prevalence of diastolic dysfunction and other frequently associated data, such as left ventricular hypertrophy and left atrial enlargement were detected.

PS189 ELEVATED SERUM LEVELS OF MACROPHAGE MIGRATION INHIBITORY FACTOR (MIF) AND STEM CELL GROWTH FACTOR BETA (SCGF BETA) IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION (PAH)

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Background: Pulmonary Arterial Hypertension (PAH) is an important vascular disease that can be either idiopathic or secondary to autoimmune diseases, in particular it represents one of the most threatening complications of Systemic Sclerosis (SSc). Macrophage Migration Inhibitory Factor (MIF) and Stem Cell Growth Factor β (SCGF-β) are pleiotropic cytokine with important proinflammatory and immunoregulatory functions. MIF appears to be important in determining the endothelial damage and seems to contribute to lung hypoxic vasoconstriction in murine models and to play a key, but controversial, role in wound repair (1,2). Moreover in SSc patients serum levels of MIF are increased compared to healthy controls and has been associated with the development of ulcers and PAH (3,4). SCGF-β is also involved in the pathogenesis of some demyelinating neuropathies and its levels increase in idiopathic dilated cardiomyopathy (5,6).
Objectives: The aim of our study was to measure serum levels of MIF and SCGF-β in SSc patients with and without PAH as well as in those with primary PAH.
Patients and Methods: We enrolled 15 SSc patients with PAH and 13 with primary PAH. We also selected 14 SSc patients without PAH, matched for sex and age. PAH was confirmed by right hearth catheterism (PAPm>25 mmHg).MIF and SCGF-β were measured by ELISA (Bio-Rad Laboratories).
Results: We found significantly higher circulating levels of MIF and SCGF β compared to those SSc patients without PAH, both in patients with primary PAH (MIF median 270 pg/ml vs 175 pg/ml, p = 0.03; SCGF-β median 18845 pg/ml vs 12054 pg/ml, p = 0.004) and with PAH secondary to SSc (MIF median 333 pg/ml vs 175 pg/ml, p = 0.02; SCGF-β median 17804 pg/ml vs 12054 pg/ml, p = 0.02). No statistically significant difference was found between the two groups of patients with PAH, either idiopathic or secondary to SSc.
Conclusions: From these preliminary data we can hypothesize that MIF and SCGF-β are able to play a role in the development of PAH in both primary or secondary forms. These circulating factors may be evaluated in the future as useful biomarkers for this serious vascular disease.

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PS190 SOME DIFFERENCES BETWEEN CONNECTIVE TISSUE DISEASE-ASSOCIATED AND IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION AT THE TIME OF DIAGNOSIS

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BACKGROUND: Pulmonary arterial hypertension associated with connective tissue disease (CTD-PAH) has certain distinct features and portends a worse prognosis in comparison with idiopathic pulmonary arterial hypertension (IPAH). We tried to determine the differences between patients with CTD-PAH and IPAH in a single centre at the time of diagnosis.
PATIENTS AND METHODS: We retrospectively analyzed 17 consecutive patients with CTD-PAH and 25 with IPAH. The underlying disease in the CTD-PAH group was systemic sclerosis in 10 pts, systemic lupus in 3, rheumatoid arthritis in 2, and other CTD in 2. In all patients, PAH was newly diagnosed by a comprehensive diagnostic algorithm including right heart catheterization and was irreversible in the acute vasodilator challenge. Age, sex, body mass index (BMI), functional class, systolic, mean and wedge pulmonary arterial pressures, right atrial pressure, cardiac index, pulmonary vascular resistance, creatinine, and NT-proBNP levels at diagnosis were compared between the groups. Differences were assessed using Student's t-test.
RESULTS: Patients in the CTD-PAH group had similar age (median 52 vs 49 years), BMI (24.2±5.8 vs. 27.8±7.3 kg/m2), functional class (3.0±0.6 vs 3.2±0.6), pulmonary artery wedge pressure (8.8±2.4 vs 9.5±2.7 mm Hg), right atrial pressure (11.5±8.3 vs. 9.7±5.4 mm Hg), cardiac index (2.3±0.5 vs 2.2±0.6 L/min/m2), as well as creatinine level (86±24 vs 88±27 umol/L) as the IPAH pts (p=n. s. for all). Systolic and mean pulmonary artery pressures were lower in the CTD-PAH than in the IPAH group (67±21 vs 85±26 mm Hg and 44±11 vs 56±19 mm Hg, resp., $p<0.05$ and $p<0.01$, resp.), as well as pulmonary vascular resistance (9.3±3.8 vs 12.5±5.7 Wood units, $p<0.05$). NT-proBNP level was significantly higher in the CTD-PAH group (4410±3320 vs 2373±2220 pg/mL, $p<0.05$).
CONCLUSION: In comparison with their IPAH counterparts, CTD-PAH patients (majory with systemic sclerosis) had lower systolic and mean pulmonary artery pressures and pulmonary vascular resistance with similar cardiac index at the time of diagnosis. Despite similar age, sex, functional class, renal function, ventricular filling pressures, and smaller right ventricular afterload and thereby systolic strain, NT-proBNP level was higher in CTD-PAH patients. This may indicate that the right ventricle fails at lower afterload in CTD, probably due to participating intrinsic myocardial damage.

PS191 PULMONARY ARTERIAL HYPERTENSION IN A CONTEMPORARY DRUG REGISTRY: RESULTS OF THE VOLT STUDY, WITH AN EMPHASIS ON PAH ASSOCIATED WITH CONNECTIVE TISSUE DISEASE

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VOLT (VOL-ibris Tracking), an EMA regulatory required study, is an open-label, prospective, observational, multicenter registry that has been structured to collect safety information on ambrisentan (AMB) to treat pulmonary arterial hypertension (PAH) when used in clinical practice. Here we present the results with an emphasis on PAH associated with connective tissue disease (CTD).

Methods: Between June 2008 and May 2011, a total of 1003 patients were included in the VOLT programme, of which 238 had a diagnosis of PAH associated with CTD. The study closed in May 2013, 2 years after the final patient was included.

Results & Conclusions: Results will include baseline demographics (aetiology, age, sex, time since diagnosis, functional class, previous PAH therapy, etc), exposure to ambrisentan, discontinuations, adverse events (with an emphasis on AEs of Special Interest (Liver Function Abnormalities, Anaemia, Pregnancy and Hypotension)), death and functional class. Conclusions will be based on the data presented.

PS192 PREVALENCE OF PULMONARY HYPERTENSION IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Introduction: This study analyzed the prevalence of Pulmonary Arterial Hypertension (PAH) in a cohort of patients with Systemic sclerosis (SSc) and correlated with the clinical form of the disease.

Objective: To describe the epidemiological profile of patients included in the study and compare the results between limited and diffuse forms of SSc.

Methods: 44 patients were included during two years. The diagnosis of PAH was considered when measurement of pulmonary artery systolic pressure (PASP) was higher than 25 mmHg at rest, by Doppler echocardiogram. The patients were divided according to the form of disease, sex, age and WHO Functional Classification of PAH.

Results: The sample consisted of 20 patients with the limited form (45.45%) and 24 (54.55%) with the diffuse form. Eleven of these (25%) were diagnosed with PAH, six (54.55%) with diffuse SSc and five (44.45%) with limited form.

Discussion: There was a relative high incidence of PAH in our series and slight predominance of PAH in diffuse form, probably due to concomitant pulmonary interstitial fibrosis. There was not a constant relationship between clinical manifestations of HAP and the values of PASP.

Conclusion: Premature screening and periodic monitoring of PASP in patients with SSc is essential for early detection of PAH. The authors didn't observed significant difference in prevalence and symptoms between limited and diffuse form of SSc.

PS193 CARDIOTHORACIC RATIO IN CHEST RADIOGRAPHY MAY FORECAST THE OCCURRENCE OF PULMONARY HYPERTENSION IN SYSTEMIC SCLEROSIS

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Background/Aims: The pulmonary hypertension of systemic sclerosis (SSc) is poor prognosis, so early diagnosis is important. The cardiac catheterization is used for diagnosis of pulmonary hypertension (PHT). But cardiac catheterization is invasive technique so echocardiography is used widely in convenient. But it is also expensive technique also. Cardiothoracic (CT) ratio measured by chest radiography is inexpensive technique and easily measured in outpatient clinic. So we investigated the correlation of increased CT ratio in chest radiography and occurrence of pulmonary hypertension in scleroderma.Method: 28 consecutive patients with confirmed SSc (22 females, 6 males, mean age 51.1±2.1 years), with mean time of 91±6.7 months from SSc diagnosis, were prospectively included in the study. Two chest radiography were obtained for each during the course of this study. first chest radiography was checked at diagnosis and second chest radiography was checked at research time. The enrolled subjects were agreement on echocardiography and measurement of brain natriuretic peptide. The statistical method was SPSS software version 11.0 (SPSS Inc., Chicago, IL, USA). Results: Four patients were estimated to pulmonary hypertension by echocardiography. The one patient who taken cardiac catheterization and confirmed to pulmonary hypertension, had severe resting dyspnea and the other had no clinical symptoms. The increased right ventricular systolic pressure is relation to the increase of CT ratio (CT ratio>0.55) in chest radiography ($p<0.05$) and increased brain natriuretic peptide in blood ($p<0.05$). Conclusion: The increased of CT ratio (>0.55) in chest radiography is relation to increased right ventricular systolic pressure in systemic sclerosis outpatients. So the periodic checked chest radiography is important for early detection of the asymptomatic pulmonary hypertension in systemic sclerosis patients.

Table 1. Characteristics of the 28 patients enrolled in this study

	High pulmonary pressure (n=4)	Normal pulmonary pressure (n=24)	p-value
sex, female(n)	4	18	< 0.05
median age(years)	60.50±11.67	50±1.22	< 0.05
median disease duration(months)	102.90±30.20	91±18.21	< 0.05
median BNP(pg/mL)	183.00±376.77	92±79.87	< 0.05
median C/T ratio	0.56±0.01	0.47±0.14	< 0.05
with ILD (n) UIP/NSIP	4 1/3	9 2/7	< 0.05
median right ventricular systolic. pr.(mmHg)	57.25±2.78	25±4.04	< 0.05
with anti-scl-antibody(n)	3	12	

BNP: Brain natriuretic peptide, C/T ratio: cardiothoracic ratio, Pulmonary a. pr.: pulmonary arterial pressure, ILD: interstitial lung disease, UIP: Usual interstitial pneumonia, NSIP: Non-specific interstitial pneumonia

Figure 1. The correlation of right ventricular systolic pressure and cardiothoracic ratio. (Pearson correlation coefficient: -0.06, p-value: 0.003, Relative risk: 4.00 (95 % confidence interval: 2.00 – 7.99))

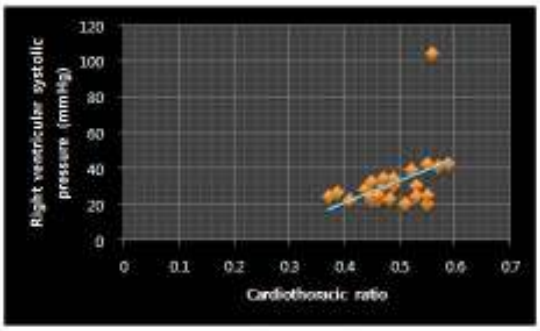


Figure 2. The correlation of pulmonary hypertension and brain natriuretic peptide. (Pearson correlation coefficient : -0.05, p-value: 0.00, Relative risk : 0.11 (95 % confidence interval : 0.01 ~ 1.28))

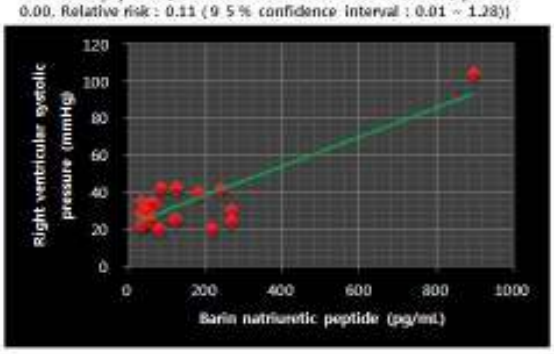
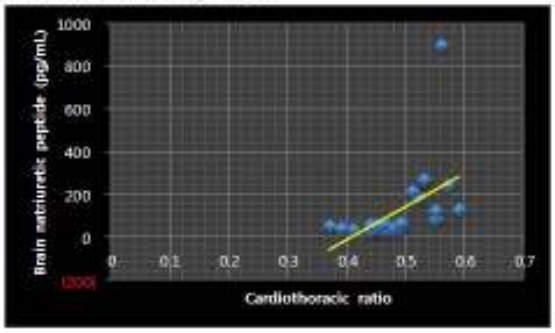


Figure 3. The correlation of brain natriuretic peptide and cardiothoracic ratio ($p<0.05$)



PS194 EARLY PULMONARY HIPERTENSION AND EARLY PULMONARY FIBROSIS: HOW CAN I TREAT? AND WHO IS THE FIRST ?

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Pulmonary Arterial hypertension and Pulmonary Fibrosis are two of the most important mortality causes in patients with systemic sclerosis. The treatment must be intense and immediate.
What we still do not know is what to do with patients that have both complications in early stages. Pulmonary hypertension has a specific treatment that should be avoided when we have evident pulmonary fibrosis, but we show a case of early fibrosis that do not demanded specific treatment and had early confirmed pulmonary arterial hypertension. Another discussion is pulmonary hypertension with small increase of pulmonary capillary pressure suggesting a concomitant myocardial dysfunction. The ideal to these patients was to have diffusion monoxide tests, dynamic cardiac catheterism to confirm initial diastolic dysfunction that echocardiogram cannot diagnose and a more accurate thorax tomography interpretation. Definitively it is not our reality. Our patient is a 38 years old woman with confirmed systemic sclerosis and a thorax computed tomography with incipient fibrosis in lower pulmonary lobes, an espirometry without restriction, no monoxide diffusion study, a cardiac catheterism with pulmonary artery median pressure of 26 mmhg , systolic pulmonary artery pressure of 35 mmhg and a capillary pulmonary pressure of 12 mmhg. A normal six minute walking test and she refers dyspnea to big efforts. The discussion is to initiate immediately sildenafila or wait to check if the fibrotic component increase and become more important than the pulmonary arterial hypertension. We decided to wait and make new echocardiogram each three months, but is that the best option?

PS195 CLINICAL USEFULNESS OF MEASURING RED BLOOD CELL DISTRIBUTION WIDTH (RDW) IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Objectives. Red blood cell distribution width (RDW) is a biomarker quantifying variability of red blood cell size in peripheral blood. Elevated RDW has been found an independent prognostic factor for cardiovascular events. Systemic sclerosis (SSc) is characterised by generalised micro- and macroangiopathy. Our aim was to investigate RDW as a potential biomarker for the assessment of the severity of vascular involvement.
Patients and Methods. One-hundred and sixty-eight consecutive SSc patients, 62 with diffuse cutaneous (dcSSc), 106 with limited cutaneous SSc (lcSSc) were investigated at baseline and after 1-year follow-up. Measurements in 93 patients with primary Raynaud's phenomenon and 40 healthy subjects served as control groups.
Results. The median RDW value of patients with SSc was higher 14.2% (13.5-14.8, 25-75% percentiles) compared both to the group of primary Raynaud's cases 13.9% (13.4-14.4; $p<0.05$) and to healthy volunteers 13.6% (13.2-13.8; $p<0.01$).
DcSSc and anti-topoisomerase antibody positive cases showed elevated RDW values compared to lcSSc and anti-topoisomerase antibody negative cases ($p<0.05$), respectively. RDW showed positive correlation with the inflammatory markers including ESR ($p<0.05$), CRP ($p<0.05$) and negative correlation with forced vital capacity ($p<0.05$) and diffusing capacity of the lung (DLCO) ($p<0.05$) during the follow-up.
A rise of RDW more than 5% during follow-up was associated with an average 8.9% decrease of ejection fraction (LVEF) and 7% of DLCO and these associations were independent from each-other.
Conclusion. RDW in SSc may represent an integrative measure of multiple pathologic processes including extensive vasculopathy, fibrosis, or ongoing inflammation. An increase in RDW value may indicate an impairment of cardio-respiratory functions.

PS196 ARRHYTHMIAS AND HEART CONDUCTION DISTURBANCES IN PATIENTS WITH SCLEROSISSYSTEMIC

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Conduction disturbances in SSc are mostly due to the fibrosis of the sinoatrial node, but direct involvement of the cardiac conduction tissue and its arterial blood supply has also been reported. Objectives: to assess conduction disturbances and cardiac arrhythmias in a consecutive and non selected series of patients with Sclerosis Systemic..Patients and Methods: a total of 142 (122Women-20Men) unselected consecutive pts with SSc were included in our study. They had mean age 51.2 years (range 13-84), disease duration 12.2 years ± 7.5 (range 1-24). All met the preliminary American College of Rheumatology classification criteria for SSc. And according skin cutaneous subsets: 16 pts (11.3%) with Early Sclerosis, 12 pts (8.4%) with intermediate cutaneous SSc, 72 pts (50.7%) with Limited cutaneous SSc, 42 pts (29.6%) with Diffuse cutaneous SSc. As expected all pts suffer from Raynaud's Phenomenon and nailfold videocapillaroscopy (NVC) was performed on all patients, and skin sclerosis was measured with Rodnan Skin Score (mRSS).All the patients were assessed for cardiac complaints according to the World Health Organization (WHO) functional class, electrocardiogram (ECG) abnormalities, trans-thoracic echocardiography (EchoCG) and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. A subset of 49 pts underwent 24 –h-Holter-ECG recording. Results Only 14 pts (9,8%) presented functional class 3-4 according to the WHO classification. Elevated NT-proBNP levels were present in 45 pts (31,6%). EchoCG abnormalities were present in 70 pts (49,2%): left atrial enlargement in 42 pts (35,2%),left heart dysfunction in 16 pts (11,2%),valve abnormalities, mostly tricuspid regurgitation, in 18 pts (12,6%). Possibly or definitely abnormal ECGs were found in 44 pts (30,9%),20 pts (14%) had AV conduction abnormalities, 5 pts with pacemaker due to AV II block. Left bundle branch block was found in 10 pts(7,0%).7 pts (4,9%) had septal q wave pattern with narrow QRS complex. Three patients (2,1%) had left ventricular hypertrophy and four patients (2,8%) unspecific ST-T wave abnormalities. A subset of 49 pts underwent 24 –h-Holter-ECG recording: thirty-three patients had normal recording, 16 /49 pts (11,2%) abnormal recording. The most common finding was an increased number of extrasystoles, eight had > 1000VES/24h,7 pts had non-sustained ventricular tachycardia,3 pts atrial arrhythmias, 2 pts AV II block.Conclusion Despite the mild clinical complaints, cardiac abnormalities in EchoCG were found in 49,2% of pts.

PS197 ECHOCARDIOGRAPHY OF THE RIGHT VENTRICLE IN PATIENT WITH SYSTEMIC SCLEROSIS AND RELATED CTD

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Systemic sclerosis has serious prognosis in the case of the development of organ complications. Epecially life limiting are both the lung impairment and the development of severe pulmonary hypertension. Echocardiography at our deparment is performed routinely in all patients with connective tissue diseases. Suspicion or diagnosis of pulmonary hypertension is found by echocardiographic screening in lower percentage of patients only. A number of authors therefore search for non-invasive predictors of pulmonary hypertension, such as exercise induced pulmonary hypertension. The aim of our study is to evaluate the importance of deformation analysis (global longitudinal strain by speckle tracking) of right vectricle free wall, and other parametres of systolic and diastolic function of the right ventricle from the point of their predictive potential in patients with systemic sclerosis and other related diseases. We present our first results and their possible benefits for the detection of pulmonary hypertension in the group of 25 patients at our centre.

PS198 ASYMPTOMATIC CARDIAC INVOLVEMENT IN THAI SYSTEMIC SCLEROSIS: PREVALENCE AND CLINICAL CORRELATION

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Background: Cardiac involvement is one of the most serious manifestations of systemic sclerosis (SSc). Its existence in asymptomatic patients has already demonstrated, however, the true prevalence and impact on clinical outcomes has never been evaluated.
Objectives: To identify the prevalence of cardiac involvement and clinical correlation in asymptomatic Thai scleroderma patients.
Methods: A cross-sectional study of adult SSc patients without signs and symptoms suggestive cardiac involvement was performed. All patients were followed up at Srinagarind Hospital, KhonKaen University, Thailand, during January 1, 2005-December 31, 2011. We excluded the patients who had symptoms overlap with other connective tissue disease, serum creatinine >1.4 mg/dl, having any atherosclerosis risk factors, history of cardiac diseases, or receiving angiotensin converting enzyme inhibitors. Among illegible patients, all tests were performed in one study visit; including echocardiography, electrocardiography, chest radiography (CXR), inflammatory biomarkers, cardiac enzymes and NT-proBNP.
Results: A total of 103 SSc patients were enrolled (female to male ratio=3:1) of which majority are diffuse SSc subset (dcSSc) (61.2%). Data analysis was done after non-specific diastolic dysfunction (73.2%), was excluded. Sixty-three patients had at least 1 test abnormality with the prevalence of 61.2% (95%CI 51.6-70.7). Rising high-sensitivity cardiac troponin-T (hs-cTnT) above 99th percentile of reference limit was the most common cardiac abnormality (33.0%) followed by cardiomegaly based on CXR (17.8%) and prolong QT interval (14.6%). By multivariate analysis, the only predictor of cardiac involvement is dcSSC subtype (OR=3.37; 95%CI 1.07-10.65), that also significantly associated with hs-cTnT level, higher CK-MB level and more prolong QT interval compared to limited subtype (p=0.01, 0.02 and 0.03 respectively). We found correlation between cardiac enzymes with modified Rodnan skin score, tendon friction rub, ground glass appearance from HRCT, NT-proBNP and QT interval; whereas negative correlation with disease duration. Rising cardiac enzymes was neither correlated with inflammatory markers nor the maximal tricuspid regurgitation velocity (p=0.29 and 0.47, respectively).
Conclusion: There was a high prevalence of cardiac involvement among asymptomatic Thai SSc particularly dcSSc subtype. Raising hs-cTnT, probably from subclinical myocardial injury, is the most common abnormality. Correlation with long term clinical outcome will be performed in our future study.

PS199 CORRELATION BETWEEN CARDIAC MAGNETIC RESSONANCE IMAGING AND ECHOCARDIOGRAPHY IN SYSTEMIC SCLEROSIS

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Objectives: To describe cardiac magnetic resonance imaging (CMRI) findings indicated in actual clinical situations, in a cohort of patients with SSc cardiac involvement (CI), and correlate them with contemporary echocardiography results held in our database.

Material and methods: Twenty one patients from a 413 subject cohort were enrolled from February 2002 to April 2013. They presented definite CI or high suspicion of it. They underwent CMRI with gadolinium contrast using a 1.5T system (Symphony, Siemens, Germany), with a 4-element phased array antenna obtaining functional sequences of multislice
cine-MRI.

Results: Seventeen patients (81%) were women. SSc subset distribution was: 10 (47.6%) limited SSc, 9 (49.2%) diffuse SSc, 1 (4.8%) sine SSc and 1 (4.8%) pre scleroderma. Immunologically, antinuclear antibodies were present 20 (95.2%) patients, anticentromere antibodies in 5 (25%) patients, and antitopoisomerase-I antibodies in 6 (30%) patients. Baseline characteristics were: digital ulcers 14 (66.7%), osteomuscular impairment 12 (57.1%), esophagic involvement 17 (81%), interstitial lung disease 15 (71.4%), pulmonary arterial hypertension 9 (42.9%) and none with scleroderma renal crisis. The frequencies of cardiovascular risk factors were: High blood pressure in 5 (23.8%) patients, dyslipidemia 7 (33.3%), diabetes mellitus 2 (9.5%) and smoking 5 (23.8%).
CI was known in 20 patients: pericardial involvement 3 (14.3%), ischemic cardiopathy 5 (23.8%), conduction alterations 6 (28.6%). Echocardiographic findings were:
left ventricle hypertrophy (LVH) in 9 (42.9%) patients, diastolic dysfunction in 19 (90.5%) and pericardial effusion in 3 (14.3%). Median tricuspid annular plain systolic excursion (TAPSE) was 20mm and median left ventricle ejection fraction (VEF) was 63%. CMRI findings were: LVH in 4 (19%) subjects, none with diastolic dysfunction, pericardial effusion in 11 (52.4%). Median right and LVEF were both 59%. Left VEF detected by echocardiography and CMRI showed a moderate reliability (Intraclass correlation coefficient=0.55, p=0.004) and a moderate correlation was found between TAPSE and Right VEF (R=0.49, p=0.033). Unweighted kappa for LVH, DD and pericardial effusion assessed by echocardiography and CMRI didn´t show significant reliability.

Conclusion: CMRI seems to have good correlation and reliability compared with echocardiography regarding functional parameters of both right and left VEF. Important differences were noted in heart structural findings (LVH and pericardial effusion), where it may be more sensible. The role of CMRI in clinical practice is still unclear, but it may be more rentable in patients strongly suspicious to have CI in order to prevent further complications.

PS200 CHARACTERISATION OF SUB-CLINICAL PRIMARY MYOCARDIAL DISEASE IN SYSTEMIC SCLEROSIS - PRELIMINARY FINDINGS FROM A CARDIAC MAGNETIC RESONANCE AND ELECTROPHYSIOLOGICAL STUDY

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Background: Clinically overt primary myocardial disease in SSc carries a poor prognosis. The natural history is poorly understood, with no clear approach to identifying the 'at-risk' patient. Cardiac MR (CMR) is a sensitive tool for detecting functional changes, tissue characterisation and perfusion changes. CMR studies in SSc have rarely correlated with disease phenotype.

Objectives: To identify the patient with SSc most at risk of primary myocardial disease and better understand the pathophysiological mechanisms, through the use of soluble cardiovascular (CV) biomarkers, electrophysiological testing and CMR. This study is a collaborative initiative between rheumatologists and CMR cardiologists.

Method: Fifty patients fulfilling SSc ACR/Le Roy criteria with no known CV disease or diabetes mellitus are being invited for clinical assessment, nail-fold capillaroscopy (NFC), soluble CV biomarker collection, echocardiography and 3T CMR with late-gadolinium enhancement (LGE) and stress perfusion. A subset (n=20) will also undergo 24-hour ambulatory ECG monitoring, autonomic testing and insertion of an implantable loop recorder (REVEAL device), repeating the electrophysiological tests and CMR yearly for 3 years. Preliminary CMR findings are reported in comparison to healthy controls.

Results: Of the 11 patients recruited to date; mean (SD) age 54 (16) yrs, 7 female, 7 limited cutaneous(lc)SSc/4 diffuse cutaneous(dc)SSc, mean (SD) disease duration (time from first non-RP) 9.6 (7.3) yrs. 2 Scl70+ve, 3ACA+ve. Mean (SD) mRSS 2.9 (2). 5 have interstitial lung disease. Smoking status: 1 current, 8 ex, 2 never. 3 have known hypertension. NFC patterns: 5 early, 3 active, 1 late and 1 non-specific.

On CMR: median (interquartile range) left ventricular ejection fraction 65% (57-66%), extra-cellular volume (ECV) fraction 33% (28-35%) and myocardial perfusion reserve (MPR) 1.77 (1.60-2.21). One hypertensive patient had LGE in the lateral, mid-ventricular wall. ECV increased and MPR decreased with age (rho=0.657, p=0.039; rho= -0.75, p=0.02 respectively). A non-significant trend for a higher ECV was noted in lcSSc (median ECV 33% vs. 28% dcSSc) and disease duration >10 years (median ECV 34% vs. 31% <10 years). MPR was lower in lcSSc (median 1.76 vs. 2.14 in dcSSc), but there was no strong association with disease duration. MPR was lower in SSc subjects compared to healthy controls (n=9) (1.77 vs. 2.80 respectively, p=0.03).

Conclusion: This initial report indicates the potential of detailed cardiovascular investigation including CMR in the detection of SSc myocardial disease and determining the at-risk patient. All patients will be recruited by early 2014 at which point additional analysis will be undertaken. This study also highlights the utility in specialist expertise collaborations.

PS201 SUBTLE IMPAIRMENT OF RIGHT VENTRICULAR FUNCTION IN SYSTEMIC SCLEROSIS WITH LUNG FIBROSIS DETECTED BY TISSUE DOPPLER

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Background. Systemic sclerosis (SSc) is an autoimmune connective tissue disease that courses with fibrosis and microvascular occlusion, involving skin and visceral organs, including lungs and the heart. It is not clear whether involvement of the right ventricle (RV) results from direct organ lesion or indirectly by pulmonary hypertension.
Objective. To assess the relationship between RV performance and lung involvement in SSc.
Methods. Fifty-one consecutive patients from the Scleroderma Outpatient Clinic were submitted to tissue Doppler echocardiography and chest high resolution computed tomography (HR-CT). RV function was evaluated by means of RV fractional area change (FAC), tissue Doppler (systolic) velocity, myocardial performance index (MPI), and tricuspid annular plane systolic excursion (TAPSE). Pulmonary artery systolic pressure (PAP) was estimated by tricuspid regurgitation. Additionally, left ventricular systolic (ejection fraction) and diastolic (transmitral Doppler and mitral annulus tissue Doppler) function was also evaluated. Chest HR-CT was used to assess interstitial lung disease (ILD). According to the CT results, patients were divided in two subgroups: Group I, including patients with ILD, and Group II with no ILD.
Results. Out of the 51 SSc patients, 37 were female, aged 52 + 12 years; all patients had normal ventricular function, as assessed by LVEF > 55% and FAC > 40%. 43 patients had chest HR-CT. There was no significant difference age or disease duration in groups I (n = 26) and II (n = 17). Except for decreased tissue Doppler velocities, all indexes of RV performance were similar for both groups.
Conclusion. In patients with SSc and ILD, tissue Doppler systolic velocities seems to identify early myocardial involvement, despite a preserved RV systolic performance

PS202 CARDIAC TROPONIN T AND ANTI-CARDIAC TROPONIN I ANTIBODIES IN PATIENTS WITH SYSTEMIC SCLEROSIS: A MONOCENTRIC, RETROSPECTIVE PILOT STUDY

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Background: Cardiac troponins (cTn) are widely used as biomarkers for the diagnosis and quantitation of cardiac injury (1). Autoantibodies against cTn, especially against cTnI (anti-cTnI), have been recently described in association with cardiac dysfunction (2). However, their clinical significance is still unclear. Systemic sclerosis (SSc) is a chronic autoimmune connective tissue disease that is associated with heart involvement, although often clinically occult (3,4). Hence, the value of elevated cTn levels and a possible autoimmune response against cTnI as biomarkers in patients with SSc were the aims of this study.

Methods: Out of our monocentric SSc cohort we retrospectively identified 113 of 190 patients in whom routine laboratory assessment including high-sensitive cTnT was performed. Stored biosamples, available for 60/113 patients (53.1%), were used to assess auto-cTnI titres as previously described (5). A 2x2 table, using chi-square test, compared the results of cTnT and anti-cTnI. If available, cardiac magnetic-resonance-imaging (cMRI) data were retrospectively evaluated to assess early myocardial gadolinium enhancement (T1 ratio, as a marker for hyperemia and capillary leakage) as well as edema (T2 ratio).

Results: Out of 113 patients with available results for cTNT, 41 patients (36.3%) had a positive and 72 (63.7%) a negative result. Biosamples were available for 21 cTNT positive and 39 cTNT negative patients. Anti-cTnI were detected in 17 samples (28.3%): in 8 (38.1%) cTNT positive compared to 9 (23.1%) cTNT negative patients (p=0.218). Anti-cTnI-titres were 1:40 in 7, 1:80 in 6 and 1:160 in 4 samples. cMRI data were available for three anti-cTnI positive patients (all diffuse cutaneous subtype). All of them had a distinct change in the T1 ratio (6.4-8.9), not in the T2 ratio. Late enhancement (gold standard for the detection of myocarditis) was present in one patient (6).

Conclusion: The preliminary results of this pilot study suggest that cTnT levels are elevated in about one third of SSc patients, and anti-cTnI are present in about a third of cTNT positive patients. Additionally, anti-cTnI can be detected in about a quarter of cTNT negative patients. Whether cTNT and/or anti-cTnI autoantibodies might serve as new biomarkers in SSc heart disease need to be evaluated in further prospective trials.

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PS203 CARDIAC VALVE MORPHOLOGY AND LEFT VENTRICULAR FUNCTION IN PATIENTS WITH SYSTEMIC SCLEROSIS (SSC) AND MATCHED POPULATION CONTROLS

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Objective: To investigate cardiac valve morphology and left ventricular ejection fraction (LVEF) in patients with systemic sclerosis (SSc) and matched population controls. We also studied the occurrence and relationship between manifest cardiovascular disease (CVD) and abnormal echocardiography findings.

Methods. 110 patients (62±12 years) with SSc were compared with 105 age and gender matched population-based controls (61±12 years). CVD was defined as a history of objectively verified angina pectoris, myocardial infarction, cerebral infarction or intermittent claudication. Echocardiography was performed to assess valvular abnormalities and left ventricular function.

Results. 44 SSc patients had an abnormal echocardiogram compared to 23 subjects in the control population (P<0.001). On group level SSc patients had lower (but normal) LVEF (P=0.02). Three of the SSc patients had undergone valve replacement and one had a significant aortic insufficiency. Two subjects in the control group had undergone valve replacement. Valve thickening or valve prosthesis was found in 28 patients and 19 controls (NS). 20 SSc patients and 7 control subjects had previous CVD (p<0.01). Seven patients had previous myocardial infarction (MI), 8 had angina (among them two with MI), 7 patients had peripheral vascular disease, among them 5 had undergone surgery (2 of them also had an MI). Among patients with CVD 8 had valve thickening or prosthesis, 5 had LV hypokinesia, 3 had LVEF < 35, six had PAH (defined as TI velocity>2.9m/s). Among controls with CVD 3 had MI, 4 had CVL. Three controls vith CVD had valve thickening, all had normal LVEF and none had PAH.

Conclusion: SSc patients have a higher prevalence of abnormal echocardiograms than population based controls and previous CVD was also more common among SSc patients. On group basis SSc patients had lower (but normal) LVEF though more SSc patients than controls had regional hypokinesia (P=0.02). Valve thickening or valve prosthesis was not more common among the SSc patients than among population controls.

PS204 PERICARDECTOMY ON CONSTRICTIVE PERICARDITIS AND DIFFUSE SYSTEMIC SCLEROSIS: FORTUITOUS ASSOCIATION?

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Aims: Asymptomatic pericardial effusions commonly occur in SSc. Moreover it's observed also large effusions causing tamponade and can even occur prior to skin thickening and the diagnosis of SSc. We report 2 singular cases of constrictive pericarditis witch are associated in the following by the appearance of diffuse SSc

Case report :

•The initial case report is referring to 47 old woman witch antecedent – 15 years ago- is characterized by pericadectomy in constrictive pericarditis presumed tuberculosis and treated in both by surgical and medical treatment (6 months of anti-tuberculosis regimen). She developed progressively fibrosis pulmonary, progressive skin tightening, sclerodactyly, characteristic scleroderma facies, aperistaltic esophagus and right heart failure (arrhythmia). The investigation established the diagnosis of diffuse SSc and the right catheterization the diagnosis of primitive pulmonary hypertension. The symptomatic and specifically treatment improve the symptoms.

•The second case is similar and is referring to 36 years old woman witch developed 2 years after pericardectomy on presumed tuberculous constrictive pericarditis a diffuse SSc. The SSc is characterized by severe malabsorption syndrome (decreased peristalsis throughout the gastrointestinal tract, leading to bloating, stasis, and pseudo-obstruction crisis). The facies is characteristic and the others syigns are suggestive of the SSc diagnosis (hyperpigmentation, sclerodactyly, contracture, Raynaud phenomenon…). The treatment is optimized referring to the actualized recommendations and improve the digestive manifestations.

Discussion: Pericardial abnormalities in scleroderma are common and usually asymptomatic. However, clinically symptomatic pericardial disease (5%-16%) is much less frequent than autopsy-demonstrated pericardial involvement (33%-72%) as reported by many authors. Large pericardial effusions are exceptional and can lead to pericardial tamponade and are a marker for poor outcome. These situations are associated to right failure in heart disease, pulmonary hypertension and renal crisis. The constrictive pericarditis is not reported as common in SSs and constitutes a singular presentation (fortuitous association?)

Conclusion: Presumed as tuberculoses - referring to the epidemiological context – or attributed to viral infections some constrictive pericarditis could be the first expression in asymptomatic SSc (misdiagnosed SSc) particularly in the forms of the SSc without scleroderma and justify early immunological tests and nailfold capillaroscopy in indeterminate etiology of constrictive pericarditis.

PS205 SERUM GROWTH DIFFERENTIATION FACTOR 15 AND TRANSFORMING GROWTH FACTOR BETA 1 IN PATIENTS WITH SYSTEMIC SCLEROSIS AND EARLY REMODELING OF THE CARDIOVASCULAR SYSTEM

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BACKGROUND: Growth differentiation factor 15 (GDF15) and transforming growth factor beta 1(TGFBETA 1) have been reported to be involved in the pathophysiology of both systemic sclerosis (SSC) and some diseases of the cardiovascular system. there are a limited data about whether the involvement of the cardiovascular system SSC can be mediated by these factors.

AIM: The aim of the study was to assess serum GDF15 and TGF BETA 1 concentration in patients with ssc and to investigate its possible relationship to ssc-induced early remodeling of the cardiovascular system.

MATERIAL AND METHODS: Forty-nine women (age 51.1±11.8 years, nyha i/ii) with diagnosed ssc and twenty healthy controls (age 34.8±9.9 years) were enrolled into the study. pulmonary arterial hypertension, pulmonary fibrosis, left ventricle (lv) systolic dysfunction and valvular heart diseases were excluded in all of the patients. the organ systems involved in ssc was investigated. echocardiography, ultrasound vascular indexes: flow mediated dilatation, nitroglycerin mediated dilatation and arterial tonometry parameters: pulse wave velocity, pulse pressure and augmentation index were measured in all subjects. the above indexes were related to the serum concentrations of GDF15, TGF BETA 1.

RESULTS: Mean serum GDF15, TGF BETA 1 levels were significantly higher in ssc patients as compared to the controls (2831±2255 pg/ml vs 745,0±202.4 pg/ml and 17.3±10.8 ng/ml vs 15.6±13.2 ng/ml, respectively).
both GDF15 and TGF BETA 1 levels correlated with the degree of the skin involvement measured with as the modified rodnan score (r=0.598, r= 0.506; p<0.05). gdf15 levels correlated with transmitral e-wave/early diastolic mitral annular velocity (e/e') ratio (r=0.327, p<0.05). there were no significant correlations between GDF15, TGF BETA 1 and other echocardiographic indices of LV systolic, RV systolic/diastolic function or ultrasound and arterial tonometry parameters.

CONCLUSIONS:
Serum GDF15 and TGF BETA 1 levels are significantly elevated in ssc patients. GDF15 seems to be related to ssc-associated heart involvement and its possible role in the pathogenesis of lv diastolic dysfunction in patients with SSC is suggested.

PS206 DESCRIPTIVE STUDY OF CARDIOVASCULAR RISK FACTORS AND ENDOTHELIAL DISFUNCTION IN PATIENTS DIAGNOSED WITH SCLERODERMA AND MIXED CONECTIVE TISSUE DISEASE

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Objectives: Detection of cardiovascular risk factors (CRFs) and endothelial dysfunction (ED) in patients diagnosed with SSc and MCTD. Final objective will be creation of a longitudinal cohort of patients, carrying out an annual or six-monthly study depending on first assessment's findings. We present a descriptive study of the patients included from April up to November 2012.
Methods: Data were collected by previously designed questionnaire including CRFs, thrombosis, strokes and ICM. ESR, CPR, Chol, LDL, HDL, TG, 25OH-D and homocysteine levels were taken. Echographic protocol: 1. Carotid study, intima-media thickness (IMT) and presence of plaques. 2. Ankel branquial index (ABI), pathologic when ABI<0.9mm. 3. Endothelial dysfunction was assessed measuring abnormal brachial artery flow-mediated dilatation after a four minutes transient ischemia period.
Results: 33 patients, 84.8% women and 15.2 % men, 30 had Scleroderma (26 SSc and 4 morpheas) and 3 MCTD. The present and diagnose mea age were 51.2 (20-69) and 46.2 years (17-67). Disease's average time was 5 years (0-37). 7 patients had HTN, 2 DM, 11 HCL, 5 HTG, 6 smokers, 8 ex-smokers, 2 thrombotic episodes and none patient had suffered strokes or ICM. Mean BMI was 25.2 (18-50) and 39.4% had a BMI>25. The mean value of the different analytic parameters was: ESR: 12.3 mm/h, PCR: 1.9 mg/L, Chol: 203 mg/dL, 25OH-D: 33 ng/mL, homocystein 12µmol/l. Furthermore 3 patients had aCL and 3 B2GPI antibodies. 69.7% patients were treated with steroids, 84.8% DMARDs and 15.1% biologic therapies.
Echographic findings: 1.The mean RCC and LCC IMT were 0.6 (0.47-0.78) and 0.63 mm (0.44-1.05) respectively. 36.4% and 45.4% of the cases had an increase of right and the left IMT respectively and 27.3% of both when it was compared with age group of reference population. 2. 18.2 % had unilateral plaques and 9.1% bilatera. 3. One patient had an ABI<9. 4. 57.6% of the patients suffered certain degree of ED which was severe in 39.4% of the cases. Of the patients suffering endothelial dysfunction 2 and 4 had left and right increased IMT respectively and 2 on both carotides. 3 people had unilateral and 2 had bilateral plaques.
Conclusions: 1.Nearly 40% of patients had BM I>25. 2. A high percentage of patients had hyperhomocyisteinemia. 3.The percentage of subjects who had increased IMT and/or carotides plaques is high, around 40%. 4. Endothelial dysfunction was found in more than half of the cases, and it was severe in almost 40%.

PS207 SCLERODERMA AND MYOCARDIAL INFARCTION: IS NOT FORTUITOUS ASSOCIATION!

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Aim: To bring back an observation characterized by myocardial infarction (MI) revealing a scleroderma in its cutaneous form.
Observation: Its about 58 years old woman, BMI at 25, hypertensive 4 years ago and stabilized by monotherapy witch in April 2012 present a myocardial infarction. The echocardiography identifies the presence of disorders of the segmentary kinetics of the LV, with deterioration of the contractile function (SEF at 50%) without obviousness of pericardial effusion, neither of intracardiac thrombus, nor of pulmonary hypertension (PH). The angiographic data highlight a thrombotic very tight stenosis of the proximal AIV at 80% extending to ostium, CD rudimentary with spasm in end of probe, vascular exploration does not show arteriosclerosis lesions (trunks supra aortic, lower extremities). The angioplasty associated with a specific treatment with its ischemic cardiopathy is initiated. In parallel a clinical expression a long time neglected made of a bilateral Raynaud phenomenon is observed. On the clinical level the patient has a cutaneous sclerosis (Rodnan modified score estimated at 13), a characteristic sclerodermas's faces and a sclerodactyly without visceral manifestations (lung, kidney) . The antinuclear antibodies are present of 1/320. The diagnosis of scleroderma in its form limited into final is retained according to the criteria of LeRoy et al.and a symptomatic treatment is added with favorable evolution.
Discussion : In spite of the absence of the other cardiovascular and metabolic risk factors usual (ponderal overload, diabetes, tobacco, dyslipidemy, oral contraception, family heredity...), like after the exclusion of the thrombogenous factors, the middle age associated with a recent arterial hypertension does not explain the MI. Nevertheless the implication of vasospasmes in the pathogenesis of these ischemic complications and the reduction of the coronary reserve with a cardiac flow preserved by vascular micro attack, remains a plausible assumption. These myocardic attacks are already most of the time present as of the first phase, cutaneous, of the disease where one finds already myocardic anomalies echocardiographic in 70% of the cases and the clinical signs at 15 20% of the patients What would partly explain the causal link between the scleroderma and which has occurred of the vascular event cardio in our patient.
Conclusion: In front of the increase in the prevalence of the atherosclerosis will infra clinical in the scleroderma, which was shown recently, all sclerodermas should profit at the beginning from the affection from a noninvasive cardiac exploration, and from a regular cardiovascular control.

PS208 DATABASE ANALYSIS OF CARDIOVASCULAR RISK FACTORS IN 123 DANISH PATIENTS WITH SYSTEMIC SCLERODERMA

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Background: Systemic scleroderma (SSc) is a connective tissue disease with abnormalities in vascular, immunological and fibrotic pathways. The vasculopathy is characterized by fibrointimal proliferation of small vessels and vasospastic episodes triggered by cold or stress. This may lead to tissue ischaemia. Primary cardiovascular involvement is well-known in SSc and is considered a leading cause of mortality in SSc patients after lung fibrosis.
Increasing evidence suggests that primary myocardial affection is associated to repeat focal ischaemic injury leading to subsequent irreversible myocardial fibrosis. However, the exact mechanism of the pathogenesis is unknown. Most available data is based upon clinical evaluation, electrocardiogram, eccocardiography and thoracic X-ray and CT-scans.

Methods: In order to describe cardiovascular involvement and evident cardiovascular risk factors we investigated an array of clinically important cardiac parameters in a Danish SSc cohort consisting of 123 patients. We obtained data such as blood pressure, ventricular function, ecco-estimated pulmonal arterial hypertension, NYHA class, cardiac and other biomarkers along with lung function, smoking history, mRodnan skin scores, Raynaud´s phenomenon during a period of one year. Statistical analyses was performed to describe any clinical relevant association of cardiovascular parameters in this population using descriptive statistics and logistic regression.

Results: Our preliminary data analysis demonstrates substantial correlations between SSc and cardiovascular risk factors and cardiac involvement per se. All data will be presented in the poster.

Conclusion: Cardiac involvement occurs in SSc patients and the information presented may constitute clinical prognostic values. Furthermore, our preliminary data may give rise for the implementation of novel cardiac monitoring techniques such as cardiac MRI suitable for the routine clinical practice.

PS209 CAN SCORES FROM ENGLISH, FRENCH AND DUTCH VERSIONS OF THE FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY-FATIGUE (FACIT-F) BE POOLED? AN ASSESSMENT OF DIFFERENTIAL ITEM FUNCTIONING

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Background: Increasingly, medical research involves patients who complete outcomes in different languages. This occurs in countries with more than one common language, as well as in international collaborations, which are utilized frequently in rare diseases such as scleroderma (systemic sclerosis, SSc). In order to pool or compare outcomes, instruments should be measurement equivalent across groups, because when measures are not equivalent metrically, it is not possible to determine if any observed differences between groups reflect real differences or are a consequence of measurement artifacts (e.g., linguistic differences). To assess fatigue in scleroderma, several instruments have been used, including the Functional Assessment of Chronic Illness Therapy- Fatigue (FACIT-F).

Objective: To assess the cross-language measurement equivalence of the English, French, and Dutch versions of the FACIT-F in SSc patients. Methods: The FACIT-F was completed by 871 English-speaking Canadian, 238 French-speaking Canadian and 230 Dutch SSc patients. Confirmatory factor analysis (CFA) was used to assess the factor structure in the three samples. The Multiple-Indicator Multiple-Cause (MIMIC) model was utilized to assess the amount of differential item functioning (DIF), comparing English versus French and English versus Dutch samples separately.

Results: A single-dimensional factor model showed good fit in all three samples. Differential item functioning analysis of the FACIT-F identified statistically significant DIF for 3 of 13 items in French and 4 items in Dutch compared with the original English version. French patients had lower fatigue scores on items 1 and 8, and higher scores on item 4. Dutch patients had higher sores (more fatigue) on items 7, 8, 9, and 13 compared to the English sample. Despite these item differences, overall, there was not evidence that the DIF items influenced fatigue scores substantially.

Conclusions: Minor DIF was found for FACIT-F items for the French and Dutch versions compared to the original English, which had only a small effect on the overall score. Therefore, scores generated with the FACIT-F in English, French, and Dutch SSc patients can be reasonably pooled without adjustment for linguistic differences. If our results are replicated, however, the translations of several items, particularly the Dutch translation of items 7 and 8, should be reconsidered, especially given the influence of the FACIT system in other approaches to measure fatigue in chronic diseases. The importance of assessing cross-language measurement equivalence prior to pooling outcomes obtained in different languages should be emphasized.

PS210 ASSESSMENT OF SENSITIVITY TO CHANGE OF THE DISEASE ACTIVITY SCORE IN SYSTEMIC SCLEROSIS

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Background: Systemic sclerosis (SSc) is a rare multi-systemic disease which may have a bad prognosis. Moreover treatment options are limited. Continuous research concerning this topic is ongoing. To improve the research in SSc and to facilitate the interpretation of clinical trials, there is a need of a standardized disease activity index as outcome measure. The Disease Activity Score (DAS), proposed by the European Scleroderma study group, meets nearly all the OMERACT-standards of truth, discrimination and feasibility. Only the sensitivity to change remains to be attested.

Aim: This study assesses sensitivity to change of the DAS in patients with early and severe Diffuse cutaneous Systemic Sclerosis (DcSSc) treated with rituximab.

Methods: 12-months follow-up (open-label study) of 14 consecutive patients with early DcSSc. Patients received an infusion of two times 1000mg rituximab at month 0 and 6, together with 100mg methylprednisolone. Low-dose prednisolone (no more than 10 mg/day) was allowed, provided patients were taking a stable dose at least 12 weeks before inclusion. All disease-modifying antirheumatic drugs (except methotrexate) were stopped 12 weeks before screening. Patients were on a stable dose methotrexate (10-25 mg/week) as background therapy since at least 12 weeks. Clinical read outs (modified Rodnan skin score, mRSS; lung function and echocardiography) and DAS were performed at month 0, 3, 6 and 12. Mixed models analyses (MMA) were used to evaluate changes in parameters over time.

Results: There was a clinical significant change in skin score with a mean (SD) mRSS of 24.8 (4.44) at baseline and 10.4 (3.12) at month 12 (MMA p <0.001), a mean/median percentage improvement over 12 months of 58%/59%. Indices of internal organ involvement remained stable throughout the study (MMA: DLCO p=0.044, FVC p=0.478, TLC p=0.206, FEV p=0.283, LVEF p=0.291, sPAP p=0.790) (see table 1). In parallel, interestingly, the DAS decreased statistically and clinically significant with a mean (SD) of 4.3 (1.79) at baseline and 0.7 (0.83) at month 12 (MMA p<0.001) (see table 2). The mean/median percentage improvement over 12 months was 84%/86% respectively. Five serious adverse events occurred, considered to be probably unrelated to the study medication.

Conclusion: A significant improvement of the DAS was observed, in line with the significant improvement of the mRSS and the stabilization of internal organ involvement. To our knowledge this is the first study to attest sensitivity to change of the DAS in a clinical trial setting in the subset of patients with early DcSSc.

Table 1. Changes in clinical parameters in patients with early and severe Diffuse cutaneous Systemic Sclerosis (DcSSc) treated with rituximab (N=14)

Variable	Statistic	0M	3M	p-value*	6M ¶	p-value*	12M	p-value*	P-value MMA
mRSS	Mean (SD)	24.8 (4.44)	18.9 (6.29)	<0.001	14.1 (4.17)	<0.001	10.4 (3.12)	<0.001	<0.001
	Median (Q1;Q3)	24.5 (21.0;28.3)	18.0 (13.8;25.0)		16.0 (9.5;17.5)		10.0 (9.0;11.5)		
	Min; max	17.0;33.0	11.0;33.0		8.0;20.0		6.0;19.0		
DLCO (% of normal)	Mean (SD)	71.9 (18.57)	65.6 (18.65)	0.007	70.0 (16.81)	0.053	71.2 (17.06)	0.212	0.044
	Median (Q1;Q3)	63.0 (56.0;86.3)	61.0 (51.0;81.0)		66.0 (58.5;87.5)		69.0 (59.5;88.5)		
	Min; max	53.0;111.0	44.0;106.0		41.0;98.0		38.0;96.0		
FVC (% of normal)	Mean (SD)	95.7 (11.21)	90.8 (12.11)	0.135	93.9 (14.65)	0.578	95.2 (14.55)	0.759	0.478
	Median (Q1;Q3)	94.5 (90.5;102.3)	94.0 (83.5;100.0)		93.0 (85.5;100.5)		97.5(86.5;107.3)		
	Min, max	76.0;117.0	68.0;105.0		71.0;125.0		64.0;113.0		
TLC (% of normal)	Mean (SD)	84.9 (9.95)	82.8 (11.20)	0.854	85.7 (14.17)	0.976	89.5 (12.72)	0.088	0.206
	Median (Q1;Q3)	84.5 (78.0;92.0)	81.0 (76.0;91.5)		86.0 (74.0;96.0)		91.0 (80.5;96.0)		
	Min, max	64.0;103.0	61.0;100.0		62.0;112.0		67.0;118.0		
FEV (% of normal)	Mean (SD)	87.6 (9.71)	84.9 (16.0)	0.314	83.9 (13.04)	0.222	88.0 (14.69)	0.637	0.283
	Median (Q1;Q3)	87.0 (81.5;94.0)	83.0 (78.5;99.5)		81.0 (73.0;95.5)		87.0 (81.5;99.0)		
	Min, max	71.0;105.0	49.0;105.0		66.0;107.0		62.0;113.0		
LVEF (% of normal)	Mean (SD)	65.5 (7.24)	67.2 (5.04)	0.368	63.8 (5.76)	0.434	64.08 (4.72)	0.527	0.291
	Median (Q1;Q3)	69.0 (60.0;70.0)	68.0 (65.0;70.5)		64.0 (59.0;68.5)		67.0 (60.5;67.5)		
	Min, max	50.0;72.0	55.0;75.0		55.0;72.0		55.0;69.0		
sPAP (mmHg)	Mean (SD)	31.3 (3.32)	29.2 (5.59)	0.373	30.2 (7.66)	0.663	29.3 (4.47)	0.413	0.790
	Median (Q1;Q3)	31.0 (29.0;34.0)	28.0 (25.3;34.8)		29.5 (25.3;35.8)		29.0 (25.0;35.0)		
	Min, max	26.0;36.0	23.0;39.0		17.0;44.0		23.0;36.0		

*p-value versus baseline; ¶One patient died so from this visit data are given for N=13; MMA=Mixed Model Analysis; mRSS: modified Rodnan skin score; DLCO: diffusion capacity for carbon monoxide; FVC: forced vital capacity; TLC: total lung capacity; FEV: forced expiratory volume; LVEF: left ventricular ejection fraction; sPAP: systolic pulmonary artery pressure.

Table 2. Changes in the Disease Activity Score (DAS) in patients with early and severe Diffuse cutaneous Systemic Sclerosis (DcSSc) treated with rituximab (N=14)

Variable	Statistic	0M	3M	p-value*	6M¶	p-value*	12M	p-value*	p-value MMA
DAS	Mean (SD)	4.3 (1.79)	2.0 (1.35)	<0.001	1.1 (0.67)	<0.001	0.7 (0.83)	<0.001	<0.001
	Median (Q1;Q2)	3.5 (3.4;5.6)	1.8 (1.4;3.0)		1.0 (0.5;1.8)		0.5 (0.0;1.0)		
	Min; max	1.5;7.5	0.0;5.0		0.0;2.0		0.0; 2.5		

*p-value versus baseline; ¶One patient died, so from this visit on data are given for N=13; MMA: mixed model analysis.

PS211 EXPLORING THE IMPACT OF FOOT DISABILITY IN SYSTEMIC SCLEROSIS

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Background: While it is established that foot pathology in patients with systemic Sclerosis (SSc) is associated with disability, the impact of such problems has yet to be determined. The aim of this study was to explore the physical and psychological consequences of foot pathology in SSc.

Methods: General and disease specific information was collected from 121 SSc patients attending the outpatient clinic at Leeds and 51 healthy controls who were invited to participate in the study. All participants completed three patient reported outcome measures: the Manchester Foot Pain and Disability Index (MFPDI); MOS SF-36, and Hospital Anxiety and Depression Scale (HADS). Data analysis was undertaken using the Mann-Whitney test for between-group comparisons and Spearman's rho to determine correlations between measures.

Results: Of the 121 patients recruited (106 female; median age 59, ranges 25 to 86 years), 96 had lcSSc, 24 had dcSSc, and one had SSc sine scleroderma, with a median disease duration of nine years (IQR:4,13) and a median modified RSS of 2 (IQR:0, 4). The control group comprised 51 healthy volunteers (43 female; median age 49, ranges 21 to 81 years). In terms of foot problems, patients with SSc had significantly greater foot-related disability than controls (median MFPDI function score 11 vs. 0), greater foot pain (median MFPDI pain score 5 vs. 0) and poorer perception of foot appearance (median MFPDI appearance score 1 vs. 0) all p values=<0.001. Of note, patients with SSc had significantly worse general functional status (SF-36 median physical score 30 vs. 56), mental health perception (SF-36 median mental health score 46 vs. 56) anxiety (HADS median anxiety score 8 vs. 5) and depression (HADS median depression score 6 vs.1) than controls (all p=<0.001).

In order to explore the specific impact of foot pathology, the MFPI subscales scores were correlated with generic physical and psychological outcomes. Not surprisingly, foot function was significantly correlated with physical subscale of the SF-36 (ρ = -0.63, 95%CI [-0.766 to -0.478]), but notably also with the mental summary subscale of the SF-36 (ρ = -0.45, 95%CI [-0.605 to -0.309]) and both anxiety (ρ=0.41, 95%CI [0.254 to 0.608]) and depression subscales of the HADS (ρ=0.60, 95%CI [0.432 to 0.735]) all p values =<0.001.

Conclusions: This study demonstrates people with SSc have significant foot disability and that this is associated with significant detrimental physical and psychological consequences. This study highlights the need for further studies aimed at improving foot outcomes in people with SSc.

PS212 TRANSITION OF CARE AND LONG-TERM OUTCOMES OF JUVENILE SYSTEMIC SCLEROSIS DURING ADULTHOOD: RESULTS FROM A FRENCH SINGLE-CENTER CASE-CONTROL STUDY

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Introduction: Juvenile Systemic Sclerosis (SSc) is a rare systemic connective tissue disorder that is responsible for a high rate of morbidity and mortality. Long-term outcomes of patients with juvenile SSc remain poorly characterized. We sought to describe the transition of care from Pediatric to an adult Internal Medicine department and long-term outcomes of patients with juvenile-onset SSc, by conducting a retrospective single-center case-control study.

Patients and Methods: Thirteen patients with SSc diagnosed before the age of 17 and previously followed in Pediatric departments were included. The control group comprised 39 patients randomly selected from all patients with a SSc diagnosed after 18 years old, matched by sex and disease duration. All patients were followed in the department of Internal Medicine of Cochin Hospital. We retrospectively collected from both pediatric and adult medical records demographic, epidemiologic, clinical, immunological data and treatments.

Results: In the juvenile-onset group, 11/13 (85%) patients were female and 7/13 presented a diffuse SSc. Mean age at diagnosis was 12.5 years (7.0-17.4). No patient had anti-centromere, 3/13 (23%) anti-Scl70 and 2/13 (15%) anti-U1RNP autoantibodies.
At the first visit to the adult department, mean disease duration was 6.6 years (0.8-12.8). While juvenile-onset patients had a significantly higher incidence of calcinosis (8/13 (62%) vs 5/39 (13%); p=0.001), they had a lower incidence of pulmonary hypertension (0/13 (0%) vs 10/39 (26%); p=0.05) and lung fibrosis (1/13 (8%) vs 16/39 (41%); p=0.039) compared to the adult-onset group.
At the time of last follow-up, mean disease duration was 10.3 years (4.5-18.6). Survival rate was lower among the juvenile-onset group but this difference was not significant (10/13 (77%) vs 37/39 (95%); p=0.092) and bowel involvement had a significantly higher incidence (7/13 (54%) vs 8/39 (21%); p=0.034). Juvenile-onset patients had received significantly more steroids > 15mg/d (8/13 (62%) vs 4/39 (10%); p=0.001) and methotrexate (7/13 (54%) vs 6/39 (15%); p=0.01), without a higher incidence of major side effects.
Factors associated with a poor prognosis in juvenile-onset SSc were lung fibrosis and pericarditis.

Conclusion: At the time of transition to adult care structures, patients with juvenile-onset SSc have more severe musculoskeletal damages and lower incidence of lung involvement than patients with adult-onset SSc. The long-term prognosis of juvenile SSc is poor. We suggest that close collaboration between adult and pediatric structures could improve both life expectancy and quality of life by standardizing the management of damage and detection of cardiac and pulmonary complications.

PS213 IN SYSTEMIC SCLEROSIS, ANXIETY AND DEPRESSION, ASSESSED BY HOSPITAL ANXIETY DEPRESSION SCALE ARE INDEPENDENTLY ASSOCIATED WITH DISABILITY AND PSYCHOLOGICAL FACTORS

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Background: Anxious and depressive symptoms are frequent in Systemic Sclerosis (SSc). Our aim is to assess their prevalence, their association with district and global disability and psychological variables and potential differences between subsets.
Methods: 119 SSc patients (14 men and 105 women; 74 with lSSc and 45 with dSSc; age: 59.46 ± 13.87 years; disease duration, 10.74 ± 7.42 years) and 50 age- and sex-matched controls were assessed by Hospital Anxiety Depression Scale (HADS) for anxious (HADS-A) and depressive (HADS-D) symptoms and for comorbity of anxiety and depression. Clinical depression and anxiety were defined for HADS score cut-off =8 or higher.
Patients were also assessed for psychological symptoms (Rosenberg Self-Esteem Scale –RSES-, Coping Orientation to Problems Experienced-New Italian Version -COPE-NIV-), hand (Hand Mobility In Scleroderma Test –HAMIS-, Cochin Hand Functional Disability Scale –CHFDS-, fist closure, hand opening) and face disability (Mouth Handicap in Systemic Sclerosis Scale-MHISS-, mouth opening), global disability and fatigue (Health Assessment Questionnaire-HAQ-, Functional Assessment of Chronic Illness Therapy-Fatigue Scale –FACIT-).
Results:
In SSc patients, HADS-D (6.14±3.97) and HADS-A (6.66±4.09) were higher than in healthy controls (4.72 ± 2.88 and 5.16 ± 3.05) ($p<0.05$), but not different in lSSc versus dSSc, (p= NS).
Both depression and anxiety in SSc were 36%: 15/ 119 patients (13%) had only depression, 15/119 (13%) presented only anxiety and 28/119 (23%) had both depression and anxiety.
Depressive patients with comorbid anxiety had significantly higher HADS-D score than patients with depression only (11.39±1.57 vs. 9.4±1.64; p=0.001).
In controls, depression and anxiety were 10% (5/50) and 20% (10/50), lower than in SSc ($p<0.05$); the co-presence of depression and anxiety, (2/50 subjects -4%-) was lower than in SSc (p=0.001) and depressive subjects with comorbid anxiety had significantly higher HADS-D score than those with depression only (9.5±2.1 vs. 4.92±2.86; p=0.001).
In SSc, by bivariate analysis, HADS-A and-D were positively correlated with HAQ, HAMIS and CHFDS, MHISS, FACIT, RSES and COPE-NIV Avoidance Strategy, and, only HADS-A, also with COPE-NIV Social Support ($p<0.05$ in all cases).
By multiple regression, HADS-D was independently associated with FACIT-F ($p<0.001$), RSES ($p<0.001$), MHISS (p=0.016), together explaining 50% of variance. HADS-A was independently associated with RSES (p=0.006), COPE-NIV Avoidance Strategy (p=0.003), COPE-NIV Social Support (p=0.008), FACIT-F (p=0.022) and MHISS (p=0.029), explaining 41% of variance.
Conclusions: in SSc, depression and anxiety are frequent and correlate to local and global disability and psychological characteristics. Depressive patients with comorbid anxiety have higher level of depressive symptoms.

PS214 SYSTEMIC SCLEROSIS DIAGNOSED IN ELDERLY : A FRENCH RETROSPECTIVE STUDY OF 27 PATIENTS

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Introduction: Mean age at the time of diagnosis for systemic sclerosis (SSc) is around 50 years (y). One study showed a peak of incidence in caucasian women aged 65-74 y, but data are lacking about specificities of SSc diagnosed in elderly. The aim of this work was to describe SSc phenotype when diagnosis is made after 70 y of age.

Patients and methods
Retrospective study from a single center French cohort over the period 1995-2013. Only patients aged 70 y and more at the time of diagnosis of SSc and fulfilling the ACR criteria for the diagnosis of SSc were included. Demographical, clinical, and paraclinical data at the time of diagnosis were retrospectively collected and analyzed.

Results
Among 246 patients, 27 (11%) were included (89% of women). At the time of SSc diagnosis, age was 78.6±4 y. Patients were caucasian in 26 cases, and no silica exposure was noted. Patients had the following comorbidities : left cardiac failure (22%), cancers (22%), including lung (n=2), breast (n=2), and colon (n=1) cancer, diagnosed on average 4.9 y before SSc. In 58% of cases, SSc had started recently suggesting a real elderly disease, whereas for 42% of patients, minor signs of SSc were present before the age of 70 without any diagnosis of SSc. SSc was mainly cutaneous limited (96%), and Rodnan score was 7.8±6. Anti-centromere Ab were detected in 76% of cases. Signs at the time of diagnosis of SSc included : Raynaud phenomenon (96%), ischaemic digital ulcers (26%), digital pitting scars (18%), telangiectasia (66%), sicca syndrome (26%), gastroesophageal reflux (59%), watermelon stomach (14%), anal incontinence (11%), extensive interstitial lung disease (30%) which was significantly more frequent among patients over 80 (p=0.046). Pulmonary arterial hypertension (PAH) was suspected in 13 patients using cardiac ultrasonography, distance at the 6-min walk test was 118±74m, and mean TLCO was 38% of expected value in theses patients. Only 5 patients underwent right heart catheterization, and 4 had PAH (mPAP=54±17, pulmonary wedge pressure=11±6 mmHg, cardiac index=2.1±1 L/min/m2.

Conclusion :
In more than 10% of patients, SSc is diagnosed after 70 y of age, which mainly correspond to real forms of disease starting in the elderly. At this age, diffuse scleroderma are uncommon and 20% of the patients have past history of cancer. Watermelon stomach seems to be frequent (14%). PAH is frequently suspected and is the first sign leading to SSc diagnosis in at least 15% of cases.

PS215 ALEXITHYMIA: UNSPEAKABLE SUFFERING, A PREVALENCE STUDY IN SYSTEMIC SCLEROSIS

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INTRODUCTION: Systemic Sclerosis (SSc) is associated with chronically painful symptoms. Patients with SSc may be at particular risk for depression due to the high levels of overall disability that may influence the emotional suffering. The psychological construct of alexithymia, literally meaning “no words for mood”, was firstly coined in 1972 to describe people who lack the ability to communicate their feelings and who seem unable to fantasize (1).

OBJECTIVE: To evaluate the presence of alexithymia in ScS patients, comparing its prevalence with that of a group of healthy subjects.

METHODS: We used the Italian validated translation of Toronto Alexithymia Scale (TAS-20) (2) to assess the alexithymic tract. It was administered to 50 ScS patients (F/M = 48/2; mean age = 59 years; diffuse form/limited form = 24/26; presence or history of digital ulcers in 20 patients and a mean disease duration 10 years) and to 37 healthy subjects (F/M = 35/2; mean age = 56 years). We also measured depressive symptoms by administering the Italian validated version of Beck Depression Inventory (BDI) to both groups.

RESULTS: In the SSc patient group a TAS-20 score indicating alexithymia (> 61) was present in 15 subjects (30%), while in 11 (22%) patients the TAS-score indicated a borderline status (50-60). The prevalence of alexithymia was significantly higher than in the healthy subject group, where it was found in 4 cases (11%) (P=0,038). The proportion of subjects with moderate to severe depression (BDI>23) was greater in the SSc patient group (12 pts, 24%) than in healthy subjects (1 pt, 3%) (P= 0,01).
The SSc group of patients showing alexithymia and borderline status (26 patients, 52%) was found to have a significant correlation with disease duration longer than 5 years (p=0,038). Moreover the SSc group with alexithymia had a strong correlation with moderate to severe depression (P= 0,0002). There was no statistically significant difference between the diffuse and the limited forms.

CONCLUSIONS: We found that SSc patients are more likely than healthy subjects to have difficulty in identifying and describing feelings, presenting higher alexithymia scores. Our data underline also that the severity of the emotional impairment of alessithimia is related with longstanding disease. Besides a moderate to severe depression is more prevalent in the patient group. These results underline the importance of considering emotions in SSc patients.

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PS216 ADHERENCE TO RECOMMENDATIONS FOR CERVICAL AND BREAST CANCER SCREENING IN SYSTEMIC SCLEROSIS

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Background. In Italy the current recommendations for the early diagnosis of the most frequent female cancers suggest screening for cervical cancer with Papanicolaou (Pap) test for women aged 25-64 years at 3-year interval and mammography for women aged 50-69 years at 2-year interval. There are no data concerning the adherence to these recommendations in Systemic Sclerosis (Ssc) women.

Objective. The aim of the study was to assess if SSc female patients underwent Pap test and mammography as suggested by current recommendations in comparison with general population.

Patients and Methods. Outpatient women affected by SSc aged 25-69 years followed at the Rheumatology Unit of Verona were consecutively enrolled for the present study. Clinical data were recorded. Female subjects attending to the office of a general practitioner were consecutively enrolled as controls. Eligible SSc patients and female controls were asked if they had undergone Pap test in the previous 3-year interval, except for patients previously hysterectomized and if they had undergone mammography in the previous 2-year interval.

Results. The cohort of SSc patients is composed of 84 subjects; 62 patients were aged 25-64 years; after exclusion of 5 cases previously hysterectomized, the eligible patients for cervical cancer screening were 57. Fifty-five patients were aged 50-69 years; only one of these was previously treated with quadrantectomy for breast cancer.

Eight out of 57 SSc patients (14.0%) had not performed Pap test during the previous 3 year interval as well 3 out of 81 female controls (3.7%). The difference was at limit of significance (P = 0.051).

Eight out of 55 SSc patients (14.5%) had not performed mammography during the previous 2 year interval. All 55 female controls reported to have regularly performed the examination. The adherence to breast cancer screening by SSc patients was lower compared to general population (P = 0.006).

There was no difference comparing SSc patients who did and who did not perform cervical and breast cancer screening in relation to age, disease duration, autoantibody profile and lung involvement.

Discussion. Our study shows that the percentage of SSc female patients who adhere to programs for the early detection of cervical and breast cancer was high (>85% of the cases), even if general population more frequently performed mammography. The elevated adherence to recommendations may be likely due to the organization of the Italian health public service which regularly invites by mail eligible subjects to undergo cancer screening with no charge.

PS217 SURVIVAL PROGNOSTIC FACTORS AND CAUSE OF DEATH IN 213 IRANIAN PATIENTS WITH SYSTEMIC SCLEROSIS

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BACKGROUND:The natural history of systemic sclerosis varies and depends on severity of organ involvement. The role of gender, race, extension of skin involvement, sclerosis in visceral organs and serologic factors has been shown in mortality of systemic sclerosis.
AIM OF THE STUDY: To determine survival and causes of death in a cohort of Iranian SSc patients and to analyze influence of demographic, clinical and immunologic variables on survival.
MATERIAL AND METHODS: The study population included 213 consecutive SSc patients first seen between February 1998 and June 2013 in Firoozgar hospital.The patient's onset was defined as the Raynaud's phenomenon or non-Raynauds scleroderma related sign or symptoms. The frequency of clinical features,organ system outcomes, and survival within patients with specific antibody were cumulative over the course of the disease. The predictive value of hypothetical prognostic variables associated with death was initially examined by univariate statistical methods for continuous or categorical data, for all patients who died versus all who survived. The variables with P<0.2 in univariate analysis were included in a Cox-proportional model; a forward strategy was used for modeling.

RESULTS: The study includes 186(87.3%) women and 27(12.3%) men. eighty three of 213 patients had diffuse SSc and 130 limited SSc. thirty one (14.5%) patients died. Deaths were due to cardiac involvement in eleven, progressive pulmonary fibrosis in four, isolated pulmonary arterial hypertension in three, cardiopulmonary and gastrointestinal bleeding in one, scleroderma renal crisis and malignancy each in two patients. Cause of death in six patients was not available. Cumulative 5 years and 10 survivals based on Kaplan-Meier analysis were 89%, 87% after the patients develop first symptoms of disease. Survival rate after 15 and 20 years were 77% and 35%.
Univariate analysis: The patients with age > 40 years, time interval from symptoms to entry> 5 years, esophageal reflux at presentation, friction rub at first visit and pulmonary arterial hypertension , scleroderma renal crisis arthritis, FVC percentage < 70%, interestial fiborosis in HRCT, hypertension >139/ 89, pericardial effusion and presence of anti-TOPO antibodies that in log-Rank test had P values<0.2, included in the Cox proportional hazard model.
Multivariate analysis: The forward conditional selection procedure in Cox proportional hazard model showed that DLCO<60% and time interval from symptoms to entry> 5 years, were independent prognostic factors.
Conclusion: The cardiac and pulmonary represented the main causes of death in this first Iranian series with systemic sclerosis.

Key words: Systemic Sclerosis. Survival

PS218 OCCUPATIONAL THERAPY IN SYSTEMIC SCLEROSIS. PRELIMINARY RESULTS OF A PILOT STUDY

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Background: Skin lesions, joint and tendon disorders characteristic of systemic sclerosis (SSc) affect significantly the autonomy of patients and compromise the quality of their life. Occupational therapy (OT) aims to improve the capacity of patients in performing activities of daily living, trying to give them the best solutions for their needs. OT has been widely used in rheumatoid arthritis, while very few data in patients with SSc have been published. The aim of this pilot project is to evaluate the effects of OT on daily life activities in a group of patients with SSc, with special attention to personal care, eating, domestic work and leisure activities.
Methods: Twenty women with SSc (age 56.6±12.1 years; disease duration 12.9± 8.1 years) were involved in this project. Thirteen patients had diffuse and 7 had limited cutaneous form. ANA were positive in all patients, with anti-Scl70 pattern in 6, anti-RNA polymerase III in 4, and ACA in 6.Ten patients partecipated to a cycle of OT, the other 10 were considered as control group. OT consisted of 6 meetings in 3 consecutive weeks, lasting 90 minutes each. The patients were educated by an expert in OT on joint and skin protection and on strategies to perform daily life activities in the most simple and effective way. All patients were evaluated by SHAQ and EDAQ questionnaires at baseline and after 6 months. Statistical comparison was performed using the t test. At the end of the cycle of OT, the patients gave their opinion on the usefulness of the meetings, by 3 items (score 0-10).
Results: Data at baseline showed an impairment of autonomy in daily life activities in all patients, without significant differences between the two groups. Meeting attendance was 96%. The patients involved in OT expressed a very favorable opinion on the organization of the meetings (score 8.5±1.2), on their conduction (8.9±0.9) and on their usefulness (8.0±0.7).
After 6 months we observed an improvement of SHAQ (mean -3.1) and EDAQ (mean -16.2) values in comparison to baseline in patients partecipating to the OT meetings, without a significant difference with the control group.
Conclusions: The preliminary results of this pilot study suggest the usefulness of OT in improving the quality of life and the autonomy of SSc patients in performing daily activities. These results allow us to continue this experience and to insert the meetings of OT in the management of SSc patients.

PS219 A SYSTEMATIC REVIEW ON THE DEVELOPMENT OF DISEASE ACTIVITY INDICES IN SYSTEMIC SCLEROSIS

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Background and aim: To improve the research in Systemic Sclerosis (SSc) and to facilitate the interpretation of clinical trials, there is a need of a standardized disease activity index as outcome measure. This study gives an overview of the present disease activity indices in SSc and reports their validation status.
Methodology: We systematically reviewed the literature on disease activity indices in SSc (development, use and validation status). The Pubmed database was searched without time limit on the following search terms: systemic sclerosis, disease activity (index) and validity (OMERACT, truth, discrimination, feasibility). The assessment of the qualitative validation status of the present indices was based on the 'Outcome Measures in Rheumatologic Clinical Trials'-filter (OMERACT filter). The filter comprises truth (face validity, credibility; content validity, covers all aspects of the construct to be measured; construct validity, represents 'biological sense', which requires comparison to a golden standard), discrimination (sensitivity to change, discrimination between situations that are of interest; reliability, high reproducibility and low inter- and intrarater variability) and feasibility (can be applied easily). The quantitative validation status of the present indices was assessed according to the definitions of the American College of Rheumatology (ACR) committee on quality measures. An index was considered 'preliminary' if no quantitative validation existed and 'provisional' if the index was quantitatively validated in previously collected cohorts. To be fully approved by the ACR, the index needs to be validated prospectively in a clinical trial setting.
Results: Three disease activity indices have been found in literature namely, the Disease Activity Score (DAS) by the European Scleroderma Study group, the 12-point index by Minier et al. and the Combined Response Index for SSc (CRISS) by the Scleroderma Clinical Trials Consortium. Of those, the DAS is the most thoroughly investigated index. There is evidence that the DAS is a valid, reliable and feasible index but its sensitivity to change still needs to be assessed. As the DAS is not yet validated prospectively in a trial setting, it is considered as a provisional index by the ACR. The 12-point activity index and the CRISS are preliminary indices.
Conclusions. Three indices to measure disease activity in patients with SSc are described in literature. The DAS is the most thoroughly assessed. Only its sensitity to change remains to be attested and it needs prospective validation to be considered as fully validated. The indices developped by Minier et al. and the CRISS are still preliminary indices.

PS220 THE VALIDITY OF THE SATISFACTION WITH APPEARANCE SCALE AND THE BRIEF SATISFACTION WITH APPEARANCE SCALE FOR PATIENTS WITH LIMITED AND DIFFUSE SYSTEMIC SCLEROSIS

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Background: The Satisfaction with Appearance Scale (SWAP) was developed to measure body image distress (BID) among burn victims, and later adapted for patients with systemic sclerosis (SSc). A short form of the measure (Brief-SWAP) was derived from the full version. Both measures yield factor-analytically derived subscales. Although both versions have been validated in SSc, their factor structures have never been compared for use with patients with limited versus diffuse SSc.

Objective: To determine the comparability of the factor structures of the SWAP and the Brief-SWAP for patients with limited versus diffuse SSc.

Methods: Participants were adults participating in the UCLA Scleroderma Quality of Life Study with rheumatologist-diagnosed limited (n = 101) or diffuse (n = 82) SSc. The 14-item SWAP evaluated BID, and the six items that comprise the Brief-SWAP were taken from the full measure. The SWAP has four subscales evaluating Social Distress, Facial Features, Non-facial features, and Perceived Social Impact; the Brief-SWAP has two subscales evaluating Social Discomfort and Dissatisfaction with Appearance. Multiple-group confirmatory factor analysis (CFA) was used to determine if the factor structures of the SWAP and the Brief-SWAP were the same for individuals with limited and diffuse SSc. Both statistical (Satorra-Bentler Chi Squared), and practical (RMSEA, CFI, SRMR) indicators of model fit were considered. For RMSEA and SRMR, values </= .08 and </=.05 were considered to indicate acceptable and good model fit, respectively. For CFI, values >/= .90, and >/= .95 were considered to indicate acceptable and good model fit, respectively.

Results: For the 14-item SWAP, fit indictors supported the proposed four-factor structure for both limited and diffuse SSc. A model in which the number of factors, item loadings for each factor, factor variances, and factor covariances were constrained to equivalence across disease subtypes satisfactorily fit the data (Chi-squared [172] = 228.59, p < .01; RMSEA = .06, CFI = .95, SRMR = .07). The Brief-SWAP fit indicators supported the two hypothesized factors for both limited and diffuse SSc. A model with these same constraints once more satisfactorily fit the data (Chi-squared [27] = 37.76, p = .08; RMSEA = .07, CFI = .97, SRMR = .08).

Conclusions: Support was found for the SWAP's four subscales and for the Brief-SWAP's two subscales. Thus, the Brief-SWAP is recommended to health professionals who want a quick assessment of BID in patients with SSc, while the original SWAP may be preferred when more detailed information is desired.

PS221 FIVE-YEAR SURVIVAL RATE AND PREDICTORS OF DEATH AND DISEASE WORSENING IN A SINGLE-CENTER COHORT OF PATIENTS WITH SYSTEMIC SCLEROSIS

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Background: Systemic sclerosis (SSc) is associated with a significant reduction in survival in comparison to the general population. This is the first report on 5-year survival and its predictors in a Romanian cohort of SSc patients.
Objective: We aimed to assess the 5-year survival in a single-center cohort of SSc patients and to identify predictors of death and disease worsening.
Methods: All patients of the EUSTAR center 100 enrolled before 2009 and who had at least 2 visits at a minimum interval of 5 years, or have died after at least 3 months of follow-up, were included. All patients were assessed according to EUSTAR recommendations. A comparison was made between the surviving and the deceased patients regarding all MEDS baseline parameters. Using age-adjusted univariate logistic regression we identified predictors for death and for several outcomes considered as disease worsening: 20% reduction in forced vital capacity (FVC); 20% reduction in DLCO; development of pulmonary arterial hypertension (PAH) as assessed by power Doppler heart ultrasound; and digital ulcers (DUs) recurrent at prospective visits.
Results: Out of 68 patients enrolled before 01/01/2009, 40 met the inclusion criteria (82,5% females, 55% limited cutaneous subset, mean±SD follow-up period 5.7±2.1 years; mean±SD age at first visit 49±11.8 years; mean±SD disease duration at first visit 4.4±6.0 years). Throughout the 5-year follow-up period there were 7 deaths (including 3 SSc-related deaths), resulting in an overall 5-year survival rate of 82,5%. In survivors, lung function tests deteriorated significantly in 11% (FVC) and 52% (DLCO), while 20% developed PAH. Recurrent or newly appearing DUs occurred in 21% of all 42 patients. Significant predictors for death were the diffuse cutaneous subset, and the presence of DUs at presentation, with hazard ratios [95% confidence interval] (HR[CI95%]) of 14,2 [1.3-151] and 38 [2.9-501] respectively. Conduction blocks on the baseline ECG predicted PAH with a HR [95%CI] of 12.8 [1.5-108]. Significant predictors for DUs were active DUs and calcinosis at presentation: HR [CI95%] 5.2 [1.1-26] and 6 [1.1-33] respectively. None of the parameters tested as potential predictors of the respiratory function decline achieved statistical significance.
Conclusions: The survival rate in our cohort was similar to other cohorts from developed countries. We identified diffuse cutaneous subset, active digital ulcers, and heart conduction blocks as predictors for a poor disease outcome.

PS222 TARGETING FEAR OF DISEASE PROGRESSION IN RHEUMATIC DISEASES: A CASE STUDY IN SYSTEMIC SCLEROSIS

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Background: Living with a recurrent chronic illness, such as a rheumatic disease, causes uncertainty and fear of the future for many patients. Patients have to deal with complications and relapses of the disease, increasing restrictions in daily functioning, progression of the disease, and for some rheumatic diseases, such as systemic sclerosis (SSc), a reduced life expectancy. Indeed, patients with SSc have reported uncertainty about the future, fear of disease progression, dependency on others, and fear of becoming physically disabled as important sources of stress, and this was found to be associated with more depressive symptoms. However, although the need for psychosocial support is high in patients with SSc and increasingly recognized by professionals, so far the evidence regarding the development and testing of psychological interventions is limited. To address the need for support, we developed a cognitive-behavioural intervention targeting concerns about the future and depressive symptoms in patients with SSc.
Objective: To illustrate an individually, tailored cognitive-behavioural protocol for the treatment of depressive symptoms and fear of progression in a patient with SSc, and to preliminary study its effectiveness.
Methods: An intervention protocol consisting of an intake interview and 10 face-to-face sessions with a psychologist was developed based on cognitive-behavioural principles. Because of the complexity of symptoms and complaints due to SSc, the psychological intervention was embedded in an interdisciplinary care program also consisting of physical therapy, occupational therapy, and specialized nurse care. A case study was conducted including a 53 years old female with a diagnosis of systemic sclerosis for 9 years. Diary measures utilizing visual analogue scales for depression, fear of progression, fatigue and pain were completed twice a week and validated questionnaires were completed pre- post and at follow-up.
Results: The diary measures showed large variability over time, and no clear effect of the intervention could be identified. The post- and follow-up measures showed substantial changes decreases in depressive symptoms and fear of progression. The secondary outcomes fatigue and helplessness showed the most remarkable changes.
Conclusion: The presented intervention is an example and starting point for the treatment of depressive symptoms and fear of disease progression in systemic sclerosis and other progressive chronic somatic diseases. Elements of the presented intervention can be integrated in psychological care in medical health settings. The effectiveness of the intervention should be established in future studies.

PS223 CORRELATIONS BETWEEN LUNG INVOLVEMENT, QUALITY OF LIFE AND FUNCTIONAL DISABILITY IN PATIENTS WITH LIMITED SYSTEMIC SCLEROSIS

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Introduction. Systemic Sclerosis (SSc) is a connective disease that usually impairs the respiratory function. Moreover many Authors have shown that SSc worsens patients' Health Assessment Questionnaire (HAQ), Short Form 36 Physical Component Summary (SF36-PCS) and Mental Component Summary (SF36-MCS).The aim of this work is to verify whether there is correlation between the quality of life and pulmonary involvement in the patients' subset with limited-SSc (lSSc).

Materials and Methods. We enrolled 27 lSSc (according to ACR criteria). SF36 and HAQ were given to each one. Pulmonary involvement was evaluated with Baseline Mahler 's dyspnea Index (BDI) - a patient self-administered scale, spirometry and semiquantitative radiological assessment of pulmonary fibrosis detectable on chest Computed Tomography (according to the method suggested by Goh et al 2008).The correlations between SF36, HAQ and lung involvement severity were investigated with Spearman's rank test. A p-value <0.05 was considered statically significant.

Results. SF36-PCS and SF36-MCS correlate with Mahler's BDI (respectively rho = -0.49 , p = 0.009 and rho = -0.40 ; p = 0.037). The best SF36 subsets which correlate with dyspnea are Vitality (rho = -0.58 , p = 0.002) and General Health (rho = -0.45 , P = 0.019). Mahler's BDI correlates also with the HAQ (rho = 0.43 , p = 0.028). No statistically significant correlation was found between SF36, HAQ and the spirometrical values nor semiquantitative radiological assessment of pulmonary fibrosis.

Conclusions. The lSSc patients enrolled in this study have an impaired quality of life as widely demonstrated in the literature. However, quality of life reduction and functional ability decrease are only related to the respiratory "subjective" impairment (assessed by the Mahler's BDI). In fact no correlation with objective lung damage (assessed by spirometry and semiquantitative radiological assessment of pulmonary fibrosis) was detected.

PS224 DEATH IN SYSTEMIC SCLEROSIS

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Aims: To study survival and causes of death in a cohort of patients with Systemic Sclerosis 'SSc'

Methods. Patients with SSc fulfilling the ACR criteria followed up between January 1997 and December 2012 in a single center of internal Medicine were included. Clinical and investigations (laboratory, radiology, anatomopathology..) data were reviewed from medical charts.

Results. We report 19 patients from cohort of 135 (14%) patients who died in the last ten years. The sex-ratio is 0.21. Among the total of 19 dead patients, 78.9% had dc SSc and 26.3% had lc SSc. Of the deaths, 89.4% were attributed directly to SSc . Four cases of non-SSc causes are attributed to stroke in arteriosclerosis (1), infectious diseases (2) and malignancy (lymphoma). The others identified cases of death were four cases attributed to pulmonary arterial hypertension, two cases to pulmonary fibrosis, one case to severe malabsorbtion with Wernicke encephalopathy, four cases to cardiac-related scleroderma causes, one case to acute congestive failure in renal crisis, one case of cirrhosis in Reynolds syndrome and a case of veino-occlusive disease. We propose to discuss the other correlations observed referring to the genre, the mean age at death, the mean duration of follow-up, the proteinuria, the skin score of Rodnan, the immunological profile and the presence of other co-morbidities.

Conclusion. Death among the patients with SSc is still high. Our data indicates an increased per cent of deaths among men affected by SSc (26.6%) compared to the women (12.5%) The majority of the cases being attributed to pulmonary arterial hypertension (despite the screening) and the primitive heart SSc diseases. The causes of mortality justify to develop the specialized centers to care the SSc recognized having the poor prognosis among the rheumatic diseases

PS225 QUALITY OF LIFE AND PSYCHOSOCIAL ASPECTS IN JUVENILE LOCALIZED SCLERODERMA: A CROSS-SECTIONAL STUDY IN 40 PATIENTS

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BACKGROUND/PURPOSE: Juvenile Localized Scleroderma (JLS) is a chronic, autoimmune disease, characterized by skin and subcutaneous tissues fibrosis, which can cause a poor quality of life and psychosocial and behavioural problems in affected children particularly when severe deformities such as face asymmetry, joint contractures, and growth disturbances of limbs develop. To date, quality of life and psychological aspects in JLS have been poorly investigated. Purpose: to evaluate quality of life and psychosocial aspects of patients with JLS as compared with healthy peers and identify specific disease characteristics possibly related to quality of life impairment and psychosocial problems.
METHODS: Two types of questionnaires (Pediatric Quality of Life Inventory 4.0™ Generic Core Scales and Child Behaviour Check List (CBCL) 6-18/Youth Self Report (YSR) 11-18) were administered to 40 consecutive patients with JLS aged 6 to 18 years and their parents. Patients' demographic and clinical data were collected during medical examination and through the review of clinical records. Same questionnaires were administered to a control group of 44 healthy children and their parents.
RESULTS: In PedsQL™ (children forms) no difference was found between JLS group and control group. In PedsQL™ (parents forms) children with JLS showed poorer quality of life as compared to control group (76.8 vs 84.8, p=0.017), especially in emotional area (64.5 vs 79, p=0.004). In CBCL/6-18 mean scores were lower in activity scale (35.2 vs 41.1, p=0,006) and higher in internalizing problems scale (58 vs 53.2, p=0.026) and depression scale (59.9 vs 55.9, p=0.038) in JLS group compared to control group. In YSR/11-18 mean scores were lower in social competence scale (44.2 vs 49.7, p=0.007) and in total competence scale (40.9 vs 42.4, p=0.028) and higher in internalizing problems scale (54.7 vs 50.9, p=0.031) in JLS group compared to healthy controls. Disease relapses, longer delay in correct diagnosis, onset of disease in adolescence and shorter disease duration significantly correlated with lower quality of life and psychosocial and behavioural problems.
CONCLUSIONS: Our study shows that quality of life is poorer in children with JLS compared to healthy peers. Emotional area and social activities are the most affected ambits and patients show also depressive and internalizing problems. Among patients with JLS, a greater need for psychological support is mainly related to disease relapses, longer diagnostic delay, shorter disease duration and onset in adolescence or pre-adolescence ages. Disease severity in terms of lesion extension or deformities and therapy related issues do not seem related to impairment in the investigated areas.

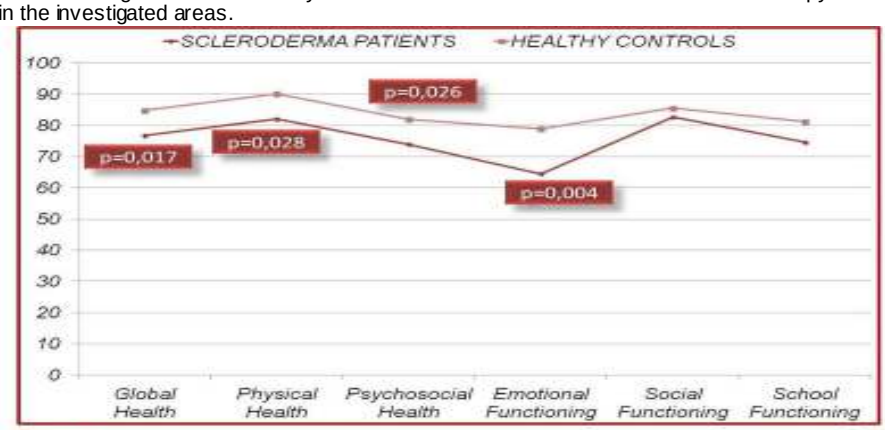

Figure 1 *Quality of life in Scleroderma patients and in healthy controls (parents forms)*

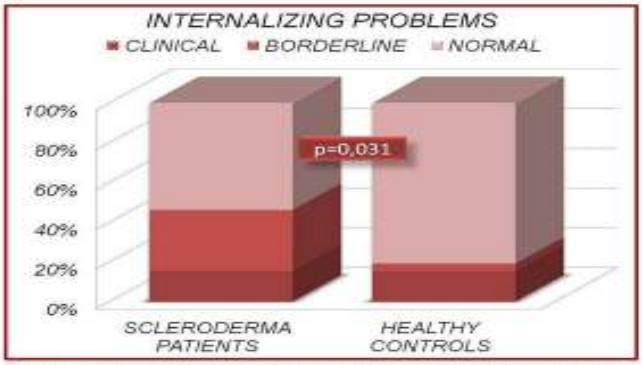

Figure 2 *Amount of internalizing problems between Scleroderma patients and healthy controls (children forms)*

PS226 MORTALITY IN SSC AND ITS ASSOCIATION WITH CLIMATE CONDITIONS – AN ANALYSIS BASED ON THE EUSTAR DATABASE

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Objective: Given the impending thread of global warming and climate change, there are no data linking climate data and especially mortality in SSc patients. With the help of the large EUSTAR database, we analysed the association of climate data and mortality in SSc patients.
Methods: The mortality of SSc patients within the EUSTAR database from 2003-2011 was analysed. For 214 deaths, a geographical location and climate data were available. The association of mortality with the month of death, the geographical location and temperature at the day of death was investigated. In addition, the risk of death at a certain temperature.
Results: Although there was some variation, deaths peaked during winter months (November-February) and there was a second peak for June/July. Most of the seasonal variation in mortality was due to mortality in female patients, which were also more numerous than male SSc patients. Mortality was highest on days with a temperature range (mean temperature) between 0 and 20° C, which was also the most common temperature. The pooled death risk analysis shows a tendency towards a higher death risk with increasing maximum temperatures. Only in few cities (Berlin, Verona, Moscow) temperatures at the end of the scale had the highest death risk. For a more profound analysis, more refined data would be needed.

PS227 THE IMPACT OF CIGARETTE SMOKING IN SYSTEMIC SCLEROSIS

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Introduction: Systemic sclerosis (SSc) is a systemic disease characterized by skin induration and thickening accompanied by diverse degrees of tissue fibrosis and chronic inflammatory infiltration in numerous visceral organs, prominent fibroproliferative vasculopathy, and alterations in adaptive immunity. Although the exact etiology of systemic sclerosis is unclear, environmental risk factors have been implicated in the pathogenesis of SSc. Previous studies have shown that smoking appears to only impact upon disease severity rather than increasing risk of development. The objective of this study was to investigate the effect of cigarette smoking on multiple visceral organs and the extent of skin disease in SSc.
Methods: Eighty four patients who fulfilled the preliminary the American College of Rheumatology criteria of SSc were enrolled the study. Patients were categorized into three groups based on smoking status, namely: ever-smoker, ex-smoker and never-smoker. All of them underwent evaluations of pulmonary function test with measurement of forced vital capacity, carbon monoxide diffusing capacity. Additionally, systolic pulmonary arterial pressure calculated by transthoracic echocardiography. Patients were evaluated by the modified Rodnan skin score (MRSS), Valentini's disease activity index, the disease severity scale of Medsger (DSS).
Results: We analyzed data from 84 patients (5 male, 79 female) with SSc. Of these, 9 were ever-smoker, 8 ex-smoker, and 67 never-smoker. %88.9, %62.5 and %80.6 of ever-, ex-, and never-smokers, respectively had limited cutaneous subtype of SSc, and the frequencies of subtypes were similar ($p>0.05$). There were no significant differences among the ever-, never-, and ex-smokers in terms of acute phase reactant levels, pulmonary function tests, MRSS, Valentini's disease activity index and the DSS of Medsger and the presence of pulmonary hypertension, pulmonary fibrosis, gastrointestinal, cardiovascular, and renal involvements ($p>0.05$). Antinuclear antibody (ANA) positivity was lower in the ever-smokers than in never-smokers (OR: 0.19, %95 CI: 0.04-0.99, $p=0.049$). The higher percent of ever-smokers had higher complement levels than in the never-smokers (OR: 6.0, %95 CI: 1.1-31.5, $p=0.034$).
Conclusion: The present study indicates that being ever-smoker has not been related to exacerbations with clinical signs of the disease. Conversely, there was lower percent of ANA positivity in ever-smokers than the other groups. The potential cause of the harmless effect of cigarette smoking might be that patients having poor clinical outcomes had to been quit smoking early by physicians. These results are not sufficient to provide a general evaluation between smoking status and SSc because of small sample size for ever-smokers in our cohort.

PS228 CAUSES OF DEATH IN A COHORT OF ARGENTINE PATIENTS WITH SYSTEMIC SCLEROSIS

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Background. Several papers addressing causes of death in systemic sclerosis (SSc) patients usually agree that between 55% (Eustar) and 65%(Brazil) are directly disease related, lung and heart involvement being the main causes. We decided to look at our experience with relation to causes of death in our cohort.
Methods. Patients with SSc seen by the Rheumatology section between 2000-2011 were retrospectively analyzed. Data on clinical manifestations, disease subtypes and antibodies were obtained. Patients were classified into diffuse cutaneous (dc) and limited cutaneous (lc) subsets (Le Roy et al´s criteria).
Results. As from the year 2000, 230 patients (194 females) were seen at our institution as out/ in patients. Sixty three (27%) had diffuse SSc and 167 (73%) limited. One hundred and nine (47%) were followed for over three years; total follow up was 688 patients-years. Seventeen of these have died under our care and 120 are being currently followed (incidence mortality rate: 25/1000 patients years, 95% CI: 15-40/1000 patients/years).Ten year survival rate was 82% for limited and 55% for diffuse variants respectively (HR: 1.56 95% CI: 0.55-4-4). Anti Scl-70 was present in 16% of overall patients and 41% of those with diffuse SSc. Anti-centromere antibodies were detected in 51% of patients overall and 70% of limited SSc.
Of the 17 patients who died, in 7 (41%) the cause was directly disease related (Table 1). Only one patient died from pulmonary fibrosis or pulmonary hypertension “alone”, versus 5 who had a combination of interstitial lung disease, pulmonary hypertension or myocardial involvement.
Two patients suffered from alveolar hemorrhage at time of death, in combination with other manifestations.
Of the 10 unrelated causes of death, 3 died from sepsis, 2 pneumonia, 2 GI hemorrhage, 1 hepatic insufficiency following primary biliary cirrhosis and 2 after heart valve replacement.
In all of these cases, underlying disease contributed to death as a fundamental comorbidity.

Conclusion. In this small series, causes of death were considered directly related to SSc in 41% of patients, lower than described elsewhere. A combination of lung and heart involvement was the main cause of death in this group. In most deaths considered to be not directly related, SSc was felt to contribute greatly as a comorbid situation towards the final outcome.

Table. Causes of death in SSc related patients

	Fibrosis	Pulmonary hypertension	Myocardial involvement	Alveolar hemorrhage	Lung transplant
1			+	–	
2	+		+		
3	+	–			
4	+				
5		–		–	
6	+				
7					+

PS229 MOOD AND ANXIETY DISORDERS IN SYSTEMIC SCLEROSIS PATIENTS

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Aim: To assess the prevalence of mood and anxiety disorders in systemic sclerosis (SSc)
Patients and methods: Between january 2011 and january 2012. 70 SSc patients fulfilling the American Rheumatism Association and/or Leroy and Medsger criteria were recruited. Mood and anxiety disorders were assessed by use of the Beck Depression Inventory (BDI) and the Hospital Anxiety and Depression Scale (HADS)
Results: 67 women and 3 men with a median age of 46 years and a disease duration (first non-Raynaud symptom) of 10.28 years. 18 patients had a diffuse scleroderma, 52 patients had a limited scleroderma. 46 patients (66%) had pulmonary fibrosis, 62 (89%) had oesophageal dismotility. The mean functional Health Assessment Questionnaire score was 0.74.
66 (94%) patients met criteria for depression, and 53 (76%) had scores above the cutoff usually taken to define moderate to severe depression. 29 (41%) patients met criteria for anxiety. Only 2 patients had a history of antidepressive drug therapy. Depression was not associated with organ involvement.
Conclusion: Systemic sclerosis is associated with a high prevalence of depression and anxiety. Lack of social support probably promotes their appearance. Adequate screening and treatment of mood and anxiety disorders in SSc are needed.

PS230 SCLERODERMIC PATIENTS: AN INTERDISCIPLINARY APPROACH

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Objectives: We experience our life through the skin: from the first loving contact to the last painful separation. Therefore the skin "reminds" all the conflicts between the individual and the external environment. Nowadays there is a great agreement in identifying these conflicts as responsible for the majority of the psychopathologies ([1]).
The present work aimed at investigating the psychosomatic features of scleroderma (i.e. the thickening and tightening of the skin) using the Analytic Psychodrama method. This method, through scenes, allows to make conscious different unconscious conflicts, as well as to interpret them.

Method: We studied a group of five women (age: 35-70 years old) for one year.
We collected the individual experiences reported by the patients, focusing on the ones that are crucial in the formation of psychosomatic symptoms: the specific relationship with the mother and with the father, the possible arrival of one or more younger siblings, the specific affection/dynamics of the primary and following milieu.
We measured the relational structures between the participants - closeness vs. distance - before and after the group work.

Results and conclusions: Collected data suggest that during the formation of their early personality patients experienced a mother affectively cold, needy or lacking of contact signals. As a result their skin was not trained to soften up, delighting in maternal warmth and protection. Conversely the skin adapted to defense itself autonomously.
The used method, the Analytic Psychodrama, allowed us to investigate different aspects of the psychic life of each participant. We identified important changes in participants' body perception as well as in physical contact with the others. We observed these changes also in the family context.
Resting on these results, we predict further long-term effects of our approach. According to the principles of psychosomatic medicine, it should affect also the specific clinical aspects of scleroderma.

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PS231 SYMPTOMS OF DEPRESSION AND ANXIETY IN CROATIAN PATIENTS WITH SYSTEMIC SCLEROSIS

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Introduction: Patients with systemic sclerosis report high levels of pain, fatigue, disability, and considerably impaired overall physical function.
Methods: We conducted a cross section study which included 16 patients with systemic sclerosis from East Croatia regions. Symptoms of depression and anxiety were evaluated using Zung , s anxiety self- assessment scale and Zung, s depression self-assessment scale.
Results: We enrolled 16 female patients (M = 62 years; range 24-78) who were treated in our Clinic during year 2013.Four patients were diagnosed with limited systemic sclerosis, and 12 with progressive systemic scleroses. Majority of the patients have an elementary school and only one patient has university degree. According to Zung, s anxiety scale twelve patients were in the normal range and only four patients were in the minimal to moderate anxiety group. Positive correlations were found between individual clinical signs and symptoms that impair physical appearance or cause pain with total anxiety. Digital ulcers, muscle pain and shortness of breath often cause discomfort, worry and anxiety in patients. Considering the small number of patients resulting data are not statistically significant. According to Zung ,s depression scale , thirteen patients were in the normal range and three patients ware in the mild depression group. We found a positive correlation between the bone pain, joints and muscular pain and higher overall depression score. Positive correlation was found, although not statistically significant, between gastrointestinal symptoms and depression.
We have found a negative correlation between body mass index and anxiety.
The analysis of individual scale items have found that 62% patients feel that their life is changing for the worse; 86% patients reported waking up with a feeling of anxiety and 94 % patients reported having had insomnia.
Conclusion: According to Zung ,s anxiety and depression scale majority of patients have no mood disorder , more detailed analysis shows that the majority of patients feel daily concerns, grief and discomfort related to their present state of health and fear for the future. Disturbances are more intense when clinical manifestations of the disease like chronic pain, fatigue and gastrointestinal symptoms are present.

PS232 PROSPECTIVE ANALYSIS OF THE CLINICAL BURDEN OF LIMITED CUTANEOUS SYSTEMIC SCLEROSIS OVER 12 MONTHS

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Introduction: Although limited cutaneous systemic sclerosis (lcSSc) is more common, the diffuse subset has generally received more attention from investigators due to its perceived greater clinical burden. The objective of this study was to evaluate the burden of disease in patients with lcSSc over a period of 12 months.

Methods: Consecutive consenting lcSSc patients attending the outpatient clinic or inpatients ward were recruited and underwent 3 study visits over a 12 month period.

Results: Over recruitment period of 3 months 44 lcSSc patients were enrolled. Of those, 88.6% were female, mean age was 55 years and mean disease duration was over 10 years (range 1-28 years). Overlap syndromes were present in 29.5% of the patients with polymyositis/dermatomyositis (20.5%) and rheumatoid arthritis (11.4%) being most frequent. Half of the patients carried anti-centromere antibodies and 16% were anti-topoisomerase I positive.

Raynaud's phenomenon was present in 89% of the patients. Over the entire follow-up period 8/44 of the patients had at some point had an active digital ulcer (year prevalence of 18%) and in 5 of the patients there were newly developed ulcers (incidence of 11% over 12 months). Those subjects developed between 1 and 3 new ulcers over the follow up period.

Some degree of pulmonary fibrosis (PF) was found in 50% of the subjects and 30% had clinically significant PF. Pulmonary hypertension had been diagnosed in 16%, cardiac SSc and renal crisis in 4.5% each. Modified Rodnan skin score varied between 0 and 14.

All had some degree of gastro-intestinal tract involvement and up to 91% of the patients suffered with reflux and abdominal distension. Diarrhoea affected 84% of the patients while constipation was reported 77%.
Half of the patients were receiving disease modifying drugs and 27.3% were treated with oral corticosteroids. Most (91%) were receiving treatment with proton pump inhibitors, 30% were taking pro-motility drugs, 16% were on laxatives and 7% were on anti-motility drugs. 66% of the patients received oral treatment for Raynaud's and 23% were admitted for treatment with Iloprost on at least one occasion during the year of follow-up.

Conclusions: Despite the relatively small number of participants in this study, the prospective design and protocolised patient assessment allowed for a more detailed record not only of clinically-significant organ-based disease, but also of non-life threatening complications of SSc, confirming the significant disease-related morbidity associated with lcSSc.

PS233 RECOMMENDATIONS FOR FUTURE PATIENT FOCUSSED TRIALS ADDRESSING FOOT PAIN IN SYSTEMIC SCLEROSIS

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Introduction: A patient initiated Randomised Control Trial was undertaken to evaluate the effectiveness of a simple cushioning and thermal insole in reducing foot pain in patients with systemic sclerosis (SSc).
A total of 560 patients were screened across four specialist sites and 141 patients were recruited to target.
Three trial contacts were required over 12 weeks, with a total of 11 patient reported assessments completed per participant.
Independent patient representatives (with SSc) participated in the trial meetings to inform trial management and design.

Findings: Compliance and completion of patient reported data was excellent; only 11 participants did not complete follow-up.
Both the intervention and a sham device yielded a reduction in pain score over 12 weeks but did not meet the pre-specified clinically significant difference. Adjusting for seasonal effect showed only a minimal and insignificant difference in pain between warm and cold months, a factor suggested by the patient representatives.
Patient diary comments highlighted severe effects of foot pain on the participant's psychological status. Much gratitude and support was shown for the trial throughout.

Recommendations: Patient and public involvement (PPI) is integral for trial success especially in severe systemic diseases and should inform the design from the outset.
To yield good recruitment rates, data collection and compliance, numbers of study visits should be minimised with flexibility and support.
The nature and source of foot pain in SSc and the interaction with footwear choice requires further evaluation.
Future intervention studies should be improved by reporting the nature and source of pain and should reflect the patient need throughout all seasons.
An additional non-treatment arm should be incorporated in future trials to explore any potential positive properties of the sham device and any gratitude effect.
Consideration of psychological support for participants is recommended when exploring new areas of chronic disease.

PS234 ROLE OF NURSING IN THE PREVENTION OF SKIN ULCERS IN SSC: A PRELIMINARY STUDY

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Skin ulcers are a frequent and disabling condition in SSc. Most of recent studies have focused on secondary prevention, but the role of primary prevention in SSc skin ulcers has been not yet fully evaluated.
The present study was an exploratory survey, in order to understand if SSc patients are aware of the measures useful to prevent skin ulcers and eventually to deal with unmet needs in the primary prevention of skin ulcers, with particular reference to educational counseling.
To this end a questionnaire was administered to 45 unselected SSc patients admitted at our unit between june and august 2013. The survey contained a number of questions related to the patient's knowledge of the disease and its complications and more specifically, questions regarding vascular and skin involvement, the use of neutral soaps to deterge skin, the use of moisturizing creams, the type of alimentation, life habits, the medications taken, the physical function.
When the patients were asked about the complications of their disease, only a minority of subjects (11%) showed to be well informed. More specifically, however, 56% of the subjects knew that skin ulcers are frequent in SSc, but only 9% of the interviewed knew the risk factors connected to the appearance of this complication.
All the patients were taking medications for their disease, mainly vasodilators and platelet antiaggregants. 40% of the patients were taking vitamin supplementation. Regarding the questions about personal hygiene, the majority of patients (98%) believed to practice a correct hygiene. However, only 20% of the patients used neutral soaps and more than 60% used alcohol containing perfumes for deodorizing. Moisturizing creams were used only by 22% of the interviewed. Only a minority of patients avoided temperature leaps (38%), but the majority (98%) protected the extremities against cold weather. 36% of the interviewed stated to have an adequate food intake, while 42% did not know and 22% stated to have an inadequate intake. 60% of the subjects stated to take at least one coffee or tea a day. A not negligible percentage of subjects (25%) acknowledged to smoke. A mild to moderate disability in common activities of daily living was present in a consistent number of patients, however only a minority of subjects had access to a rehabilitation program.
The informational gaps identified by the survey will be the basis to design a pamphlet to be used by nurses for educational purpose.

PS235 SSC CLINICAL PROFILE OBSERVED IN A SINGLE INTERNAL MEDICINE DEPARTMENT

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Aim: To review through an single center Internal Medicine the SSc profile observed and to compare ours results in data literature.
Patients and methods. Adult's patients presenting for various symptoms from January 1997 to December 2012 fulfilling the ARA criteria for SSc were included. Investigations including immunological tests (ANAs), , liver and kidney functions, imaging (thoracic angio-tomodensitometry, barium swallow..), pulmonary function test (spirometry), echocardiography, digestive investigations (esophageal manometry, endoscopy) were done. Others explorations are dictated by the clinical context (right cardiac catheterization, cardiac MRI, liver or kidney biopsy, vascular Doppler…).
Results. 120 women and 15 men were studied, mean age is 41.7 years (2 cases diagnosed in the childhood). The mean duration of SSC is 5.97 years. Most common presenting symptoms were skin binding-down (85%), Raynaud's phenomenon (95%), characteristic facies (48%), and digital abnormalities (ulcers, ischemia, and amputation : 37%) pigmentary changes morphoea and pruritus (70%). Other symptoms revealing SSc are dyspnoea (48%), joint complaints (30%), muscles weakness (17%), dysphagia (37%), abdominal pains (14%), first heart disease (15%), lung diseases (40%) and kidney disease (3.7%). Various and multiple symptoms are often intricate. The data analysis showed an association with auto immune's diseases (31%). Morbid associations is a type 2 diabetes (12%), a type C hepatitis (2%), a valvular disease (7%), an ischemic stroke (4%) and tuberculosis (4%). We observed a severe malnutrition by intestinal malabsorption (8%), a major esophageal stenosis (5%), myocardial infarction (2.9), and digital amputation (4.4%). The immunological profile finds positive ANAs (89%), antiScl70 antibody (51%), ACAs (30%), anti-mitochondria (7%) and anti-SSSA (15%). Pulmonary function tests showed restrictive (48%) and obstructive pattern (6%). Diffuse SSc are dominant (74%). The treatment (medical and surgery) is symptomatic referring to the manifestations observed. We haven't use news therapies and only five patients were selected for immunosuppressive drugs. The global quality of life is poor essentially by global pain and the hand handicap.
The causes of 19 total death observed are attributed directly to SSc in 15 cases (11%) and identified cases of death were pulmonary arterial hypertension (4), lung disease (3), severe malabsorbtion (1), heart failure (5), acute renal crisis (1) and liver failure (1).

Conclusion: The clinical profile in our cohort is similar in those reported in the literature and the increase cases of heart disease observed are probably explained by the way of the recruitment. Some singular presentations will be detailed in others works (veino-occlusive disease, constrictive pericarditis, childhood SSc…).

PS236 NAILFOLD VIDEOCAPILLAROSCOPY FINDINGS IN SYSTEMIC SCLEROSIS AND PRIMARY RAYNAUD'S PHENOMENON – 12 MONTHS FOLLOW UP STUDY

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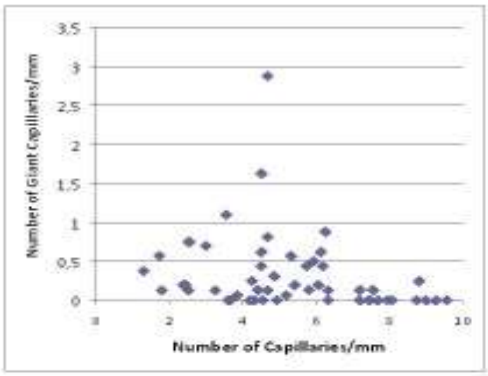
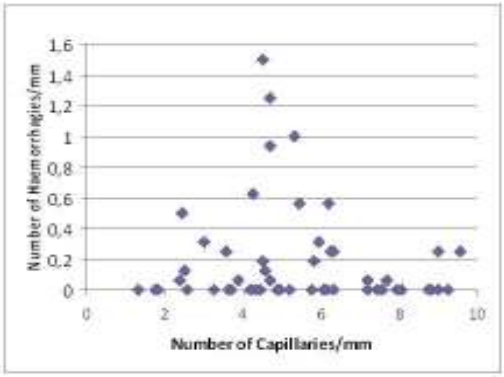
The aim of the study: We aim to compare nailfold videocapillaroscopy (NVC) findings between systemic sclerosis (SSc) patients and patients with primary Raynaud's phenomenon in a Finnish prospective study cohort. NCV status will be evaluated at 0, 6, and 12 months. In addition, clinical findings, laboratory data, functional test results, and radiological findings will be analyzed. Here, we describe the baseline characteristics and NVC findings of the study patients with SSc diagnosis.

Methods: We enrolled consecutive 152 patients with Raynaud's phenomenon and SSc patients that were not examined with NVC before. Nailfold capillaries of II-V fingers were examined from both hands by using an optical probe videocapillaroscope mounted with x200 magnification contact lens. Images were analyzed with Videocap software (DS MediGroup, Milan, Italy). The number or capillary loops (NCL), giant capillaries, and hemorrhages in the range of 1 mm field were calculated. The average of two consecutive 1 mm fields was calculated. The average of the eight fingers was calculated. In the future, all of these patients will have their Hamis, health assessment questionnaire, and Rodnan skin score evaluated.

Results: 51 patients out of 152 patients with Raynaud's phenomenon were diagnosed with SSc. The year of the diagnosis varied between 1970's to present. Some of the patients were diagnosed during this study. The mean age of the SSc patients was 56.4 years (±13.8 SD, range 24-76 y), and the most of the patients were female (90%). The average of number NCL in one finger was ranging between 1.3 and 9.6 and the average NCL of the eight fingers was 5.3 (SD 2.1), median 4.9, IQR25% 4.0, IQR75% 6.8. The number of hemorrhages was ranging from 0 to 1.5 with average of 0.2 (SD 0.34), median 0, IQR25% 0, IQR75% 0.25. The number of giant capillaries average was 0.32 (SD 0.50), median 0.13, IGR25% 0, IQR75% 0.44. Range of the number of the giant capillaries varied between 0 and 2.9.

Conclusions: The following charts from our material (one dot representing one patient) demonstrate that the SSc patients are in different disease stages. As expected, a small number of hemorrhages and giant capillaries were associated with very early stage of the disease when the number of capillaries was high or alternatively, in the very late stage of the disease with small number of capillaries. We are now waiting for the rest of the results for further analyze.





PS237 UTILITY OF NAILFOLD CAPILLAROSCOPY FOR THE VERY EARLY DIAGNOSIS OF SYSTEMIC SCLEROSIS

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Background: A scleroderma-pattern on nailfold capillaroscopy (NFC) evaluation of the microvasculature is predictive of the development of systemic sclerosis (SSc). The proposed European League Against Rheumatism criteria for the very early diagnosis of SSc (VEDOSS) include NFC findings, SSc-specific autoantibodies and clinical manifestations.

Aims: To determine the utility of NFC for the very early diagnosis of SSc in an Asian cohort

Methods: Patients not fulfilling the American College of Rheumatology criteria for SSc were referred for NFC and consecutively recruited based on the presence of (A) Raynaud's phenomenon (RP) with or without positive ANA>1/800 (B) Undifferentiated clinical features to suggest SSc, polymyositis or dermatomyositis (C) Asymptomatic isolated positive ANA>1/400. Scleroderma-pattern NFC is defined by the presence of >1 giant capillary, avascular areas or >2 dilated capillaries with areas of haemorrhage.
Results: Ninety patients were consecutively recruited from March 2010 to May 2013 (mean age 55 years, 87% female; 76% Chinese, 7% Malay, 10% Indian, 7% other ethnicity). Taking into consideration NFC patterns, the clinical outcomes were normal in 32 patients (35.6%), connective tissue disease (CTD) suspected in 33 patients (36.7%), and definite CTD in 25 patients (27.8%). Forty-one patients had a scleroderma-pattern on NFC, of whom 22 fulfilled VEDOSS criteria, and 19 were suspected to have a CTD, giving an overall diagnostic yield of 24.4% (22/90) for VEDOSS. ANA was positive in 74 (82.2%) patients (n=25 anti-centromere, n=3 anti-Scl70). When stratified according to reasons for referral (Groups A-C above), VEDOSS was most frequently diagnosed in Group A (8 of 20, 40.0%) followed by Group B (11 of 37, 29.7%) and Group C (3 of 33, 9.1%).

Conclusions: NFC is useful for the very early diagnosis of SSc with a diagnostic yield of 24.4%, especially in the subgroup of patients with Raynaud's phenomenon with or without positive ANA>1/800.

PS238 FINGER SKIN VASCULARIZATION IN PATIENTS WITH SYSTEMIC SCLEROSIS – COMPARISON OF ULTRASONOGRAPHY AND CAPILLAROSCOPY

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Objectives: To assess the level of skin vascularization in hand fingers of patients with SSc using ultrasonography and capillaroscopy, and to estimate the clinical value of these findings.
Methods: The cross-sectional clinical study enrolled 35 pts who fulfilled ACR criteria for classification of SSc. Ultrasound examination was performed using VOLUSON 730 machine equipped with 10 - 16 MHz linear probe. The appearance of Power Doppler (PD) skin signal and dorsal digital artery (DDA) flow of the second (II) and fourth (IV) finger at the level of intermediary (IMF) and distal phalanges (DF) of both hands, were analyzed separately. The dorsal digital artery flow was rated as: 0º intact, when blood flow can be continuously visible in whole examined area, 1º reduced, as blood flow was not visible in 1/3 of examination area; 2º reduced, when blood flow was not visible in 2/3 of examination area; 3º reduced, when blood flow was invisible in whole examined area. Capillaroscopy findings were described by both methods: Maricq and Cutolo.
Result: Thirty-two pts (32/35) were females, mean age of pts was 55.3±10.7 yrs. The mean duration of Raynaud's phenomenon was 104.3±10.1 months. PD soft tissue signal of right hand finger was present in 14 (40.0%) pts and in 17 (48.5%) pts of left hand finger summary. Reduced DDA flow had 24 (68.6%) pts. analyzed.

Tab.1 dorsal digital artery flow in the 2nd and 4th hand fingers of patients with SSc.

DDA flow	2nd right hand finger (N of pts)	2nd left hand finger (N of pts)	4th right hand finger (N of pts)	4th right hand finger (N of pts)
Intact (0°)	3 (9.3%)	2 (5.7%)	6 (17.1%)	2 (5.7%)
1° reduced	16 (45.7%)	12 (34.2%)	15 (42.8%)	13 (37.1%)
2° reduced	13 (37.1%)	14 (40.0%)	10 (28.5%)	10 (28.5%)
3° reduced	3 (8.5%)	7 (20.0%)	4 (11.4%)	5 (14.2%)

Only two pts. had normal or type 1 (Maricq) capillaroscopy findings. Early changes (type 2) were found in 17 (48.6%) pts whereas type 3 (active changes) were present in 9 (25.7%) pts. Five (14.3%) pts had changes of type IV. We found strong significantly positive correlation of ultrasonografic and capillaroscopy findings (p= 0.001, r= 0.547). Rank correlation between level of DDA flow and Raynaud's phenomenon (r= 0.276) and age of pts. (r= 0.137) either with presence PD skin signal were not statistically significant (r= 0.250)
Conclusion: Dorsal digital artery flow estimated by ultrasonography was reduced in large number of our patients with systemic sclerosis, and it was mostly of severe intensity. Power Doppler skin signal was often present in finger soft tissue and could probably point to enlarged capillary loops in the examined part of skin. Ultrasonography could be useful tool in estimation of the level of finger vascularisation in patients with systemic sclerosis.

PS239 VIRTUAL TOUCH IMAGING AND QUANTIFICATION: A NEW NON-INVASIVE IMAGING METHOD TO MEASURE SKIN STIFFNESS FOR SCLERODERMA

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Background: Skin involvement is of major clinical and prognostic relevance in systemic sclerosis (SSc) and often the primary outcome in clinical trials. Nevertheless, an objective and sensitive measure of skin involvement is lacking. Virtual Touch Imaging and Quantification (VTIQTM) is a new elastography imaging method that provides qualitative and quantitative information about absolute skin stiffness.
The present study evaluated VTIQTM as a potentially method for determining absolute skin stiffness in SSc.
Methods: Skin thickness was clinically assessed by the modified Rodnan Skin Score (mRSS) in SSc patients. Absolute skin stiffness was measured at all mRSS anatomical sites using VTIQTM to quantify the shear wave velocity (in m/s). The same quantification was also performed in age and gender-matched healthy controls. Intraobserver reliability was calculated in four SSc patients and two healthy controls (HC), in two different scanning sessions, one week apart. Correlations between absolute skin stiffness and mRSS, and comparison between patients and controls were statistically assessed using SPSS software. P values <0.05 were considered significant.
Results: Twenty-six SSc patients were included (mean age 55.3 ±12.1 years, mean disease duration 12.5 years (range 0.5–36), and mean mRSS 11.8 (range 0–33). Seventeen age and gender matched controls were recruited. Absolute skin stiffness measurements were statistically significantly higher in SSc than in HC, in 11 out of 16 mRSS sites of analysis (see table 1). The absolute skin stiffness was strongly correlated with the local mRSS in the following anatomical sites: forearm, r= 0.688, p= 0.0001; hand, r= 0.577, p= 0.0001; and, phalanx, r= 0.748, p= 0.0001].
The technique showed an excellent intraobserver reliability in our small sample (intraclass correlation coefficient >0.8).
Conclusions: Shear wave velocities showed a significant positive correlation with mRSS in four sites. The lack of correlation at other sites may be due to the high proportion of cases with mRSS=0 and suggests that the clinical assessment has low sensitivity at the lower levels of skin involvement. VTIQTM represents an innovative and promising technique that provides, for the first time, a non-invasive, absolute quantification of tissue stiffness. Further studies of VTIQTM are required, but this early study supports the clinical and scientific potential this new measure of skin involvement in SSc.

Figure 1

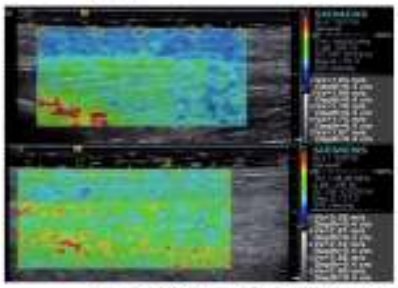

Figure 1 - VTIQ™ of the dorsal aspect of the hand in a control (A) and in a patient with SSc (B). Absolute shear wave velocities (in m/s) within the sample gate (yellow box) are shown quantitatively on the right side. The colour scale depicts graphically the absolute stiffness of all tissues within the region of interest (redhard tissue, and blueroft tissue).

PS240 A STUDY COMPARING VIDEOCAPILLAROSCOPY AND DERMOSCOPY IN THE ASSESSMENT OF NAILFOLD CAPILLARIES IN PATIENTS WITH SYSTEMIC SCLEROSIS-SPECTRUM DISORDERS

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Background. Nailfold videocapillaroscopy (NVC), is the current 'gold standard' for detecting capillary abnormalities suggestive of a systemic sclerosis (SSc)-spectrum disorder, however it is not widely available: a key question is whether lower magnification, easy-to-use dermoscopy compares favourably. Our objectives were to examine the classifiability of capillaries and the evaluation of abnormality(severity), by both NVC and dermoscopy(and to determine whether these differ between (i) general and specialist rheumatologists (ii) the thumbs and fingers and (iii) the left and right hands) and to compare intra- and inter-rater reliability of both techniques.
Methods. NVC and dermoscopy images were acquired from all 10 nailbeds of 32 subjects with a range of capillary abnormalities. Images were graded (on a web-based interface) on a 0-3 scale of severity: normal, mildly, definitely and grossly abnormal, and an unclassifiable category. Raters graded images from four subjects (40 nailbeds) using each technique, with 5 repeated images to estimate intra-rater reliability.
Results. Forty-eight rheumatologists from 12 countries participated in the study (22 generalist, 26 specialist). While most images could be graded by both techniques, more were graded (Table 1) by NVC (86% vs.73%) and were systematically scored higher (Table 1) by NVC (mean difference of 0.422 between the ratings). General and specialist rheumatologists performed similarly, however generalists were less likely to grade dermoscopy images. Intra- and inter-rater reliability was comparable for the two techniques in the classifiability of images and the grading of severity. The thumb was twice less likely to be graded, images from the left hand were slightly more likely to be classified and there was a small increase in the scoring of severity of images obtained from the right hand.

		Videocapillaroscopy scores						
		normal [0]	*mildly abnormal [1]*	*definitely abnormal [2]*	*grossly abnormal [3]*	*unable to classify*	Sub-total	Total
Dermoscopy scores	*normal [0]*	92 (4.8)	130 (6.8)	62 (3.2)	18 (0.9)	*24 (1.3)*	326 (17.0)	**1,394 (72.6)**
	mildly abnormal [1]	65 (3.4)	140 (7.3)	169 (8.8)	87 (4.5)	*30 (1.6)*	491 (25.6)	
	definitely abnormal [2]	18 (0.9)	50 (2.60)	135 (7.0)	128 (6.7)	*35 (1.8)*	366 (19.1)	
	grossly abnormal [3]	1 (0.1)	12 (0.6)	51 (2.7)	131 (6.8)	*16 (0.8)*	211 (11.0)	
	unable to classify	*60 (3.1)*	*106 (5.5)*	*112 (5.8)*	*82 (4.3)*	*166 (8.6)*	*526 (27.4)*	***526 (27.4)***
	Sub-total	236 (12.3)	438 (22.8)	529 (27.6)	446 (23.2)	*271 (14.1)*		***1920 (100.0)***
	Total	**1,649 (85.9)**				***271 (14.1)***		

Table 1: Cross-tabulation of frequency of ratings (with percentages): by NVC and dermoscopy (severity scores are indicated by square brackets).

Conclusion. Our results suggest that dermoscopy is comparable to NVC. NVC images were more likely to be classifiable, and were graded more severely. Intra- and inter-rater reliability were similar for both techniques. Small, yet significant differences were noted in the classifiability and the grading of severity between the left and right hands and the thumbs and fingers. Further research is warranted to validate dermoscopy in the assessment of patients with SSc-spectrum disorders.

PS241 LONGITUDINAL ASSESSMENT OF SCLERODERMA SKIN BY OPTICAL COHERENCE TOMOGRAPHY: PRELIMINARY VALIDATION OF SENSITIVITY TO CHANGE OVER-TIME

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Background: Optical coherence tomography (OCT) is a quantitative reliable tool to assess skin involvement in Systemic Sclerosis (SSc) (1). However the sensitivity to change over-time has not been evaluated. The present study aimed to compare skin assessment by OCT over-time in patients with SSc.
Methods: We performed 52 OCT scans of dorsal forearms on 26 sites of analysis from 17 SSc patients (9 dcSSc, 8 lcSSc; 6±4.5years disease duration) at 0 and 24 months.Clinical skin involvement was assessed using the modified Rodnan skin score (mRss). Minimum and Maximum Optical Density (Min and Max OD) of the mean-A scans were calculated employing Matlab software (1).Comparison of the local mRss with Min and Max OD at the 2 time-points was performed by two-tailed paired t-test.
Results: Fourteen sites with local mRss=0 did not change over 24 months. Accordingly, both Min and Max OD showed an average +2.98% and -0.05% change, respectively (p>0.05). Six sites of analysis improved by 2 mRSS points (three from “2” to “0”, three from “3” to “1”). In these sites Min OD showed an average increase of 23.92% (p=0.0084) and Max OD of 25.13% (p=0.008).In 4 sites of analysis mRss improved by 1 point (two from “3” to “2”, one site from “2” to “1”, one site from “1” to “0”). In these sites Min OD and Max OD showed no significant improvement (Min OD 1.93% and Max OD of 8.15%; p>0.05 for both). Furthermore, both Min and Max OD showed a trend forward a decrease (-3.54%, -5.41% respectively) at the 2 sites of analysis with worsening mRSS (one point increase) but the low sample size did not allow to perform a statistical evaluation.
Conclusions: Although preliminary for the low number of observations, this study provides the first evidence suggesting that OCT of the skin is sensitive to change over time and it changes consistently with mRss. The lack of improvement of OCT in sites with a mRSS of 1 deserves further studies to determine whether this is correlated with poor accuracy of mRSS or room for improvement in OCT analysis. Studies including a larger number of patients and sites of analysis with different grades of skin involvement and improvement/deterioration of clinical score are needed to reach a definitive validation.

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PS242 CONE BEAM CT SCAN IN THE MONITORING OF LINEAR SCLERODERMA OF THE FACE: PRELIMINARY RESULTS

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Background: Up to now there are no reliable outcome measures for Linear Scleroderma of the Face (LSF) in its two subtypes, Parry Romberg syndrome (PRS) and Scleroderma En coup de sabre (ECDS). Cone Beam CT Scan (CBCT) has been recently introduced in pediatric odontostomatology as an useful and safe instrument for the clinical practice. CBCT is a fast procedure showing both soft and hard tissue abnormalities with 50 times reduction of the irradiation dose, as compared to a conventional CT.
Objective: Our study was aimed to define the symmetry cut-off for the two hemifaces and to quantify the sensitivity of the CBCT Scan for the assessment of LSF between the affected and non-affected side of the face.
Methods: Patients with LSF followed at the Department of Pediatrics, University of Padua, were evaluated by CBCT Scan. Each image was evaluated choosing 5 different axial planes (supraorbital margin, mandibular condyles, floor of the maxillary sinus, mandibular hole and mandibular symphysis). Control subjects affected by Benign Joint Hypermobility Syndrome was enrolled in order to support the correct choice of a symmetry cut-off. The sensitivity of CBCT was compared with physician's clinical judgment, sequential clinical pictures and thermography.
Results: 18 patients (11M, 7F) with LSF entered the study. Eleven patients had PRS, 4 ECDS, 3 progressive emifacial atrophy. CBCT Scan was sensitive in detecting the degree of facial asymmetry in different spatial planes, coincident with those affected by the disease (upper planes for patients with ECDS and lower planes for those with PRS). In addition, CBCT better evidenced the presence of disease evaluating the soft tissue thickness as compared to bone involvement.
Conclusions: This preliminary data show that CBCT is a reliable and safe technique to quantitate the asymmetry of the face in disease affected areas, particularly for the soft tissue. CBCT may have a potential role as gold standard for the assessment of the disease course. A sensitive to change study is in progress.

PS243 NON-INVASIVE ASSESSMENT OF SILENT LIVER FIBROSIS IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Background. Although up to 90% of patients systemic sclerosis (SSc) have been estimated to have gastrointestinal involvement, liver disease (without any cause other than SSc itself) has been reported only rarely in this disease. Liver biopsy is considered the gold standard for an accurate assessment of liver fibrosis. However, it is an invasive and expensive tool, so there has been increasing interest in non-invasive assessment evaluation of liver stiffness (LS) by transient elastography (TE) which have been recently demonstrated to be useful for the diagnosis of various grades of fibrosis in the course of chronic liver diseases.
Objectives. To evaluate the presence of liver fibrosis in a series of SSc patients, without any functional sign of liver disease and any cause other than SSc itself, and to identify any possible associations with demographic data, disease duration and disease phenotype.
Methods. Thirty-nine SSc patients (33 females and 6 males) without liver diseases, mean age 63.4±13.2 years, disease duration 10.5±8,67 years, and a sex- and age-matched control group, were consecutively studied. LS was evaluated using TE (Fibroscan; Echosens, Paris, France) and measured in kPa. We adopted 5.3 kPa as the cutoff for abnormal LS values.
Results. Seventeen (43.5%) SSc patients had abnormal LS values when patients were classified into two groups according to the cutoff (group A <5.3 kPa, group B > 5.3 kPa); the median LS value was 4 kPa in group A and 7.1 kPa in group B . There were no significant differences between the two groups in disease duration, demographics, laboratory variables or disease characteristics. Among medications, a significant difference for patients on endothelin receptor antagonist therapy was seen in group B (P = 0.02).
Conclusions. TE suggested, in a non-invasive fashion, liver fibrosis in 43.5% of our SSc patients, as a result of a primary hepatic involvement. LS measurement could be suggested for checking silent liver fibrosis in SSc, even in absence of abnormal liver function serological tests. However, further studies are required to investigate whether treatment regimens can influence the progression of liver fibrosis, or if they should be modified when abnormal LS values are identified.

PS244 CHANGES IN THE THICKNESS AND STIFFNESS OF PALMO-PLANTAR SOFT TISSUES IN PEOPLE WITH SYSTEMIC SCLEROSIS

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Objective: To compare thickness and relative stiffness of palmo-plantar soft tissues between people with systemic sclerosis (SSc) and healthy controls (HC).
Methods: Soft tissue thickness and stiffness, at one palmar site [third metacarpophalangeal joint (3rdMCPJ)] and two plantar sites [third metatarsophalangeal joint (3rdMTPJ) and heel], were measured by high-frequency ultrasound and compression-elastography, respectively, in 25 SSc patients and in 18 HC.
Results: Twenty-five SSc patients (23 females, 2males) with a mean age of 56.6 (9.9) years and mean disease duration of 11.1 (7.0) years; and 18 controls with a mean age of 51.9 (10.6) years were included. Nineteen patients had limited SSc and six had diffuse SSc.
Palmar skin was thicker in SSc cases than controls: 0.15 mm (0.13 to 0.16) vs. 0.11 mm (0.10 to 0.12), $p<0.001$) and fibro-fat pad in the plantar surface of 3rdMTPJ was thinner: 0.41 (0.35 to 0.47) vs. 0.52 (0.44 to 0.59), $p<0.05$, in the SSc group than in the control group.
Fibro-fat pad at the palmar site was stiffer in the SSc group than in the control group: 0.7 (0.6 to 0.9) vs. 0.5 (0.4 to 0.6) and plantar heel: 0.9 (0.7 to 1.1) vs. 0.5 (0.4 to 0.6) (all $p<0.05$),.
Conclusion: Measurements of soft tissue relative stiffness by compression-elastography add a new dimension to the clinical assessment of soft tissue in SSc. Changes in thickness and stiffness of palmo-plantar soft tissues may lead to functional limitations as well as a decrease in shock attenuation properties and ability to distribute foot-ground contact load affecting the foot during walking. Furthers studies are needed to define the role of compression-elastography in SSc patients with hand and foot problems.

PS245 DO HEATING AND HYDRATION IMPROVE THE QUALITY OF NAILFOLD CAPILLAROSCOPY IMAGES?

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Background. Nailfold videocapillaroscopy helps identify which patients presenting with Raynaud's phenomenon have an underlying systemic sclerosis (SSc)-spectrum disorder. However, in some patients the nailfold capillaries can be difficult to visualise clearly.
Objective. To investigate the hypothesis that heating and hydration will improve image quality in those patients in whom nailfold capillaries are difficult to visualise.
Methods. 29 patients with SSc and nailfold capillaries that were difficult to visualise clearly were recruited (24 female; median age 58 years, range 20-71). At an ambient temperature of 23C, nailfold videocapillaroscopy was performed on the ring finger of the non-dominant hand using a KK Technology (Honiton, UK) microscope under 4 conditions:

1. Baseline.
2. After heating the hand in a box (temperature 30C) for 10 minutes.
3. Post hydration (after drinking 1 litre of water/juice, and further 20 minute acclimatisation).
4. After a second 10 minute period of rewarming in the heated box (i.e. post hydration and heating).

To assess the quality of the nail fold image, two specialist raters scored each image on a 10 point scale, with the higher score representing an image of higher quality. The mean of the two raters' scores was used to estimate image quality. The Freidman test was applied to these mean scores over the 4 test conditions.
Results. The median (IQR) score was 5 (2 to 7.5) for condition 1, 5.5 (3 to 7.5) for condition 2, 5.5 (3.5 to 7.5) for condition 3 and 5.5 (4 to 7.5) for condition 4. A statistically significant difference across the 4 test conditions was identified ($p = 0.04$). Post-hoc Wilcoxon tests performed for each pair of test conditions (with Bonferroni adjustment) indicated that the only significant difference was between baseline and 'hydration + heating' ($p = 0.02$). However, the median difference between baseline and 'hydration + heating' was only -1 (95% CI -1.5, -0.5) which, given the subjective nature of the rating scale, was unlikely to be clinically relevant. Descriptive analysis demonstrated that in some patients, scores increased over the 4 test conditions.
Conclusion.

1. Heating and hydration have minimal (if any) effect on image quality, although there was a trend for imaging quality to be rated more highly after the combination of both heating and hydration.
2. The possibility remains that in a proportion of patients with poorly visualised capillaries, a combination of heating and hydration is helpful, and could be considered in cases of diagnostic uncertainty.

PS246 VIDEO-CAPILLAROSCOPY OF PERI-CALCINOTIC SKIN INDICATES SPECIFIC FEATURES OF SEVERE MICRO-VASCULOPATHY ASSOCIATED WITH CALCIUM DEPOSITS IN SYSTEMIC SCLEROSIS

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Objective: To determine whether the presence of calcinotic lesions is accompanied by local features of micro-vasculopathy by investigating the video-capillaroscopic pattern of peri-calcinotic skin in Systemic sclerosis.

Methods: We adopted an Optilia Digital video-capillaroscopy system equipped with 200x magnification lens. 144 images were collected in 4 surrounding quadrants within 3mm of calcinotic lesions and at their contra-lateral unaffected skin in the same Region of interest (ROIs). Two rheumatologists blinded to the clinical details independently analysed the images for presence of: non-specifically enlarged capillaries, Giant capillaries, Haemorrhages, loss of capillaries, disorganisation and ramifications. Images were scored and data were analysed by non-parametric tests.

Results: Eighteen calcinotic lesions and contra-lateral ROIs were analysed from 11 patients. Loss of capillary areas were observed in all calcinotic lesions vs 7 contra-lateral ROIs (p=0.0001). Non-specifically Enlarged capillaries were observed at 17 lesions vs 11 ROIs (P=0.031), giant capillaries, disorganisation and capillary ramifications were observed at 7, 9 and 5 lesions, respectively, while none were observed in any ROIs (P =0.016, p=0.004, p=0.063). Haemorrhages were observed at 5 lesions and 2 ROIs (P = 0.25).

Conclusion: Features of severe micro-vasculopathy are observable in plain skin by video-capillaroscopy and may be specifically associated with calcinotic lesions in SSc.

PS247 THYMIC FINDINGS BEFORE AND AFTER AUTOLOGEOUS STEM CELL TRANSPLANTATION FOR SEVERE SYSTEMIC SCLERODERMA – A RETROSPECTIVE STUDY USING COMPUTED TOMOGRAPHY IN THE PRE- AND POST-TRANSPLANTATION SETTING

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Introduction: The underlying pathogenesis of systemic scleroderma (SSc) is still a matter of discussion but alterations of the immune system definitely play an important role. Recent studies on incomplete thymic involution in patients with SSc raised the suspicion that thymic abnormalities might be associated with increased risk for autoimmune diseases. Resetting the "immunologic clock" by autologous stem cell transplantation (aSCT) is a promising therapeutic option. Aim of this study was to evaluate thymic alteration in Ssc patients before and after aSCT.
Methods: All patients underwent non-enhanced chest-CT both in the pre- and post-transplantation setting. CT examinations were carried out at suspended end-inspiratory volume from apex to base on multidetector CT-scanner (SOMATOM Sensation 16/64 or 128 Siemens, Germany). All images were assessed by an experienced chest radiologist reviewed at a mediastinal window. We used following criteria for definition of an abnormal thymus: a length and/or thickness >13mm for diffuse enlargement or a length >7mm for multinodular thymic enlargement.
Results: We evaluated 28 (16 female, 12 male, mean age at transplantation 38.75 years) who all have had a chest-CT scan within 3 months before transplantation. 57.1% (n=16) of these patients showed incomplete involution of the thymus at baseline, with 10 patients showing hyperplastic and 6 nodular thymus. If we exclude those who were <25years at the time of transplantation 14/25 or 56% showed an incomplete involution. In 16 of these patients follow up CT scans were available, showing a non significant reduction of the thymic surface over the median follow up period of 11 (2-48) months.
Conclusion: More than half of the patients considered for transplantation for severe Ssc showed incomplete involution of their thymus by means of CT scan. This very high percentage is most probably explained by the negative selection of very ill patients considered for transplantation. This goes in line with previous reports of abnormal enlarged thymus especially in patients with progressive disease. Transplantation leads to a downsizing of the thymus, an observation which will be further evaluated

PS248 SCLERODERMA CAPILLAROSCOPIC PATTERNS IN AUTOIMMUNE DISEASES WITH RAYNAUD'S PHENOMENON. REPORT OF 100 PATIENTS

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Summary: Nailfold capillarmicroscopy allows to visualize and study the capillaries by simple transillumination.The presence of megacapillaries and a decreased capillary density are the hallmarks of the scleroderma capillary pattern, which can be detected by nailfold capillarmicroscopy.
Objectives:
- research the scleroderma capillaroscopic patterns in the various autoimmune diseases with Raynaud's phenomenon.
- prevalence of the other non specific capillaroscopic anomalies.
Patients and methods: One hundred patients were investigated: 26 cases with undifferentiated connective tissue disease (UCTD), 20 patients with systemic lupus erythematosus (SLE), 4 patients with dermato/polymyositis, 10 with rheumatoid arthritis, 16 cases with primary Sjögren's syndrome and 24 patients with systemic sclerosis (SSc) ., 99 of these patients are female, the average age is 40,3 years. These patients were all explored by capillarmicroscopy .
Results: All patients (100%) with dermatomyositis showed the scleroderma capillaroscopic pattern, 70.8% of systemic sclerosis , 42.3% of undifferentiated connective, 30% of lupus disease, 31.2% of Sjogren's syndrome and one case (10%) of patients with rheumatoid arthritis also exhibited the same pattern.
Conclusion: Scleroderma capillaroscopic pattern is often present in systemic sclerosis and dermatomyositis. Furthermore, it has also been described in other autoimmune disease such as Sharp syndrome, patients with Raynaud's phenomenon and UCTD may also exhibit this pattern. Therefore, capillarmicroscopy seems to be a useful tool for the early selection of those patients who are potential candidates for developing scleroderma spectrum disorders.

PS249 RELATIONSHIP BETWEEN ELASTONOSONOGRAPHY AND CAPILLAROSCOPIC PATTERNS IN SYSTEMIC SCLEROSIS

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Background: Vascular damage and fibrotic process represent the pathophysiological hallmarks of systemic sclerosis (SSc). Peripheral microangiopathy can be early detected by nailfold videocapillaroscopy, whereas modified Rodnan skin score (mRSS) is the most extensively validated technique to estimate the severity of skin involvement. Recent studies have considered the role of ultrasound elastosonography, suggesting that this technique can identify the reduction of dermal elasticity[1]. Our study was aimed to explore possible correlation between nailfold capillaroscopic patterns and finger dermal stiffness evaluated with elastosonography in SSc patients.

Methods: For the present study 20 subjects, who met the ACR criteria for scleroderma, were recruited. They underwent complete clinical examination, NVC and ultrasound evaluation. NVC was performed in each patient as reported elsewhere [2]. Patients were divided according to 3 described patterns of microvascular damage on the basis of NVC: 'Early', 'Active' and 'Late' [2]. Ultrasound elastography was performed at palmar surface of each finger tip. Images were obtained by applying repetitive skin compression as previously described[1]. The elastogram, which reflects the relative elasticity of the tissues, was created as a color coded map (i.e. blue= areas of great stiffness, red= areas of low stiffness). Images were analyzed by a proprietary software (Esaote elastosonography module, Esaote, Inc., Italy) that allows to obtain a numeric evaluation of stiffness expressing the global percentage of hardness. 'Skin stiffness' was computed by considering the average of eight fingers for each patient.

Results: Mean age of patients was 61 ±12.3 years. Mean disease duration was 7.3±5.7 years. A significant positive correlation (r=0.43, p=0.02) was found between Skin stiffness and NVC. For the case control analysis, we compared subjects showing 'Late pattern' (n=12) with subjects showing 'Active and Early pattern' (n=8) . Table shows that subjects were comparable for age and both disease and Raynaud's phenomenon duration (p=NS) . Finally, the highest skin stiffness were found in patients showing the late pattern when compared to the subjects showing 'Active and Early pattern' (p=0.03).

Table. Case control-analysis: Comparison between subjects with 'Late Pattern' and subjects with 'Active and Early pattern'

	Early + Active (N=8)	*Late (N=12)*	*P*
Age (years)	56.3±9.0	64.3±13.8	NS
RP duration (years)	11.5±9.8	16.2±12.8	NS
Disease duration (years)	6.1±4.8	8.1±6.5	NS
Skin Stiffness	46.7±6.2	55.7±9.3	0.03

All data are reported as mean ± SD. RP= Raynaud's phenomenon; NS= not significant

Conclusion: According to our data, although partially influenced by the relatively low number of subjects, elastosonographic findings in SSc patients are strictly correlated with NVC patterns of microvascular damage. Our observation if validated in subsequent studies involving a greater number of patients could lead to better define a novel role of elastosonography in skin evaluation during the course of SSc.

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PS250 MUSCULOSKELETAL ULTRASONOGRAPHY FINDINGS IN SCLERODERMA PATIENTS

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Objective: To determine and characterize the sonographic abnormalities in joints and tendons of patients with scleroderma(SSc).

Methods: Ten patients with the diagnosis of scleroderma (2 dcSSc, 8 lcSSc) regardless of whether or not have arthralgia and/or arthritis were recruited to the study and examined with musculoskleletal sonography. Sonographic evaluation was performed to the patients from the wrist, metacarpal and proksimal interphalangeal joints of both hands in dorsal and volar sides and ankle with the examination of periarticular structures. Erosive changes were evaluated from the lateral longitudinal and transvers view of the 2nd MCP, 5th MCP, 2nd PIP and ulnar styloid of the both hands. The presence of synovitis (synovial hypertrophy and/or joint efffusion), tenosynovitis, erosions and Doppler signal were investigated. Changes according to definitions of OMERACT group study were recorded (Wakefield 2005). My Lab 70 (Esaote Biomedica, Italy) sonography machine was used with a 6-18 mHz probe for the sonographic evaluation.

Results: Median disease duration and age were 9.8(2-21), 52(31-60) years respectively. All the patients fullfilled American college of rheumatology classification criteria for SSc.
Synovitis of the carpal recesses were found in 10 of the 20 evaluated wrists. In 6 of the 10 wrists with synovitis had PDS. None of the MCP joints have synovitis. On the other hand, synovitis has been observed in 13 of 100 PIP joints and 7 of them had PDS.
Extensor tenosynovitis was detected in 8 wrists and 5 of them with the hypertrophy of tendon sheath. Erosion was detected in 4 of 2nd and 5thMCP (4/ 40), 6 of 2nd PIP (6/ 20) and 7 of ulnar bone (7/20). Physical examination was determined only 4 tender, 2 swolen wrist joints .
Synovitis has been detected in 6 of 20 examined ankle and 2 of them with PDS signal. Tenosynovitis was detected in 4 of them and all with the tendon sheath thickness. More then one tendon was involved in all 4 ankle. On the other hand 2 swollen, 4 tender ankle joints were determined with the clinical examination.

Conclusion: Sonography may be a useful method to detect and categorize musculoskeletal pathologies in SSc since joint and tendon involvement can be silent and challenging for the clinician to assess by physical examination only. Tendon pathology was a frequent finding at wrist extensor and ankle tendons in SSc. Ankle joint and tendon pathology as common as wrist joints and tendon pathology in SSc.

PS251 INTERSTITIAL LUNG DISEASE ASSOCIATED WITH SINE SCLERODERMA SYSTEMIC SCLEROSIS: A CASE PRESENTATION

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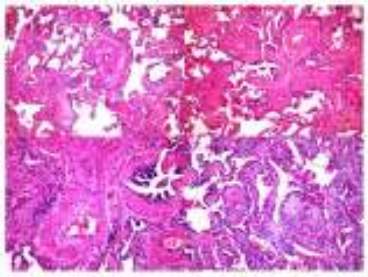
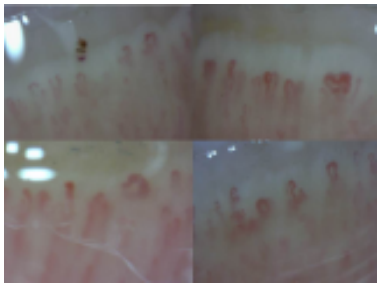
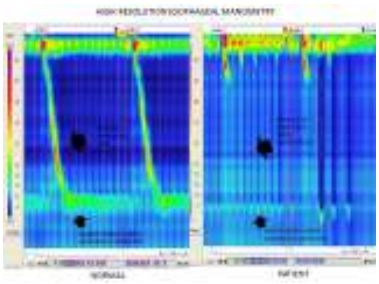
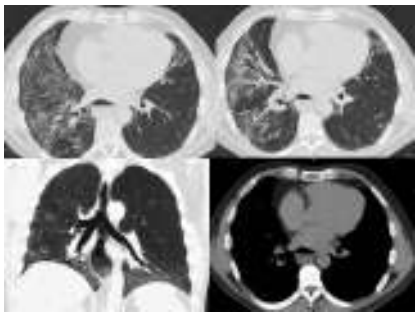
Introduction: Interstitial lung disease (ILD) may be the first manifestation of systemic sclerosis (SS) in a previously healthy patient, since the association between ILD and SS has a prognosis and therapeutic implications, this association must be evaluated at the initial approach of ILD.

Case Presentation: A 51 year old male patient with a diagnosis of idiopathic nonspecific interstitial pneumonia (NSIP) (figure 1) since 2 years ago was referred to our institution for a lung transplant evaluation. He was under treatment with azathioprine 75 mg / day, meprednisone 10 mg / day, N -aceltylcysteine 1200 mg / day.
During the evaluation symptoms consistent with gastroesophageal reflux, post prandial dyspepsia and discoloration of the fingers with pallor, cyanosis and erythema triggered by exposure to cold were detected. Physical examination revealed crackles Velcro, digital pallor and acrocyanosis compatible with Raynaud's phenomenon, digital pitting scars of finger tips (Figures 2 and 3) and no evidence of skin sclerosis, slcerodactyly or puffy fingers.
A naillfold videocapillaroscopy was performed showing an active scleroderma pattern with frequent giant capillaries, capillary microhemorragies, mild disorganization of capillary architecture and mildly ramified capillaries (figure 4). A high-resolution esophageal manometry revealed absence of peristalsis (aperistalsis) of the smooth muscle esophageal segment and hypotensive lower esophageal sphincter (Figure 5). A chest CT was performed showing a pattern of NSIP and significant esophageal dilatation in the distal third with an air-fluid level (Figure 6). An antinuclear antibody (ANA) showed a speckled pattern 1/640, anti-centromere and anti-topoisomerase I antibodies were negative.
The diagnosis of systemic sclerosis sine scleroderma was made with pulmonary, esophageal and vascular involvement.
The patient started with nifedipine, proton pump inhibitors and cyclophosphamide with good clinical response.
Discussion: In a patient with a new ILD the diagnosis of SS may be difficult when some of frequent signs of this illness are absent, like cutaneous sclerosis, sclerodactyl or puffy fingers. The presence of Raynaud Phenomenon, digital pitting scars of finger tips, dysphagia and symptoms of gastroesophageal reflux are clinical clues for the association between ILD and SS. In this case an interdisciplinary assessment directed to evidence vascular, gastrointestinal involvement and the presence of antibodies was required to making the diagnosis.
Conclusion: At the initial approach of an ILD, the association with a collagen disease, particularly SS, must be considered since this association has prognostic and therapeutic implications.
A prompt interdisciplinary evaluation must be done in order to make a right diagnosis.



PS252 TOLERABILITY OF INTRAVENOUS PROSTANOID ILOPROST THROUGH ELASTOMERIC PUMP DEVICE IN SCLERODERMA PATIENTS

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Background and purposes: Intravenous prostanoids are commonly used in the treatment of complicated Raynaud's phenomenon (RaP). Those drugs are overall moderately tolerated and their use through long-term infusion require daily admission in dedicated facilities. Furthermore, traditional peristaltic pumps (12 hours infusion protocol) do not allow complete emptying of iloprost vials.
Our aim is to describe a case series of scleroderma patients treated with iloprost through elastomeric pump, avoiding hospitalization.

Methods: Prostanoid therapy (iloprost 50 mcg) was loaded into the elastomeric pump at hospital, setting infusion rate at 24-48 mL/hour. Patients were instructed to avoid even mild physical activity, then returned to their homes for the period of administration (24 hours). A telephone alert system was enabled in order to quickly provide assistance in case of side effects.
Clinical notes of scleroderma subjects admitted to Clinical Immunology Branch were reviewed. Complete data about their condition are reported. Tolerance to treatment was classified into none, poor, moderate and good. Improvement rate of digital ulcers are given as well.

Results: Data were available for 14 patients (71.4% female), median age 53.5 years (IQR 48-60). Six cases were systemic sclerosis (one complicated by heart involvement). Six cases had RaP, 35.7% had digital ulcers.
Median duration of therapy was 33 months (IQR 15-84). Ten subjects (71.4%) showed good tolerance, while one patient suspended because of poor tolerance. Side effects were common, including headache (21.3%), dizziness (both 14.2%) or arterial hypo/hypertension (14.2%).
Only one patient was not able to receive the whole vial of iloprost as scheduled.
RaP was at least relieved in 55% of cases. Out of 5 cases with digital ulcers, 2 showed improvement or full recovery.

Conclusions: Elastomeric pump administration of prostanoids in scleroderma subjects seems a safe procedure with impressive tolerance. Our experience revealed minimized toxicity and hospital stays, allowing improved quality of life and better resources use (including the whole emptying of iloprost vials). Full patient compliance and adequate surveillance systems are deemed mandatory in order to avoid adverse events.
Our data support the need for larger study of a promising technique aimed to improve the managing of prostanoid therapy.

PS253 **COMPARISON BETWEEN NORMAL INTRAVENOUS INFUSION AND INTRAVENOUS INFUSION THROUGHT ELASTOMERIC PUMP OF ILOPROST: EVALUATION OF THE EFFECTIVENESS AND SIDE EFFECTS**

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Iloprost, a stable prostacicline analogue, is indicated for treatment of Raynaud's phenomenon in systemic sclerosis.
Particulary, this treatment has been shown to be effective for the prevention of new acral skin ulcers.
Iloprost is usually administered monthly, (6-hour continuous intravenous infusion, 0,5-2 ng/Kg/min) . Alternatively, the same total dose of iloprost can be administered in outpatients, by using a portable elastomeric pump during 24-hour continuous intravenous injection. This treatment can be performed at home while the 6-hour infusion need hospital stay.
The aim of this analysis was to compare the tolerability, the treatment compliance and the effectiveness in reducing the rate of new ulcers in patients undergoing these 2 different modalities of iloprost administration.
The study has been approved by the local Ethic Committee and all participants gave their written informed consent.
We considered 25 patients (2 females, mean age 58 ± 15 years) affected with systemic sclerosis (diagnosed according to the ACR criteria). The subjects were devided into 2 groups (13 inpatients and 12 outpatients) according to their preference of being treated during hospital stay (6 hour infusion) or at home (24 hour infusion).
The 2 groups resulted homogeneous as far as gender, treatment duration and clinical conditions are concerned but the inpatients resulted older than the outpatients (63,6 ± 14 versus 54 ± 16 years, $p < 0,05$).
We have considered for each patient a follow up period of 11 months (11 treatments), the patients of the 2 groups received the same mean monthly dose of iloprost.
At the end of each treatment day we assessed the numbers and the intensity of side effects and the treatment compliance. During each pre-treatment visit we evaluated the appearance of new acral ulcers.
Statistical analysis has been performed by using the Fisher's exact test.
Main results are summarised in the table.

Symptom	Outpatients	Inpatients	p value
Headache (patients No)	10	10	NS
Hypotension (patients No)	1	1	NS
Nausea (patients No)	0	4	<0,05
Headache (No of episodes)	46	52	NS
New skin ulcers	0	0	NA

Both treatment options resulted highly effective in the prevention of new acral ulcers. No significant difference in the number and the severity of side effects, except for nausea, were observed between the 2 groups. In fact, the inpatient group, nausea were complained by 4 patients in each treatment session while in the outptient group none referred any digree of nausea.
In conclusion, our data show that iloprost injection by using an elastomeric pump, performed at home seems to be, at least, as safe and effective as traditional infusion. However,it seems that a slower infusion rate of iloprost might avoid the occurrence of nausea.

PS254 BIOLOGICAL THERAPY IN SYSTEMIC SCLEROSIS

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Aims: To analyze our experience of biological therapy (BT) in a cohort of 228 patients with systemic sclerosis (SS) in a third level university hospital.
Material and Method: Retrospective study. BT treated patients were sought in our own database of patients with SS and their medical records were reviewed.
Results (table 1): seven patients were treated with BT: five of them with anti-TNF and the other two with rituximab (RTX).
1) Patients treated with anti-TNF: Two patients with diffuse systemic (dSS) and with a very aggressive onset were treated with anti-TNF in order to stop the quick evolution of the cutaneous sclerosis (one with imfliximab and the other with adalimumab), with no response. The three other patients with erosive arthritis who did not respond to previous treatment (methotrexate and leflunomide) did respond well to etanercept (two patients) and adalimumab (one patient). In one of these three patients the therapy was able to be discontinued after two years but not in the other two who remain in treatment until today (years).
2) Patients treated with RTX: Case 1: RTX was indicated because of an advanced interstitial lung disease (ILD) with respiratory failure and secondary pulmonary hypertension that didn´t respond despite previous treatment with cyclophosphamide (CYM) and mycofenolate (MFN). The RTX treatment was able to slow down the progression. Case 2: A patient with dSS and interstitial lung disease with anti-Scl70 y pANCA (anti- MPO) antibodies suffered a severe pulmonary hemorrhage with a complete response to RTX (2011, July); in 2013 July she suffered a glomerulonephrytis together with high titles of anti-MPO antibodies and again with a good response to RTX.

Conclusion: In our experience anti-TNF treatment is a suitable option for erosive arthritis treatment SS patients. On the other hand, aggressive cutaneous sclerosis did not respond to anti-TNF treatment. Our impression, in the case of aggressive interstitial lung disease, was that RTX slows down the clinical worsening. In the case ANCA vasculitis associated with dSS clinical response to RTX was favorable for both renal and lung manifestations.

Case	Gender	Age*	Years#	SE	Antibody	BT Indication	BT	Response
1	M	54	0	Diffuse	ANA (nucl)	Cutaneous sclerosis	Infliximab	-
2	F	42	0	Diffuse	ANA (fs.)	Cutaneous sclerosis	Adalimumab	-
3	F	35	9	Diffuse	Scl70	Arthritis	Etanercept	+
4	F	59	6	Limited	ACA	Arthritis	Etanercept	+
5	M	47	1	Diffuse	Scl70	Arthritis	Adalimumab	+
6	F	58	1	Diffuse	Scl70, ANCA	ANCA Vasculitis	Rituximab	+
7	M	41	19	Diffuse	Scl70	Interstitial lung disease	Rituximab	+/-

*age at diagnosis; # years from diagnosis; SE: systemic sclerosis; nucl: nucleolar, fs: fine speckled; BT: biological therapy

PS255 ILOPROST AS CYCLIC SIX-DAY PER MONTH. LONG TERM EFFACACY IN SCLERODERMA PATIENTS

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Introduction: Scleroderma is a treatable but not curable disease, characterized by a poor prognosis. Previous studies have defined prognostic indicators useful for assessing the severity of the clinical picture and to predict patient survival. So, stabilizing the disease as long as possible may represent an important therapeutic goal. The aim of the study is to evaluate the evolution of the disease and to identify possible prognostic factors in a group of consecutive patients accessed to the Unit of Rheumatology Catania's hospital, Italy, from 2006 to 2013.
Methods: Retrospective analysis of a database of 44 patients (44F, 50.8 +/- 12.5 years), treated with iloprost for a mean duration of 28.0 +/- 16.5 months. Iloprost was administered with a regimen of daily infusion for six consecutive days per month, for a duration of 6 hours, at a dose of 0.5 - 2.0 ng/kg/min to treat secondary Raynaud's phenomenon, diagnosed at an average age of 45 +/- 14.8 years. At baseline, 10 (23.3%), 23 (53.5%) and 10 (23.3%) patients had an early, active and late pattern, respectively, and 14 (32.6%) had interstitial lung disease. The parameters evaluated were: skin score (SS), systolic pulmonary arterial pressure (PAPs), plane tricuspid annular systolic excursion (TAPSE), lung diffusing capacity of carbon monoxide (DLCO), forced vital capacity (FVC), alveolar volume (VA), DLCO / VA, pro-brain natriuretic peptide (pBNP), and NYHA class.
Results: SS showed statistically significant improvement from baseline (5.0 vs. 4.5, p = 0.0015) and TAPSE showed a trend toward improvement (21.5 vs 22.5, p = 0.088). None of the other parameters showed significant changes, in particular: PAPs (32.2 vs 32.7, NS), DLCO (82.2 vs 77.9, NS), FVC (106.2 vs. 107.1, NS), VA (92.2 vs 90.1, NS), DLCO / VA (88.1 vs 87.8, NS), pBNP (122.7 vs. 136.7, NS), and NYHA class (1 vs 1, NS).
Discussion: The results showed stabilization of the clinical picture of the patients evaluated. The natural course of scleroderma tends to a progressive and inexorable worsening, until death, usually from cardiopulmonary causes. The main variable introduced in this group of patients was the administration of iloprost, a drug approved for the treatment of secondary Raynaud's phenomenon; in particular, iloprost seems to confirm the hypotesis that monthly iloprost infusions for six hours a day during six consecutive days could have a beneficial effect against PAH development or worsening, according to the results of the study and in agreement with many previous evidences.

PS256 TOCILIZUMAB IN SYSTEMIC SCLEROSIS, A SINGLE CENTRE EXPERIENCE

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BACKGROUND: there are few report in literature about the efficacy of the monoclonal antibody against IL-6 Tocilizumab (TCZ) for cutaneous involvement in Systemic Sclerosis (SSc), these data seem encouraging.

METHODS: we enrolled SSc patients with an active skin disease according EULAR/EUSTAR criteria (δmRSS > 14) who failed previous recommended therapies for cutaneous involvement. These patients released informed consent and underwent preliminary investigations including Quantiferon test, skin biopsy and nailfold capillaroscopy.
They were treated with a standard TCZ amount of 480 mg/month i.v. despite weight.
mRRS was re-evaluated after 3, 6 and 12 month, capillaroscopy was controlled after 12 month.
Concomitant steroid therapy was administered but no steroid-bolus were performed before TCZ treatment.

MATERIALS: three patients were enrolled. Two patients presented DcSSc, one LcSSc.
Patient 1 had LcSSc with mRRS = 25 in July 2010 treated with three methylprednisolone bolus and methotrexate; despite therapy, after 1 year, mRRS was = 20
Patient 2 had DcSSc with mRRS = 22 in July 2011 treated with three methylprednisolone bolus and methotrexate; after 6 months mRRS was = 20 despite therapy.
Patient 3 had a DcSSc with mRRS > 20 from 2009 treated with Cyclophosphamide followed by azathioprine and mycophenolate mofetil for 1 year. In 2012 she started methotrexate and after 6 month her mRRS was = 18.
All patients underwent skin biopsy (both clinically involved and healthy skin) studied in morphological way and by immunoistochemistry with anti-IL-6 antibodies.
After 6 months of therapy we observed an improvement in skin involvement in all three patients
(pt 1 mRRS from 20 to 13; pt 2 mRRS from 20 to 12; pt 3 mRRs from 18 to 11), but we weren't able to stop prednisone therapy (mean dosage 5 mg/daily).
The most interesting observation was a decrease in Raynaud phenomenon intensity (pt 1 stopped Iloprost infusions) and in the number of digital ulcers (DU) (pt number 3 had a mean DU number of 6 before therapy, actually 3 without pain and complication).
After 12 month of therapy patient number 1 has stopped steroidal therapy and maintain a good response both on skin than in vascular involvement.

CONCLUSIONS: Tocilizumab proved good efficacy in obtaining improvement in skin involvement in Systemic Sclerosis also in patients who underwent many different therapies in personal history; besides Tocilizumab showed an encouraging efficacy reducing vascular manifestation of the disease, including Raynaud phenomenon and digital ulcers, but this data have to be confirmed with serial nailfold capillaroscopy.

PS257 ALTERNATIVE BIOLOGICAL MODEL FOR PRECLINICAL TESTING

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Development of each novel formulation needs to pass the essential step of preclinical testing. To make this phase more comprehensive and animal friendly, here we propose an alternative biological model based on the choriallantoic membrane of the fertilized chicken egg (CAM) [1]. It is suitable for a wide range of applications such as treatment efficacy, personalized medicine, phototherapy, xenografts and angiogenesis development. The CAM model brings advantages of a low cost experimental setup, fast accumulation of experimental data, applicability of a wide range of investigated substances, high repeatability of data.
The immune system of the chicken embryo is not active till the certain egg development day (EDD), assisting an effective tissue adaption on the CAM. Diverse cell samples taken directly from patients or hybrid cell culture lines can be easily transferred to the next stage of preclinical trails [2]. The CAM is a biological model that can match the mouse model in in vivo investigations, having additional advantages in the experimental time frame. The natural cellular barriers and circulation are present in a way easily accessible for treatment and observation.

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PS258 MACITENTAN IN THE TREATMENT OF DERMAL FIBROSIS IN PATIENTS AFFECTED BY LIMITED SYSTEMIC SCLEROSIS: IN VITRO EVIDENCES

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Systemic Sclerosis (or Scleroderma) is an autoimmune disease characterized by skin and internal organ fibrosis, caused by microvascular dysfunctions. The microvascular damage seems to be a consequence of endothelium autoimmune response, followed by inflammatory cascade and massive deposition of collagen. Endothelin-1 (ET-1) is involved in the inflammatory and fibrotic processes by increasing the concentration of pro-inflammatory and pro-fibrotic cytokines and it is considered one of the most relevant mediators of vascular damage in scleroderma. It is indeed found in very high concentration in serum of sclerodermic patients. Moreover, in these pathological conditions there is an increased expression of ET-1 principal receptors (ETA and ETB), which mediate the detrimental action of ET-1, often resulting in a change of ETA/ETB ratio. The aim of the present study is to evaluate the in vitro effect of macitentan, an orally active tissue-targeting dual endothelin receptor antagonist, and its major metabolite (ACT-132577) on alpha smooth muscle actin (αSMA) expression, evaluated on dermal fibroblasts from healthy subjects and on dermal fibroblasts from lesional and non-lesional skin from sclerodermic patients. The combination of macitentan and its major metabolite reduced the levels of αSMA after 48 hours in sclerodermic fibroblasts from lesional skin. No relevant changes in αSMA levels were found in fibroblasts from non-lesional skin, whose behavior is similar to that of dermal fibroblasts from healthy patients.

PS259 OPTIMIZED FORMULATION OF ENDOGENOUS NEUROPROTECTIVE AGENT

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The pilot biochemical studies demonstrated the ability of carnosine to increase the efficacy of the standard therapy for the patients with discirculatory encephalopathy. At the same time, the efficacy of carnosine in the organism is limited due to its hydrolysis, accomplished by a specific enzyme – carnosinase. Currently, in order to achieve a stable therapeutic level of carnosine, application of excessive dosage is required. To avoid the drug loss during transportation an improved drug delivery advanced drug formulation is needed.

The aim of the present study is to develop a liposomal carnosine formulation for a better drug protection from degradation in blood and more efficient delivery to the target tissue. Carnosine loaded liposomes were developed characterized and tested in vivo. Obtained liposomal formulation has a diameter of 120 nm and was stable in solution for 5 days. REM and TEM imaging showed round shaped. The carnosine ability to protect cells against oxidative stress was tested in vitro on a neuronal cell line model. The oxidative stress was induced by polyamines and treated with carnosine and liposomal carnosine formulation. We have shown that carnosine encapsulated in liposomes could better protect neuronal cells and supports cell viability. In our opinion, this formulation has a great perspective to improve treatment of neuronal damage.

PS260 RAPID RESPONSE OF DIGITAL ULCERS TO BOSENTAN IN SYSTEMIC SCLEROSIS

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Systemic sclerosis is a multisystem disorder of unknown aetiology. Pulmonary and cutaneous manifestations of the disease cause significant morbidity, affect quality of life and are resistant to therapeutic interventions. The aim was to describe two cases of systemic sclerosis patients with digital ulcers who were successfully managed by the administration of the dual endothelin receptor antagonist bosentan.

A patient, male, aged 67 years, presented with systemic sclerosis. He was diagnosed three years ago, having presented with Raynaud's phenomenon, cutaneous thickening and hardening over the digits, weight loss, muscle involvement and positive ANA. He had been treated with cyclophosphamide and nifedipine. Subsequently he was lost to follow up for two years presenting thereafter with cutaneous manifestations of systemic sclerosis, small mouth opening, Raynaud's phenomenon, cutaneous thickening and hardening over the digits and digital ulcers. A chest CT scan performed revealed mild pulmonary manifestations while a cardiac echogram was normal. Clinical examination revealed multiple digital ulcers affecting both hands. Iloprost i.v. infusion was administered, followed by bosentan 62.5 mg twice daily and nifedipine 30 mg. A month later the digital ulcers were healed. Bosentan was continued and the patient remains free of ulcers.

A patient, female, aged 50 years, with a history of limited cutaneous systemic sclerosis and digital ulcers appearing intermittently presented with a digital ulcer in the right hand. Laboratory evaluations revealed a negative Scl 70 and positive SSA-Ro. She was treated with iloprost i.v. and antibiotics, the ulcer persisting. Bosentan 62.5 mg twice daily was administered for a month, being increased thereafter to 125 mg twice daily. A month later the digital ulcer healed, bosentan is continued and the patient remains free of ulcers.

Systemic scrlerosis is a multisystem disorder which was treated symptomatically until recently. Digital ulcers, which may appear during the course of the disease, are resistant to treatment and even if treated they may recur. In the cases described the rapid response of the digital ulcers to the administration of bosentan is noted. The dual endothelin receptor antagonist bosentan appears to act on digital ulcers in systemic sclerosis and may prevent recurrence of these difficult to treat cutaneous manifestations of systemic sclerosis.

PS261 SUCCESSFUL TREATMENT OF SYSTEMIC SCLEROSIS DIGITAL ULCERS WITH BOSENTAN

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Systemic sclerosis is a multisystem disorder characterized by cutaneous, pulmonary and cardiac manifestations. Until recently treatment of the disorder was symptomatic and patients finally succumbed to the complications of pulmonary involvement.

The aim was to describe the case of a female patient with systemic sclerosis, pulmonary fibrosis and a digital ulcer who was successfully treated with bosentan.

A female patient aged 56 years, non-smoker, childless, presented with Raynaud's phenomenon, skin thickening observed in the upper and lower extremities, soft tissue calcification over the elbows, facial telangiectasia, dyspnea on exertion, and a digital ulcer in the left index finger. Clinical and laboratory evaluation revealed positive Scl 70, normal C3 and C4 levels, negative ANA, resorption of the distal phalangeal tufts on X-ray examination, pulmonary fibrosis, restrictive pulmonary disease and severe osteoporosis. Azathioprine 50 mg twice daily, prednisone 5 mg, and iloprost infusions were administered, the digital ulcer persisting. Bosentan 62.5 mg twice daily was administered for 4 weeks thereafter being increased to 125 mg twice daily. After 2 months the digital ulcer was completely healed and Raynaud's phenomenon improved.

The dual endothelin receptor antagonist bosentan is a novel agent mainly indicated for the treatment of pulmonary disease in systemic sclerosis. Bosentan seems to have a beneficial effect on the digital ulcers observed during the course of systemic sclerosis.

PS262 SAFETY AND EFFECTIVENESS OF MYCOPHENOLATE IN SYSTEMIC SCLEROSIS: A SYSTEMIC REVIEW

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Background. Mycophenolate reduces chronic allograft nephropathy and interstitial fibrosis by inhibiting TGF-?, which is an important molecule in the pathogenesis of systemic sclerosis (SSc). The main side effects observed are gastrointestinal disturbance, myelosuppression, and increased risk of infection. This maybe a limitation of its use in SSc patients since gastrointestinal involvement is very common. The objective of this study is to evaluate the safety, in particular gastrointestinal adverse events, of mycophenolate in SSc. Secondarily we evaluated the effectiveness of mycophenolate in SSc skin and lung disease.
Methods. A literature search of Medline, Embase, Cochrane Central Register of Controlled Trials, and CINAHL (inception - September 2012) was performed. Titles and abstracts were screened to identify studies that described the use of mycophenolate in SSc patients. Inclusion criteria included exposure to mycophenolate, and reporting of modified Rodnan skin score (MRSS), forced vital capacity (FVC), diffusing capacity of carbon monoxide (DLCO); or adverse events. The primary outcome was gastrointestinal events occurring after the initiation of mycophenolate. Secondary safety outcomes included myelosuppression, infection, malignancy, and death occurring after the initiation of mycophenolate.
Results. 616 citations were identified and 20 were included in the analysis. 477 patients have been exposed to mycophenolate. The mean disease duration ranged between 0.8-14.1 years. There were 89 non-lethal adverse events, of which 43 (48%) were gastrointestinal and 46 (52%) were non-gastrointestinal adverse events. The most commonly reported gastrointestinal events included diarrhea (n=18 (20%)), nausea (n=12 (13%)), and abdominal pain (n=3 (3%)). The most commonly reported non-gastrointestinal adverse events were infections (n=33 (37%), and 6 cytopenias (n=6, (7%)). The reported rate of discontinuation ranged between 8-40%. Seven observational studies report mycophenolate is effective improvement or stabilization in FVC, and 5 observational studies report stabilization or improvement in MRSS.
Conclusion. Observational studies report mycophenolate is effective in improving or stabilizing interstitial lung disease, and may be effective for skin involvement. However, gastrointestinal adverse events are common in SSc patients.

PS263 TREATMENT OF SYSTEMIC SCLEROSIS WITH TOCILIZUMAB

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Background: Systemic sclerosis (SSc) is a multiorganic autoimmune disease characterized by connective tissue fibrosis and vascular injury with dysfunctional angiogenesis and vasculogenesis. Interleukin-6 (IL-6) is being increasingly recognized as a potential target to modulate disease progression. This is supported by the acknowledgement of the multiple actions of this cytokine, which have been associated with endothelial cell dysfunction and fibroblast activation.

Methods: Three patients with SSc were treated with tocilizumab after a succession of previous treatment attempts. Tocilizimab was given at a dosage of 8 mg/Kg every four weeks. A follow-up evaluation six months after treatment initiation comprised clinical (weight, modified Rodnan skin score, digital ulcer healing and global health score) and laboratorial parameters (blood count, ESR, renal and liver biochemistry, and lipid profile). After nine months of treatment with tocilizumab lung function tests and chest computed tomography were also reassessed.

Results: The three patients had diffuse SSc, were female, and had a mean age of 46,3±10,7 years. The involved organs were: skin (3 cases), digital vasculature (3 cases), lung (3 cases), gastrointestinal tract (2 cases), and joints (3 cases). The altered laboratory tests were: anemia (2 cases), increased erythrocyte sedimentation rate (ESR) (2 cases), positive antinuclear antibodies (3 cases), positive anti-topoisomerase I antibodies (2 cases), and positive anti-PM-Scl antibodies (1 case). Tocilizumab was well tolerated and all the patients experienced an improvement in global health score. Weight increased in two patients. Skin thickness assessed by the 17 site modified Rodnan skin score (mRSS) decreased in all patients. The two patients with refractory digital ulcers showed complete heal. Hemoglobin levels increased in the two patients with anemia, and erythrocyte sedimentation rate (ESR) decreased. With respect to pulmonary function, diffusing capacity (DLCO) did not change in two patients, but further decreased in one. All patients had non-specific interstitial pneumonia pattern that remained stable in two and worsened in one case.

Conclusions: Our mini-series suggests that tocilizumab might be a valuable treatment for SSc patients particularly because there are no clear effective alternatives. All the clinical aspects of the disease present in these patients showed a relevant improvement and even lung involvement did not progress in two out of three patients. These results reinforce the need for clinical trials using tocilizumab in diffuse SSc.

PS264 IDENTIFICATION OF ICD-9 CODES ASSOCIATED WITH SCLERODERMA RENAL CRISIS

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Background: Scleroderma renal crisis (SRC) is a rare complication of systemic sclerosis (SSc) associated with high morbidity and mortality. Large administrative databases are useful for epidemiologic studies of rare conditions, but often rely on International Classification of Diseases-Clinical Modification-9 (ICD-CM-9) codes for case definitions. We sought to identify the most common ICD-9 codes associated with definite SRC cases for use in future epidemiologic studies.

Methods: We identified patients with SRC from our database of 429 patients with SSc evaluated at Stanford University Medical Center from 2005 to 2012. All patients with SRC had a rapidly progressive oliguric renal insufficiency with no other explanation and/or rapidly progressive hypertension occurring during the course of SSc. We collected demographic information, clinical features, symptoms and complications of SRC, autoantibodies, treatments, outcomes, and ICD-9 codes associated with each SRC case.

Results: Ten patients with SRC were identified (9 female, 8 diffuse cutaneous SSc, mean age at SRC 54.2±10.8 years). Nine patients were ANA positive, 7 with nucleolar pattern, 2 patients were Scl-70 positive, and 1 was Anti-RNA polymerase III positive. Mean time from first non-Raynaud's symptom to SRC was 3.3±4.7 years. Six patients (60%) used prednisone before SRC (with a mean dose of 43 mg/day). Mean systolic and diastolic blood pressure at SRC onset was 200±33 mmHg and 115±27 mmHg; one patient was normotensive. Nine patients required hospitalization, with a mean length of stay of 16.5±13.5 days. Mean creatinine, hemoglobin, and platelet count at SRC presentation was 3.0±1.6 mg/dl, 10.2±1.6 mg/dl and 147± 67, respectively. Five patients had active urine sediment with proteinuria, hematuria or casts. Nine patients were treated with angiotensin converting enzyme inhibitors, although 7 needed combination anti-hypertensives to control blood pressure. Five patients required dialysis during hospitalization and only 1 was able to discontinue dialysis 13.8 months later. Eight patients developed end-stage renal disease after SRC. We identified ICD-CM-9 codes associated with the SRC episode in 7 patients. All had ICD-CM-9 code 710.1 corresponding to scleroderma, 6 (86%) had ICD-CM-9 code 401.9 (hypertension), 3 (43%) had ICD-CM-9 code 584.9 (acute renal failure). Given the similar clinical features seen in SRC and thrombotic thrombocytopenic purpura (TTP), it is not surprising that 3 (43%) SRC cases had ICD-CM-9 code 446.6 for TTP.

Conclusions: The combination of ICD-CM-9 codes 710.1, 401.9, 584.9 and/or 446.6 may be helpful to identify cases of SRC using large administrative databases, but our results require validation in another cohort.

PS265 INFORMATICS CAN IDENTIFY SYSTEMIC SCLEROSIS PATIENTS AT RISK FOR SCLERODERMA RENAL CRISIS

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Background: Systemic sclerosis (SSc; scleroderma) is a rare, complex autoimmune disease in which a poor prognosis is most closely related to organ fibrosis and/or hypertensive crisis. Hypertension is the key factor in the development of sudden kidney failure in SSc, which is called scleroderma renal crisis (SRC). It is critical to detect SRC in its earliest stages because prompt treatment with the BP-lowering class of drugs called angiotensin-converting enzyme inhibitors (ACE-inhibitors) can help to prevent progression to serious kidney failure. A significant risk factor for SRC is recent use of prednisone. A delay in diagnosis of SRC unfortunately can result in high morbidity and mortality due to unnecessary delays in the referral process.
Electronic medical records (EMR) provide an ideal opportunity for the detection, diagnosis, and management of SSc patients within VHA. The Veterans Informatics and Computing Infrastructure (VINCI) and Consortium for Healthcare Informatics Research (CHIR) have shown that the EMR can be effectively utilized for patient safety and quality measurement. The objective of this project was to use informatics to identify potential SSc patients in the Veterans Health Administration (VHA) that had a diagnosis of hypertension and were on prednisone, in order to inform an outreach project to prevent SRC.

Methods: The EMR and VINCI were used to identify SSc cases in the VHA through ICD-9 code (710.1) and natural language processing (NLP) of the terms “scleroderma” or “systemic sclerosis” in the clinical note to identify potential SSc patients on prednisone doses > 10 mg and/or hypertensive crisis. The use of prednisone in the clinical document was confirmed as active medication of the prescription list. We manually reviewed cases to validate this process and determine recall (sensitivity) and precision (positive predictive value) of our methodology.

Results: In the VHA, there are 4,272 patients that have a diagnosis of SSc determined by the presence of an ICD-9 code and NLP. Of these patients, 1,118 patients (21%) had the use of prednisone > 10 mg. Of these patients, 26 had a concurrent diagnosis of hypertension.

Conclusions: Current rheumatology guidelines emphasize early detection and effective management of hypertension and highlight the risk of prednisone for SSc patients. Advances in informatics allow identification of SSc patients potentially at risk for SRC and provides the opportunity to improve quality of care in these patients.

PS266 JUVENILE SCLERODERMA: TREATMENT EXPERIENCE OF A SINGLE ONE CENTER

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Treatment consensus in Juvenile scleroderma (JS) is hard to be achieved due to low incidence, heterogenity of JS, lack of controlled studies.
Efficacy of 5 treatment regiments (TR) was analysed retrospectively in 426 JS patients(pts), among them 375 pts with localized JS (JLS),30- systemic sclerosis (JSS), 21- Mixed connective tissue disease (MCTD).Follow up period was 1 - 10 years (M=5).TR efficacy was estimated by skin score, skin thickness (Durometr), square of skin lesion, joint immobility, laboratory,instrumental data.
1 TR - Penicillamine (PA) 8-10 mg\kg\d along 3-4 years was used in 70 JLS pts (32- circumscribed deep morphea (CDM), 10- generalized morphea (GM), 10 - "en coup de cabre" (ECDS),8- linear morphea on limbs(LM). PA was effective in 98% of CDM.
2 TR - PA 8-10 mg\kg\d for 3-5 years + Prednisone(Pr) 1mg\kg\day for 6-10 weeks, then taped and stopped in 12 mo.- in 165 JLS pts (46-LM,45-unilateral GM (UGM), 44-GM,30- ECDS and 30 JSS pts. 2 TR was effective in 90% of UGM & LM pts,48% ECDS pts, 87% JSS pts.
3TR- Methotrexate (MTX) 10-15 mg\m2 \wk for 2-5 years we used in 68 JLS pts (28- LM, 23- GM, 17- ECDS. 3TR was benefit in 92% LM & GM pts,50 % ECDS.
4TR-MTX 10-15 mg\m2 \wk for 2-5 years + Pr 1mg\kg\day for 8-10 weeks, then taped and stopped in 12 mo. - in 70 JLS (33- UGM, 14- LM, 12- GM, 11- ECDS) & 21 MCTD pts.
4TR was effective in 97% of UGM, LM, GM pts, in 60% ECDS, in 90% MCTD pts.
We prefer parental use of MTX (Metoject/Metex),it was effectively & safely used in 80 JS pts, with no relapses despite permanent pricks of skin with injections, side effects occurred in 0,3% in contrary to 4% in oral MTX pts.
5 TR - Cyclophosphamide (CYC) IV 20mg\kg + Pr 1mg\kg for 6 mo - in 6 pts with interstitial lung disease (ILD).We achieved reverse of ILG in all pts.
SNPs of NOS3(G894T), MMP 1(G-1607GG), MMP 9(C-1562T), MTHFR, SLC(19A1), GGH were genotyped in 216 of our JS pts, as potential predictors of treatment response. Polymorphism GG in NOS3(G894T) showed strong correlation with clinical efficacy of PA in our cohort.
Our data suggests that PA & PA+Pr are still effective TR for several forms of JLS (CDM,UGM, JSS) especially usefull in pts with recurrent infections, tuberculosis,those who live in cold climate, endocrine disorders, intolerance to MTX. TR with MTX are more effective than TR with PA.ILD is rare in JS, recover under CYC+Pr treatment. Treatment results in ECDS are the poorest, better at edema skin disease stage, in elder children on MTX+Pr protocol.

PS267 SYSTEMIC SCLEROSIS AT THE CROSSROAD OF POLYAUTOIMMUNITY

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Objectives: Several epidemiological studies have revealed the co-occurrence of other autoimmune diseases (AIDs) within patients with systemic sclerosis (SSc). However, some of these studies were based on small cohorts and wide ranges of prevalence were reported. Therefore to overcome these limitations of individual studies, we sought to perform a meta-analysis to determine the accurate prevalence of polyautoimmunity in SSc.
Methods: We performed a systematic review and a meta-analysis of literature in MEDLINE and Embase databases from January 1960 to March 2013. All cohort studies reporting on prevalence of other AIDs known to be associated with SSc were analyzed. Prevalence of polyautoimmunity and of each AID were then calculated by dividing the number of patients with polyautoimmunity (or the specific AID investigated) by the number of patients studied. We then calculated the pooled estimate for all studies (with 95% confidence interval (CI95%)), which was backtransformed afterward using the DerSimonian and Laird method. With the prevalences calculated, aggregation for different AIDs was calculated by dividing the prevalence of a given AID in SSc-patients by the prevalence in the general population.
Results: Ten studies reporting polyautoimmunity were identified, corresponding to a total of 6102 SSc patients (women 87.1%, 35% of diffuse cutaneous subtype). Mean age at assessment was 57.6 (± 3.1) years and mean disease duration 10.6 (± 2.3) years. Overall 1432 patients with at least one AID were identified corresponding to a weighted prevalence of polyautoimmunity equal to 25.7 % [CI 95%: 20.1%-31.6%]. 208/5139 SSc-patients had at least two additional AIDs resulting in a weighted prevalence of 3.9% [3.3%-4.4%]. Patients with polyautoimmunity were more frequently women (607/654 (92.8%) vs. 1524/1755 (86.8%); $p<0.01$) and of limited cutaneous subtype (314/385 (81.6%) vs. 925/1439 (64.3%); $p<0.01$). The most prevalent associated AIDs were autoimmune thyroid disease (10.4%) followed by Sjögren's syndrome (7.7%) and dermatopolymyositis/polymyositis (5.6%). Primary biliary cirrhosis and rheumatoid arthritis were detected in 3.0% and 4.2% of SSc-patients, respectively, whereas prevalence of systemic lupus erythematosus was equal to 2.6%. Recurrence risk values were calculated to approximately 1120 for dermatopolymyositis/polymyositis, 750 for primary biliary cirrhosis, 108 for systemic lupus erythematosus, 26 for Sjögren's syndrome, 5 for autoimmune thyroid disease and 4 for rheumatoid arthritis.
Conclusion: Our results confirm that polyautoimmunity is a frequent condition in SSc, affecting a quarter of SSc-patients. The impact on the phenotype and also on the management and therapy will need to be addressed now in further works.

PS268 CLINICAL AND SEROLOGICAL COMPARATIVE ANALYSIS OF SYSTEMIC SCLEROSIS WITH OR WITHOUT OVERLAP SYNDROMES IN A LARGE BRAZILIAN COHORT

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Background: There are scarce data comparing clinical and serological features in patients with systemic sclerosis (SSc) and SSc overlap syndromes (SSc-OS) due to the rarity of these associations.
Objective: To analyze clinical and SSc-associated serological profiles including a panel of novel described antinucleolar antibodies (ANoA) in a large cohort of Brazilian patients with SSc and SSc overlap syndromes.
Methods: Three-hundred twenty-eight SSc patients attending the Scleroderma Outpatient Clinic of a tertiary referral university hospital from 2000 to 2011 were enrolled. Clinical and demographic data were obtained from an electronic register database. Serum samples were analyzed for the presence of antinuclear antibodies (indirect immunofluorescence on HEp-2 cells), antibodies to Scl-70, PM-Scl, RNA-Pol III, CENP-A/CENP-B, and Ro/SS-A (52 and 60 kDa) (ELISA), and antinucleolar antibodies (ANoA) fibrillarin, Ku, Th/To and NOR90 (immunoblotting using commercial available standardized kits).
Results: Two-hundred ninety seven patients were classified as SSc and thirty-one patients as SSc-OS (13 with systemic lupus erythematosus, 10 with polymyositis, 7 with rheumatoid arthritis, and 1 with both systemic lupus erythematosus and polymyositis). Both groups (SSc-O and SSc) were similar regarding mean age at onset, female predominance, disease duration and ethnicity ($p>0.05$). Concerning clinical features, there were no significant differences related to the occurrence of pitting scars, digital amputation, calcinosis, telangiectasia, interstitial lung disease, pulmonary hypertension, cardiovascular disease, renal crisis, and Sjögren syndrome ($p>0.05$). Conversely, SSc-OS patients had lower mean modified Rodnan skin score (4.1±5.8 vs. 9.0±11, $p=0.015$) and esophageal involvement (71 vs. 91%, $p=0.003$), but higher percentage of joint (55 vs. 20%, $p<0.001$) and muscle involvement (42 vs. 7%, $p<0.0001$) compared to SSc group. There was no difference regarding the frequency of all ten autoantibodies tested in the two groups ($p>0.05$). Although SSc-OS patients had lower mean titlers of anti-Scl70 ($p=0.04$), the percentage of patients with pulmonary interstitial disease was similar in both groups (23% vs. 31%; $p>0.05$).
Conclusion: This study identified a comparable occurrence of major organ involvement and ischemic lesions in SSc-OS and SSc. This finding is strengthened by the observation of a similar frequency of all scleroderma autoantibodies in both groups and suggests that SSc determines the clinical manifestation in overlap syndromes in spite of a less extensive skin involvement in these patients.

PS269 PREVALENCE OF A CHRONIC WIDESPREAD PAIN IN LOCALIZED AND DIFFUSE SYSTEMIC SCLEROSIS PATIENTS

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Background/Purpose: Chronic widespread pain (CWP) is a healthcare problem with great impact on mental health, professional and family life of the patient. It can be a consequence of many disorders; however, there are few reports concerning its prevalence during the course of other diseases. Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by vascular injury and progressive skin and organ fibrosis. Moreover, the patients quality of life can be worsened by the presence of CWP. The aim of this study was to compare the prevalence of CWP in patients with limited (l-SSc) or diffuse SSc (d-SSc). Methods: The study evaluated 111 consecutive patients with SSc (females 91%; mean age 60.8, range [23-84], overall mean disease duration 92±61 m.). All of the patients were evaluated in terms of the disease activity, markers of inflammation, the presence of antibodies, serum vitamin D levels, and disease duration. Manchester definition of CWP was used for diagnostic reasons; pain must be reported in at least two frequency of two contralateral limbs and in the axial skeleton, and have been present for at least 3 months. All of the subjects completed a psychic stress test (the Kessler 10-item test) (KT), a test of the quality of sleep and fatigue (Flinder's Fatigue Scale) (FFST), and the pain catastrophizing scale (PCS).
Results: The overall prevalence of CWP in the patients was 27.1%, much higher than that expected in the general population. The prevalence of CWP in the patients with l-SSc and d-SSc was respectively 17.6% and 32.3%, but the difference was not statistically significant (p=0.318). There was no correlation between the prevalence of CWP and the degree of cutaneous involvement (modified Rodnan Skin Score) and ESR (p=0.48), but there was a correlation with older age (p=0.0196). No significant difference was observed on KT, FFST and PCS between d-SSc and l-SSc patients. Logistic regression showed that the only variable favouring the development of CWP was the presence of anti-centromeric antibodies (ACAs, p<0.0001; OR=8.1 [3.3-19.8]).
Conclusion: The higher prevalence of CWP among patients with SSc does not correlate with the clinical manifestations of the disease. However, it does correlate with advanced age. The presence of ACAs is a risk factor for CWP, which suggests that patients with l-SSc develop CWP more frequently than those with d-SSc.

PS270 SERUM ADROPIN LEVEL AND ENHO EXPRESSION IN SYSTEMIC SCLEROSIS

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Introduction: Systemic sclerosis (SSc) is an autoimmune multisystemic disease characterized by vasculopathy, inflammation and progressive fibrosis of the skin and internal organs. However, the pathogenesis of SSc is still not fully understood. Adropin, a secreted protein, is encoded by the Energy Homeostasis Associated (ENHO) gene. It is expressed by a variety of tissues and cells. It has been implicated in the several physiological and pathological processes such as angiogenesis, apoptosis. Adropin-treated endothelial cells exhibited greater proliferation, migration and capillary-like tube formation and less permeability and tumor necrosis factor alpha-induced apoptosis via altering PI3K-Akt and ERK1/2 pathways and activating VEGFR2. If so, adropin may have the potential role in the pathogenesis of SSc. Therefore, in the present study, we investigated the serum adropin levels and ENHO expressions in patients with SSc.

Methods: The study included 27 patients with SSc, 39 patients with Behçet's disease (BD) as patient controls, and 20 healthy controls (HC). The patients were fulfilling the established classification criteria. For each SSc patient, modified Rodnan skin score, Valentini disease activity index and Medsger disease severity scale were assessed. Serum adropin levels were analyzed by ELISA method. ENHO and GAPDH gene expressions by peripheral blood mononuclear cells were analyzed by real-time PCR. One-way ANOVA, post-hoc Tukey test and chi-square test were applied to statistical analysis.

Results: The serum adropin levels were higher in the SSc and BD groups than in the HC group ($p=0.023$ and $p<0.001$, respectively, Table 1). However, there were no significant differences among the groups in terms of ENHO expressions ($P_{ANOVA}=0.149$). 15 of the SSc patients had limited cutaneous subtype. There was no significant difference between the limited and diffuse cutaneous subtypes in terms of serum adropin level and ENHO expression. Moreover, serum adropin level and ENHO expression were not associated with the disease activity and severity indices. ENHO expression was correlated with the triglyceride levels in the BD group ($r=-0.426$, $p=0.027$), and with the total cholesterol ($r=-0.580$, $p=0.007$) and LDL-cholesterol ($r=-0.542$, $p=0.014$) levels in the HC group.

Conclusion: The augmented serum adropin levels may be expected in the chronic inflammatory disease, and seem not to be characteristic of only SSc. Moreover, although it increases in SSc, it is not associated with any activity and severity indexes of the disease. Therefore, it may be concluded that adropin is not involved in the pathogenesis of SSc. However, further studies are needed to explain the precise role of adropin in SSc.

Table 1. The demographics, serum adropin level and ENHO expression in the study groups

	HC (n=20)	BD (n=39)	SSc (n=27)	P_{ANOVA}
Mean age (years)	44.0±13.1	37.1±10.9	48.9±13.7[c]	0.001
Mean disease duration (years)	-	6.7±6.1	7.5±4.7	-
BMI (kg/m²)	27.3±5.0	25.7±4.3	24.9±5.0	0.102
Adropin (ng/ml)	1.12±0.52	1.92±0.81[b]	1.67±0.65[a]	0.001
ENHO expression	1.19±0.11	1.25±0.12	1.21±0.08	0.149

HC: healthy control, BD: Behçet's disease, SSc: systemic sclerosis, BMI: body mass index.
When compared to the HC group; [a]$p=0.023$ and [b]$p<0.001$.
When compared to the BD group; [c]$p<0.001$.

PS271 PREVALENCE AND PREDICTIVE VALUE OF SCLERODERMA –SPECIFIC SERUM AUTOANTIBODIES IN THE GENERAL POPULATION OF A NORTHERN ITALIAN AREA

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Background. The prevalence of scleroderma (SSc)-specific serum autoantibodies (autoAbs) is generally obtained from large datasets including blood donors or employees, thus resulting poorly representative of the general population. Similarly, it is challenging to determine the risk of developing a connective tissue disease (CTD) in subjects positive for serum autoantibodies in the absence of an adequate observation. Our aim is to determine the prevalence and predictive value of anti-centromere (ACA), anti-Scl70, and anti-CENP-B autoAbs in a large cohort of Italian subjects participating in a 13-year longitudinal study.

Methods. The general population of a Northern Italian area was randomly selected 1:4 and enrolled in 1999 in a clinical epidemiology study and 71% of resident subjects (age 18-75) participated to the study (mean age 42, female/male 1.15). In 2011 serum samples (n=2690) were blindly tested for ANA and anti-ENA including anti-Scl70 and anti-CENP-B using commercially available indirect immunofluorescence and ELISA. Administrative data were then analyzed to determine if study subjects had developed SSc over the following 13 years.

Results. Serum ANA were detected by IIF in 18.1% (titer >1:80) and 5.7% (titer>1:160) of tested samples and the pattern was speckled in 5.2% of cases and centromeric in 0.3%. The prevalence of anti-Scl70 was 1.45% and anti-CENP-B 0.3% by ELISA. In all cases, prevalence rates were higher in women but predominance was lower than classically reported for CTD. The predictive value of autoantibodies was obtained from the analysis of copayment exemptions, even if this approach does not account for 11% of the population with total expense waiver for low income or advanced age. The relative risk (RR) of developing a CTD over 13 years for ANA positive individuals is 1.78 (95% confidence interval -CI- 1.16-2.73; p=0.0001). The RR of developing a CTD for individuals with high-titer ANA is 12.26 (95% CI 2.52-59.62; P<0.0001). No cases of SSc were observed during the follow-up period using this low-sensitivity approach.

Conclusions. Prevalence of serum ANA and anti-ENA may be higher than reported when a general unselected population is investigated with sufficient power. Serum positivity for autoAbs confers a significant risk of developing an autoimmune disease when subjects are observed for a long period of time.

PS272 OSTEOPOROSIS AND FRACTURE RISK IN OUTPATIENTS WITH SYSTEMIC SCLEROSIS

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Background/Purpose:Osteoporosis (OP) is a frequent complication of a number of chronic inflammatory diseases. Only Rheumatoid Arthritis (RA) is included in the FRAX algorythm to calculate fracture risk but also Systemic Sclerosis (SSc) displays many disease-specific OP risk factors (chronic inflammation, malnutrition, steroid use, etc.).
Aim:To determine OP frequency and fracture risk by FRAX in outpatients with SSc.
Methods: After consent, in outpatients with SSc (le Roy criteria) of a University Hospital, bone mineral density (BMD) was calculated by Dual Energy X-Ray Absorptiometry (DEXA) at the femoral neck and lumbar spine and FRAX was obtained by the calculation tool (http://www.shef.ac.uk/FRAX). A routine SSc evaluation (according to EUSTAR) was performed as well. Age- and BMI-matched early RA (ACR/EULAR 2010 criteria) patients were enrolled as controls.
Results: Seventy-one SSc patients (3:68 M:F, age 66±9yrs, 57:14 limited:diffuse cutaneous, median disease duration 8.5, 2.4-14.7yrs, median disease activity 1, 0.25-2) and 44 RA (11:33 M:F, age 62±12yrs, median DAS28 4.42, 3.94-5) were enrolled. OP was detected in 42/71 (59%) SSc patients. Disease duration was significantly higher in SSc-OP patients (10.5, 4.3-16.6 vs 5.5, 1.6-9.8, $p<0.01$) and it was also significantly associated to OP (OR 1.4, 1.1-1.7, $p<0.01$), even when corrected at a multivariable analysis for other disease-specific features (skin and gastrointestinal involvement, autoantibody subset, median mRSS, disease activity) and OP risk factors (steroid use, smoke, BMI, chronic renal insufficiency). OP in RA patients was significantly lower than in SSc (9/44, 20%, $p<0.001$). Mean femoral BMD was 0.58 (0.53-0.7) in SSc vs 0.72 (0.64-0.82) in RA ($p<0.001$), lumbar mean BMD 0.82 (0.75-0.9) in SSc vs 0.92 (0.81-1) in RA. FRAX for major fracture was not significantly different between groups (low in 47% and 50%, medium in 28% and 40%, high in 25% and 10% of SSc and RA respectively). A diagnosis of SSc was significantly associated to OP (OR=13.2, 4-42.4), even when corrected for steroid use.
Conclusion: We have detected a very high OP frequency in our SSc patients, significantly higher than a control early RA cohort and significantly associated to disease duration. Routine DEXA evaluation and risk factors for OP should always be considered and treated when possible in every SSc patient, especially after 5 years of disease duration.

PS273 ARE THERE DIFFERENCES IN LIMITED SSC ACCORDING TO EXTENSION OF SKIN INVOLVEMENT?

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Background: There is consensus in classifying Systemic Sclerosis (SSc) according to extension of skin involvement as limited and diffuse, using the elbows and knees as "limits" to distinguish between them. Decades ago, Barnett classified SSc as Type 1 (only sclerodactyly), Type 2 (acrosclerosis - distal but may reach up to elbows and/or knees plus face) and Type 3 (diffuse skin involvement). Patients with Type 2 had an intermediate degree of organ involvement compared to Type 1 (less) and Type 3 (more). This issue has not been recently addressed. We examined the characteristics of our patients with limited disease to see if we could find differences between Barnett Type 1 and Type 2 subsets.

Methods: electronic medical records of patients registered between years 2000-2011 with the problem: scleroderma, SSc or CREST and those with anti Scl-70, anticentromere or anti nucleolar antibodies in laboratory database were reviewed. Cases fulfilling ACR 1980 criteria were included and were classified as diffuse or limited according to LeRoy`s criteria with limited being separated into sclerodactyly (only fingers) and acrosclerosis (fingers and up to elbows and/or knees) (Barnett´s Types 1 and 2).

Results: 234 SSc patients (216 females) fulfilled criteria. Female/male ratio was 12:1; 24% had diffuse SSc and 76% limited (64% sclerodactyly and 12% acrosclerosis). Total follow up was 688 patients-years. Over half (55.1%) are still under our care and 17 died during this period. Ten year survival rate was 80% for limited and 70% for diffuse variants respectively (HR: 0.88 95% CI: 0.7-1.1). Table 1 shows clinical and serological profile of this cohort.

Anti Scl-70 was present in 16%, anticentromere in 53% and nucleolar ANA in 7% of overall patients. Within the limited group, several characteristics in the acrosclerosis (Type 2) group were more similar to the diffuse than the Type 1 (sclerodactyly) patients. Duration of Raynaud was shorter, and they had significantly more anti Scl-70 and less anti centromere antibodies than those with Type 1. In particular, interstitial lung disease (ILD) was significantly more prevalent in Type 2 group, and similar to Type 3. Other characteristics did not reach statistical differences.

Conclusion: These results appear to confirm that extension of skin involvement within limited SSc may identify two different subsets with clinical and serologic characteristics. Indeed, Type 2 as defined by Barnett appears to have intermediate organ involvement, and serology may be more similar to the diffuse type.

Type of systemic sclerosis	Limited (n=178)			Diffuse (n=56)	
	Sclerodactyly (n=149)	Acrosclerosis (n=29)	p		p
Females, n (%)	142 (95.3)	25 (86.2)	0.06	49 (87.5)	0.13
Age at diagnosis, years mean (SD)	59.8 (15.2)	54.9 (16.2)	0.14	53 (15.3)	0.038
Duration of raynaud before diagnosis, years median (SD)	9.2 (3.4)	5.5 (1)	0.018	1.9 (0.8)	0.008
Anti Scl-70, %	6.4	39.3	<0.001	43.9	<0.001
Anticentromere,%	82.3	17.9	<0.001	4.8	<0.001
Nucleolar ANA, %	5.7	3.6	0.54	20.9	0.001
Other autoantibodies, %	26.3	23.5	0.54	25.9	0.70
GI involvement, %	65.9	81.3	0.22	64.3	0.45
Interstitial lung disease, %	17.1	50	<0.001	65.3	<0.001
Pulmonary hypertension with ILD,%	5.5	0	0.34	15.4	0.03
Pulmonary hypertension (without ILD), %	9.1	4.8	0.45	2.6	0.39
Echocardiographic abnormalities (other than PH), %	5.7	4.5	0.65	10	0.26
Digital ulcers, %	26.9	34.5	0.44	52.1	0.86
Renal Crisis, n	0	0		1	
Pregnancy after diagnosis, n	3	1		3	
Patient-year, years (SD)	462 (3.1)	81.2 (3.1)		144.8 (3.6)	
Currently followed, n (%)	88 (59.5)	15 (51.7)		26 (46.4)	
Died under our care, n	11	2		4	

PS274 CORRELATION AMONG WHOLE BLOOD VISCOSITY, HEMATOCRIT AND CAPILLAROSCOPIC PATTERNS IN SYSTEMIC SCLEROSIS

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Background: Microvascular alterations represent the pathophysiological hallmark of systemic sclerosis (SSc). As known, hemorheological features such as blood viscosity strongly influence vessel tone, structure and function through interaction of blood with the endothelial surface. Previous investigations reported an impaired rheological profile in SSc patients. The present study was aimed to investigate whether alterations in blood viscosity contribute to microvascular damage in subjects with SSc. In addition, possible differences in blood rheology between patients with 'late' pattern and patients with 'early/active' pattern were explored.

Methods: 16 women who met the ACR criteria for scleroderma and 16 healthy controls were recruited for this study. Hematocrit (Ht), hemoglobin (Hb), fibrinogen, erythrocyte sedimentation rate (ESR) were measured by standard methods. Whole blood viscosity (WBV) was calculated according to the formula: (0.12 . haematocrit) + 0.17 . (plasma proteins - 2.07). Nailfold videocapillaroscopy (NVC) was performed in each participant as reported elsewhere. Afterwards, patients were distributed into two groups based on the presence of late or early/active pattern. Variables among these groups and controls were compared using either ANOVA or Kruskal-Wallis test.

Results: Overall mean age of patients was 57.5±12.2 years, while mean disease duration was 8.1±6.3 years. Significant inverse correlations were found between Ht (r=- 0.53, p=0.033), Hb (r=- 0.63, p=0.027), WBV (r=- 0.54, p=0.031) and NVC patterns. In the case control analysis, patients showing 'late pattern' had significant lower Hb concentration, Ht and WBV than control group and 'early/active' patients.

Conclusion: Our study demonstrates an inverse association among WBV, Hb, Ht and capillaroscopy patterns providing further evidence about the effects of hemorheology on vascular properties in SSc patients. The possible mechanisms responsible for these findings can be only hypothesized. Blood viscosity and hematocrit strongly influence shear stress, that is the frictional force that flowing blood generates tangentially to the endothelial surface. Wall shear stress is an important regulator of the nitric oxide synthesis and strongly influences vessel tone and angiogenesis. It is likely that low hematocrit and WBV, through a reduction in shear stress, contributes to capillaries loss in SSc.

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Table: Clinical characteristics and hemorheological parameters of subjects

	Late	*Early/Active*	*Control Group*	*ANOVA*
Number	8	8	16	---
Age (years)	58.0±15.8	55.0±8.7	54.3±15.1	NS
RP duration (years)	15.8±11.0	12.2±11.0	---	NS
Disease duration (years)	11.0±9.0	7.2±5.2	---	NS
Hematocrit (%)	36.3±4.5*	41.0±3.2	42.0±2.5	0.004
Hemoglobin (g/dL)	10.7±1.4*	12.8±1.4	13.4±1.2	0.001
Fibrinogen (mg/dL)	392±55	340±92	352±82	NS
ESR (mm/h)	44.5±28.5§	20.0±12.9	17.9±11.5	0.020
Whole blood viscosity (cP)	3.5±0.5*	4.0±0.4	4.2±0.3	0.002

ANOVA Tukey post-hoc test *p<0.01 group 'Late' vs control; p=0.03 group 'Late' vs group 'Early/Active'. § p=0.02 group 'Late' vs control

PS275 AUTOANTIBODIES IN SYSTEMIC SCLEROSIS MAY PREDICT DISEASE SEVERITY, COMPLICATIONS, AND MORTALITY: A SINGLE EUSTAR CENTER (042) EXPERIENCE

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To assess the association between scleroderma (SSc) specific autoantibodies (Abs, antinuclear (ANA), anti-topoisomerase (ATA), anti-centromere (ACA)), clinical features, and mortality in SSc patients registered at our EUSTAR site (042).

In 219 out of 230 registered SSc patients clinical or laboratory data were available. According to Abs profile patients were divided: ATA+ (37%), ACA+ (34%), and ANA+ (29%, ATA negative and ACA negative). There was no difference in gender or nationality between subgroups. ACA+ patients were significantly older and had the longest disease duration. Diffuse SSc was significantly more often in ATA+ and ANA+ patients. Rodnan skin score was lowest in ACA+ and highest in ATA + patients. ATA+ and ANA+ patients had higher incidence of arthritis and sclerodactyly. ATA+ patients had more often digital ulcers (DU), gangrene, and CK elevation. Digestive system was involved equally in all patients. Above 50% of ATA+ and 26% ANA+ patients had significant pulmonary fibrosis (PF). PF was rare and mild in ACA+ patients. Heart involvement was reported in 12% of ATA+ and 6.8% of ACA+ patients. ATA+ and ACA+ patients had similarly high incidence of pulmonary hypertension (PAH, pulmonary artery pressure more than 45 mm Hg on ECHO-Doppler): 22.9% and 20.5%. Ten patients developed renal crisis (SRC): 5 ATA+ and 5 ANA +. During follow-up 43 patients died (19.6%) with higher mortality in ATA+ (24.1%) and lower in ANA+ (11.1%). Among ATA+ patients 25% died from PF, 15% from heart, digestive system, and SRC each; among ACA+ patients 43.8% died from PAH and 31.3% from heart involvement; among ANA+ patients 8.7% died from PAH, 13/4% from heart failure, 8.4% from SRC. 41.6% of patients died from cancer: 66% of ATA+ and 50% of ACA+.

In SSc patients Abs profile is associated with different clinical features. ATA positivity was associated with diffuse SSc, arthritis, complicated DU, and risk for severe lung, heart, and kidney involvement. Presence of ACA+ was associated with severe PAH but not with PF or SRC. ANA+ patients had often SSc-overlap syndromes, severe skin, joint and muscle involvement, multiple DU, PF, GIT involvement, and SRC. Awareness regarding malignancy should be high, especially among ATA+ and ACA+ SSc patients.

PS276 SSC-OVERLAP SYNDROMES: A DISTINCT CLINICAL SUBGROUP WITH SIGNIFICANT DIFFERENCES IN DISEASE PROGRESSION COMPARED TO LSSC AND DSSC PATIENTS

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Background: SSc-Overlap syndromes are a very heterogeneous and remarkable subgroup of SSc-patients, who present at least two connective tissue diseases (CTDs) at the same time, usually with a specific autoantibody status.
Objectives: To determine whether patients, classified as SSc-overlap syndromes, represent a distinct SSc subgroup with a disease course different from patients with limited (lSSc) and diffuse cutaneous SSc (dSSc).
Methods: The data of 3240 prospectively included patients, registered in the database of the German network for systemic sclerosis and followed between 2003 and 2013, were analyzed. The following statistical methods were used: Kaplan-Meier analysis, logistic regression and chi-square-test.
Results: Among 3240 registered patients, 10% (325/3240) were diagnosed as SSc-overlap syndrome. Of these, 82.5% (268/325) were female with a mean age of 49.2 ±1.2 years and carried significantly more often other antibodies (71.1%; p<0.0001), including U1RNP- (33.5%), PmScl- (16.9%), Ro-(24.7%), La- (11.0%), as well as Jo-1- (4.1%) and Ku-antibodies (3.8%).
These patients developed musculoskeletal involvement earlier and more often, than patients diagnosed as lSSc and dSSc (37.8 %, 47.8%; p<0.0001). The onset of lung fibrosis and heart involvement in SSc-Overlap patients was significantly earlier than in patients with limited SSc and occurred later in patients with dSSc. Interestingly patients with anti-PmScl- (51.4%), -Ku- (50%), -Jo1- (55.6%) and anti-topoisomerase antibodies (53.7%) suffered more frequently from lung fibrosis, compared to patients with anti-U1RNP- (27.8%) and anti-centromer-antibodies (11.1%). Oesophagus, kidney and PAH progression was similar to lSSc patients, whereas dSSc patients had a significantly earlier onset. Patients with SSc-overlap syndromes were significantly more frequently treated with corticosteroids and immunosuppressive agents than other SSc subsets. Additionally, this specific subset also had a significantly lower mRSS compared to dSSc patients (6.7 ± 0.4 versus 15.8 ± 0.3; p<0.0001), but a very similar mean mRSS to lSSc patients (7.2 ± 0.2).
Conclusions: These data support the concept, that SSc-overlap syndromes should be regarded as a separate SSc subset, distinct from lSSc and dSSc.

PS277 SYSTEMIC SCLEROSIS-RELATED AUTO-ANTIBODIES ARE MARKERS OF NEW CLINICAL ASSOCIATIONS IN A COHORT OF 328 BRAZILIAN PATIENTS

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Background: Systemic Sclerosis (SSc) shows a heterogeneous clinical presentation, characterized by marked skin and internal organ fibrosis and vascular dysfunction, associated with immunological abnormalities. A varied panel of SSc-related auto-antibodies has been described, and there is a growing interest to establish their prevalence and clinical associations in populations of different ethnicities.
Objective: To evaluate the frequency and the putative associations of a panel of SSc-related auto-antibodies with demographic and clinical features in a large SSc cohort.
Methods: We analyzed serum of 328 consecutive SSc adult patients attended at the Scleroderma Outpatient Clinic of a tertiary referral university hospital in Brazil; Clinical and demographic data were obtained through a review of the electronic register database. SSc-related auto-antibodies were determined by indirect immunofluorescence, ELISA, and immunoblotting.
Results: ANA positivity was 88%, and anti-Ro/SSA was positive in 96 patients (29%). Anti-Scl70 was present in 92 (28%), anticentromere (ACA) in 83 (25%), anti-fibrillarin in 39 (12%), anti-RNA Pol III in 23 (7%), anti-Th/To in 17 (5%), anti-PM-Scl in 16 (5%), anti-Ku in 12 (4%), and anti-NOR in 6 (2%) patients. ACA was associated with female gender ($p < 0.001$), white ethinicity (trend; $p = 0.076$), limited cutaneous SSc ($p < 0.001$), calcinosis ($p = 0.002$), asymptomatic ILD ($p < 0.001$), and isolated PAH ($p < 0.001$). Otherwise, anti-Scl70 was associated with male gender ($p = 0.034$), diffuse cutaneous SSc ($p < 0.001$), digital ulcers ($p < 0.001$), symptomatic ILD ($p < 0.001$), and use of immunosuppressive drugs (cyclophosphamide, azathioprine, mycophenolate mofetil ($p < 0.001$). Only three patients were diagnosed as scleroderma renal crisis and all of then presented anti-RNA pol III, that was associated with diffuse cutaneous SSc ($p = 0.036$). Anti-fibrillarin was associated with symptomatic ILD (trend; $p = 0.072$). Anti-Ku was associated with finger amputation ($p = 0.019$) and esophageal involvement ($p = 0.032$). Anti-PM-Scl, anti-Th/To and anti-NOR90 did not show any specific association. Anti-Ro/SSA was associated with Sjogren Syndrome ($p = 0.001$) and PH ($P = 0.026$). The concomitance of anti-Scl70 and anti-Ro, present in 19 patients (6%), was associated with ILD ($p = 0.008$), use of cyclophosphamide ($p = 0.040$) and death ($p = 0.037$).
Conclusion: Among the different SSc-related auto-antibodies, anti-Scl70 and ACA clearly characterize distinct demographic and clinical presentations. Our study also identified new clinical associations, among anti-Ku and digital amputation and esophageal involvement, as well as the concomitance of anti-Ro/SSA with anti-Scl70 being associated with poor prognosis.

PS278 THE AUTOANTIBODY PROFILE OF THE WAIKATO HOSPITAL SYSTEMIC SCLEROSIS COHORT (WHSSC COHORT)

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Introduction: Systemic Sclerosis (SSc) is a heterogeneous autoimmune connective tissue disease (CTD). The two subtypes of SSc are limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc). SSc can overlap with other CTD and is called systemic sclerosis overlap syndrome (SOS).
Association of specific autoantibodies with the subtypes and specific phenotypes is well recognized with some geographic and ethnic variation.
So far the autoantibody profiles in SSc have not been assessed in the New Zealand population.

Objective: To characterize the autoantibody profile of the WHSSc cohort.

Methods: Sixty patients had the autoantibody profile checked within allocated time. The SSc was defined per ACR criteria.
Autoantibodies were tested with Euroline (IgG) Systemic Sclerosis Immunoblot. Antibodies to Scl-70, CENP-A, CENP-B, RNA Polymerase III (RP-11 and RP155), Fibrillarin (U3-RNP), NOR-90, Th/To, PM-Scl 100 and 75, Ku, Ro52 and PDGFR were tested.

Results: 60 patients were reviewed (56 females) with median age 61 (range 29-81) years. Cohort consisted of 54 Europeans, 2 Indians, 2 Maoris, 1 Tongan and 1 Southeast Asian. 41 had lcSSc, 15 dcSSc and 4 SOS.
Of lcSSc, 31(75.6%) were positive for CENP-A and CENP-B, 12(29.3%) for Ro-52, 5(12.2%) for RP11 and RP155, 4(9.8%) for Scl-70, 1(2.4%) for Fib and 1(2.4%) for Th/To. Of 15 dcSSc patients, 7(47.6%) were positive for RP11 and RP155, 4(26.7%) for Scl-70(26.7%), 4(26.7%) for Ro-52, 2(13.3%) for Ku and 1(6.7%) each for NOR90 and Fib. In the 4 SOS group, 1 was positive for CENP-A and CENP-B, 1 for Ro-52 and 1 for Ku.
Both Maori patients with lcSSc were positive for CENP-A & B. Our 2 Indian patients had dcSSc but no detectable autoantibodies.

Discussion: 27.6% of dcSSc patients had anti-Scl-70 antibodies. This is less than the French group (35%) but similar to UK and US prevalence (22%).
There was a higher prevalence of CENP-A & B in our lcSSc group (75.6%).
Anti-RP11 & RP155 prevalence was 20%, similar to Denmark (22%), but different from France (9.4%), UK (12%), Spain (16%) and USA (25%).
There was a higher prevalence of anti-Ro52 (28.3% vs quoted 10%) with increased co-existence of anti-Ro52 with anti-RP11 & RP155 (33%) in our cohort
RP11 & RP155, Scl-70 and anti-CENP-A and CENP-B were mutually exclusive except for one.

Conclusion: This is the first study to look at the autoantibody profile of SSc patients in New Zealand. Our findings support the suggestion that antibody prevalence vary geographically and ethnically. There possibly are different (yet undetected) antibodies in local Indian ethnic group.

PS279 HIGH PREVALENCE OF ANTI-THYROID ANTIBODIES IN A NEW ZEALAND COHORT OF PATIENTS WITH SYSTEMIC SCLEROSIS

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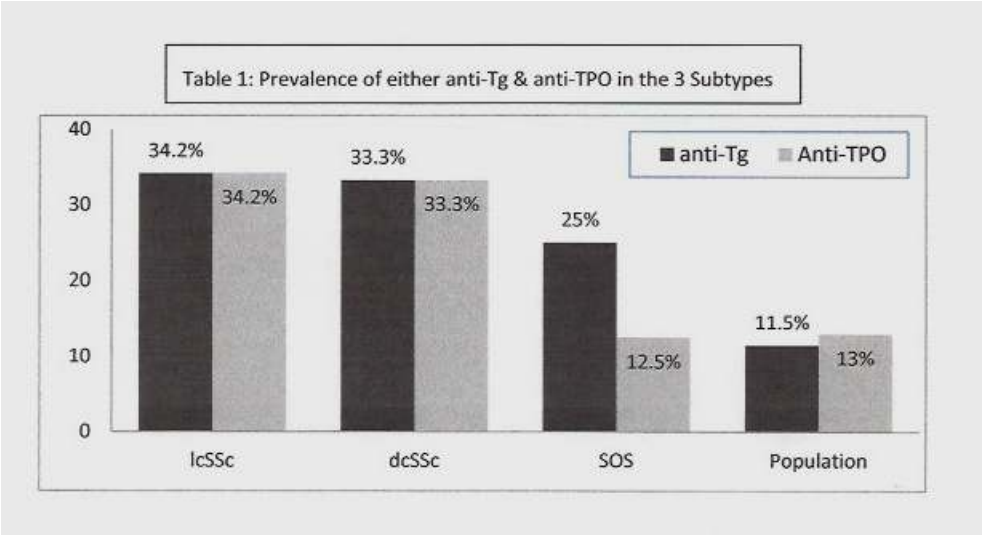
Background: Autoimmune thyroid disease is common and affects 1% of general population with thyroid antibodies being found in up to 15% of healthy subjects. Autoimmune conditions tend to cluster.
Objectives: We hypothesized that Systemic Sclerosis (SSc), being an autoimmune disorder was associated with higher prevalence of thyroid autoantibodies.
Method: Our SSc Clinic patients were prospectively tested for the thyroid autoantibodies as part of their assessment. 75 patients with SSc and 10 patients with Overlap Syndrome (SOS) were randomly chosen. The anti-thyroglobulin (anti-Tg) and anti-thyroid peroxidase (anti-TPO) antibodies were tested utilizing SERODIA-ATG and SERODIA-AMC Haemagglutination tests respectively. Data was analyzed in SPSS (Chi square analysis).
Results: Our cohort comprised 76 females (89.5%). 53(61.6%) patients had limited cutaneous Systemic Sclerosis (lcSSc) (4 males), 22 patients (25.6%) had diffuse Systemic Sclerosis (dcSSc) (3 males); and 10 patients (11.6%) had SOS (1 male). Median age was 60 years, range 25-82 years.
Anti-Tg and anti-TPO were tested prospectively in 61 of 85 patients (70.6%). 38 patients with lcSSc, 15 with dcSSc and 8 with SOS.
Anti-Tg antibodies were present in 20 patients (32.8%). 13 patients with lcSSc (34.2%), 5 patients with dcSSc (33.3%), 2 patients with SOS (25%). Anti-TPO antibodies were present in 19 patients (31.15%). 13 patients with lcSSc (34.2%), 5 patients with dcSSc (33.3%), 1 patient with SOS (12.5%). (See table 1)
Chi-Square analysis identified no significant association between Anti-thyroid antibodies and the two sexes or subtype of SSc, nor was there any statistical difference in the prevalence of anti-Tg and anti-TPO in our cohort.
At follow up at 18 months, one patient (female with lcSSc) positive for both Anti-Tg and TPO antibodies developed hypothyroidism requiring treatment whereas none of those without these antibodies did.
Conclusion: Anti-thyroid antibodies are increased in Systemic Sclerosis compared to the general population. Our study did not show any preferential increase of Anti-TPO as seen in some earlier studies.
Further prospective follow up is ongoing for 5 years to see the translation of these autoantibodies into clinical manifestations.
We suggest screening patients with systemic sclerosis for the presence of both these antibodies.



PS280 LOW DOSE MODIFIED-RELEASE PREDNISONE TREATMENT AND A THERAPIST-GUIDED EXERCISE PROGRAM IN UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE PATIENTS: OUR 24-MONTH RESULTS

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Undifferentiated Connective Tissue Disease (UCTD) is a pathologic condition characterized by signs and symptoms suggestive of a connective tissue disease (CTD) that have not fulfilled the diagnostic criteria for any of the defined connective tissue disorders for at least three years.
UCTD is characterized by a mild clinical picture and rarely involves major organs, but many patients, initially diagnosed with UCTD, may go on to develop a specific connective tissue disorder within one or two years from diagnosis.
Capillaroscopy have a predictive value in UCTD and may help to select patients at risk of developing a CTD.
In managing CTDs and other conditions Corticosteroids (CS) have a pivotal role, due to their anti inflammatory and immunosoppressive properties.
In recent years, it has been shown that a low-dose of oral Modified-Release Prednisone (PDN) may lead to a better control of the disease activity, thanks to a long-term sustainable effect synchronized to blunt the circadian rhythm of the release of inflammatory cytokines.
The objective of our study was to analyse the effects of a 24-month treatment with 1 mg per day of Prednisone MR combined with a therapist-guided exercise program in 30 UCTD patients (female gender, mean age:58±11 yrs and mean duration: 3±5 yrs) at risk of developing SLE or other CTDs.
Nailfold capillaroscopic examination showed elongated capillaries in 43% of the cases (13/30), an increased tortuosity in 70% (21/30), a prominent subpapillary plexus in 60% (18/30), dilated capillaries in 80% (24/30) and haemorrhages in 16.6% (5/30).
The patients were assessed at baseline (T0) and at the 2-year follow up (T1) by Health Assessment Questionnaire (HAQ), Time Up-and-Go (TUG) test and 6-min walking test (6MWT). At T0 patients had low TUG test and impaired 6MW test.
They were treated with therapist-guided exercises twice a week for 1 hour, three times in a year for 5 weeks.
At T1 patients showed improvement in the TUG and 6MWT tests and the parameters of capillaroscopic examination with a potential significant predictive value for the development of UCTD (apical limb width, capillary width and capillary length) showed no tendency to be larger, as in those who develop CTDs, in any of the patients.
These encouraging findings suggest that clinical remission might be a realistic end point of UCTD treatment and Prednisone MR may be effective for both induction and maintenance of remission in these patients, also improving compliance to the programme of therapist-guided rehabilitation exercises .

PS281 NEUTROPHIL-LYMPHOCYTE AND PLATELET-LYMPHOCYTE RATIOS IN SYSTEMIC SCLEROSIS

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Introduction: Inflammatory process and autoimmunity affect the haemopoetic system and alter the counts and figures of peripheral blood cells in chronic inflammatory diseases. The indices of the complet blood cell count (CBC) analysis such as mean platelet volume (MPV), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) are reported to be associated with a variety of cardiovascular and oncological diseases. Therefore, the aim of the present study was to evaluate the potential association of these indices on the disease course of systemic sclerosis (SSc) which is a connective tissue disease characterized by widespread fibrosis.
Method: The study included 39 patients with SSc and 51 patients with systemic lupus eritematosus (SLE) as patient controls, and 50 healthy controls (HC). The patients were fullfilling the established criteria. Modified Rodnan skin score (MRSS), Valentini disease activity index and Medsger disease severity scale in the SSc patients and SLE disease activity index (SLEDAI) and Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index in the SLE group were assessed. Routine laboratory analyses were applied by the standart methods. NLR and PLR were calculated. One-way ANOVA, post-hoc Tukey test and chi-square test were applied to statistical analysis.
Results: When compared to the HC group, the neutrophil counts were higher in the SS group and the lymphocyte counts were lower int the SLE group (Table 1). Correspondingly, the NLR was higher in the SSc and SLE groups than in the HC group ($p=0.008$ and $p<0.001$, respectively). The platelet counts and MPV were similar among the study groups. However, when compared to the HC group, PLR was higher in the SLE group ($p<0.001$), while it was not higher in the SSc group ($p=0.104$). %53.8 of the SSc patients had limited cutenous subtype. NLR, PLR and MPV of limited and diffuse cutaneous subtypes were similar ($p>0.05$ for all). NLR, PLR and MPV in patients with the positive for anti-nuclear, anti-centromer or anti-Topo I antibodies were not significantly different from the patients negative ones ($p>0.05$ for all). Moreover, they were not correlated with the MRSS, disease activity index and severity scale ($p>0.05$ for all).
Conclusion: These indices maybe useful to differantiate the SSc patients from healthy subjects and SLE patients. However, they do not seem to predict the activity and/or severity of the SSc. Further studies are needed to explain the precise roles of NLR and PLR in SSc.

Table 1. The demographics and laborotory parameters in the study groups

	HC (n=55)	SLE (n=51)	SSc (n=39)	P_{ANOVA}
Mean Age (years)	45.1±13	33±9.6*	49.2±13.2×	<0.001
Sex (Female percents)	80	92.2	89.7	-
BMI (kg/m²)	27.4±4.8	25.8.1	25.4±5	0.113
Mean disease duration (years)	-	4.6±5.2	8.5±5.8	-
Haemoglobin (g/dL)	13.5±1.2	11.5±1.9*	12.4±1.7**××	<0.001
WBC (10^3/µL)	6.48±1.48	5.77±2.52	7.57±2.53**×	0.001
Neutrophil (10^3/µL)	3.72±1.04	3.93±1.99	4.56±2.02**××	0.002
Lymphocyte (10^3/µL)	2.09±0.61	1.26±0.66*	1.85±1.04×	<0.001
NLR	1.9±0.7	3.9±3.1*	3.4±3.1**	<0.001
Platelet (10^3/µL)	272.3±75.2	251.4±93.5	293.7±95.5	0.084
MPV (fL)	8.8±1.5	9.5±1.7	8.8±1.1	0.044
PLR	138.9±49.6	277.9±225.1*	207.2±165.1	<0.001

HC: healthy controls, SLE: systemic lupus erythematosus, SSc: systemic sclerosis, BMI: body mass index, WBC; white blood cell count, NLR: neutrophil-lymphocyte ratio, MPV: mean platelet volume, PLR: platelet-lymphocyte ratio.
*P<0.001, **P<0.01 when compared to the HC group
×P<0.001, ××P<0.05 when compared to the SLE group

PS282 COEXISTENCE OF ANTITOPOISOMERASE I AND ANTICENTROMERE ANTIBODIES IN 3 PATIENTS WITH SYSTEMIC SCLEROSIS

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Antibodies targeting DNA topoisomerase I (ATA) or centromere proteins (ACA) are associated with different clinical subsets of systemic sclerosis (SS). Those antibodies are considered to be mutually exclusive and very few cases of association of these two antibodies have been reported. We herein describe three additional cases. We screened ACA positive serum samples (detected by indirect immunofluorecence using HEp2 cells) and ATA positive serum samples (detected by ELISA) in Bordeaux University hospital. Between July 2011 and July 2013, out of 181 ACA positive samples and 283 ATA positive samples, 3 patients were found to have both antibodies (0.7%). Table 1 sums up clinical characteristics of these patients.

Autoantibodies are found in about 95% cases of SS. ACA and ATA are associated with subgroups that have distinctive clinical symptoms and prognosis. These two antibodies are regarded as mutually exclusive. However, few cases of ATA and ACA coexistence in individual patients have been reported. In previous reports prevalence of ATA/ACA coexistence ranges from 0.05% to 5.6%. Dicks et al. reviewed 56 reports from 1985 to 2000, regarding 5423 patients with SS and 28 patients were found to have both antibodies (0.52%). The EUSTAR database reports a similar prevalence 29/4867 (0.6%). Our own findings (3/461= 0.7% prevalence) are consistent with those reports.

The clinical significance of such association is still unknown. Do those patients simply have both diseases independently? Do they represent a rare clinical subset of the disease with peculiar clinical and prognostic characteristics? Definite conclusions cannot be drawn from the literature data since most patients reported had heterogeneous clinical features, internal organ involvement and outcome. In our study, all our patients had internal organ involvement but different extent of skin disease. Patient 1 had diffuse skin involvement with mild pulmonary fibrosis and renal disease. Patient 2 had only sclerodactyly but severe pulmonary disease. Patient 3 had a mild disease for 19 years with only Raynaud's phenomenom and sclerodactyly but then developed rapidly mild pulmonary fibrosis, severe renal and cardiac disease. Further studies with a larger number of patients and thorough analysis of clinical features, skin and systemic symptoms are needed to draw conclusion on the significance of ATA/ACA association.

Table 1 Clinical data of patients (NDA: No Data Available)

Sex	F	F	F
Age (years)	50	75	75
Age of onset (years)	46	61	56
Scleroderma	diffuse	limited	limited
Raynaud's phenomenom	yes	yes	yes
Fingertip necrosis	yes	no	yes
Calcinosis	NDA	No	yes
Telangiectasia	NDA	yes	yes
Oesophageal hypomobility	yes	yes	yes
Sicca syndrome	NDA	yes	yes
Arthralgia	yes	no	yes
Pulmonary fibrosis	mild	severe	mild
Pulmonary hypertension	No	no	no
Renal disease	yes	no	yes
Cardiac disease	no	no	Yes

PS283 EFFECTS OF ILOPROST ON T-LYMPHOCYTE ACTIVATION PATHWAY IN EARLY SYSTEMIC SCLEROSIS (ESSC)

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Introduction: Systemic Sclerosis (SSc) is an autoimmune disease characterized by fibrosis and vasculopathy. In patients with active SSc increasing values of the Th17 subset and of pro-fibrotic interleukins such as IL6, IL1 and IL17 were demonstrated, as compared to healthy controls.
Iloprost, a stable prostacyclin analogue, has been shown to down regulate pro-inflammatory cytokines, but its role on T cells modulation is not completely understood.
The aim of this study was to evaluate functional T cells subsets in patients with early SSc (eSSc) in basal conditions and after Iloprost treatment.
Patients and Methods: a total of 7 previously untreated female patients with eSSC (mean age 41.7 years) were enrolled in this study. Two patients were positive for anti-scl70 autoantibodies and five for anti-centromer antibodies, with a mean skin score of 12 (nobody presented digital ulcers) and Medseger score of 5.1 (range 4.8 – 6.7). All patients were treated with i.v. Iloprost (0.3ng/kg for 6 hours in continuous infusion for 5 days). The analysis of T cells subsets, including Th1, TH2, Th17, quiescent CD8 (CD8+/CD38-/HLADR-) and activated CD8 (CD8+/CD38+/HLADR+) was carried out on peripheral blood samples by 8-color flow cytometry. Patients were studied first in basal condition and after 5 days of therapy. Fifteen healthy subjects were studied as controls.
Results: Our results shown: a) Low basal absolute values of CD4+T cells in patients with eSSc (mean 776.5/mL, range 424.8/mL-1520.4/mL) vs control group (mean 1048.1/mL, range 642/mL -1683/mL); b) Lower values of percent and absolute CD4+TH17+ cells in the eSSc group, mean 7.66% vs 12.59% (range 4.2% - 12.1% vs 2.7% - 20.3%, $p<0.05$) and mean 53.92/mL vs 123.1/mL (range 26.34/mL – 87.47/mL vs 45.44/mL-257.8/mL, $p<0.05$), respectively; c) Reduced baseline quiescent CD8+T cells values and increased activated CD8+T cells after treatment (baseline mean quiescent CD8+ cells: 86.71% and 494.7/mL vs post therapy mean CD8+ cells: 74.54% and 478.3/mL, basal activated CD8+ cells: 1.86% and 13.4/mL vs after treatment activated CD8+ cells: 2.41% and 18 /mL), respectively.
Conclusion: The literature data on T cell regulatory subsets in eSSc are scanty. Our approach included the phenotypic evaluation of CD4+Th17+ cells using CCR6 and CXCR3, so that our measured levels may be higher than those using direct intracellular IL17 evaluation. The low baseline level of CD4+Th17+ cells may be related to the very early phase of the disease, whereas the increase in activated CD8+ cells can be related to the anti-inflammatory and anti-fibrotic effects of Iloprost.

PS284 DISTRIBUTION OF BODY MASS INDEX AND METABOLIC SYNDROME IN PATIENTS WITH SYSTEMIC SCLEROSIS: STUDY OF A SINGLE ITALIAN CENTRE

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Background: Obesity is at now considered as a mild, long-lasting inflammatory disease associated with an increased cardiovascular (CV) risk. Systemic Sclerosis (SSc) and other rheumatic diseases have been associated with increased CV risk, but despite an increasing interest regarding the prevalence and the effects of obesity and metabolic syndrome in these patients, conclusive data are lacking.
Objectives: To evaluate the prevalence of overweight, obesity and metabolic syndrome (MS) in a cohort of patients with SSc.
Methods: Body mass index (BMI) was assessed in 296 SSc patients. BMI was categorized into 4 classes, i.e <25 kg/m2 (under-weight), 18-25 kg/m2 (normal weight), 25-30 kg/m2 (overweight), and >30 kg/m2 (obese). Levels of total cholesterol, HDL-cholesterol, triglycerides, fasting glucose were evaluated, as well as the presence of arterial hypertension and diabetes mellitus. Metabolic syndrome was defined according to the American Heart Association/Updated NCEP criteria (1). We considered central obesity as a BMI>24 kg/m2 for women and BMI>25 kg/m2 for men (2).
Results: In the SSc cohort (88.2% female, age 58.5±14.2 years, mean disease duration 11.4±8.6 years) the mean BMI was 24.4±4.8 and the prevalence of obesity was 10.4%. According to BMI, 136 SSc patients (46.1%) were normal-weight, 125 (42.2%) were overweight, 31 (10.4%) where obese, while only 4 (1.3%) were underweight. The analysis of individual cardiovascular risk factors highlighted that 50 patients (16.9%) presented hypertriglyceridemia, 107 (36.1%) had low HDL-cholesterol levels and/or were taking a specific treatment for lipid abnormalities and 25 (8.44%) had arterial hypertension. The prevalence of metabolic syndrome was 14.2%. The prevalence of obesity and MS was comparable in patients with diffuse and limited cutaneous disease. Considering the immunological autoantibodies profile and the organ involvement no differences emerged in the prevalence of obesity and MS. Nineteen (6.4%) patients of our cohort presented myocardial involvement, but only 3 of them had a MS and none of theme was obese.
Conclusions: SSc-patients have a lower prevalence of both obesity and MS with respect to the general population as well as to patients with other rheumatic diseases such as rheumatoid arthritis, according to available data (3,4). The weight of well-known CV risk factors and of specific disease abnormalities, leading to the SSc micro-and macrovascular damage, has to be further defined.

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PS285 COMPROMISE OF FOREARM BONE MASS IN PATIENTS WITH SYSTEMIC SCLEROSIS: ASSOCIATION WITH DISEASE DURATION, RANGE OF MOTION, QUALITY OF LIFE AND SYSTEMIC BONE INVOLVEMENT

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Introduction. Skin thickening associated with forearm and hand joint involvement can contribute to functional disability, with consequent disuse and worsening of bone loss in patients with systemic sclerosis (SSc).
Objective. To evaluate prognostic factors that can contribute to forearm bone loss in patients with diffuse cutaneous SSc.
Methods. Prospective study analyzing 38 female patients with the diagnosis of SSc attended at the scleroderma outpatient clinic of the University of São Paulo (May 2012-May 2013). Patients were interviewed about disease symptoms and examined regarding modified Rodnan skin score (mRSS), measurement of total passive range of motion (ROM) of wrists and fingers joints, Health Assessment Questionnaire (HAQ), nailfold capillaroscopy, bone mineral density (BMD by DXA) and high-resolution peripheral quantitative computed tomography (HRpQCT) of distal forearm.
Results. Mean age was 40,18±7,27 years and mean disease duration was 8,25±4,96 years. Clinical and laboratory findings revealed interstitial lung disease in 79%, esophageal hipomotility in 63%, and anti-Scl70 antibody in 53% of patients. Modified Rodnan skin score was 6,42±4,78 and nailfold capillaroscopy score was 5,48±2,24. Osteoporosis was found in 39%, and BMD of left forearm with T-score<=-2,5 was present in 13% of patients. Left forearm BMD was negatively correlated (Pearson) with disease duration (r=-0,328; p=0,043); HAQ (mainly eating; r=-0,323; p=0,047); radius trabecular structure [trabecular separation (r=-0,498; p=0,001) and trabecular non homogeneity of network (r=-0,436; p=0,006)] and positively with: ROM of left hand fingers thumb (r=0,350; p=0,031); index (r=0,351; p=0,030); middle (r=0,372; p=0,021); ring (r=0,354; p=0,028); little (r=0,258; p=0,117); ROM of right hand fingers thumb (r=0,342; p=0,035); index (r=0,359; p=0,026); middle (r=0,325; p=0,046); ring (r=0,320; p=0,049); little (r=0,338; p=0,037); BMD of L1-L4 (r=0,780; p<0,0001); BMD of femoral neck (r= 0,571; p=0,0002); BMD of total hip (r=0,779; p<0,0001); trabecular bone volume / tissue volume (r=0,645; p<0,0001), trabecular thickness (r=0,624; p<0,0001); trabecular volumetric bone density (r=0,647; p<0,0001) and cortical radius thickness (r=0,632; p<0,0001). There was no correlation between left forearm BMD with mRSS and nailfold capillaroscopy.
Conclusion. Bone forearm involvement was associated with disease duration, impairment in daily living activities (eating), ROM of hands and involvement of trabecular and cortical bone.

PS286 LEVELS OF VITAMIN D, PTH AND CALCIUM IN PATIENTS WITH SYSTEMIC SCLEROSIS IN LIMITED AND DIFFUSE FORMS

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INTRODUCTION:The importance of the vitamin D in patients with Systemic Sclerosis (SSc) has been reported in some studies, but its role is not yet well established. Recently it was concluded that vitamin D deficiency is very common in patients with SSc .

OBJECTIVES:Conduct a prospective comparative study related with the dosage of vitamin D 25 (OH) D3, ionized calcium and parathyroid hormone (PTH) among female patients who have SSc in limited and diffuse forms.

METHODOLOGY: A prospective study between years 2012-2013, with 32 patients followed up at Rheumatology ambulatory, with a diagnosis of Systemic Sclerosis. The study included female patients with a mean age of 44.4 years, both limited and diffuse forms, living in the same city, during mild winter, to assess dosage of vitamin D by a competitive method based on steroid use and labeled binding protein; parathyroid hormone and ionized calcium. According to the consensus of the Endocrine Society of 2011, the reference ranges for deficiency, insufficiency and sufficiency of vitamin 25 (OH) D3 were < 20ng ml , 20-30ng/mL and >30ng/mL, respectively. Criteria for exclusion: patients on supplementation of calcium and vitamin D, intestinal or renal involvement or presence of malignancy bone disease and osteoporosis or osteopenia confirmed by bone densitometry.

RESULTS:Of the 32 patients who were evaluated, 13 (40,6%) have diffuse form and 19 (59,4%) limited form. Regarding the dosage of vitamin 25 (OH) D3 in patients with diffuse form, we founded 6 (46%) patients with deficiency, 3 (23%) with insufficiency, and 4 (31%) with sufficiency. In the limited form group, we found 7 (36,8%) patients with deficiency, 11 (58%) with insufficiency, and 1 (5,2%) with sufficiency. Considering together limited and diffuse forms, 12 (38.7%) patients had deficiency, 14 (43,7%) had insufficiency and 5 (16.1%) had sufficiency. With regard to PTH and ionized calcium values were normal in both forms.

DISCUSSION:Studies evidenced a high prevalence of vitamin D deficiency in these patients. More studies are necessary to identify the exact role of vitamin D in different manifestations of the disease, including pulmonary artery hypertension, disease activity and the presence of pulmonary fibrosis.

CONCLUSION: Decreased levels of vitamin D were found in 26 of 32 patients with SSc in this study. It was more prevalent in limited form than diffuse form of SSc. These findings may be important hereafter, correlating with some aspects of the disease and perhaps a perspective of treatment.

PS287 BONE MINERAL DENSITY IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Studies of bone mineral density (BMD) in patients with systemic sclerosis (SSc) showed its decreasing in comparison with healthy control. Prevalence of low bone mass and severity of BMD decreasing differ significantly between patients from different countries and vary from 17% in China (Mok CC, et al. 2012) to 77% in Spain (Rios-Fernández R, et al, 2012).

Aim: To assess BMD and frequency of osteoporosis (OP) in patients with SSc in Russia.

Methods. In case-control study BMD was evaluated in 52 postmenopausal women with SSc (16 – diffuse and 36 – limited form) , mean age 57,6±7,1yrs and mean disease duration 11±8 yrs. Forty four healthy postmenopausal women (mean age 59,2±6,6yrs) served as control. BMD was measured at the lumbar spine (LS), femoral neck (FN) and total hip (TH) by DXA (Hologic 4500A). BMD decreasing grade was determined in according to WHO criteria.

Results. BMD was significantly decreased in SSc women in comparison with control group: in LS – 0,804±0,090 vs 0,861±0,092 g/sm2 (p=0,025); in FN – 0,670±0,128 vs 0,736±0,112 g/sm2 (p=0,037), and in TH – 0,801±0,160 vs 0,884±0,124 g/sm2 (p=0,03). Frequency of OP in SSc group was significantly more often than in control group (59% vs 11%, p<0,0001).

BMD didn't differ between pts with diffuse or limited SSc. Decreasing of BMD in LS, FN and TH associated with age (r=-0,40, p<0,001; r=-0,48, p<0,001; r=-0,38, p=0,002, respectively), duration of postmenopausal period (r=-0,44, p<0,001; r=-0,42, p<0,001; r=-0,33, p=0,016, respectively), duration of SSc (r=-0,21, p=0,033; r=--0,37, p=0,001; r=-0,36, p=0,004, respectively) and hsCRP level (r=-0,22, p=0,041; r=-0,26, p=0,045; r=-0,35, p=0,011). BMD of FN and TH correlated also with daily dose of glucocorticoids (GC) (r=-0,34, p=0,025; r=-0,37, p=0,023, respectively). T-score was significantly lower in pts treated with GC than in GC free pts in LS (-2,01±1,52 vs -1,17±1,42, p=0,012), FN (-2,38±1,18 vs -1,26±1,25, p=0,003) and TH (-1,98±1,34 vs -0,84±1,19, p=0,011).

Conclusion. OP occurs in more than half cases of SSc pts. Low BMD in SSc pts apart from traditional risk factors of OP is associated with disease duration and inflammatory activity.

PS288 BONE MICROARCHITECTURE ASSESSMENT BY TRABECULAR BONE SCORE, IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Current data on bone mineral density (BMD), in patients with Systemic sclerosis (SSc) is discrepant. Trabecular Bone Score (TBS) is a novel software application for bone quality assessment, in addition to BMD measurement.
Aim: To examine the micro architectural bone status by TBS in SSc patients and its relation to the bone mineral density and clinical features of the disease.
Methods: The cross sectional study included 40 female SSc patients. The parameters of lumbar spine BMD and total body were examined by X-ray absorptiometry (DXA) on Hologic Discovery device, TBS analysis was carried out by Insight TBS ® - MedImaps. Demographic data and clinical characteristics of SSc patients were collected from the EULAR Scleroderma Trials and Research (MEDS EUSTAR) database. SSc activity was determined using Valentini's questionnaire (SSAS). We examined the correlation between the TBS and demographic and clinical characteristics of the patients.
Results: The average age of the patients (N = 40) was 57.22 (36 - 73.2 ± 8.69) years, postmenopausal 37/40, menopause duration: 10.00 (1-23 ± 6.85) years, duration of disease 9.06 (1-26 ± 6.8) years. Diffuse disease subtype (dSSc) had 19/40 (47.5%), limited (lSSc) 21/40 (52.5%) pts, 4/40 had fractures (10%), glucocorticoids (GC) users were 10/40 (25%), current smoking was recorded in 10/40 (25%), ATA +18 / 40 (45%), ACA +19 / 40 (47.5%). The most frequent clinical features were: Raynaud phenomenon (100%), sclerodactily (98%), digital ulcers (81.5%), esophageal dysfunction (80.3%), joint contractures (78.8%), etc. Average disease activity by SSAS = 6.5. Lumbar spine BMD was 1.03±0,321gr/cm2, TBS 1.364 ± 0.034, calcium content 2.25 ± 0.03 kg. There was no statistically significant correlation between the BMD, BMC and TBS. TBS values were inversely correlated with the age and use of GC in the treatment (r = -0.330, -0.385, p = 0.03), while positively correlated with SSc activity, presence of digital ulcerations and calcinosis (r = 0.342, 0.341, -0,367, respectively; p<0.05).
Conclusions: The TBS values are not associated with BMD parameters in SSc patients. Lower TBS is associated with age and the use of steroids in the treatment. Higher TBS values are associated with the presence of digital ulcers, calcinosis and higher disease activity.

PS289 SEXUAL DYSFUNCTION AND LOWER URINARY TRACT SYMPTOMS IN 74 PATIENTS WITH SYSTEMIC SCLEROSIS

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Objective: To estimate the frequency of lower urinary tract symptoms (LUTS) and sexual dysfunction in patients with systemic sclerosis (SSc) and correlate these symptoms with clinical and functional parameters including disability and quality of life.
Patients and methods: SSc patients fulfilling the American College of Rheumatology and/or the Leroy and Medsger criteria, received by mail self-administered questionnaires assessing for clinical symptoms, LUTS using Urinary Symptom Profile (USP) scale, sexual dysfunction using Feminine Sexual Function Index (FSFI), International Indication for the Erectile Function (IIEF-5), disability using Health Assessment Questionnaire (HAQ) and McMaster Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR), anxiety and depression using Hospital Anxiety and Depression scale (HAD) and quality of life using the Short Form Health Survey (SF-36).
Results: 74 patients (61 females) were included. The most frequent LUTS were overactive bladder (n=11, 84.6%) and dysuria (n=8, 61.5%) in males and overactive bladder (n=52, 85.3%) and incontinence (n=30, 49.2%) in females.
Thirty two females were sexually active, 20 (62.5%) of whom presented sexual disorders with a mean ± SD FSFI score of 16.3 ± 6.2; the most compromised domains being mean ± SD arousal (2.5 ± 1.4)) and mean ± SD desire (2.6 ± 1.3). Sexual disorders were associated with a lower disease duration (p=0.01) and a higher depression (p=0.04) and anxiety (p=0.05) score. Dysuria was indirectly correlated with sexual disorders in women (r=-0.48). Seven of 8 men (87.5%) had erectile dysfunction, with a mean ± SD IIEF-5 score of 16 ± 5.3.
Conclusion: LUTS are more frequent in SSc patients than in the general population. The most frequent symptom is overactive bladder. Sexual disorders are similarly frequent in French SSc women than in Canadian.

PS290 ANTI-NUCLEAR AUTOANTIBODIES IN 200 IRANIAN PATIENTS WITH SYSTEMIC SCLEROSIS: CORRELATION WITH CHARACTERISTIC CLINICAL FEATURES

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Objectives: To investigate correlation of different antinuclear antibodies (ANA) in patients with systemic sclerosis and its clinical features.
Methods: Sera of 200 patients with systemic sclerosis (SSc) were analyzed by an indirect immunofluorescence (IIF) technique with HEp-20-10 liver (monkey) cells as a substrate. Specific ANA such as anti-centromere antibodies (ACA), anti-topoisomeraseI(TOPO), anti-RNA Polymerase III (Pol 3), anti-Pm/Scl (Pm/Scl) and anti-Histone were determined by ELISA technique.Presence and frequency of clinical features associated with a specific antibody (ab) group was reported cumulatively over the follow-up period. We compared frequency of specific clinical features across different auto-antibody types.
Results: We detected ANA in sera of 91.5% of the patients (ACA:11.5% ;anti-TOPO:78% ; anti-pol3:11% ; anti-Pm/Scl:3.5% ;anti-Histone: 4.5%). ACA was related to a high prevalence of Raynaud's phenomenon as first symptom, esophageal reflux, lung fibrosis in HRCT of chest and low prevalence of diarrhea. Anti-TOPO abs were associated with higher prevalence of diffuse subtype of SSC, digital ulcer/gangrene, pulmonary fibrosis, calcinosis and reduction of pulmonary diffusion (DLCO<60%).Patients with anti-pol3 were older at time of first symptom had more diffuse subtype, showed significant relation to Raynaud's phenomenon and had less pulmonary fibrosis.Positive anti-Pm/Scl abs correlated with younger age at disease onset but not with specific clinical features. Positivity for ani-Histone was associated with pulmonary fibrosis.
Conclusions: Anti i-TOPO abs showed higher prevalence and correlation with diffuse disease subtype. Age at disease onset associated with anti-pol3 and anti-Pm/Scl abs positivity. The anti-TOPO abs was showed high prevalence as previously describe in a group of Iranian SSc patients.

Key words: Systemic sclerosis. Auto-antibodies

PS291 SEVERITY OF NAILFOLD CAPILLARY MICROSCOPY CORRELATE WITH BONE MINERAL DENSITOMETRY BY ULTRASONOGRAPHY AND RODNAN SKIN SCORE IN SSC PATIENTS

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Systemic Sclerosis is characterized by autoimmunity and vasculopathy leading to tissue fibrosis;osteopenic syndrome might be an important complication of complexed pathogenesis in SSc
Objective: to perform bone ultrasonography assessment in SSc Patients and to correlate with capillaroscopy findings and the pattern of skin thickness. Methods: BMD by bone ultrasonography of every patients, all digits capillaroscopy and clinical data were carefully analyzed in 44 consecutive SSc patients fulfilling Leroy and Medsger criteria.
Results: we include 44 post-menopausal consecutive women (average age 58,6 years) with an average duration of disease 8 years; 22 pts(50%) were diffuse SSc, 40% with digital ulcers, 18% smokers, 58% were treated with glucocorticoids and 9% suffered from fractures earlier.75% presented T-score <-1,00 (osteopenic) and 25% were osteoporotic. Nail fold capillaroscopic pattern was found Late in all osteoporotic patients (100%). In 33 osteopenic patients nail fold capillaroscopic pattern was found active in 20 pts (60,6%), Early in 10 pts (30,3%), Late in 3 pts (9,1%).Another association was found between both lower BMD, Late capillaroscopic pattern and modified Rodnan Skin Score >18. Our study point to a significant role of capillaroscopy in osteoporotic SSc pts and in evaluating the role of capillaroscopy in discriminating between osteoporotic and osteopenic SSc pts. We did not observe any association between bone fragility and age, duration of disease, smoking, glucocorticoid therapy or some other feature of disease. Conclusion Capillaroscopic study was indicative regarding the Clinical pathological context with a specifity 100% scleroderma pattern late in all osteoporotic pts. According to data we believe that evaluation of SSc pts with BMD searching for bone fragility is a priority.

PS292 CALCINOSIS PREFERENTIALLY AFFECTS THE THUMB COMPARED TO OTHER FINGERS IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Background: Systemic sclerosis (SSc)-related calcinosis (which is well demonstrated on plain X-rays), frequently affects the fingers, and can be a major source of pain and disability. Although Raynaud's phenomenon often spares the thumb, clinical experience suggests that conversely the thumb is frequently affected by calcinosis. We set out to investigate the hypothesis that in patients with SSc, thumbs are more commonly affected than other digits by calcinosis.

Methods: Hand radiographs from patients with SSc from a single tertiary referral centre were selected for analysis on the basis that at least one area of calcinosis was identified. Each finger on both hands of each patient was assigned a severity score on a 0 to 3 scale (0 = no calcinosis, 3 = most severe): scores were then analysed. The scoring was completed twice, including and excluding the metacarpals.

Results: Hand X-rays of 68 patients with SSc (90% female, median age 62 years [range 55-68], 81% limited cutaneous and 19% diffuse cutaneous) showed calcinosis. When metacarpals were excluded, the overall trend in scores across digits for both hands suggested that there was decreasing severity from the thumb to the little finger (finger 5). There were a particularly large number of 3 scores for thumbs on right hands (15%) compared to left hands (4%). A Friedman test of difference in median scores across fingers (testing for an overall difference between fingers) was statistically significant for both left hands and right hands (both $p < 0.0001$). Post-hoc tests of the difference in paired medians between thumbs and other fingers showed, for left hands, significant differences in severity between the thumb and fingers 3, 4 and 5 and for right hands, significant differences between the thumb and each of the other fingers. For example, for right hands the median difference in calcinosis scores between the thumb and finger 5 was 1.5 (95% confidence interval [CI] 1.0 to 2.0, $P < 0.0001$), and between the thumb and finger 2 the median difference was 0.5 (95% CI 0.0 to 1.5, $P = 0.037$). When the analysis was repeated for scores including the metacarpals, the same broad trends were apparent.

Conclusions:
1. The thumb is affected by calcinosis more than other digits, followed by the index finger.
2. This observation provides insight into the pathogensis of SSc-related calcinosis, which may relate more to repetitive trauma than to ischaemia.

PS293 SMOKING AND ITS EFFECT ON SKIN OF PATIENTS WITH SYSTEMIC SCLEROSIS

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Objective: To evaluate the effect of smoking on the extent of cutaneous involvement in patients with systemic sclerosis.

Patients and Methods: Smoking history was surveyed on consecutive patients diagnosed with Systemic Sclerosis (ACR 1980) attending to their routine clinical evaluation during july and august 2013. To measure the degree of exposure to tobacco smoke during this time, the index packs / years (cigarettes smoked per day x number of years of consumption / 20) was used. Meanwhile cutaneous involvement was objectively assessed using the modified Rodnan score (0-51).

Descriptive statistics, t-test, linear correlation and multiple regression were used. Was considered significant a p <0.05.

Results: We included a total of 72 patients, all female, with a mean age of 54.80 (± 13.37) years and an average of 7.11 (± 7.04) years of disease duration. The 70.84% (51) of the patients were limited variations of the disease and 29.16% (21) diffuse forms.

Of the total of patients, a 65.28% (47) never smoked and 34.72% (25) had current or past exposure to tobacco smoke with an average of pack / years of 16.6 (± 11.06). The 20.83% (15) were former smokers and 13.88% (10) current smokers.

There were significant differences between the Rodnan scores of patients exposed to tobacco and the scores of patients who never smoked (5.92 ± 4.48 vs 9.02 ± 6.25, p 0.0314). Also a significant negative linear correlation was found between Rodnan scores of patients exposed and tobacco consumption expressed in pack / years (r -0.4211, p 0.0361).

A multiple regression model showed that smoking is a significant predictor of the extent of cutaneous involvement, even adjusted by years of disease duration (R2 0.44, b -0.1643, p 0.0067).

Conclusions: Smoking was found to be associated with a less severe cutaneous involvement in patients with systemic sclerosis. A higher current or past exposure to tobacco smoke gave less cutaneous involvement extension. Previous studies confirmed that there is an association between smoking and cutaneous atrophy which may explain the beneficial effect on the skin thickening in this patient group.

PS294 CORRELASTION BETWEEN CHRONIC WIDESPREAD PAIN OR FIBROMYALGIA AND ACTH AXIS ALTERATIONS IN PATIENTS WITH LOCALISED AND DIFFUSE SYSTEMIC SCLEROSIS

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Objective: The aim of this study was to evaluate the prevalence of FM and CWP in SSc patients, and the correlations between the adrenocorticotropic hormone (ACTH) axis alterations and clinical and laboratory parameters.

Methods: We enrolled 40 consecutive outpatients fulfilling the American College of Rheumatism (ACR) criteria for SSc. All of the patients were evaluated in terms of disease activity, inflammation markers, the presence of antibodies, and disease duration.

They were all classified as having FM on the basis of the 1990 and 2010 ACR FM criteria.

The Manchester definition was used for the diagnosis of CWP (CWP[M]). Pain had to be reported in at least two contra-lateral limbs and the axial skeleton, and had to have been present for at least three months. All of the subjects completed a psychic stress test (the Kessler 10-item test, KT), a test of the quality of sleep and fatigue (Flinder's Fatigue Scale, FFS), and the pain catastrophising scale (PCS), and their modified Rodnan skin scores (mRSS) were recorded.

Serum cortisol levels were assessed in the morning and afternoon by means of ECLIA (Immunoassay in electrochemiluminiscience); Roche, Germany). Urinary free-cortisol levels and ACTH levels were assessed using also a ECLIA.

Results: Most of the 40 SSc patients (34 females and six males; 23 with localised SSc and 17 with diffuse SSc; disease duration 48.4± 63.9 months) were being treated with azathioprine (AZA) at a mean dose of 150 mg/day (range 50-200), or methotrexate (MTX) and mycophenolate mofetil . All of the patients were ANA and Scl-70 or anti-centromeric antibody positive, and had high CRP and ESR values.

Thirteen patients (32.5%) suffered from CWP and nine (22.5%) also met the FM criteria. The clinical and the laboratory parameters were similar in the patients with SSc and concomitant CWP or FM, but their pain VAS scores were 18.4±12.4 vs 18.7±13.6, Kessler test scores 25.9±10.2 vs 33.0±20.8, and tender point (TP) counts 15.0±1.4 vs 11.8±4.9 . The pain correlated negatively with mRSS (R= -0.55; p= 0.01) and positively with TP count (R=0.468; p=0.05), but not with baseline serum levels of cortisol or ACTH, which correlated with each other (R=-0.700, P<0.001).

Conclusion: CWP in SSc patients correlates with the clinical manifestations of the disease, but not with serum levels of cortisol or ACTH. Moreover, skin fibrosis assessed through mRSS seems to be inversely related to pain VAS score, suggesting a possible protective effect in nociception.

PS295 INFLUENCE OF GENDER, ETHNICITY AND AGE AT ONSET IN THE CLINICAL PRESENTATION OF SYSTEMIC SCLEROSIS IN A LARGE BRAZILIAN COHORT OF 1017 PATIENTS

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Background: Although systemic sclerosis (SSc) is a systemic connective tissue disease characterized by female predominance, male adult patients are frequently associated with higher disease severity. There are no data assessing these variables in a Brazilian population with heterogeneous genetic background.
Objective: To characterize SSc clinical presentation according to gender, ethnicity and age at onset in a large cohort of Brazilian patients.
Methods: Retrospective study analyzing demographic variables in a cohort of 1017 patients with SSc from the Scleroderma Outpatient Clinic of two referral University centers in Brazil in the period between 1990 and 2012. Clinical and demographic data were obtained through chart review from 1990 to 2000, and through an electronic register database after 2001. Regarding ethnicity, patients were considered as white (with European ancestry), African-Brazilians (including mullatos/mestizos, i.e., originating from the mixture of white and black individuals, and black patients of unmixed ancestry), and Asian descendants. Juvenile SSc was defined when the age at onset was < 16 years, and adult SSc when age at onset was > 16 years. Patients were classified as limited SSc and diffuse SSc according to LeRoy et al criteria, and as SSc sine scleroderma according to Poormoghin et al criteria.
Results: There were 88.4% females, with 75.7% white, 22.2% African-Brazilians and 2.3% of Asian ancestry. Male gender was significantly associated with diffuse SSc ($p < 0.001$), higher skin score ($p < 0.001$), interstitial lung disease ($p = 0.01$), scleroderma renal crisis ($p = 0.019$), neurologic involvement ($p = 0.004$), and death ($p = 0.022$), whereas females presented more calcinosis ($p = 0.043$), telangectasia ($p = 0.021$), and joint involvement ($p = 0.050$). African-Brazilian ethnicity was associated with diffuse SSc ($p < 0.001$), interstitial lung disease ($p = 0.008$), myositis ($p < 0.001$) and higher skin score ($p = 0.001$), while white patients had higher age at diagnosis ($p = 0.003$) and telangectasias ($p = 0.002$). Patients with juvenile SSc were associated with diffuse SSc ($p < 0.001$), calcinosis ($p < 0.001$), and myositis ($p = 0.026$), although they were also associated with lower frequency of interstitial lung disease ($p = 0.050$), pulmonary hypertension ($p = 0.035$), interstitial lung disease ($p = 0.050$), pulmonary hypertension ($p = 0.035$), esophageal ($p = 0.005$), and joint ($p = 0.047$) involvement.
Conclusion: Male gender and African-Brazilian ethnicity presented distinct clinical features characterized by major organ involvement, while juvenile SSc was associated with lower frequency of visceral involvement.

PS296 ARTERIAL STIFFNESS IN SSC PATIENTS- A SINGLE CENTRE EXPERIENCE

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Background: Systemic sclerosis (SSc) is characterized by endothelial dysfunction, microangiopathy and macrovascular damage. Aortic pulse wave velocity (aPWV) is known to be a reliable indicator of arterial stiffness and a useful prognostic predictor of cardiovascular events.

Objective: The aim of this study was to evaluate aPWV alterations in a series of SSc patients.

Methods: A total of 33 patients diagnosed with SSc (30 females and 3 males, mean age 51,81 years) were included in the study. We determined parameters of aortic stiffness - pulse wave velocity (PWV) and augmentation index (Aix) in all subjects using Arteriograph device (Tensio Med Ltd., Budapest, Hungary).
In our cohort more than half had a limited SSc (60,6%) and 51,51 % had an elevated aPWV. 10 out of 33 patients had one or more classic cardiovascular risk factors, 30% with limited SSc and only 7,69% (1 patient) with diffuse SSc , but with no proof of microangiopathy correlated with these comorbidities. These patients also had an elevated average of aPWV (10,99), signifficatly higher compared to those with no C-V risk factors (9,12). 18,18% of patients with limited SSc had no C-V risk associated and high aPWV, respectively 12,12% of those with diffuse disease. Also, in the group with no C-V risk, patients had a higher Aix (-9,11 vs -1,94).

Conclusion: As expected, patients with high aPWV were classified as having limited SSc and also had conventional cardiovascular risk factors. Aortic pulse wave velocity can be easily measured by non-invasive, user-friendly tool and can be used as a marker of damage, still further prospective studies are required for better validation of this method.

PS297 JUVENILE SCLERODERMA INTERNATIONAL NETWORK (JUSINET) DATABASE: A RELIABLE INSTRUMENT FOR CLINICAL RESEARCH IN JUVENILE SCLERODERMA SYNDROMES

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Background The conduct of Clinical Research in rare diseases, such as Juvenile Systemic Sclerosis (JSSc) and Juvenile Localized Scleroderma (JLS), requires an adequate number of patients and a fruitful collaboration between international centers. The clinical management of young patients suffering from these diseases is also often difficult to achieve in an effective and shared matter.
Objective: We propose a web-based registry (www.jusinet.org) to prospectively collect data on demographic, epidemiological, clinical, and laboratory features of patients with JSSc and JLS from adult and paediatric rheumatology centres and to educate physicians to a more standardized approach to these conditions
The purpose is to provide a well-characterized cohort of scleroderma patients according to the current classification criteria and collect adequate information enabling to uniform clinical assessment and diagnostic tests, to stimulate clinical and basic research projects.
Methods The Database was evaluated by some international experts who provided us with valuable advice for improvement.
JUSINET has an administrative structure including a Database Executive Committee (DEC), who evaluates progress of the project and discuss management issues.
The Database Coordinator (DC) assisted by a Research Assistant (RA), and a Database Manager (DM, statistician) form the Local Administrative Structure (LAS).
In order to verify the performance of JUSINET at national and international level, four centers in Italy, one in Slovenia, Argentina and Turkey, have tested and validated the system including real patients cases. Compilers were required to express their opinion on 3 variables, clarity of information, ease of data entry and completeness of information, for each section of the database. The 324 opinions expressed for the 22 sections of JUSINET, in a range between 1-5, reached a mean value of 4.62. The mean time to enter a new patient data was 14 minutes for JSSc, and 8 minutes for JLS; to update data was 8 minutes for JSSc and 5 minutes for JLS.
Conclusions The JUSINET Database represents a valuable instrument to better characterize patients childhood onset scleroderma and facilitate research on pathogenesis and treatment of this relatively rare condition. It also provides a simple and reliable tool for the daily clinical management of these patients

PS298 MODIFIED RODNAN SKIN SCORE: A NEW TECHNOLOGICAL APPROACH

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Systemic sclerosis (SSc) is an autoimmune disease characterized by vascular alterations, especially Raynaud's phenomenon, and by progressive skin and visceral fibrosis.
Usually sweat glands and hair follicles are also affected, resulting in a decreased sweat secretory function and hair loss that associate to skin alterations.
In a context in which the entire surface of the body may be affected, according to the extent of affected skin are classified two types of systemic sclerosis with different clinical behavior and systemic involvement: limited and diffuse SSc.
To quantify precisely the cutaneous sclerosis the practitioners all over the world use the RSS (Rodnan Skin score). RSS is the most used for its accuracy and reproducibility, expecially the Modified version (MRSS), wich consider 17 body areas, scoring each of them on a scale of 0-3 for thickness, by clinical skin evaluation (0=absent sclerosis, 1=mild, 2=moderate, 3=severe), obtaining a total score with a maximum value of 51. This score allows to monitor the disease activity and the response to treatment, thus improving prediction of prognosis.
In collaboration with Actelion, our Center has developed an application (APP) for iOSystem available for iPhone and iPad devices, that allows a quick and easy calculation of MRSS.
In addition, this APP (called “MRSS”) consent to record every patients’ MRSS in a proper database always available for evaluations and comparisons.
The use of this APP is really handy and allows the clinician to be more accurate: in a single step take place the clinical assessment, the scoring of MRSS and the recording of data, avoiding this performance being in different phases, and avoiding the final data transcription on paper or on computer, which are not bedside.
Results
In our experience all the medical and nursing staff, even without specialized computer skills nor experience on devices of this type (iPhone, iPad), they all appreciated the comfort of use, preferring the APP to the traditional papery approach mostly because of the routine-time saving, but also for the manageability of the instrument.
Conclusions
Currently this Application is the first and only one available for calculation of MRSS. In our experience, this application has proven itself to be a great help for clinicians, and we hope this informatic tool will soon be followed by similar applications that will certainly be useful for a more accurate clinical monitoring, in reducing the waste of routine-time and for a better patient-centered care of the disease.

PS299 SIGNIFICANCE OF IGG LEVELS IN THE WAIKATO HOSPITAL SYSTEMIC SCLEROSIS COHORT

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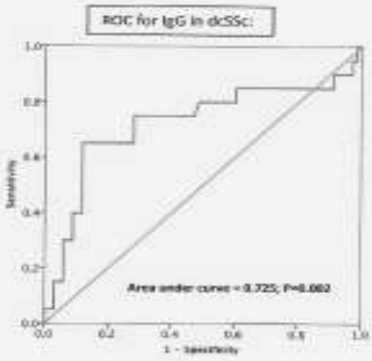
Background: Systemic sclerosis (SSc) is a heterogeneous autoimmune disease which affects predominantly women. SSc is subclassified by the extent of skin involvement into diffuse cutaneous (dcSSc) and limited cutaneous systemic sclerosis (lcSSc). The main difference between the two types of systemic sclerosis is the rate of disease progression, the severity of skin and visceral involvement along with a few characteristic phenotypic differences. It has a variable course and a guarded prognosis.
The association between autoantibodies (immunoglobulins) and the two major subsets of SSc is well known. Anti-centromere antibodies (ACA) are highly specific for limited cutaneous systemic sclerosis (lcSSc) and anti-topoisomerase 1 (scl70) antibodies are highly specific for diffuse cutaneous systemic sclerosis (dcSSc) which carries a poorer prognosis. However, the role of the above autoantibodies in the pathogenesis of SSc remains elusive.
There is a paucity of literature on the association between isotypes of autoantibodies and their clinical implications.
Objective: We aimed to evaluate the significance of immunoglobulin isotypes and their association with clinical features in our cohort of patients with SSc.
Method:

- Patients with SSc and SSc-Overlap Syndrome (SOS) were identified from the Waikato Systemic Sclerosis database and the most recent immunoglobulin and complement levels recorded.
- Diagnosis of Systemic Sclerosis was established as per 1980 ACR criteria in all cases.
- Immunoglobulin and complement levels were estimated by Nephelometry (Beckmann Immage).
- Association of Ig levels with SSc subtype and SOS were assessed with one way analysis of variance (ANOVA) & a receiver operating characteristic curve was generated for the significant result
- Association of complement levels with SSc subtype and SOS was tested with Chi square analysis

Results: The cohort comprised of 78 female and 10 male patients (60 lcSSc, 20 dcSSc and 8 SOS)
The mean immunoglobulin levels in the three groups are as tabulated.
Conclusion: We have demonstrated that the IgG levels were significantly higher in dcSSc than other subtypes (ROC for IgG as above). This is consistent with previous work by Tamby MC[1] et al who showed higher (but not significant) mean IgG & IgA levels in patients with anti-scl70 positive dcSSc compared to lcSSc. No significant difference in complement levels and the three groups were found.
An IgG level of 11.85 g/L had a sensitivity of 85% and specificity of 72% (Positive Likelihood Ratio of 3.04) in the diagnosis of dcSSc.
References:
[1] Tamby MC[1] et al , Biologics: Targets & Therapy 2008:2(3) 583-591

The mean immunoglobulin levels in the three groups are as tabulated.

		Mean (g/L)	SD	95% CI
IgG Level (NR=7.0-16g/L)	lcSSc	11.1	3.82	10.1 – 12.1
	dcSSc	14.8	5.46	12.2 – 17.3
	SOS	12.5	3.78	9.3 – 15.7
IgA Level (NR=0.8-4.0g/L)	lcSSc	2.5	1.25	2.2 – 2.9
	dcSSc	2.8	1.36	2.1 – 3.4
	SOS	2.9	1.52	1.6 – 4.1
IgM Level (NR=0.4-2.5g/L)	lcSSc	1.5	0.9	1.3 – 1.8
	dcSSc	1.2	1.03	0.76 – 1.7
	SOS	1.9	0.89	1.3 – 1.7



PS300 SEVERE VITAMIN D DEFICIENCY IN SYSTEMIC SCLEROSIS

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Introduction: In recent years a role of vitamin D as immune modulator factor has been proposed, consistently low levels of this hormone have been observed in several autoimmune diseases including systemic sclerosis (SSc).
Objective: To evaluate the prevalence of low serum vitamin D levels in a large series of SSc patients and the possible correlation with clinical features of the disease.

Methods: We retrospectively analyzed the serum levels of vitamin D in 140 consecutive SSc patients (F/M 119/21; age 11.06±6.65 yrs) followed in our Rheumatology Unit. In particular, serum 25-hydroxyvitamin D (25OHD) dosage was performed in 90 patients (group 1) without vitamin D supplementation (F/M 77/13, mean age at the moment of the 25OHD dosage 49.89±15.65 years, mean disease duration 10.64±6.27 yrs) and in 50 patients (group 2) receiving conventional dosages of vitamin D (800 IU cholecalciferol/day and oral calcium) (F/M 42/8, l/d 40/10, mean age at the moment of the 25OHD dosage 50.38±13.57 yrs, mean disease duration 82±7.28 yrs). Serum levels of 25OHD, which represents the major circulating form of vitamin D and standard indicator of vitamin D status, were defined as normal (>30 ng/ml), vitamin D deficiency (<10 ng/ml), or insufficiency (>10, <30 ng/ml).

Results: In the group 1, the mean 25OHD levels were 9.84±4.17; 50 patients showed vitamin D deficiency (<10 ng/ml), 40 patients showed insufficiency and among these only 3 had mild hypovitaminosis (>20, <30 ng/ml).
In the group 2, including patients with vitamin D supplementation, the mean serum concentration of 25OHD was 25.59±8.51 ng/ml; only 12 patients presented level of 25OHD >30 ng/ml, while 13 remained <20 ng/ml despite supplementation.
The observed low levels of 25OHD did not correlate with the main clinical features in whole SSc patients series in both subsets with/without vitamin D supplementation.

Conclusion: The results of the present study confirm previous reports focusing on hypovitaminosis D in SSc patients. In addition, our 90 patients without vitamin D supplementation show 25OHD deficiency in 55% cases.
The severe hypovitaminosis D observed in our SSc patients may be multifactorial: insufficient sun exposure, skin sclerosis, insufficient intake, malabsorption and/or vitamin D receptor resistance. Moreover, standard oral vitamin D supplementation is inadequate to normalize serum levels of the hormone, suggesting an important role of gut malabsorption and/or vitamin D utilization. Finally, the possible correlations of low 25OHD levels with clinical features should be thoroughly evaluated in larger series of SSc patients with relatively shorter disease duration.

PS301 ENVIRONMENTAL FACTORS AND INDUCTION OF SYSTEMIC SCLEROSIS: ANALYSIS OF 211 CONSECUTIVE PATIENTS

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Introduction: Many environmental factors can be involved as triggering agents in the etiopathogenesis of systemic sclerosis (SSc).
Objective: To analyse the presence of environmental factors in the clinical picture of a cohort of patients with SSc attended in a reference center in Brazil.
Methods: A consecutive group of 211 patients with the diagnosis of SSc was interviewed about exposition to infectious (viral, bacterias), occupational (exposition to sílica or organic solvents) and non infectious or occupational (drugs, pesticides, silicone prothesis) environmental factors. Those groups with and without positive environmental factors were compared regarding demographic, clinical and laboratory variables.
Resultados: Twenty-one patients (10%) referred possible triggering environmental factors: organic solvents 14 (67%), sílica 4 (19%), pesticides 4(19%), bacterial infections, silicone and drugs 1 each (5%). Three patients (15%) referred exposition to more than one environmental factor. Regarding demographic and clinical characteristics, it was not observed statistical association among the different variables. Patients with previous exposition to pesticides showed statistical trend to association with anti-Scl70 antibody ($p = 0.066$).
Conclusion: Exposition to environmental factors can represent a potential triggering factor to the development of SSc in Brazilian patients, especially positive anti-Scl70.

PS302 UTILITY OF THE 6 MINUTE WALKING TEST IN SYSTEMIC SCLEROSIS, EXPERIENCE FROM 20 CROATIAN PATIENTS

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Introduction: Interstitial lung disease and pulmonary vasculopathy are the current leading causes of death in patients with systemic sclerosis. 6 minute walking test (6MWT) has failed to provide information about pulmonary function in systemic sclerosis patients. Despite the above, the 6MWT is often used in everyday practice for the simple reason that we do not have better tools to assess pulmonary status of patients.
Methods: We performed 6 minute walking test in 20 patients.
Results: All enrolled patients were women, four were diagnosed with limited systemic sclerosis and 16 with diffuse systemic sclerosis, 10 patients have anti-topoisomerase antibodies and 3 anti –centromere antibodies. The mean weight was 62 kg (42 -85), height 159 cm (150-173), and BMI 24,3 kg/m2 (17-35,5).
Mean distance in the 6MWT was 312 meters (125-610). The oldest patient (age78) walked the shortest distance, 125 meters. Mean distance for five patients with a restrictive pattern on spirometry was 412 meters .Mean distance for four patients with obstructive and restrictive pattern was 245 meters; mean distance for 11 patients with a reduced DLCO was 315 meters. Four patients who have lung fibrosis and reduced DLCO but with no pulmonary hypertension, walked (mean) 353 meters.
The relationship of the level of shortness of breath and level of fatigue before the test and walked distance in meters was negative($r = -0.19$, $p = 0.42$, $r = -0.05$, $p = 0.85$, respectively). Similarly, the level of shortness of breath and level of fatigue after the test was negatively related to the walked distance in meters ($r = -0.19$, $p= 0.46$, $r= -0.42$, $p = 0.06$, respectively). This indicates that patients with better exercise capacity feels less fatigue and shortness of breath before and after the test, and on average have better results of the 6MWT.However, due to the small sample size statistical significance was not reached.
We found a negative correlation between BMI and walked distance in meters ($r =-0.16$, $p=0. 52$).
However, the walked distance was not related to the patient's weight suggesting that BMI maybe a better predictor of walked distance.
Conclusion:Although the 6MWT cannot provide reliable data to assess lung function in systemic sclerosis patients, it can offer useful information on the overall exercise capacity in systemic sclerosis. Reduced exercise capacity in systemic sclerosis, measured by the 6MWT, is not entirely due to reduction in lung function, but also due to the affection of other organs and systems.

PS303 PARTICULARITIES OF SCLERODERMA IN MALE PATIENTS

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Aim : To analyze clinical profile of the systemic sclerosis (SSc) observed in male patients.
Patients and Methods: is about retrospective study on the review of patients' cases observed in specialized consultation and hospitable stay in an internal medicine department from January, 1997 till December, 2011. All patients SSc referring to the ACR criteria and appropriate investigations allowing the data analysis.
Results: 15 patients on a troop of 117 patients (12%); the average age is of 31.2 (19-51) years, the diagnosis delay is established about 15.2 months. It is about a diffuse SSC in 11cas (73%). Triggering factors are associated as medication taking (statine in secondary prevention of recurring stroke at a smoking patient) (1), a silicosis exposure (1) and a tymectomy for myasthenia (1). The cutaneous achievements are dominated by Raynaud's phenomenon (100 %), a diffuse scleroderma (3), a sclerodactyly (5), cutaneous ulcerations s (7) ischemic digital amputations (2), calcinosis (4). The systemic manifestations are dominated by a lung interstitial syndrome of variable severity (9), constant esophageal achievement is observed complicates by ulcerations (3) and stenosis (2). We find a syndrome of pseudo-obstruction (2) at the origin of a syndrome of sever malabsorption (1). A cirrhosis is noted (2) realizing a Reynolds syndrome (1) and in a cardiac cirrhosis (1). The myocardium infringement is present (5) as restrictive cardiomyopathy (2), pulmonary hypertension complicated with right cardiac insufficiency (4) on definite post embolic heart diseases (2) and an ischemic cardiomyopathy (1). The renal infringement is found (2) and justifies a kidney biopsy (1). The associated autoimmune diseases are Thyroiditis (4), a dry syndrome of Gougerot-Sjogreen (3), a myathenia (1) and a primitive biliary cirrhosis (1). The immunological profile shows the presence of antiScl70 (11) and anti-centromeres antibodies (4). The medical treatment is dictated by the clinical context and justifies specific treatments as inhibitors of the receptors of the endotheline (3), immunosuppressive drugs (3), esophageal dilation (1), octreotide (2). The evolution is fatal medium-term (4), by cardiorespiratory failure (2), cirrhosis (1) and severe malnutrition (1).
Conclusion: The male SSc is rare (12%) and sever with high mortality (26%). The diffuse restrictive lung disease is the dominant manifestation. The cardiovascular causes constitute the second cause of morbi-mortality and appears mostly associated to an embolic event. The associated autoimmune diseases are various and often infra-clinical so its justify to be detected by the appropriates investigations (biological, morphological, histological explorations…).

PS304 CLINICAL UTILITY OF SALT & PEPPER SKIN CHANGES IN THE WAIKATO HOSPITAL SYSTEMIC SCLEROSIS COHORT

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Background: Systemic sclerosis (SSc) is sub-classified by the extent of skin involvement into diffuse cutaneous (dcSSc) and limited cutaneous systemic sclerosis (lcSSc). The main difference between the two types of SSc is the rate of disease progression, the severity of skin and visceral involvement along with characteristic phenotypic differences.
Cutaneous involvement is an almost universal manifestation. Skin changes include non-pitting oedema, sclerosis, calcinosis, telengiectasias and hypo and hyperpigmentation (known commonly as "Salt and Pepper skin" or pseudovitiligo) and the accompaniment of pruritus.
Objective: To investigate the diagnostic utility of salt and pepper skin in SSc and the association with specific autoantibodies.
Methods: Patients with SSc followed up from 2005 until present were selected from the SSc database at Waikato Hospital, Hamilton, NZ. All patients met the 1980 ACR criteria for systemic sclerosis.
Modified Rodnan Skin Score (mRSS), skin pigmentary changes and pruritus were prospectively recorded at patient reviews in the SSc Clinic.
Autoimmune profiles were tested with the Euroimmun (IgG) Systemic Sclerosis Immunoblot which tested for: Scl-70, CENP A, CENP B, RP11 (RNAP-11), RP155 (RNAP-155), Fibrillarin (U3RNP), NOR-90, Th/To, PM-Scl 100, PM-Scl75, Ku, PDGFR and Ro-52.
Data was processed using SPSS version 21. Continuous variables were described as mean ± sd or median, range where appropriate. The association of skin pigmentation with SSc subtype was assessed using the chi-squared test (or Fisher's exact test where numbers were small). Student's t-test was used for between group comparison of mean mRSS.
Results:
Demographics:
87 patients were reviewed as in the table below.
Salt and Pepper Skin and SSc Subtypes:
Presence of salt and pepper skin changes was associated with dcSSc subtype, $X2=47.9$, $p=<0.001$ with the positive likelihood ratio of 8.81 (PPV 74.07%; NPV 96.55%). In addition, the presence of salt and pepper skin changes was also associated significantly with pruritus, $X^2=9.07$, $p=0.004$.
No association was found between pruritus or salt and pepper changes and the other autoantibodies.
The mean mRSS in dcSSc was 19.28 compared to 4.74 in lcSSc ($t=9.5$, $p<0.001$). Those with pruritis had a higher mean mRSS, $t=2.1$, $p=0.03$.
Conclusion: There is a significant association between the presence of salt and pepper skin and dcSSc, Scl70 antibody and pruritus. The presence of pruritus is associated with higher mean mRSS. There was no gender differences noted in these respect.

Subtype	Females (Mean age, SD)	Males (Mean age, SD)	Subtotal
lcSSc (mean age 58.80 yrs)	58 (58.9, 12.8)	6 (58, 14.7)	64
dcSSc (mean age 53.74 yrs)	19 (54.8, 10.9)	4 (48.8, 18.2)	23
Total	77	10	87

PS305 MUSCULAR INVOLVEMENT IN PATIENTS WITH SYSTEMIC SCLEROSIS: MYOSITIS RELATED TO SSC OR TO OTHER AUTOIMMUNE DISEASE?

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Introduction: systemic sclerosis (SSc) is an inflammatory disease of the connective tissue associating a vasculopathy. Several organs are involved. Skeletal muscle involvement is not rare and can be due to a specific scleroderma myositis, to an associated autoimmune disease or iatrogenic. The aim of our study is to review the cases of myositis in patients with SSc.

Methods: Files of patients with SSc (fulfilling ACR critera) were studied. Patients with myopathy (defined by muscle weakness associated to increased creatine kinase and/or myopathic electromyography) were indentified from the records. Demographic, clinical and immunological characteristics were analyzed. Outcome and associated autoimmune diseases were also investigated.

Results:

Twelve patients with myositis were included (11.7%). The average age of SSc diagnosis was 43.25 years. The mean delay between the myositis and SSc diagnosis was 0.7 months; skeletal muscle involvement revealed the disease in 2 patients and was discovered on admission in 8 others. Nine patients complained of myalgia and 10 of muscle weakness. Muscular enzymes increased in all patients. Electromyography showed myositic features in 70% of cases. Two patients had left ventricular dysfunction. Raynaud's phenomenon was experienced in 10 patients with geant capillaries in 7 cases. Interstitial lung disease with reduced forced vital capacity (< 70%) was objectified in 8 cases. Eleven patients had gastro-oesophageal reflux and 6 had arthralgia. Three patients were classified as diffuse cutaneous SSc and 9 as limited cutaneous SSc. Antinuclear antibodies were positives in all cases; anti-Scl 70 in 5 patients, anti-PM- Scl in 1 patient (they aren't routinely done), ACA were not found in any patient. Three patients were also diagnosis a Sjogren's syndrome (SS), 3 had a systemic lupus erythematosus (SLE) and one had a real dermatomyositis (DM) with specific cutaneous features. All patients were treated with corticosteroids and outcome was good in all cases (there was no muscle weakness and creatine kinase was normal). Patients with myocarditis had a stable left ventricular ejection fraction. There was no scleroderma renal crisis.

Discussion: Skeletal muscle involvement is common in SSc since muscle weakness is found in up to 90% SSc patients when systematically assessed. Clinical, biological and electromyographic features are similar to those of polymyositis or dermatomyositis and histological findings include interstitial fibrosis, microangiopathy and inflammatory infiltrate. When scleroderma is associated to other systemic disease (SS, SLE), it is difficult to attach the myopathy to one of them (except DM: it's more likely related to DM then SSc).

Conclusion: There are no uniform criteria for the diagnosis of SSc-associated myopathy, Treatment with high doses of corticosteroids is usually sufficient. An associated cardiomyopathy must be screened.

PS306 PERIPHERAL NEUROPATHY IN SYSTEMIC SCLEROSIS PATIENTS: A PILOT STUDY

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The etiology of neuropathy in systemic sclerosis (SSc) is unknown. An autopsy of a patient with systemic sclerosis and neuropathy showed severe sclerosis of the spinal peripheral nerves with extensive degeneration of nerve fibers.
The aim of this study was to determine the prevalence of peripheral neuropathies (PN) in SSc patient and possible relationship between PN with activity and clinical manifestations of the disease.
21 consecutive patients [19 women and 2 men, mean age 47.3 (11.8) years, median disease duration 6 years with minimum–maximum range 1–20 years] which fulfilled the ACR criteria for SSc were recruited in this study. Apart from the usual history and physical examination, a full neurological examination by a neurologist was carried out. The patients had no other known cause of peripheral neuropathy except SSc. The neurologic assessment included a neurologic history, neurologic examination; nerve conduction studies (NCS) and electromyography (EMG). We evaluated the clinical manifestations of SSc according to the Medsger Severity Scale. The level of SSc activity was evaluated according to Valentini activity score.
The frequency of abnormal electrophysiological findings was 63%. The frequency of polyneuropathy (defined as abnormality in 2 or more nerves) was 52%. The skin involvement evaluated by modified Rodnan skin score was highly variable between SSc patients with or without PN ($P<0.05$). No significant differences were found for the distribution of age, disease duration, autoantibody profile, estimated sPAP, hemoglobin and creatinine levels between SSc patients with or without PN. Severity of joint/tendon involvement was different between SSc patients with or without PN ($p=0.02$). Activity score according to Valentini was higher in SSc patients with PN than in the SSc patients without ($p<0.05$).
The prevalence of PN is relatively high in SSc and occurs more frequently in patients with grater skin and joint/tendon involvement and high disease activity. Larger, prospective studies using the more sensitive tools as well as pathologic studies of nerve, including cutaneous innervation, are needed to further assess the characteristics and etiology of the neuropathy in SSc.

PS307 PROTECTIVE EFFECTS OF SUPPLEMENTATION WITH 25-HYDROXYVITAMIN D AND AN INDIVIDUALIZED REHABILITATION PROGRAM IN SYSTEMIC SCLEROSIS PATIENTS: OUR 2-YEAR EXPERIENCE

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In recent years evidence emerging indicates that, in addition to their known role in bone metabolism, steroid hormones derived from Vitamin D (vit D2 and vit D3) exert many biological activities, including a moderating effect on the immune system.
Numerous studies have demonstrated a significant association between Vitamin D deficiency and increased incidence of autoimmune disorders including Systemic Sclerosis (SSc), a connective tissue disease characterized by immune system activation, widespread microangiopaty with endothelial dysfunction and fibrosis of the skin and internal organs.
The aim of our study was to estimate the effects of a 2-year period with calcifediol (25-hydroxyvitamin D) daily treatment associated with an individualized rehabilitation program in 25 female patients (mean age: 57.4 yrs, mean disease duration: 8.2yrs), fully fitting the ACR criteria for diffuse SSc and with a progressive disabling condition.
Nailfold capillaroscopic patterns were classified according to Maricq criteria: 9 early (36%), 6 active (24%) and 10 late (40%).
Laboratory evaluation showed hypovitaminosis D in all patients (mean serum Vit D level: 17.5 ±10.8ng/ml) and secondary hyperparathyroidism in 72% (18) of them.
SSc patients were assessed at baseline (T0) and at 24 months follow up (T1) by Health Assessment Questionnaire (HAQ), Hand Mobility in Scleroderma Test (HAMIS), Time Up-and-Go (TUG) test, and 3-mt walk (3MWT) test.
They were treated with therapist-guided exercises, manual lymph drainage and finger stretching for 1 hour, twice a week, for 5 weeks, 3 times in a year.
At T0 patients had low hand grip strength and mobility, impaired TUG and 3MW test.
At 24 months follow up (T1) they showed a significant improvement in hand mobility, exercise tolerance, TUG and 3MWT tests. HAQ score for hand functions, such as eating and gripping, was decreased with a positive influence on the Quality of Life (QoL).
Oral daily intake of calcifediol resulted in a short-term increase of 25 (OH) serum levels in all patients, achieving parathyroid hormone suppression in all patients with secondary hyperparathyroidism.
At the 2-year follow-up, the evolution of microvascular damage and skin involvement was significantly reduced and in 65% of patients (16) the regression of some capillaroscopic alterations [capillary disarrangement (45.8%) and capillary loss (52.7%)] was observed, too.
These encouraging findings suggest that prevention of hypovitaminosis D by a long term calcifediol supplementation might reduce the prevalence of autoimmune diseases, particularly in those believed to be Th1 induced, thanks to the Vit D immunosoppressive effect on Th1 profile and B-cell proliferation.

PS308 JOINT INVOLVEMENT IN SYSTEMIC SCLEROSIS AND ITS RELATIONSHIP WITH AUTOANTIBODY TO ANTI-CYCLIC CITRULLINATED PEPTIDE

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Introduction: The presence of anti-cyclic citrullinated peptide antibodies (anti-CCP) has a high specificity for the diagnosis of rheumatoid arthritis (RA). Different cross-sectional studies estimated the point prevalence of anti-CCP antibodies in patients with systemic sclerosis (SSc), wich ranged from 1% to 15%.
Objectives: To investigate joint involvement in SSc and its relationship with autoantibody to anti-cyclic citrullinated peptide.
Patients and methods: One hundred fifty (150) patients attending the rheumatology department at Ben Aknoun Hospital, as part of a prospective study and fulfilling the ACR and/or Leroy and Medsger criteria for systemic sclerosis were evaluated. Joint involvement was determined by clinical, radiological and ultrasonographical evaluation. All autoantibody analyses were performed in the Laboratory of Beni Messous hospital. The presence of anti-CCP2 IgG was evaluated with commercially available enzyme-linked immunosorbent assay (ELISA) kit. The test kit was used following the procedures suggested by the manufacturer. The samples were classified as negative (<5 units), positive (>5 units). The analysis of results was performed by the Epidata analysis. Data were expressed as the median and range or mean ± standard deviation (SD) and 95% confidence interval (95% CI), when appropriate. The statistical significance for the various associations was calculated using the Khi 2 test. The difference was significant when p value < 0.05.
Results: 139 women and 11 men with a median age of 45.12±13.59 years and a disease duration (first non-Raynaud symptom) of 9.7 years. 42 patients had a diffuse scleroderma, 108 patients had a limited scleroderma. 60 patients had arthritis. 21 patients had erosive arthritis, An overlap with Rheumatoid Arthritis (RA) was found in only 7 patients. The presence of anti-CCP 2 was found in sera of 9.4%.
Anti-CCP2 was positive in 16.5% patients with arthritis and in 4.5% patients without arthritis (p=0.01). Anti-CCP2 was positive in 33.3 % of patients with erosive arthritis and in 7.7 % of patients without erosive arthritis (p = 0.01). in 71.4% of patients with overlap syndrome SSc-RA (p<10-5).
A statistically significant association was found between anti-CCP2 positivity and the presence of arthritis (p=0.01), erosive arthritis (p=0.01) and overlap syndrome (p<10-5). High titres of anti-CCP2 antibodies were found in patients having an overlap syndrome SSc–RA. The presence of anti-CCP2 antibodies was not associated with interstitial lung disease and pulmonary arterial hypertension
Conclusion: Anti-CCP2 antibodies were associated with the presence of arthritis, erosive arthritis and overlap syndrome. The finding of high titres of anti-CCP antibodies may help to define the diagnosis of overlap syndrome SSc-RA

PS309 22 YEARS EXPERIENCE OF PATIENTS WITH SYSTEMIC SCLEROSIS ON HOME PARENTERAL NUTRITION

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Introduction: Patients with systemic sclerosis (SSc) may develop significant gastrointestinal involvement (GI). When severe, this can lead to intestinal failure (IF) requiring home parenteral nutrition (HPN). However, few outcome data are reported for these patients.

Objective: To review the characteristics and outcomes of all patients with SSc who had received HPN.

Methods: Records were reviewed of all patients with SSc who required HPN, at a national IF centre, between 1990 and 2012. Disease characteristics and survival/outcome data were evaluated.

Results: 25 patients (5 male, median age: 55 (range 24-76)) with SSc received HPN (37,200 catheter days). Median time from SSc onset to HPN was 113 months (range 14-389).
All had small intestinal involvement. 80% had proven bacterial overgrowth. 44% had experienced at least one episode of pseudo-obstruction. 16% had a small intestinal resection.
Prior to HPN initiation, 6 patients failed a naso-enteric feeding trial. 10 patients had a gastrostomy or jejunostomy inserted; 7 of whom received enteral feeding for less than 1 year. The remaining 9 patients commenced HPN directly, without enteral tube feeding, because of the severity of their dysmotility/associated co-morbidity.
Only 2 patients were weaned off HPN (after 8 and 29 months) following successful medical optimisation. After 1 year, median body mass index rose from 18.5 to 21.3.
3 patients received HPN for more than 10 years. The cumulative survival on HPN after 1, 5 and 10 years were 75%, 37% and 23% respectively.
No patients died from HPN-related complications. 16 died from causes related to their SSc. 1 died from malignancy. 8 patients survive, 7 of whom remain on HPN (median duration: 40 months, range 9-178).
9 patients were trained to manage their central venous catheters and self-administer HPN. 16 patients relied on others for their HPN administration. Reported catheter complications included non-thrombotic occlusion (0.70/1,000 catheter days), sepsis (0.19/1,000 catheter days) and central venous thrombosis (0.11/1,000 catheter days). The sepsis rate for all HPN patients, at the same IF centre, is 0.39/1,000 catheter days. No one developed IF-associated liver disease.

Conclusions: This is the largest reported series of patients with SSc requiring HPN, which is life-saving in patients with severe bowel involvement. Our data shows that HPN offers a safe means of nutritional support for patients with severe SSc-related GI involvement, but that SSc-related mortality remains high. Patients with SSc had a low catheter-related sepsis rate. Additionally, the majority relied on others for their catheter care.

PS310 ESOPHAGEAL INVOLVEMENT IN SYSTEMIC SCLEROSIS: CLINICAL CORRELATIONS

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Introduction: systemic sclerosis (SSc) is an autoimmune disorder characterized by fibrosis, inflammation and vasculopathy. Gastrointestinal involvement is the third most common clinical manifestation. Esophageal dysfunction affects 50-90% of SSc patients. A correlation has been proposed between severity of esophageal involvement, Raynaud phenomenon, specific autoantibodies and capillaroscopy patterns.
Objective: to investigate the correlation between severity of esophageal dysfunction and clinical features of SSc.
Patients and Methods: we evaluated 18 adult patients (17 female) who fulfilled the ACR criteria for SSc according to Le Roy. All underwent esophageal manometry and endoscopy. We considered hypotensive lower esophageal sphincter (LES) pressure <10mmHg; hypoperistalsis defined by <70% propulsive waves or wave pressure <50mmHg; akinetic esophagus when absence of peristaltic activity was found. The presence of one out of 3 criteria defines esophageal involvement by SSc. Endoscopic esophagitis followed Los Angeles classification. Heartburn, regurgitation and dysphagia were assessed at the time of manometry. Microvascular involvement was evaluated by capillaroscopy and classified through patterns early, active and late defined by Cutolo. Clinical and laboratory findings were reviewed: autoantibody profiles, pulmonary hypertension, modified Rodnan skin score (MRSS) and digital ulcers. Statistical analysis: Mann-Whitney, chi-square Fisher test $p<0.05$.
Results: all patients had Raynaud phenomenon, 39% had diffuse (dsSSc) and 61% limited (lcSSc) systemic sclerosis. Mean age was 54.05±14 years. Positivity of antinuclear autoantibody was 83.4%, antiScl-70 11.1%, anticentromere 50% and anti-SSA/Ro 11.1%. Peristaltic abnormalities were found in 76% consisting in hypoperistalsis 38% and aperistalsis 38%. In 27% of patients hypotensive LES was detected, 60% of them had aperistalsis too. All patients with dcSSc had esophageal motor abnormalities, while 63% of lcSSc cases did, $p=0.06$. Two thirds of patients with aperistalsis had late SD pattern, $p=0.079$. A significant correlation was found between MRSS and severity of peristaltic alteration, $p<0.02$. No correlation was found between digestive clinical symptoms and peristaltic abnormalities. All patients with digital ulcers had manometric abnormalities, although not reaching statistical significance.
Conclusions: manometric findings in SSc are both frequent and severe. In our series of patients we did not find a correlation between digestive clinical symptoms, manometric abnormalities and esophagitis. However, esophageal peristaltic abnormalities are constantly present in patients with digital ulcers, dcSSc and severe skin involvement.

PS311 COMPARISON OF MID UPPER ARM ANTHROPOMETRY TO BODY MASS INDEX IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Introduction: Patients with systemic sclerosis (SSc) may develop disease-related malnutrition. Mid upper arm anthropometry (MUAA), such as triceps skin-fold thickness (TSF) and mid-arm muscle circumference (MAMC), may be used for early detection of malnutrition in a variety of disease groups, but there is limited data on the role of these measures in conditions involving muscle and skin, such as SSc.

Objective: To evaluate the role of MUAA in a large cohort of patients with SSc.

Methods: Patients were studied in the outpatient department of a tertiary SSc centre. Demographics and disease characteristics were recorded. Weight, height, non-dominant mid arm circumference and TSF were measured, from which Body Mass Index (BMI) and MAMC were calculated. TSF and MAMC measurements <5th age and gender-specific centiles were identified.

Results: 168 patients (82% female, median age 61 (range 25-81)) were studied. 76% had limited cutaneous SSc. The remainder had diffuse cutaneous SSc. Median interval from SSc onset was 120 months (range 0-666 months). 34% were anti-centromere positive. 16% were anti-topoisomerase positive.
Median BMI was 23.7kg/m2 (range 15.6-39.8). 10% had a non-dominant MAMC <5th centile; 23% had a non-dominant TSF <5th centile. Notably, 11% of patients with a BMI >20 had a TSF <5th centile; by contrast, only a minority (2%) of these patients had a MAMC <5th centile (Table 1).

Conclusions: Our study demonstrates that many patients with SSc have a low BMI, highlighting their significant risk of malnutrition. However, MUAA, particularly TSF, as an indication of malnutrition, may be misleading in patients with SSc and should not be used in isolation. Additional studies are needed to assess patients to investigate if a change in BMI corresponds to a change in MUAA.

Table 1: MUAA results according to BMI group

BMI	<18.5	18.5-20.0	>20.0
all patients (n=168)	7% (n=12)	13% (n=22)	80% (n=134)
patients with MAMC <5th centile (16/168)	50% (6/12)	32% (7/22)	2% (3/134)
patients with TSF <5th centile (38/168)	92% (11/12)	55% (12/22)	11% (15/134)
patients with TSF and MAMC <5th centile (9/168)	50% (6/12)	9% (2/22)	1% (1/134)

PS312 OBESITY: A NEW ASPETC OF MALNUTRITION IN SYSTEMIC SCLEROSIS

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Objective. Systemic Sclerosis (SSc) is a rare connective tissue disease characterized by small vessel vasculopathy, autoantibody production and excessive collagen deposition in the skin and internal organs.
Denutrition is present in SSc patients from 15% to 56%, according to the diagnostic method; many factors may contribute to the development of nutritional impairment, including gastrointestinal involvement and psychobehavioral aspects.
The aim of this study is to evaluate the prevalance of malnutrition in a cohort of SSc patients and to identify sub-groups at elevated risk for disease progression.

Methods. 93 SSc patients were enrolled at Day Hospital of San Luigi Hospital (TO). Nutritional status was assessed by a combination of antropometric, biochemical parameters and specific scores as MUST (Malnutrition Universal Screening Tool), INA (Instant Nutritional Assessment), NRI (Nutritional Risk Index), MI (Maastricht Index). Food intake was assessed by a 24-h recall.

Results. Overall, BMI (Body Mass Index) ranked 10 patients (11%) as underweight and 44 (47%) as overweight/obese. These conditions were not associated to the main clinical characteristics.
The nutritional tools identified 18-60% of patients at high risk of malnutrition: 18% using MUST, 31% INA, 60% NRI, 39% MI. None of the score was associated to the main disease characteristics, gastrointestinal involvement included. Moreover, INA, NRI and MI ranked patients as malnourished and did not show significant differences in BMI values.
All the six patients affected by pulmonary hypertension were identified as malnourished, as the patients with ulcer by INA.
Biochemical parameters did not show any significant difference across the groups, except for haemoglobin and B 12 vitamin, despite being in normality range.

Conclusion. The risk of malnutrition in SSc is high-moderate, particularly evaluating this shape in its wider maining. It appears as not associated to disease activity, gastrointestinal involvement, psychobehavioral aspects or nutritional intake. Patients affected by ulcers or pulmonary hypertension could be at high risk, but further studies are needed to define this association.
Our results show that, contrary to what we thought, a high proportion of patients are obeses, according to BMI growth pattern of Italian population. Obesity increases the risk of cardiovascular disease in healthy subjects. SSc patients have an increased risk for cardiovascular disease, likely due to inflammatory and fibrotic mechanisms affecting the macrovasculature and microvasculature. Obesity, in this population, could be an aggravating element which worths to be corrected.

PS313 ASSESSMENT OF VALIDITY OF GASTROINTESTINAL MOTILITY PROCEDURES USED IN SYSTEMIC SCLEROSIS, BASED ON OMERACT CRITERIA

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Background: The gastrointestinal tract (GI) is involved in nearly all patients with systemic sclerosis (SSc) and causes significant morbidity and mortality. There is no single objective measure to assess the extent and severity of GI involvement in SSc patients. The evaluation of the morphology and motility and absorptive/ secretory functions of the GI tract by dedicated tests, provides a systematic approach to the assessment of GI involvement in SSC.
Objectives To assess the validity of the motility measures used to examine the GI tract in SSc, using the OMERACT criteria.
Methods: We performed a systematic literature search for published data on GI involvement in SSc, using the PubMed database for English-written articles and the Cochrane library from 1966 through the end of 2012. The keywords used were “systemic sclerosis” (SSc) and “scleroderma “and they were combined with text words such as esophagus, stomach, small bowel, colon, anorectal, dysmotility and procedures used for motility assessment (eg manometry,, scintigraphy, pH monitoring, breath test), randomized controlled studies (RCT), clinical studies. The articles were reviewed for additional references. Case reports or case series of less than 8 patients, articles with non separable data for SSc patients and reviews were excluded. The validity of the tests was evaluated according to the OMERACT principles.
Results: The search identified 427 titles or abstracts. Only 82 articles which answered the inclusion criteria and demonstrated at least one type of validation, were included. Of the 29 motility tests examined only 6 tests (esophageal manometry, esophageal scintigraphy, esophageal pH monitoring, stomach manometry, small bowel manometry and scintigraphy) are fully validated. Esophageal impendance, stomach EGG, lactulose breath test, large bowel scintigraphy and radio-opaque markers, anal ultrasound and anorectal manometry are partially validated.
Conclusions: Impaired GI motility is the hallmark of visceral involvement in SSC. Technologic advance lead to the introduction of new tests in GI motility with better spatial and temporal resolution. However only a minority of motility tests are partial or fully validated in SSc, conforming OMERACT principles. Proper validation in SSC of the modalities reviewed will provide valuable tools to improve our understanding of SSC and to be used as outcome measures in interventional studies.

PS314 ESOPHAGEAL ABNORMALITIES IN VERY EARLY SYSTEMIC SCLEROSIS. A CASE SERIES

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Introduction: The esophagus is affected in up to 90% of patients with systemic sclerosis (SS), and generates symptoms in half of them. Alterations of esophageal motility and lower esophageal sphincter hypotonicity trigger gastroesophageal reflux disease (GERD) that is more severe than in patients without SS, and has been related to lung disease.
Objective: To determine if esophageal abnormalities are present in patients with very early systemic sclerosis (VESS)
Methods: We retrospectively analyzed 17 patients with SS. Clinical features, high-resolution esophageal manometry (HREM), barium esophagram (BE), esophagogastroduodenoscopy (EGD), serum antibodies, pulmonary function tests and high-resolution CT scans (HRCT) were analyzed. Patients with VESS were analyzed separately and compared with patients with limited systemic sclerosis (LSS) and sine escleroderma systemic sclerosis. (SESS)
Results: Four patients with VESS were identified. All were asymptomatic and had normal EGD. Only 1 had evidence of gastroesophageal reflux on BE. However the HREM showed lower esophageal sphincter hypotonicity (HLES) in 3 of them (3/4), one of which also had weak peristaltic waves with large peristaltic defect (WPWLPD). HRCT showed no esophageal dilatation, air-fluid level or pulmonary infiltrates in this group.
Thirteen patients with SSL or SESS were identified, all of them had esophageal involvement and symptomatic GERD, that was evident on BE on 8/10 patients. EGD showed alterations in 9/12 and consisted on esophagitis in 8 cases and stenosis with Barret's esophagitis in the remaining one.
In SSL/SESS group 10/11 patients had alterations in the HREM, the abnormalities encompass HLES, HLES+WPWLP and more pronounced alterations like aperistalsis (AP) in 8 patients. In the HRTC, the esophagus were dilated in 12/13 cases and was evidence of fluid level in 6 cases. The prevalence of lung interstitial infiltrates were 11/13, 2 patients had nonspecific interstitial pneumonia; the remaining has no significant alterations in lung function tests.
Discussion: Comparing the VESS group with SSL/SESS group these patients seems to have asymptomatic esophageal involvement, and poorly evidence of alterations in UDE and BE. The HREM seems to be more adequate to detect early esophageal alterations. This group could not show structural alterations in the esophagus at the EGD and HRCT whereas in SSL/SESS are more prevalent clinical disease, evidence of esophageal motors dysfunctions and structural alterations.
Conclusion: Despite a small number of patients, the VESS group seems to have a subclinical esophageal involvement with an important prevalence of early esophageal motility disorders evidenced principally by HREM.

RESULTS

	VESS GROUP (N: 4)		LSS/SSSS (N:13)		P value	
	PATIENTS / N	%	PATIENTS / N	%		
Female	4/4		12/13		ns	1
Age (years)*	51 (43-59)		60 (28-73)		ns	0.776
Time of disease (years)*	1		9.5 (3.5-15.5)		0.006	
SYMPTOMS of GERD	0/4	0	13/13	100	<0.001	
GER ON BE	1/4	25	8/10	80	0.095	
ABNORMAL EGD	0/3	0	9/12	75	0.044	
ALTERED HREM	3/4	75	10/11	100	ns	0.267
ESOPHAGEAL DILATATION HRCT	0/4	0	12/13	92.3	0.002	
FLUID LEVEL IN ESOPHAGUS	0/4	0	6/13	46.1	ns	0.237
INTERSTITIAL LUNG INFILTRATES	0/4	0	11/13	84.6	0.006	

Fisher exact test for categorical variables and U-Mann Whitney for continuous variables.
*Mean (95% Confidence Interval)
GERD: gastroesophageal reflux disease
BE: barium esophagram
EGD: esophagogastroduodenoscopy
HREM: high-resolution esophageal manometry
HRCT: high-resolution CT scans

PS315 SMALL INTESTINAL BACTERIAL OVERGROWTH IN PATIENTS WITH SYSTEMIC SCLEROSIS, CLINICAL DATA RELEVANCE

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Background: Gastrointestinal involvement is frequent in systemic sclerosis (SSc), occurring in 75 to 90% of patients with diffuse or limited cutaneous SSc. Small bowel involvement in SSc occurs in 17 to 57% of patients. The intestinal migrating motor complexes are reduced or absent, predisposing to small intestinal bacterial overgrowth (SIBO). Malabsorption syndrome is related in SIBO. The aim of the study was to investigate frequency of SIBO in relevance with age, age of SSc onset, organ manifestation and disease classification.
Methods: 37 (9 man, age range 57-77 years, median 61 age) patients with SSc were examined. SSc pacients, according ACR criteria, underwent hydrogen breath testing. After 12 hours fasting end-expiratory air was collected by means of QUINTRON GaSampler two-bag system with T-valve (Quintron Instrument Company, Milwaukee, WI, USA). After collection of baseline sample, patient ingested substrate (75g of glucose of 10g of lactulose) and subsequent samples were collected in 20 minutes intervals for a total of 4 hours. Breath samples were analyzed by special gas chromatograph QUINTRON Microlyzer DP Plus (Quintron Instrument Company, Milwaukee, WI, USA). Subtype and severity of scleroderma involvement, actual medication, TLCO, echocardiography, weight loss were recorded.
Results: 14 (37,8%) patients have positive SIBO test. Patients with SIBO had higher age p=0,037, time of first SSc symptom (p=0,05) using T-test. There was no significant difference between the scleroderma type, frequency of pulmonary arterial hypertension, digital ulcers, Rodnan skin score. Patients with SIBO had a significantly hight frequency of TLCO decrease (p=0,005).
Conclusion: The SIBO is frequent finding in SSc. The results of this study suggest that SIBO in SSc patients is associated with age, disesase duration and interstitial lung disease. These findings should be of interest to clinician and investigator alike.

PS316 SYSTEMATIC EVALUATION OF ESOPHAGEAL AND ANORECTAL DAMAGE IN SYSTEMIC SCLEROSIS : PRELIMINARY RESULTS

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Introduction: Esophageal and anorectal damages are common in scleroderma and are often associated. Since 2008, Health French High Authority made recommendations and suggested the creation of functional tests based on symptoms (1). However, in clinical practice, it seems that if the esophageal examination is regularly prescribed, anorectal evaluation is rarely offered. In the literature, when lower gastro-intestinal abnormalities is documented, an esophageal concomitant disease is always described (2, 3). Nevertheless, this involvement was often unrecognized and unexplored so that early detection of anorectal disorders in these patients could prevent the occurrence of pelvic floor disorders and disabling symptoms. The main purpose of our study is to systematically detect esophageal and anorectal damage in scleroderma by high resolution esophageal manometry (MOHR) and anorectal high resolution three-dimensional manometry (MHR3D).
Patients and Methods: All patients followed for systemic scleroderma or CREST syndrome in one department of internal medicine of the University Hospital of Marseille were included. Symptomatic and quality of life self-administering questionnaires have been given to patients. Two questionnaires are interested in upper gastrointestinal symptoms: dysphagia (DYMUS) and reflux (REQUEST), two in the lower gastrointestinal symptoms: constipation (KESS) and anal incontinence (Wexner); the latter is an overall quality of life questionnaire(SF-36). All patients underwent the same day the various examinations: MOHR , MHR3D and endo -anal ultrasound, and autoimmune serological profile was also studied.
Results: To date, 17 patients (15 women), mean age 51 years were evaluated and the mean follow-up of patients from diagnosis of the disease was 7 years . Five showed a diffuse scleroderma and 10 a limited damage (CREST syndrome). Combined high and low manometric dysfunction was found in 6 patients : 5 with symptoms of both high (4 Gastroesophageal reflux disease (GERD) and dysphagia, only one GERD) and low (3 constipation and incontinence,1 incontinence alone, 1 constipation alone) and 1 asymptomatic patient. Quality of life (physical and mental) of 2 symptomatic patients was impaired. An isolated esophageal manometric dysfunction was found in 4 patients with 3 symptomatic (1 GERD and dysphagia, 2 GERD only). Of these 3 patients, two reported an alteration of the overall quality of life.On immunological results, 4 patients had anti-Scl 70 and 13 patients anti-centromere B positive profile.
Conclusion: These preliminary results confirm that the anorectal disease appears closely linked to oesophageal involvement. Its screening, as for the esophageal damage, appears necessary to limit the occurrence of disabling symptoms such as fecal incontinence.

PS317 TRANSLATION, CROSS-CULTURAL ADAPTATION, AND VALIDATION OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES SCLERODERMA CLINICAL TRIAL CONSORTIUM GASTROINTESTINAL TRACT INSTRUMENT 2.0 INTO THE DUTCH LANGUAGE

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Objective: To translate and adapt the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument 2.0 (UCLA SCTC GIT 2.0) into Dutch and validate it among Dutch systemic sclerosis (SSc) patients.
Methods: First, the UCLA SCTC GIT 2.0 questionnaire was translated and adapted according to international guidelines. The resulting Dutch GIT 2.0 was, in combination with the SSc Health Assessment Questionnaire (SHAQ) and Short Form-36 (SF-36) administered to SSc patients participating in a standardized medical assessment. Moreover, all previous clinical examinations and confirmed medical diagnoses related to GIT were extracted from the medical records. Internal consistency was determined by calculating Cronbach's alpha. To determine the reliability, the questionnaire was re-administered with an interval of two weeks to a subgroup of patients and the intraclass-correlation coefficient (ICC) was computed. Spearman correlation coefficients between GIT scores, SF-36 and SHAQ were computed. GIT scores were compared among patients with and without previous gastrointestinal examinations and/or diagnoses.
Results: Eighty-nine patients with a mean age of 53.6 (SD 12) years, and predominantly female (76%) were included. The median total GIT score was 0.17 (Cronbach's alpha 0.921). The test-retest reliability of the total GIT score was good (n=27; ICC 0.749). Overall, the GIT total scores correlated significantly with the SHAQ visual analogue scale intestinal complaints and the SF-36. Significant differences between GIT total and subscale scores of patients with and without previous gastrointestinal examinations and diagnoses were present.
Conclusion: The Dutch GIT 2.0 questionnaire showed good internal consistency, construct validity and test-retest reliability.

PS318 GIT MANIFESTATIONS OF SYSTEMIC SCLEROSIS AS THE MOST FREQUENT. IS IT THE MOST IRRITANT TOO?

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Introduction: Gastrointestinal (GIT) manifestation of scleroderma (SSc) is a common complication, with major impact on quality of life and morbidity, (UCLA) Scleroderma Clinical Trial Consortium GI Tract Instrument (UCLA SCTC GITI) was developed to measure gastrointestinal tract disease in (SSc).

Patients and METHODS: twenty eight patients of (SSc) recruited from two rheumatology clinics in Sohag and Assiut university hospitals, all patients completed UCLA SCTC GITI, a self-administered questionnaire with 7 scales and an overall score. An evaluation of gastro-esophageal reflux diseases (GERD) has been done by barium swallow, upper endoscopy and esophageal manometry.

Results: 20 female and 8 male patients, with mean disease duration 9.3 years, mean age 46 years, 19 patients were dcSSc, and 9 patients were lcSSc, Mean questionnaire scores showed that patients have a wide range of GI symptoms, 85.7% of patients reported upper and 75% lower GI symptoms, and 3.57 % of patients reported no symptoms. There was no association between disease subtype and GI symptoms.

With reclassification of the patients' symptoms under the UCLA SCTC GITI to "Non- to- Mild", "Moderate" and "Severe-to- Very severe", 78.6 % were reported as severe to very severe category, 14% were mild, while 7% were non to mild symptoms, these reports showed positive correlation with the barium swallow and upper endoscopy.

Conclusion: the frequency of GIT symptoms in SSc patients whether upper or lower is high . UCLA SCTC GITI focused questionnaire is an effective way to assess not only gut symptoms but also severity of the gut involvement.

PS319 CHARACTERIZATION OF SYSTEMIC SCLEROSIS PATIENTS FOLLOWED IN A SYSTEMIC IMMUNE MEDIATED DISEASES CLINIC - 4 YEAR RETROSPECTIVE ANALYSIS

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Background: Systemic sclerosis (SSc) is a rare autoimmune disease, characterized by fibrosis of skin and internal organs and obliterative vasculopathy.
Aim: to characterize patients with SSc in a systemic immune mediated diseases clinic.
Methods: retrospective analysis of patients with SSc, followed in our clinic, between June 2009 and November 2013.
Results: forty patients were identified (37 female, 3 male), mean age of 52 (±15) years. The mean disease duration was 10 (±11) years, and the mean age of Raynaud's Phenomenon (RP) beginning was 43 (±23) years. 9 patients had diffuse SSc, 9 limited SSc, 9 mixed connective tissue disease (MCTD), 8 overlap syndrome, 3 very early SSc, 1 SSc sine scleroderma and 1 CREST syndrome. 87% fulfilled the ACR/EULAR 2013 criteria. 92.5% were ANA positive, 35% anti-centromere positive, 25.7% anti-U1-RNP positive and 20.6% anti-Scl70 positive. RP was the first clinical manifestation in 65% of the patients, followed by polyarthritis in 25%. Peripheral vascular involvement was frequent: 82.5% with RP, 37.5% with digital ulcers (DU) - active DU in 1 patient. Nailfold capillaroscopy revealed an early pattern in 26% of the patients, an active pattern in 50% and a late pattern in 24% (patients with a late pattern had a prolonged mean disease and RP duration compared to the early pattern). Cutaneous involvement was limited in 42.5% and diffuse in 25%. Gastrointestinal involvement was frequent with 57.5% of the patients with oesophageal dysmotility. 45% had interstitial lung disease (ILD) on high resolution thoracic scan (67% usual interstitial pneumonia pattern and 33% non-specific interstitial pneumonia pattern). 35% had a decrease in diffusing capacity of carbon monoxide, in lung function tests. According to the scoring system proposed by Wells for evaluation of ILD in SSC, 67% had a limited disease and 33% an extensive disease. 17% had pulmonary hypertension (evaluated by pulmonary artery pressure on echocardiogram), 50% of them with MCTD. 2 patients had scleroderma renal crisis. The preferred immunosupressor strategies were cyclophosphamide (30%), methotrexate (23%), azathioprine (20%) and biologics (13% - 3 tocilizumab, 2 rituximab). The most used vasodilator therapies were calcium channel blockers (34%), endothelin receptors antagonists (20%) and prostacyclin analogs (15%).
Conclusions: our patients had a high prevalence of vascular involvement and ILD, which explains the high percentage of treatment with cyclophosphamide and endothelin receptors antagonists. Both capillaroscopy and Wells scoring system for ILD in SSc were useful for a better characterization of the disease. We also highlight the significant percentage of patients under biologic therapeutics.

PS320 CHARACTERIZATION OF INTERSTITIAL LUNG DISEASE IN A COHORT OF SYSTEMIC SCLEROSIS PATIENTS - 4 YEAR FOLLOW-UP DATA

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BACKGROUND: Interstitial lung disease (ILD) is a frequent manifestation of systemic sclerosis (SSc), associated with significant morbidity and mortality. Its evaluation in clinical practice, whether defining its presence or ascertaining its severity, is still not standardized.
OBJECTIVES: To characterize interstitial lung disease in SSc patients.
METHODS: SSc patients with interstitial lung disease followed in our clinic for a 4 year period of time were retrospectively analyzed.
RESULTS: 40 subjects were included, with mean age of 53±16 years and mean duration of disease since first manifestation of SSc of 9,1±10,3 years. Of these, 9 had mixed connective tissue disease (MCTD) and 8 had an overlap syndrome. 18 (45%) had ILD by lung CT scan (LCT), 6 (33%) with usual interstitial pneumonia pattern (UIP) and 12 (67%) with non-specific interstitial pneumonia pattern (NSIP). Pulmonary function tests (PFT) revealed changes in lung volumes and CO diffusion in 4 (22%) and 10 (56%) respectively. Using the validated semi-quantitative evaluation of lung involvement by LCT described by Wells, et al, 12 (67%) subjects had limited disease, and 6 (33%) had extensive disease. The NSIP pattern in LCT was associated with more limited disease (75%) than the UIP (50%). Interestingly, although MCTD patients had a greater prevalence of ILD (67%) when compared to SSc (35%), they had more limited disease (83% vs. 62%) and a greater proportion had NSIP (67% vs. 50%). Patient subgroups based on autoantibodies patterns did not differ from the overall ILD prevalence, with the exception of anti-centromere (ILD in 10%). There were no differences in the mean disease duration between those with and without ILD, neither between those with limited and extensive disease.
CONCLUSIONS: In this cohort, there was a relevant proportion of patients with ILD and no changes in lung volumes on PFT. In order to rigorously evaluate lung involvement, semi-quantitative methods, such as the one used, are practical and effective. NSIP pattern in LCT seems to be associated with a less extensive disease and to MCTD. Mean duration of disease does not seem to be associated with ILD or its severity.

PS321 THE TYROSINE KINASE INHIBITOR DASATINIB EFFICIENTLY BLOCKS PDGF-INDUCED ORBITAL FIBROBLAST ACTIVATION: A POTENTIAL NOVEL THERAPEUTIC AGENT IN FIBROTIC DISEASE?

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Fibrosis is a leading cause of morbidity and mortality in the Western World. The hallmark of fibrosis is abnormal and exaggerated fibroblast proliferation and deposition of extracellular matrix components. In Graves' disease (GD), autoantibodies directed against the thyroid stimulating hormone receptor activate the thyroid gland, resulting in hyperthyroidism. The orbital tissues are frequently affected in GD, referred to as Graves' Orbitopathy (GO). Excessive orbital fibroblast activity, driven by locally produced platelet-derived growth factor (PDGF), plays a central role in GO which is similar to fibrotic diseases involving other organ systems such as idiopathic pulmonary fibrosis and systemic sclerosis. So far, treatment options are limited. The effects of small-molecule tyrosine kinase inhibitors (TKIs) imatinib mesylate and nilotinib to block aberrant tyrosine kinase activity in in vitro and animal models have been explored by researchers including ourselves. However, results were variable and these compounds are associated with adverse effects like peri-orbital edema and peripheral artery occlusion. The second-generation TKI dasatinib displays a higher pIC50 for the PDGF-receptor and ABL tyrosine kinases and may therefore be a more promising compound. The aim of this study is to compare the prophylactic and therapeutic effect of imatinib mesylate and dasatinib on PDGF-BB-induced proliferation, hyaluronan, IL-6, IL-8 and CCL2 production by orbital fibroblasts. Orbital fibroblasts were obtained from orbital tissue of four GO patients and five healthy controls. Prophylactic effect was evaluated by overnight pre-incubation with TKI before PDGF-BB (50 ng/ml) stimulation for 24 hours, while TKI was added together with PDGF-BB for estimation of therapeutic effects. Proliferation was assessed by colorimetric assay, and hyaluronan and cytokine production were measured by ELISA. Dasatinib dose-dependently inhibited PDGF-BB-induced orbital fibroblast proliferation, hyaluronan, and cytokine production much more efficiently than imatinib mesylate in the prophylactic setting, reaching statistical significance from a concentration of 0.04 µg/ml. Under therapeutic conditions, lowest concentration dasatinib tested (0.04 µg/ml) inhibited PDGF-BB-induced orbital fibroblast activation as efficient as in the prophylactic condition, with the exception of IL-8 production that was only reduced at the higher dasatinib concentration (2.5 µg/ml). Imatinib mesylates was less efficient than dasatinib and was unable to block fibroblast activation at a concentration of 0.04 µg/ml. The strong anti-fibrotic effects of dasatinib in our study may provide a basis for its introduction in treatment of GO and its clinical implications may be extended to other fibrotic diseases as well. Further clinical studies are warranted to evaluate its potential clinical effects.

PS322 UPDATE ON THE JUVENILE SYSTEMIC SCLEROSIS INCEPTION COHORT. WWW.JUVENILESCLERODERMA.COM

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Background: Juvenile systemic sclerosis (jSSc) is a orphan autoimmune disease. Currently just retrospective data is existing without a standardized assessment of the organ involvement. Our project is the first projects, where prospectively and with a standardized assessment data of early jSSc patients are collected.
Objectives: to learn about the evolvement of juvenile systemic sclerosis
Methods: Patients with less the 18 months of disease duration, after the first Non-Raynaud symptomatic, are prospectively assessed, using the proposed standardized patient assessment protocol.
Results: 45 centers from 24 countries applied to participate on the project. The assent and consent forms were translated into the local native languages (9). We report the characteristics of the patients at the entry to the cohort. Up till now 23 patients were enrolled, the mean follow up of the patients in the cohort are 3.2 years. Seventeen of the 23 patients were female. The mean age of the onset of Raynaud symptomatic was 11.1 years, the youngest 4.2 years old. The mean age at the onset of the non-Raynaud symptomatic were 11.6 years. 15 of the 22 have diffuse subtype, 5 of them have an overlap symptomatic. At the time of the inclusion the mean modified Rodnan Skin Score was 19.9. ANA positive were 19, and 6 of them were anti-Scl 70 positive. None of them was anticentromere positive. 19 of them have Raynaud´s, 15 of them have capillary changes and 7 of them already ulcerations.12 of them have cardiopulmonary involvement, 10 of them have interstitial lung disease. Two of them have renal involvement. Eight of them have gastrointestinal involvement, and 5 of them oesophageal involvement. Nineteen of them have musculoskeletal involvement.
Conclusion: We present the data on the first 23 prospectively assessed patients with jSSc. The current recruitment data confirms that pediatric patients are different from the adult patients. We are only at the first phase of this project and hope to recruit up to 50 patients and follow them prospectively over the next 5 years at least.

PS323 SYSTEMIC SCLEROSIS IN OVERLAP WITH RHEUMATOID ARTHRITIS: A RATHER FREQUENT ASSOCIATION IN SCLERODERMA PATIENTS

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Background: Patients with systemic sclerosis (SSc) may sometimes simultaneously have consistent disease features of another connective tissue disease (CTD). These patiens may represent disease subsets with distinct prognosis and management options. Musculoskeletal symptoms are a common complaint in ScS patients and the existence of a SSc overlap with rheumatoid arthritis (RA) has been cited in the literature.
Objective: We aimed to define in a cross-sectional study the clinical particularities of patients with SSc who also satisfy classification criteria for RA.
Methods: In a single-center cohort of patients with SSc, as defined by the 1980 ACR classification criteria, we selected the subjects who also satisfied the 1988 ACR classification criteria for RA and compared these overlap patients with the ones having pure SSc (SSc patients who satisfied classification criteria for myositis, systemic lupus and mixed connective tissue disease have been excluded from the analysis).
Results: Among 122 consecutive patients satisfying the 1980 ACR classification criteria or SSc we identified 11 subjects (9%) also satisfying the 1988 ACR classification criteria for rheumatoid arthritis (SSc-RA overlap patients). Five SSc patients satisfied classification criteria for CTDs other than RA and Sjogren's syndrome and have thus been excluded from the SSc control group.
Compared to the 106 SSc control patients, the 11 SSc-RA overlap patients had less skin involvement as assessed by the modified Rodnan skin score (4,2±6,3 vs. 11,4±8,9 in controls), greater musculoskeletal involvement including higher tender and swollen joint counts, and more severe hand involvement as shown by higher finger contracture counts (9.3±8,5 vs. 5.3±6.4) and higher finger-to-palm distance on maximal finger flexion (28±23 mm vs. 13±15 mm), all $p<0.01$ by Mann-Whitney U test. There was a tendency towards lower prevalence of the SSc difuse cutaneous subset and less peripheral vascular involvement (telagiectasiae, digital ulcers, digital scars) in SSc-RA overlap patients vs. SSc patients, without reaching statistical significance. Demographic data, interstitial lung disease and SSc-associated GI involvement were similar between groups. Methotrexate treatment was significantly more frequent in SSc-RA patients (54.5% vs. 5.7%, $p<0.001$ by Fisher's exact test).
Conclusion: Patients with SSc-RA overlap may have milder skin fibrosis, less vascular involvement but more severe hand musculoskeletal damage than patients with SSc who do not satisfy RA classification criteria. These findings should be confirmed on a larger SSc cohort.

PS324 EVOLUTION OF SYSTEMIC SCLEROSIS OVERLAP SYNDROME

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Objective: To study evolution and outcome of SSc-RA and SSc-PM/DM.
Material and methods: There were 100 pts SSc overlap syndrome: 68 SSc-PM/DM and 32 SSc-RA (17 male, 83 females; mean age 45±14,4; disease duration 7 [2-10] years; follow-up 10 years).
Results: 71 % pts has had SSc-PM/DM and SSc-RA within the first three years of disease and in 40% of them during the 1st year after onset. The first symptoms of pts were Rainaud's syndrome, edema hands, arthralgia and rare isolated joint and musculskeletal involvement (7% and 2%). All pts were treated corticosteroids and 74% of them received cytotoxic (methotrexate 48%; cyclophosphamide 10%; azathioprine 5%), hydroxychloroquine 11%, D-penicillamine 7%.
Identified two variants of evolution: I- favorable 79%; II unfavorable 21% (includ deaths (10%)). The favorable evolution was observed in pts with onset before 40 years, the relative stabilization of the process - from the onset of the disease before the age of 25 years, an unfavorable outcome - in pts with age of onset of the disease for more than 40 years, where pts SSc-PM/DM prevailed.
The peripheral symptoms SSc-RA has not progressed for 10 years and has decreased: skin induration (lSSc/dSSc 97%/3% and 100%/0%), hyperpigmentation (34% and 9%), flexion contractures (81% and 72%), arthritis (100% and 78%), rheumatoid nodules disappeared. Rainaud's syndrome was less expressed. Howere clinical features SSc increased: telangiectasias (37,5% and 47%), calcinosis (31% and 47%), osteolysis (25% and 28%), conduction blocks(53% and 56%) and arrhythmia (9% and 19%), interstitial lung disease (9% and 19%), esophageal involvement (66% and 69%). Decrease of ESR was observed in 1/3 of pts.
The SSc-PM/DM pts has decreased skin induration (lSSc/dSSc 68%/32% and 100%/0%), hyperpigmentation (27% and 18%), skin symptoms of DM (44% and 7%), joint involvement (56% and 15%) for 10 years. PM was in remission in all patients. Rainaud's syndrome progressed with the development mainly scars (18% and 37%), increased telangiectasias (50% and 59%), calcinosis (32% and 56%), osteolysis (23,5% and 26%), conduction blocks(53% and 57%) and arrhythmia (15% and 18%), interstitial lung disease (12% and 15%), esophageal involvement (78% and 88%). Decrease of ESR was observed in 2/3 of pts.
Conclusion: Adverse prognostic factors of SSc overlap syndrome: age of onset after 40 years, rapidly progressive acute with generalization of the process and features of the PM in the first year of the disease, late diagnosis of the disease and inadequate therapy

PS325 ASSOCIATION BETWEEN SYSTEMIC SCLEROSIS AND SJÖGREN'S SYNDROME

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Background: Systemic Sclerosis (SSc) is an autoimmune disease characterized by vasculopathy, inflammation, and fibrosis that can lead to loss of organ function. It is frequently associated to other autoimmune disease. This present report aims to describe the clinical presentation, immunological features and outcome of patients with the association SSc and Sjögren's syndrome (SS).
Patients and methods: We retrospectively investigated 102 patients with SSc and 133 patients with SS hospitalized in our internal medicine department from 2000 to 2012. All patients fulfilled ACR criteria for SSc and the Americano-European Consensus Group criteria for SS. Only patients with the 2 diagnoses were included. Demographic, clinical and serologic characteristics were analyzed.
Results: We identified 15 women with SSc and SS. The mean age of onset of SSc and SS was respectively 53.6 years (range:29-74) and 54 years (range:29-74). Diagnosis of SSc was prior to SS in 8 cases (53.3%), they were concomitant in 4 patients. Thirteen patients were classified as diffuse SSc and 2 others as limited SSc. All patients had sicca syndrome (xerophthalmia et xerostomia). Grade 3 or 4 sialoadenitis was detected in all patients. Raynaud's phenomenon was constant and giant capillaries were noted in 9 patients. Only 3 patients had digital ulcers. Rheumatologic involvements were as follows: arthralgia (n=11), arthritis (n=1), calcinosis (n=1). Electromyogram showed myositis in 3 patients and peripheral neuropathy in 3 others. Interstitial lung disease was found in 8 patients with a decreased forced vital capacity in 5 of them. Cardiac ultrasonography showed pulmonary arterial hypertension in 2 patients and pericardial effusion in 1 case. All patients were positive for AAN [ACA (n=7), Scl70 (n=4), SSA (n=6), SSB (n=3), RNP(n=4) and Sm (n=2)]. Other autoimmune diseases were found in 3 different cases: dermatomyositis, grave's syndrome and primary biliary cirrhosis. Treatment consisted of calcic blockers in 14 patients, corticosteroids in 7 and other immunosuppressive agents in 10. Mean follow up period was 70 months. The outcome was favorable in 7 cases; while we noted stabilization in 4 and impairment in 2. Two patients were lost to follow-up.
Conclusion: SSc and SS are connective tissue disorders with different pathogenetic mechanisms. However, they have several common manifestations, particularly sicca syndrome, rheumatologic involvement, interstitial lung disease and Raynaud's phenomenon. In our report, the association does not seem to impair SSc's clinical course. Similar results have been reported in other studies.

PS326 SJOGRENS SYNDROME IN SYSTEMIC SCLEROSIS

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Background: The clinical manifestations of systemic sclerosis are very divers both in the amount and in the clinical signs and symptoms. The clinical prognosis and the quality of patients' life with systemic sclerosis depend mostly on the possession of Sjogrens syndrome. The majority of the scientist who studied the problem with the Sjogrens syndrome in the patients with systemic sclerosis emphasizes the high level of difficulty of prognosis for this syndrome.
Objectives: tracking the factors that contribute to the development of Sjogrens syndrome in the patients with systemic sclerosis.
Materials and methods: 150 patients with systemic sclerosis where examined, of which only 6 were males. The average age of the subjects included in the examination was 42.3 ages. The average duration of the disease – 13.6 ages. 121 (80.7%) from the patients manifested SS in a limited form while 29 (19.3%) had the diffuse form of the disease. The diagnosis of Sjogrens syndrome was established according to the diagnostic criteria of SICCA (Sjogren's International Collaborative Clinical Alliance), proposed in 2012. The clinical dates of the patients within the examination were analysed according to the static discriminatory analysis.
Results: Sjogrens syndrome was diagnosed in 28 (18.6%) of the examined patients, of which 20 (71.4%) with a limited form of the disease and 8 (28.6%) with the diffuse one. Sjogrens syndrome's development was noticed in average at 11.7± 1.2 years from the onset of the disease. Using the static discriminatory analysis, the following factors proved the influence on the development of the Sjogrens syndrome in the patients with systemic sclerosis: the length of the disease of more than 10 years, arthralgia and arthritis in the clinical manifestations of the disease, the presence of interstitial lung disease, the presence of the rheumatoid factor in the blood, a high activity of the base disease (EUSTAR scale (EULAR Scleroderma Trials and Research Group) higher than 3). Using the same factors the development of the Sjogrens syndrome can be predicted in the patients with systemic sclerosis with an accuracy of 78.2%, and with its absence – 71.6%.
Conclusion: The presence of some factors in the patients with systemic sclerosis can predict the development of the Sjogrens syndrome with an accuracy of 78.2%, namely the length of the disease of more than 10 years, arthralgia and arthritis in the clinical manifestations of the disease, the presence of interstitial lung disease, the presence of the rheumatoid factor in the blood, a high activity of the base disease.

PS327 EFFECT OF AMBRISENTAN ON DIGITAL ULCERS IN SYSTEMIC SCLEROSIS: A CASE REPORT

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In May 2011 a 72 year old man with Systemic sclerosis (SSc) complicated by pulmonary artery hypertension (PAH) and DUs (digital ulcers) came to our observation complaining of dyspnea on exertion. His medical history included Raynaud's phenomenon (RP) diagnosed in 1988, a definitive diagnosis of SSc in 2002, followed by occurrence DUs on the first, second and third digits of the left foot. He already failed therapy with bosentan (62.5 mg twice daily for the first month, followed by 125 mg twice daily) for marked elevation of hepatic transaminases and with intravenous iloprost (at maximum tolerated dose once monthly) for absence of DUs healing. During this hospitalization the patient underwent diagnostic work-up for PAH, with evidence of severe pulmonary hypertension at right heart catheterization, with a negative vasoreactivity test performed by intavenous epoprostenol. He was in WHO class III, and began therapy with warfarin and ambrisentan 5 mg daily, on-label for PAH associated with connective tissue diseases such as systemic sclerosis. After only 3 months of ambrisentan therapy we observed complete healing of DUs (Fig. 1 DUs before (a), at 1 month (b) and 2 months (c) after starting ambrisentan). Oral endothelin receptor blockers are a second-line therapy in the treatment of SSc-related DUs; this treatment is able to prevent new DUs and the only randomized clinical trial is limited to bosentan. Ambrisentan, a selective blocker of the ETA receptor, has proven to be effective in SSc-PAH. Preliminary data from a prospective open label, single centre study enrolling 20 patients with DU secondary to SSc treated with ambrisentan revealed the efficacy of this drug on the healing of DUs. A recent study on six SSc patients with DUs and without PAH suggested that ambrisentan might be useful in the treatment of DUs in the case of previous failure of bosentan therapy. There is also a case report concerning the use of selective ETA receptor antagonist sitaxentan for the treatment of DU, with a complete healing after four months. These data could explain the class-effect mechanism of ETA receptor antagonist drugs. Currently, ambrisentan is an off-label drug for the treatment of DU, but it may be considered an alternative to bosentan, at least in cases of adverse effects. However, there is a need for randomized, double-blind, placebo-controlled trials to further evaluate the efficacy of ambrisentan in the prevention and treatment of DU.

PS328 IMPROVEMENT OF PULMONARY FUNCTION IN A PATIENT WITH INTERSTITIAL LUNG DISEASE SECONDARY TO SYSTEMIC SCLEROSIS AFTER TREATMENT WITH TOCILIZUMAB

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Background: Systemic sclerosis (SSc) is a connective tissute disease characterized by activation of the immune system, vasculopathy and deposition of collagen and extracellular matrix in the skin and internal organs. Interleukin-6 (IL-6), has a major impact on immune regulation, haematopoiesis and inflammation. Increased levels of IL-6 have been described in sera from SSc patients, correlating with the extent of skin involvement; moreover, serum IL-6 levels appear to be predictive of early disease progression in patients with mild interstitial lung disease (ILD).
Methods: We report the case of a patient with a diagnosis of diffuse cutaneous SSc (dcSSc) anti-Topoisomerase I positive, with ILD as assessed by high resolution computed tomography (HRCT) and hypermetabolic pulmonary lesions on PET-CT, previously treated with oral cyclophosphamide (CYC) 2 mg/kg/day plus medium dose of steroid (0.3-0.5 mg/kg/day of prednisone) for 12 months with no avail. CYC was deemed ineffective due to progressive deterioration of the forced vital capacity (FVC, from 55% to 47% of predicted) and of the diffusing capacity for carbon monoxide (DLco, from 31% to 23%) and persistence of inflammatory area at the PET scan.
Due to concurrent arthritis with DAS28 ESR > 3.2 patient was given tocilizumab (TCZ) 8 mg/kg monthly intravenous infusion plus ongoing steroids (prednisone 12.5 mg/die). After 6 months of therapy with TCZ we observed a complete remission of articular symptoms with a DAS28 ESR < 2.6; prednisone was then gradually tapered to 5 mg/die. Pulmonary function tests improved with FVC that rose to 70% of the predicted values and DLco that rose to 35% of the predicted values; PET scans also normalized with complete regression of the inflammatory areas.
Conclusion: The case we present suggests that IL-6 blockade may be beneficial in selected SSc patients with ILD unresponsive to conventional therapy with CYC. Further studies are needed to better assess who may benefit from this therapeutic option and/or to define its role in larger cases series.

PS329 CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME AND SYSTEMIC SCLEROSIS- A RARE ASSOCIATION

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Introduction: Antiphospholipid antibodies (aPL) are commonly found in patients with scleroderma but the typical clinical manifestations of antiphospholipid syndrome are not frequently seen in these patients. Catastrophic antiphospholipid syndrome (CAPS) is a rare form of antiphospholipid syndrome resulting in multiorgan failure with a high mortality rate. In the majority of the cases the trigger factors remain unknown and sometimes CAPS occurs in patients without any previous thrombotic history.
Case report: A 32-year-old woman diagnosed with diffuse systemic sclerosis in 2010 was admitted to the hospital with a 4-days history of dry cough, subfebrile status and dyspnoea on exertion. Because of the severe skin involvement, with poor response at Methotrexate therapy, three months previously she was started on Cyclophosphamide (600mg monthly). She had no pulmonary or renal involvement but cardiac MRI revealed minimal fibrosis with normal ejection fraction. On admission she had low grade fever 37,3 ºC, WBC was 11000/ul, ESR and CRP were normal, muscle enzymes (CPK, LDH) and procalcitonin were slightly elevated. Upon admittion she had reduced ejection fraction (40%) on echocardiography, pleural and pericardial effusion on X-Ray. In the following days her status worsened, with reduction of ejection fraction to 15% and elevation of pro-BNP. Cardiac MRI showed an increase of fibrotic lesions, left apical thrombus and no signs of myocarditis. Because she developed three episodes of ventricular fibrillation, a subcutaneous implantable cardioverter-defibrillator was implanted. She also developed severe thrombocytopenia, hemolytic anemia, acute renal failure in the presence of positive aPL and aaCL(high titer).CAPS was diagnosed. She was treated with plasmapheresis, dialysis, corticosteroids, intravenous gamma globulins. This regimen proved to be ineffective and patient died of multiple organ failure.
Conclusion: Apart from diagnostic difficulties, we decided to present this case because there is relative sparse data pertaining to this complication in the course of scleroderma. Although this patient was under careful clinical supervision and received intense treatment her status rapidly deteriorated.

PS330 SYSTEMIC SCLEROSIS WITH SYSTEMIC LYMPHADENOPATHY COMPLICATED BY ADENOCARCINOMA PROSTATE AND TUBERCULOSIS

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Systemic sclerosis (SSC) is an autoimmune disease which involves internal organs. Limphadenopathy is often observed in different connective tissue diseases. In SSC limphadenopathy often coexists with interstitial lung disease (ILD). We present a case report of a patient with the diagnosis of overlap syndrome: polymiositis and SSC. When he was 53 years old the diagnosis of SSC was established. He presented Raynaud's phenomenon, sclerodactylia, ulcers of the fingers and Scl70 antibodies. The HRCT revealed enlargement of the mediastinal lymph nodes, without coexisting ILD. Other tests confirmed generalized limphadenopathy. Bronchoscopy, bronchoalveolar lavage (BAL), endobronchial ultrasound (EBUS) biopsy of mediastinal lymph nodes, microbiological tests, cytological study were undertaken to exclude tuberculosis and neoplasm. Immunosuppressive treatment was administered. One year later prostatic cancer was diagnosed and one month after finishing radical radiotherapy the symptoms of active infiltrative tuberculosis appeared.

PS331 SUCCESSFUL TREATMENT OF MEDICALLY REFRACTORY SCLERODERMA DIGITAL GANGRENE WITH LONGTERM CONTINUOUS BRACHIAL PLEXUS BLOCK

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Introduction: Raynaud Phenomenon (RP) is the earliest and most common clinical manifestation of scleroderma, occurring in 90 to 98% of patients. A combination of sympathetically mediated vasospasm and vasoocclusive disease has been implicated in the etiology of digital ischemic phenomenon and treatment of RP is directed towards relieving vasospasm and restoring blood flow. Thoracoscopic symapthectomy and digital sympathectomy would be a limited treatment option because of a recurrent ulcer , delayed wound healing and development of complex regional pain syndrome . An alternative less invasive treatment for blocking the sympathetic outflow would be a sympathetic block with local anesthetics.Case Report :We report a case of 75 years old woman affected by diffuse systemic sclerosis and digital ulcers refractory to medical therapy. She came to our observation complaining persistent left sided RP with severe ischemic pain (VAS 9 -10) and rapidly evolving digital ulcers onto 2°, 3° and 4° finger o f left hand. The angiogram was performed and revealed a distal ulnary obstructive lesions, radial segmental occlusion with reperfusion of the arch handheld by interosseossus artery , narrowing of multiple digital arteries.Medical therapy (iloprost, low molecular weight heparin, opioid) was started without benefit. Methods: A diagnostic single shot axillary brachial plexus block with ropivacaine 0.375 30 ml was performed; the block showed immediate effectiveness with pain disappearance (VAS 0) for 12 hours; the left hand also regained temperature and perfusion and return of interdigital flow revealed with continuous waves Doppler.We decided to perform a continous brachial plexus block. Infusion was started with Ropivacaine 0.2% 5 ml/hr and then reduced to 0.15% because of persistent and limitating motor block; at week 4 after block despite complete regression of algic symptoms (VAS 0), ischemia and termic gradient between right and left hand persisted. So a series of 4, weekly, stellate ganglion blocks were performed and continous infusion of local anesthetic was continued with bupivacaine 0.125%. Results: We observed a demarcation of digital necrosis and the amputation of the distal phalanges of 3° and 4° finger was performed at week 9 after positioning. Continous infusion of Bupivacaine was continued allowing wound dressing and healing. On week 18 healing process improves and pain absent (VAS 0). Conclusion: Continuous longterm brachial plexus block can provide a significant effect on improving blood flow for wound healing of an otherwise medically refractory gangrenous ulcer in patients with RP and systemic sclerosis.

PS332 A CASE OF LONG-STANDING LIMITED CUTANEOUS SCLERODERMA WITH CHRONIC INFECTION – DIAGNOSTIC CHALLENGES

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Here, we present a case of 74-year-old woman with long-standing limited cutaneous systemic sclerosis (SSc) (skin and vascular involvement, pulmonary arterial hypertension, histologically proven secondary SÖgren syndrome) who presented in our clinic with complaints of accelerated dyspnoea on exertion and at rest and 2 weeks duration of intermittent abdominal pain and fever up to 39℃. At clinical examination, it was found vesicular respiration with crepitation in the basal and middle parts of the lungs bilaterally, several enlarged neck lymph nodes with size up to 6 cm in diameter, hepatosplenomegaly, pain on percution in the kidney area.
Laboratory investigations revealed mild leucocytosis 10.8G/l with absolute granulocytosis 8.6G/l, elevated inflammatory markers e. g., CRP – 39.4, ESR – 110mm/1st hour, elevated creatinine - 149µmol/l , positive urine culture (E. coli). An infectious agent from blood culture was not found. Computed tomography showed inflamed bronchiectasis and pulmonary infiltrates. Vegetation on cardiac valves were not detected on echocardiography. Right heart catheterization showed increased pulmonary arterial pressure 78 mm/Hg. Treatment with combination of intravenous antibiotics (ceftriaxone and ciprofloxacin) as well as therapy with bosentan at initial dose of 62.5mg bid, vasodilators, aspirin 100mg was initiated. 24 hours after the admission in the hospital ward, diffuse haemorrhagic rash appeared at the extremeties and trunk. Intravenous methylprednisolon at the dose of 1mg/kg was started and bosentan was discontinued. A consultation with haematologist with morphological analysis of blood smear revealed reactive changes in the context of chronic inflammation without signs of lymphoproliferative disease.
20 days after treatment with intravenous intravenous antibiotic and corticosteroid, the patient was permanently afebrile, skin rash significantly improved, neck lymph nodes - returned to normal size, with decreased dyspnoea. Control laboratory and microbiologic investigations revealed normal value of CRP – 1.1, normal creatinine – 91, sterile urine culture, resorption of pulmonary infiltrates. The final diagnosis of chroniossepsis (not proved microbiologically with evidence of pulmonary and renal infectious foci) with allergic vasculatis was made. Reactive lymphadenomegaly and hepatosplenomegaly in this case should be differentiated from malignant transformation of SjÖgren syndrome in limphoproliferative disease. The manifested allergic vasculitis may manifest in the context of various conditions some of the major being infections and drugs. In our case, the attempt to start treatment treatment with bosentan one month later after suppression of the infection was well-tolerated from the patient, which led us to conclusion, that the leucocytoclastic vasculitis has been a manifestation of the infectious process.

PS333 COMPLEX PATHOPHYSIOLOGY OF PULMONARY HYPERTENSION ASSOCIATED WITH SYSTEMIC SCLEROSIS: MERITS AND DEMERITS OF AGGRESSIVE TREATMENT WITH PULMONARY VASODILATORS

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Pulmonary arterial hypertension (PAH) is an intractable complication of systemic sclerosis (SSc). Over the past 10 years, PAH-specific pulmonary vasodilators have become available, and their implementation has led to clinical improvement and prolonged survival. Early diagnosis and initiation of aggressive treatment are recommended to favorably impact on the natural history of the disease. However, a combination therapy of PAH drugs does not always achieve favorable outcomes. We here report 3 patients with SSc-PAH, who had adverse clinical course potentially caused by the aggressive therapy.

Case #1: A 67-year-old woman with limited cutaneous SSc (lcSSc) was diagnosed as having PAH by active screening program followed by right heart catheterization (RHC). She had minimum dyspnea of WHO functional class (FC) II with mean pulmonary arterial pressure (mPA) of 39 mmHg and pulmonary arterial wedge pressure of 10 mmHg. She was treated with sildenafil and beraprost, resulting in gradual improvement of 6-minute walking distance (435m to 525m) and reduction of mPA (28 mmHg). Three years later, the patient experienced deterioration of symptoms and hemodynamics, which required addition of ambrisentan. Soon after, she was rushed to the emergency unit because of severe oxygen desaturation with pulmonary edema and pleural effusion. RHC showed remarkable improvement of PAH (mPA 37 to 25 mmHg), but moderate diastolic myocardial dysfunction was apparent by echocardiogram with tissue Doppler imaging.

Case #2: A 75-year-old woman with lcSSc and PAH (WHO-FC II) was treated with sildenafil and beraprost. Hemodynamics had been gradually improved (mPA 35 to 21 mmHg), but her symptoms had never improved. Addition of bosenten resulted in oxygen desaturation with pulmonary congestion. High-resolution CT scan of the chest revealed typical features of pulmonary veno-occlusive disease (PVOD) including centrilobular groundglass opacities, septal lines, and lymph node enlargement.

Case #3: A 72-year-old woman with lcSSc was referred to our hospital because of progressive dyspnea. Diagnosis of PAH with WHO-FC III was made. Treatment with sildenafil and bosentan resulted in improvement of symptoms and hemodynamics. However, her symptoms worsened because of anemia with repeated episodes of gastrointestinal bleeding. Colonoscopy revealed oozing from multiple teleangiectasias, but repetitive endoscopic clipping procedure failed to control bleeding.

A combination therapy of PAH drugs successfully improved PAH, but paradoxically unmasked subclinical other complications of SSc, such as diastolic myocardial dysfunction, PVOD, and bleeding from intestinal telangiectasias. We should be cautious about these adverse effects after increase in the dosage or sequential addition of PAH drugs.

PS334 COEXISTENCE OF SYSTEMIC SCLEROSIS AND SARCOIDOSIS: A CASE REPORT

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Introduction: Sarcoidosis is a Th1-related multisystem granulomatous disease characterized by lymphadenopathy, skin lesions and various internal organ involvement. Systemic sclerosis is a chronic autoimmune disease characterized by skin thikness and fibrosis of various internal organs and vascular abnormality. During the early and active stage of the disease, the presence of Th2-immune response was shown. This presentation reports a female patient presented with symptoms of granulomatous dermatitis, interstitial lung disease and Raynaud's phenomenon and the association of sarcoidosis with systemic sclerosis.
Case report: 52-year-old female patient was complaining of Raynaud's phenomenon,arthralgia, morning stiffness, and dyspnea on exercise was admitted to our rheumatology out-patient's clinic. Physical examination revealed telangiectasia on the face, reduction in mouth opening, sclerodactyly and pallor phase of Raynaud's phenomenon and brown-red colored skin lesion on the right pretibial area (Figure 1). Auscultation of the lung revealed basal crepitan lung crackles in both lungs. Laboratory tests were as follows; ESR 38mm/h, C-reactive protein: 3.5mg/dl, RF was negative. Liver and kidney function tests were normal. Routine urine analysis was normal. Serological tests reported nucleon and homogeneous positive ANA, positive anti-Scl70, normal C3 and C4 complements, and anti-CCP, anti-Ro, anti-La, anti-Sm, anti-ribosomal P antibodies were negative. Serum ACE level was 65U/L (normal values: 8-52 U/L). Fine reticular pattern was captured in lung graphy. Chest HRCT reported images of frosted glass and honeycombing in accordance with interstitial AC disease. The patient was presented to a pulmonologist, bronchoscopy and BAL were performed and mixed alveolitis was detected. Skin biopsy was performed and non-caseating granulomas, granulomatous dermatitis consistent with sarcoidosis was determined. There were no acid fast bacilli and fungus in Ziehl-Neelsen and PAS histochemistry respectively. The patient was diagnosed as scleroderma and sarcoidosis according to the clinical, laboratory and histological findings. Therapy with corticosteroid 16mg/day, hydroxychloroquine 200mg/day and azathyoprine 150mg/day was started. It was noticed on the follow-up pulmonary function tests and DLCO test that dyspnea on exercise was decreased and there was a significant regression in skin lesions. Clinical condition of the patient is stable at the moment and outpatient follow-up is continuing.
Conclusion: Coexistence of sarcoidosis with systemic sclerosis is a rare entity. Th1/Th2 paradigm is one of the most important reasons for this entity. Since each of these syndromes can do similar clinical presentation, the differentiation of actual overlap of syndromes is important in predicting prognosis and planning the treatment.

PS335 RENAL THROMBOTIC MICROANGIOPATHY TRIGGERED BY LUNG CANCER IN LIMITED SSC-A CASE REPORT-

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Background. Scleroderma renal crisis, whose pathophysiology is thrombotic microangiopathy (TMA), is a life-threatening complication of SSc, occurring much more frequently in diffuse type than in limited type. Malignancy, especially lung cancer, could cause TMA as well.
Objectives. We report a rare of renal TMA induced by lung cancer in a patient with limited SSc.
Results. A 68-year-old Japanese woman with 30-year history of Raynaud phenomenon began to have her finger tip ulcers 2 months ago. She noticed a right cervical mass a month ago and admitted because of her renal function worsening with normal blood pressure. She was diagnosed with limited SSc based on skin sclerosis distal to her wrist and positive anti-centromere antibody. A cervical lymph node biopsy and imaging studies of the chest revealed an advanced lung adenocarcinoma. Renal function gradually worsening, hemodialysis was started. Renal biopsy showed TMA which could be attributed to SSc or lung cancer.
Conclusion. We speculated that preexisting mild endothelial injury of renal vasculature with SSc was accelerated to the overt TMA by lung adenocarcinoma.

PS336 PRIMITIVE HEART DISEASES IN SYSTEMIC SCLEROSIS : REVIEW OF 05 CASES

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Introduction: The heart is one of the major organs involved in systemic scleroderma (SSc) witch compromises the prognosis and justifies the appropriate screening and treatment in this patient population. Cardiac involvement can be manifested by myocardial disease (systolic and diastolic dysfunction), conduction system abnormalities (arrhythmias, heart blocks) and pulmonary hypertension (PH).
Aims : To summarize through some reported cases of heart SSc the clinical profile and the types and the mechanisms of abnormalities observed. All patients' benefits from a cardiac exploration including echocardiography, thallium scintigraphy, MRI, coronarography etc… We have excluded from this study the cases of right heart failure resulting of PH.
Results: 5 cases referring to a man and 4 women are studied. The middle-aged is 39 years (19-55) and the SSc evolves on average for 7.1 years (2-15). The clinical presentation type of SSc corresponding in a diffuse cutaneous sclerosis (4) and a limited cutaneous sclerosis (1). The cardiac involvement is associated with a Rodnan skin score over 13 comes along with an involvement of lung (3), of digital ulcerations (3), of gastrointestinal achievement (4) and of liver disease (2). The immunological profile showed high titers of antibodies topoisomerase type (4), anti centromeres type (1) and anti-RNP type (3). The cardiac symptomatology is of insidious (3) and quickly progressive (2). Main symptoms observed are common with dyspnoea (5), congestive failure (2) associated to arrhythmia (1) and right heart failure (3). The determining explorations are the echocardiography (3) realized by transesophageal way (2), the heart MRI (5), the myocardial scintigraphy (2) and high-resolution computed tomography of the chest. The prognosis is evaluated by the titers of troponines and the BNP and some echocardiography index (TAPSE, TEI), left ventricular ejection fraction and the pericardial effusion. The mechanism of heart disease are attributed a direct endomyocardial fibrosis (4) and an ischemic cardiomyopathy (1). The course is quickly unfavorable by congestive failure (2) and thromboembolism event (1) despite of an optimized symptomatic therapeutics (diuretics, calcium inhibitors, angiotensine converting enzyme inhibitor drugs anticoagulant…).
Conclusion: The primitive heart disease in SSc is rare but a severe situation characterized by heart fibrosis and diastolic dysfunction. The mechanism implicated is the microcirculation alteration. The abnormal perfusion early detection will allow us to improve quality of life and the prognosis in patients with cardiac involvement in SSc. The algorithm of the screening and the treatment of primitive heart disease in SSc remain to be codified.

PS337 DIGITAL NECROSIS IN SYSTEMIC SCLEROSIS NOT ONLY A MICROVASCULAR DISEASE: A CASE REPORT

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Systemic sclerosis (SSc) is a connective tissue disease characterized by immune system alterations, skin and internal organs fibrosis and diffuse microangiopathy. This latter is responsible for digital ulcers (DU), renal crisis and pulmonary arterial hypertension; while macrovascular involvement is less frequently reported in the clinical practice.

Here we describe a patient with severe ischemic lesions due to both micro- and macrovascular involvement successfully treated with a combined therapy: systemic vasoactive treatment, local medications and angioplasty with distal revascularization.

A 60 y.o. woman was first diagnosed as SSc in 1996 on the basis of Raynaud's phenomenon, diffuse skin sclerosis, capillaroscopic scleroderma pattern, anti-Scl70 positivity and interstitial lung disease. In 2012 exertion dyspnea markedly worsened due to pulmonary artery hypertension (mean precapillary pulmonary artery pressure of 48 mmHg at right heart catheterization) treated with bosentan in association to the ongoing prostanoid therapy. In January 2013 the patient was hospitalizated in the Emercengy Departement for respiratory failure and pneumonia. She developed distal ischemic lesions localized at the right hand and an amputation of the distal phalanxes of 2nd, 3rd, 4th fingers of the right hand was carried out. Then she was admitted to our Rheumatology Unit because of a severe relapse of ischemic lesions with gangrene involving all the fingers of the right hand treated with prostanoid infusions and intensive local medications. Therefore, an attempt of treatment with sildenafil and heparin was started in association with prostanoids. Due to the resistence to systemic and local treatment, the patient underwent to angioplasty of both radial and ulnar arteries leading to dital revascularization.
The patient is still treated with continue prostanoid infusive therapy and regular local medications with progressive improvement of ischemic lesions of the right hand. During the follow-up also pulmonary arterial hypertension remained stable.
The present report describes the case of a SSc patient with fingers ischemia severely impaired by surgical approach. The role of microvascular impairment in course of SSc is well-known, but less attention is paid to macrovascular abnormalities. An increased prevalence of peripheral macrovascular disease has been observed in SSc in early phases with trend to progression.
The case here described underline the role of macrovascular involvement that may severely contribute to the ischemic complications generally associated to typical scleroderma microangiopathy, as well as the relevance in the clinical practice of a whole vascular assessment, especially in those patients with severe ischemic lesions scarcely responsive to standard treatment.

PS338 SCLERODERMA MODEL OF CARE – TEAM MEETINGS

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Background: The allied health and medical team of the Scleroderma Clinic at St Vincent's Hospital, Melbourne, have devised a simple but effective method to organise and expedite multiple resources for more complex patients.

Objective: When Allied Health Professionals approached the Clinical Nurse Consultant (CNC) in Scleroderma they proposed meeting for collaborative care as an alternative to the pre-existing written referral process. The belief was that involvement of multiple health care personnel would facilitate care particularly in most complex clinical cases. These patients have a challenging combination of wounds, contractures and aggressive disease states. As an example, a patient may not receive maximum benefit from a physiotherapy program because unsuitable footwear hampers their exercise program. Input from podiatry, prosthetics and orthotics with guidance from the consulting Rheumatologist in an open forum and review of progress was the aim for this case.

Implementation: The model of an existing virtual clinic was duplicated where the involved health care team met to discuss the complexity of care needed by nominated patients on a regular basis; to discuss treatment options, on-going care planning and coordination needs. In this case, allied health personnel regularly involved with complex scleroderma patients (either inpatients or outpatients) were contacted via email to propose logistics around regular meetings for this purpose. Discussion with interested parties took place in March 2013 and the first meeting was held in April 2013. Each was approximately an hour length, involved education when required, in-service planning, multidisciplinary and interdisciplinary planning of care, review of problems solved, etc. Patients were nominated via email prior to the meeting with additional patients accepted during the meeting, time-permitting.
Minutes of meetings were emailed to participants and notes were also stored in the Medical Records Online system which is accessible hospital-wide.

Conclusion: Since April 2013 five meeting have taken place. The meetings have been effective in facilitating cross-consultative care, expediting referral processes and education of relevant personnel through direct contact with the consultant rheumatologist and nurse consultant.
As a bonus, this process has achieved results previously not even considered possible. The in-depth knowledge of the patient by the consultant and nurse allows them to petition with or on behalf of allied health, and explain in terms that patients find acceptable why particular things are necessary.

PS339 A PARTICULAR CASE OF SEVERE SYSTEMIC SCLEROSIS, PROCEEDED BY BULLOUS MANIFESTATIONS IN APPARENTLY QUIESCENT SCLERODERMA

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Introduction: scleroderma (laterally skin induration) is usually divided into two forms: localized scleroderma (morphea, linear scleroderma) generally confined to skin and subcutaneous tissues and Systemic sclerosis (SSc) affecting internal organs too. Morphea consists of various variants, including nodular morphea (NM), keloidal morphea (KM), morphea profunda (MP), diffuse morphea (DM) and pansclerotic morphea (PM). NM and KM are used synonymously. SSc is divided into two major categories: diffuse cutaneous Systemic Sclerosis (dcSSc) and limited cutaneous Systemic Sclerosis (lcSSc). In contrast to SSc, the scleroderma variant conditions generally carry a good prognosis and are often self-limited. We present a 56-year-old Caucasian female, the first case of scleroderma, who first developed bullous lesions on pre-existing sclerotic plaques, and then dcSSc.
Case report: A 56 years old woman presented to our Rheumatologic Clinic. Five months earlier, she developed some cutaneous thick and discoloured areas on the chest, abdomen, dorsal-lumbar region, arms and legs. After two months she developed bollous lesions on the legs, on pre-existing sclerotic plaques, that have hesitated into crusted lesions. Histology was compatible with a bullous presentation of scleroderma (complete detachment dermo-epidermal, edema of dermis and superficial inflammation accompanied by fibroblast proliferation of deep dermis and hypodermic septa) and other entities in the differential diagnosis were ruled out. ANA, anti-Ro, anti-La, Sm, dsDNA, Scl-70, neoplastic markers, complement fractions (C3, C4) and Borrelia antibody test were negative, as all infectivological exams.
The patient had no Raynaud's phenomenon neither sclerodactyly or telangiectasia. Contemporary to the appearance of bullous skin lesions, she developed dyspnoea and dysphagia and the extenshion of skin induration. From the chest CT scan and spirometry, a restrictive pulmonary pattern was evidenced. BAL was negative for neoplastic cells, cultural exams for common germs and Mycobacterium tuberculosis. An esophageal scintigraphy showed slowed emptying of the esophagus. She was given cyclophosphamide (50 mg bid to take orally) and prednisone (5 mg/die). In consideration of the lack of response, the steroid therapy was increased at 1 mg/kg/die, with the improvement of skin thickness and dyspnoea.
Conclusion: the rapid worsening of the clinical conditions of patient and the bullous lesions, that are a very uncommon presentation of sclerodermal cutaneous manifestations, made SSc diagnosis difficult and represented a challenge for physicians. Moreover, these skin lesions may be activity disease index, both cutaneous and visceral. Therefore they should be made known to clinicians so that activity and progression of the disease can be recognized and treated to avoid complications.

PS340 THYROID DYSORDERS IN PATIENTS WITH SYSTEMIC SCLEROSIS: BIOCHEMICAL AND SONOGRAPHIC CHARACTERISTICS

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Background: Previous studies have shown elevated risk for thyroid autoimmune diseases in patients with systemic sclerosis (SSc). Increased risk for thyroid nodules and cancer was demonstrated in other autoimmune disease like systemic lupus erythematosus.
Aim: The aim of our study was to evaluate the thyroid gland in consecutive SSc patients using biochemical and sonographic tools.
Methods: Thyroid-stimulating hormone (TSH), free thyroxine (fT4), antithyroglobulin (aTG; normal range 1-40 IU per L) and antiperoxidase (aTPO; normal range 1-35 IU per L) autoantibodies as well as thyroid ultrasound were performed to consecutive patients with SSc classified according to the American College of Rhematology 1980 criteria.
Results: Fifty patients (44F, 6M; age 50.4 ± 14.6 years) with dsSSC and lsSSC (40, 10) were evaluated. Median duration of the disease was 6.5 years (range 0.5-38 years) with clinical manifestations involving mainly the skin, gastrointestinal tract and musculoskeletal systems (in 90.4%, 82.7%, and 69.2%, respectively). Ten patients were previously diagnosed with hypothyroidism, 2 had hemithyroidectomy, one had procor-induced hypothyroidism and seven had autoimmune thyroid disease. A third of patients had first degree relatives with autoimmune thyroid disease. TSH level was 2.24±1.18 mIU per l (normal range 0.23-4) and fT4 1.28±1.76 (normal range 0.8-2.0 ng per dL). Out of forty thyroid disorder-naive patients 3 had mildly elevated TSH level (5.2±0.76 mIU per l), and 15% and 5% were positive for aTPO and aTG antibodies, respectively. Twenty two patients had 1-6 thyroid nodules, which were >1 cm in 24% of the patients. Two nodules were hypoechoic, and 2 others were calcified. Overall 6 patients underwent fine needle aspiration procedures: 5 were diagnosed as colloid nodules, and one as papillary carcinoma.
Conclusions: In this screening study no evidence of thyroid autoimmune disease was found in this unique group of patients. Yet, almost half of the patients had thyroid nodules. The clinical significance of these findings is to be determined in long-term studies.

PS341 EXERCISE TRAINING IN SYSTEMIC SCLEROSIS – FIVE SSC PATIENTS FINISHED THE BERLIN MARATHON

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Exercise training can improve aerobic capacity and muscle function in patients with connective tissue diseases e.g. rheumatoid arthritis, inflammatory myositis, systemic lupus and primary Sjögren syndrome. There are only few data concerning the usefulness of exercise training in patients with systemic sclerosis. In 10/2010 we started a 12 months aerobic exercise training program for patients with systemic sclerosis as part of the long term rehabilitation process. 5 patients were enrolled in this uncontrolled single center pilot study, 4 women, age 35 – 48 years, and 1 man age 38 years. 3 patients were Scl70+, 2 patients ACA+. 3 patients suffered from limited SSc, and 2 patients from diffuse SSc for at least 2 to 4 years.
The individual training program consisted of 3-4 jogging units per week at 50-70% VO2 max and was intensively supervised by two sport scientists from a Swiss Olympic Medical Center in Basel. Exercise training was administered over an online training platform where participants uploaded their heart rate and GPS data after each training.
Baseline tests included clinical evaluation, spiroergometry, lactate threshold testing, capillaroscopy, blood and urine tests, lung function tests, Holter ECG, echocardiography, Raynaud severity analogue scale, and the SF12 Qol test. Tests were repeated every 4 months. After 11 months of exercise training all 5 SSc patients finished the 42,195 km Berlin Marathon with no evidence of adverse events, no changes in muscle enzymes, and no deterioration of the disease.
Results: The most striking results were complete suppression of Raynaud attacks in 4/5 patients. There was also a reduction of finger swellings in 2/5 patients. Both patients could wear rings again. There was a reduction of ANA titer in 4/5 patients. In the other patient with very early SSc ANA and Scl70+ antibodies became negative during the training period and this result was stable for at least 12 months after the marathon. All patients noticed a reduction of their fatigue syndrome.
We will present test results in detail and show a short videoclip with the SSc patients running the 2011 Berlin Marathon.
Conclusion: Professionally supervised exercise training might become a useful adjunct therapy in patients with early SSc but controlled studies are needed.

PS342 SYSTEMIC SCLEROSIS ASSOCIATED TO SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective: The aim of this study was to describe clinical, immunological features and outcome of patients with systemic sclerosis (SSc) and Systemic lupus erythematosus (SLE).
Methods: A retrospective study of patients' files with SSs, only patients who fulfilled the ACR criteria for both SSc and SLE were included. Demographic, clinical and immunological characteristics were studied.
Results: Twelve Patients have SSc associated to SLE (11.7 % of patients with SSc), all of them were female. The average age at the diagnosis of SSc and SLE was respectively 38.33 and 36.08 years. The mean delay between the 2 diagnoses was 40 month. SSc preceded SLE in 5 patients. Five patients had diffuse cutaneous scleroderma and 7 had limited cutaneous scleroderma. Ten patients complained of arthralgia and 4 of myalgia. Glomerulonephritis (GN) and pericarditis were both diagnosed in 5 patients. Eleven patients complained of Raynaud's phenomenon and 3 had digital ulcers. Three patients had interstitial pneumonia and 5 had esophageal involvement. Antinuclear antibodies were positives in all patients; 9 patients had anti-DNA antibodies, 6 had anti-topoisomerase I (50%) and one had anti-Pm-scl. Anti-Smith, anti-SSA and anti-RNP antibodies were positives respectively in 7, 5 and 3 cases. All patients were treated by corticosteroids (for GN, pericarditis, myositis, arthralgia or neurological involvement), no scleroderma renal crisis was noted. Eight patients were treated with immunosuppressant agents (GN, interstitial pneumonia or arthralgia). The outcome was good in 9 cases, 2 patients were stables and one died.
Conclusion: Connective tissue diseases may overlap with each other or be associated during the disease course. Serial follow-up for clinical symptoms as well as serological changes is recommended.

PS343 BK VIRUS ASSOCIATED HAEMORRHAGIC CYSTITIS IN A SCLERODERMA PATIENT AFTER CYCLOPHOSPHAMIDE THERAPY

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INTRODUCTION: Haemorrhagic cystitis (HC) is characterized by haemorrhage of the bladder mucosa with painful micturation which ranges from microscopic haematuria to clot retention and renal failure. HC is either an early-onset event arising from chemotherapeutic agents, particularly metabolites of cyclophosphamide (CTX) and/or irradiation, or a late-onset event viral-associated. The majority of these HC are due to reactivation of BKV, but may also arise from cytomegalovirus and adenoviruses. HC-associated reactivation of BKV is a frequently encountered condition in immunocompromised haematopoietic stem cell transplant recipients leading to significant morbidity and occasional mortality.
HISTORY: years old woman. Beginning of disease in 2011 with polyarthralgias, Raynaud's phenomenon, digital ulcerations and diffuse skin involvement. Serology testes: positive ANA and antiENA (Scl-70). Diagnosis: diffuse cutaneous systemic sclerosis. Staging of disease: HRCT is negative for active alveolitis, barium contrast study is negative for esophageal involvement, echocardiogram is negative for pulmonary hypertension. Due to the rapid progression of the disease it was decided to establish immunosuppressive therapy with CTX iv. The patient has not shown any problem until to infusion of third bolus after which, at a distance of few weeks, is appear HC. Chemical and physical urine examination and urine culture are negative, quantitative search of urine BKV is positive. The ultrasound of the urinary tract has not been documented hydronephrosis. The patient was hospitalized and was placed 3-way catheter for bladder washings. Set treatment with Immunoglobulins iv (20 mg daily for 5 consecutive days) for a total of 6 cycles (from December 2011 to September 2012). Bladder instillation of Tranexamic acid + Hyaluronic acid on a weekly basis. Slow but progressive regression of the clinical picture for which no therapy was started with Cidofovir.
DISCUSSION: Polyomaviruses (PyV) are small, nonenveloped, circular, double-stranded DNA viruses of the family Polyomaviridae. The first two PyV which were discovered in immunosuppressed patients were: JCV was identified in brain tissue from a patient with progressive multifocal leukoencephalopathy (PML), and BKV from the urine of a renal transplant. The increased incidence of JCV/PML in association with the HIV-1 pandemic and the emergence of BKV-associated-nephropathy in association with renal transplantation and HC in bone marrow transplant recipients, highlighted the importance of the host immune system in the control of these latent infections and the pathogenesis of these diseases.
CONCLUSION: in case of HC during treatment with cyclophosphamide in scleroderma patient is necessary to exclude the reactivation of BKV.

PS344 SPECIFIC ATROPHY OF THE VOCAL FOLD DURING SCLERODERMA : UNDERESTIMED IMPACT ON QUALITY OF LIFE, ABOUT 2 CASES

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There are few reports about hoarseness during systemic sclerosis. Except esophageal reflux, a specific atrophy of the vocal fold can occur with significative impact in patient's quality of life. We report two cases of hoarseness due to specific atrophy.

Case 1: A 37 year-old woman was addressed to the internal medicine department for a severe acrosyndrome with pulpal ulcer. She was also complaining about a sclerosing skin on the neck and the arm (Rosner's score from 3 to 4). Biological data showed anti nuclear antibodies at a high level. The diagnosis of systemic sclerosis was retained. During the follow up she started to report a dry cough with hoarseness: her voice was less strong, she could not scream at all. She did not complain about dyspnea and the pick flow was in normal range. She was obliged to eat slowly mixed food because she was choking with dry food.

Maximum phonation time was five seconds. Endoscopy showed normal mobility of vocal fold but the right one was generally atrophied . Voice therapy has been effective and now his voice is more powerful than before.

Case 2: A 54 year-old teacher was followed in internal medicine departement for systemic sclerosis (anti SCL70 antibodies) with esophageal involvment and pulpar ulcer. For several months she was complaining of her voice that was low and hoarse with impact in her job. There was a harmonic impoverishment associated with irregularity. The left vocal cord was concave with a specific muscle atrophy

The more common cause of hoarseness during systemic sclerosis is gastro esophageal reflux in connection with a sclerosis of esophageal damage. Endoscopy shows oedema and thickening of the inter arytenoid region (1).In case of specific atrophy of the vocal fold, first occurs an oedema of the vocal fold, followed by its infiltration, induration and finally a general atrophy (2).

Voice therapy is one of the most effective therapeutic methods. Impact on patient's everyday life is underestimed.

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PS345 RITUXIMAB TREATMENT IN DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS: A CASE REPORT

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Introduction: Recent evidence supports the B-cells involvement in the fibrotic process of systemic sclerosis (SSc). Rituximab (RTX), a B-cell depletion therapy, is being used in the treatment of this disease and becoming a promising therapy, because of the encouraging results of clinical studies and analysis of the EUSTAR database.
We present a case of a patient with rapid progressive diffuse cutaneous SSc (dSSc) unresponsive to conventional therapy, who exhibited significant improvement following RTX administration.

Case presentation: We present a case of a 40-year-old woman with severe and rapidly progressive dSSc. The initial clinical manifestations were new-onset Raynaud's, weakness and generalized pain. On the first examination she presented puffy hands since 4 months ago, without skin thickening. Speckled anti-nuclear antibodies were positive with high-titer anti-topoisomerase antibodies. Within 2 months of the beginning of the symptoms, she had a mRSS (modified Rodnan skin score) of 22 and a FVC and DLCO of 93 and 71% of predicted values, respectively. The chest high-resolution CT scan (HRCT) revealed focal ground-glass appearance, predominantly in the lower lobes. She was treated with cyclophosphamide for 6 months. However, a progression of the skin involvement was observed, with a mRSS of 51 and a worsening of the PTFs, with a FVC and DLCO of 70 and 54%, respectively. Her chest HRCT now revealed diffuse ground-glass appearance.
Since worsening was observed despite immunosuppressive therapy, she was administered RTX (1 g, 2 weeks apart). She had a good subjective symptomatic improvement. Three months after the RTX infusion, the mRSS had improved to 37 and the FVC and DLCO were of 79 and 78%, respectively. Chest HRCT scan was similar to the one realized in the baseline.
Six months after the first RTX infusion, she was re-treated with the same regimen. Three months after the second RTX treatment, mRSS was decreased to 33 and FVC and DLCO reached values of 86 and 78%, respectively. She is now on mycophenolate mofetil as maintenance therapy for 5 months and her clinical situation remains stable.

Conclusions: RTX had a beneficial effect in our patient, as indicated by the improvement of mRSS, pulmonary function tests and even the chest HRCT. The clinical improvement of skin thickening and pulmonary function after RTX, which may indirectly support the role of B-cells in the pathogenesis of dSSc, supports the need for formal evaluation of this promising therapy.

PS346 SPARING EFFECT OF HEMIPLEGIA ON SCLERODERMA-LIKE MICROVASCULAR INVOLVEMENT AND SKIN FIBROSIS: A CASE REPORT

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Background. Sparing effect of hemiplegic syndromes has been often described in rheumatic diseases, but reports on systemic sclerosis (SSc) are exceptional.
We describe the uncommon case of a hemiplegic patient who developed SSc-like disease with asymmetric skin and microvascular involvement of the non-paretic limb.
Case report. A 61-year-old woman came to our observation in March 2013 for new-onset Raynaud's phenomenon in her left hand only.
Her medical history was notable for left parieto-temporal ischaemic stroke in 2001, and residual right hemiplegic syndrome, dysarthria, and proximal dysphagia. The stroke was defined as "cryptogenic" since no evident causes were found (negative thrombophilia screening, including genetic and immunologic triggers such as antiphospholipids antibodies). No comorbidities were identified. Hitherto, chronic antiplatelet therapy is ongoing.
Physical examination revealed right-sided neurological signs and sclerotic skin changes only on the left hand.
Routine laboratory tests were normal. Immunological studies showed antinuclear antibodies 1:640 granular pattern and anti-RNP (141 UA). Nailfold capillaroscopy pointed out scleroderma pattern on all fingers of the left hand, while no capillary alterations were present in the spastic one.
Recently, isolated basal ground glass opacities have been detected bilaterally on chest CT with normal lung volumes and slightly reduced DLCO (65%, and DLCO/VA 74%). Transthoracic echocardiographic PAPs assessment was near to upper value (33 mmHg) and barium swallow was normal. Thus, a diagnosis of SSc-like undifferentiated connective tissue disease has been made and follow-up planned.
Discussion. This is the first description of asymmetric microvascular damage in a hemiplegic patient with new-onset SSc-like disorder. So far, two analogous cases have been described in literature: the former clinically assessed the absence of sclerosis on the paretic limbs; the latter reported the unilateral acroosteolysis on X-ray of the non-paretic hand. In none capillaroscopy was performed. For the first time we have documented the capillaroscopic SSc-like changes of nailfold vessels of the "healthy" limb while sparing the paretic one.
The reason of such a "protective" factor is elusive. The mechanobiological dysregulation of dermal fibroblasts in SSc and the abnormal mechanical stimuli such as disuse of paretic limbs is an intriguing yet speculative hypothesis. Besides, evidence supports the mediation of nervous system in inflammatory response.
This clinical case points out the possible role of a "cross-talk" between nervous system and microvascular immuno-mediated disorders and suggests areas of research interest for future directions in pathogenetic studies and target therapy advancement for SSc.

PS347 A RARE CASE OF CHRONIC EFFUSIVE-CONSTRICTIVE PERICARDITIS IN LIMITED CUTANEOUS SYSTEMIC SCLEROSIS

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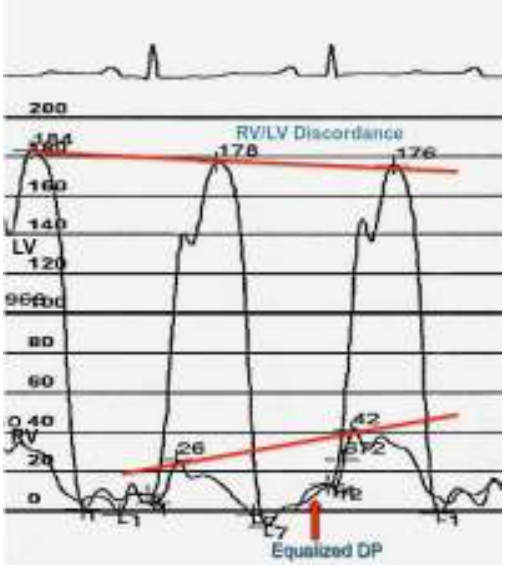
Background: Systemic Sclerosis (SSc) is a heterogeneous autoimmune disease with propensity for internal organ involvement. Mild pericardial effusion is common especially in diffuse cutaneous systemic sclerosis. However significant pericardial effusion with tamponade or constriction is rare.
We report a case of a chronic effusive-constrictive pericarditis.
Case: A 52 year lady was diagnosed with limited cutaneous systemic sclerosis (lcSSc) whilst living in Australia (then 31 years old) with positive antinuclear antibody (> 1280 anticentromere pattern), telengiectasias, calcinosis, raynauds, sclerodactyly, oesophageal dysmotility. She had penicillamine, omeprazole and was screened annually with pulmonary function tests (PFTs) and echocardiogram (ECHO).
In 2004 she moved to New Zealand. Her initial ECHO and PFTs were normal. She was lost for follow up until late 2008 when she represented to the peripheral hospital with primary biliary cirrhosis. Her ECHO showed mild pericardial effusion (PcE). Repeat ECHO (2009) showed mild and stable PcE and rest of her cardiac function including LV and RV function were normal with no evidence of pulmonary hypertension. Her ECG and blood tests including inflammatory markers were unremarkable. She was followed up with repeat PFTs and ECHO at 4 to 6 monthly intervals.
In mid 2011 her ECHO showed an increase in PcE which progressed to severe degree and required pericardial window by December 2011 her ECHO showed PcE of 1.7cm in diastole (was 1.2 cm in June 2011) and she was beginning to get symptomatic.

Following this she developed further palpitations, chest pain and shortness of breath and was transferred to our tertiary hospital in January 2012. Clinically she had effusive-constrictive pericarditis. Her transthoracic and transoesophageal ECHO revealed a small PcE (post-pericardial window the pericardial space of 0.9cm) mild RV dysfunction and doppler inflows in MV & TV showed a change of more than 25% with respiration. She proceeded to simultaneous right and left heart catheter studies (figure1) which confirmed constrictive pericarditis (with normal coronary arteries). Thereafter she had open pericardiectomy with improvement in her symptoms. Histological analysis of pericardium ruled out calcified, infective and granulomatous causes.
Discussion: We believe our case is one of extremely few cases of SSc presenting with chronic effusive-constrictive pericarditis and the only one reported in lcSSc.
Our case also illustrates that significant PcE does occur in lcSSc. Apart from slow worsening of the effusion there was development of constriction with fibrinous pericarditis (noted on histology) with a lag in presenting symptoms. Though our patient had calcinosis cutis none was evident in pericardium.



PS348 A RARE PRESENTATION OF SCLERODERMA RENAL CRISIS FOLLOWING SILICONE BREAST IMPLANT RUPTURE

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Background: Systemic sclerosis (SSc) is an autoimmune disorder of unknown aetiology. Exposures to environmental factors may play a role. Silicone breast implants have been postulated as a cause for autoimmune diseases including SSc. This remains unconfirmed.

Case Presentation: 47 year old lady developed ridging in her silicone breast implants four years after implantation. Ultrasound confirmed ruptured implants.
In 2011 she developed raynauds which worsened following the silicone breast re-implantation (mid 2012) associated simultaneously with puffiness of her fingers followed thereafter with rapid thickening of the skin over her fingers, forearms, arms as well as chest wall.
In early 2013 she presented with breathlessness. Physical examination and chest x-ray confirmed acute pulmonary oedema. Her NT-proBNP was elevated (>4,000pmol/L). Her blood pressure (BP) was 180/110 mmHg. Her blood tests confirmed acute renal failure with serum creatinine (Scr) 313 micromol/L (NR= <90 micromol/L). She had decreased complement levels, positive antinuclear antibody (speckled pattern at 1:640), and positive anti-RNA Polymerase III (anti-RNAP III) antibody screen.
She was commenced on escalating doses of captopril. Frusemide, labetalol and amlodipine were required for optimal control.
Her pulmonary function tests (PFT) revealed FVC 89%, FEV1 85%, FEV1/FVC ratio 80% and TLCO of 44% predicted. HRCT scan ruled out fibrotic lung disease. Echocardiography (ECHO) revealed pericardial effusion (1.55cm width) with right ventricular systolic pressure of 47.1 mmHg and ejection fraction of 60%.
She was discharged at day 16. Review at 4 weeks confirmed her BP and Scr was stable (149 micromol/L).
Repeat PFT and ECHO have been requested to establish the baseline status after stabilization.

Discussion: This is the first reported case of dcSSc (and presence of anti-RNAP III antibodies) in a lady with a history of silicone breast implant rupture, presenting with SRC.
Autoimmune diseases such as SSc, inflammatory arthritis, human adjuvant syndrome and SLE have been reported following silicone implants. ANA, dsDNA and RF are the commonly reported autoantibodies.
Published cases reveal the mean time from silicone implantation to symptom onset was 13.2 years. In our case, the first non-Raynaud developed 9 years after implantation (5 years after rupture).
Bekerecioglu et al[1] demonstrated in asymptomatic patients with previous silicone implants a significantly higher concentrations of immunoglobulins (IgG and IgM) and anti-silicone antibodies around the implant suggesting that silicone is not biologically inert.
The link between silicone breast implants and SSc is attractive but tenuous on current evidence. There is a biological plausibility. Larger studies are required to see if there is any definite association.

PS349 A CASE OF SYSTEMIC SCLEROSIS PATIENT THAT HAD SEVERE HYPOTENSION WITH ACUTE RENAL FAILURE DUE TO THE SILDENAFIL

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A 54-year-old man was re-admitted to severe dizziness and fatigue. At time previous admission, he was diagnosed systemic sclerosis that accompanied severe digital ulcer with gangrene and borderline pulmonary hypertension. He was improved digital ulcer treated with I.V antibiotics (Cefazolin) and I.V. prostacyclin (Eglandin) and P.O sildenafil (20mg TID), and discharge with P.O medication (Beraprost, Sildenafil 20mg TID). Two weeks after, he felt severe intermittent dizziness and low back contusion at the bus, but initial vital sign was normal blood pressure (120/80 mmHg) rapid rhythm (HR 108), and had not anemia or abnormal finding in complete blood count, chemical, electrolyte. But, he had progressive lowering the blood pressure to 60/40mmhg rapidly in a day. He was discontinued the sildenafil, started vigorous hydration with normal saline, and administered norepinephrine via intra venous. His blood pressure was maintained at the level of 90/70mmHg, But He had showed oliguria and then anuria for 22 hours, and revealed BUN/ creatinine 21.7/1.7 IU/L, AST/ALT 111/53 IU/L, Pro-BNP 587.7 IU/L. There was no abnormal heart motion and normal ejection fraction in echocardiographic finding, and normal EKG finding. After anuria state, he had showed large amount urination with 300~ 600cc/hour on day after, and then massive urination in 5 days 29000cc~ 323000/day, we performed the vigorously I.V hydration for balance of body fluid. Body weight change of patient was just 2kg in first day that the time showed anuria. The 6th hospital day, he had stable vital sign and input- output ratio (3350/2880cc) without I.V hydration or norepinephrine, and revealed the BUN/Cr 11.4/0.7 IU/L, AST/ALT 32/53 IU.

In this case was suggested that the patient was suffered the acute renal failure due to severe hypotension that may be use of sildenafil citrate. Sildenafil citrate is used in systemic sclerosis with pulmonary hypertension or digital ulcer, but in our knowledge, there is no reports severe hypotension with acute renal failure in systemic sclerosis patients. There was a report that temporal association sildenafil by a healthy subject and his presentation several days later with symptoms of acute renal failure. And a case of fatal hypotension by sildenafil in an end-stage renal disease patient was reported. And a case reported that In intermittent WPW syndrome patient, sildenafil induced atrial fibrillation and continuous hypotension.

No yet, the relationship was not clear, but usage of sildenafil in scleroderma patients may have attention of severe hypotension.

PS350 SYSTEMIC SCLEROSIS WITH EXTENT NECROSIS AND LOST OF PART OF THE FOOT– A CASE REPORT

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Introduction: The vascular involvement in Systemic sclerosis (SSc) is an early manifestation and represents a central event in the pathogenesis of the disease. Structural and functional abnormalities of blood vessels, include changes in the control of vascular tone, endothelial damage and dysfunction, intimal proliferation of small arteries and arterioles, Raynaud's phenomenon, digital ulcers, gangrene and amputation of extremities. We describe an important lesion on the foot of a patient with SSc with a very extensive necrosis and lost of three fingers. Case report: MVOE, female, married, born in Itaperuna - RJ, black, 35 years, housewife, introduced himself to the service of Rheumatology of Gaffrée e Guinle Universitary hospital (RJ). She had diagnosis of Systemic sclerosis (SSc) since 1998. Clinical findings were: Raynaud's phenomenon, digital ulcers, claw-like hands, fingers and toes acrosteolisis. At february 2009 she developed an enormous ulceration with gangrene of the 1st, 2nd and 3rd right toe, covering the distal extremity of the right foot (Figure 1). We referred her to surgery for debridement. She was taking the follow medicaments: captopril, cilostazol, low-dose prednisone (5mg/day), pentoxifylline, nifedipine and aspirin 100 mg/day. It was added sildenafil 50 mg/day and bosentan, but irregularly and for short time. Since September 2010 she had joined regular use of bosentan, initially at a dose of 62,25 mg 12/12/hs for four weeks, increasing to 125 mg 12/12hs, with gradual improvement, but maintaining open sore, with smaller diameter and granulation tissue (Figure 2). Discussion: Digital ulcers are more frequentely described in hands than feet. It is not common a so large lesion like this one observed in the patient. New forms of treatment such as phosphodiesterase-V inhibitors and endothelin receptor blockers have proven effective in patients with ischemia of the extremities as a manifestation of SSc.Conclusion: Ischemic ulcers represent a severe and extremely debilitating condition affecting up to 50% of patients with SSc, most commonly on the hands. This patient had severe involvement of the feet, with gangrene and loss of extensive part of right foot, a rare feature in SSc.

Figure 1: Aspect of the foot of the patient at the onset of the injury.
Figure 2: Present aspect of the patient's foot after two years of treatment.

PS351 AN ALTERNATIVE APPROACH TO THE MANAGEMENT OF A PATIENT WITH SSC-MYOSITIS ASSOCIATED WITH DYSPHAGIA

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Dysphagia commonly occurs in patients with systemic sclerosis (SSc), but is uncommonly due to pharyngeal muscle myositis. Oropharyngeal dysphagia leads to recurrent, potentially life-threatening, aspiration pneumonia. As such, management strategies involve the avoidance of oral nutrition, through temporary percutaneous endoscopic gastrostomy (PEG) placement, whilst the myositis is medically optimised. We present a patient with SSc, myositis-overlap and oropharyngeal dysphagia, who declined PEG placement.

A 44 year old female was referred to our centre for specialist review with a 2 month history of dysphagia to liquids, which she localised to her pharyngeal region. She also reported nasal regurgitation on swallowing liquids. Two years earlier she had been diagnosed with diffuse cutaneous SSc (PM Scl +ve 75/100), associated with pulmonary involvement. This had been preceded by a 6 month history of Raynaud's phenomenon. Our clinical suspicion was of pharyngeal myositis.

Investigations were performed. Pulmonary function tests (FVC 53%; DLCO 51.4% predicted) and CT thorax showed pulmonary fibrosis. Serum creatinine kinase (CK 1011U/L [reference range 24-170]) and quadriceps muscle MRI confirmed myositis. Videofluoroscopy showed aspiration. Swallowing assessment demonstrated incomplete laryngeal elevation, marked pharyngeal residue and aspiration on swallowing food of all consistencies.

Thus, recurrent aspiration from pharyngeal myositis was diagnosed and a multi-disciplinary approach presented to the patient. In light of previous success at our centre, placement of a temporary PEG was proposed to reduce the risk of feeding-related aspiration, while the myositis was treated. However, after careful consideration, she declined PEG placement. Instead, she chose to continue on a modified oral diet and take care on swallowing, whilst starting prednisolone and mycophenolate mofetil for her myositis.

To-date, using this approach, she has successfully maintained her weight and has had no serious episodes of aspiration pneumonia. Meanwhile, her myositis has clinically and biochemically (CK 144) improved. However, given her precarious situation, due to her high risk of aspiration whilst immunosuppressed, she remains under close supervision by both gastroenterologists and rheumatologists. Should her swallowing deteriorate, she is aware that PEG placement may need to be reconsidered. However, in light of her current improvement, she is likely to have a successful outcome.

In summary, this case highlights the possibility of patients with SSc-myositis overlap developing oropharyngeal dysphagia, and describes the success of an alternative management strategy, when PEG placement is declined.

PS352 A MULTI-DISCIPLINARY APPROACH TO THE MANAGEMENT OF A PATIENT WITH RAPIDLY PROGRESSIVE SSC, SEVERE GASTROINTESTINAL INVOLVEMENT AND MALNUTRITION

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Patients with systemic sclerosis (SSc) may rapidly develop malnutrition, associated with morbidity and increased risk of mortality. Thus, when detected, early nutritional intervention is essential. We describe a case highlighting the benefit of a carefully coordinated approach by cross-speciality, multi-disciplinary teams.

A 59 year old female presented with Raynaud's phenomenon, dry cough, hand swelling and weight loss (5kg over 2-3 months). On examination, she had dilated nailfold capillaries, distal skin thickening, bibasal crackles and proximal muscle weakness. She weighed 65.1kg, body mass index (BMI) of 23.9kg/m2.

Investigations showed a raised ESR (40mm/hour), creatinine kinase (214U/L [24-170]) and cardiac troponin (66ng/L [0-14]), but normal full blood count, renal profile and albumin (42g/L). ANA and ENA were negative. Pulmonary function tests showed a restrictive pattern (FVC 1.45 L [49%]; DLCO 80.2% predicted). CT thorax showed basal interstitial changes and a dilated, fluid-filled oesophagus. Quadriceps muscle MRI showed bilateral, multi-focal, low grade myositis. Thus, SSc-myositis overlap was diagnosed. Prednisolone and azathioprine were commenced.

However, 2 months later, she returned with refractory vomiting and diarrhoea. On examination, her abdomen was distended and tympanic. She now weighed 62kg (BMI 22kg/m2). Albumin was low (26g/L). Barium follow-through showed a markedly dilated small bowel. A CT scan revealed considerable colonic barium retention. She failed to tolerate a hydrogen breath test. Therefore, rapidly progressive SSc-myositis overlap with extensive small intestinal and colonic involvement, causing pseudo-obstruction and delayed colonic transit, was diagnosed.

Given this significant gastrointestinal involvement, associated with her rapid weight loss (>10% in <6 months), a combined gastroenterology, rheumatology and dietetic/nutrition support approach was taken. As she failed to tolerate a trial of nasogastric feeding, total parenteral nutrition (TPN) was initiated. Meanwhile, she was empirically treated for small intestinal bacterial overgrowth (cyclical antibiotics). As a result, her gastrointestinal symptoms dramatically improved, whilst her nutritional needs were supported. She discontinued TPN after 2 weeks. Upon discharge, her weight was maintained on small, frequent meals (low fibre and food fortification) with enteral supplementation.
Now, 6 months later, she continues on cyclical antibiotics and a lower dose of prednisolone and has started cyclophosphamide (substituted for azathioprine in view of her pulmonary fibrosis). Albumin (35g/L), creatinine kinase (38U/L) and cardiac troponin (22ng/l) have all improved.

In summary, we highlight the need for the prompt, aggressive treatment, of patients with rapidly progressive SSc, by multi-disciplinary teams. In this case, the carefully coordinated inter-speciality multi-disciplinary approach was life-saving.

PS353 ANGIOSARCOMA OF THE SCALP IN A PATIENT WITH SYSTEMIC SCLEROSIS

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Angiosarcoma is a rare tumor which consists less than 1% of all soft tissue sarcomas. It most commonly affects elderly men with a poor prognosis. Angiosarcoma is known to have an association with some conditions such as injury, lymphedema and prior radiation therapy.

We report a case of cutaneous angiosarcoma in a 67-year-old woman with limited cutaneous systemic sclerosis (SSc). She noted Raynaud's phenomenon from decades years before. She admitted our hospital claiming of the rapid growing tumor in the scalp. Clinical examination revealed multiple granulomatous tumors up to 8 cm in diameter. Skin sclerosis was observed on her fingers and dorsa of the hands, and also on the face and the scalp surrounding the tumor with salt-and-pepper like depigmentation. A biopsy of the tumor showed a proliferation of atypical polygonal tumor cells. Immunohistologically, the tumor cells showed strong immunoreactivity for CD31, vimentin and D2-40. We diagnosed the tumor as angiosarcoma of the scalp. Although computed tomography revealed lymphadenopathy in the both cervical nodes, no visceral metastasis was evident. We conducted docetaxel monotherapy. As a result, all the tumors including lymph node metastases regressed completely after 9 cycles of weekly and 5 cycles of monthly administration of docetaxel. During the treatment, she developed interstitial pneumonia but recovered by discontinuation of the treatment.

To the best of our knowledge, no case of angiosarcoma have been reported to be associated with other connective tissue diseases such as systemic lupus erythematosus, dermatomyositis, Sjogren's syndrome or rheumatoid arthritis. Although rare, our case is the third reported case of angiosarcoma in a patient with SSc. All three cases developed in an area of sclerodermatous skin. Increasing evidence indicates that vascular damage is the primary event in the pathogenesis of SSc. This vascular damage causes the overexpression of the potent angiogenic mediator vascular endothelial growth factor (VEGF) in the skin and circulation of patients with SSc. One of the receptors of VEGF, VEGF receptor-3 has been reported to be positive for 50% to 80% of angiosarcoma. Recent studies on pathogenesis of angiosarcoma have indicated the possibility that malignant transformation occurs in benign endothelial cells characterized by overexpression of VEGF in the presence of p53 mutation. Thus, the overexpression of VEGF in SSc could play a causative role in the progression of angiosarcoma. It is important to recognize the association with angiosarcoma and SSc and perform a biopsy when suspicious lesion developed on sclerodermatous skin.

PS354 WHEN DOES SYSTEMIC SCLEROSIS IN CHILDOOD REALLY START? AN ORIGINAL CASE REPORT

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We report the case of a boy who first presented to clinical attention at the age of 4 years old, with an hyperpigmented scleroderma-like skin lesion on the upper left limb. Laboratory findings showed an ANA (titer 1:320 on Hep-2) and anti-Scl70 antibodies positivity. Clinical assessment did not reveal any sign of systemic involvement while the skin lesions were attributed to lichen aureus.

At the age of 8 years, the patient developed a second, hyperpigmented, linear scleroderma-like lesion on the contra lateral arm. The clinical and laboratory assessment showed no systemic involvement but persistence of the autoantibodies abnormalities.

At the age of 13, the patient experienced a Raynaud's phenomenon followed, one year later, by joint stiffness at the upper limbs.

At the age of 15, the patient came to our observation. Clinical examination revealed diffuse skin induration with bilateral elbows and wrists contractures, the mRodnan skin score was 17/51, digital tip scars and bilateral malleolar ulcerations were also present. On the right arm, a linear hyperpigmented atrophic skin lesion was still evident. The overall organs system revealed a scleroderma active pattern on capillary microscopy, a slow esophageal distal tract transit and a right bundle branch block with right axis deviation. Pulmonary function tests and chest HRCT were normal. Laboratory findings confirmed a positivity of ANA (>1:640), anti-Topoisomerase1 (Scl70) antibodies.

At the best of our knowledge, this is the first report of a patient developing specific autoantibodies positivity several years before the onset of SSc. Indeed, the role of linear scleroderma-like lesions far before the disease onset should be elucidated.

In the large cohort of 127 patients with paediatric onset systemic sclerosis, included in the PRES database, 18 (14.4%) showed the first clinical signs before the age of 4 years. Among these patients, only 2 (11,1%) were male; 94.4% ANA+ positivite and 4/15 patients (26.7%) in which anti-topoisomerase I antibodies test were performed were positive; none of these patients had renal involvement.

PS355 A RARE PRESENTATION OF NECK PAIN WITH RADICULOPATHY IN DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS

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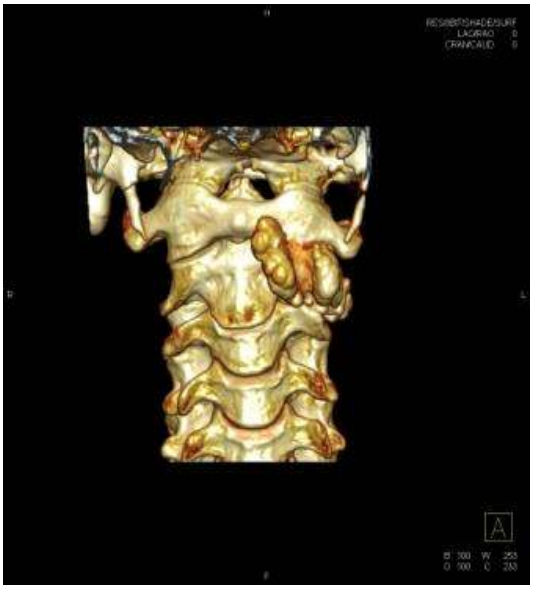
Background: Systemic sclerosis (SSc) is a chronic multisystemheterogeneous autoimmune disorder of unknown aetiology. Calcinosis is one of the manifestations which may occur in up to 25% cases.. It may vary from mild to severe and tumorous in nature especially in limited cutaneous systemic sclerosis (lcSSc). It is not so common in diffuse cutaneous systemic sclerosis (dcSSc). The precise cause and treatment of calcinosis remains elusive.

Case Presentation: 56 year lady with dcSSc (Scl-70 positive) with onset of puffy fingers and skin thickening as 1st non-raynaud manifestation three and half years ago and current problems of severe raynauds (despite Sildenafil), digital pitting, sclerodactyly, joint and tendinopathy (finger to palm test 2cm), usual interstitial pneumonitis and upper gastrointestinal manifestations along with primary nodal osteoarthritis presented with progressive worsening of neck pain with radiation of pain with tingling to lateral aspect of her face and neck without focal weakness or reflexic changes around mid 2012.
Light touch sensation was decreased over lateral aspect of neck and over C2-C3 dermatome region without tenderness in her spine. Cervical spine X-ray (fig. 1) showed degenerative changes and heterotrophic calcification. MRI of brainstem and cervical spine revealed abnormal marrow signal in the left lateral C2 vertebral body involving the articular facet along with extensive calcified mass with severe narrowing of left C2/C3 neural exit foramen as well as encroachment of the lateral aspect of pharynx.
She was referred to neurosurgeon and had CT of head & neck stealth scan (fig. 2) and angiogram as a preoperative workup.
Thereafter she had two stage procedures initially the lateral C1-C2 bony mass excision, C2 neural foramen decompression and thereafter the occipitocervical stabilization. She was on cervical hard collar for 6 weeks and mobilized thereafter with resolution of her symptoms.
Histology of the excised mass confirmed calcified material (von Kossa stain) within fibrocollagenous tissue with foreign type giant cell reaction without any evidence of caseating granulomatous inflammation or malignancy
Discussion: Heterotrophic calcification is known to occur in lcSSc as part of CREST syndrome and tends to occur in soft tissues over areas of trauma or repeated friction like extensor surfaces of phalanges, forearm and around bony prominences. They may occur in unusual sites such as intracerebral and paraspinal (at times leading to serious consequences such as spinal instability given the proximity to facet joints, erosions and even cord compression) and Guyon's canal leading to nerve entrapment. Very rarely dcSSc patients may have this phenomenon.
Plain X-rays are usually sufficient to reveal calcification, but CT scans allows better definition of calcification around the facet joints as well any erosive changes. MRI is usually undertaken to rule out possible intraspinal extension, cord or nerve compression.
Our lady had dcSSc rather than lcSSc and presented relatively early (compared to greater duration of SSc) with significant symptoms of nerve entrapment in the cervical region secondary to tumorous calcification which is rare and less well recognised complication of SSc.
We would suggest incorporating specific questions regarding any axial discomfort or symptoms of radiculopathy or nerve entrapment in the history and examination of all patients with SSc.



PS356 CONVINCING EFFECT OF BOTULINUM TOXIN A TO TREATMENT RESISTANT DIGITAL ULCERS ON TOES IN A PATIENT WITH SYSTEMIC SCLEROSIS. A CASE

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Digital ulcers on toes in patients with systemic sclerosis can be very painful, debilitating and reduce the quality of life significantly. Lack of understanding of the disease and treatment options can lead to unnecessary amputations or other surgical prodecures.
In this case we describe a successful combined treatment with local anesthetics and botulinum toxin A.
A 61 year old man with systemic sclerosis of limited type presented treatment refractory digital ulcers on toes. There was a poor response to conventional treatment with nifedipine, tadalafil, sidenalafil and ileoprost and the patient complained of severe pain and disturbed sleep. A combined treatment as above mentioned prevented a threatening amputation. The treatment was repeated every 12 week. The patient was satisfied with the treatment and expressed a significantly improved quality of life, reduction of pain and healing of wounds.
Using botulinum toxin A combined with local anesthetics to severe digital ulcers in patients with systemic sclerosus could be another option, when other treatments have been ineffective.
The mechanism appears to be related to the paralysis of the blood vessel innervation which improve the availability of oxygen.

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Because of rapid advances in the medical sciences, we recommend that independent verification of diagnoses and drug doses should be made.

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