POSTER SESSION

BASIC (PS01–PS58)

PS01. SERUM AND SPUTUM CAVEOLIN-1, TGF-β AND ET-1 LEVELS IN SCLERODERMA PATIENTS

N. Yilmaz[1], S. Olgun[2], R. Ahiskali[3], S. Karakurt[2] and S. Yavuz[1]
[1]*Department of Rheumatology,* [2]*Department of Chest Medicine and* [3]*Department of Pathology, Marmara University, Faculty of Medicine, Istanbul, Turkey*

Aim. Scleroderma (SSc) is a connective tissue disease characterized by diffuse endothelial damage and interstitial fibrosis. Despite the pathogenesis of SSc is unknown, some studies implied the role of caveolin-1 (Cav-1), TGF-β and ET-1 in interstitial fibrosis and vasculopathy. The aim was evaluate a non-invasive marker to determine interstitial lung involvement and its progression in the SSc patients.
Methods. he study population consisted of 55 SScs, 25 asthma patients and 16 healthy volunteers (HCs). All SSc patients were evaluated in every 6 months for clinical and laboratory parameters. ILD diagnosis and progression were determined pulmonary function tests and high-resolution CT. Serum and sputum Cav-1, TGF-β and ET-1 levels were measured by ELISA technique for all patients and controls.
Results. The mean (S.D.) age was 48 (25–72 years) years and the mean disease duration was 5 (1–29 years) years in SSc patients. Forty-five (81.8%) patients had interstitial lung disease, 8 (14.5%) had pulmonary hypertension and 22 (40%) had digital ulcer. The mean disease activity score was 5.4 (2.6). Forty-five (81.8%) patients were taking immunsppuressive treatment and seven (12.7%) patients were taking endothelin receptor antagonist treatment.
Serum Cav-1 levels were lower in SSc and asthma patients compared with HC [SSc 0.29 (0.11), asthma 0.27 (0.07) *vs* HC 0.39 (0.1) ng/ml] ($P < 0.01$).On the other hand sputum Cav-1 levels were lower in SSc patients compared with both groups [SSc 0.19 (0.04) *vs* asthma 0.24 (0.07), HC 0.28 (0.07) ng/ml] ($P < 0.001$). Although, there was no difference for serum TGF-β levels among the groups {SSc [8176 (4298)], asthma [7979 (4055)] and HC [8497 (3574 pg/ml)]}, the mean sputum TGF-β was significantly higher in the asthma patients compared with the other groups {Asthma [156.8 (147.5)] *vs* SSc [85.6 (85.6)] and HC [89.5 (83.7 pg/ml)]} ($P < 0.05$).Only mean serum ET-1 was significantly higher in the SSc patients compared with control groups {SSc [3.43 (6.05)] *vs* asthma [0.73 (0.53)] and HC [0.58 (0.29) fmol/ml)]} ($P < 0.01$).
Neither serum or sputum Cav-1 abnormality nor TGF-β or ET-1 levels correlated with disease activity, disease subsets, pulmonary hypertension and presence of digital ulcer or interstitial lung disease. No association was observed between alveolitis index, fibrosis index, total skor and Cav-1, ET-1 ve TGF-β serum and Cav-1, ET-1 sputum levels ($P > 0.05$). Only sputum TGF-β levels positively correlated with alveolitis index ($r = 0.34$) and inversely correlated with FVC measurements ($r: = -0.44$, $P < 0.05$). In SSc patients, Cav-1 levels decreased significantly in serum samples at 0, 6 and 12 months, whereas fibrosis score increased at chest CT scan at follow-up.
Conclusion. These results suggest that Cav-1 plays a role in the pathogenesis of the SSc and sputum TGF-β levels may be used as a marker for severity of interstitial lung involvement.

PS02. Th 17 CELLS ARE INCREASED IN THE SKIN OF SSc INDIVIDUALS

M. Truchetet[1], E. Raschi[2], C. Lubatti[3], L. Fontao[4], P. Meroni[2,3] and C. Chizzolini[1]
[1]*University Hospital – Immunology and Allergy, Geneva, Switzerland,* [2]*IRCCS – Istituto Auxologico Italiano,* [3]*Istituto Gaetano Pini – Rheumatology, Milan, Italy and* [4]*University Hospital – Dermatology, Geneva, Switzerland*

Background. In SSc inappropriate T-cell responses are thought to participate in initiating events ultimately leading to excessive extracellular matrix deposition and fibrosis. The recently described Th 17 subset has been shown to be increased in the peripheral blood of SSc individuals. The aim of our study was to assess the presence of Th17 cells in the SSc and healthy skin.
Material and methods. Upon informed consent and approval by the ethical committee, skin samples were obtained from eight SSc and eight healthy donors used as controls (ctrl). T-cell lines from the skin of all the individuals were grown in the presence of IL-2, each in four independent replicates. Intracellular localization of IL-17A, IL-22, IL-4 and IFN-γ in CD4+ T cells as well as the surface expression of chemokine receptors were assessed by multiparametric FACS analysis. Paraffin embedded skin biopsies were stained for CD3/IL-17 or α-smooth muscle actin/IL-17 and positive cells frequency determined by laser scanning confocal microscopy.
Results. In T-cell lines generated from the skin 79.1% (10.5) and 73.7% (16.9) were CD4+ T cells in SSc and ctrl, respectively. Production of IL-17A, IL-22, IL-4 and IFN-γ was detected in all T-cell lines. Statistically significant differences were observed in the subsets co-producing IL-17A and IL-22 [5.6% (7.9) *vs* 2.5 (1.6)] as well as IFN-γ and IL-4 [7.8% (4.6) *vs* 2.4% (1.8)], which were more frequent in SSc compared with ctrl. As expected, T-cell lines generated from the skins were skewed for high expression of CCR4 compared with counterparts from the peripheral blood. In addition, the percentage of CXCR3+ cells was higher in SSc [48.1% (17.9] compared with ctrl [29.5% (13.0)]. Finally, histological identification of CD3+IL-17+ cells was possible in both SSc and ctrl skin, and Th17 cells were more frequent in SSc (3.5 cells/field) than ctrl (1.7 cells/field) ($P = 0.05$). Furthermore, myofibroblasts were only found in SSc samples and always in proximity with IL-17 positive cells.
Conclusions. Our preliminary data indicate that Th17 co-producing IL-17A and IL-22 are increased in SSc skin, which may suggest a role for these cells in the pathogenesis of the disease, particularly since myofibroblasts were preferentially located in proximity of IL-17 positive cells. These results provide new rationale for targeting IL-17 and the Th17 differentiation pathway as novel approaches to harness the clinical course of SSc.

PS03. S100A4 IS A NOVEL MEDIATOR OF TGF-β DRIVEN FIBROBLASTS ACTIVATION AND DERMAL FIBROSIS IN SSc

M. Tomcik[1], K. Palumbo[2], P. Zerr[2], B. G. Fuernrohr[2], J. Avouac[3], A. Horn[2], C. Dees[2], A. Akhmetshina[2], C. Beyer[2], L. Andres Cerezo[1], R. Becvar[1], O. Distler[4], M. Grigorian[5], L. Senolt[1], G. Schett[2] and J. H. W. Distler[2]
[1]*Department of Clinical and Experimental Rheumatology, Institute of Rheumatology, 1st Faculty of Medicine, Charles Univ, Prague, Czech Republic,* [2]*Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany,* [3]*Rheumatology A Department, Paris Descartes University, Cochin Hospital, Paris, France,* [4]*Experimental Rheumatology and Zurich Center of Integrative Human Physiology, University Hospital, Zurich, Switzerland and* [5]*Institute of Cancer Biology, Danish Cancer Society, Copenhagen, Denmark*

Background. S100A4 is a calcium-binding protein exerting regulatory functions in diverse biological processes. It promotes cancer progression and metastasis by regulating remodelling of extracellular matrix.
Objectives. To investigate the role of S100A4 in SSc and experimental dermal fibrosis.
Methods. Expression of S100A4 was determined by real-time PCR, immunohistochemistry and western blot. Collagen synthesis was quantified by real-time PCR, SirCol- and hydroxyproline assay. Bleomycin-induced dermal fibrosis and tsk-1 model were used to evaluate the role of S100A4 *in vivo* using mice deficient for S100A4 (−/−) and wild-type littermates (+/+).
Results. Expression of S100A4 was increased in the skin of SSc patients compared with healthy controls and clearly colocalized with α-smooth muscle actin-positive fibroblasts and phospho-Smad3 expression. Over expression of S100A4 persisted in cultured SSc fibroblasts and might contribute to their activated phenotype. S100A4 expression was similarly increased in the skin of both bleomycin-challenged and tsk-1 mice. TGF-β stimulation of human fibroblasts increased expression of S100A4 protein. siRNA-mediated knockdown

of S100A4 fully abrogated the stimulatory effects of TGF-β on collagen synthesis of SSc fibroblasts. Stimulation of fibroblasts with S100A4 increased collagen production in a dose-dependent manner; this effect was abrogated in fibroblasts transfected with Smad3 siRNA. Similarly, endogenous overproduction of S100A4 in fibroblasts transfected with plasmid construct overexpressing S100A4-increased collagen production and expression of pSmad3, and luciferase activity of col1a2 promoter reporter and Smad3 (CAGA) adenovirus reporter. Consistent with the role of S100A4 as a novel mediator of profibrotic effects of TGF-β, mice lacking S100A4 were protected from experimental dermal fibrosis. In bleomycin-induced dermal fibrosis and tsk-1 model, respectively, knockdown of S100A4 decreased dermal thickening by 74 (3)% ($P < 0.01$) and 66 (8)% ($P < 0.001$), hydroxyproline content by 56 (4)% ($P < 0.01$) and 39 (5)% ($P < 0.01$) and myofibroblast counts by 91 (17)% ($P < 0.01$) and 64 (5)% ($P < 0.001$). Reduced induction of dermal fibrosis in S100A4 −/− mice might result from inhibition of TGF-β signalling as evidenced by reduced nuclear accumulation of pSmad 3 in the skin of S100A4 −/− mice and decreased mRNA expression of TGF-β target genes PAI-1 and Smad 7.

Conclusions. This is the first study demonstrating the role of S100A4 in SSc. We show that S100A4 is up-regulated in SSc in a TGF-β-dependent manner, and that inhibition of S100A4 reduces collagen synthesis in activated SSc fibroblasts. Knockdown of S100A4 protected from experimental fibrosis in bleomycin-induced dermal fibrosis and tsk-1 model due to inhibition of TGF-β signalling. Thus, S100A4 might be a candidate for novel anti-fibrotic therapies.

PS04. NOVEL BIOMARKERS OF DYSREGULATED ANGIOGENESIS ARE NOT SPECIFIC TO PULMONARY ARTERIAL HYPERTENSION IN SSc

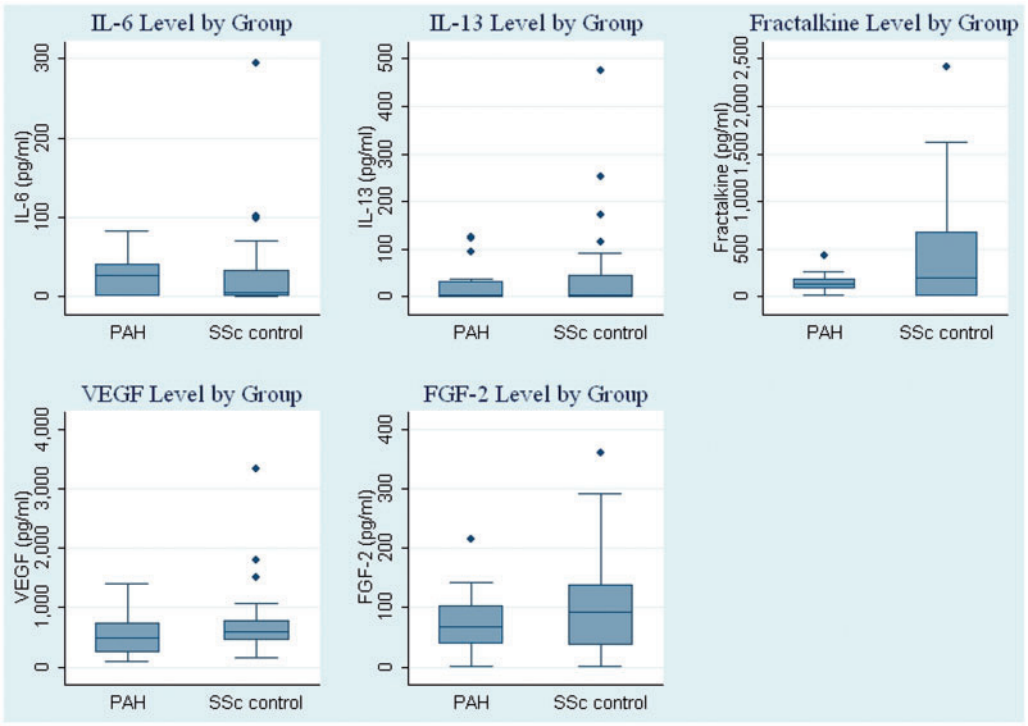
V. Thakkar[1], K. Patterson[2], W. Stevens[1], J. Byron[1], O. Moore[1], J. Roddy[3], J. Zochling[4], J. Sahhar[5], P. Nash[6], K. Tymms[7], P. Youssef[8], S. Proudman[9], M. Nikpour[1] and P. Hissaria[2]
[1]*Department of Rheumatology, St Vincents Hospital, Melbourne,*
[2]*Royal Adelaide Hospital – Immunology Directorate, Adelaide,*
[3]*Department of Rheumatology, Royal Perth HospitalPerth,*
[4]*Department of Rheumatology, The Menzies Institute, Hobart,*
[5]*Department of Rheumatology, Monash Medical Centre, Melbourne*
[6]*Sunshine Coast Rheumatology – Research Institute, Maroochydore,*
[7]*Department of Rheumatology, Canberra Rheumatology, Canberra,*
[8]*Department of Rheumatology, Royal Prince Alfred Hospital, Sydney and* [9]*Department of Rheumatology, Royal Adelaide Hospital, Adelaide, Australia*

Introduction. Dysregulated angiogenesis mediated by cytokines, chemokines and growth factors has been postulated to underlie the pathogenesis of SSc-related pulmonary arterial hypertension (PAH). We undertook an exploratory study of these factors evaluating whether a single serum measurement could be used as a biomarker in SSc-PAH.

Methods. Two main clinical groups were selected from the Australian Scleroderma Cohort Study (ASCS): Group 1 ($n = 20$) had definite PAH defined by Dana Point criteria on RHC; Group 2 ($n = 26$) were SSc controls with no evidence of cardiopulmonary disease. Serum IL-6, IL-13, FGF-2, VEGF and fractalkine levels were measured with the commercially available Millipore Milliplex MAP Human cytokine/chemokine panel (Millipore Corporation, Billerica, MA, USA). All sera were prospectively collected in the ASCS and frozen at −80°C until the time of measurement. All patients in Group 1 had their pre-treatment sera assayed. Statistical analysis was performed using a two-tailed Mann–Whitney U-test and $P < 0.05$ were considered as statistically significant.

Results. Patients in Group 1 (PAH) were older at the time of study [62 (10.3) *vs* 48.4 (10.1) years] and had a longer disease duration [20.4 (2.9) *vs* 7.6 (1.3) years] than patients in Group 2 (controls). There were no significant differences in gender and disease subtype between groups. The mean echocardiography defined systolic pulmonary artery pressure (PAP) was 65.3 (27.8) mmHg (Group 1) *vs* 26.3 (2.6) mmHg (Group 2). The mean PAP in Group 1 at RHC was 39.5 (±12.4) mmHg. There were no significant differences seen in levels of IL-6 ($P = 0.23$), IL-13 ($P = 0.97$), VEGF ($P = 0.14$), FGF-2 ($P = 0.34$) and fractalkine ($P = 0.12$) in SSc patients with and without PAH. Patients with diffuse disease appeared to have higher VEGF levels ($P = 0.05$) than those with the limited subtype.

Conclusions. We did not find an association between serum IL-6, IL-13, FGF-2, VEGF, fractalkine and SSc-PAH. While these factors may play a role in the pathogenesis of SSc and SSc-PAH, their serum levels do not appear to correlate with clinical PAH.



PS05. SERUM ICAM-1 LEVELS ARE RELATED TO THE PRESENCE OF INTERSTITIAL LUNG DISEASE IN SSc

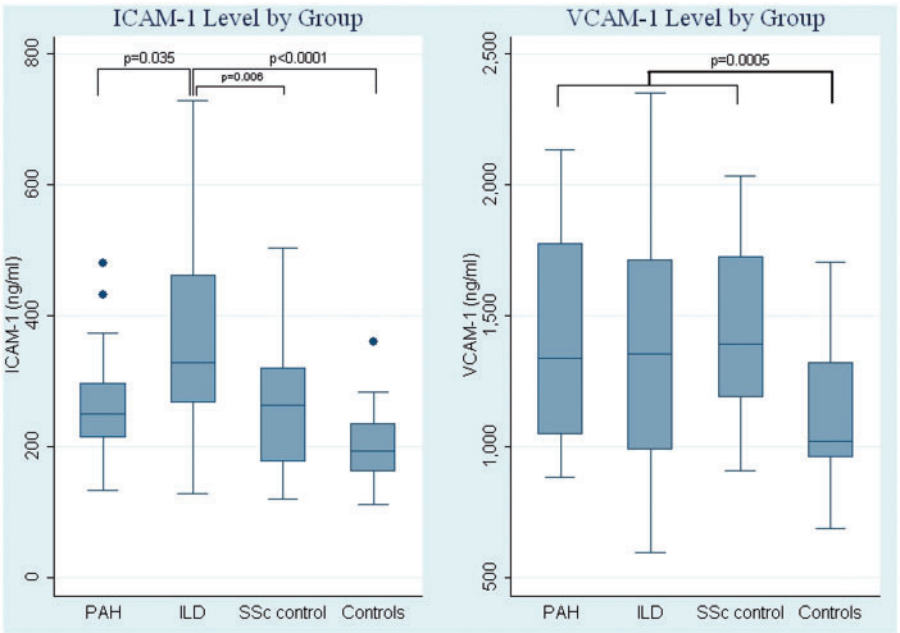
V. Thakkar[1], K. Patterson[2], W. Stevens[1], J. Byron[1], O. Moore[1], J. Roddy[3], J. Zochling[4], J. Sahhar[5], P. Nash[6], K. Tymms[7], P. Youssef[8], S. Proudman[9], P. Hissaria[2] and M. Nikpour[1]
[1]*Department of Rheumatology, St Vincents Hospital, Melbourne,* [2]*Royal Adelaide Hospital – Immunology Directorate, Adelaide,* [3]*Department of Rheumatology, Royal Perth Hospital, Perth,* [4]*Department of Rheumatology, The Menzies Institute, Hobart,* [5]*Department of Rheumatology, Monash Medical Centre, Melbourne,* [6]*Sunshine Coast Rheumatology – Research Unit, Maroochydore,* [7]*Department of Rheumatology, Canberra Rheumatology, Canberra,* [8]*Department of Rheumatology, Royal Prince Alfred Hospital, Sydney and* [9]*Department of Rheumatology, Royal Adelaide Hospital, Adelaide, Australia*

Introduction. Recent studies have suggested elevated intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) levels may be markers of pulmonary arterial hypertension in SSc (SSc-PAH).
Methods. Four clinical groups were selected from the Australian Scleroderma Cohort Study: Group 1 ($n = 20$) had definite PAH defined by Dana Point criteria on right heart catheterization; Group 2 ($n = 18$) had interstitial lung disease (ILD) defined by moderate or severe ILD on HRCT and an FVC $< 85\%$; Group 3 ($n = 23$) were SSc controls with no evidence of cardiopulmonary complications; Group 4 ($n = 34$) were normal healthy controls. In selecting patients for this study patients were excluded if they had LV dysfunction or eGFR < 30 ml/min. Serum VCAM-1 and ICAM-1 levels were measured using the Millipore Milliplex MAP Human 2-Plex Panel (Millipore Corporation, Billerica, MA, USA). All sera were prospectively collected and frozen at -80°C until the time of measurement. In Group 1, sera were collected pre-treatment for PAH. For statistical analysis, data were transformed to obtain a normal distribution and analysis of variance with two-group comparisons was used to determine differences in the clinical characteristics and soluble adhesion molecule levels between and within groups.
Results. As seen in Fig. 1, mean ICAM-1 levels were significantly higher in the ILD group compared with the PAH [380.4 (168.3) *vs* 266.4 (88.4) ng/ml, $P = 0.035$), SSc control [380.4 (168.3) *vs* 257.3 (97.8) ng/ml, $P = 0.006$] and healthy control [380.4 (168.3) *vs* 201.8 (57.2) ng/ml, $P < 0.0001$) groups. Notably, there was no significant difference between the PAH group and SSc or healthy normal controls. Among those with ILD there were no significant differences in ICAM-1 levels between those who did or did not have previous CYC treatment for SSc–ILD ($P = 0.36$). The significantly increased ICAM-1 level in the ILD group was independent of disease subtype ($P = 0.69$). VCAM-1 levels were shown to be significantly higher in SSc patients than normal healthy controls [1420.0 (53.4+) *vs* 1125.6 (46.9) ng/ml, $P = 0.0005$) but were not shown to be associated with a particular disease phenotype or subtype.
Conclusions. ICAM-1 levels are associated with the presence of significant SSc–ILD. However, ICAM-1 level does not appear to be a specific marker for the presence of PAH. VCAM-1 levels are raised in SSc patients but are not specific to ILD or PAH. Further studies of ICAM-1 in SSc–ILD are warranted.

PS06. TRIDIMENSIONAL RECONSTRUCTION, BIOCHEMICAL AND MOLECULAR PROFILE OF COLLAGEN V IN SKIN AND LUNG FIBROBLASTS CULTURE FROM SSc INDICATE A FAILING IN FIBRILOGENESIS

W. Teodoro[1], J. Morais[1], P. Martin[1], A. P. P. Velosa[1], S. Carrasco[1], R. B. C. Souza[1], M. L. Katayama[2], C. Goldeinstein-Schainberg[1], E. R. Parra[3], V. L. Capelozzi[3] and N. H. Yoshinari[1]
[1]*Division of Rheumatology,* [2]*Division of Oncology and* [3]*Department of Pathology, School of Medicine, University of São Paulo, São Paulo, Brazil*

Background. The type V collagen (COL V) mutations are involved in collagen vascular diseases, such as SSc, in which an unusual accumulation of this collagen was demonstrated (Pathol Res Pract 2004; 200:681). In this context, our purpose was to analyse the 3D reconstruction, biochemical and molecular profile of COL Vα1 and α2 chains in skin and lung fibroblasts culture from patients with SSc.
Methods. Lung biopsies of seven patients, skin of six patients and respective matched controls were obtained from SSc according ACR. For fibroblast culture skin and lung evaluations were used the following score: intense expression (1–4), fibroblast number/field (1, 2) and collagen fibres architecture (1–3). The total evaluations were: mild (3–5), moderate (6, 7) and severe (8, 9). COLV 3D reconstruction was performed by confocal microscopy, COL Vα1 and Vα2 gene expression in fibroblasts of skin and lung was performed in PCR–RT and COLV protein expression by immunoblotting.
Results. The structure of COL V fibre in 3D reconstruction showed distorted and strongly thickened fibres in skin and lung fibroblasts with irregular bundles of COL V distributed in parallel and perpendicular arrangements resulting in a dense network in SSc patients compared with thin fibres pattern from the healthy controls. Collagen quantification showed increase of COL V fibres expression in SSc cutaneous fibroblast [82.5 (9.5)% *vs* 47.5 (9.5)%, $P = 0.002$] and lung fibroblast 38.87 (2.99)% *vs* 20.33 (7.50)%, $P = 0{,}002$) compared with respective controls. The molecular evaluation demonstrated an increased of COL Vα1 and α2 mRNA expression in SSc fibroblast skin when compared with control [1.375 (0.373) au *vs* 0.0047 (0.0013) au, $P = 0.05$). Similar results were observed in lung [1.61 (0.654) *vs* 0.99 (0.51) au; $P = 0.05$).The proportion COL Vα1/COL Vα2 mRNA in fibroblast lung and skin was higher in SSc than in controls being the chains ratio 1 : 2.



COL V chains from skin and lung fibroblasts presented alteration of molecular weight of the quoted chain.
Conclusion. The overexpression and the unusual organization of COLV fibres, besides the biochemical changes, suggest an interference with the fibrillogenesis process in skin and pulmonary fibrosis from SSc patients, reinforcing the participation of this collagen in pathogenesis of SSc and open new therapeutic perspectives for these patients.

PS07. COLLAGEN V AND DECORIN INTERACTION ARE INVOLVED IN PULMONARY FIBROSIS OF SSc

W. Teodoro[1], A. Marcelino[1], I. C. Brindo da Cruz[1], A. P. P. Velosa[1], P. Martin[1], S. Carrasco[1], C. Goldenstein-Schainberg[1], E. R. Parra[2], V. L. Capelozzi[2] and N. H. Yoshinari[1]
[1]*Division of Rheumatology and* [2]*Department of Pathology, School of Medicine, University of São Paulo, São Paulo, Brazil*

Aims. Type V collagen (COL V) is involved in SSc pathogenesis since immunization of health rabbits with this protein induces an experimental model reproducing the main pathogenic manifestation of this disease. We have demonstrated an increased amount of unusual COL V fibrils deposition in lung of SSc patients indicating an important role for this protein in fibrosis. Formation of fibrotic tissue can be induced both by cytokines and cell–matrix interaction involving signalization mechanism. COL V and decorin participate of this mechanism interfering with fibrilogenesis. The aim was to evaluate COL V and decorin expression in pulmonary tissue and to characterize biochemical profile of COLV from lung fibroblasts culture from SSc patients.
Methods. We evaluated COL V and decorin expression as well as 3D reconstruction using IF in lung specimens from six patients with SSc without pulmonary hypertension and six normal individuals died from trauma. The amount of COL V in lung sections was evaluated with software Image Pro-Plus 6.0 in Olympus-BX51. Quantitative immunoblotting was used to characterize COL V biochemistry from lung fibroblasts culture.
Results. It was found that the structure of COL V fibres was distorted and strongly thickened in lung tissue from SSc patients compared with thin fibres pattern in the healthy controls. Decorin was distributed around COL V fibrils in the bronchovascular interstitium and vascular walls. Histomorphometric analysis of SSc lung demonstrated increased expression of both COL V and decorin when compared with the control ($68.52 + 7.36\%$ *vs* $5.01 + 2.12\%$, $P < 0.01$ and $22.99 + 0.59\%$ *vs* $32.93 + 3.81\%$, $P = 0.01$, respectively). The semiquantitative immunoblotting detected an increased high molecular weight COL V fraction in patients when compared with the controls ($P = 0.02$).
Conclusions. The overexpression and unusual organization of COL V fibres with biochemical changes associated to increased decorin indicates that matrix signalization pathway is involved in COL V fibrillogenesis process in SSc pulmonary fibrosis.

PS08. NOTCH PATHWAY IS ACTIVATED IN SSc

K. Takagi[1], Y. Kawaguchi[1], Y. Ota[1], A. Tochimoto[1], C. Fukazawa[1] and H. Yamanaka[1]
[1]*Institution of Rheumatology, Tokyo, Japan*

Objective. SSc is a chronic disease of unknown aetiology characterized by autoimmunity, vascular damage and progressive fibrosis of the skin and internal organs. However, it has not been elucidated how the fibrosis is achieved. Therefore, any effective treatments have not been established. Recently, it has been reported that Notch signalling pathway was activated in lesional skin of SSc patient. Notch signalling pathway has been known to be associated with human development process and differentiation. Alterations in Notch signalling are implicated in the pathogenesis of several human diseases such as T-cell acute lymphoblastic leukaemia, melanoma. On the other hand, Notch pathway is context dependent, and the effects for fibrosis may depend on the cellular and physiological environment in which fibroblast or connective tissue is placed. The aim of our study is to investigate whether Notch signalling pathway contributes to the uncontrolled activation of fibrosis in SSc.
Methods. The expression of Notch receptor and its ligand was determined by RT–PCR, western blot (WB) analysis and flow cytometry (FCM) in cultured skin fibroblasts derived from SSc and healthy controls (HC). To investigate functional significance of Notch signalling pathway, Notch intracellular domain was retrovirally transduced with SSc-derived fibroblast. Then, concentrations of type I procollagen in the fibroblast supernatants were measured using EIA kit. After stimulating by TGF-β and PDGF, the expression of Notch was determined by real-time PCR and WB.
Results. Expression of Notch 1, 2 and 3 mRNAs was lower in SSc-derived fibroblast than HC. WB and FCM analysis revealed that SSc-derived fibroblasts showed reduced expression of Notch 1 than fetal-derived control fibroblast. However, even in HC-derived fibroblasts, Notch expression was variable. These indefinites results prompt us to investigate procollagen type 1C levels in supernatants of cultured mock or NICD-transduced SSc-derived fibroblasts. NICD transduction into SSc-derived fibroblasts slightly augmented procollagen type 1C production. Expression of Notch was up-regulated after TGF-β stimulation, but not by PDGF stimulation.
Conclusion. Importance of Notch signalling pathway for aetiology of fibrosis in SSc was provided. Nevertheless, obvious relationship between Notch signalling pathway and fibrosis was not elucidated. Complexity and context dependency of Notch signalling pathway contributing to fibrosis was speculated.

PS09. A MUC5B PROMOTER POLYMORPHISM AND PULMONARY FIBROSIS IN SSc

C. Stock[1], H. Sato[1], C. Fonseca[2], G. E. Lindahl[1], T. M. Maher[1], A. U. Wells[1], C. P. Denton[2], D. J. Abraham[2] and E. A. Renzoni[1]
[1]*Interstitial Lung Disease Unit, Royal Brompton Hospital and* [2]*Centre for Rheumatology, Royal Free Hospital, London, UK*

Introduction. Mucin 5, subtype B (MUC5B), is one of the main gel-forming mucins expressed in the airways. A single-nucleotide polymorphism (SNP) (rs35705950) located 3-kb upstream of MUC5B has been shown to be strongly associated with both familial interstitial pneumonia (FIP) and sporadic idiopathic pulmonary fibrosis (IPF). Although SSc-associated interstitial lung disease (SSc-ILD) differs from IPF in many respects, including better survival for equivalent disease severity, alveolar epithelium abnormalities occur in both diseases. We therefore investigated if this MUC5B polymorphism also represented a risk factor for pulmonary fibrosis in SSc.
Methods. To investigate involvement of this variant in susceptibility to pulmonary fibrosis in SSc, UK Caucasian patients (SSc, $n = 460$; IPF, $n = 95$) were genotyped for rs35705950 using a commercially available assay (TaqMan, C__1582254). Pulmonary fibrosis was defined on the basis of chest imaging and the presence of a restrictive lung function pattern.
Results. The minor allele frequency (MAF) of rs35705950 in the IPF cohort (0.28) was similar to that published by Siebold *et al.* (0.37), while the frequency in the SSc cohort (0.12) was similar to that reported for the general population (0.09). The frequency in the UK SSc and IPF cohorts were significantly different from each other ($P < 0.0001$). There was no significant difference ($P = 0.47$) in the SNP frequency in the SSc patients who did ($n = 232$, MAF = 0.11) and did not ($n = 228$, MAF = 0.12) have pulmonary fibrosis. A subgroup of SSc patients with pulmonary fibrosis were categorized as having either limited ($n = 36$, MAF = 0.15) or extensive ($n = 98$, MAF = 0.12) lung disease according to a validated staging system. No significant difference between the groups was observed ($P = 0.44$). There was also no significant difference seen when the SSc cohort was analysed according to autoantibody; presence ($n = 113$, MAF = 0.12) or absence ($n = 301$, MAF = 0.11) of ATA ($P = 0.31$), presence ($n = 119$, MAF = 0.13) or absence ($n = 295$, MAF = 0.12) of ACA ($P = 0.65$) or presence of either ATA or ACA ($P = 0.94$).
Conclusion. In contrast to FIP and IPF, we find no evidence that the MUC5B promoter SNP rs35705950 is associated with susceptibility to, or severity of, pulmonary fibrosis in SSc, further highlighting differences in disease pathogenesis of idiopathic and SSc-associated ILD.

PS10. SILENCING OF THE WNT SIGNALLING INHIBITOR GENE, WIF1, IN FIBROBLASTS DERIVED FROM SSc PATIENTS: ROLE OF OXIDATIVE STRESS AND DNA DAMAGE

T. Spadoni[1], S. Svegliati[1], G. Marrone[2], A. Grieco[1], L. DeGennaro[1], A. Gabrielli[1] and E. Avvedimento[3]
[1]*Dipartimento di Scienze Cliniche e Molecolari, Università Politecnica delle Marche, Ancona,* [2]*Oncogenomic Center, NOGEC, CEINGE and* [3]*Dipartimento di Biologia e Patologia cellulare e molecolare, Università Federico II, Naples, Italy*

Background. SSc is an autoimmune disease characterized by extensive fibrosis and vascular lesions. WNT family is a large group of highly conserved glycoproteins implicated in developmental processes and recently in carcinogenesis, ageing and fibrosis.

WNT signalling is tightly controlled by several negative regulators, such as WIF1, WNT inhibitor factor 1. WIF1 is frequently silenced in human cancer by DNA methylation and, recently, its inhibition has been associated to ageing of mesenchymal stem cells and fibrosis, attributed to unrestrained WNT signalling.
We have recently demonstrated that WIF1 expression was consistently down-regulated in fibroblasts derived from SSc patients, through histone deacetylation and not through DNA methylation, as occurs in cancer.
Objective. In order to identify the primary cause of silencing of WIF1 in SSc, we have analysed its expression in normal fibroblasts subjected to severe oxidative stress and the role of proteins involved in DNA damage response, such as ATM and 53BP1.
Methods. Total RNA was isolated and reverse transcribed, according to the manufacturer's instructions (Bio-Rad). Quantitative real-time PCR reactions were performed using SYBR Green PCR Master Mix (Bio-Rad). To analyse protein expression, cells were lysed with RIPA buffer and subjected to western blot with specific antibodies. For immunocytochemistry, cells were fixed in PFA, permeabilized and labelled with specific antibodies to be evaluated through fluorescence microscopy.
Results. SScIg silenced WIF1 expression via PDGFR. On the other hand, PDGF stimulated acutely WIF expression. These effects were mediated by ROS. Incubation of normal fibroblasts with high doses of hydrogen peroxide (1 mM) down-regulated WIF1 expression and increased ATM activation and 53BP1 protein levels. These alterations were reverted by ATM kinase inhibitor.
Conclusions. Our data indicate that WIF1 expression is directly linked to oxidative stress and DNA damage and is selectively down-regulated in cells incubated with SScIg or insulted by oxidative stress. All these data suggest that the ultimate cause of silencing WIF-1 in SSc is DNA damage.

PS11. SSc AND POLYMOPHYISMS IN GENES RELATED TO COMPLEMENT REGULATORY PROTEINS

C. Scambi[1], V. La Verde[1], S. Jokiranta[2], L. De Franceschi[1], P. Caramaschi[1], P. Guarini[1] and D. Biasi[1]
[1]*Department of Clinical and Experimental Medicine, University of Verona, Verona, Italy and* [2]*Department of Bacteriology and Immunology, Haartman Institute, University of Helsinki, Helsinki, Finland*

Studies on pathogenesis of SSc suggest that endothelial cell damage may be the initiating event in SSc (Abraham DJ, Rheumatology 2009]. In different clinical conditions such as early stage or diffuse pattern, an abnormal complement activation may contribute to an inadequate protection of the endothelial cell surface. In SSc patients higher plasma levels of C3d, C4d and Ba (Senaldi, Arthr Rheum 1989) and lower levels of C3 and C4 have been observed compared with healthy controls (Cuomo, Reum 2008).
Recently, we have reported alteration of alternative complement pathway activation possible due to complement factor H (CFH) dysfunction in SSc patients, (Scambi, PLos One 2010]. In addition, Venneker *et al*. have previously shown that endothelium of lesional and non-lesional skin of SSc patients expressed decreased amounts of membrane cofactor protein (MCP) and decay-accelerating factor (Venneker, Lab Invest 1994).
In order to evaluate whether the abnormality of FH function observed in SSc patients was related to molecular defect of FH or other partners involved in the complement pathway regulation such as MCP or factor-I (FI), we screened six patients with SSc for mutations and polymorphisms (SNPs) in CFH, MCP and FI genes. The enrolled patients were affected by dcSSc pattern and resulted positive to the sheep red blood cells lysis test that evaluates the activation of complement via the alternative pathway.
Genomic DNA was extracted from buffy coat by using Maxwell 16 Instrument (Promega) and Maxwell 16 Blood DNA purification Kit (Promega) according to manufacturer's instruction. The genetical analysis was outsourced from Secugen Diagnostic (Spain). Exons and promoter regions of CFH, MCP and FI genes were analysed and compared with the DNA reference in the databases Ensemble, NCBI and aHUS database. Genotypes for common SNPs in these genes were also analysed.
The full-length CFH, FI and MCP genes were sequenced and no mutations were found, except for a patient, who presents a nucleotide change in heterozygosis in the FI gene (c.1534 + 5G > T). The following SNPs for MCP gene: c.-652G, c.-366G, c.989-78A and *897C were found in four patients and the c.-184A and c.-1204C SNPs for CFH gene were found in two patients with SSc
This finding suggests that SNPs in genes related to complement regulatory proteins might be involved in the pathogenesis of the disease; a further study in a larger SSc population is ongoing.

PS12. OVERPRODUCTION OF EXTRACELLULAR MATRIX IN SCLERODERMA KERATINOCYTES IS NOT ASSOCIATED WITH ACTIVATION OF TGF-β/SMAD SIGNALLING

A. Philip[1], K. W. Finnson[1], I. Fanelus[1], M. Baron[2] and X. Y. Man[1]
[1]*Department of Surgery and* [2]*Department of Rheumatology, McGill University, Montreal, Canada*

Previous mechanistic studies have focused on the fibroproliferative process in the dermal fibroblasts in scleroderma (SSc). However, emerging evidence suggests that other cell types also play a crucial role in the pathogenesis of SSc. Although the mechanism underlying the excessive fibrosis in SSc is poorly understood, TGF-β is thought to play a critical role in this process in SSc fibroblasts. However, whether TGF-β signalling pathways play a role in extracellular matrix (ECM) production in SSc keratinocytes remains to be determined. In the present study, we examined the production of ECM components in epidermal keratinocytes and the potential role of the TGF-β/Smad signalling pathway in this process. We hypothesized that (i) epidermal keratinocytes exhibit increased production of ECM in SSc, thereby contributing to the pathogenesis of SSc; and (ii) excessive ECM production by SSc keratinocytes is associated with enhanced activation of TGF-β/Smad pathways. Our approach involved determining the levels of ECM proteins [type I collagen, plasminogen activator inhibitor-1 (PAI-1) and fibronectin], TGF-β type I receptors (ALK5 and ALK1) and phosphorylated Smads (Smad2/3 *vs* Smad1/5) in SSc and normal skin by immunohistochemistry and in SSc and normal human skin keratinocytes by western blot analysis. Our results show that SSc keratinocytes display increased type I collagen, PAI-1, fibronectin and connective tissue growth factor expression *in vivo* and *in vitro*, as compared with normal keratinocytes. Contrary to our expected results, SSc keratinocytes exhibit decreased TGF-β type I receptor (ALK5 and ALK1) expression levels and reduced phosphorylated levels of Smad2/3 and Smad1/5 *in vivo* and *in vitro*, as compared with normal keratinocytes. These data suggest that epidermal keratinocytes contribute to the fibrotic process in SSc. Moreover, the excessive ECM production by SSc keratinocytes is not associated with activation of TGF-β/Smad pathways. Our findings highlight a major difference in the mechanism by which keratinocytes and fibroblast aberrantly overproduce ECM components in SSc.

PS13. COLLAGEN V-INDUCED NASAL TOLERANCE PROMOTES DECREASE IN TOPO I PROTEIN SYNTHESIS AND PULMONARY FIBROSIS OF SSc MODEL

A. P. Velosa[1], W. R. Teodoro[1], M. R. Callado[1], A. S. Filho[1], S. M. Fernezlian[2], M. L. Katayama[3], E. R. Parra[2], V. L. Capelozzi[2] and N. H. Yoshinari[1]
[1]*Division of Rheumatology,* [2]*Department of Pathology and* [3]*Division of Oncology from Departmento os Radiology, School of Medicine, University of São Paulo, São Paulo, Brazil*

Background. Autoantibodies against topo I (anti-Scl-70) are found to be associated with increased mortality and correlate with the extent of pulmonary fibrosis in SSc. To evaluate anti-Scl-70 antibodies and topo I expression in lung and to correlate with pulmonary fibrosis in experimental SSc after collagen V (COL V)-induced nasal tolerance.
Methods. Female New Zealand rabbits ($n = 12$) were immunized with 1 mg/ml of COL V in Freund's adjuvant (IM). After 150 days, six immunized animals were tolerated by nasal administration of type COL V (25 μg/day) (IM-TOL), daily during 60 days. Anti-Scl-70 antibodies were evaluated by ELISA. Immunohistochemistry, histomorphometry and RT–PCR evaluated pulmonary topo I expression, types I, III and V collagen and TGF-β expression in pulmonary parenchyma.
Results. A significant decrease in topo I expression by pulmonary endothelial cells was found comparing IM-TOL *vs* IM [29.86 (10.48) *vs* 76.11 (20.91), $P = 0.019$]. No difference was found for the anti-Scl-70 frequency after tolerance. Type V collagen content around the small vessels [0.371 (0.118) *vs* 0.874 (0.282), $P < 0.001$] and bronchioles [0.294 (0.139) *vs* 0.646 (0.172), $P < 0.001$], beyond mRNA expression to types I [0.10 (0.07) *vs* 1.0 (0.528), $P = 0{,}002$] and V [1.12 (0.42) *vs* 4.74 (2.25), $P = 0{,}009$] collagen decreased in IM-TOL, when compared with IM TGF-β expression decreased in endothelial [10.77 (4.3) *vs* 43.5 (5.7), $P < 0{,}0001$] and smooth muscle cells [9.93 (3.77) *vs* 53.68 (4.06), $P < 0{,}0001$] from pulmonary vessels, epithelial cells [6.03 (1.47) *vs*

13.65 (1.39), $P < 0{,}0001$] and interstitial fibroblasts [11.55 (1.88) *vs* 20.13 (1.60), $P < 0{,}0001$] in IM-TOL compared with IM.
Conclusions. The results showed that a direct link between nasal type V collagen tolerance and a decline in topo I expression may reduce pulmonary fibrosis, suggesting that strategies aimed at preventing the increase of the type V collagen synthesis, or the local responses to increased topo I expression, may have a greater impact in SSc.

PS14. ATORVASTATIN ATTENUATES SKIN FIBROSIS THROUGH THE PI3K PATHWAY

Y. Ota[1], Y. Kawaguchi[1], K. Takagi[1] and H. Yamanaka[1]
[1]*Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan*

Background/Purpose. Atorvastatin, a member of the statin class of drugs, is an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. This drug offers several beneficial effects in treating conditions with vascular involvement, such as RP and digital ulcers in patients with SSc, by recruiting circulation endothelial progenitor cells. In addition to their well-known effects in down-regulation of serum cholesterol, statins induce pleiotropic effects at the cellular level, regulating intracellular signalling systems. Recently, it was reported that statins ameliorated liver and heart fibrosis. The aim of the present study was to investigate the anti-fibrotic effects of atorvastatin on skin fibroblasts from patients with SSc.
Method. Skin fibroblasts from five patients with dcSSc were cultured with increasing concentrations of atorvastatin for various times. The resulting supernatants were collected and stored at -80°C. Procollagen type I C-peptide and IL-6 levels were then measured using commercial ELISA kits. In addition, mRNA levels of collagen1α (II) and IL-6 were estimated using real-time PCR. The phosphorylation of Akt (Thr308) was evaluated by western blot analysis using specific monoclonal antibodies.
Results. In the supernatants of fibroblasts cultured with 10 μM of atorvastatin for 72 h, the levels of procollagen type I C-peptide and IL-6 were significantly suppressed ($P < 0.001$, Fig. 1) as compared with those in supernatants obtained from cultures lacking atorvastatin. In skin fibroblasts cultured with LY294002 (PI3K inhibitor), procollagen type I C-peptide and IL-6 production were significantly suppressed ($P < 0.05$, and $P < 0.01$, respectively). IL-6 production was significantly suppressed ($P < 0.01$) upon the administration of Y27632 (Rho kinase inhibitor), although procollagen type I C-peptide levels were not suppressed. Treatment with U0126 (Erk1/2 inhibitor) did not affect the levels of collagen or IL-6. The results from western blot analyses indicated that atorvastatin inhibited the phosphorylation of Akt (Thr308), which is regulated by the PI3K signalling pathway.
Conclusion. Our results showed that atorvastatin attenuates, via the PI3K pathway, collagen and IL-6 production in skin fibroblasts from patients with SSc. Atorvastatin may represent a novel therapy not only for vasculopathy but also for fibrosis in patients with SSc.

PS15. CIRCULATING ADIPOKINES AND DIGITAL ULCERS IN SSc PATIENTS

A. Olewicz-Gawlik[1], **D. Trzybulska**[1], A. Danczak-Pazdrowska[2], P. Hrycaj[1], W. Silny[2], B. Kuznar-Kaminska[3] and H. Batura-Gabryel[3]
[1]*Department of Rheumatology and Clinical Immunology,*
[2]*Department of Dermatology and* [3]*Department of Pulmonology, Alergology and Pulmonary Oncology, Poznan University of Medical Sciences, Poznan, Poland*

Background. There are evidences that adipokines may play a role in the pathogenesis of endothelial dysfunction, which is a key feature of SSc.
Objective. To compare serum adipokines concentrations in patients with SSc and healthy controls. To find possible relationships between serum adipokines concentrations and presence of digital ulcers.
Methods. Serum samples from 30 patients with SSc and 30 healthy controls were examined for resistin, adiponectin, leptin and insulin with use of commercially available ELISA kits.
Results. We found no statistically significant differences in serum resistin, leptin and adiponectin concentrations between SSc patients and the healthy controls. However, resistin levels were significantly increased in patients with digital ulcers ($P = 0.03$) and serum adiponectin levels negatively correlated with modified Rodnan skin score ($P = 0.01$). Moreover, serum leptin and insulin concentrations correlated with the onset of SSc symptoms other than RP ($r = 0.67$, $P = 0.001$ and $r = 0.53$, $P = 0.01$, respectively).
Conclusions. The results of presented study indicate that adipokines may be involved in a process of skin fibrosis and ulcer development in SSc patients. However further studies, preferably on tissue level, are needed to confirm these results.

PS16. INNATE IMMUNITY PROTEINS AND LUNG INVOLVEMENT IN SSc PATIENTS

A. Olewicz-Gawlik[1], D. Trzybulska[1], A. Danczak-Pazdrowska[2], P. Hrycaj[1], W. Silny[2], B. Kuznar-Kaminska[3] and H. Batura-Gabryel[3]
[1]*Department of Rheumatology and Clinical Immunology,*
[2]*Department of Dermatology and* [3]*Department of Pulmonology, Alergology and Pulmonary Oncology, Poznan University of Medical Sciences, Poznan, Poland*

Background. Little is known about the role of innate immunity proteins in the pathogenesis of SSc. Elafin, secretory leucocyte protease inhibitor (SLPI) and clara cell protein 16 (CC16) can protect human airways against inflammation; therefore, can play a role in a development of lung involvement in SSc.
Objective. To evaluate serum levels of innate immunity proteins in SSc patients and to correlate the obtained results with functional and radiological lung involvement parameters.
Methods. Serum samples from 30 patients with SSc and 30 healthy controls were examined for elafin, SLPI and CC16 using commercially available ELISA kits. Lung involvement of SSc patients was assessed both functionally [diffusing capacity of the lung for carbon monoxide (DL_{CO}), body plethysmography] and radiologically (high-resolution CT of lungs, evaluated according to Warrick's score by an experienced radiologist).
Results. The serum elafin concentration was significantly elevated in the SSc patients (median 94.32 ng/ml, interquartile range 73.09–112.05 ng/ml) as compared with the healthy control (48.92 and 29.0–64.1 ng/ml) ($P = 0.000002$). The median serum level of SLPI in SSc patients was 7.28 ng/ml, interquartile range 5.44–10.33 ng/ml *vs* 5.52 and 4.22–6.82 ng/ml in the healthy control group ($P = 0.007$) and was significantly inversely correlated with DL_{CO} ($r = -0.41$, $P = 0.02$), total lung capacity (TLC) ($r = -0.46$, $P = 0.01$) and 6 min walk test ($r = -0.52$, $P = 0.004$) and positively correlated with ESR ($r = 0.57$, $P = 0.001$) and EUSTAR score ($r = 0.42$, $P = 0.02$). Serum concentration of CC16 did not differ between the two investigated groups, but significantly negatively correlated with DL_{CO} ($r = -0.43$, $P = 0.02$), TLC ($r = -0.4$, $P = 0.03$) and 6 min walk test ($r = -0.47$, $P = 0.01$) in SSc patients.
Conclusion. Our data indicate that innate immunity proteins: elafin, CC16 and SLPI may play an important role in the disease process in SSc. Investigated proteins seem to be also potential markers of SSc (elafin) or lung involvement in this disease (SLPI, CC16). This finding is of special interest as these proteins could be a target for drug delivery. However further studies, preferably on large group of patients, are needed to confirm these results.

PS17. T CELL-DERIVED IL-6 AND IL-13 DRIVE FIBROBLAST FIBROSIS: IMPLICATIONS FOR SSc

S. O'Reilly[1], T. Hugle[1], B. Griffiths[1], A. Krippner[1] and J. M. Van Laar[1,2]
[1]*Institute of Cellular Medicine, Newcatle University, Newcastle and* [2]*James Cook Hospital, North East NHS, Middlesbrough, UK*

SSc is an autoimmune disease of unknown aetiology that is characterized by inflammation and excessive extracellular matrix deposition. The immune abnormalities include T- and B-cell activation and a host of proinflammatory cytokines that may mediate the fibrotic response characteristic of SSc. TNF-α is a proinflammatory cytokine that may be involved in disease pathogenesis and has been demonstrated to be up-regulated in SS. TNF-α signals through two receptors causing a variety of downstream effects that depends on cell type. The aim was to investigate the role of TNF-α in T cells and the role of proinflammatory cytokines in scleroderma and matrix deposition. We used T cells from SSc and controls and analysed these for the TNF-α receptor using flow Cytometry to examine expression, both in skin and PBMCs. Specific mutant ligands that are recombinant for TNF-α receptor subtypes or soluble TNF was used to examine downstream effects. T cell-conditioned medium was added to normal dermal fibroblasts and markers of fibrosis were examined including collagen type I by RT–PCR. T cell-derived cytokines were measured using ELISA and subsequent cytokines neutralized with antibodies or isotype controls and collagen I measured.
Results. T cells were present in high numbers in the skin of patients. Also TNF-αR II was elevated in T cells from both the skin of affected patients and also T cells from PB compared with healthy controls. Mutant ligands to receptor subtypes leads to elevated IL-6 and also

IL-13 expression from healthy and scleroderma donors. However, scleroderma donors have a much higher constitutive level of both cytokines without the addition of TNF-α ligands suggesting activation of T cells. Conditioned medium leads to up-regulated α-smooth muscle actin content in dermal fibroblast and also up-regulated collagen I expression by 20-fold after incubation with TNF-R subtypes both R1 and R2. A differential response was seen between 'activated' and non-'activated' T cells in collagen expression. Suppression of T cell-derived cytokines IL-6 and IL-13 in combination by neutralizing antibodies leads to an attenuated increase in collagen I mRNA expression, indicating a pivotal role of these cytokines in fibrogenesis. There is also a differential response between patients and controls. SSc T cells expressed elevated TNF-R 2 expression, this maybe an activation marker in scleroderma. T cells are activated '*in vivo*' and secrete the cytokines IL-6 and IL-13. IL-6 and IL-13 work in a synergistic fashion leading to enhanced extracellular matrix deposition.

PS18. ABSENCE OF EPITHELIAL TO MESENCHYMAL TRANSITION DESPITE ACTIVATION OF KERATINOCYTES IN SCLERODERMA SKIN

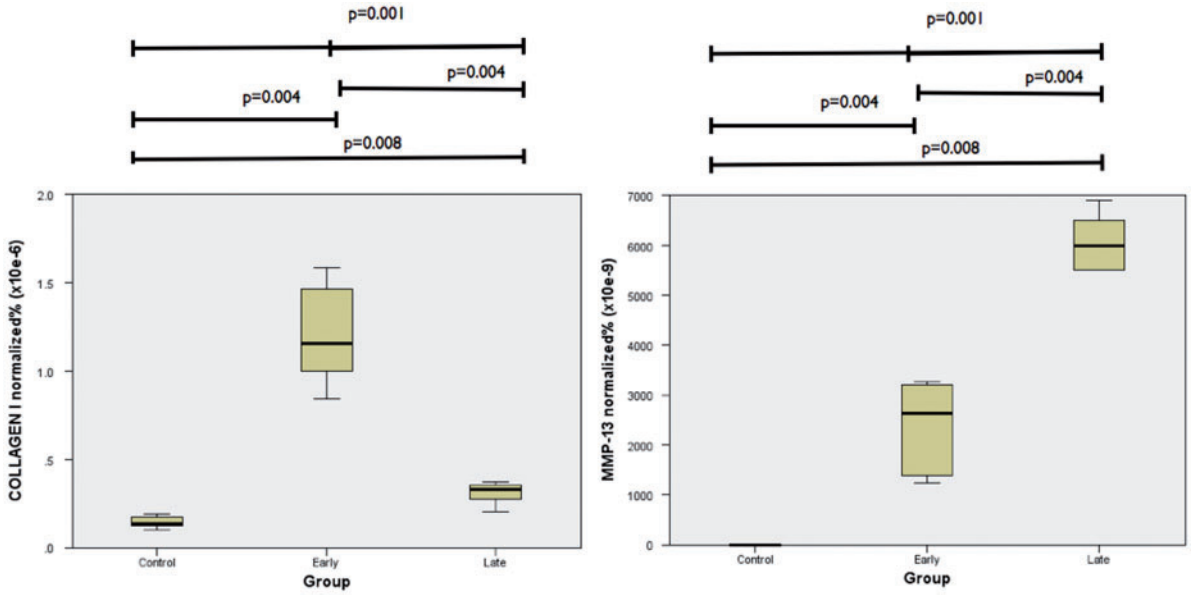
J. Nikitorowicz Buniak[1], X. Shiwen[1], D. Abraham[1], C. Denton[1], C. Black[1] and R. Stratton[1]
[1]*Centre for Rheumatology, UCL Medical School, London, UK*

Background. We have recently shown that scleroderma (SSc) epithelial cells exhibit an activated phenotype similar to wound healing. The interplay between keratinocyte–fibroblast is important in health and disease including epithelial to mesenchymal transition (EMT). EMT is regarded as an important mechanism potentially contributing to lung, liver and kidney fibrosis. In the SSc epidermis, we found active HGF signalling via c-Met and SMAD phosphorylation consistent with TGF-β signalling, both mechanisms implicated in driving EMT. Also, we found increased vimentin levels in whole skin biopsy by proteomics. Therefore, we decided to look for evidence of EMT in the skin of scleroderma patients to determine if the skin fibrosis in scleroderma might involve EMT process.
Materials and methods. Forearm skin biopsies taken from scleroderma patients diffuse subset ($n=6$) and age matched healthy controls (HCs) ($n=6$) were analysed by immunohistochemical staining using antibodies against epithelial markers, K14 and E-cadherin as well as mesenchymal cell markers such as: vimentin, FSP-1, α-SMA. Collagen IV was also identified in the sections to determine integrity of the basement membrane. The epidermal thickness and cell area was measured using Axiovision 4.8 software.
Results. Immunohistochemistry results showed activated skin phenotype. Epidermal thickness was increased from 51.27 μm in HC to 88.85 μm in SSc skin, ($P=0.005$). The mean area of basal cells was 73.37 μm^2 in HC and 111.71 μm^2 in SSc ($P=0.0016$). While spinous layer keratinocytes were 89.26 μm^2 in HC and 173.6 μm^2 in SSc ($P=0.0038$). We did not observe any loss of E-cadherin or gain of vimentin in basal keratinocytes. However, HC subepidermal cells in a 50-μm area adjacent to epidermis had increased vimentin staining. The collagen IV layer in the basal membrane was not compromised. Although we observed increased levels of FSP-1 expression in scleroderma skin when compared with HC skin, the level of smad2/3 activation in the area showed no difference.
Conclusions. Our results indicate that despite keratinocytes activation and HGF signalling, EMT is not taking place in scleroderma skin. Although, FSP-1 was increased the marker is not specific to fibroblasts and also detects dendritic cells and macrophages. EMT process is an important step in tumour development and the findings are consistent with the clinical observation that skin cancers are not seen at increased frequency in scleroderma patients. However, more investigations should be done to fully explore the cell and molecular mechanisms underlying the activated epidermis seen in SSc.

PS19. MATRIX METALLOPROTEINASE-13 CONTRIBUTES TO IMPROVE DERMAL FIBROSIS IN SSc

J. Muñoz-Ortego[1], L. Tio[1], A. Pros[1], J. Monfort[1], J. Sanchez[2], J. Carbonell[1] and V. Fonollosa[3]
[1]*Servicio de Reumatología,* [2]*Servicio de Dermatología, Parc de Salut Mar. IMIM. PRBB and* [3]*Servicio de Medicina Interna. Hospital Vall Hebrón. Universitat Autònoma de Barcelona, Barcelona, Spain*

Background. The fibrosis in SSc is characterized by uncontrolled excessive deposition of type I collagen attributed to an imbalance between production and degradation. MMPs are the major enzymes responsible for degradation of extracellular matrix components. MMP-13 is a member of the collagenase family, which degradates fibrillar collagens of types I, II, III, IV, X, XIV and play a key role in the MMP activation cascade.
Objective. To quantify MMP-13 levels and collagen type I in skin tissue of patients with SSc at different stages of the disease.
Material and methods. Skin biopsies in forearm of 11 patients (ACR criteria; diffuse form): 6 early disease (<2 years of first symptom attributable to SSc), mean age: 55.3 (14.1), modified Rodnan skin thickness score (mRSS) 27 (25–30); 5 late disease (>10 years) mean age: 65.2 (10.5), mRSS 12 (11–15) and 5 healthy controls mean age: 65.2 (7.5). Extractions of skin matrix proteins were performed and ELISA quantifications were normalized by total soluble protein via Braford's method.
Results. We observed a significantly higher expression of MMP-13 in late SSc patients compared with early stage: 2639% (1341–3217) *vs* 5991 (4648–6694); $P=0.004$). MMP-13 was not detected in healthy controls. Collagen I expression was higher in SSc group than in healthy, with more elevated levels in early disease than in late ones: 1.157% (0.961–1.494) *vs* 0.326% (0.238–0.363) *vs* 0.137% (0.112–



0.183); $P = 0.001$). mRSS was correlated with disease duration ($P = 0.004$).
Conclusion. MMP-13 may be involved in the mechanisms of homeostasis against dermal fibrosis, mainly at late stages of this disease.

PS20. PROTEOMES OF HUMAN UMBILICAL VEIN AND MICROVASCULAR ENDOTHELIAL CELLS REFLECT DISTINCT BIOLOGICAL PROPERTIES THAT INFLUENCE IMMUNE RECOGNITION

L. Mouthon[1], H. Dib[1,2,3], P. Chafey[1,2,3], G. Clary[1,2,3], C. Federici[1,2,3], M. Le Gall[1,2,3], N. Tamas[1,2,3], G. Bussone[1,2,3], C. Broussard[1,2,3], L. Camoin[1,2,3], V. Witko-Sarsat[1,2,3] and M.C. Tamby[1,2,3]
[1]*INSERM U1016, Institut Cochin,* [2]*CNRS UMR 8104,* [3]*Université Paris Descartes and* [4]*Université Paris Descartes, Pôle de Médecine Interne, hôpital Cochin, Paris, France*

Rationale. Human umbilical vein endothelial cells (ECs) (HUVECs) are widely used as a source of ECs because of easy access to tissue and simplicity of isolation. However, there are differences among the different EC types and we suspect that the results obtained with a given EC type cannot be extrapolated to other types of ECs.
Objective. To compare the proteomes of microvascular ECs and HUVECs.
Methods and results. Proteomes of HUVECs and human microvascular pulmonary ECs (HMVEC-Ps) and microvascular dermal ECs (HMVEC-Ds) from healthy Caucasian donors (four for each cell type) were compared by 2D differential in-gel electrophoresis and mass spectrometry. In pH 4–7 and 3–11 gels, 17 and 64 proteins were found to have at least 2-fold change in expression between HUVEC and HMVEC-P and between HUVEC and HMVEC-D samples, respectively. In the same gels, 14 and 3 protein spots, respectively, showed 2-fold changed expression between HMVEC-D and HMVEC-P samples, respectively. Among these proteins, six and three, respectively, were found to correspond to cytoskeleton proteins or enzymes implicated in glycolysis. Ingenuity pathways analysis revealed that proteins differentially expressed between HMVEC-D and HUVEC samples were involved in susceptibility to retinoic acid. *In vitro* tubulogenesis assays showed a dose-dependent and differential effect of retinoic acid on angiogenesis. Moreover, serum IgG from patients with SSc showed distinct reactivity profiles in HUVEC and HMVEC-D protein extracts.
Conclusions. The proteome profiles of HUVECs and microvascular ECs differ, which reflects distinct biological properties that influence immune recognition.

PS21. NOVEL GENETIC VARIANTS IN SCLERODERMA SUBPHENOTYPES IDENTIFIED BY IMMUNOCHIP IN A COMBINED US AND SPANISH COHORT

M. Mayes[1], O. Gorlova[2], L. Bossini-Castillo[3], E. Martin[3], J. Ying[2], P. Gregersen[4], A. Lee[4], S. Assassi[1], S. Agarwal[1], F. Tan[1], J. Reveille[1], X Zhou[1], F. Wigley[5], L. Hummers[5], F. Arnett[6], C. Simeon[7], P. Carreira[8], N. Ortego[9], M. Gonzalez-Gray[10] and J. Martin[3]
[1]*University of Texas Health Science Center, Houston, USA,* [2]*University of Texas – M.D. Anderson Cancer Center, Houston, USA,* [3]*Consejo Superior de Investigaciones Cientificas, Granada, Spain,* [4]*Feinstein Institute, North Shore University Hospital, Manhasset,* [5]*Johns Hopkins University, Baltimore,* [6]*Emeritus, University of Texas Health Science Center, Houston, USA,* [7]*Hospital Valle de Hebron, Barcelona,* [8]*Hospital 12 de Octubre, Madrid,* [9]*Hospital Clinico San Cecilio, Granada and* [10]*Hospital Marques de Valdecillas, Santander, Spain*

Objective/Background. The goal of this study was to identify the single nucleotide polymorphisms (SNPs) that are associated with SSc subphenotypes and to identify shared susceptibility loci between SSc and other diseases represented on the Immunochip.
Method. Genotyping: genotyping was performed using the Immunochip, which is a custom chip developed by the Immunochip Consortium and which contains 196 524 SNPs that provide deep coverage of loci previously reported from GWAS and candidate gene studies of multiple autoimmune and inflammatory diseases.
Method. Cases and controls: after quality control measures were applied, a total of 1868 SSc cases and 4774 controls were included in the analysis. Case samples included European–Caucasian subjects from the USA Scleroderma Registry and US GENISOS cohort ($n = 981$, 88.6% female) and from the Spanish Scleroderma group (903 cases, 89.3% female). Control data on 4774 matched subjects were obtained from the Immunochip consortium. *P*-values reported are adjusted for multiple comparisons by FDR-BH (False Discovery Rate using the step-up procedure of Benjamini and Hochberg).
Result. After quality control measures, the genotyping rate was 99.8% and 140 871 SNPs were included in the analysis.
As expected and previously reported, the most highly associated loci included the MHC region on chromosome 6, STAT4 on chromosome 2, TNPO3/IRF5 on chromosome 7 and BLK on chromosome 8.
In addition, seq-VH-988 in the gene SCHIP1 on chromosome 3 encoding for schwannomin interacting protein 1 (adjusted $P = 8.65 \times 10^{-7}$) was associated with lcSSc. Similarly, seq-VH-1269 in IL12A, coding for IL-12 subunit α on chromosome 3, was also associated with the lcSSc subgroup (adjusted $P = 1.34 \times 10^{-6}$).
The SNP imm_3_58178554 in DNASE1L3 on chromosome 3 was associated with the ACA-positive group (adjusted $P = 2.71 \times 10^{-9}$).This gene encodes a member of the DNase family that mediates the breakdown of DNA during apoptosis.
The SNP imm_20_47978447, found in the SPATA2/ZnF313 intergenic area of chromosome 20, was associated with the anti-topoisomerase antibody-positive group (adjusted $P = 4.56 \times 10^{-6}$)
Conclusion. This Immunochip analysis has provided confirmation of previously reported genetic loci in SSc. In addition, novel gene regions have been identified as potential susceptibility loci for SSc subphenotypes. Although the role of these variants in disease is not yet understood, the strong association suggests that these pathways are important in SSc pathogenesis.

PS22. IDENTIFICATION OF MAJOR HISTOCOMPATIBILITY COMPLEX CLASS II ALLELES ASSOCIATED WITH SSc THROUGH IMPUTATION STRATEGY

J. Martin[1], C. P. Simeon[2], N. Ortego-Centeno[3], P. Carreira[4], M. A. Aguirre[5], F. J. Garcia-Hernandez[6], M. C. Vonk[7], A. J. Schuerwegh[8], G. Riemekasten[9], N. Hunzelmann[10], S. Assassi[11], F. K. Tan[11], F. C. Arnett[11], X. Zhou[11], T. R. D. J. Radstake[7], M. D. Mayes[11], P. I. W. de Bakker[12], J. Martin[1] and B. P. C. Koleman[12]
[1]*Instituto de Parasitologia y Biomedicina Lopez-Neyra, CSIC, Granada,* [2]*Servicio de Medicina Interna, Hospital Valle de Hebron, Barcelona,* [3]*Servicio de Medicina Interna, Hospital Clínico Universitario, Granada,* [4]*Servicio de Reumatologia, Hospital 12 de Octubre, Madrid,* [5]*Servicio de Reumatologia, Hospital Reina Sofía, Cordoba,* [6]*Servicio de Medicina Interna, Hospital Virgen del Rocío, Sevilla, SPAIN,* [7]*Department of Rheumatology, Radboud University Nijmegen Medical Center, Nijmegen,* [8]*Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands,* [9]*Department of Rheumatology and Clinical Immunology, Charité University Hospital, Berlin,* [10]*Department of Dermatology, University of Cologne, Cologne, Germany,* [11]*The University of Texas Health Science Center, Houston, Texas, USA and* [12]*Department of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands*

Background. Different alleles of MHC class II molecules (namely, HLA-DRB1, DPB1 and DQB1) have been described to be associated either with risk to SSc or its subphenotypes. Due to the high cost of HLA typing, studies have been limited to small sample sizes, preventing definitive statements as to which HLA alleles are likely causal.
Methodology. We have imputed the MHC class I and II alleles of 2296 cases and 5356 controls from the USA, Spain, Germany and The Netherlands with a method previously developed, which uses genotype data from ~2000 SNPs in the MHC region and an independent reference panel of dense SNP and classical HLA typing data in >2700 unrelated Europeans. We obtained actual HLA typing data for both class I and II molecules for the Spanish and US cohorts, and compared the accuracy of the imputation. Besides classical HLA alleles, we also imputed amino acid changes encoded by genetic variants within the different MHC molecules. We compared the frequencies of the different alleles between cases and controls for SNPs, amino acids and classical HLA alleles.
Results. The accuracy of the imputations ranged from 90 to 98% depending on the alleles being imputed with an average of 93% for all alleles in both populations. We confirmed previous associations of HLA alleles with SSc or its auto-antibody-positive subgroups (HLA-DRB1*0701, HLA-DPB1*1301, HLA-DRB1*1104, HLA-DQB1*0501). We define in deeper detail some of these associations down to the level of amino acid positions that affect epitope binding. Furthermore, we describe new associations of HLA alleles with auto-antibody-positive subgroups, HLA-DRB1*0801, with the presence of ACAs and

HLA-DQB1*0301 with the presence of anti-topo I auto-antibodies. No associations in the MHC class I molecules was found.
Conclusion. Our data indicate that most associations of HLA alleles (and more precisely amino acid positions within them) are specific to the presence of auto-antibodies. Also, only MHC class II alleles are associated and not MHC class I.

PS23. MESENCHYMAL STEM CELLS FROM SCLERODERMA PATIENTS BEHAVE AS PERICYTES: TOOLS FOR CELLULAR CROSS-TALK STUDIES AND STEM CELLS REGENERATIVE MEDICINE

P. Cipriani[1], **A. Marrelli**[1], P. Di Benedetto[1], V. Liakouli[1], F. Carubbi[1], P. Ruscitti[1] and R. Giacomelli[1]
[1]*Dep Internal Medicine and Public Health, Rheumatology, L'Aquila, Italy*

Objective. Vascular involvement is a key feature of SSc. Although the pericytes endothelial cells (ECs) cross-talk may regulate vessels formation no evidences about the contribution of pericytes to ineffective angiogenesis during SSc are available. Recent findings showed similarities between pericytes and bone marrow mesenchymal stem cells (BM-MSCs).
Due to difficulties in dermal pericytes isolation, the aim of this work is to explore the possibility to use BM–MSCs as pericytes surrogate to clarify their possible role in supporting neo-angiogenesis during SSc.
Methods. To demonstrate the potential of BM–MSCs to differentiate into cells with pericytes phenotype and function, healthy controls (HCs) and SSc BM–MSCs were treated with PDGF-BB and TGF-β for 7 days. The expression of pericytes specific markers (αSMA and NG2) was assessed by qPCR and IF; chemioinvasion and capillary morphogenesis were also performed by using a specific 3D matrigel assay.
Results. Our results showed that BM–MSCs isolated from HC and SSc patients displayed the same pericytes phenotype and functional ability before and after PDGF-BB, TGF-β alone or in combined administration. Confirming data on HC BM–MSc, we showed that during SSc, both TGF-β and PDGF-BB can specifically modulate and activate BM–MSCs towards pericytes behaviour in different phase of angiogenesis. Using BM–MSCs/MVECs co-culture system we observed that BMMSCs improve ECs tube formation ability in stressed condition, possibly acting as paracrine source of angiogenic molecules.
Conclusions. The ability of BM–MSC to behave as functional pericytes and to improve the Ecs tubular formation potential suggest that they could be candidates for regenerative medicine during SSc.

PS24. FIBRILLIN-1, MAGP-1 AND FOCAL ADHESION MOLECULES EXPRESSION BY DERMAL BLOOD AND LYMPHATIC MICROVASCULAR ENDOTHELIAL CELLS CHALLENGED WITH SSc SERA

M. Villano[1], A. Borghini[1], P. Sestini[2], A. Rossi[1], E. Gabbrielli[1], M. Manetti[3], A. F. Milia[4], S. Guiducci[4], **M. Matucci-Cerinic**[4], L. Ibba-Manneschi[3] and E. Weber[1]
[1]*Molecular Medicine Section, Department of Neuroscience,* [2]*Division of Respiratory Diseases, University of Siena, Siena,* [3]*Anatomy Section, Department of Anatomy, Histology and Forensic Medicine, University of Florence and* [4]*Department of Biomedicine, Division of Rheumatology, University of Florence, Florence, Italy*

Background. SSc is a connective tissue disorder of unknown aetiology characterized by three major features: vascular endothelial injury, inflammation/autoimmunity and massive deposition of collagen. Many extracellular matrix proteins are altered in SSc, including fibrillin. Fibrillin microfibrils form anchoring filaments in lymphatic endothelium. In the wall of arteries they constitute a scaffold for elastin deposition and also sequester in the matrix TGF-β, whose active form stimulates matrix protein deposition by fibroblasts. Fibrillin alterations have been described in SSc: (i) fibrillin microfibrils are disorderly arranged in human dermis of SSc patients; (ii) the fibrillin molecules produced by cultured SSc fibroblasts are unstable; and (iii) alterations of the gene encoding for fibrillin-1 on chromosome 15q have been reported in two populations with a high prevalence of SSc. Autoantibodies to fibrillin-1 have been found in 31% of Caucasic patients affected by SSc.
Objective. The aim of this study was to evaluate the effect of SSc sera on the deposition of fibrillin-1 and microfibril associated glycoprotein-1 (MAGP-1) and on the expression of focal adhesion molecules (FAK) by human adult dermal blood (BHMVEC) and lymphatic (LyHMVEC) microvascular endothelial cells.
Materials and methods. HMVECs were cultured on gelatine-coated coverslips in EBM containing 15% of serum of lSSc or dSSc patients, naïve or under pharmacological therapy (CYP) and of controls. Cells were fixed at days 2 and 4 of confluence. Double IF was performed for fibrillin-1 and MAGP-1, αvβ3 integrins and phosphorylated FAK, vinculin and phalloidin. The expression of these molecules was quantified on 30 random photographic fields/slide.
Results. Fibrillin-1 and MAGP-1 colocalized in BHMVEC and LyHMVEC in all experimental conditions. They formed a honeycomb pattern in BHMVEC and a dense mesh of short segments in LyHMVEC. Fibrillin-1 and MAGP-1 production significantly increased with time in culture in BHMVEC but not in LyHMVEC. In BHMVEC, fibrillin-1 and MAGP-1 production also significantly increased in presence of sera of both lSSc and dSSc patients treated with CYP *vs* naïve. A significant increased expression of αvβ3 integrin only in BHMVEC challenged with sera from SSc CYP-treated patients *vs* naïve was observed.
Conclusions. CYP treatment effectively promoted fibrillin-1 deposition by BHMVEC but not LyHMVEC. Due to its role in sequestering TGF-β in the extracellular matrix, a normal fibrillin-1 deposition might limit collagen fibre production by fibroblasts and fibrosis.

PS25. INCREASED SERUM LEVELS AND TISSUE EXPRESSION OF MMP-12 IN PATIENTS WITH SSc: CORRELATION WITH SEVERITY OF SKIN AND PULMONARY FIBROSIS AND VASCULAR DAMAGE

M. Manetti[1], S. Guiducci[2], E. Romano[2], S. Bellando-Randone[2], M. L. Conforti[2], L. Ibba-Manneschi[1] and M. Matucci-Cerinic[2]
[1]*Department of Anatomy, Histology and Forensic Medicine and* [2]*Department of Biomedicine, Division of Rheumatology, University of Florence, Florence, Italy*

Objective. SSc is a life-threatening connective tissue disease characterized by widespread vasculopathy, lack of angiogenesis and fibrosis of the skin, lung and other internal organs. Increasing evidence indicates that matrix metalloproteinase-12 (MMP-12) plays an important role in pulmonary inflammation and fibrosis. MMP-12 also suppresses angiogenesis through different mechanisms. In this study, we evaluated serum levels of MMP-12 and their correlation with clinical features in patients with SSc.
Methods. Sera were obtained from 72 SSc patients and 42 healthy volunteers. SSc patients were assessed for disease subset (lcSSc)/dcSSc), disease stage (early/late SSc), extent of skin sclerosis [modified Rodnan skin thickness score (mRSS)], autoantibodies, interstitial lung disease (ILD), pulmonary arterial hypertension and peripheral vascular involvement [digital ulcers (DU), nailfold videocapillaroscopy). Serum MMP-12 levels were measured by ELISA. Immunohistochemical expression of MMP-12 was analysed in skin biopsies from SSc patients ($n = 15$) and healthy subjects ($n = 10$), and lung biopsies from three patients with SSc-related ILD and three controls.
Results. Circulating levels of MMP-12 were significantly increased in SSc patients compared with controls ($P < 0.0001$). Serum MMP-12 levels were significantly higher in both lcSSc and dcSSc than in controls (both $P < 0.0001$), and a trend towards a significant elevation in dcSSc *vs* lcSSc was observed ($P = 0.06$). MMP-12 was significantly increased in both early- and late-stage SSc compared with controls (both $P < 0.0001$), and in late-stage *vs* early-stage SSc ($P < 0.0001$). Patients with mRSS >10 had significantly elevated levels of MMP-12 compared with patients with mRSS ≤10 ($P < 0.0001$). Moreover, MMP-12 levels correlated positively with mRSS ($r = 0.62$, $P = 0.01$). MMP-12 levels were significantly raised in SSc patients with ILD compared with patients without ILD ($P = 0.02$). Elevated levels of MMP-12 were also significantly associated with presence of DU ($P = 0.004$). Circulating MMP-12 was significantly higher in patients with 'late' nailfold capillaroscopic pattern than in those with 'early' and those with 'active' patterns ($P < 0.0001$ and $P = 0.009$, respectively), as well as in 'active' *vs* 'early' patterns ($P = 0.02$). In contrast to almost undetectable MMP-12 expression in healthy skin, in SSc skin MMP-12 was strongly expressed in keratinocytes, dermal endothelial cells, fibroblasts and inflammatory cells. Affected lung tissues from patients with SSc-related ILD showed strong MMP-12 expression in capillary vessels, inflammatory cells, alveolar macrophages and fibroblasts in the thickened alveolar septa, while faint expression was observed in normal lungs.
Conclusion. MMP-12 levels are increased in SSc patients and are associated with severity of skin and pulmonary fibrosis and peripheral vascular damage.

PS26. DECREASED ADIPONECTIN LEVELS IN THE SKIN AND SERA OF dcSSc PATIENTS

T. Makino[1], M. Jinnin[1], H. Arakawa[1], I. Kajihara[1], K. Makino[1], N. Honda[1], K. Sakai[1], S. Fukushima[1] and H. Ihn[1]
[1]*Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan*

Adiponectin is protein hormone produced by visceral and subcutaneous fat cells. In many past studies, adiponectin plays some roles in inflammation, angiogenesis and tissue remodelling, and induces the production of the anti-inflammatory mediators.
In this study, we determined the adiponectin expression in the serum and lesional skin of patients with SSc. Serum adiponectin concentrations were measured in 32 patients with SSc, 10 patients with SLE, 12 patients with dermatomyositis and 13 healthy subjects with specific ELISA. Adiponectin mRNA was determined in skin tissues of five patients with dcSSc, seven patients with lcSSc and seven healthy subjects with real-time PCR. There was a significant reduction in serum adiponectin levels in patients with dcSSc. SSc patients with decreased serum adiponectin levels had higher total skin thickness score and higher incidence of pulmonary fibrosis. Adiponectin mRNA levels in skin tissues from patients with dcSSc were also reduced. Serum adiponectin levels may be a useful biomarker for fibrotic condition in patients with SSc. Clarifying the role of adiponectin in collagen diseases may lead to further understanding of the pathogenesis and new therapeutic approach.

PS27. PTEN KNOCKOUT MICE: A NOVEL MODEL OF LUNG FIBROSIS IN SCLERODERMA

S. Liu[1], S.I.K Parapuram[1], W. Sha[1], X. Shi-Wen[2], D. Abraham[2] and A. Leask[1]
[1]*Division of Oral Biology and Department of Physiology and Pharmacology, University of Western Ontario, London, Canada,* [2]*University College London, Centre for Rheumatology, London, UK*

Background. Fibrosis is characterized by excessive production of collagens and their contraction by fibroblasts. Lung fibrosis is the major cause of death in scleroderma. There is no effective therapy till now. The protein phosphatase and tensin homologue (PTEN) acts to dephosphorylate proteins, which promotes tissue repair. Our previous study showed that deletion of PTEN in fibroblasts resulted in skin fibrosis. However, the effect of PTEN deletion on internal organ such as lung is not clear.
Materials and methods. Fibroblast specific PTEN knockout mice were created by crossing mice carrying floxed pten with mice carrying a tamoxifen-inducible Cre-recombinase under the control of a fibroblast-specific regulatory sequence from the proα2(I) collagen gene. Deletion of PTEN was induced by injection of tomoxifen at age of 3 weeks. Two months after gene deletion, animals were sacrificed and lungs were analysed by histology, collagen production, CTGF expression and myfibroblast formation [α-smooth muscle actin (α-SMA) positive staining].
Results. Loss of PTEN resulted in significant increase of lung fibrosis indicated by increased collagen production, CTGF expression and the number of α-SMA-positive myofibroblasts.
Conclusion. Our results indicate that deletion of PTEN in fibroblasts promotes lung fibrosis and targeting PTEN may be of benefit in combating fibrotic disease such as in scleroderma.

PS28. A SYNONYMOUS VARIANT IN TREX1 IS ASSOCIATED WITH AN INCREASED RISK OF SSc

J. Little[1], A. Herrick[1], S. Pushpakom[1], H. Ennis[1], H. McBurney[1], J. Worthington[1] and W. Newman[1]
[1]*Manchester University, Manchester, UK*

Objectives. Variants in TREX1, the major three DNA exonuclease in mammalian cells, can cause a number of conditions including the neurodevelopmental disorder, Aicardi–Goutières syndrome, familial chilblain lupus and SLE. Patients with these conditions can be affected by chilblain-like vasculitic lesions. Many patients with SSc, and especially those with the lcSSc, have severe digital ischaemia with RP progressing to digital ulceration, scarring and sometimes to gangrene necessitating amputation. Our objective was to examine a cohort of patients with SSc to look for associations with TREX1, in particular in those with lcSSc and in those with severe digital ischaemia.
Methods. DNA sequencing of TREX1 was undertaken in 80 patients with lcSSc. Subsequently, genotyping of a synonymous TREX1 variant, 51-Ser (rs11797) was undertaken in an additional cohort of 172 white British individuals with SSc and 115 healthy controls. The clinical characteristics of the entire cohort were: lcSSc = 193 (77%); dcSSc = 59 (23%). 98 patients (39%) had a history of severe digital ischaemia as defined by a history of admission for intravenous prostanoids, digital debridement or digital amputation. Twenty-two patients (9%) had had amputations. Eighty-nine of 251 patients (35%) were ACA positive (ACA is associated with severity of digital ischaemia in patients with SSc).
Results. The synonymous TREX1 variant 51-Ser was present more commonly in patients with SSc than in healthy controls (OR = 1.4; $P = 0.03$). This association was confined to lcSSc (OR = 1.4; $P = 0.02$). The minor allele was most strongly associated in SSc patients who had a history of amputations (OR = 2.1; 95% CI 1.08, 4.27; $P = 0.02$). There was no association with ACA.
Conclusion. The TREX1 51-Ser variant is associated with an increased risk of SSc. This association was strongest in the patients with lcSSc and particularly in those with a predisposition to the most severe digital vascular disease.

PS29. PROFILES OF EFFECTER AND REGULATORY T CELLS IN SSc

E. Lee[1], H. Kim[2], J. A. Park[1], H. W. Kim[1], B. Cho[2] and J. H. Sim[2]
[1]*Department of Internal Medicine and* [2]*Department of Anatomy, Seoul National University College of Medicine, Seoul, South Korea*

Introduction. SSc is an autoimmune disease characterized by excessive fibrosis of skin and internal organs. Immune modulation of lymphocytes and vascular dysfunction play important roles in the process of fibrosis. We explored the characteristics of peripheral blood T lymphocytes in SSc.
Methods. A total of 35 patients with SSc and 22 healthy controls were enrolled. Frequencies of CD4+/CD8+ T cells and differentiation status of T cells were investigated based on CCR7 and CD45RA. The distribution of Th1, Th2, and Th17 cells was investigated with intracellular IL-4, IFN-γ and IL-17 cytokine staining. Three subsets of regulatory T cells were measured, including CD4+CD25++, CD4+NKG2D+ and CD8+CD28− T cells.
Results. Distribution of CD4+/CD8+ T cell was comparable between SSc patients and healthy individuals. Minimal increases were observed in central memory CD4+ T cells in lcSSc and in terminal effector CD8+ T cells in dcSSc. There were no significant differences in Th1, Th2 and Th17 cells between SSc patients and healthy controls. However, there were significant increases of all regulatory T cell subsets in SSc patients compared with healthy controls.
Conclusion. Regulatory T cells are expanded in SSc patients compared with healthy controls. Our results suggest that regulatory T cells may contribute to fibrosis through their pertinent cytokines.

PS30. THE CD163/TWEAK RATIO IS INCREASED IN PBMC CULTURES FROM PATIENTS WITH SSc AND CORRELATES WITH THE SEVERITY OF SSc

M. Bielecki[1], P. Bernatowicz[2], L. Chyczewski[2], K. Kowal[3] and **O. Kowal-Bielecka**[4]
[1]*Department of Orthopedics and Traumatology,* [2]*Department of Medical Pathomorphology,* [3]*Department of Allergology and Internal Medicine and* [4]*Department of Rheumatology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland*

Background. CD163 is a new potential scavenger receptor of TNF-like weak inducer of apoptosis (TWEAK) that elicits diverse biologic actions involved in SSc. We have recently shown that capacity of the peripheral blood mononuclear cells (PBMCs) from SSc patients to produce TWEAK inversely correlates with the severity of vascular damage in SSc.
Aim of the study. In the present study we hypothesized that CD163/TWEAK interactions might play a role in the development of SSc.
Methods. To address this hypothesis the production of soluble (sCD163) and soluble TWEAK (sTWEAK) by PBMC from 20 patients with SSc and 15 healthy controls (HCs) has been measured by commercially available ELISA kits. The sCD163/sTWEAK ratio was calculated and its association with disease parameters was assessed.
Results. PBMC from SSc patients tended to release greater amounts of sCD163 as compared with HC ($P = 0.07$). There was no significant correlations between sCD163 and clinical or laboratory parameters of SSc except for CRP concentration in the peripheral blood ($r = 0.52$). As reported by us previously, the production of sTWEAK was comparable between PBMC from SSc patients and HC ($P > 0.05$) and sTWEAK correlated inversely with duration of RP and capillary

damage as assessed by capillaroscopy. The sCD163/sTWEAK ratio was however significantly increased in SSc-PBMC cultures in comparison with HC and correlated with mRSS ($r = 0.49$) and, inversely, with FVC values (per cent of predicted) ($r = -0.49$). The sCD163/sTWEAK ratio was significantly higher in SSc patients with SLD as compared with SSc patients without SLD and in those with greater capillary damage ('active' pattern in capillaroscopy) than in those with less capillary damage ('slow' pattern).
Conclusion. We show, for the first time, that PBMC form SSc release significantly greater amounts of sCD163 than do PBMC from healthy subjects. Moreover, correlation of sCD163/sTWEAK ratio in PBMC supernatants with the severity of skin, lung and vascular damage in SSc indicates that relationship between these two molecules might play a role in the development of SSc and represent a new target for therapy in SSc. In addition sCD163/sTWEAK ratio might serve as a new biomarker of the severity of SSc-related organ involvement.

PS31. ANTI-AT(1)R AND ANTI-ET(A)R AUTOANTIBODIES IN SSc: CLUES FOR POSSIBLE INVOLVEMENT IN DISEASE PATHOLOGY

A. Kill[1], M. O. Becker[1], J. Günther[1], D. Dragun[2], G.R. Burmester[1] and G. Riemekasten[1]
[1]*University Hospital Charité, Rheumatology and Clinical Immunology and* [2]*University Hospital Charité, Nephrology, Transplantology and Intensive Care, Berlin, Germany*

Background. Autoantibodies that target the angiotensin-II type-1 receptor (AT1R-Abs) and the endothelin-1 receptor type A (ETAR-Abs) were recently identified in SSc. They were associated with clinical symptoms such as vascular and fibrotic complications. In addition, the presence of both autoantibodies predicted mortality due to cardio-pulmonary complications, thus implicating their contribution to SSc pathogenesis. Here, different autoantibody-mediated effects and their blockade by receptor inhibitors were studied in an *in vitro* analysis setting.
Methods. Human microdermal endothelial cells-1 (HMEC-1) were treated with IgG from SSc patients containing anti-AT(1)R and anti-ET(A)R autoantibodies and with IgG of healthy donors as a negative control. In parallel, cells were pre-treated with various receptor antagonists alone and in combination. Regulative effects on different cytokines, growth factors, cell signalling molecules and cell viability were measured by e.g. toxicity test, qRT–PCR and ELISA.
Results. Treatment of cells with SSc-IgG led to a strong up-regulation of several mediators compared with negative control treatment. In case of IL-8, the mRNA and protein expression levels were up-regulated. Moreover, expression of mRNA was down-regulated and partially reduced on the protein levels using pre-treatment with receptor inhibitors. There was a high variability in the response to the blockers exhibiting responders and non-responders. Interestingly, treatment with natural ligands did not result in IL-8 up-regulation. Treatment with SSc-IgG led also to a significantly reduced cell viability compared with negative control treatment. These effects were partially abolished by pre-treatment with AT(1)R-inhibitor, but completely abolished using one but not another ET inhibitor.
Conclusion. Our results suggest an autoantibody-driven cytotoxicity and inflammatory activation of endothelial cells by angiotensin/endothelin-receptors *in vitro*. The data suggest also a high heterogeneity of the antibody-mediated effects, a role of other possible autoantibodies, and different responses to inhibitors and natural ligands. Whether these *in vitro* data could be used to identify responders or non-responders to therapy remains to be studied. *In vivo* experiments are underway to give better insight into the complex nature of the SSc-antibody-mediated effects.

PS32. GUT FIBROSIS IS ASSOCIATED WITH REDUCED COLONIC CONTRACTILITY IN A TGF-β MOUSE MODEL

K. Khan[1], N. Thoua[1], A. Dooley[1], E. Derrett-Smith[1], V. Ong[1], D.J. Abraham[1] and C.P. Denton[1]
[1]*UCL Medical School, London, UK*

Background. Significant gastrointestinal (GI) involvement occurs in up to 90% of patients with SSc. Animal models have helped to study different disease aspects such as systemic disease manifestations as well as organ damage such as lung fibrosis and pulmonary arterial hypertension. However, no mouse model to date has specifically investigated the GI tract. The transgenic mouse strain TβRIIk-fib is characterized by ligand-dependent up-regulation of TGF-β signalling and has been shown to develop skin, lung fibrosis and diminished aortic ring contractility associated with adventitial fibrosis. We investigated if similar changes are observed in gut tissue in this model.
Method. Colonic tissue was examined using histology, immunohistochemistry and isolated organ bath studies. Gross tissue architecture was examined by haematoxylin and eosin (H&E), picrosirius red (staining for collagen) and immunohistochemical markers for α-smooth muscle actin (αSMA), phospho-Smad 2/3 (pSmad2/3) and Ki-67 (cell proliferation marker). To investigate the enteric nervous system, tissue was stained with PGP 9.5 (marker for general neural tissue) and S-100 (glial marker). Fibrosis was quantified using the NIS Elements BR 2.30 system (Nikon) allowing for quantification of the various colour wavelengths with pixels as the unit of measure. Colonic strip contractile responses to potassium chloride (KCl) and carbachol (a cholinergic agonist) were assessed in isolated organ baths and data were presented as per cent of maximal contraction.
Results. H&E staining showed no architectural differences between transgenic and wild-type (WT) mice gut tissue. However, a marked increase in collagen deposition in the transgenic mice compared with WT controls [per cent of tissue stained red: WT: 3.95 (0.7) *vs* TG: 9.71 (2), $P = 0.05$]. No significant difference was observed immunostaining for SMA, Ki-67, pSmad2/3 between transgenic and WT control mice. There was no obvious difference in neural tissue staining. Organ bath studies showed colonic strip contractility was diminished in transgenic (TG) mice compared with WT controls to both KCl 80 mM [WT: 53.5 (14.2) *vs* TG: 13.5 (12.8), $P = 0.022$] and carbachol at the higher concentrations [10^{-5}: WT: 90.4 (8.7) *vs* TG: 50.6 (17.8); $P = 0.025$ and 10^{-4}: WT: 64.6 (7.2) *vs* TG: 31.97 (13.9); $P = 0.023$].
Conclusion. We have shown that this transgenic mouse model previously shown to develop skin, lung and cardiac fibrosis also develops colonic fibrosis with associated effect in colonic tissue contractility. This may offer further insight in pathological processes leading to the development of gut fibrosis as well as the effect in the GI tract of therapies targeting fibrosis.

PS33. CHRONIC ASPIRATION PNEUMONIA AS A PULMONARY MANIFESTATION OF SCLERODERMA-DIAGNOSTIC DIFFICULTIES. CASE REPORT

A. Kempisty[1], I. Bartoszuk[1], P. Radwan-Rohrenschef[1], D. Wyrostkiewicz[1], R. Langford[2], K. Blasinska-Przerwa[3], R. Jagiello[4] and J. Kus[1]
[1]*Department of Lung Diseases,* [2]*Department of Pathology,* [3]*Department of Radiology and* [4]*Department of Thoracic Surgery, National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland*

Introduction. The most common pulmonary manifestation of scleroderma are: interstitial pneumonia and pulmonary hypertension. There are also another changes in lungs in scleroderma patients. We present a case of a female patient with aspiration pneumonia as a pulmonary manifestation of scleroderma and difficulties in this diagnosis.
Case report. A 47-year-old women with scleroderma was admitted to the hospital with a 7-month history of dry cough, subfebrile status and dyspnoea on exertion. She improved for a short time after antibiotic therapy. On admission she was afebrile. On auscultation bilateral basal, crepitations were noted. WBC was normal, ESR and CRP was elevated. High-resolution CT revealed infiltrations with air bronchogram in the lower lobes, and diffuse small nodules and ground-glass opacities localized in the upper and middle zones of the lungs. Flexible fibre optic bronchoscopy was performed: transbronchial lung biopsy (TBLB) showed active interstitial inflammatory infiltration with focal fibrosis, culture was negative. Because of no correlation between clinical and TBLB result the surgical biopsy of the lung was performed and revealed purulent bronchitis a bronchiolitis with areas of acute bronchopneumonia. The patient was diagnosed as having chronic aspiration pneumonia. She was treated with ceftazidime and amikacin for 2 weeks and clindamycin for 4 weeks and proton pump inhibitor. Symptomatic and radiological improvements were noted.
The oesophago-gastroduodenoscopy confirmed oesophagitis, and results of barium swallow study showed oesophageal dysmotility. No recurrence was observed in the longitudinal follow-up.
Conclusion. Apart of diagnostic difficulties, we decided to present clinical, radiological and histopathological features of aspiration pneumonia, because to our knowledge, there is relative sparse data pertaining to this complication in the course of scleroderma.

PS34. MICROSOMAL PROSTAGLANDIN E SYNTHASE-1 NULL MICE EXHIBIT DEFECTS IN WOUND HEALING RESPONSE *IN VIVO*

P. Ghassemi[1], L. Crofford[2], M. Blati[1], G. Perez[1] and **M. Kapoor**[1]
[1]*University of Montreal, Montreal, Canada and* [2]*University of Kentucky, LX, USA*

Aim. Microsomal PGE synthase (mPGES)-1 is an inducible enzyme that acts downstream of cyclooxygenase and specifically catalyses the conversion of PG H2 to PGE2. We have previously shown that mPGES-1 is induced during the inflammatory phase of normal wound healing process. Here for the first time, we determined the effects of genetic deletion of mPGES-1 on normal wound repair response using full-thickness incisional model of wound healing in mice.
Methods. Wild-type (WT) and mPGES-1 null mice were subjected to the full-thickness incisional model of wound healing in mice and wound healing parameters were determined.
Results. WT mice subjected to wound healing model showed increased wound PGE2 levels during inflammatory phase of wound healing. However, mPGES-1 null mice showed no significant increase in the levels of PGE2 throughout the time course of wound healing. Results further showed that genetic loss of mPGES-1 in mice was associated with reduced inflammatory response, delayed re-epithelialization and wound closure, reduced new blood vessel formation associated with reduced levels of VEGF, reduction in wound collagen (hydroxyproline) production associated with reduced myofibroblast formation (assessed by α -smooth muscle actin (α-SMA) staining) and delay in transition of granulation tissue to scar formation during normal wound repair response. We then determined if the loss of PGE2 upon genetic deletion of mPGES-1 was responsible for this delay in wound repair response. Indeed, intradermal injections of PGE2 at the wound site were able to reverse the delay in transition of granulation tissue to scar formation.
Conclusion. These results suggest that mPGES-1 and its derived PGE2 are essential for driving normal wound repair response.

PS35. PLATELET-MEDIATED ENDOTHELIAL APOPTOSIS IN SSc: A POSSIBLE ROLE FOR THROMBOSPONDIN 1–CD36 PATHWAY

B. Kahaleh[1] and Y. Wang[1]
[1]*Department of Medicine, University of Toledo, Toledo, OH, USA*

Objectives. Sequential pathological observations in the early stages of SSc demonstrated an early evidence for platelet aggregation and binding to blood vessels, which is largely followed by vascular effacement and the development of SSc vasculopathy. In this study, we thought to investigate the effects of platelet constituents on microvascular endothelial cells (MVEC) apoptosis. We particularly investigated the role of thrombospondin 1 (TSP1) as a possible platelet-derived signal since it is a potent angiogenic inhibitor; mediates endothelial apoptosis; activate TGF-β and is overexpressed in SSc. Moreover, we investigated the role of CD36 since TSP1 vascular effects are known to results from its interaction with the CD36 receptors.
Methods. MVEC were isolated from involved SSc skin and matched control subjects. Platelets were collected from healthy subjects, sonicated, ultracentrifuged and the resulting supernatant (PLSN) was used in MVEC cultures. MVEC apoptosis was evaluated by TUNEL and active caspases-3 staining. CD36 expression in MVEC was measured by quantitative RT–PCR and CD36 expression was knocked down using CD36-specific siRNA.
Results. The following results were observed in this study:

1. Addition of PLSN to MVEC cultured in 0.5% serum concentration resulted in a dose-dependent apoptosis of MVEC. SSc-MVEC manifested higher degree of apoptosis than control MVEC, thus at 20% PLSN concentration, MVEC apoptosis was 20% (5) and 48% (8) in control *vs* SSc MVEC, respectively [mean (S.D.) of three cell lines].
2. Addition of TSP1 neutralizing antibody to PLSN significantly reduced PLSN-induced MVEC apoptosis, suggesting that TSP1 in PLSN mediate MVEC apoptosis.
3. CD36 expression levels were significantly higher in SSc-MVEC than in control MVEC [7.4 (2.3)-folds, mean (S.D.) of three cell lines].
4. CD36 knockdown using CD36-specific siRNA but not ir-siRNA resulted in >90% decrease in CD36 expression and the inhibition of TSP1- and PLSN-induced MVEC apoptosis.

Conclusions. Platelet interaction with MVEC results in MVEC apoptosis. This effect is largely mediated by interaction of TSP1 with CD36. SSc-MVECs are more susceptible to this effect possibly because of an up-regulated CD36 expression levels in SSc cells. The data propose the platelet as a possible source for the initial MVEC apoptotic signal in the early stages of SSc vasculopathy and suggest TSP1 as a crucial player in SSc pathogenesis in view of its abundance in SSc and its documented role in the genesis of vasculopathy and tissue fibrosis.

PS36. PLASMACYTOID DENDRITIC CELLS INFILTRATE THE LUNG AND SKIN OF PATIENTS WITH SSc

S. Kafaja[1], A. Divekar[1], D. Khanna[1], R. Saggar[1], D.E. Furst[1] and R.R. Singh[1]
[1]*UCLA Department of Medicine, Division of Rheumatology, LA, USA*

Introduction. Mechanisms that drive immune-mediated inflammation leading to vasculopathy and fibrosis in patients with SSc remain largely unclear. While many studies have suggested a role for T cells particularly those that produce type 2 cytokines in the pathogenesis of SSc, little is known about the role of dendritic cells (DCs) in this disease.
Objective. (1) To examine the phenotype of DCs in skin and lung tissues and bronchoalveolar lavage (BAL) of patients with SSc and correlate these findings with clinical disease.
(2) To investigate mechanisms whereby plasmacytoid DCs (pDCs) might participate in SSc pathogenesis, we sought correlation between pDCs and an array of profibrotic cytokines and growth factors.
(3) To investigate the clinical significance of pDC infiltration in tissues of patients with SSc.
Results. (1) Flow cytometry analysis showed that the frequencies of pDC, a subset of DC cells, were 5-fold lower in peripheral blood of SSc patients compared with healthy controls ($P < 0.05$), whereas Myeloid DCs (mDC) were not different between the two groups. In contrast, immunohistochemistry staining of skin biopsies showed abundant staining for pDC cells in SSc patients, whereas rare cells stained for pDCs in control skin. A similar trend was noted in lung biopsies of SSc patients when compared with lung controls. In BAL, the frequencies of pDCs correlated with high-resolution CT (HRCT) scores of SSc-interstitial lung disease (SSc-ILD) ($r > 0.4$), whereas myeloid CD11c+ DCs negatively correlated with SSc-ILD scores ($r = 0.4$).
(2) The frequency of pDCs correlated with a set of proteins involved in inflammation, leucocyte migration, and wound repair ($r > 0.4$).
(3) To further evaluate the clinical significance of pDC infiltration in tissues of patients with SSc, we enumerated pDCs in BAL of patients with SSc before and after treatment with imatinib mesylate and elicited a modest improvement in skin score and lung function in a pilot clinical trial that we recently reported (Khanna *et al*., Arthritis Rheum 2011, in press). pDCs were significantly reduced in BAL after 12 months of treatment with imatinib mesylate ($P < 0.05$).
Conclusion. Taken together, these data suggest a possible and important role of pDCs in SSc pathogenesis. Ongoing studies are directly examining a causal relationship between pDCs and SSc pathogenesis.

PS37. INCREASED CONCENTRATIONS OF ANNEXIN V NEGATIVE SUBSETS OF CIRCULATING MICROPARTICLES IN PATIENTS WITH SSc AND LUNG INVOLVEMENT

L. Iversen[1], C.T. Nielsen[2], O. Østergaard[2], S. Ullman[1], P. Halberg[1], T. Karlsmark[1], S. Jacobsen[3] and N. H. H. Heegaard[2]
[1]*Department of Dermatology, University Hospital Bispebjerg,* [2]*Department of Clinical Biochemestry and Immunology, Statens Serum Institut,* [3]*Department of Rheumatology, University Hospital Rigshospitalet, Copenhagen, Denmark*

Background. Microparticles (MPs) are small membranous vesicles released by apoptotic or activated cells. Autoantigens in SSc have been identified in blebs released from cells undergoing apoptosis *in vitro*. This may link MPs to the development of systemic autoimmunity. Here, we characterize the circulating MPs in a large group of clinically well-defined patients with SSc.
Methods. One hundred and twenty-one ($n = 121$) unselected SSc patients, 49 sex- and age-matched healthy controls and 29 SLE patients were included in the study. Samples were analysed by flow cytometry for MPs directly from citrated platelet poor plasma (PPP). MPs were characterized by Annexin V-binding (AnxV+) in combination with antibodies to either platelet, leucocyte or endothelial cell surface markers.
Results. Total concentrations of MPs in the three groups did not differ. The concentration of AnxV+ MPs and MPs derived from platelets (PMPs), leucocytes (LMPs) and endothelial cells (EMPs) was

significantly lower in SSc patients than in healthy controls. In contrast, the concentration of AnxV− MPs (AnxV− MPs) including the AnxV− cell-derived subsets of MPs did not differ between healthy controls and SSc patients.
An inverse correlation was found between lung function (diffusion capacity and vital capacity) and AnxV− MPs, including AnxV− LMPs and AnxV− EMPs. Patients with lung fibrosis had significantly increased numbers of AnxV− MPs EMPs. The concentration of AnxV− MPs was higher in men than in women, but the sex difference was uncertain for AnxV+ MPs.
Conclusion. In this study, the concentration of AnxV− MPs, including AnxV− LMPs and AnxV− EMPs, increased in scleroderma patients with abnormal lung function i.e. decreased diffusion capacity and vital capacity and in the patients with pulmonary fibrosis as seen by chest X-ray. These findings call for further characterization of AnxV− MPs in SSc and underline the importance of including analysis of the AnxV− subset of cell-derived MPs in microparticle studies.

PS38. DIRECT VESICLE TRANSMISSION BY MAST CELLS TO FIBROBLASTS AND LYMPHOCYTES IN SSc

T. Hügle[1], K. White[2] and J. M. van Laar[3]
[1]*Department of Rheumatology, University Hospital Basel, Basel, Switzerland,* [2]*EM research services and* [3]*Musculoskeletal Research Group, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK*

Background. SSc is a connective tissue disease of unknown origin. We have shown that mast cells are the main source of TGF-β in the dermis of SSc patients. Recently, *in vitro* data revealed intercellular communication between fibroblasts and mast cells directing fibroblast activity.
Objective. To investigate whether mast cells interact with fibroblasts and immune cells in SSc dermis via cell–cell contact, thus efficiently delivering vesicle content.
Methods. Four millimetre dermal punch skin biopsies were obtained from seven SSc patients (four diffuse, three with limited SSc) and one healthy control. For electron microscopy, skin biopsies were fixed in 2% glutaraldehyde and embedded in epoxy resin. Mast cell origin was confirmed by toluidine blue staining.
Results. Substantial cell–cell contact between activated mast cells and fibroblasts was predominantly detected in samples from progressive diffuse SSc patients but not in the control. Cell–cell contact of mast cells with fibroblasts was characterized by gap junctions. We found direct transmission of mast cell vesicles into fibroblasts. Cell–cell contact and vesicle transition was also encountered between mast cells and lymphocytes. Interestingly, an inter-twining cell membrane contact between mast cells and the effector cells was found.
Conclusion. Mast cells stimulate fibroblasts and effector cells by cell–cell contact and direct transmission of vesicle content. Cell–cell interaction and vesicle transfer of mast cells is a mechanism that potentially involved in fibrogenesis and autoimmunity and therefore might reveal new therapeutic approaches in SSc.

PS39. IDENTIFICATION OF BONE MARROW-DERIVED MESENCHYMAL STEM CELLS IN SSc

Y. Hou[1], X. Y. Huang[1], M. T. Li[1], Q. Wang[1], D. Xu[1], Y. Zhang[2], Y. F. Liu[2] and X. F. Zeng[1]
[1]*Department of Rheumatology, Peking Union Medical College Hospital and* [2]*Institute of Basic Medical Sciences, Academy of Military Medical Sciences, Beijing, China*

Objective. To identify the characteristics of mesenchymal stem cell (MSC) in patients of SSc.
Methods. MSCs were isolated and expanded from bone marrow samples of SSc patients and identified by morphology, phenotype and function. Mixed lymphocyte reaction and lymphocyte transformation test were performed and expression of immune cytokines was detected with RT–PCR for evaluation of immunomodulation function of MSCs.
Results. MSCs were successfully isolated and expanded with an ageing process after six passages. Phenotype assay confirmed a high purity of MSCs. Cell cycle assay demonstrated that >90% of SSc and control MSCs remained in G0/G1 phase without significant difference between passages. Some patient inclined to osteogenic differentiation. Both SSc-derived and control MSCs acted as stimulate to allogeneic T cells when MSC:T > 1:80 ($P < 0.05$), but inhibited mitogen-induced T-cell proliferation when MSC:T > 1:160 ($P < 0.05$). SSc-derived MSCs presented an immune expression profile of cytokines, with reduced expression of macrophage colony-stimulating factor (M-CSF) and TGF-β1 (TGF-β1) in some patients.
Conclusion. MSCs of SSc patients possessed limited expansion and immunomodulation function.

PS40. SSc-AGONISTIC AUTOANTIBODIES DIRECTED AGAINST THE ANGIOTENSIN RECEPTOR TYPE 1 AND THE ENDOTHELIN RECEPTOR TYPE A AND THEIR EFFECTS ON IMMUNE CELLS

J. Günther[1], M. O. Becker[2], A. Kill[1,2] and G. Riemekasten[2]
[1]*German Rheumatism Research Center, a Leibniz Institute and* [2]*Charité University Hospital, Rheumatology and Clinical Immunology, Berlin, Germany*

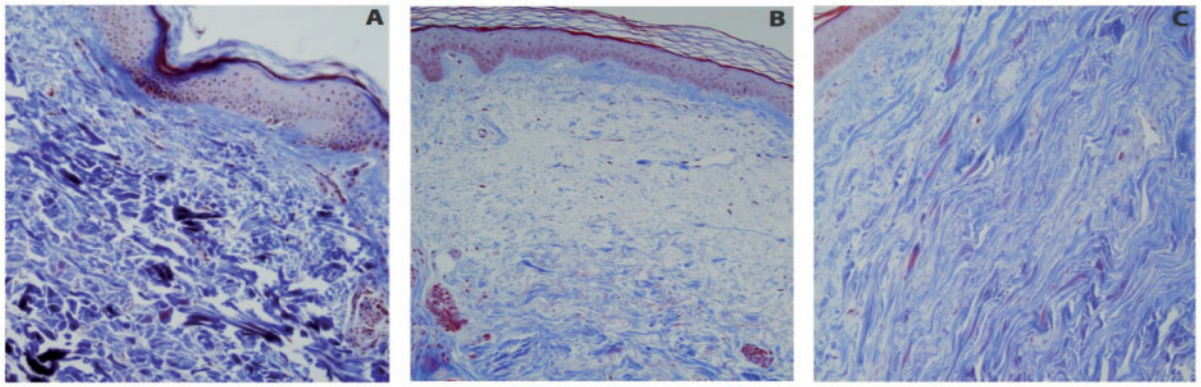
Background. Autoimmunity, vasculopathy and fibrosis are features of SSc. The functional link between these three pathophysiological components is still missing. Research suggests an involvement of ET-1 and angiotensin II, and of the activation of their receptors by the natural ligands as well as by agonistic autoantibodies against these receptors in SSc-associated vasculopathy and fibrosis.
Objective. We found autoantibodies against the angiotensin receptor type 1 (AT1R) and the endothelin receptor type A (ETAR) in SSc patients. Additionally, we could show the expression of these receptors on immune cells. The pathophysiological effects of the autoantibodies on immune cells and their association with clinical data have not been studied so far.
Methods. Peripheral blood mononuclear cells (PBMCs) from healthy donors were isolated by gradient centrifugation and stimulated *in vitro* by affinity-purified IgG from SSc patients containing anti-AT1R and anti-ETAR antibodies as well as by IgG from healthy donors. After stimulation the expression of markers and cytokines were measured by flow cytometry or ELISA.
Results. Stimulation of PBMCs by SSc patients, IgG resulted in a significantly increased expression and secretion of IL-8 compared with the stimulation by IgG of healthy donors. This effect was blocked by commercial AT1R and ETAR blockers. Correlation analysis of the IL-8 expression with clinical data of the SSc patients whose IgGs were used revealed a negative correlation of IL-8 expression with the time since onset of SSc features like RP and skin fibrosis.
Conclusion. SSc patient IgG-containing anti-AT1R and anti-ETAR antibodies seem to have effects on inflammation and immune regulation. IL-8 is a strong inflammatory cytokine mainly secreted by monocytes among the immune cells, and may play an important role in the early stage of SSc contributing to vascular inflammation and injury, which are regarded to be the first events leading to tissue damage and fibrosis.

PS41. VASCULAR LEAK IS A CENTRAL FEATURE TO THE PATHOGENESIS OF SSc

T. Frech[1], M. P. Revelo[2], S. Drakos[1], M. Murtaugh[1], B. Markewitz[1], A. Sawitzke[1] and D. Li[3]
[1]*Department of Internal Medicine,* [2]*Department of Pathology and* [3]*Department of Internal Medicine and Molecular Medicine, University of Utah, Salt Lake City, USA*

Objective. SSc (scleroderma) is a clinically defined disease of unknown aetiology, which is thought to be the result of vasculopathy, immune dysfunction, and subsequent fibrosis. Previous histopathology descriptions of SSc have well characterized the process of fibrosis. While it is recognized that there can be decreased numbers of blood vessels in SSc skin biopsies, a description of vasculopathy using whole-field digital microscopy has not been previously reported. We report the use of whole-field digital microscopy for description of vasculopathy in SSc.
Methods. Twenty consecutive SSc patients were biopsied on the left or right medial forearm with a 6-mm punch biopsy. Biopsy specimens in the same location were obtained from four healthy controls. These specimens were processed with haematoxylin and eosin (H&E) and histochemical stains, and immunohistochemistry was performed. The Aperio ScanScope with standardized colour deconvolution and microvessel density algorithms were used to quantify vascular abnormalities. Electron microscopy (EM) was used to examine endothelial cell features, basal lamina and tight junctions.
Results. Whole-field digital microscopy and EM of SSc skin biopsies revealed that endothelial abnormalities are a universal feature regardless of clinical features and/or duration of disease. These features were not seen in the healthy control specimens. The Aperio ScanScope with standardized colour deconvolution and microvessel density algorithms identified interstitial oedema (weak trichrome,

Fig. 1 Trichrome stain shown in panel A donor skin biopsy without abnormalities in the epidermis and dermis without inflammation, edema or significant fibrosis. In panel B edema is present in the superficial dermis and appears as clear blue staining. In panel C diffuse dermal fibrosis is demonstrated.



$P = 0.03$) and fibrosis (strong trichrome, $P = 0.01$) in all SSc patients when examined by vessel area. Perivascular and interstitial infiltrate of mast cells were present in all SSc specimens.
Conclusions. Whole-field digital microscopy offers a means of rapidly carrying out quantitative, reproducible measurements of microanatomical features of SSc vasculopathy. The universal morphologically abnormal endothelial cells and interstitial oedema in all SSc patients who were biopsied regardless of their clinical characteristics suggests that SSc may be an intrinsic disease of the endothelium with fibrosis as the result of antecedent vascular leak. Whole-field digital microscopy should be considered in characterizing SSc patients for research and clinical care.

PS42. ANALYSIS OF A POLYMORPHISM (RS763361) IN THE CD226 GENE IN UK PATIENTS WITH SSc

C. Fonseca[1], B. Ahmed[1], V. Ong[1], C. P. Denton[1] and D. Abraham[1]
[1]*Centre for Rheumatology, University College Medical School, London, UK*

Background. Scleroderma or SSc is a complex disease. The aetiology of SSc remains unknown but it is likely to be multifactorial, with the interaction of environmental and genetic factors playing a central role to the pathogenesis of the disease role. The rs763361 polymorphism in the CD226 gene has been identified as a susceptibility locus for SSc in a European ancestry population.
Purpose. To investigate whether the association of the rs763361 polymorphism in CD226 gene previously reported in patients with SSc, is also present in an independent set of UK Caucasian patients.
Methods. Seven hundred and twenty-eight scleroderma patients and 260 healthy controls were genotyped for the rs763361 polymorphism. All patients and controls were UK Caucasian. Patients were categorized according to three mutually exclusive autoantibody statuses: anti-topo I (ATA), anti-centromere (ACA) and anti-RNA-polymerase (ARA) or none of them. We also classified the groups according to a major organ involvement; pulmonary fibrosis (assessed by HRCT and lung function test with a restrictive pattern), pulmonary arterial hypertension (defined as an elevation in the mean pulmonary artery pressure >25 mmHg with normal pulmonary capillary wedge pressure (<15 mmHg) on right heart catheterization) and renal crisis (defined by a rapidly progressive renal failure, new onset accelerated hypertension). Genotyping was performed by the KASPar system (allele-specific PCR, KBiosciences, UK).
Results. Of the SSc patients, 511 (70.2%) were lcSSc and 217 (29.8%) were dcSSc. There were 273 (37.5.1%) patients with lung fibrosis, 111 (15.2%) with pulmonary arterial hypertension and 63 (8.6%) with renal crisis. One hundred fifty-five patients (21.3%) were positive for ATA, 255 (35.0%) for ACA and 97 (13.32%) ARA. The SSc and control groups' genotyping were in Hardy–Weinberg equilibrium. Although there was no difference in the distribution of the genotype between SSc and the control group, when analysed for organ involvement a difference was found between patients with FA and without FA ($P = 002$ OR = 0.784 CI 95% 0.63, 0.97). This difference was also observed when the PAH group was compared with the group with no PAH ($P = 0.02$ OR = 1.38 95% CI 0.149, 1.036).
Conclusion. We confirmed the association of the CD226 polymorphism with SSc in the UK Caucasian population. CD226 encodes DNAX accessory molecule 1 that is involved in T-cell co-stimulation pathways. Our results provide further evidence for the important influence of genetic factors in the autoimmune component of SSc.

PS43. EXPRESSION PROFILING OF SKIN AND LUNG TISSUE AND EXPLANTED FIBROBLASTS IN A TRANSGENIC MOUSE MODEL OF SCLERODERMA

E. Derrett-Smith[1], R. Hoyles[1], P. Moinzadeh[1], C. Chighizola[1], K. Khan[1], D. Abraham[1] and C. Denton[1]
[1]*Centre for Rheumatology and Connective Tissue Diseases, UCL Medical School, Royal Free Campus, London, UK*

Background. Gene expression profiling of skin or lung tissue and fibroblasts in explant culture have been used to study intrinsic subsets and pathogenic mechanisms in SSc. There are technical challenges integrating the results of whole tissue and fibroblasts, although the methods are often complementary. We have applied a similar strategy to analysis of a transgenic mouse model that is a phenocopy of many of the histological and biochemical features of SSc. This mouse strain has ligand-dependent up-regulation of TGF-β signalling due to altered TβRII receptor expression in fibroblasts.
Methods. In the present study, we have analysed gene expression profiles of whole skin and lung from littermate TβRIIδk-fib mice and fibroblasts cultured from neonatal or adult skin and lung tissue ($n = 3$ in each group) using the illumina gene platform. RNA was extracted, quantified and assessed for quality using standard methods. Technical validation of the data and additional quantitation of key gene expression were performed using quantitative RT–PCR assay using technical and biological replicate samples.
Results. Cluster analysis identifies key gene profiles that are specific for skin or lung fibroblasts and also that are altered in whole tissues. In general, the differential gene expression was much more marked in whole tissue and differences were more marked in neonatal compared with adult fibroblasts consistent with the higher levels of transgene expression previously described in younger mice. In particular, genes related to cytoskeletal and extracellular matrix structure and function (αSMA, troponin, tropomyosin 1, collagens type I, III, VI, VIII, XVII, matrix metalloproteinases 3, 9, 10, 13, 17, Timp3), endothelin (ET-1, Ednrb, Ednra), TGF-β (Ltbp1, TGF-β1, 2, 3, Ctgf), BMP (Bmp2, 4, Bmpr1) and VEGF (Vegfa, Vegfc) signalling axes and innate immunity (Il-6, Il-11, Il-13, Il-1r, Crp, Saa) were found to be differentially expressed both in transgenic whole skin, lung and explanted fibroblasts. In addition, genes coding for Pecam1 ($P = 0.03$) and Elastin ($P = 0.003$) were up-regulated strongly in whole lung and skin. Some of these key genes that demonstrated significantly dysregulated expression in transgenic mouse skin and lung are summarized in more detail in Table 1.

TABLE 1. Representative genes that demonstrate dysregulated expression in transgenic skin and lung

Gene	Tissue examined	Relative transgenic expression	P
Mus musculus matrix metallo-proteinase 3 (Mmp3), mRNA	Lung fibroblast	1.94	0.02
Mus musculus TGF−β 1 (Tgfb1), mRNA	Lung fibroblast	1.14	0.01
Mus musculus pleiotrophin (Ptn), mRNA	Skin fibroblast	−0.59	0.1
Mus musculus dual specificity phosphatase 1 (Dusp1), mRNA	Skin fibroblast	0.28	0.0004
Mus musculus homeo box B7 (Hoxb7), mRNA	Skin fibroblast	−0.49	0.01
Mus musculus annexin A1 (Anxa1), mRNA	Whole lung	−0.43	0.05
Mus musculus integrin α–6 (Itga6), mRNA	Whole lung	−1.89	0.02
Mus musculus collagen, type XII, α–1 (Col12a1), mRNA	Whole skin	0.82	0.01
Predicted: Mus musculus similar to fibrillarin, transcript variant 1 (LOC100044829)	Whole skin	0.40	0.02
Mus musculus vascular endothelial growth factor (Vegfa) transcript variant 2, mRNA	Whole skin	−1.86	0.05

Conclusions. These data are reminiscent of studies of human SSc tissue and illustrate another potential complementary strength for mouse models in better understanding the disease.

PS44. SYSTEMIC VEGF INHIBITION INDUCES PULMONARY ARTERIAL HYPERTENSION IN A TRANSGENIC MOUSE MODEL OF SCLERODERMA

E. Derrett-Smith[1], A. Dooley[1], R. Baliga[2], A. Hobbs[2], D. Abraham[1] and C. Denton[1]
[1]*Centre for Rheumatology and Connective Tissue Diseases, UCL Medical School and* [2]*Centre for Cardiovascular Pharmacology, UCL, London, UK*

Purpose. PAH complicates up to 15% of SSc cases and occurs throughout the disease suggesting that a second vascular event occurring in the context of a systemic disease may be responsible. A role for altered VEGF signalling in PAH-SSc is supported by data that correlate circulating VEGF with mPAP at diagnosis. We have previously shown that a transgenic mouse model develops many features of SSc including susceptibility to vasculopathy and lung fibrosis. We have inhibited VEGF signalling using SU5416 to induce endothelial apoptosis in this model.
Methods. The transgenic mouse strain TβRIIδk-fib expresses a kinase-deficient type II TGF-β receptor driven by a fibroblast-specific promoter leading to balanced ligand-dependent up-regulation of TG-Fβ signalling. The constitutive pulmonary vasculopathy was confirmed by histological assessment of vessel architecture, isolated organ bath and *in vivo* haemodynamic studies. Biochemical analysis of the VEGF signalling axis by quantitative PCR and western blotting was performed using cultured pulmonary artery smooth muscle cells, and by immunostaining of tissue sections. *In vivo* SU5416 administration to transgenic and wild-type animals was compared with vehicle administration alone ($n = 6$ each group). Post-mortem RV mass index measurements were taken, and histological and immunohistochemical stains (H&E, SR, CD31) were performed.
Results. Within the transgenic pulmonary arterial circulation, hypertrophy of the smooth muscle layer was increased (mean wild-type vessel thickness: circumference ratio 0.66 (0.02), mean transgenic 0.88 (0.04), $P < 0.05$). Pulmonary arterial ring responses to direct and receptor-mediated contractile stimuli were reduced in the transgenic animals (in response to endothelin contraction at 10-5 M wild-type 1.10 mN (0.02), transgenic 0.62 (0.12), $P < 0.05$) and right ventricular pressures were elevated in transgenic animals [wild-type mean 29 mmHg (4), transgenic mean 37 mmHg (3)]. Explanted transgenic PASMC showed up-regulation of VEGF and VEGFR1. RV mass index in transgenic animals was increased after treatment with SU5416 [transgenic, vehicle only 0.19 (0.01), SU5416 treated 0.29 (0.03), $P < 0.05$]. Histological and immunohistochemical analysis revealed evidence of obliterative endothelial proliferation in transgenic SU5416-treated animals similar to human plexiform lesions, which was not seen in any other group.
Conclusion. Treatment with SU5416 exacerbates the underlying constitutive pulmonary vascular defect of this transgenic mouse model and replicates the key histological and pathophysiological features seen in human PAH-SSc. These findings support a role for perturbed TGF-β and VEGF activity in the pulmonary circulation in SSc, supporting the concept of a second pulmonary endothelial injury leading to PAH in SSc. This model may provide a valuable platform for future therapeutic studies *in vivo* as well as providing insight into pathogenic mechanisms.

PS45. INDEPENDENT REPLICATION AND META-ANALYSIS ESTABLISH TNFSF4 AS A SUSCEPTIBILITY GENE PREFERENTIALLY ASSOCIATED WITH THE SUBSET OF PATIENTS WITH POSITIVE ACAs IN SSc

B. Coustet[1], M. Bouaziz[2], P. Dieude[3], M. Guedj[2], L. Bossini-Castillo[4], P. R. Gourh[5], G. Chiocchia[1] and Y. Allanore[1]
[1]*Rheumatology A Department, Paris Descartes University, Sorbonne Paris Cités, Cochin Hospital, Inserm U1016, Paris,* [2]*Laboratoire Statistique et Génome UMR CNRS-8071/INRA-1152/Université d'Evry Val d'Essonne, Evry,* [3]*Paris Diderot University, Bichat Hospital, Inserm U699, Paris, France,* [4]*Consejo Superior de Investigaciones Científicas (CSIC), Armilla, Spain and* [5]*UTHSC-Houston Medical School, Houston, USA*

SSc is a complex genetic disorder for which susceptibility genes are being discovered. As expected for this model, signal for association are frequently weak and therefore very large cohorts are needed to confirm and validate first findings.
The TNFSF4 locus, encodes the co-stimulatory molecule OX40 ligand, involved in T-cells regulatory functions. Genetic studies have found genotype–phenotype association with SLE, with influence on auto-antibodies production. In SSc, TNFSF4 risk locus has been investigated in two studies that both identified association signal. However, ORs were weak and conflicting results with regards to genotype–phenotype correlation association were reported.
Objective. To perform a large and independent replication study of the TNSF4 variants in SSc and to perform a meta-analysis of available data in order to clarify the level of association and subsets with preferential associations.
Method. Known lupus and SSc TNFSF4 susceptibility variants (rs2205960, rs1234317, rs12039904, rs10912580 and rs844648) were genotyped in a French cohort consisting of 1031 SSc patients and 1014 controls of European Caucasian ancestry. Genotype–phenotype association analysis and meta-analysis of available data were performed (providing a population study of 4989 SSc patients, 1526 SSc patients with ACA+, 949 SSc patients with anti-topoisomerase antibodies (ATA+) and 4661 controls, all of European Caucasian ancestry).
Results. In the French cohort, the TNFSF4 SNPs were at Hard–Weinberg equilibrium in the control population. No variant showed allelic association with the overall SSc, however, the rs2205960 TT genotype was found to be associated. In addition, the five SNPs showed association or trend for association with the lcSSc subset and even most strongly with the subgroup of SSc patients having ACA+. In this latter subset, rs2205960 had the highest level of association (TT genotype $P_{corr} = 0.00042$; OR 2.98; 95% CI 1.73, 5.1; T allele $P_{corr} = 0.015$; OR 1.37; 95% CI 1.12, 1.66). Haplotype analyses led to the identification of three common haplotypes (frequency >5%).
Meta-analysis of the three most strongly associated SNPs according to the previous reports strengthened results with global association and both lcSSc and ACA+ subsets (rs220590 T allele in SSc $P = 0.0021$; OR 1.19; 95% CI 1.064, 1.324; in lcSSc $P = 0.0003$; OR 1.25; 95% CI 1.11, 1.42 and ACA+ $P = 0.00013$; OR 1.33; 95% CI 1.15, 1.54).
Conclusion. Our data confirm association signal of TNFSF4 with SSc and preferentially with ACA+ subset, the mostly associated with other autoimmune diseases. That makes sense for a polymorphic auto-immune susceptibility gene. Therefore, ACA+ patients may represent a subgroup that could be treated by future drugs targeting T-cell pathway.

PS46. USING PROTEOMIC ANALYSIS FOR STUDYING THE SKIN FIBROBLAST PROTEIN PROFILE IN SSc

P. Coral-Alvarado[1], G. Quntana[1,2], C. A. Cardozo[2], A. Cepeda[2], A. Iglesias[2] and E. Caminos[2]
[1]*Universidad de Los Andes – Fundacion Santa Fe de Bogota and* [2]*Universidad Nacional de Colombia, Bogota, Colombia*

Introduction. Despite recent advances having been made in understanding some molecular pathways involved in SSc, its aetiopathogenesis remains unknown. A proteomics study of fibroblasts in SSc was thus proposed to observe the expression profile and determine changes in their profiles in relation to different phases of the illness, serology and treatment, trying to determine the proteins involved in the illness' aetiopathogeny that could have potential therapeutic implications.

Objective. Studying the fibroblast protein expression profile in patients suffering from SSc during different stages of the illness and comparing it with clinically healthy areas in the same SSc patient and with fibroblasts from healthy individuals.
Methods. Eleven patients diagnosed with SSc at different stages of their illness were included according to ACR criteria; skin biopsies of areas with and without clinical involvement were taken from three healthy people. A cell culture was made, obtaining fibroblast growths; proteins having a differential pattern were identified by means of mass spectrometry.
Results. Differentially expressed proteins (spots) between controls and SSc patients were isolated and digested with trypsin and the peptides so produced were analysed by mass spectrometry (peptide mass fingerprints) (MALDI-TOF). The spots analysed from the stained gels mainly corresponded to different isoforms from the haptoglobin protein, having a protein score CI% >99%.
Conclusion. The results suggested that high haptoglobin levels or its differential expression were associated with the presence of SSc.

PS47. ILOPROST ENHANCES TH22 AND TH17 WHILE DECREASING TH1 CELL RESPONSES IN SSc INDIVIDUALS: INVOLVEMENT OF THE IP RECEPTOR AND MONOCYTES

M. E. Truchetet[1], Y. Allanore[2], E. Montanari[1], C. Chizzolini[1] and **N. C. Brembilla**[1]
[1]*Immunology and Allergy, University Hospital and School of Medicine, Geneva, Switzerland and* [2]*Université Paris Descartes, Service de Rhumatologie A, Hopital Cochin, Paris, France*

Objective. Iloprost, a prostacyclin analogue, is currently used as vasodilating agent to treat SSc-related vascular events. However, the capacity of iloprost to affect the adaptive immune response remains poorly characterized. Our purpose was to assess whether iloprost could impact on the production of lineage-specific cytokines by Th cells in SSc and healthy donors (HDs).
Methods. Peripheral blood mononuclear cells (PBMCs) were obtained from 30 SSc and 29 age- and sex-matched HDs. None of the patients was under immunosuppressant agents at the time of blood sampling. Cytokine levels in the supernatant of iloprost-treated PBMC cultures and autologous monocytes/CD4+ T cells co-cultures were quantified by ELISA and multiplex technology. Frequencies of IL-17A, IL-22, IFN-γ and IL-4-producing CD4+ T cells were assessed upon 7 days of polyclonal expansion by multiparametric flow cytometry. Selective IP and EP4 receptor antagonists were used to identify the receptors mediating iloprost effects.
Results. Iloprost significantly enhanced IL-22 and IL-17A while decreasing IFN-γ production in a dose-dependent manner in PBMC from both HD and SSc individuals. Analysis at the single cell level confirmed these results and revealed that iloprost treatment consistently favoured the expansion of Th17 ($P < 0.0001$) and Th22 cells ($P < 0.0001$) while strongly decreasing Th1 cells ($P < 0.0001$). No effects of Iloprost were observed on IL-4-producing Th2 cells. Importantly, these effects were specifically reversed by a peptide inhibitor of the IP (CAY10449) but not of the EP4 (AH23848) receptor. Of interest, monocyte depletion abrogated the effect of iloprost on IL-17A and IFN-γ production, which was re-established after monocyte reintroduction. The simultaneous enhanced production of IL-6 and IL-23 observed when CD4+ T cells were co-cultured with monocytes in the presence of iloprost may explain the enhancement of Th17 responses.
Conclusion. Our results show that iloprost, at pharmacological relevant doses, enhances Th22 and Th17 while decreasing Th1 cell responses in humans, mainly via the IP receptor with a mechanism partially dependent on monocytes. This immunological role distinct from its action on endothelial cells and fibroblasts should be taken into account in current iloprost-based therapies and could be exploited to develop novel therapeutic approaches.

PS48. A MULTICENTRE STUDY CONFIRMS CD226 GENE ASSOCIATION WITH SSc-RELATED PULMONARY FIBROSIS

L. Bossini Castillo[1], C. P. Simeon[2], L. Beretta[3], J. Broen[4], R. Ríos-Fernández[5], P. Carreira[6], M. A. González-Gay[7], Spanish Scleroderma Group, T. Witte[8], A. Kreuter[9], A. J. Schuerwegh[10], A. M Hoffmann-Vold[11], R. Hesselstrand[12], C. Lunardi[13], J. M. van Laar[14], M. M. Chee[15], A. Herrick[16], C. Fonseca[17], T. R. D. J. Radstake[4] and J. Martin[1]
[1]*Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Granada,* [2]*Servicio de Medicina Interna, Hospital Valle de Hebron, Barcelona, Spain,* [3]*IRCCS Fondazione Policlinico-Mangiagalli-Regina Elena & University of Milan, Allergy, Clinical Immunology and Rheumatology, Milan, Italy,* [4]*Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands,* [5]*Servicio de Medicina Interna, Hospital Clínico Universitario, Granada,* [6]*Servicio de Reumatología, Hospital 12 de Octubre, Madrid,* [7]*Servicio de Reumatología, Hospital Universitario Marqués de Valdecilla, IFIMAV, Santander, Spain,* [8]*Hannover Medical School, Hannover,* [9]*Ruhr University of Bochum, Bochum, Germany and* [10]*Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands,* [11]*Department of Rheumatology, Rikshospitalet, Oslo University, Oslo, Norway,* [12]*Department of Rheumatology, Lund University, Lund, Sweden,* [13]*Department of Medicine, Università degli Studi di Verona, Verona, Italy,* [14]*Institute of Cellular Medicine, Newcastle University, Newcastle,* [15]*University of Glasgow, Glasgow,* [16]*Arthritis Research UK Epidemiology Unit, The University of Machester, Manchester Academic Health Science Center, Manchester and* [17]*Center for Rheumatology, Royal Free and University College Medical School, London, UK*

Introduction. CD226 genetic variants have been associated with a number of autoimmune diseases and recently with SSc. The aim of this study was to test the influence of CD226 loci in SSc susceptibility, clinical phenotypes and autoantibody status in a large multicentre European population.
Methods. A total of seven European populations of Caucasian ancestry were included, comprising 2131 patients with SSc and 3966 healthy controls. Three CD226 single nucleotide polymorphisms (SNPs), rs763361, rs3479968 and rs727088 were genotyped using Taqman 5′allelic discrimination assays.
Results. Pooled-analyses showed no evidence of association of the three SNPs neither with the global disease nor with the analysed subphenotypes. However, haplotype block analysis revealed a significant association for the TCG haplotype (SNP order: rs763361- rs34794968- rs727088) with lung fibrosis-positive patients [$P_{Bonf} = 1.78E\text{-}02$, OR 1.29 (1.07, 1.56)].
Conclusion. Our data suggest that the tested genetic variants do not individually influence SSc susceptibility but a CD226 three-variant haplotype is related with genetic predisposition to SSc-related pulmonary fibrosis.

PS49. PATHOGENIC EFFECTS OF AUTOANTIBODIES AGAINST VASCULAR RECEPTORS IN PATIENTS WITH SSc

M. Becker[1], A. Kill[2], R. Undeutsch[2], C. Tabeling[3], M. Witzenrath[3], W. Kuebler[4], S. Bock[4], R. Sampati[4], H. Heidecke[5], H. Ghofrani[6], M. Hoeper[7], I. Lukitsch[8], D. Dragun[8] and G. Riemekasten[1,2]
[1]*Department of Rheumatology and Clinical Immunology, University Hospital Charite,* [2]*German Rheumatism Research Centre (DRFZ, a Leibniz Institute),* [3]*Department of Infectiology and Pulmonology, University Hospital Charite,* [4]*University Hospital Charite – Institute of Physiology, Berlin,* [5]*CellTrend GmbH, Luckenwalde,* [6]*Department of Pulmonology, University Hospital Giessen, Giessen,* [7]*Department of Pulmonology, Hannover Medical School Hospital, Hannover and* [8]*Department of Nephrology and Intensive Care, University Hospital Charite, Berlin, Germany*

Objective. We have recently discovered functional cross-reacting autoantibodies against the angiotensin II type 1 receptor (AT1R) and against the ET-1 type A receptor (ETAR) in the majority of patients with SSc linked with vascular and fibrotic complications and predicting disease-related mortality (Riemekasten *et al.,* ARD 2010). The association between the presences of these antibodies with clinical SSc symptoms suggest a contribution of these antibodies in SSc pathogenesis. Due to the high homology of the receptors in different species, we hypothesized comparable effects of the antibodies on pathogenesis in different species. Our aim was to investigate the effects of the antibodies on pathogenesis of SSc-specific pathology *in vitro* and *in vivo*.
Methods. The association of vascular events and positivity for AT1R and the ETAR autoantibodies was investigated in SSc patients. In addition, we examined the pathogenic effects of these antibodies in cell culture *in vitro* and in animal models *in vivo*.
Results. Anti-AT1R and anti-ETAR autoantibodies were able to predict development of pulmonary arterial hypertension (PAH) as well as digital ulcers in SSc patients. They could contribute to an increased vascular tone and activated endothelial cells (e.g. via calcium influx). Other signalling cascades were also activated in cultured endothelial cells. In addition, we tested the effect on fibroblasts and found a profibrotic effect of these antibodies *in vitro*. The pathogenic capacity of the antibodies was also tested in a murine model with transfer of high-titre SSc-IgG and initial experiments revealed a role for these antibodies in the development of alveolitis/fibrosis.

Conclusions. Functional, stimulatory autoantibodies against AT1R and ETAR are common in patients with SSc. They could contribute to disease pathogenesis and may serve as biomarkers for risk assessment of disease progression. Long-term *in vivo* experiments and long-term blockade will be performed to identify the full spectrum of the effects.

PS50. PSORIASIN SALIVARY LEVELS IN CONNECTIVE TISSUE AND OTHER RHEUMATIC DISEASES

L. Bazzichi[1], F. Sernissi[2], M. Doveri[1], L. Giusti[2], C. Giacomelli[1], F. De Feo[1], A. Consensi[1], A. Rossi[2], A. d'Ascanio[1], A. Della Rossa[1], R. Neri[1], A. Lucacchini[2] and S. Bombardieri[1]
[1]*Department of Internal Medicine, Rheumatology Unit and* [2]*Department of Psychiatry, Neurobiology, Pharmacology and Biotechnology, University of Pisa, Pisa, Italy*

Background. Psoriasin (S100A7) is a small calcium-binding protein of the S100 family, originally identified as a 11.4 kDa protein expressed in psoriatic skin, where it is up-regulated. It has also been found in saliva samples at three different molecular weights (12, 24 and 50 kDa), corresponding to one monomeric and two multimeric forms. The aim of this study was to evaluate psoriasin levels, through ELISA technique, in SSc, PM and DM, SLE, EF patients, *vs* RP patients, active RA, PsA and healthy controls.
Materials and methods. Fifty-nine SSc patients were consecutively enrolled: 35 with lcSSc and 24 with dcSSc. Twenty-four matched patients for age and sex were included in the CTD group: 17 PDM, 6 SLE and 2 EF. The control group consisted of 11 PA, 5 RA and 19 age-matched healthy volunteers. Twenty-nine RP patients were also evaluated.
Results. The statistical comparison of CTD *vs* RP and *vs* control group (ANOVA and Dunnett's *post hoc* test) showed a significant difference between CTD and controls. No statistical differences within CTD, between CTD and RP, and within controls were found. Finally, we found that RP patients with a suspect for a secondary form had higher psoriasin levels than primitive RP, though the difference was not statistically significant. The result seemed to be independent of clinical features such as lung and skin involvement, RP, capillaroscopy pattern and autoantibodies profile.
Conclusion. With this preliminary study we confirmed the elevated levels of salivary S100A7 in SSc and in patients characterized by a skin fibrotic activation (PDM, EF and SLE), stressing the concept that psoriasin is typically involved in flogosis process of vasculitis nature. This result is also supported by the low levels observed in RA and PA patients. The lack of correlation between psoriasin and lung involvement could be explained considering that only the monomeric form is linked to reduced DL_{CO}, pulmonary fibrosis and ground-grass opacity, as previously observed, and that ELISA assay can't discriminate between the three forms. Thus, the development of a quantitative technique, selective for 12 kDa S100A7, assumes a crucial importance in the progress of this research. The actual assay is nonetheless useful as it highlighted elevated psoriasin levels in vasculitis diseases and so it could turn into being a simple predictive tool of secondary evolution of early RP patients.

PS51. THE SYNTHETIC CANNABINOID AJULEMIC ACID EXERTS POTENT ANTI-FIBROTIC EFFECTS IN EXPERIMENTAL MODELS OF SSc

E. Balistreri[1], E. Garcia Gonzalez[1], E. Selvi[1], S. Lorenzini[1], C. Baldi[1], A. Akmestshina[2], K. Palumbo[2], M. Galeazzi[1], F. Laghi Pasini[3], P. E. Lazzerini[3] and J. H. W. Distler[2]
[1]*Department of Clinical Medicine and Immunological Sciences, Unit of Rheumatology, University Of Siena, Siena, Italy,* [2]*Department of Internal Medicine III. University of Erlangen, Erlangen, Germany and* [3]*Immunology Unit – Department of Clinical Medicine and Immunological Sciences, Siena, Italy*

Cannabinoids are able to modulate fibrogenesis in SSc. Ajulemic acid (AjA) is a non-psychoactive synthetic analogue of tetrahydrocannabinol (THC), able to bind the peroxisome proliferator-activated receptor-γ (PPAR-γ). PPAR-γ receptor activation has been recently demonstrated to modulate fibrogenesis. In addition, a reciprocal inhibitory cross-talk between PPAR-γ signalling and the profibrotic cytokine TGF-β has been suggested. On this basis the aim of this study was to investigate whether AjA could modify fibrogenesis in scleroderma
Material and methods. Skin fibrosis was induced in two groups of DBA/2J mice by local injunction of bleomycin (BLM). One group of BLM challenged mice received orally AjA 1 mg/Kg/day. Skin fibrosis was evaluated by quantification of skin thickness and hydroxyproline content. As a marker of fibroblast activation, α-SMA was examined. Fibroblasts from scleroderma were cultured and treated with increasing concentrations of AjA (0, 1, 1, 5 and 10 μM) in the presence or absence of the PPAR-γ irreversible antagonist GW9662 (1 and 10 μM) in order to evaluate procollagen production. We evaluated PPAR-γ protein expression, as well as the supernatant level of its endogenous ligand, 15d-PGJ2 and TGF-β, prior or after AjA treatment.
Results. AjA treatment was able, *in vivo*, to significantly prevent experimental dermal fibrosis, consistently dermal thickness and hydroxyproline were significantly reduced. Upon AJA (1 mg/kg) treatment was observed a strong reduction of α-SMA-positive cell in lesional skin. *In vitro* treatment of scleroderma fibroblasts, with increasing concentration of AjA, prevent collagen neosynthesis in a dose-dependent manner. This effect was completely reverted by the PPAR-γ antagonist GW9662 (10 μM). The same treatment was able to induce an increase of PPAR-γ and its endogenous ligand15d-PGJ2 expression and a reduction of the supernatant level of TGF-β.
Conclusions. We demonstrate that AjA exerts potent anti-fibrotic effects *in vivo* and *in vitro* by stimulating PPAR-γ signalling. Since therapeutics doses of AjA are well tolerated in humans, we suggest AjA as an interesting molecule targeting fibrosis in patients with scleroderma.
Acknowledgements. We are grateful to Professor Robert B. Zurier (MA, USA) for advices. We thank JB Therapeutics (MA, USA) that kindly provided Ajulemic Acid for all experiments presented in this work.

PS52. THE NUCLEAR RECEPTOR CAR MEDIATES THE PRO-FIBROTIC EFFECTS OF TGF-β AND CONTRIBUTES TO THE DEVELOPMENT OF EXPERIMENTAL DERMAL FIBROSIS

J. Avouac[1], M. Tomcik[1], K. Palumbo[1], P. Zerr[1], C. Dees[1], A. Akhmetshina[1], C. Beyer[1], O. Distler[2], G. Schett[1], Y. Allanore[3] and J. Distler[1]
[1]*Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen, Germany,* [2]*Center of Experimental Rheumatology and Zurich Center of Integrative Human Physiology, University Hospital Zurich, Zurich, Switzerland and* [3]*Paris Descartes University, Rheumatology Department and INSERM U1016, Cochin Hospital, Paris, France*

Background. Tissue fibrosis caused by pathological activation of fibroblasts is a major hallmark of SSc. The constitutive androstane receptor (CAR), a member of the nuclear receptor superfamily, is involved in shear and xenobiotic stress. CAR activation has been shown to exacerbate hepatic fibrosis.
Objectives. To investigate whether CAR might contribute to the pathological activation of fibroblasts in SSc and to the development of experimental dermal fibrosis.
Methods. Expression of CAR was determined in human skin by immunohistochemistry and in fibroblasts by real time PCR and western blots. SSc and healthy dermal fibroblasts were stimulated with TGF-β and incubated with CITCO, a selective agonist for the human CAR. Collagen release from fibroblasts was evaluated by mRNA levels of col1a1 and col1a2 and by the SirCol collagen assay. Col1a2 transcriptional activity was assessed by transfection assays performed with a luciferase reporter construct under control of the −772-bp to +58-bp col1a2 promoter. The synthetic agonist of mouse CAR TCPOBOP was used to evaluate the profibrotic potential of CAR *in vivo* in the mouse model of bleomycin-induced dermal fibrosis or in the model of dermal fibrosis induced by local injections of replication deficient adenoviruses overexpressing a constitutively active TGF-β receptor I.
Results. Up-regulation of CAR was detected in the skin and dermal fibroblasts of SSc patients. Stimulation of healthy fibroblasts with TGF-β increased the expression of CAR mRNA by 93 (11)% and protein by 81 (14)% ($P < 0.05$ for both). Treatment of healthy or SSc fibroblasts with CITCO significantly increased the stimulatory effects of TGF-β on collagen synthesis. CITCO also amplified the stimulatory effects of TGF-β on col1a2 transcriptional activity by up to 41 (5)% ($P = 0.03$). Consistently, activation of CAR with TCPOBOP exerted potent profibrotic effects in different models of experimental fibrosis. In the mouse model of bleomycin-induced fibrosis, activation of CAR increased dermal thickening by 35 (1)% ($P < 0.05$). The collagen content and the number of myofibroblasts were also significantly increased [42 (3)% and 69 (11)%, respectively, $P < 0.05$]. In the TGFBRI model, activation of CAR also exerted potent profibrotic effects and increased dermal thickening, collagen content and myofibroblast counts by 51 (5)%, 46 (7)% and 42 (3)%, respectively ($P < 0.05$).

Conclusion. We demonstrate that CAR is activated in a TGF-β-dependent manner in SSc and mediates the effects of TGF-β on collagen synthesis. In addition, activation of CAR contributed to the development of experimental dermal fibrosis. Thus, CAR might be a promising new molecular target for the treatment of SSc and other fibrotic processes.

PS53. BOSENTAN REVERSES THE PROFIBROTIC PHENOTYPE OF SSc DERMAL FIBROBLASTS THROUGH INCREASING THE DNA BINDING ABILITY OF TRANSCRIPTION FACTOR FLI1

Y. Asano[1], K. Akamata[1] and S. Sato[1]
[1]*University of Tokyo Graduate School of Medicine, Tokyo, Japan*

SSc is a multisystem autoimmune disease characterized by vascular injuries and fibrosis of skin and certain internal organs. Although the pathogenesis of SSc still remains unknown, mounting data have demonstrated the possible contribution of ET-1 to the development of fibrosis and vasculopathy in SSc. ET-1 is indispensable for the profibrotic effect of TGF-β on fibroblasts and bosentan, a dual ET receptor antagonist, reverses the profibrotic phenotype of SSc fibroblasts. Clinically, bosentan prevents the development of new digital ulcers in SSc. Thus, ET-1 may be involved in the mechanism responsible for the constitutive activation of fibroblasts and endothelial cells in SSc.
Fli1 is a member of Ets transcription factor family, which functions as a potent repressor of type I collagen gene in dermal fibroblasts and as a pivotal regulator of angiogenic process in endothelial cells. In SSc skin, Fli1 is constitutively down-regulated in these cells, especially through the epigenetic mechanism in dermal fibroblasts, suggesting that Fli1 is a genetic factor in SSc. Supporting this idea, gene silencing of Fli1 activates fibroblasts and endothelial cells *in vitro* and a series of Fli1 mutant mice reproduce the histopathological features of SSc skin, including collagen deposition and abnormal vascular structure.
Based on these backgrounds, the purpose of this study is to clarify the mechanism responsible for the anti-fibrotic effect of bosentan on SSc fibroblasts especially by focusing on Fli1.
mRNA levels of COL1A2 gene were increased by ET-1 around 15 min in normal fibroblasts. A responsive element of ET-1 was located between −353 and −264 bp of the COL1A2 promoter, where Fli1 binding site is located, suggesting that ET-1 increases the promoter activity of COL1A2 gene by decreasing the DNA binding ability of Fli1. Consistent with the previous finding that the DNA binding ability of Fli1 is diminished by phosphorylation at threonine 312, ET-1 stimulation increased the phosphorylation levels of Fli1 at threonine 312. In SSc fibroblasts, phosphorylation levels of Fli1 were constitutively elevated compared with normal fibroblasts. Furthermore, a responsive element of bosentan was located between −353 and −264 bp of the COL1A2 promoter in SSc fibroblasts. Moreover, bosentan decreased the phosphorylation levels of Fli1 and increased the DNA binding ability of Fli1 in SSc fibroblasts.
Collectively, these results indicate that bosentan reverses profibrotic phenotype of SSc fibroblasts at least partially by increasing the DNA binding ability of Fli1.

PS54. CAPILLAROSCOPIC CHANGES DO NOT ASSOCIATE WITH SERUM LEVELS OF VASCULAR ENDOTHELIUM GROWTH FACTOR

R. Alekperov[1], E. Korzeneva[1], E. Alexandrova[1] and L. Ananyeva[1]
[1]*Institute of Rheumatology, Moscow, Russia*

Background. SSc is characterized by considerable reduction of microvessels. On the other hand, in SSc the increased levels of angiogenic factors are observed.
Aim. To study the association angiogenic factors with capillaroscopic changes in SSc.
Methods. Forty patients with established SSc according to ARA criteria were enrolled. In all the patients nailfold videocapillaroscopy (NVC) was performed and its parameters were scored, including total number of capillaries, number and percent of dilated or bushy capillaries, presence of haemorrhages and avascular areas. Serum levels of VEGF and its type 2 receptor (VEGFR2) were measured.
Results. There were not find correlations of levels of VEGF and VEGFR2 in the serum with any analysed capillaroscopic characteristics, such as total number of capillaries, number and percent of dilated or bushy capillaries, presence of haemorrhages, and avascular areas. Levels of VEGF and VEGFR2 did not differ between patients with different sclerodermic patterns of capillaroscopic changes, as well as between active an inactive patterns. Capillaroscopic parameters did not among patients with the highest and the lowest levels of VEGF and VEGFR2.
Conclusion. Capillaroscopic changes in SSc do not associate with serum levels of VEGF and VEGFR2. It is possible that such association exists between capillaroscopic changes and local levels of VEGF and VEGFR2. It is necessary further investigations with the greater number of patients.

PS55. ALLOGRAFT INFLAMMATORY FACTOR-1 AND CAVEOLIN-1 COLONIC EXPRESSION IN COLLAGENOUS COLITIS ASSOCIATED WITH SSc

G. Abignano[1,2], N. Scott[3], P. Emery[1], M. Buch[1] and F. Del Galdo[1]
[1]*Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK* [2]*Rheumatology Unit, Second University of Naples, Naples, Italy and* [3]*Histopathology Department, St James's Hospital, Leeds, UK*

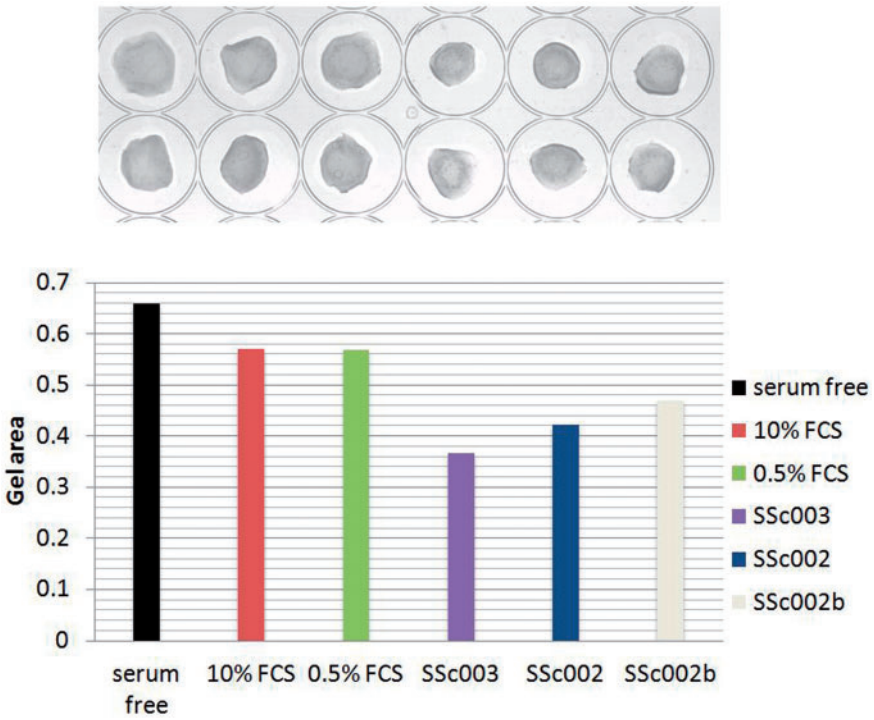
Background. Collagenous colitis (CC) is a large bowel inflammatory condition of unknown aetiology, characterized, clinically, by chronic watery and non-bloody diarrhoea, abdominal pain and weight loss and, macroscopically, by normal colonic mucosa. The diagnosis is essentially based on the typical histopathological findings of a thickened subepithelial collagen layer >10 μ, intraepithelial lymphocytes, inflammatory infiltrate in the lamina propria and epithelial damage such as flattening and detachment. SSc has been associated with CC only in few cases. The pathogenetic mechanism underlying both conditions is not well known. Several mechanisms have been proposed to explain the collagen deposition occurring in CC. Some of them are common to SSc and include abnormalities of the subepithelial myofibroblast function, increased CTGF and VEGF expression. In SSc, an increased expression of allograft inflammatory factor-1 (AIF-1) (1) and a decreased expression of caveolin-1 (CAV-1) (2) have been previously demonstrated in skin and lung. No previous studies have investigated their expression in the colonic mucosa of SSc and CC.
Objective. Starting from a clinical case of a SSc patient with CC, the aim of this study was to analyse the expression of AIF-1 and CAV-1 in colonic biopsies.
Methods. Paraffin-embedded sections from colon biopsy specimens were obtained from one patient with SSc-CC, three patients with CC and three healthy (H) controls. IF studies were performed for AIF-1 and CAV-1. The sections were analysed using a Zeiss LSM 510 META confocal laser scanning microscope system and software (Zeiss, Wetzlar, Germany).
Results. AIF-1 and CAV-1 expression was analysed by IF in the colon specimens from three H controls, one SSc-CC and three CC patients. The H and CC specimens did not show any expression of AIF-1. On the contrary, we observed AIF-1 expression in the SSc-CC colonic specimen. The CC and SSc-CC specimens showed a decreased expression of CAV-1 compared with H specimens.
Conclusion. Our IF studies found AIF-1 expression in the inflammatory cells of SSc-CC colon specimens whereas in CC and H it was not identifiable. This finding suggests that CC and SSc associated with CC may have different pathogenetic mechanisms. In addition, CAV-1 was overexpressed in CC and SSc-CC colon specimens consistent with a common profibrotic mechanism.

PS56. ANALYSIS OF SPECIFIC PDGFRα AND PDGFRβ SIGNAL TRANSDUCTION PATHWAYS IN SSc FIBROBLASTS AND EXAMINATION OF CUTANEOUS WOUND HEALING AND FIBROSIS IN A PDGFRα KNOCKOUT MOUSE

J. Donovan[1], C. P. Denton[1], J. Norman[1] and D. A. Abraham[1]
[1]*University College London, UCL Medical School, London, UK*

Background. PDGF isoforms (PDGF-AA, PDGF-BB, PDGF-CC, PDGF-DD and PDGF-AB) are potent activators of migration and proliferation in mesenchymal cells, including fibroblasts. PDGF ligands signal with varying specificities and affinities via dimeric receptors (PDFGRαα, PDGFRββ and PDGFRαβ). Activation of the PDGF pathway has been implicated in the pathogenesis of fibrotic diseases including SSc. Although recent studies have demonstrated stimulatory PDGFR autoantibodies present in SSc, and clinical trials to assess the impact of PDGFR antagonism in SSc are ongoing, it is unclear which ligand/receptor combinations and downstream signalling pathways contribute to the SSc pathology.
Objectives. Use neutralizing antibodies to PDGFRα and PDGFRβ to examine the differences in signal transduction and cellular responses of SSc fibroblasts. To generate a conditional inducible PDGFRα KO mouse to analyse the impact of PDGFRα deletion in fibroblasts on cutaneous wound healing and fibrosis.

FIG. 1



Methods. SSc and healthy control fibroblasts were treated with neutralizing antibodies against PDGFRα or PDGFRβ. Western blotting was used to examine the efficacy of the antibodies and differences in downstream signalling pathways. Differences in the contraction and migration of these cells were assessed by scratch wound and gel contraction assays.
To further investigate the effect of PDGFRα in wound healing and fibrosis, a fibroblast-specific, tamoxifen-inducible PDGFRα knockout mouse were generated and wound repair assessed (3, 7 or 10 days) and analysed by immunohistochemistry. Depletion of PDGFRα was shown by western blot of fibroblasts from explant cultures.
Results. Signal transduction through PDGFRα or PDGFRβ was abrogated by the neutralizing antibodies in SSc and control fibroblasts. Cell migration was reduced in the presence of PDGFRα or PDGFRβ neutralizing antibodies; this was more pronounced in occurred more for PDGFRα and in SSc fibroblasts.
Wound healing studies in PDGFRα conditional KO mice exhibited a reduction in wound size at Day 3 [1956 μm (S.E.M. 250.4 μm) compared with 1352 μm (S.E.M. 282.3 μm) in the control] and in the dermal boundary [1299.93 μm (S.E.M. 128 μm) compared with 713.44 μm (S.E.M. 226 μm) in the control $P > 0.05$].
Conclusions. PDGFRα and PDGFRβ neutralizing antibodies reveal important insights in to the difference signal transduction pathways and cellular function between SSc and control fibroblasts. Specific depletion of PDGFRαα in mouse fibroblasts appears to slow the rate of cutaneous wound closure.

PS57. USE OF FIBROBLAST POPULATED COLLAGEN LATTICES TO ASSAY FIBROCYTE ACTIVITY IN SSc

S. Kia[1], K. Khan[1], R. Yu[1], X. Shiwen[1], J. Nikitorowics-Buniak[1], J. Watson[1], C. P. Denton[1], D. J. Abraham[1] and R. J. Stratton[1]
[1]*Institute of Rheumatological Reseach, Royal Free Hospital, London, UK*

Introduction. Fibrocytes are bone marrow-derived circulating mononuclear cells capable of differentiating into collagen-producing contractile cells, and implicated in tissue regeneration and fibrosis. Fibrocyte levels are increased in SSc patients, and it is possible that fibrocyte activation and migration into disease tissues promotes fibrosis in the disease. It is not known whether fibrocytes are directly responsible for extracellular matrix production within fibrotic lesions, or if they are inducing resident tissue fibroblasts.

Material and methods. Mononuclear cells (PBMC) were isolated from blood samples from SSc patients and healthy controls, and cultured on six-well plates coated with fibronectin (<10 μg/ml) with 2 ml of media containing DMEM with 10% heat inactivated fetal calf serum (FCS). Non-adherent cells were washed from the plate at 48-h intervals. Cells were seen to adhere, elongate and take on a spindle-like morphology attributed to fibrocyte differentiation by Day 7 which increased by Day 14 and more frequent in SSc cultures.
After 14 days of primary cultures fibrocytes from SSc patients and controls in 0.5% FCS, were added to the surface of fibroblast populated collagen lattices cultured on 24-well plates. The collagen gels were released from adhesion to the well perimeter at 24 h and contraction assayed by imaging at 48 h. Gel contraction was quantified by weight at 48 h.
Results. Fibrocytes from three SSc patients and one healthy control were analysed. Fibrocytes from SSc patients demonstrate more aggressive features by promoting gel contraction at 48 h. Our preliminary data showed surface area of the gel was 2.35 mm^2 original gel, 0.657 mm^2 serum free, 0.569 mm^2 10% FCS, 0.365 mm^2 SSc patient 1, 0.42 mm^2 SSc patient 2, 0.468 mm^2 SSc patient 3.
Conclusion. We found that PBMC from SSc patients more frequently take on fibrocyte morphology when cultured adherent to fibronectin. SSc-derived firbrocytes were capable of promoting gel contraction are more likely to promote gel contraction compared with control. Further work is in progress to obtain more data and determine the underlying pathophysiology.

PS58. PROFILING OF CYTOKINE INDUCTION IN HACAT CELLS BY SSc AUTOANTIBODIES

J. Watson[1], S. Kia[1], J. Nikitorowicz-Buniak[1], X. Shiwen[1], D. Abraham[1], C. Denton[1] and R. Stratton[1]
[1]*Department of Rheumatology, University College London, London, UK*

Aims. We found that in SSc the epidermis is an activated IL-1α dominated tissue capable of inducing fibroblasts in co-culture. Because SSc is autoimmune, we wondered if SSc autoantibodies (IgG) were binding to keratinocytes and inducing inflammatory cytokines. We assayed SSc and control sera for IgG-dependent binding to fixed keratinocytes. Also, we investigated the effect of SSc IgG's on cultured keratinocytes, looking at the induction of various inflammatory cytokines. Chloroquine has previously been found to inhibit lysosomal Toll-like receptor (TLR) activation so we used

chloroquine to determine whether SSc IgG's activate TLR's leading to an increase in the release of inflammatory cytokines.
Methods. Fixed human keratinocytes were used as target antigen in a cell-based ELISA of 30 dcSSc sera, 30 lcSSc sera, and 30 healthy control sera. We also grew keratinocytes in the form of the immortalized HaCat cell line. We took serum from five scleroderma patients and isolated IgG antibody from the serum by protein A column. We then cultured the IgG's (100 μg/ml) with the HaCat cells for 24 h with and without chloroquine in DMEM with fetal calf serum. We used antibody from five healthy patients' serum as control. Media was removed and using a Luminex array we assayed for the expression of IL-1α, IL-1β, IL-1ra, IL-6, IL-8, MCP-1, PDGF-AA, PDGF-AB and PDGF-BB.
Results. Anti-keratinocyte ELISA binding titre was increased in both dcSSc and lcSSc sera when compared with control samples (Table 1). Treatment of HaCat cells with control IgG failed to cause induction of cytokines or growth factors. One out of five SSc patients' IgG (severe diffuse SSc skin score 40) caused induction of IL-1α, IL-8 and IL-1ra, which was blocked by pre-treatment with chloroquine. One further SSc patients' IgG caused induction of IL-6, not antagonized by chloroquine.
Conclusions. SSc patients' sera contain IgG capable of binding to human keratinocytes. Some but not all SSc IgG lead to induction of inflammatory cytokines in HaCat cells via differing mechanisms. We propose to more systematically screen a large number of SSc IgG for their ability to induce IL-1α or IL-6 in keratinocytes. In addition, we will extract cytoplasmic and nuclear proteins in a time course following antibody exposure, in order to test which phosphorylation signalling pathways are being induced by SSc IgG in these cells.

TABLE 1. ELISA binding titres

	Anti-epithelial cell ELISA, median (interquartile range)	*P vs* control (Wilcoxon rank sum test)
Healthy control ($n = 30$)	6.1 (0.00–28.3)	
lcSSc ($n = 30$)	23.8 (5.65–43.20)	$p < 0.025$
dcSSc ($n = 30$)	18.8 (10.00–35.60)	$q < 0.027$

CLINICAL (PS59–PS306)

PS59. A PRELIMINARY DISEASE SEVERITY SCORE FOR JUVENILE SSc

F. Zulian[1], F. La Torre[1], G. Martini[1], M. M. Katsicas[2], F. Corona[3], G. Calcagno[4], F. Falcini[5], F. Vittadello[1] and R. Russo[2]
[1]*Department of Pediatrics, University of Padua, Padua, Italy,* [2]*Department of Pediatrics, University of Buenos Aires, Buenos Aires, Argentina,* [3]*Department of Pediatrics, University of Milan, Milan,* [4]*Department of Pediatrics, University of Messina, Messina and* [5]*Department of Rheumatology, University of Florence, Florence, Italy*

Objective. To develop a preliminary disease severity score for juvenile onset SSc (JSSc).
Methods. We conducted an evidence and consensus-based study that included four phases: (i) prospective data collection of demographic and clinical characteristics of patients with JSSc, followed for at least 4 years or until death; (ii) blinded evaluation of the disease course profiles of these patients by JSSc experts to be used as 'gold standard'; (iii) definition of candidate severity indexes to be included in potential scores; (iv) selection of the score with the best statistical performance, in terms of face validity and sensitivity to change, by its ability to classify individual patients as having improvement or worsening of the disease when compared with the 'gold standard' profiles. This score was then compared with the modified Medsger severity score (MSS) for adults.
Results. Thirty-five patients, classified as having an aggressive ($n = 8$), moderate ($n = 10$) and mild ($n = 17$) course entered the study. The selected paediatric score, defined as Juvenile Systemic Sclerosis Severity Score (J4S), included indexes of nine organ systems (general, peripheral vascular, cutaneous, osteoarticular, muscular, gastrointestinal, respiratory, cardiac and renal) scored from 0 to 4. To weight the importance of the different organ involvement, a coefficient of severity was introduced. Compared with the modified MSS, J4S performed significantly better in detecting change in severity, both in patients with moderate (0.89 *vs* 0.52) and aggressive disease course (0.82 *vs* 0.75).
Conclusion. The J4S is a reliable and sensitive instrument to assess SSc in childhood. The use of variables adapted to the paediatric age and the inclusion of coefficients to appropriately weight the importance of the different organs involvement represent innovative features.

PS60. RELATIONSHIP BETWEEN PULMONARY HYPERTENSION AND HEART INVOLVEMENT IN SSc

M. Zlatanovic[1], D. Kalimanovska-Oštrić[2], B. Ivanovic[2], M. Tadic[2] and N. Damjanov[1]
[1]*Institute of Rheumatology and* [2]*Institute for Cardiovascular Disease, Clinical Center of Serbia, Belgrade, Serbia*

Background. Primary heart involvement in SSc is result of microvascular alterations and myocardial fibrosis. Pulmonary and heart involvement frequently coexists in SSc and has major impact on survival and prognosis.
Objective. To assess relationship between pulmonary hypertension (PAH) and heart involvement in patients with SSc.
Methods. Group of 80 patients, 22 with dcSSc and 58 with lcSSc, mean age 53.32 (10.75) years and mean duration of disease 8.68 (6.33) years were included in the study. All patients underwent the physical examination, evaluation of skin involvement, chest X-ray, complete Doppler echocardiographic assessment and PFTs (VC, FVC, FEV1, DL_{CO} and DI_{CO}/VA). Echocardiographic signs of PAH were compared with findings of cardiac and pulmonary function. Data were analysed using Mann–Whitney test, χ^2 test and Pearson's correlation coefficient in SPSS 11.0 program.
Results. Fifty (64.5%) patients were found to have right ventricular systolic pressure (RVSP) > 35 mmHg and inverted tricuspid (Tr) and mitral (Mt) E/A ratio (E/Atr, mt ratio <1) was detected in 31(40%) and 40(50%) patients. There was no significant difference in presence of PAH and inverted E/A ratio between lcSSc and dcSSc patients. RVSP was found to be correlated positively to Atr ($r = 0.37$; $P = 0.001$) and inversely to E/Atr ($r = -0.38$; $P = 0.001$). E/Atr ratio was found to be positively correlated to E/Amt ratio ($r = 0.26$; $P = 0.02$). Moreover, RVSP was found to be inversely correlated to VC, FVC, FEV1 and DL_{CO} ($r = -0.31$, -0.36, -0.38, -0.38, $P < 0.02$) and positively correlated to thickness of the septum, left ventricular posterior wall, diameter of left atrium, right ventricle and pulmonary artery ($r = 0.33$, 0.25, 0.42, 0.27, 0.40, $P < 0.03$).
Conclusion. In this study, pulmonary hypertension and impaired left and right ventricular filling have been detected in a significant percentage of our SSc patients, whatever the subset. Right ventricular diastolic dysfunction is related to pulmonary hypertension, but also to left ventricular diastolic dysfunction and primary heart involvement in SSc.

PS61. SEMIQUANTITATIVE EVALUATION OF HIGH-RESOLUTION CT IN SSc: PRELIMINARY APPLICABILITY OF A SIMPLE SCORE IN CLINICAL PRACTICE

A. Zimmermann[1], E. Pizzichini[2], L. F. Nobre[1] and M. M. M. Pizzichini[2]
[1]*Department of Rheumatology, University Hospital, Federal Universisty of Santa Catarina, Florianopolis and* [2]*Federal Universisty of Santa Catarina – NUPAIVA (Asthma and Ayrways Inflammation Research Center), Florianopolis, Brazil*

Background. High-resolution CT (HRCT) represents the gold standard in diagnosis and monitoring of interstitial pneumonias. Many authors have elaborated different scoring systems to interpret HRCT findings, but they have not been properly validated or are too complex to be routinely used in clinical care. We propose a simplified HRCT scoring system that evaluates simultaneously severity and extension of pulmonary involvement and includes different lesions that may be important in SSc patients.
Methods. Forty-five SS patients were submitted to a HRCT scan protocol and performed spirometry and pulmonary plethysmography. Tomographic index (TI) evaluated severity (weighted as 1, 2 or 3 for each observed lesion, depending on its relevance) and extension, as follows: 0 = absent, 1 = mild (involving up to 20% of the lung field's area), 2 = moderate (between 20 and 50%) and 3 = severe (>50% of lung involvement). So (TI) = 2× (ground glass opacities, possible score 0–3) + 3× (honeycombing, 0–3) + 3× (intralobular reticulation, 0–3) + 1× (bronchial structure alterations: 0 = absent, 1 = bronchiolectasis, 2 = bronchiectasis, 3 = both) 2× (interlobular septal thickening: 0 = absent; 1 = present) + 1× (centrilobular nodules, 0 or 1) + 1× (air trapping, 0 or 1). Although not included in the score, oesophageal dilation was registered whenever present. Statistical analysis: Pearson's coefficent was used to test correlations between TI and pulmonary function tests. A *P* value inferior to 0.05 was considered significant.

Results. The most prevalent lesions were ground glass opacities, which occurred in 55.1% of the cases, followed by bronchial structure alterations, seen in 40.8%. Honeycombing and intralobular reticulation were present in 16.6 and 14.3% of the scans, respectively. Centrilobular nodules and air trapping were observed in 8.2% of the cases. Oesophageal dilation was more frequent in patients with abnormal CT scans. TI was inversely correlated with carbon monoxide diffusion ($r = 0.31$, $P = 0.04$), total pulmonary capacity ($r = 0.55$, $P < 0001$), residual volume ($r = 0.33$, $P = 0.02$), vital forced capacity ($r = 0.40$, $P = 0.005$) and final expiratory volume ($r = 0.31$, $P = 0.03$).
Conclusion. TI is a reliable and simple tool to evaluate pulmonary involvement in SSc. Its validation and specific role in sequential monitoring of these patients will be addressed in future prospective studies.

PS62. LUNG INVOLVEMENT IS ASSOCIATED WITH GASTRO-OESOPHAGEAL REFLUX AND MICROASPIRATION IN SSc

A. Zimmermann[1], E. Pizzichini[2], I. A. Pereira[1], G. G. Ribeiro[1], O. E. C. Regis[3], P. M. G. Gomes[3], E. Usuy[3] and M. M. M. Pizzichini[2]
[1]*Department of Rheumatology, University Hospital, Federal University of Santa Catarina,* [2]*Federal Universisty of Santa Catarina – NUPAIVA (Asthma and Airways Inflammation Research Center) and* [3]*CEMAD (Digestive Medical Center), Florianopolis, Brazil*

Background. Oesophageal dysmotility leading to gastro-oesophageal reflux (GER) is common in SSc patients, potentially originating chronic microaspiration of digestive contents. It has been suggested that this could cause or aggravate pulmonary lesions in SSc, but a causal relationship remains to be demonstrated. We aimed to investigate the association of GER, oesophageal dysmotility and lung involvement in SSc patients and correlate it to airway microaspiration.
Methods. Forty-five SSc patients performed pulmonary function tests [spirometry and carbon monoxide diffusion (DL_{CO})], sputum induction, oesophageal manometry, 24 h pH monitoring and high-resolution CT (HRCT) scan. The lipid laden macrophage index (LLMI) in sputum was considered as a surrogate marker of microaspiration and was scored according to its original description. Pulmonary lesions were recorded using a semiquantitative scoring system (tomographic index, TI). Statistical analysis: data are expressed as mean and standard deviation or median and interquartile range. Parametric (Student's *t*-test) or non-parametric tests (Wilcoxon/Mann–Whitney) were applied. Pearson's chi-square or exact Fisher's tests were used to compare categorical variables, as appropriate. Correlations between continuous parameters were tested using Pearson's coefficient. Significance was set in 5%.
Results. GER was diagnosed in 69.7% of SSc patients and 86.6% of them had manometry abnormalities, while 64.4% of the individuals had symptoms. Patients with manometry abnormalities, aperistalsis and an abnormal HRCT had a higher prevalence of GER ($P < 0.05$). DL_{CO}, but not vital forced capacity (VFC), was reduced in patients with GER ($P = 0.05$). TI was higher in patients with GER ($P = 0.03$) and ineffective peristaltic waves ($P = 0.002$). TI was also significantly higher in male subjects, patients with dcSSc and a positive anti-SCl 70 ($P < 0.01$). A higher modified Rodnan skin score was observed in patients with HRCT abnormalities ($P < 0.0001$). Sputum neutrophil count was inversely correlated with DL_{CO} ($r = 0.32$, $P = 0.03$). Patients with an abnormal LLMI had more frequently aperistalsis ($P = 0.02$) and different manometry abnormalities ($P = 0.059$). There were no correlations between pH monitoring results and LLMI.
Conclusion. Oesophageal dysmotility and GER are associated with functional and anatomic pulmonary abnormalities in SSc patients. In addition, we also found that a higher LLMI, although not related to with GER diagnosis by pH monitoring, is associated with manometry abnormalities and with neutrophilic airway inflammation. This suggests a causal relationship between microaspiration and lung disease in SSc and should be confirmed by larger, prospective studies.

PS63. AIRWAYS HYPERRESPONSIVENESS AND INFLAMMATION IN PATIENTS WITH SSc: ASSOCIATION WITH OESOPHAGEAL DYSMOTILITY AND MICROASPIRATION

A. Zimmermann[1], E. Pizzichini[2], T. S. Veras[2], I. A. Pereira[1], G. R. W. Castro[1] and M. M. M. Pizzichini[2]
[1]*Department of Rheumatology, University Hospital, Federal University of Santa Catarina and* [2]*Federal University of Santa Catarina – NUPAIVA (Asthma and Airways Inflammation Research Center), Florianopolis, Brazil*

Background. Airways hyperresponsiveness (AHR) is characteristic but not exclusive of asthma. Gastro-oesophageal reflux (GER) is thought to be associated with AHR even in adults without asthma. Patients with SSc) frequently present with oesophageal dysmotility leading to acid gastro-oesophageal reflux and probably non-acid reflux as well. We hypothesize that microaspiration may cause upper airways inflammation and AHR in SSc patients, what has never been investigated.
Methods. Forty-five SSc non-smoking patients with no medical history of asthma or allergy were compared with 38 age-matched non-smoking healthy controls. The subjects were submitted to sputum induction, spirometry, bronchial provocation test to methacholine and oesophageal manometry. AHR was regarded positive if a provocative concentration of methacholine to cause a 20% falls in FEV1 ($PC20 < 8$ mg/ml). Sputum was induced and processed as described by Pizzichini *et al.* The lipid laden macrophage index (LLMI) was used as a marker of microaspiration and regarded positive when >100.
Statistical analysis. Parametric (Student's *t*-test) or non-parametric tests (Wilcoxon/Mann–Whitney) were applied and Pearson's chi-square or exact Fisher's tests were used to compare categorical variables, as appropriate. Significance was set in 5%.
Results. AHR was present in 25.6% of the patients and in none of the controls ($P < 0.001$, Fisher's exact test). Compared with controls, SSc patients had a lower forced vital capacity (FVC) [89.47 (19.82) *vs* 101.37 (11.63), $P = 0.001$] and a lower forced first second expiratory volume (FEV1) [86.47 (19.13) *vs* 97.34 (11.24), $P = 0.002$] but similar FEV1/FVC ratio. SSc patients had a higher sputum total cell count (TCC) [6.0 (7.6) *vs* 3.5 (4.1) $\times$ 106, $P = 0.008$] and higher neutrophil count [54.0 (35.3) *vs* 25.0 (16.5), $P < 0.0001$] than controls, respectively. LLMI was positive in 24% of the patients and it was significantly associated with aperistalsis ($P = 0.02$) and with percentage of ineffective peristaltic waves ($P = 0.03$). Induced sputum neutrophils and TCC were significantly higher in patients with a positive LLMI ($P = 0.04$ and $P = 0.001$, respectively).
Conclusion. These results demonstrate that microaspiration, as measured by the LLMI, is prevalent in SSc patients and is associated with neutrophilic airways inflammation. Although a quarter of SSc patients have AHR, this was not associated with microaspiration or oesophageal dysmotility. The significance of these findings in progression of pulmonary disease in SSc patients deserves further investigation.

PS64. DYSEXECUTIVE SYNDROME; A SPECIFIC PATTERN OF COGNITIVE IMPAIRMENT IN SSc

N. Yilmaz[1], A. Mollahasanoglu[2], H. Gurvit[3], M. Can[1], N. Tuncer[2], N. Inanc[1] and S. Yavuz[1]
[1]*Department of Rheumatology, Marmara University, Faculty of Medicine,* [2]*Department of Neurology, Marmara University, Faculty of Medicine and* [3]*Department of Neurology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey*

Background and aim. SSc is a connective tissue disorder that is characterized by microvascular damage and tissue fibrosis. Although nervous system involvement is unusual in SSc, cerebral hypoperfusion has been shown in imaging studies. Here, we aimed to evaluate cognitive functions in SSc patients who had no previous or current history of neurological involvement.
Methods. Thirty-one scleroderma patients (24 lcSSc, 4 dcSSc, 3 overlap) were examined. Fifteen RA patients and 20 healthy controls (HCs) were selected as aged and sex-matched controls. To evaluate of different areas of cognition six neuropsychological tests were performed.
Results. Five out of 6 test scores including Wechsler Memory Scale digit span (WMS), Wisconsin Card Sorting Test (WSCT), Stroop Colour-Word interference test, Controlled Oral Word Association test (COWAT), California Verbal Learning Test (CVLT) were different among the groups ($P < 0.005$). WSCT categories completed test (HC *vs* SSc and RA *vs* SSc, $P < 0.0001$), WSCT preservative responses (HC *vs* SSc, $P < 0.0001$; RA *vs* SSc, $P = 0.005$), WSCT percentage preservative errors (HC *vs* SSc, $P < 0.0001$; RA *vs* SSc, $P = 0.003$), WSCT percentage conceptual level responses (HC *vs* SSc, $P < 0.0001$; RA *vs* SSc, $P = 0.001$) and CVLT perseveration (HC *vs* SSc, $P < 0.0001$; RA *vs* SSc, $P = 0.001$) test scores were significantly impaired in SSc patients compared with both RA patients and HC subjects. On the other hand, WMS, Stroop test, COWAT and CVLT scores were found to be impaired in both SSc and RA patients compared with HCs ($P < 0.005$).
Conclusion. Our results suggest that a specific pattern of cognitive impairment that is the dysexecutive syndrome seemed to be specific to the cognitive impairment in SSc, whereas attentional and memory problems might arise from other confounders such as disease duration

and chronic drug use. SSc may be a rare cause of vascular cognitive impairment.

PS65. CLINICAL EFFICIENCY OF ROSUVASTATIN IN PATIENTS WITH SYSTEMIC SCLERODERMA

R. Yatsyshyn[1], Y. U. Delva[1], Y. A. Sandurska[1] and N. Yatsyshyn[1]
[1]*Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine*

Background. The most often clinical features of systemic scleroderma (SSc) is the pathology of microcirculation, lungs and kidney. Endothelial dysfunction is an early and crucial feature in the pathogenesis of SSc. Different studies found that patients with SSc have fewer circulating endothelial progenitors (EPCs) than healthy controls. New useful therapy for SSc vasculopathy might be addressed to drugs capable to induce mobilization and migration of EPCs to sites of ischaemia. Among these, statins have been shown to have proangiogenic actions by promoting mobilization and differentiation of bone marrow EPCs in addition to well-known directvascular effects.
Objectives. Aim of this study was to evaluate the effects of rosuvastatin on both vasculogenesis and peripheral vascular function in patients with SSc.
Methods. Twenty-eight patients with SSc were randomized: 14 SSc patients with normal cholesterol levels and 14 hypercholesterolemic subjects. The patients received 10 mg/day of rosuvastatin for 24 weeks. Peripheral blood samples were obtained at 0 (pre-treatment) and 24 weeks. Five-parameter, 3-colour flow cytometry was performed with a FACScan. In addition, levels of soluble E-selectin, ICAM1 and ET-1 were assessed by ELISA. Baseline endothelial dysfunction was documented by decreased brachial artery ultrasound endothelium-dependent, flow-mediated dilatation (FMD <6%).
Results. ET-1 mean level was 6.4 (S.E. 0.6) pg/dl before treatment. ET-1 levels in patients with pitting ulcers of finger were higher than patients without it ($P < 0.001$, 6.9 *vs* 4.4). Evaluation of ET-1 levels in patients with scar tissue and without scar showed the higher level of ET-1 in whom with scar tissue (18 patients) comparing to those without it (10 patients) ($P = 0.01$, 4.9 pg/ml *vs* 3.7 pg/ml) if pull out cases with pitting ulcers through patients with scar tissue, the difference would be dissolved. Rosuvastatin treatment significantly increased EPCs from the baseline ($3.1 + 2.3$ cells/ml) to $7.8 + 3.9$ cells/ml ($P = 0.03$) at 24 weeks in the hypercolesterolemic group, but failed to improve the EPC levels in the SSc patients. FMD increased significantly from $3.6 + 2.3$ to $9.1 + 1.8$. Regarding other markers of endothelial damage, we found that soluble levels of E-selectin and ET-1 ($P < 0.05$ for all comparisons) but not ICAM1 decreased in a statistically significant manner in the treated patients. No changes in cholesterol levels were observed.
Conclusion. Treatment with low doses of rosuvastatin results in rapid and significant improvement in FMD and parameters of endothelial damage in the SSc group, further suggesting a direct effect of statin on SSc vasculopathy.

PS66. DISEASE-MODIFYING EFFECT OF ILOPROST THERAPY IN SYSTEMIC SCLERODERMA

R. Yatsyshyn[1] and M. Yatsyshyn[1]
[1]*Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine*

Background. Iloprost is a chemically stable prostacyclin analogue that causes vasodilation and inhibits platelet aggregation. Iloprost infusions are well established in the treatment of peripheral vascular disease and have also been successfully used in the treatment of severe RP associated with systemic scleroderma (SSc).
Objectives. The aim of the study was to evaluate the role of iloprost as a possible disease-modifying agent for SSc.
Methods. Forty-two consecutive SSc patients [33 women and 9 men, aged 38.02 (2.77) years, duration of disease was 5.32 (1.03) years] treated for a median time of 2 years with cyclic infusion of iloprost, for severe RP and ischaemic ulcers, were compared with 41 SSc control patients, matched for age, sex, disease subset and duration. Diagnosis of SSc was made according to the ACR criteria. Control patients were similar to the iloprost group also as far as autoantibody status, presence of major disease-related organ manifestations at baseline, and use of other treatments. The evolution of lung function test, the frequency of major disease-specific complications and the survival of the cohorts were the objects of this analysis.
Results. All patients showed a clinical reduction in severity and number of RP attacks. But no significant difference was observed comparing the two groups as far as: changes of lung function tests during time; number of patients who presented the onset of active interstitial lung disease, pulmonary arterial hypertension or scleroderma renal crisis. Survival was not different between the two groups. However, since no case of severe pulmonary arterial hypertension was observed in patients treated with iloprost, further studies are warranted, as far as a possible preventing action of iloprost on worsening of SSc-associated mild pulmonary arterial hypertension.
Conclusion. Venous infusion of Iloprost reduces frequency and severity of vasospastic episodes, reliefs the pain and heals digital ulcers. The evolution of lung function test, the frequency of major disease-specific complication and the survival of patients with SSc treated for a median time of 2 years with iloprost was not significantly different than those observed in a group of patients matched for sex, age, disease subset and duration.

PS67. LONG-TERM SURVIVAL AND CAUSES OF DEATH IN 177 JAPANESE PATIENTS WITH SSc: A RETROSPECTIVE STUDY IN A SINGLE INSTITUTE

Y. Yamasaki[1], H. Yamada[1], A. Maeda[1], K. Suzuki[2] and S. Ozaki[1]
[1]*Division of Rheumatology and Allergology and* [2]*Division of Cardiology, St Marianna University, School of Medicine, Kawasaki, Japan*

Objective. SSc frequently involves multiple internal organs and they have considerable impact on its survival. The aim was to analyse long-term survival and causes of death in patients with SSc in our patient population. We also evaluated incidence of pulmonary hypertension (PH) during the study period and its prognosis.
Methods. We retrospectively investigated SSc patients who visited to our hospital from 2006 through 2011. Diagnosis of SSc and classification of dcSSc and lcSSc were made by the LeRoy–Medsger criteria. Pulmonary arterial hypertension (PAH) was diagnosed according to the Dana Point classification. We also regarded as PH in patients with estimated right ventricular systolic pressure elevated >40 mmHg by echocardiography when septal flattening was accompanied.
Results. A total of 177 patients were included. Mean age (S.D.) and follow-up period (S.D.) were 57.3 (13.0)-year-old and 89 (74) months, respectively. Kaplan–Meier survival analysis showed that patients aged 60 years or older ($P < 0.0001$) and interstitial lung disease (ILD) ($P = 0.0268$ by Gehan–Breslow) at the initial presentation had significantly lower survival than those without them. Out of the 177 patients, 50 (28.2%) and 127 (71.8%) patients were classified as dcSSc and lcSSc, respectively. Patients with dcSSc had significantly lower survival compared with lcSSc with 5-year survival rate of 89% in dcSSc and 98% in lcSSc. ($P = 0.0320$). ILD was more commonly observed (86 *vs* 38%, $P < 0.0001$) and percent vital capacity was significantly lower (79 *vs* 103%, $P < 0.0001$) in patients with dcSSc compared with those with lcSSc. During the follow-up, dcSSc patients more frequently developed borderline or manifest PH than lcSSc patients (17.0 *vs* 7.3% at 5 years, $P = 0.0290$). Surprisingly, only two patients with dcSSc (1.1%) developed renal crisis. Thirteen patients (7.3%) (seven dcSSc/six lcSSc) died during the follow-up. The main causes of death was cardiopulmonary complications in six patients (two dcSSc/four lcSSc) due to PAH (one/one), ILD-associated PH (zero/two) and progressive ILD (one/one). Notably, death of three patients with dcSSc was related with chronic intestinal pseudo-obstruction (CIPO). Two (one dcSSc/one lcSSc) patients and one dcSSc patient died in association with heart failure and renal crisis with thrombotic microangiopathy, respectively. Another one patient died from pneumonia.
Conclusion. Progressive ILD and heart failure as well as PAH were the most important cause of death in SSc. CIPO was also fetal complication especially in patients with dcSSc. Renal crisis was rare in our patient population.

PS68. CLINICAL CHARACTERISTICS OF SSc PATIENTS WITH DIGITAL ULCER, AN ANALYSIS OF CHINESE EULAR SCLERODERMA TRIAL AND RESEARCH GROUP (EUSTAR) DATABASE

D. Xu[1], M. T. Li[1], Y. Hou[1], Q. Wang[1], Z. J. Hu[1] and X.F. Zeng[1]
[1]*Department of Rheumatology Peking Union Medical College Hospital, Beijing, China*

Objective. To investigate the clinical and laboratory characteristics of SSc patients with digital ulcer (DU) in Chinese.
Method. The data of 166 consecutive SSc patients based on Eular Scleroderma Trial and Research Group (EUSTAR) database in Peking Union Medical College Hospital from February 2009 to August 2010 were prospectively collected, the patients with DU were analysed with

those without DU. All patients fulfilled ACR classification criteria in 1980 for SSc.
Results. Out of 166 SSc patients, 1.49 (29.5%) had DU with the onset age 36.3 (11.7) years (8.1–61.7 years). All had RP.2
Demographic data. There were significant difference between patients with and without DU in the sex (F/M 40/9 *vs* 112/5, $P = 0.005$), age [40.4 (11.6) years *vs* 46.2 (12.1) years, $P = 0.005$], RP age [33.0 (11.6) years *vs* 39.0 (12.7) years, $P = 0.005$] and the time from RP to the first non-RP manifestations [17.6 (14.9) months *vs* 114.8 (307.2) months, $P = 0.002$].3
Clinical manifestations and laboratory findings There were more rates of dcSSc patient (dc/lc 32/17 *vs* 48/69, $P = 0.006$) and more oesophageal involvements (65.3 *vs* 44.4%, $P = 0.017$) in patients with DU.
Conclusions. DU in SSc patients is common, especially in male and dcSSc patients. It should be attentive of DU in SSc patients with earlier age of RP and earlier non-RP manifestations.

PS69. SSc AND ORGAN-SPECIFIC ANTIBODIES

E. Wielosz[1], M. Dryglewska[1] and M. Majdan[1]
[1]*Department of Rheumatology and Connective Tissue Diseases Medical University, Lublin, Poland*

Introduction. SSc and some thyroid or liver disorders are of autoimmune origin. It is known that systemic- and organ-specific diseases of autoaggression often overlap. According to literature some organ-specific antibodies such as anti-thyroid antibodies or anti-mitochondrial antibodies may be present in course of SSc.
The objective. The objective of this study was to assessment the prevalence of anti-thyroid antibodies [anti-thyroid peroxidase (anti-TPO) and/or anti-thyroglobulin (anti-TG)] and AMAs in SSc patients.
Material and methods. Analysis involved 86 consecutive patients with SSc (according to ACR criteria) hospitalized in the Department of Rheumatology and Connective Tissue Diseases, Medical University, Lublin, Poland. Patients were observed for autoimmune thyroid diseases (ATDs) and primary biliary cirrhosis (PBC). They were classified according to the criteria of Le Roy *et al.* as having either lcSSc or dcSSc subset of the disease: 32 patients had dcSSc and 54 had lcSSc. The mean age was 53.00 (±13.07) years (range 19–81 years). The mean disease duration was 6.8 (6.3) years (range 0.5–30 years). Anti-TPO and anti-TG antibodies were detected using of direct chemiluminescence methods on Advia Centaur XP Systems. AMA antibodies were assessed by using immunoblotting method. The data regarding coexistence of ATD or PBC were obtained retrospectively based on available medical records and anamneses from previous hospitalizations.
Results. According to our observation 27/86 patients (31%) had positive anti-thyroid antibodies and 11/86 patients (13%) had positive AMA. ATD was diagnosed in 26/86 patients (30%) and PBC in 10/86 patients (12%) with SSc. In dcSSc group positive anti-thyroid antibodies occurred in 11/32 patients (34%), ATD was diagnosed in 10/32 dcSSc patients (31%). The prevalence of AMA in dcSSc was in 2/32 patients (6%) and PBC was diagnosed in 2/32 patients (6%). In lcSSc group positive anti-thyroid antibodies were detected in 17/54 patients (32%), 16/54 lcSSc patients (30%) had ATD. In this group the prevalence of AMA was in 9/54 patients (17%) and PBC was diagnosed in 8/54 patients (15%). We did not find significant intergroup differences dcSSc *vs* lcSSc in the prevalence of anti-thyroid antibodies and AMA.
Conclusions. We conclude that the prevalence of organ-specific antibodies in SSc is relatively high. The prevalence of AMA is higher in lcSSc compare with dcSSc group but these results are not statistically significant. Patients with SSc should be evaluated for coexisting ATDs and PBC.

PS70. DEPRESSION AND COGNITIVE STATUS IN PATIENTS WITH SSc

T. Dziewit[1], **M. Widuchowska**[1], M. Kopec-Medrek[1], A. Kotulska[1], B. Dutkiewicz[1] and E.J. Kucharz[1]
[1]*Department of Internal Medicine and Rheumatology, Medical University of Silesia, Katowice, Poland*

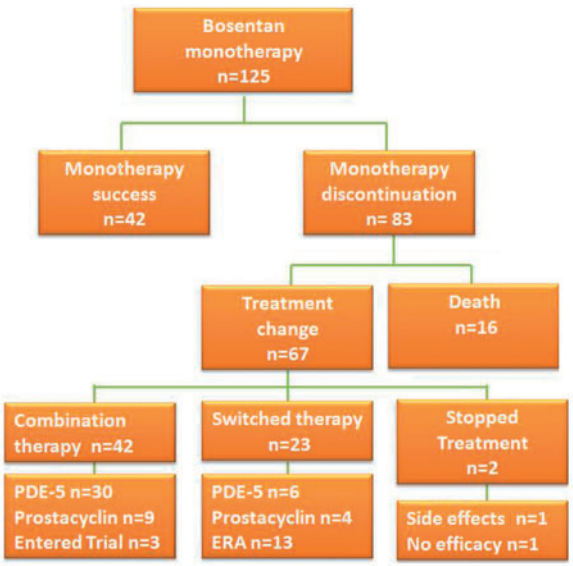
Introduction. SSc is a chronic connective tissue disorder characterized by progressive fibrosis of the skin and subcutaneous tissue, occurrence of RP and other vascular abnormalities as well as internal organ involvement due to fibrosis, especially within the lungs, heart, kidneys and alimentary tract. CNS involvement is still relatively unknown. Vascular changes in the CNS are detected in MRI in 50% of SSc patients; however, the correlation of the detected changes with neurological manifestation is unclear.
Aim of the study. Evaluation of severity of depression and cognitive dysfunction in patients with SSc.
Materials and methods. The study group included 30 patients with SSc. The severity of depression was measured with the use of Beck Depression Inventory (BDI). Cognitive function was evaluated with the use of the mini mental state examination (MMSE). The results were correlated with the HAQ, the modified Rodnan skin score and with the disease duration.
Results. Mean BDI score in all patients ($n = 30$) was 10.46. In 60% of the patients ($n = 18$) no depression was observed (BDI score 0–11). Mild depression (BDI score 12–26) was observed in 33% of the patients ($n = 10$), and moderate depression (BDI score 26–49) in 7% of the patients ($n = 2$).
Mean MMSE score in the study group ($n = 30$) was 26.4. In 53% of the patients ($n = 16$) no cognitive impairment was observed (MMSE score 30–27). Cognitive impairment without dementia (MMSE score 26–24) was observed in 37% of the patients ($n = 11$) and mild cognitive impairment (MMSE score 23–19) in 10% of the patients ($n = 3$). There was no significant correlation between the severity of depression, cognitive dysfunction and the modified Rodnan skin score. Positive correlation was found between the functional status and depression.
Conclusions. Mild depression and cognitive dysfunction without dementia are observed in ~40% of patients with SSc. Functional status but not the severity of skin thickening has an impact on the incidence of the signs of depression. The cognitive dysfunction does not correlate with the functional status, severity of the skin thickening and the disease duration.

PS71. PREDICTORS OF BOSENTAN MONOTHERAPY DISCONTINUATION IN SSc-PAH PATIENTS

C. Warrell[1], D. Dobarro[1], C. Handler[1], C. P. Denton[1], B. E. Schreiber[1] and J. G. Coghlan[1]
[1]*Royal Free Hospital, London, UK*

Purpose. Bosentan monotherapy is commonly used as first line therapy in SSc-associated pulmonary arterial hypertension (SSc-PAH). Predictors of discontinuation of the treatment have not previously been described.
Methods. A retrospective analysis of consecutive patients with newly diagnosed SSc-PAH at a large regional centre from 2005 to June 2010. Inclusion criteria were: SSc and treatment naïve PAH (mPAP ≥ 25 mmHg, PCWP ≤ 15) when starting bosentan monotherapy. Patients with evidence of interstitial lung disease on imaging (HRCT) or lung function tests (FVC $< 70\%$) were excluded. Discontinuation of

Fig. 1 Outcome of patients at 1 year after first-line treatment with bosentan monotherapy.



therapy was defined as any change from bosentan monotherapy or patient death. Use of immunosuppressants at any point during the course of bosentan therapy was recorded. Logistic regression analysis was used to determine which characteristics predicted treatment failure.

Result. One hundred and twenty-five patients were identified. The mean age was 62 years (range 28–84 years) and 85% were female (ratio F : M 5.6 : 1). Disease subtype was lcSSc in 114 patients (91%) and dcSSc in 11 patients (9%). Mean haemodynamic values at initial right heart catheterization were mPAP 40 mmHg and PVR 586 dyns s/cm^5 (7.4 wood units). Median survival was 36 months.

Only 34% of patients remained on Bosentan monotherapy at 1 year (Fig. 1). In the 66% in whom treatment failure occurred at 12 months, 19% died, 3% had stopped therapy due to intolerance or lack of efficacy and 78% had switched to another drug or combination therapy. Univariable logistic analysis showed the following factors were not associated with discontinuation of monotherapy: gender ($P = 0.545$), age ($P = 0.068$), lcSSc ($P = 0.633$), baseline NTproBNP ($P = 0.169$), mPAP ($P = 0.227$) PVR ($P = 0.158$), WHO functional class ($P = 0.177$) and immunosuppressant therapy ($P = 0.367$). No variables investigated were found to be predictive of bosentan monotherapy discontinuation in the first year of treatment.

Conclusion. We found that 66% of SSc-PAH patients treated with first-line bosentan monotherapy had changed their treatment by 1 year. It is instructive that baseline haemodynamics cannot help to predict which patients these are, although treatment failures are more common in the elderly. The high rate of monotherapy treatment discontinuation highlights the importance of assessing whether patients with up-front combination therapy fair better.

PS72. RELEVANCE OF OESOPHAGEAL DILATATION ON HIGH-RESOLUTION CT IN SSc-ASSOCIATED INTERSTITIAL LUNG DISEASE

S. Wangkaew[1], S. Patiwetwitoon[1], J. Euathrongchit[2], N. Kasitanon[1] and W. Louthrenoo[1]
[1]*Division of Rheumatology and* [2]*Division of Diagnostic Radiology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*

Purpose. To evaluate the correlation of oesophageal dilatation (EsD) with high-resolution CT (HRCT) findings in SSc-associated interstitial lung disease (SSc-ILD).

Methods. Seventy-one SSc-ILD patients who underwent HRCT of the chest were retrospectively identified at Chiang Mai University Hospital between June 2005 and March 2010. Data abstracted include clinical characteristics and HRCT variables. The HRCTs were read by one experienced chest radiologist. The amount of ground glass (GG), lung fibrosis (Fib), and honeycombing (HC) was calculated by using radiographic definition established by Zisman *et al.* 1. Scoring of each lobe was performed by using a Likert scale based on Kazerooni *et al.*'s method 2. Total (t)-GG, t-Fib and t-HC were computed by summing the score from all five lobes. All scores were aggregated to produce a total CT perfusion score (CT-total). The widest oesophageal diameter (WED) was measured at three levels (mid-arch of aorta, main carina and diaphragmatic hiatus). EsD was defined as WED $\geq$10 mm presented wherever the regions. Pearson's correlation coefficients were used to determine the correlations between WED and the HRCT scores.

Results. Mean (S.D.) age was 54.8 years (11.8 years) and mean disease duration 3.9 years (4.2 years). 69.0% were female and 67.6% were classified as dcSSc. 60 of 71 (84.5%) patients had EsD. Mean (S.D.) values were: t-GG 5.8 (3.8); t-Fib 8.7 (3.8); t-HC 2.6 (3.7); CT-total 17.2 (7.0); WED at mid-arch of aorta 1.0 cm (0.6), main carina 1.2 cm (0.7) and diaphragmatic hiatus 1.6 cm (0.8). There was low correlation between WED at diaphragmatic level and t-HC score ($r = .33$, $P < 0.01$). There were no significant correlations of WED at mid-aortic arch and carina level with any of the HRCT scores. SSc with EsD had significant longer disease duration [4.5 years (4.3) *vs* 1.1 years (1.1), $P < 0.01$] than SSc without EsD. There were significant correlations between disease duration and the WED at three levels where their correlation coefficients were 0.42 ($P < 0.01$), 0.29 ($P < 0.05$) and 0.38 ($P < 0.01$), respectively.

Conclusions. In SSc-ILD patients, there was no marked correlation between oesophageal dilatation and the HRCT scores. However, the widest oesophageal diameter showed significant correlation with disease duration.

PS73. CORRELATION BETWEEN HIGH-RESOLUTION CT FINDINGS AND PULMONARY HYPERTENSION IN PATIENT WITH SSc-ASSOCIATED INTERSTITIAL LUNG DISEASE

S. Wangkaew[1], S. Patiwetwitoon[1], J. Euathrongchit[2], N. Kasitanon[1] and W. Louthrenoo[1]
[1]*Division of Rheumatology and* [2]*Division of Diagnostic Radiology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*

Purpose. To determine the correlations between chest high-resolution CT (HRCT) findings and estimated systolic pulmonary artery pressure (sPA) in SSc-associated interstitial lung disease (SSc-ILD).

Methods. Fifty SSc-ILD patients who had echocardiography performed within 24 weeks of the corresponding HRCT were retrospectively identified at Chiang Mai University Hospital between June 2005 and March 2010. Data abstracted include clinical characteristics, HRCT variables and sPA. The HRCTs were read by one experienced chest radiologist. The amounts of ground glass (GG), lung fibrosis (Fib) and honeycombing (HC) were calculated by using radiographic definition established by Zisman *et al.* 1. Scoring of each lobe was performed by using a Likert scale based on Kazerooni *et al.*'s method 2. Total (t)-GG, t-Fib, t-HC were computed by summing the score from all five lobes. All scores were aggregated to produce a total CT perfusion score (CT-total). The maximum diameter of the main pulmonary artery (MPAD) and ascending aorta (AD) were measured. The ratio of MPAD and AD (MPAD/AD) was calculated. Pulmonary artery hypertension (PAH) was defined as sPA $\geq$ 45 mmHg. Pearson's correlation coefficients were used to determine the correlations between sPA and the HRCT scores.

Results. Mean (S.D.) age was 54.9 years (11.5 years), mean disease duration 3.8 years (4.2 years) and mean duration between HRCT and echocardiogram was 0.2 months (2.1 months). Sixty-six per cent were female and 68.0% were classified as dcSSc. Mean (S.D.) values were: t-GG 5.5 (3.7); t-Fib 8.6 (3.6); t-HC 2.9 (3.8); CT-t 17.1 (6.9); MPAD 3.0 cm (0.5); AD 3.1 cm (0.4); MPAD/AD 0.9 (0.1) and sPA 40.6 mmHg (13.9). Eighteen of 50 (36.0%) patients had sPA $\geq$45 mmHg. In total group, there were significant correlations between sPA and t-Fib and CT-total where their correlation coefficients were 0.36 ($P < 0.05$) and 0.31 ($P < 0.05$), respectively. In sPA $\geq$45 mmHg subgroup, there were significant correlation between sPA and t-GG and t-Fib where their correlation coefficients were 0.55 ($P < 0.05$), and 0.68 ($P < 0.01$), respectively. In sPA <45 mmHg subgroup, there were no significant correlations between sPA and any of the HRCT scores.

Conclusions. In total group, correlations between calculated HRCT scores and sPA, if significant, were low. In PAH-subgroup, the total lung fibrotic score showed a marked degree of correlation with sPA. The lack of correlations between sPA and MPAD or MPAD/AD was found. The total lung fibrotic score offers promise as a measure of outcome in SSc-ILD-PAH.

PS74. CORRELATIONS BETWEEN CHANGES IN BIOMARKERS AND CLINICAL OUTCOMES FOR EARLY PHASE (PROOF OF CONCEPT) TRIALS IN ACTIVE DCSSc USING DATA FROM AN IMATINIB STUDY

J. Pope[1], K. Walker[2], F. De Leon[3], D. Mcbain[1], L. Vanderhoek[1], S. Mifflin[3] and K. Summers[4,5]
[1]*Department of Medicine, Division of Rheumatology, University of Western Ontario – Schulich School of Medicine and Dentistry, London, Canada,* [2]*Trinity College Dublin – School of Medicine, Dublin, Ireland,* [3]*McMaster University, Hamilton,* [4]*Lawson Health Research Institute and* [5]*Department of Microbiology and Immunology, University of Western Ontario, London, Canada*

Objective. Imatinib has been studied in the treatment of SSc and data from one study were used to determine if biomarker changes were related to changes in clinical parameters (as some patients improved, others worsened or were stable).

Methods. A small blinded placebo-controlled study with imatinib in SSc-obtained serum samples and skin biopsies at baseline and 6 months analysing samples for fibrotic and inflammatory cytokines. Correlations between changes in cytokines and clinical outcomes [modified Rodnan skin score (mRSS), physician and patient global assessments and HAQ] were performed.

Results. In serum, only VCAM-1 ($P < 0.001$) decreased significantly after 6 months of imatinib treatment but the medication was not well tolerated so half did not receive the recommended dose. In tissue homogenates, soluble intercellular adhesion molecule-1 (sICAM-1) ($P = 0.009$) was significantly different with an increase after 6 months. There were strong correlations for: fold-changes in some serum biomarkers and in changes in clinical parameters: patient global and IL-13 ($P = 0.000$, $r = 0.964$), physician global and PDGF ($P = 0.041$,

$r = 0.774$), IFN-γ ($P = 0.022$, $r = -0.825$), sCD40L ($P = 0.002$, $r = 0.937$) and TGF-β1 ($P = 0.021$, $r = 0.830$) and HAQ with IL-17 ($P = 0.045$, $r = 0.764$). Fold-change correlations in tissue were mRSS and VEGF ($P = 0.020$, $r = 0.831$), patient global and E-selectin ($P = 0.004$, $r = 0.913$) and physician global with CD40L ($P = 0.008$, $r = -0.883$).
Conclusion. Biomarkers may have a role in early phase clinical trials of SSc as some changes correlate strongly with changes in clinical parameters.

PS75. TREATMENT OF SSc: WHAT TO USE WHEN FIRST-LINE TREATMENT FAILS. A CONSENSUS OF EXPERTS

K. Walker[1] and J. Pope[2]
[1]*Trinity College Dublin – School of Medicine, Dublin, Ireland,* [2]*Department of Medicine, Division of Rheumatology, University of Western Ontario – Schulich School of Medicine and Dentistry, London, Canada*

Background. There is a need for standardization in SSc management, particularly after usual (first-line) treatment.
Method. SSc experts ($n = 118$) were sent four surveys to gain consensus for SSc management. Cases were given for mild and severe organ involvement in order to construct treatment algorithms. Experts were surveyed to determine the rate of agreement with each algorithm. Good agreement (consensus) was considered >70%.
Results. Fifty-five responded to all surveys (47% response rate). After ACEi use for mild scleroderma renal crisis (SRC; 97%), second-line was to add either a CCB (37%) or ARB (35%), then an α-blocker (20%) in severe SRC. Treatment of mild and severe SRC was similar (75% agreement). ERAs were first-line in mild PAH (72%) and proceeded by adding PDE5i (77%) and then a prostanoid (73%). For severe PAH, initial treatment was any of: prostanoid (49%), combination of ERA and PDE5i (19%) or ERA and prostanoid (16%) (71% agreed). For mild RP, CCB (92%) were followed by adding a PDE5i (35%), then an ARB (32%) and finally a prostanoid (23%). For more severe RP, 54% agreed on adding a PDE5i or a prostanoid (32%). For prevention of digital ulcers (mild history) treatment was a CCB (73%), then to add a PDE5i (57%) then an ERA (47%) and a prostanoid (38%) (50% agreed). A severe history was similar. For ILD, induction was usually iv CYC (65%) or occasionally oral (64%) or MMF (48%) or AZA (45%). For maintenance, MMF was chosen by three-fourths (56% agreed). For skin involvement after MTX, MMF was usually chosen (38% agreed). For GERD, half would exceed the maximum recommended PPI dose if required (72% agreed). For joint involvement after MTX (60%), CSs (37%) or HCQ (31%) and then biologics (20%) should be considered (62% agreed).
Conclusion. Discrepancies in drug choices occurred after first-line treatment in SSc. Not all algorithms had good agreement. This study provides some guidance for SSc management.

PS76. PULMONARY ARTERIAL HYPERTENSION IN SSc IS ASSOCIATED WITH PROFOUND IMPAIRMENT OF MICROVASCULAR ENDOTHELIUM-DEPENDENT VASODILATATION

H. Hofstee[1], **A. Voskuyl**[1], A. Vonk Noordegraaf[1], Y. Smulders[1], B. Dijkmans[1], P. Postmus[1] and E. Serne[1]
[1]*VU University Medical Center, Amsterdam, The Netherlands*

Objective. Impaired microvascular function may contribute to organ complications in patients with SSc. This study was undertaken to investigate whether SSc patients without and with pulmonary arterial hypertension (PAH) show a graded impairment of microvascular endothelium-dependent vasodilatation compared with healthy controls.
Methods. Twenty-two SSc patients and 22 controls were included. All patients underwent right-heart catheterization; 6 had no PAH (SSc-non-PAH) and 16 had PAH (SSc-PAH). Acetylcholine (ACh)-mediated endothelium-dependent vasodilatation and sodium nitroprusside (SNP)-mediated endothelium-independent vasodilatation were assessed by iontophoresis combined with laser Doppler fluxmetry.
Results. Compared to sex- and age-matched controls, the percentage increase in ACh-mediated vasodilatation was reduced in SSc-non-PAH (340.4 *vs* 79.5%, $P < 0.01$), but not in SSc-non-PAH (392.3 *vs* 340.4%, $P = 0.63$). No significant differences in SNP-mediated vasodilatation between the groups were present.
Conclusion. Systemic microvascular endothelium-dependent vasodilatation is markedly reduced in SSc complicated by PAH.

PS77. A MULTICENTRE STUDY ON THE RELIABILITY OF QUALITATIVE AND QUANTITATIVE NAILFOLD VIDEOCAPILLAROSCOPY ASSESSMENT

H. Hofstee[1], **E. Serne**[1], C. Roberts[2], R. Hesselstrand[3], A. Scheja[3], T. Moore[2], M. Wildt[3], J. Manning[4], A. Vonk-Noordegraaf[1], A. Voskuyl[1] and A. Herrick[2]
[1]*VU University Medical Center, Amsterdam, The Netherlands,* [2]*University of Manchester, Manchester, UK,* [3]*Lund University, Lund, Sweden and* [4]*Salford Royal NHS Foundation, Salford, UK*

Objective. To investigate the inter- and intraobserver reliability of both qualitative and quantitative parameters used in the assessment of nailfold capillaroscopy images.
Methods. Fifty mosaic nailfold images of healthy controls ($n = 10$), patients with primary RP ($n = 10$) and SSc ($n = 30$) were randomly assessed by two blinded observers on two occasions at centres in Sweden, UK, and The Netherlands. Each image was therefore scored by six observers twice.
Results. Inter- and intraobserver reliability of quantitative parameters showed substantial to almost perfect agreement (inter-and intraobserver weighted kappa's for the number of mega capillary 0.75 and 0.87, giant capillary 0.84 and 0.92, capillary density 0.87 and 0.92 and total loop width 0.94 and 0.98). Qualitative parameters including architecture, avascularity, haemorrhage, crossed, ramified and bushy capillaries showed moderate to substantial interobserver agreement (weighted kappa's ranging from 0.47 to 0.73), and substantial intraobserver agreement (weighted kappa's ranging from 0.71 to 0.80), whereas the scoring of tortuous and bizarre capillaries showed poor interobserver and substantial intraobserver agreement (interobserver ICCs 0.39 and 0.21, and intraobserver weighted kappa's 0.68 and 0.76, respectively).
Conclusion. All quantitative and certain qualitative parameters are highly reliable in terms of inter- and intraobserver agreement. A combination of parameters with the highest reliability should be incorporated into future capillaroscopic scoring systems in studies of prediction and monitoring of SSc-spectrum disorders.

PS78. COLOMBIAN EXPERIENCE WITH HAEMATOLOGICAL STEM CELL TRANSPLANTATION IN SEVERE AND REFRACTORY SSc: THREE CASE-REPORT AND LONG-TERM FOLLOW-UP

C. Velasquez[1], F. Vargas[2] and L. A. Ramirez[3]
[1]*Rheumatology Section, Hospital Pablo Tobon Uribe, Universidad Pontificia Bolivariana,* [2]*Rheumatology Section, Universidad de Antioquia and* [3]*Rheumatologist, Reumalab and Reumatologya SA, Medellin, Colombia*

Background. Haemopoietic stem-cell transplantation (HSCT) is a potential treatment for SSc and relies on early intervention during immune activation. Previous studies of HSCT for SS sclerosis showed significant improvements in modified Rodnan skin score (mRSS), and some studies suggested improvement of lung function. The ASSIST trial concluded that non-myeloablative autologous HSCT improves skin and pulmonary function in patients with SSc for up to 2 years and is preferable to the current standard of care with CYC. In the First Systemic Sclerosis World Congress, we presented our successful experience with HSCT in two patients with scleroderma.
Objective. To report the results, safety and long-term follow-up with HSCT in three Colombian patients with severe and refractory SSc. Table 1 describes the baseline characteristics of the patients.
Procedure. HSCT was performed in all the cases (March 2007, October 2008, and January 2011, respectively).
Conditioning regimen. CYC 50 mg/kg for 4 days and anti-thymocyte globulin 2.5 mg/kg for 2 days.
Mobilization: Filgastrim 10 μg/kg/day. Apheresis with CD34 cells.

Case 1 presented a CMV infection 24 h post-HSCT and received treatment with vanganciclovir 900 mg daily, with total resolution.
Case 2 presented an episode of neutropenia and fever 24 h after HSCT. There was no infection documented.
Case 3 presented an episode of acute pulmonary oedema 24 h thereafter, with total resolution.

Response. A rapid and sustained response was obtained in all the cases (see Table 2).
Conclusion. The response of these cases to HSCT confirms the findings of long-term follow-up of this procedure in refractory SSc. In selected patients, without relevant cardiopulmonary involvement, there is a rapid and sustained skin response with stabilization and non-progression of organic involvement with HSCT.

Table 1. Baseline characteristics of patients

Characteristics	Patient 1	Patient 2	Patient 3
Age	29	30	45
Date of diagnosis	28/07/2003	01/04/2008	21/01/2010
Skin involvement	Yes	Yes	Yes
Modified Rodnan skin score	42	34	34
Oral aperture	2.3 cm	2.2 cm	2.1 cm
Cardiac involvement	No	No	No
Pulmonary hypertension	No	No	No
Pulmonary involvement	Yes	No	Yes
HRCT	Ground-glass appearance	Normal	Ground-glass appearance
VEF1 (predicted %)	72.5	95	91
CVF (predicted %)	72.8	97	92
Gastrointestinal involvement	Gastro-oesophageal reflux disease, oesophageal dilatation)	Dysphagia	Oesophagitis
WHO functional class	III	I	I
Previous immunosuppression	MTX 25 mg/week (4 months) CYC 1 g i.v./month (5)	MTX 25 mg/week (3 months) CYC 1 g i.v./month (4) MMF 2 g/day (3 months)	CYC 1 g i.v./month (6)

Table 2. Response to HSCT in SSc patients

Characteristic	Patient 1	Patient 2	Patient 3
Follow-up period (months)	49	34	7
Modified Rodnan skin score	12	11	18
Oral aperture	3.2 cm	3.3 cm	3 cm
Pulmonary involvement	No	No	No
HRCT	Normal	Normal	Normal
VEF1 (predicted %)	82	96	91
CVF (predicted %)	85	97	93
Gastrointestinal involvement	Symptomatic relief of GERD	None	Persisted
WHO functional class	II	II	I
Initial Response Time (months)	17	6	2

PS79. NAILFOLD CAPILLAROSCOPIC STUDY IN FIRST AND SECOND DEGREE RELATIVES OF PATIENTS WITH SSc

M. Vasile[1], K. Stefanantoni[1], I. D'Arcangelo[1], N. Iannace[1], V. Riccieri[1] and G. Valesini[1]
[1]*Dipartimento di Medicina Interna e Specialita' Mediche, Reumatologia, Sapienza Universita' di Roma, Roma, Italy*

Aim. Relatives of SSc patients present a higher risk of autoimmunity. Nailfold videocapillaroscopy (NVC) is a useful tool in order to make an early diagnosis of SSc. Aim of our study was to carry out NVC in a group of relatives of SSc patients to detect potential abnormalities that could be related to an autoimmune disease.
Methods. We enrolled 35 subjects (mean age 45 years, range 14–73 years), first and second degree relatives of SSc patients. In all cases, we looked for the presence of acrovascular symptoms and performed NVC. NVC abnormalities were evaluated using a semiquantitative grading scale.
Results. None of the relatives was suffering for RP, while acrocyanosis was present in nine (26%).
Twenty-three subjects (65.8%) showed a normal capillaroscopic pattern, while 11 (31.4%) had minimal and unspecific changes, 1 (2.8%) showed evident unspecific abnormalities. Only four subjects suffering for acrocyanosis had NVC abnormalities. In the case showing evident-unspecific abnormalities, giant capillaries were present.
NVC-unspecific findings were represented by an irregular distribution of the capillary loops in 8.5% of cases, a variable length of capillary loops in 40% of cases, a reduced length of the loops in 5.7% of cases, microhaemorrhages in 20% of cases, a reduced blood flow in 11.4% of cases; multiple crossings of the loops were present in 8.5% of cases, mild enlargement of the loops in 60% of cases.
Conclusions. In our group of first and second degree relatives of SSc patients, 26% of the subjects were affected by unspecific acrovascular symptomatology, in agreement with the prevalence of such symptoms in the general population (4–20%). NVC abnormalities resulted to be minimal and unspecific in 31.4% of cases, so that no further investigations were needed. The only patient with major abnormalities had ANA positive and 'cold finger' and underwent vasodilator therapy. Due to the presence of SSc familiarity, meaning a higher risk of developing an autoimmune disease, we decided to follow all the subjects till 1 year in order to detect any early pathological transition of the NVC pattern.

PS80. THREE YEAR-FOLLOW UP OF THE JOINT INVOLVEMENT IN 131 HUNGARIAN PATIENTS WITH SSc

Z. Bálint[1], H. Farkas[1], N. Farkas[2], T. Minier[1], G. Kumánovics[1], L. Czirják[1] and **C. Varjú**[1]
[1]*Department of Rheumatology and Immunology and* [2]*Department of Analytical and Environmental Chemistry, University of Pécs, Pécs, Hungary*

Objectives. To observe effects of instruction of home exercise on changes in range of motion and contracture development in a 3-year follow-up study in patients with SSc.
Methods. One hundred and thirty-one consecutive patients, 119 females and 12 males, 41 with dcSSc, 90 with lcSSc were evaluated at baseline, with 111 patients re-evaluated at 1 and 3 years. Mean age was 55.9 (11.6) years (±S.D.) with a mean disease duration was 8.1 (7.2) years. ROM, Modified Rodnan skin score (MRSS), HAQ-DI, hand anatomic index (HAI) and clinical characteristics were recorded. Additionally, every patient at our centre receives education for home exercises of hands, mouth and large joints. This education is repeated at least every 6 months.
To determine differences between subgroups Mann–Whitney U-test were performed. Spearman's rank correlation coefficient was calculated to assess parametric correlation.
Results. Limitation in ROM >25% was considered 'contracture' and >50% as 'severe contracture'.
At baseline, MCP II and III were the most commonly affected joints, in 90–95% of patients. Wrist flexion-extension was impaired in 69–75%, shoulder flexion-extension in 49–50%, PIP II-III flexion-extension in 34–43%, wrist adduction-abduction in 18–22%, knee flexion-extension in 15–17%, shoulder adduction-abduction in 13–15%, rotation in 9–11%, ankle extension-flexion, hip rotation and flexion-extension in 7–8%, abduction in 1–2%.
Over a 3-year-follow-up period, differences favouring the non-dominant hand in ROM were statistically significant while there was no difference in laterality of the large joints.
Comparative subgroup analysis of lcSSc and dcSSc, early- (<4 years) and late (>4 years)-phase SSc patients concorded that in all groups only the small joints (MCP II, III and PIP II, III) of the hands and the HAI showed significant improvement throughout the 3-year follow-up of repetitive teaching. However the large joints, again, revealed no significant difference.
The number of severe contractures of the upper extremities positively correlated with ESR, CRP, HAQ-DI and the 10-m walk test and negatively with forced vital capacity (FVC) at baseline and 3-year-follow up.
Conclusions. Across disease subgroups, the interval teaching of simple 'routine' stretching exercises performed at home may be beneficial for small joint function, but does not have a noticeable effect on large joint function.
Prominent use of the dominant hand may explain its increased impairment in ROM compared with the non-dominant hand; suggesting that excessive use may provoke an adverse effect on hand mobility.

PS81. SUSTAINABLE IMPROVEMENT CAN BE ACHIEVED WITH INTRADERMAL INJECTIONS OF BOTULINUM TOXIN A (BTX-A) IN A PATIENT WITH LIMITED SCLERODERMA: 3-YEARS FOLLOW-UP

S. Tosounidou[1], H. MacDonald[2] and T. P. Sheeran[3]
[1]*Cannock Chase Hospital, Cannock,* [2]*Birmingham City Hospital, Birmingham and* [3]*Cannock Chase Hospital, Cannock, UK*

Introduction. The pathophysiology of RP is not fully understood but likely to be multifactorial due to vascular, i.v. and neural factors. Agents interacting with α-adrenoreceptors have been implicated

blocking vasodilatation thus causing vasoconstriction. BTX-A possibly acts by preventing recruitment of α-2 receptors to vascular smooth muscle thus increasing the blood flow leading to healing of digital ulcers.

Case report. In 1982 a 30-year-old female was diagnosed with limited scleroderma. Her Raynaud's syndrome and recurrent digital ulcers, proved intractable despite a variety of treatments.

In 1982, captopril and nebulized salbutamol was followed by a right cervical sympathectomy (1984), a right stellate ganglion block in 1989 plus three infusions of C-GRP; all failed. Despite AZA, prednisolone, captopril and nicotinic acid, symptoms remained severe. In 1994, nifedipine was added.

The patient received 4 monthly infusions of Iloprost since 1990. This ceased in 1994 due to infusion reactions, and difficulties obtaining peripheral venous access. A central venous line was not tolerated. The patient was treated with inhaled monthly nebulized Iloprost, with some benefit.

In 2006, she developed a digital pulp infection in her right index finger, which required numerous courses of oral antibiotics over the next 2 years. Her pain scores were very high and she was often unable to sleep. Fluoxetine and topical GTN paste were tried with no benefit.

In 2008, she had two intradermal injections of 10U BTX-A to the base of her right index finger. Within 3 days the pain had disappeared. Her infection cleared up and she stated 'I've slept for the first time in two years'.

She now has intradermal digital injection every 3–4 months and the response is still maintained.

Discussion. The use of BTX-A is an established treatment for focal and dystonic syndromes and has been also effective in focal hyperhidrosis. It has been tried in RP with variable success. BTX-A produces a digital artery smooth muscle neuromuscular blockage by blocking the release of acetylcholine presynaptically.

However, there is no consensus on the way to administer BTX-A. In our case, a sustainable effect was achieved by performing intradermal injections locally to the finger.

Conclusion. Additional studies are needed for optimization of this technique. Randomized, controlled studies are required to evaluate the clinical importance of BTX-A. We believe that injection technique is the most important aspect of BTX-A therapy for digital ulceration in scleroderma

PS82. SUCCESSFUL TREATMENT OF CALCINOSIS WITH INFLIXIMAB IN A PATIENT WITH SSc/MYOSITIS OVERLAP SYNDROME

S. Tosounidou[1], H. Macdonald[1], P. Ferguson[1] and D. Situnayake[1]
[1]*Sandwell and West Birmingham NHS Trust, Birmingham, UK*

Introduction. Diffuse calcinosis is a disturbing complication affecting patients with connective tissue diseases in particular, SSc and DM. We present a case of severe subcutaneous calcinosis in a patient with SSc/myositis overlap syndrome, where introduction of anti-TNF therapy produced a sustained clinical and radiological improvement.

Case report. The patient was diagnosed with limited SSc/myositis overlap syndrome in 2007, based on clinical presentation and positive immunology (ANA 1 : 1600, PMScl positive). Creatinine kinase was 352–701, and EMG showed low-grade myositis. No muscle biopsy was performed.

Arthritis, myositis and moderate pulmonary fibrosis debilitated the patient, but her principle concern was severe subcutaneous calcinosis. Lesions occurred though out her body, particularly affecting fingers and pressure areas including buttocks and hips. Intratendon calcification was proven radiologically.

Multiple therapeutic approaches including i.v. CYC and methylprednisolone failed to halt calcification progression. Minocycline and MTX improved finger lesions and rendered the myositis subclinical, but calcific deposits remained unimproved. Surgical excision of lesions resulted in dehiscence and poor healing. Specialist consensus in 2008 was to obtain objective baseline assessment by pelvic CT, and then to commence infliximab. Six infusions were given >6 months, according to the RA protocol.

After 6 months there were no new lesions, pre-existing lesions had regressed and the patient felt more independent and energetic. Follow-up pelvic CT demonstrated reduced calcification with no new lesions, muscle enzymes normalized and CRP decreased. In view of clinical and radiological improvement, the patient continues to receive Infliximab on an eight weekly basis. No further progression of pulmonary fibrosis was noted.

Discussion. Diffuse calcinosis is a common manifestation of SSc and DM, yet no currently approved medical treatment exists. Our understanding of the pathogenesis of calcinosis is still very limited. Recent findings showed association of calcinosis with inflammation. Unlike adult DM, increasing calcinosis in JDM is considered to be a sign of active disease. TNF-α has been found in high levels in JDM patients with a long disease course and calcinosis.

Blockage of TNF-α-mediated action has been successful in treatment of various rheumatic diseases. Its effectiveness has been also described in adults with myositis and JDM. On the contrary, currently routine use of TNF-α blocker is not recommended in SSc and can be considered only for treatment of refractory arthritis.

Our case represents a successful treatment of calcinosis with anti TNF agent but further studies required to validate this observation.

PS83. SSc SINE SCLERODERMA AND lcSSc: SAME DISEASE SUBSET?

L. Morera-Morales[1], C. Tolosa-Vilella[1], C. P. Simeón-Aznar[2], L. Gabarró-Julià[1], A. Fernández-Codina[2], B. Marí-Alfonso[1], M. Campillo[2], V. Fonollosa-Pla[2] and M. Vilardell-Tarrés[2]
[1]*Parc Taulí Hospital, Sabadell and* [2]*Vall d'Hebrón Hospital, Barcelona, Spain*

Introduction. To describe the characteristics of a great cohort of patients with SSc sine scleroderma (ssSSc) and compare them with a group of patients with lcSSc.

Patients and methods. It is a prospective study of 45 patients with ssSSC and 186 patients with lcSSc. We compared the following items: demography, fulfilment of preliminary ACR criteria for SSc, organ involvements, immunological parameters, nailfold capillary pattern and average survival.

Results. There were no significant differences between ssSSc and lcSSc in the prevalences of gender (women: 93.3 *vs* 89.8%), mortality (24.2 *vs* 11.1%), age at onset (46.8 *vs* 44.7 years), age at diagnosis (55.2 *vs* 54.5 years), interval between onset and diagnosis (8.7 years *vs* 9.8 years), telangiectasias (62.2 *vs* 75.5%) and RP as first manifestation of disease (95.6 *vs* 94.1%). Fulfilment of ACR criteria for SSc were different between ssSSc and lcSSc subsets (13.3 *vs* 77.4%, $P < 0.0001$). Organ involvements: there were no differences in articular (57.8 *vs* 71%), gastrointestinal (71.1 *vs* 78%), interstitial and/or vascular pulmonary disease (84.4 *vs* 76.3%), cardiac (57.8 *vs* 57%), renal (4.4 *vs* 3.8%), myopathy (4.4 *vs* 4.3%), palpable tendon friction rubs (0.0 *vs* 1.1%),and development of neoplasia at follow-up (8.9 *vs* 7.0%). However, there were differences in the presence of sicca syndrome (30.1 *vs* 13.3%; $P = 0.024$), digital ulcers (15.6 *vs* 50.5%; $P < 0.0001$), calcinosis (11.1 *vs* 25.8%; $P = 0.047$) and acroosteolysis (0 *vs* 9.7%; $P = 0.028$). Immunology: prevalence of anti-nuclear and anti-centromere antibodies was similar between subsets (91.1 *vs* 96.8% and 46.5 *vs* 53.1%, respectively). Capillaroscopy: slow pattern was the most prevalent in both groups with no differences between them (80.5 *vs* 82.7%). Average survival at 5, 10 and 15 years was also similar (100 *vs* 98%, 100 *vs* 98% and 92 *vs* 89%, respectively).

Discussion. We compared a large series of ssSSc patients with a group of lcSSc and we confirm that ssSSc patients have great similarities in most of the parameters evaluated and also in the average survival. However, some differences were found in lower fulfilment of ACR criteria for SSc as well as lower presence of digital ulcers, calcinosis and acrosteolysis in ssSSc individuals.

Conclusions. ssSSc patients respect to lcSSc patients: (i) have similar demographic parameters; (ii) rarely fulfil the preliminary ACR criteria for SSc; (iii) have lesser incidence of digital vascular involvement but similar nailfold capillary pattern on capillaroscopy; (iv) have similar organ involvement; (v) have similar average survival.

PS84. CARDIOVASCULAR EVALUATION IN SSc: A PRELIMINARY REPORT OF A CASE–CONTROL STUDY

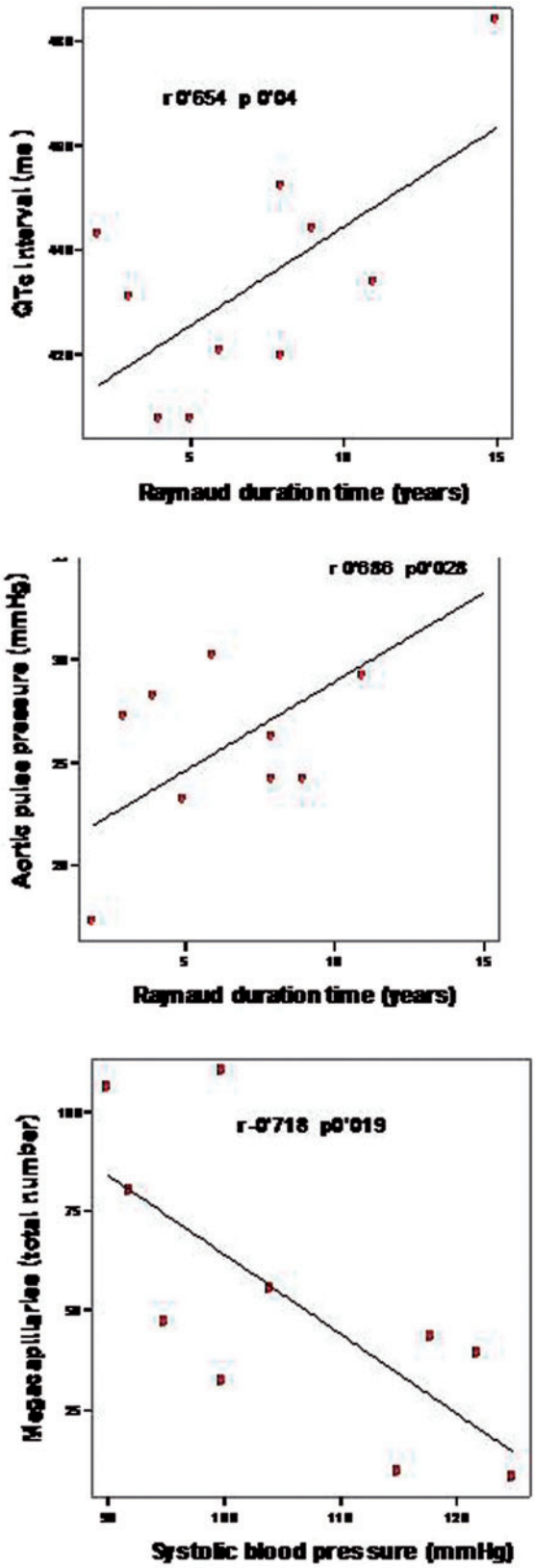
A. Toro-Parodi[1], J. Todoli-Parra[1], C. Ballester-Valles[2] and J.R. Calabuig-Alborch[1]
[1]*Internal Medicine Department and* [2]*Radiology Department, Hospital Universitario Y Politecnico La Fe, Valencia, Spain*

Objectives. To analyse the prevalence of cardiovascular risk factors and subclinic cardiovascular disease in a group of patients with SSc.

Material and methods. Case–control prospective study from October 2010 to August 2011. Ten patients with the diagnosis of SS (ACR criteria and LeRoy and Medsger 2001 subclassification), sex- and age-matched with 10 healthy controls.

Study design. (i) cardiovascular risk factors and established cardiovascular disease clinical history. (ii) Clinical data related to SSc. (iii) Physical exam and modified Rodnan score estimation. (iv) Blood and urine analysis sample. (v) Cardiovascular evaluation: (a) blood pressure measurement (Omron M6 HEM-7000-E); (b) EKG, Sokolow–Lyons and Cornell index and QTc interval; (c) ankle-brachial index (WatchBP

FIG. 1



Office ABI); (d) 24 h blood pressure registry (Spacelabs 90207); (e) nailfold videocapillaroscopy; (f) carotid-ultrasonography (Siemens Antares Sonoline, multifrequence transducer W 13-5) and intima media thickness (IMT); (g) arterial stiffness and pulse wave velocity by arterial tonometry (SphygmoCor. Software 8.2 Version:SPT-301 Millar tonometre).

Statistical analyses. SPSS 15.0 version for Windows. Chi-square and Contingency tables, Mann–Whitney test and Pearson's coefficient correlation when indicated.

Results. We did not find any statistical difference in traditional cardiovascular risks factors prevalence and neither in history of cardiovascular events between both groups.

Concern to laboratory data, we uniquely found higher haematocrit values in the control group (41.25 *vs* 39.12%; $P < 0.03$). Cardiovascular patients profile is showed in Table 1.

RP duration is positively correlated with QTc interval, aortic pulse pressure and systolic blood pressure (Fig. 1). The number of megacapillaries shows a negative correlation with systolic ($r = -0.718$, $P = 0.019$) and diastolic ($r = -0.644$, $P = 0.042$) blood pressure and BMI ($r = -0.800$, $P = 0.005$); and a positive correlation with ABI ($r = 0.735$, $P = 0.0015$).

Respect to pulse wave velocity results, we obtained a positive correlation with systolic blood pressure, cardiac frequency and waist circumference.

Conclusions. Pulse wave velocity shows in SSc patients a positive correlation with other cardiovascular risks factor with statistical significance (systolic blood pressure, cardiac frequency, systolic and diastolic blood pressure by 24 h-ABP and waist circumference)

ABI is an adequated instrument for cardiovascular study in SSs patients, showing a negative correlation with cardiac frequency, waist circumference, systolic and diastolic blood pressure by 24 h-ABP and pulse wave velocity.

The number of megacapillaries estimation could be a useful tool because of its association with other cardiovascular risk factors, but its utility at this setting needs to be elucidated.

TABLE 1.

VARIABLES	Controls $n = 10$ (X and S.D.)	Cases $n = 10$ (X and S.D.)	*P*
Age (years)	47.5 (14.62)	47.2 (13.67)	NS
EKG			
Sokolow index (mm)	14.6 (4.16)	14.8 (4.15)	NS
Cornell index (mm)	11.5 (3.5)	11.6 (3.09)	NS
QTc interval (ms)	418.3 (13.9)	433.5 (22.92)	
ABI*			
Right ABI	1.26 (0.12)	1.25 (0.16)	NS
Left ABI	1.3 (0.1)	1.28 (0.12)	NS
24 h-ABP**			
Systolic BP 24 h-ABP (mmHg)	106.9 (10.9)	104.3 (14.47)	NS
Dyastolic BP 24 h-ABP (mmHg)	66.1 (3.9)	65.9 (9.46)	NS
Median BP 24 h-ABP (mmHg)	81.8 (5.99)	79.6 (10.77)	NS
Capillaroscopy			
Megacapillary total number	0	51.9 (35.78)	0.001
Megacapillary mean number	0	6.69 (4.5)	0.001
Tortuosity (%)	22.8 (12.97)	15 (20.72)	NS
Ramification (%)	0.69 (1.35)	17.1 (25.26)	NS
Capillary mean number	11.38 (1.49)	5.1 (1.29)	0.001
Carotid-Ultrasonograp			
Intima-media thickness	0.64 (0.15)	0.66 (0.17)	NS
Arterial Stiffness			
Arterial central pressure (mmHg)	104.9 (10.6)	92.5 (9.57)	0.028
Aortic pulse pressure (mmHg)	34.6 (12.53)	26.4 (5.01)	NS
Pulse wave velocity (m/s)	7.11 (1.63)	6.6 (2.08)	NS
Augmentation Index (%)	26.7 (12.6)	22.44 (11.4)	NS

PS85. DIGITAL ULCERS SEVERELY IMPACT WORK AND DAILY ACTIVITIES— RESULTS FROM THE DUO REGISTRY

L. Guillevin[1], C. P. Denton[2], E. Hunsche[3], D. Rosenberg[3], B. Schwierin[3], M. Silkey[3], T. Krieg[4] and M. Matucci-Cerinic[5]
[1]*Department of Internal Medicine, University of Paris, Paris, France,* [2]*Royal Free Hospital – Centre for Rheumatology, London, UK,* [3]*Actelion Pharmaceuticals Ltd, Allschwil, Switzerland,* [4]*Department of Dermatology, University of Koln, Koln, Germany and* [5]*Department of Internal Medicine, University of Florence, Florence, Italy*

Background. Digital ulcers (DUs) are frequent and persistent clinical manifestations, which occur in up to 30% of all SSc patients and cause

considerable disability. The DUO Registry is an international, multicentre, observational study that aims to assess disease course in patients with DU associated with SSc.
Objectives. To assess the impact of DU on work, daily activities and help needed, in patients enrolled in the DUO Registry.
Methods. A functional impairment questionnaire was completed by patients upon enrolment into the DUO Registry. The questionnaire included three topics: work impairment (sum of work time missed + - work time attended multiplied by % of impairment while at work), daily activity impairment (%) and help needed (paid and unpaid in hours), all with regard to the past month. Patients were stratified according to number of DU at enrolment (0 DU, 1–2 DU, ≥3 DU; per DUO Registry protocol all patients require a history of DU).
Results. From April 2008 to August 2010, 2180 patients were enrolled into the DUO Registry. Of the patients, 1465 (69.6%) completed at least one part of the questionnaire and were included in this analysis. Of the 1465 patients 84.4% (1236/1465) were female. 409 (27.9%) had no DU, 639 (43.6%) had 1–2 DU, and 408 (27.8%) had ≥3 DU (missing data 62). The mean age was similar across all groups (55.7, 54.2 and 52.6 years, respectively). These baseline characteristics were similar to that observed in the overall registry population (82.8% female patients and mean age of 53.6 years1). Work impairment increased with the number of DU [0 DU: 31.9%, (95% CI 26.3, 37.5); 1–2 DU: 40.7%, (35.9, 45.5); ≥3 DU: 47.9% (42.2, 53.5)]. Impairment of daily activity also increased with the number of DU. Unpaid help needed due to DU increased with the number of DU present [unpaid help (95% CI), 0 DU: 17.4 h (9.9, 24.9); 1–2 DU: 33.4 h (27.5, 39.3); ≥3 DU: 62.5 h (48.0, 77.0)].
Conclusions. This analysis, from patients enrolled in the DUO Registry, shows that DU severely impacts work and daily activities. Functional impairment appears to increase with the number of DU present, reflected by higher impairment of work and daily activity, and increased hours of unpaid help needed.
We gratefully acknowledge all investigators involved in this study. The DUO Registry and the preparation of this abstract were supported by a grant from Actelion Pharmaceuticals Ltd, Allschwil, Switzerland.

PS86. PATIENTS WITH ONGOING DIGITAL ULCERS HAVE HIGHER DISEASE BURDEN COMPARED TO PATIENTS WITH A HISTORY BUT NO CURRENT DIGITAL ULCERS: FINDINGS FROM THE DUO REGISTRY

M. Matucci-Cerinic[1], L. Guillevin[2], C. P. Denton[3], B. Schwierin[4], D. Rosenberg[4], M. Silkey[4] and T. Krieg[5]
[1]*Department of Internal Medicine, University of Florence, Florence, Italy,* [2]*Department of Internal Medicine, Paris Descartes University, Paris, France,* [3]*Royal Free Hospital – Centre for Rheumatology, London, UK,* [4]*Actelion Pharmaceuticals Ltd, Allschwil, Switzerland and* [5]*Department of Dermatology, University of Cologne, Cologne, Germany*

Background. Digital ulcers (DUs) are a frequent, persistent and debilitating manifestation of SSc. The DUO Registry is a European, multicenter, prospective, observational cohort study of SSc patients with ongoing DU disease.
Objectives. To describe the ongoing complications, history of interventions and organ manifestations in SSc patients with ongoing DU disease, presenting with and without DU at enrolment into the DUO Registry.
Methods.. This registry enrols consenting patients with current or a history of DU. Patients are clinically assessed and receive medical care, as determined by their physician. Since April 2008, data collected have included demographics, SSc and DU medical history and interventions/complications associated with DU, including medications.
Results.. Till 19 November 2010, 1426 had ≥1 DU (58.5%) and 951 (39.0%) had 0 DU at enrolment [62 (2.5%) missing DU number]. All patients with no DU at enrolment had a history of DU disease. Mean age S.D. of the patients with ≥1 DU and the patients with zero DU was 53.5 (14.26) and 56.1 (13.72) years, respectively; >80% in either group were female [≥1 DU: 1200/1426 (84.2%); 0 DU: 762/951 (80.1%)]. The group with ≥1DU had a higher proportion of diffuse SSc compared with the group with zero DU [599/1408 (42.5%) *vs* 266/939 (28.3%), respectively] and a lower proportion of limited SSc [685/1408 (48.7%) *vs* 537/939 (57.2%)]. Mixed CTD was equally distributed across subgroups [≥1 DU: 87/1408 (6.2%); 0 DU: 77/939 (8.2%)]. In patients with ≥1 DU compared with 0 DU, there were a greater number of previous DU hospitalizations [≥1 DU: 620/1339 (46.3%) 0 DU: 354/883 (40.1%)], ongoing critical digital ischemia [≥1 DU: 172/578 (29.8%); 0 DU: 33/447 (7.4%)] and ongoing use of antibiotics for soft tissue infection [≥1 DU: 221/1396 (15.8%); 0 DU: 17/940 (1.8%)]. In both subgroups more than half of the patients had a previous diagnosis of gastrointestinal manifestations [≥1 DU: 805/1426 (56.5%); 0 DU: 527/951 (55.4%)], similar proportion of pulmonary arterial hypertension [≥1 DU: 219/1426 (15.4%); 0 DU: 144/951 (15.1%)] and more than one-third suffered from lung fibrosis [≥1 DU: 651/1426 (45.7%); 0 DU: 335/951 (35.2%)].
Conclusion. Both patients with and without DU have suffered high rates of previous SSc-related complications. Larger proportions of patients with current DU have ongoing DU complications and previous hospitalizations for DU compared to patients with no DU at enrolment.
We gratefully acknowledge all investigators involved in this study. The DUO Registry and abstract preparation were supported by a grant from Actelion Pharmaceuticals Ltd, Switzerland.

PS87. SSc IN MOROCCO: MONOCENTRIC STUDY OF 65 CASES

L. Lamzaf[1], H. Harmouche[1], M. Maamar[1], M. Adnaoui[1], M. Aouni[1] and Z. Tazi Mezalek[1]
[1]*Internal Medicine Department, Ibn Sina Hospital, Rabat, Morocco*

Introduction. SSc is an auto-immune disease that involves immune cells, fibroblasts and endothelial cells. This connectivity has rarely been studied in the North African countries. The aim of our study is to describe SSc in a Moroccan population.
Methods. A retrospective study conducted in the internal medicine department of a University Hospital between 2000 and 2011, concerned patients with SSc. Diagnosis was made according the ACR criteria.
Results. Sixty-five patients were included with 56 (86%) women and a mean age at time of diagnosis of 40.5 years (16–72 years). The mean diagnosis delay was 2.75 years. RP revealed the disease in 60% of cases and was reported in 58 (89%) patients. Fifteen cases (23%) of digital ulcers have been reported. Cutaneous sclerosis, present in 98% of cases was limited in 56% and diffuse in 44%. Joint involvement was present in 40 patients (61.5%). Contractility disorders on oesophageal manometry have been detected in 37 patients (57%), including 33 with swallowing disorders. Pulmonary interstitial involvement was objective by thoracic scan in 35 (56.5%) patients (62 scans), among them 34 (52%) had dyspnoea and 27 (41.5%) restrictive syndrome in pulmonary function testing. Pulmonary hypertension was noted in nine cases (14%). ANAs were positive in 36 patients with anti-Scl 70 in 18.5%. Associated auto-immune diseases were found in 17 cases. Calcium antagonists were initiated in 40 (61.5%) cases, converting enzyme inhibitor in 13 (20%) cases and colchicine in 28 (43%). Oral corticosteroids were given in 34 cases (52%) suffering from diffuse cutaneous sclerosis, pulmonary disease and/or articular manifestations. Thirty-one patients with pulmonary involvement (47.7%) received CYC. The mean follow-up was 5 years and the evolution was characterized by stabilization in 41 cases (63%). Four patients (6%) developed pulmonary hypertension and 8 (12%) pulmonary fibrosis. Digital amputations were necessary in four patients (6%). Two patients had a renal scleroderma crisis, one at the initial presentation of the disease and the other after initiation of corticosteroid therapy. Four deaths (6%) were noted, two from pulmonary hypertension, one from pulmonary fibrosis and one after renal crisis.
Discussion. All those results provide a better definition of the presentation of SSc patients in our country. The SSc seems to have similar characteristics to those observed in other countries. The severity of pulmonary hypertension, pulmonary fibrosis and renal involvement in SSc justify a systematic screening and regular follow-up.

PS88. THROMBIN—A POSSIBLE ALTERNATIVE THERAPEUTIC TARGET IN SCLERODERMA PATIENTS WITH PULMONARY LUNG DISEASE

C. Tanaseanu[1], M. Popescu[1], A. Dumitrascu[1], I. Tiglea[1] and S. T. Tanaseanu[1]
[1]*University of Medicine Carol Davila Hospital 'St Pantelimon' Internal Medicine Department, Bucharest, Romania*

Scleroderma-associated interstitial lung disease (SSc-ILD) is an irreversible and progressive complication of SSc often leading to respiratory failure and death. Lung involvement include at least two

entities—interstitial lung disease and pulmonary hypertension, many patients having elements of both.
Thrombin exerts a number of proinflammatory and profibrotic cellular effects that are predominantly mediated via proteolytic activation of PAR (proteinase-activated receptor).
PARs are expressed in lungs on a variety of cells, some of them recruited in the lung following injury.
Aim. We try to asses the effects of a reversible direct thrombin oral inhibitor (Dabigatran) in patients with SSc and pulmonary disease.
Methods. Four patients with diffuse SSc were selected form 10 SSc patients with pulmonary involvement, according to progressive decline of DL_{CO}, FVC, TLC, FEV1 and right ventricular dysfunction (Etr/Atr <1, systolic tricuspid flow velocity 2.5–3 m/s, TAPSE $<$ 20 mm). Pulmonary fibrosis was attested by HRCT. Two patients were scheduled for RHC. Patients were symptomatic (progressive severe dyspnoea) despite conventional therapy with CYC (pulse therapy 1 g/monthly for 12 months followed by CYC i.v.1 g at 3 month interval).
All patients received treatment with low dose of prednisone (10 mg/day), losartan 25 mg/day, amlodipine 2.5–5 mg/day, spironolactone 25 mg/day, pentoxifiline (800 mg/day), anti-osteoporotic and gastro protective treatment. One patient received Ilomedin 20 μg/day for 7 days, monthly, but for the other three patients the values of blood pressure were too low for prostanoid treatment.
The usual anti-coagulant treatment (acenocoumarol, clopidogrel) was replaced by Dabigatran 110 mg/day. The following tests were performed at base line and 12 weeks: ECG, transthoracc echocardiogram, 6-min walk distance, Borg dyspnoea index, pulmonary tests. Blood sampling for routine biochemistry was done at baseline and 4-weeks interval.
Results. The results are reported at 12 weeks. All patients presented an improvement in 6-min walk distance [with 25(±5) m] dyspnoea functional class (NYHA II), improvement in pulmonary tests: DL_{CO} with 6% (1), 5, FEV1 with 4 (2)%, TLC NS.
Right ventricular function measured as TAPSE, Etr/Atr, RAP and systolic regurgitant tricuspid flow velocity presented mild improvement, but no more decline.
Conclusions. The small number of patients in this study provides limited power to attest the importance of this treatment, but even in these conditions, the mild improvements or the slowing of the progression of pulmonary functional decline, have to be mentioned. Further clinical experience is needed for Dabigatran to be defined as a possible therapeutic option in the management SSc patients.

PS89. THE PREVALENCE AND EFFECTS OF ERECTILE DYSFUNCTION AMONGST MEN WITH SSc

T. Ngcozana[1], C. Chighizola[2], L. Parker[1], C. M. Black[1], C. D. Denton[1] and V. Ong[1]
[1]*UCL Medical School and Royal Free Hospital, London, UK and* [2]*University of Milan, Milan, Italy*

Introduction. SSc is associated with significant co-morbidities including erectile dysfunction (ED). Sexual dysfunction amongst men with SSc has been poorly reported. Previous studies suggest that frequency of ED in SSc ranges from 12–81%. The aims for this study were to examine the frequency of ED in a UK cohort of male patients with SSc, evaluate psychological effect on sexual relationships and we explored interaction with key health professionals with regards to ED.
Methods. One hundred men with lcSSc and dcSSc were asked to complete a validated international Index of Erectile Function Questionnaire (IIEF). The questionnaire was expanded to assess the psychological effects of sexual difficulties in SSc patients' relationships and interaction with health professionals.
Results. Sixty-two patients responded to the questionnaire of which the mean age (S.D.) was 54 (11.1) years. The mean disease duration (S.D.) was 8.4 (8.0) years and 11.4 (7.3) years for patients with dcSSc and lcSSc, respectively. Seventy-one per cent of the respondents reported sexual difficulties in at least one of the domains. Thirty-nine per cent of this cohort was considered as severe in all five domains of which half had diffuse disease. Interestingly, 34% developed sexual difficulties before they were diagnosed with SSc. For those who developed ED after the onset of SSc, the mean duration (S.D.) from emergence of ED to disease onset was 4.0 (3.1). As shown in the Table 1, intercourse satisfaction fared the worst of all the five domains with a score of 45% in the severe dysfunction category. As a consequence of ED, 55% of the respondents reported that their sexual difficulties had caused a significant strain on their relationships with their partners. Forty-five per cent of the patients reported that they had never been asked about their sexual health by a health professional. However, 65% of the men would have discussed these issues had they been given the opportunity to do so.
Conclusion. ED is a difficult subject to broach; patients and health professionals are reluctant to talk about it. ED is a common yet unexplored complication in scleroderma, our results show that sexual functioning is an integral part of determining quality of life for these patients. Our results imply that ED may occur even before diagnosis of SSc, suggesting that it could be an early feature especially in the diffuse subset. Therefore, multidisciplinary teams treating scleroderma patients should be aware of and actively enquire about sexual dysfunction.

PS90. ROSUVASTATIN IMPROVES IMPAIRED ENDOTHELIAL FUNCTION, BUT DOES NOT EFFECT ARTERIAL STIFFNESS IN PATIENTS WITH SSc—A NON-CONSECUTIVE, PROSPECTIVE CASE-SERIES STUDY

G. Szucs[1], O. Timar[2], G. Y. Kerekes[2], J. Vegh[2], S. Z. Szamosi[1], P. Soltesz[2] and Z. Szekanecz[1]
[1]*Department of Rheumatology and* [2]*3rd Department of Internal Medicine, University of Debrecen, Debrecen, Hungary*

Objective. Endothelial dysfunction and vasculopathy of the small and large vessels are crucial pathogenic factors in SSc. Statins display pleiotropic effects on endothelial function that may potentially retard vascular injury. The aim of this study was to evaluate the potential efficacy of rosuvastatin therapy on endothelial and macrovascular function as well as arterial stiffness in patients with SSc.
Methods. Twenty-eight patients who fulfilled the American College of Rheumatology criteria for classification of SSc were treated with 20 mg/day rosuvastatin for 6 months. Endothelium-dependent, flow-mediated dilatation (FMD) as well as endothelium-independent, nitroglycerin-mediated dilatation (NMD) of the brachial artery, common carotid intimal–medial thickness (ccIMT), aorto-femoral pulse wave velocity (PWV) and augmentation index (AIx) were measured before and after the 6-months of rosuvastatin treatment period. Parallel plasma levels of circulating von Willebrand factor antigen (vWF), a marker of endothelial cell activation, high-sensitivity CRP and lipid parameters was assessed before and after therapy.
Results. FMD significantly improved after 6 months of rosuvastatin therapy [2.2 (3.1) *vs* 5.7 (3.8)%, $P = 0.00033$]. Neither aorto-femoral, nor carotid–femoral PWV showed significant improvement upon rosuvastatin treatment as compared with pre-treatment values. When assessed the clinical forms of SSc separately, patients with limited cutaneous form exhibited significantly higher baseline PWV velocities than those with dcSSc. Changes in the ccIMT during the therapy were also not significant. Laser Doppler analysis of the forearm skin flow during post-occlusive reactive hyperaemia testing revealed a decrease in the acceleration and deceleration slope of the curves following rosuvastatin therapy compared with pre-treatment values [acceleration slope: 14.6 (14.8) *vs* 10 (10.3) U/s; $P = 0.081$; deceleration slope: -1.13 (0.92) U/s *vs* -0.64 (1.09 P); $P = 0.0211$]. Also, we observed a significant decrease in the mean area of occlusion after rosuvastatin treatment [2227 (2139) *vs* 1626 (1307) U*s; $P = 0.033$]. Analysing laboratory parameters, total cholesterol and LDL-C levels decreased significantly, while mean HDL-C and CRP levels remained unchanged. Baseline circulating vWF antigen levels

TABLE 1. Percentage of severity of Dysfunction

Domain	Severe Dysfunction (%)	Moderate (%)	Mild-Moderate Dysfunction (%)	Mild Dysfunction (%)	No Dysfunction (%)
Erectile Function	37	6	5	18	26
Orgasmic Function	35	13	8	2	34
Sexual Desire	10	18	16	26	10
Intercourse Satisfaction	45	8	18	5	16
Overall Satisfaction	39	5	8	26	15

were abnormally high (compared with the 160% laboratory reference range) in 63% of patients and although mean vWF antigen levels showed a slight but not significant decrease after rosuvastatin treatment.
Conclusion. Our results showed that rosuvastatin improved brachial FMD but did not reduce increased arterial stiffness or carotid IMT following a 6-month treatment period in SSc patients with intermediate cardiovascular risk. To determine the place of rosuvastatin in the therapy of SSc patients, however, repeated and large-scale studies need to be performed in the future.

PS91. SUCCESSFUL MANAGEMENT OF SEVERE PULMONARY ARTERIAL HYPERTENSION WITH INTRAVENOUS TREPROSTINIL THERAPY—A CASE REPORT

S. Szamosi[1], A. Nemeth[1], Z. Szekanecz[1] and G. Szucs[1]
[1]*Department of Rheumatology, University of Debrecen, Debrecen, Hungary*

Introduction. Pulmonary arterial hypertension (PAH) is a devastating disease with a poor prognosis. Treatment guidelines recommend targeted therapies depending on the disease severity. The use of prostacyclin analogues as replacement therapy improves the physical function and survival of PAH patients, and it is currently considered the most effective treatment available for moderate-to-severe PAH. However, prostacyclin therapy is underutilized in the majority of eligible patients.
Case history. A 55-year-old female with 10-year history of diffuse SSc developed PAH in 2004. She was included in a clinical trial and introduced endothelin receptor antagonist (ERA) ambrisentan therapy that she responded well as her clinical status, 6-min walk test (6-MWT) and diffusing capacity of the lung (DL_{CO}) improved in the next 5 years. A remarkable deterioration became evident in 2009 with a marked limitation of physical acitivity despite increased dose of ambrisentan (10 mg). In 2009 sildenafil therapy was introduced, but she did not tolerate it because of severe side effects. In January 2010, she was admitted to our department because of NYHA functional class IV dyspnoea. At this time s.c. treprostinil therapy was administered as a third-line therapy, since she failed to respond to ERA and PDE-5 inhibitors. After a 5 days' period, s.c. treprostinil had to be discontinued, since the patient showed severe local skin reaction and pain at the site of the infusion. In March 2010, continuous i.v. treprostinil therapy was started via central venous catheter, but she was refused to be eligible for lung transplant. Since then, a significant reduction in the pulmonary arterial pressure has been documented with an acceptable quality of life.
Conclusion. The i.v. prostaglandin treatment and lung transplantation should be reserved for a small population of patients with refractory illness. Patients and clinicians have to face a lot of difficulties during the treatment of severe PAH cases, since therapeutic strategies have to be developed individually. Presenting this case we wanted to demonstrate that a much longer survival might be achieved with careful patients' follow-up and by choosing optimal targeted therapy.

PS92. CLINICAL SIGNIFICANCE OF SERUM ADIPONECTIN LEVELS IN PATIENTS WITH SSc

H. Sumida[1], Y. Asano[1], Y. Masui[1] and S. Sato[1]
[1]*Department of Dermatology, Faculty of Medicine, The University of Tokyo, Tokyo, Japan*

Adiponectin has been demonstrated to be one of anti-inflammatory and anti-fibrotic factors, suggesting the potential of this cytokine to be involved in the developmental process of SSc. Serum adiponectin levels in dcSSc patients were significantly lower than those in lcSSc patients and healthy controls. dcSSc patients with disease duration of <5 years had significantly decreased serum adiponectin levels than those with disease duration of >5 years, lcSSc patients with disease duration of <5 years, lcSSc patients with disease duration of >5 years and healthy controls. Longitudinal studies in five patients with early dcSSc treated with oral prednisone demonstrated that serum adiponectin levels inversely correlate with the activity of progressive skin sclerosis in dcSSc patients.
Interstitial lung disease (ILD) is a leading cause of death in SSc. Therefore, we further investigate the clinical significance of monitoring serum adiponectin levels during i.v. pulse CYC (IVCY), which is currently the first-line treatment against SSc-ILD. Serum adiponectin levels were significantly decreased in SSc patients before IVCY compared with healthy controls. However, serum adiponectin levels in SSc patients showed statistically significant increase after the therapy compared with the initial levels. Moreover, the change in serum adiponectin levels inversely and greatly correlated with the change in ILD scores between before and after the whole IVCY therapy.
Serum levels of adiponectin may serve as a useful marker to evaluate the activity of progressive skin sclerosis in dcSSc. Together, serum adiponectin levels may reflect the efficacy of IVCY against SSc-ILD.

PS93. CORRELATIONS BETWEEN DERMAL THICKNESS AND BOTH MICROANGIOPATHY EXTENT AND PERIPHERAL BLOOD PERFUSION DEGREE IN SSc PATIENTS

A. Sulli[1], B. Ruaro[1], C. Pizzorni[1], M. Parodi[1], C. Ferrone[1], G. Zampogna[1], M. A. Cimmino[1] and M. Cutolo[1]
[1]*Department of Internal Medicine, Research Laboratory and Academic Unit of Clinical Raheumatology, University of Genoa, Genoa, Italy*

Background. Dermal thickness is a typical clinical aspect of SSc. High frequency US is able to detect digital dermal thickening in SSc, giving reliable and reproducible results [1].
Objectives. To investigate possible correlations between dermal thickness evaluated by US and both microangiopathy extent and peripheral blood perfusion in SSc patients.
Methods. Thirty-three SSc patients were enrolled [mean (S.D.) age 64 (12) years, mean disease duration 7 (5) years]. Dermal thickness was measured using a My Lab 25 US system (Esaote, Genoa, Italy) with an 18 MHz probe, by evaluating the dorsum of middle phalanx of both right and left third finger [1]. Nail-fold microangiopathy was detected by nail-fold videocapillaroscopy (NVC) at the level of the same fingers, and the scores for the capillaroscopic parameters were calculated, as well as the proper pattern of microangiopathy [2–4]. Peripheral blood perfusion (PBP) was analysed by laser Doppler flowmetry (Periflux System 5000, Perimed, Milan, Italy) at the central area of the fingertip of the same digits, and the values of PBP were recorded as perfusion units (PUs) [5].
Results. Dermal thickness was found progressively higher in patients with early, active and late NVC pattern of microangiopathy (median 0.81, 0.93, and 1.10 mm, respectively) ($P = 0.04$), and a positive correlation was observed between dermal thickness and microangiopathy score ($P = 0.01$). A negative correlation was observed between dermal thickness and PBP, but this was not statistically significant possibly due to little study population and wide distribution of perfusion values ($P = 0.10$). Dermal thickness was found greater in patients with diffuse skin SSc than in those with limited skin disease ($P = 0.02$). A strong statistically significant correlation was observed for dermal thickness values between left and right hand fingers ($P < 0.0001$). The study confirmed a statistically significant correlation between nail-fold microvascular damage extent and PBP degree ($P < 0.0001$).
Conclusions. This study demonstrates a positive correlation between digital dermal thickness and nail-fold microvascular damage extent in scleroderma patients. Patients showing the Late NVC pattern of microangiopathy and/or a high microangiopathy score are likely to have greater dermal thickness. Peripheral blood perfusion seems negatively correlated with dermal thickening, but larger studies need to confirm this observation.

PS94. NAIL-FOLD MICROANGIOPATHY AND AUTOANTIBODIES IN SSc

A. Sulli[1], V. Smith[2], C. Pizzorni[1], B. Ruaro[1], E. Alessandri[1], G. Zampogna[1] and M. Cutolo[1]
[1]*Department of Internal Medicine, Research Laboratory and Academic Unit of Clinical Rheumatology, University of Genoa, Genoa, Italy and* [2]*Department of Rheumatology, Ghent University Hospital, Ghent, Belgium*

Background. Nail-fold microvascular damage is a characteristic aspect of SSc, and the evolution from early to active and to late capillaroscopic pattern of microangiopathy was recently demonstrated in 34 and 13% of SSc patients, at 28 and 36 months, respectively [1].
Objectives. Longitudinal study to investigate the association between nail-fold capillaroscopic patterns of microvascular damage and autoantibodies occurrence.
Methods. Thirty-eight SSc patients [mean (S.D.) age 52 (10) years; mean disease duration from the onset of the first SSc symptom different from RP 1 (1) year] with the Early pattern of nail-fold microangiopathy at baseline were followed-up by nail-fold videocapillaroscopy (NVC) for a mean time of 8 (1) years. The proper pattern of

NVC microangiopathy (early, active, late) was recorded as previously reported [2, 3], and ANA, ACA and anti-topo (Scl70) autoantibodies were tested.
Results. At the end of the follow-up the NVC pattern was found Late in 7 patients (17%), Active in 17 patients (42%), and still early in 14 patients (35%). In the seven patients whose microangiopathy showed a progression from early to late NVC pattern through the active pattern, three patients were found positive for Scl70 antibodies, one patient was ACA positive and three patients were ANA positive (two patients presenting a nucleolar, and the other a homogeneous pattern). ACA (positive in 39% of total patients) were found significantly more frequent in SSc patients showing either the early or the active NVC patterns of microangiopathy at the end of follow-up (90% of patients) ($P = 0.0001$), confirming previous observations that ACA are likely to be associated with a slower disease progression. Opposite results were obtained for the Scl70 autoantibodies, which were found more frequent in patients with active and late NVC patterns of microangiopathy. Other SSc-specific autoantibodies were not investigated.
Conclusions. The results of the study confirm the progressive transition of the SSc microvascular damage through different NVC patterns of microangiopathy. The progression of nail-fold microangiopathy to the late pattern (more advanced stage of microvascular damage) associates with different autoantibody specificities and larger longitudinal studies need to better identify them (including other SSc-specific autoantibodies). ACA seem associated to a microangiopathy with a slower progression rate.

PS95. QUALITY OF LIFE AND FATIGUE IN SSc: EVALUATION OF THE EUROQUOL-5D AND FACIT-F ASSESSMENT TOOLS

G. Strickland[1], J. Pauling[1], J. McHugh[2] and N. McHugh[3]
[1]*Department of Rheumatology, Royal National Hospital for Rheumatic Diseases,* [2]*Bath Institute for Rheumatic Diseases and* [3]*Department of Pharmacy and Pharmacology (also Institution 1 and 3), University of Bath, Bath, UK*

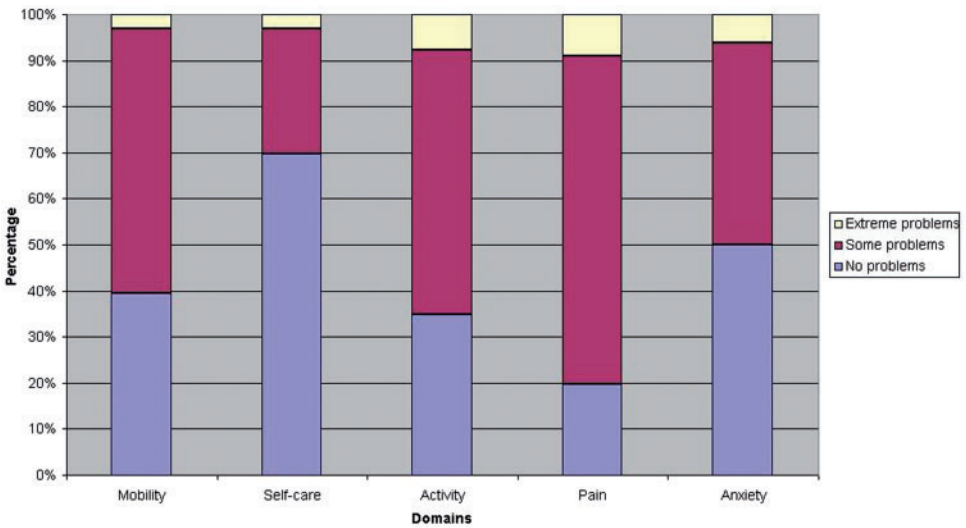
Objectives. Reduced quality of life (QoL) and fatigue are recognized features of SSc. We have evaluated predictors of reduced QoL and fatigue in SSc using two novel self-report indices; the EuroQual-5 domain health questionnaire (EQ-5D®) and the Functional Assessment of Chronic Illness Therapy – Fatigue scale (FACIT-F).
Methods. A cross-sectional study of patients with SSc was undertaken using a postal questionnaire that included the Scleroderma Health Assessment Questionnaire (SHAQ), EQ-5D and FACIT-F. The SHAQ encompasses the HAQ-DI and six visual analogue scores (VAS) assessing RP, digital ulcers, pain, gastrointestinal and respiratory symptoms, and patient global assessment. The EQ-5D assesses five domains of health quality (mobility, self-care, activity, pain/discomfort and anxiety/depression) that is converted into a time trade-off (TTO) value using population-based normograms (higher scores indicative of better health quality), in addition to a patient global assessment (0–100 VAS). The FACIT-F is a 13-item questionnaire converted into a summary score between 0 and 52 where higher scores are indicative of lower fatigue. Case notes were scrutinized for details including patient demographics, disease duration, serology and clinical phenotype.
Results. Sixty-eight patients with SSc [60 females, mean (S.D.) age 62.6 (11.5) years] completed the questionnaires (~70% response rate). The mean (S.D.) disease duration was 12.8 (7.2) years and 72% had lcSSc. Unweighted EQ-5D scores are presented in Fig. 1. Pain was the most frequently reported health problem (80%) in contrast to self-care (30%). There was good correlation between fatigue levels and QoL ($r = 0.78$ and 0.77 for EQ-5D VAS and TTO respectively, $P = 0.01$). Similarly, higher fatigue correlated well with disability assessed using the HAQ-DI ($r = -0.74$, $P = 0.01$). SHAQ-VAS scores correlated well with the FACIT-F, EQ-5D and HAQ-DI scores ($P < 0.05$). There was also excellent correlation between the EQ-5D and HAQ-DI ($r = 0.83$, $P = 0.01$). Few associations were identified between self-report measures and age, disease subtype, disease duration, most recent pulmonary function test results or highest Rodnan skin score. Only the absence of upper-gastrointestinal involvement predicted better QoL and lower levels of fatigue and disability ($P < 0.05$).
Conclusions. This is the first comparative study of the SHAQ, EQ-5D and FACIT-F in SSc. There is a strong correlation between the three self-report indices, possibly reflecting similar perceptions of health quality across the three measures. Few associations with objective assessments of organ-specific manifestations and patient demographics were identified. The absence of upper gastrointestinal symptoms appears to be associated with improved health quality with lower levels of fatigue, disability and improved QoL.

PS96. LUNG DISEASE IS THE MAJOR CAUSE OF DEATH IN THE AUSTRALIAN SSc COHORT STUDY

W. Stevens[1], V. Thakkar[1], O. Moore[1], J. Byron[1], S. Proudman[2], J. Zochling[3], J. Roddy[4], J. Sahhar[5], P. Nash[6], P. Youssef[7], G. Major[8], K. Tymms[9], A. Sturgess[10] and M. Nikpour[1]
[1]*Department of Rheumatology, St Vincents Hospital, Melbourne,* [2]*Department of Rheumatology, Royal Adelaide Hospital, Adelaide,* [3]*Menzies Research Institute, Tasmania, Hobart,* [4]*Department of Rheumatology, Royal Perth Hospital, Perth,* [5]*Department of Rheumatology, Monash Medical Centre, Melbourne,* [6]*Sunshine Coast Rheumatology, Maroochydore,* [7]*Department of Rheumatology, Royal Prince Alfred Hospital, Sydney,* [8]*Department of Rheumatology, John Hunter Hospital, Newcastle,* [9]*Canberra Rheumatology, Canberra and* [10]*Department of Rheumatology, St George Hospital, Sydney, Australia*

Objectives. To determine the cause of death among a cohort of patients with SSc
Methods. The Australian scleroderma cohort study is a national multicentre prospective study of patients with SSc. Comprehensive

Fig. 1 Descriptive profile of the five domains of the EQ-5D® reported by 66 patients with SSc



disease data are captured at least annually on all recruited patients. Deaths are recorded and the treating centre is required to provide details on the cause of death and other comorbidities. Data from this database have been used for this analysis. We used univariate methods to determine differences in demographic and disease-related characteristics of patients who have died, compared with survivors.
Results. Since the inception of the database in 2007, 1136 patients have been enrolled. Mean (S.D.) follow-up is 2.13 (0.88) years. Sixty-nine deaths have been reported. Mean (S.D.) age at death was 67.3 (10.1) years. Disease duration at time of death was significantly shorter in patients with diffuse SSc than in patients with limited SSc [mean 12.0 (13.0) *vs* 20.0 (14.1) years, $P = 0.006$].
Cause of death was determined to be SSc related in 39 (57%), unrelated to SSc in 29 (42%) and unknown in one case. The leading cause of SSc related death was lung disease, accounting for 43% of total deaths and 76% of SSc related deaths. Among the 30 lung-related deaths, 20 patients had isolated pulmonary hypertension (PAH), 3 had interstitial lung disease (ILD) and 7 had both ILD and PAH. Other SSc-related deaths were classified as multiorgan involvement in three cases, sepsis related to SSc in two, GIT involvement in two, renal crisis in one and SSc myocardial disease in one.
The second most common cause of death was cancer, accounting for 14 deaths (20% of total deaths). Cardiovascular event were responsible for deaths in 8 patients (11.6% of total deaths).
Among the cancer deaths, there were six with lung cancer, four GIT malignancies, three haematopoietic malignancies and one ovarian cancer. Among the lung cancer deaths, four had interstitial lung disease and two had smoked previously.
Conclusion. Lung disease is the most common cause of death in our SSc cohort. In particular, despite the advent of new therapies, PAH remains a major cause of death in our patients. Earlier detection and treatment of this complication through screening may improve survival. As cancer is the second most common cause of death among our patients, further studies are needed to determine the risk factors for malignancy in SSc, and the value of screening.

PS97. HYPOCOMPLEMENTAEMIA IN THE PATIENTS WITH SSc

M. Starovoytova[1], O. Desinova[1], O. Koneva[1] and L. Ananieva[1]
[1]*Institution of Rheumatology RAMS, Moscow, Russia*

Background. SSc is an autoimmune inflammatory disorder of unknown aetiology. Although complement fixation is not commonly thought to be part of the pathogenesis of SSc, hypocomplementaemia has been associated with SSc. Hypocomplementaemia is one of the variables in one SSc disease activity index.
Objectives. The aim of this study was to evaluate hypocomplementaemia in patients having SSc and it correlations with clinical features, serological marks and activity of disease.
Methods. Eighty SSc patients (65 females and 8 males) with mean age of 44.5 (11.7) underwent clinical evaluation and were analysed for their complement levels. Patients had diffuse (32.5%) or limited (57.5%) or overlap (10%) form of SSc, all fulfilling the ACR preliminary criteria for SSc. Disease activity was measured using Valentini Scleroderma Disease Activity Index.
Results. Hypocomplementaemia (low C3 and/or C4) was found in seven patients (8.8%). Based on hypocomplementaemia detection 80 patients were classified into two groups. Group A consists of 73 patients without hypocomplementaemia. Group B consists of seven patients with hypocomplementaemia. The female/male ratio was 8:1 and 5:1 in Group A and in Group B, respectively; the mean age was 44.9 (11.4) and 42.6 (14.8) of the patients in the Groups A and B, respectively. The mean duration of disease from the first non-RP was 7.55 (6.8) in Group A *vs* 3.5 (2.23) years in Group B. Group B did not have SSc-overlap form. There were 20 patients (25%) with disease activity more than 3. Disease activity score ranges from 0 to 7, mean 2.12 (1.75). The mean disease activity score was 3.1 (1.8) in normocomplementic patients. No significant association was found between the presence of hypocomplementaemia and the clinical-demographic and laboratory parameters, including specific autoantibodies and variables of SSc disease activity index.
Conclusion. In this study, we found that in SSc, hypocomplementaemia was rare. The meaning of hypocomplementaemia for evaluation of SSc activity requires further studying.

PS98. THE ASSOCIATION OF ANTI-CITRULLINATED PEPTIDE ANTIBODIES WITH EROSIVE ARTHRITIS IN PATIENTS WITH SSc: CLINICAL, RADIOGRAPHIC AND MAGNETIC RESONANCE IMAGING EVALUATION

B. Stamenkovic[1], A. Stankovic[1], A. Dimic[1], N. Damjanov[2], D. Menkovic[1], J. Nedovic[1], S. Stojanovic[1] and S. Milenkovic[1]
[1]*Department of Rheumatology, Institute Niska Banja, University of Nis, Nis and* [2]*Institute for Rheumatology,Belgrade University, Belgrade, Serbia*

Anti-citrullinated peptides antibodies (ACPAs) are highly specific for RA and important prognostic markers for development of erosive arthritis. A small number of studies have proved their presence in scleroderma.
Objective. To determine the frequency of ACPA in SSc, the association with clinical arthritis of the hand, radiographic changes and inflammatory findings in MRI in patients with SSc
Methods. The study included 82 SSc patients with an average age of 54 years, 59 with lSSc, 23 with dSSc and 28 healthy control group subjects (CG). ACPA and RF were determined in all SSc patients and controls. Standard RTG of the hands was performed in all the patients. MRI of the dominant hand was done in all the patients with SSc on the device of Artroscan 0.2 T MRI unit (Esaote Biomedica) with contrast agent bolus i.v. injection of 0.1 mmol/kg gadolinium.
Results. ACPA were found in 11/82 (13.4%) patients with SSc: 4/59 with lSSc and 7/23 with dSSc; they were not found in CG group of patients. Significantly higher percentage of dSSc patients had positive ACPA, compared with lSSc patients (30.4 *vs* 6.8%, $P = 0.009$). Positive RF was found in 13/82 (15.9%) patients with SSc: 9/59 (15.2%) with lSSc and 4/23 (17.4%) with dSSc; not found in CG.
Arthritis was found in 14/82 (17.1%) SSc patients, marginal erosions on RTG in 14/82 (17.1%) SSc patients. Statistically significant association was determined between positive ACPA and arthritis ($P < 0.0001$) and positive ACPA and erosion ($P = 0.0002$). The MR examination determined the prevalence of erosions in 9/11 (81.8%) SSc patients with positive ACPA, while the RTG examination showed their lower frequency, at 7/11 patients (63.6%), without statistical significance ($P = 0.635$). There was a statistically significant difference in the frequency of erosion in SSc patients with positive, as compared with those with negative ACPA [9/11 (81.8%) *vs* 34/71 (47.8%), $P = 0.037$). Precursors of erosive changes were present in almost all the SSc patients with positive ACPA and in lower percentage of ACPA negative, with no statistically significant difference: synovitis in 10/11 (90.9%) ACPA-positive and 50/71 (71.4%) ACPA-negative SSc patients($P = 0.273$); bone oedema in 10/11 (90.9%) ACPA-positive and in 44/71 (61.9%) ACPA-negative SSc patients ($P = 0.088$).
Conclusion. ACPA are associated with arthritis, erosions by radiography and with inflammatory changes by MRI of the hands in SSc. Considering that there has not been any standardized therapy of arthritis in SSc, our research may contribute to deciding on early, aggressive treatment of arthritis in scleroderma.

PS99. DO WORSENING SCLERODERMA CAPILLAROSCOPIC PATTERNS PREDICT FUTURE SEVERE ORGAN INVOLVEMENT? A PILOT STUDY

V. Smith[1], S. Decuman[1], A. Sulli[2], C. Bonroy[3], Y. Piette[1], E. Deschepper[4], F. De Keyser[1] and M. Cutolo[2]
[1]*Department of Rheumatology, University Hospital, Ghent, Belgium,* [2]*Research Laboratory and Academic Unit of Clinical Rheumatology, University of Genova, Genova, Italy,* [3]*Department of Clinical Chemistry, Microbiology and Immunology, University Hospital and* [4]*University Biostatistics Unit, Ghent, Belgium*

Objective. Assessment of associations of NVC scleroderma patterns ('early', 'active' and 'late') with future severe clinical involvement in a SSc population.
Methods. Sixty-six consecutive patients with SSc according to the LeRoy and Medsger criteria underwent nail-fold videocapillaroscopic (NVC) assessment at baseline. Videocapillaroscopic images were classified into 'normal', 'early', 'active' or 'late' NVC pattern. Clinical evaluation was performed for nine organ systems (general, peripheral vascular, skin, joint, muscle, gastrointestinal tract, lung, heart and kidney) according to the disease severity scale of Medsger (DSS) at 18–24 months of follow-up. Severe clinical involvement was defined as categories 2–4 per organ of the DSS.
Results. NVC patterns were significantly associated with future severe, peripheral vascular disease ($P = 0.040$) and lung involvement ($P = 0.016$) at 18–24 months. More specifically, the number of patients having future severe peripheral vascular disease significantly differed according to baseline NVC pattern. In this way, 13% of patients with 'normal' baseline NVC pattern, while 20/33/63% of patients with 'early'/'active'/'late' scleroderma pattern had future severe peripheral disease. Also the number of patients having future severe lung involvement significantly differed according to baseline NVC patterns: 13% of patients with 'normal' baseline NVC pattern, while 40/48/74%

with 'early'/'active'/'late' scleroderma pattern had future severe lung disease.
The odds ratio raised steadily throughout the patterns. The odds ratio for future severe peripheral disease was 1.75 (95% CI 0.084, 36.29) for 'early', 3.50 (95% CI 0.36, 34.33) for 'active' and 11.67 (95% CI 1.23, 110.95) for the 'late' NVC scleroderma pattern *vs* the 'normal' NVC pattern. The odds ratio for future severe lung involvement was 4.67 (95% CI 0.30, 73.38) for 'early', 6.36 (95% CI 0.66, 61.20) for 'active' and 19.83 (95% CI 2.00, 196.381) for 'late' NVC pattern.
Conclusions. This pilot study is the first demonstrating an association between baseline NVC patterns and future severe, peripheral vascular and lung involvement. Moreover, it suggests a stronger association according to worsening scleroderma patterns. This may indicate a putative role of capillaroscopy as a biomarker.

PS100. THE DIFFERENCIES IN CLINICAL CHARACTERISTICS OF SSc SUBTYPES (CENTRE 055 EUSTAR DATABASE)

K. Simic Pasalic[1], I. Jeremic[1], N. Damjanov[1] and G. Marinkovic[2]
[1]*Institute of Rheumatology and* [2]*Primary Health Center Zvezdara, Belgrade, Serbia*

Background. SSc is a multisystemic, heterogenic, unpredictable disease, with pathogenesis based on alterations in endothelial, epithelial cells, fibroblasts, innate and aquired immune system, thus, there is a great variety of clinical manifestations, combining under basic disease subtypes, diffuse (dSSc) and limited (lSSc). Aim of this study is to explore the differencies in clinical characteristics of dSSc and lSSc.
Patients and methods. The cross-sectional study included 160 patients with SSc, from EULAR Scleroderma Trials and Research (EUSTAR). As a disease onset, we considered the appearance of any other SSc manifestation other than RP. We analysed the differences in demographic and clinical characteristics of the patients with dSSc and lSSc disease subtypes Appropriate statistic tests were applied in SPSS14.
Results. The study group comprised 160 SSc patients from EUSTAR Centre 055, of whom 141 were females (88.1%). A total number of 90 (56.2%, among them 95.5% females) patients were clasified as lSSc, while 70 (43.7%, 78.5% females) had the dSSc subtype. The average patient's age was 59.1 (27–78) years, mean disease duration 9.2 (1–28), while mean RP duration was 13.2 (1–22) years. There were no statistical differencies in demografic characteristics, between the patients with limited and diffuse subtype of the disease. Highly statistically significant difference was found in modified Rodnan skin score (MRSS) between dSSc and lSSc patients (16.9 *vs* 8, $P = 0.000$). Within dSSc subtype of the disease, there were significantly more frequently ACR SSc diagnostic criteria fulfilled, compared with lSSc (100 *vs* 89.5%, $P < 0.05$). Statistically significant difference was found in the presence of dyspnoea: 48.5 *vs* 30.6%, joint contractures: 78.8 *vs* 60%, anti-topo (ATA) positivity: 73.1 *vs* 30.2%, diastolic dysfunction of the left ventricle: 36.9 *vs* 21.2%, muscle atrophy: 24.2 *vs* 11.8% (all, $P < 0.05$), as well as tendon friction rub: 30.3 *vs* 2.4%, lung fibrosis 47.7 *vs* 18.6% (both, $P < 0,01$) in dSSc patients compared with lSSc patients, while in lSSc subtype there were ACA positivity significantly more frequently found (59.3 *vs* 15.2%, $P < 0.05$).
Conclusions. In SSc patients from our EUSTAR database, we found lung fibrosis, diastolic dysfunction of left ventricle, dyspnoea, muscle atrophy, tendon friction rub, joint contractures, ATA positivity, higher values of MRSS, significantly more frequent in dSSc subtype, compared with lSSc, yet, in lSSc patients there were significantly more ACA positivity.

PS101. BOSENTAN IN PAEDIATRIC AUTOIMMUNE DISORDERS: THREE CASE REPORTS

V. Silva[1], C. Esteves[1] and N. Fernandes[1]
[1]*Centro Hospitalar Barreiro Montijo – Auto-Immune Diseases Group, Barreiro, Portugal*

Background. Approach to RP in paediatrics remains a challenge, mostly in adolescence that refuse to accomplish general measures to prevent it, like using gloves. We report three cases in which bosentan, appears as a therapeutic option to consider in these cases.
Case 1: a 13-year-old girl was diagnosed with SSc, with RP and digital ulcers, muscle/joint and gastrointestinal involvement with dysphagia. She was started on bosentan with an enormous improvement of digital ulcers and RP.
Case 2: a 14-year-old girl was diagnosed with SSc, with RP, gastrointestinal, pulmonary and muscle/joint involvement. She had no ulcers but was started on bosentan with a great improvement of RP; she progressed to hip arthritis with gait impairment and severe abdominal pain. Refractory to conventional treatment, completed four cycles of rituximab with clinical enhancement and CD19 depletion.
Case 3: a 14-year-old girl was diagnosed with primary RP medicated with nifedipine and experienced hypotension, headaches and dizziness. Three months laters she got pulp fingers reduction. She had no ulcers but was started on bosentan with a great improvement of RP. She repeated capillaroscopy that revealed a secondary RP but no antibodies.
Conclusion. Bosentan seems to be an important therapeutic approach in SSc in paediatrics even when there are no digital ulcers, preventing deformities of the fingers in such a young age.

PS102. ENDOTHELIUM DYSFUNCTION ASSESSMENT: A USEFUL TOOL AS AN ALERT SIGN FOR MICROVASCULAR COMPLICATIONS IN RP

I. Silva[1], T. Loureiro[1], J. Oliveira[2], M. Matos[3], C. Vasconcelos[4] and R. Almeida[1]
[1]*Serviço de Angiologia e Cirurgia Vascular,* [2]*Serviço de Química Clínica,* [3]*Departamento de estudo de populações ICBAS and* [4]*Unidade de Imunologia Clínica UIC, Porto, Portugal*

RP is a clinical marker for microangiopathy. Frequently only as a functional vasculopathy, it can in a subgroup of patients (secondary RP) gradually evolve to structural changes in the microcirculation with reduction in blood flow to the fingers, leading to ischaemia and digital ucers. The aim of this study was to identify biomarkers and functional assessment of endothelium dysfunction in patients with RP with or without peripheral microvascular complications, in order to try to predict development of digital ulcers in RP patients.
Methods. We reviewed a cohort of RP patients attending our Raynaud's Clinic. Demographic and epidemiological data, autoimmune serological screening, inflammatory protein screening, Biomarkers for endothelium dysfunction (ET-1), assymetric dimetilarginine (ADMA), capillaroscopy and flow-mediated dilation (FMD), were analysed in all patients. In an attempt to define the risk of a patient with RP to develop digital ulcers, we crossed clinical, analytical, haemodynamic and capillaroscopic data.
Results. Four groups of patients were compared: primary RP, secondary RP with and without digital ulcers and healthy controls. Data analysis showed that patients with RF and ANA > 1/1280 anticentromere mottled pattern, Sscl 70 positive, VS increased, CRP > 30, pitting of the digital pads of the fingers, calcinosis lesions and changes of digital capillaroscopy stages (early/active or active/late) have a high risk of developing digital ulcers. Endothelium dysfunction was confirmed: ET-1 was elevated in all RP patients, but a significant difference was detected in secondary RP patients when compared with the primary RP and control group. We found no differences in ADMA between the groups. FMD was reduced in patients with digital ulcers. The brachial artery diameter at 15 s after cuff deflation had statistical differences ($P = 0.008$) between RP patients with digital ulcers and primary RP. End diastolic volume was significantly different between groups ($P = 0.001$) suggesting an increase in peripheral resistance in patients with DU.
Conclusions. In our cohort, we identified patients at risk of developing DUs as having ANA >1/1280 anti-centromere mottled pattern, Sscl 70 positive, increased vasoconstrictor ET-1 and decreased bioavailability of nitric oxide, caused by an decrease in production, rather than inhibition of it's generation. These data may help us in understanding the pathogenesis and natural history of RP and DUs and defining a correct target therapy in patients without active ulcer but at risk of developing ulcers.

PS103. LONG-TERM OUTCOMES OF PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION AND CONNECTIVE TISSUE DISEASE TREATED WITH INTRAVENOUS EPOPROSTENOL

Y. Shirai[1], H. Yasuoka[1], T. Takeuchi[1], T. Satoh[2,3] and M. Kuwana[1]
[1]*Division of Rheumatology,* [2]*Division of Cardiology, Department of Internal Medicine, Keio University School of Medicine and* [3]*Department of Cardiology, Kyorin University School of Medicine, Tokyo, Japan*

Objectives. Pulmonary arterial hypertension (PAH) still remains an intractable condition in patients with CTD, including SSc. This study was undertaken to assess outcomes and predictors for mortality in patients with PAH-CTD, who were treated with i.v. epoprostenol.

Methods. We studied 16 patients with PAH-CTD, who were treated with continuous i.v. epoprostenol at Keio University Hospital between 2000 and 2009. Right heart catheterization was performed before initiation of epoprostenol and 6 months later. Baseline clinical characteristics, haemodynamic parameters, and serum BNP level were registered at introduction of epoprostenol, and serial WHO functional class and concomitant PAH drugs used were prospectively recorded. Cumulative survival rates were calculated using the Kaplan–Meier method and survival rates between two groups were compared using the log-rank test. Multivariate analysis using the Cox proportional hazards regression model was performed to select independent predictors for mortality.
Results. Underlying CTDs included SLE in six, MCTD in five, SSc in four, and primary SS in 1. Age at PAH diagnosis was 42 (14) years, and the time interval between PAH diagnosis and initiation of epoprostenol was 12 (23) months (range 0–69 months). Only 6 patients (38%) were classified as having WHO functional class IV at the introduction of epoprostenol, and the remaining patients were in Class III (56%) or Class II (6%). Prior PAH drugs included beraprost alone in 10, and beraprost in combination with sildenafil and/or bosentan in 4, whereas 2 patients received epoprostenol as the first-line treatment. Sildenafil or bosentan were added after introduction of epoprostenol treatment in 19 or 6%, respectively. Four patients died within 6 months after initiation of epoprostneol. Cumulative survival rates at 1, 3, and 5 years were 69, 69 and 55%, respectively. In multivariate analysis, cardiac index at baseline $\geq$1.4 l/min/m^2, 20% reduction of mean pulmonary arterial pressure at 6 months and increase in CI at 6 months were selected as independent predictors for favourable outcomes at 5 years ($P = 0.03$, 0.02 and 0.03, respectively).
Conclusion. Long-term outcomes in epoprostenol-treated patients with PAH-CTD were still poor. Rapid increase in epoprostenol dosage to improve haemodynamic parameters within 6 months would be a key to further increase a long-term survival rate in patients with PAH-CTD.

PS104. EFFECTIVE TREATMENT OF DEGOS DISEASE WITH TREPOSTINIL: EARLY EXPERIENCE

L. Shapiro[1], A. Toledo[2] and J. Farrell[3]
[1]*Steffens Scleroderma Center, The Center for Rheumatology, Saratoga Springs,* [2]*The Center for Rheumatology and* [3]*Albany College of Pharmacy and Health Sciences, Albany, NY, USA*

Degos disease (malignant atrophic papulosis) is an uncommon endotheliopathy with pathological findings similar to the vascular lesions of SSc. These two disorders can overlap. When associated with visceral lesions, Degos disease has been considered almost universally and rapidly fatal. A recent report described dramatic response to treatment with eculizumab, but disease progression after initial response to therapy has occurred.
We describe the clinical and pathological findings in two patients with Degos disease who received treatment with s.c. trepostinil. One had experienced life-threatening disease progression despite ongoing eculizumab therapy. During this treatment, he had developed multiple CNS and bladder lesions with neurological symptoms and gross haematuria. Therapy with trepostinil was temporally associated with clearing of haematuria, resolution of CNS symptoms and improvement in MRI findings.
The second patient had an overlap syndrome with features of SLE and scleroderma and severe pulmonary hypertension. She also had very extensive cutaneous lesions of Degos disease. There was no evidence of CNS disease and laparoscopy revealed no visible Degos lesions on the serosa of the small bowel. She was placed on therapy with trepostinil for her pulmonary hypertension, but in the months subsequent to initiation of treatment, dramatic and near-complete clearing of cutaneous Degos lesions occurred with resolution of disabling digital pain.
Trepostinil may offer a second effective treatment approach to individuals with Degos disease or 'rescue' therapy to those in whom eculizumab treatment has failed to maintain suppression of disease activity.

PS105. COMPARISON OF WIDE FIELD NAIL-FOLD CAPILLAROSCOPY AND VIDEOCAPILLAROSCOPY IN THE ASSESSMENT OF THE MICROCIRCULATION IN PATIENTS WITH RP: PRELIMINARY RESULTS

J. Sekiyama[1], C. Camargo[1], L. Andrade[1] and **C. Kayser**[1]
[1]*Rheumatology Division – Universidade Federal de São Paulo, São Paulo, Brazil*

Purpose. Capillaroscopy is a well-established method for the assessment of the microcirculation in patients with RP and SSc. Several equipments such as wide field nail-fold capillaroscopy (NFC) and digital videocapillaroscopy are currently used. This study aimed to compare the different parameters evaluated by wide field NFC with those obtained by videocapillaroscopy, as well as to evaluate the reliability of both methods in the assessment of the microcirculation in RP patients.
Methods. One hundred and fifty patients with primary RP ($n = 34$), RP secondary to SSc ($n = 80$), and undifferentiated CTD ($n = 36$) (23 men and 177 women in total) were included. Fifty healthy controls matched for sex and age were also evaluated. Wide field NFC was performed using a stereomicroscope (Olympus-SZ40) under 10–25$\times$ magnification. The following parameters were analysed in eight digits of the hands (excluding the thumb): number of capillary loops/mm, number of enlarged and giant capillary loops, number of microhaemorrhages and vascular deletion score (score 0–3). Videocapillaroscopy was performed under 200$\times$ magnification contact lens connected to an image analysis software (Videocap 8.14, DS-Medica, Italy). The following parameters were measured over 32 fields (four fields per finger in eight fingers): presence of enlarged and giant capillaries, microhaemorrhages and capillarie loss. The mean score based on a semiquantitative rating scale (score 0–3) of every parameter was used. Intra- and inter-observer reliability was evaluated by performing both exams in 20 individuals in two different days and with two different observers, respectively.
Results. There was a significant correlation ($P < 0.000$) between wide-field NFC and videocapillaroscopy in comparison of all parameters: number of capillaries ($r = 0.733$), enlarged capillaries ($r = 0.922$), giant capillaries ($r = 0.752$), microhaemorrhages ($r = 0.601$) and vascular deletion/capillaries loss ($r = 0.784$). For NFC the inter- and intra-observer agreement was 0.754 and 0.970 for number of capillary loops/mm; 0.971 and 0.977 for number of enlarged loops; 1.0 and 0.705 for giant capillary loops; 0.920 and 0.562 for microhaemorrhages; and 0.853 and 0.937 for vascular deletion score, respectively. For videocapillaroscopy the inter- and intra-observer agreement was 0.850 and 0.923 for enlarged capillaries; 0.817 and 0.805 for giant capillary loops; 0.644 and 0.624 for microhaemorrhages; and 0.751 and 0.937 for capillaries loss, respectively.
Conclusions. In the present study, both wide-field NFC and videocapillaroscopy showed to be reproducible and reliable methods and could be equally useful for the peripheral microangiopathy evaluation in RP patients.

PS106. SKELETAL AND HEART MUSCLE INVOLVEMENT IN SSc

L. Schade[1], E. S. Paiva[1] and **C. S. Muller**[1]
[1]*Hospital de Clinicas da Universidade Federal do Paraná, Curitiba, Brazil*

Patients with SSc may present with muscle involvement, including myositis or no-inflammatory myopathy. In SSc patients with muscle abnormalities, left ventricular dysfunction can be found, leading to a worse prognosis in these cases. Eighty-seven SSc patients from the Hospital de Clínicas of the Universidade Federal do Paraná were evaluated, concerning the muscular manifestations and their association with left ventricular dysfunction. The prevalence of muscle involvement in our sample was 42.5%, with a positive correlation with the presence of diffuse SSc. In patients who were found to have left ventricular dysfunction, when other causes where ruled out, three of four patients had muscular weakness, muscle atrophy and/or muscle enzymes elevation.

PS107. SSc: RELATIONSHIP BETWEEN CAPILLAROSCOPY, CLINICAL RISK FACTORS AND BONE MINERAL DENSITOMETRY

Y. Ju[1], S. Visentini[1], S. Veiga[1], C. Laurito[1] and J. Scali[1]
[1]*Durand Hospital – Rheumatology Unit, Buenos Aires, Argentina*

Autoimmunity aetiology in Collagen diseases (scleroderma) have not yet entirely clarified and express complex interactions between genetics, immune system, hormone levels, etc., that could generate susceptibility to suffer them. At the same time patients with SSc can suffer from comorbidities or related problems. Osteoporosis is one of them. This led us to study our patients with SSc because at present, the data is very poor. Thinking in this aspect we include our SSc patients involving bone mineral densitometry (BMD) and its correlation with factors allegedly predictive to suffer it or considering associated with.

Methods. BMD (by DEXA) of every patient, all digits capillaroscopy and clinical data were carefully analysed in SSc patients fulfilling LeRoy and Medsger criteria.
Results. We include 44 patients, 6 men and 38 women (average age: 59.9 years, range: 21–81 years), with an average duration of disease: 8 years. Half of the patients were diffuse and 75% had extra-cutaneous manifestations and 40% digital ulcers. It was found as risk factors for osteoporosis: 18% smokers, 69% were post-menopausal women, 58% were treated with glucocorticoids (average dose: 10 mg/day) and by 15% suffered from fractures earlier. Level of BMD: 33 patients (75%) presented t-score < -1.00, and 11 patients (25%) were osteoporotic (t-score < -2.5) in lumbar spine and/or in hip. Seven patients had fractures (vertebral, wrist, ankle, humerus) and all have low BMD (osteopenia), except two patients with normal BMD at hip level. We did not observe any association between bone fragility and age, duration of disease, smoking or menoage, glucocorticoid therapy or some other feature of the disease. Capillaroscopic study was indicative regarding the clinical–pathological context (normally is not included in diagnostic criteria) with an specificity almost 100% (scleroderma pattern).
Conclusions. Low-range DXA BMD is very common in SSc (75%) and 25% of patients present osteoporotic range on Lumbar and/or Hip, without be able settling Predictive factors for this fragility. We need more data from other pathogenic factors that we already started to look particularly at intestinal level (whether by commitment SSc or other disease causing malabsorptive condition and hence hipovitaminosis D). According to data we believe that evaluation of SSc patients with BMD searching for bone fragility is a priority. Capillaroscopy remain a simple and rapid method for the differential diagnosis between primary and secondary Raynaud, also effective in diagnosing different stages of SSc.

PS108. ULNAR ARTERY INVOLVEMENT IN SCLERODERMA PATIENTS

R. Sarov[1], I. Tiglea[1], A. Dumitrascu[1] and C. Tanaseanu[1]
[1]*Internal Medicine Department, Clinical Emergency Hospital St Pantelimon, Bucharest, Romania*

Background. Vascular lesions are crucial in determing the prognosis of patients with scleroderma. Although most of the attention has focused on small-vessel disease, macrovascular disease has been recently described.
Objective. The aim of the study was to investigate the presence of large artery involvement, respectively ulnar artery occlusion, in a small number of patients diagnosed with SSc.
Methods. Retrospective study on seven scleroderma patients, all of whom exhibited RP and digital ulceration together with a positive modified Allen test, compared with seven negative patients, matched for age, sex, smoking habit, arterial hypertension and diabetes.
Results. Comparing the two groups, the positive one had a significant ulnar artery involvement and there was no significant difference in risk factors of macrovascular disease between ulnar artery-involved patients and not-involved subjects.
Conclusion. As previous studies showed, ulnar artery is frequently involved in patients with scleroderma, therefore its status should be assessed on patients with severe RP and refractory digital ulcer using modified Allen test or Doppler sonography if available.

PS109. SECONDARY SSc TO SILICOSIS OR TO NEOPLASM?

M. Saracco[1], R. Vitetta[1], C. Lomater[1], E. M. Marucco[1] and R. Pellerito[1]
[1]*Rheumatology Unit, Ospedale Mauriziano di Torino, Turin, Italy*

A 62-year-old man arrived to our observation in March 2010 because of RP since July 2009 and arthralgia since December 2009. He was a mason, a smoker of 60 cigarettes/day; had a car accident in 1986 resulting in costal infraction and pneumothorax.
At clinical evaluation he presented a diffuse (Dc) scleroderma with a modified Rodnan skin score (TTS) of 18, puffy hands, arthralgia; additionally he reported an increase in dyspnoea in the last 3 months. He was diagnosed with dcSSc.
A nail-fold capillaroscopy was performed revealing an 'active scleroderma pattern'. The immunology test revealed PMSCL 100 and Th/To positivity. The HRTC detected presence of a 20-mm mediastinal limphoadenophaty and 2-cm pleural effusion at the right basis. Nothing else. An abdomen TC evidenced normal parenchyma and lymphnodes. A bronchoalveolar lavage was negative for neoplastic cells, and a mediastinoscopy revealed a black lung disease with silicosis nodules histologically. This suggested the diagnosis of SSc secondary to silicosis according to literature.
Because of the increasing skin involvement (TTS 25 in July 2010) we started therapy with i.v. CYC (750 mg every 2 week for eight infusions with 6 g total dose) plus steroid (three infusions of 500 mg of 6-methylprednisolone followed by 25 mg/day of prednisone orally). We also started an anti-tuberculosis prophylaxis according to local guidelines for immunosuppressant therapy in silicosis.
In November 2010, TTS decreased to 15 and he started maintenance therapy with AZA 150 mg/day.
In January 2011, an abdomen US control revealed normal parenchyma, absence of adenophaty and no ascites; a thorax X-ray the persistence of pleural effusion.
In March 2011, we detected TTS 12 but persisting puffy hand and RP despite calcium-channel blockers. He reported abdomen distension without ascites; the haematic exams revealed increased levels of liver enzymes (1.5 fold the normal). We decreased prednisone to 5 mg/day and give an appointment in June 2011.
He did not attend the visit and we call him to ask for his conditions. In June 2011, he was diagnosed a hepatic carcinoma and in September 2011 he was at home under a morphine therapy.
In literature, several papers underline the increased risk of neoplasm in scleroderma patients but there are not clear data about temporal and causal correlations. Two recent studies describe the association of Anti-RNA polymerase III antibodies with Ssc and synchronous onset of malignancies. In our experience, this is the first case of such time-linked occurrence of SSc and neoplasm.

PS110. ENCOURAGING RESULTS FROM AUTOLOGOUS FAT INJECTION (LIPOFILLING) OF THE LIPS IN SSc

M. Saracco[1], M. Raso[2] and R. Pellerito[1]
[1]*Rheumatology Unit, Ospedale Mauriziano di Torino,* [2]*Plastic Surgery Unit, Ospedale Mauriziano di Torino, Turin, Italy*

Background. SSc leads to several deep changes in physical aspect of patients with psychological discomfort and embarrassment in social life other than functional limitations. One of these changes is the classic scleroderma facies with microstomia and loss of lip tenderness and mobility. Driven by our patients we decided to create a collaboration with plastic surgeon.
Methods. We reviewed the literature to understand the better way to work. We found some interesting experiences of few cases treated with autologous fat injection (lipofilling) in the lips. No difficult wound healing or graft reaction was reported.
We decided to treat patients with isolated lip tightening without perioral bar code, despite a successful case of deep phenol peeling is described in literature, and only patients with non-active disease.
Two patients affected one by LcSSc ACA+ and one by DcSSc Scl70+, with disease duration of 7 and 10 years, respectively, underwent this treatment between May and July 2011. According to the recent literature, 50 cc of fat tissue were prelevated and centrifugated, then injected in the lips in two different interventions with a month of interval in between (20 cc each one).
Results. None of the patients had post-surgery complications. Despite a little change in the aspect of our patients their subjective sensation was greatly positive. They referred improvement in psychological aspect with greater self-confidence in social life; furthermore they noted a better capacity in mimics' movement, functional aspect of life like eating and drinking and the ability in pronounce labial letters.
We have then created a 10-item questionnaire, and now we are submitting it to several patients, to evaluate functional and psychological mouth involvement in SSc patients.
Conclusions. Despite more effective kinds of interventions are available in plastic surgery to reduce ageing and functional limitation of perioral region, these techniques are not applicable in SSc patients because the possibility of graft reaction and late healing of surgical wounds. The lipofilling intervention seems to be a good effort to improve the quality of life in patients which are in large part young women. In fact it is well tolerated and it can be repeated many times. Other cases and a long period of follow-up are needed to define the safety and effectiveness of this approach.

PS111. EARLY OESOPHAGEAL TREATMENT MAY BE ASSOCIATED WITH A DECREASED FREQUENCY OF GASTROESOPHAGEAL SURGERY IN A LARGE BRAZILIAN COHORT OF PATIENTS WITH SSc

P. Sampaio-Barros[1], I. Nascimento[1], L. Seguro[1], A. L. Foelkel[1], A. P. Del-Rio[2], L. R. Lopes[3], N. A. Brandalise[3], N. Andreollo[3] and J. F. Marques-Neto[2]

[1]*Division of Rheumatology, University of São Paulo, São Paulo,* [2]*Unit of Rheumatology and* [3]*Division of Gastric Surgery, University of Campinas, Campinas, Brazil*

Background/Purpose: Oesophagus is the most frequently involved organ in SSc. Despite the clinical treatment, some patients can need a surgical approach for gastroesophageal reflux disease (GERD). The present study analyses the surgery for GERD during the last two decades in a large cohort of SSc patients.
Methods. One thousand and six SSc patients attended at the Scleroderma Outpatient Clinic at two referral university centres in Brazil during the period 1991–2010 were retrospectively studied. All the patients fulfilled the diagnosis of SSc according to the ACR criteria. Demographics, clinical and imaging data related to TGI involvement were obtained from medical records. Continuous treatment with prokinetic drugs and gastric protectors was prescribed for all patients with SSc and oesophageal involvement in these two referral university centres since 2001. Fisher's exact test was used to analyse the data; $P < 0.05$ was considered statistically significant.
Results. Among the 1006 SSc patients, 42 (4.2%) patients with severe GERD were submitted to surgery, predominantly gastrofundoplicature (Lind and Nissen techniques). In the patients submitted to GERD surgery, there was predominance of female gender (95.2%), Caucasians (88.1%) and limited SSc (73.8%). Thirty-five patients (83.3%) were submitted to surgery in the period 1991–2000, while seven patients (16.7%) had surgery in the period 2001–10 ($P < 0.001$). There was statistical significance among GERD surgery and limited SSc ($P = 0.011$) and Caucasian race ($P = 0.046$).
Conclusion. An early and continuous treatment for the oesophageal involvement may be responsible for a decreased number of GERD surgeries in the last decade in this large cohort of SSc patients.

PS112. GASTROINTESTINAL INVOLVEMENT IN A LARGE BRAZILIAN COHORT OF PATIENTS WITH SSc

P. Sampaio-Barros[1], I. Nascimento[1], L. Seguro[1], A. L. Foelkel[1], A. P. Del-Rio[2] and J. F. Marques-Neto[2]
[1]*University of São Paulo, São Paulo and* [2]*University of Campinas, Campinas, Brazil*

Background/Purpose: Gastrointestinal (GI) involvement is significantly common in patients with SSc, but its frequency according to specific organ (oesophagus, stomach and intestines) is quite variable. The present study analyses the frequency of GI involvement in a large cohort of SSc patients.
Methods. One thousand and six SSc patients attended at the Scleroderma Outpatient Clinic at two referral university centres in Brazil were retrospectively studied. All the patients fulfilled the diagnosis of SSc according to the ACR criteria. Demographics, clinical and imaging data related to TGI involvement were obtained from medical records. Fisher's exact test and chi-square were used to analyse the data; $P < 0.05$ was considered statistically significant.
Results. Among the 1006 SSc patients there was predominance of female gender (88.6%), Caucasians (75.1%) and limited SSc (54.9%). Oesophageal involvement affected 83.5% of the SSc patients; 51.6% referred dysphagia and 62.1% heartburn. The contrasted radiography of oesophagus revealed hypomotility in 57.6% and gastroesophageal reflux in 51.7%. Stomach (9.7%) and intestines (8.9%; 8.4% with malabsorption syndrome, 5.1% with severe constipation, and 2.2% with fecal incontinence) were less common. Among the drugs specific for the GI tract, proton pump inhibitors were prescribed for 68.4% patients, prokinetics for 41.8% and ranitidine for 25.9%.
Conclusion. In this large cohort of SSc patients, oesophageal involvement was very common, although stomach and intestines were rarely involved.

PS113. LOW FREQUENCY OF MALIGNANCIES IN A LARGE BRAZILIAN COHORT OF PATIENTS WITH SSc

P. Sampaio-Barros[1], L. Rocha[1], R. Marangoni[1], A. P. Del Rio[2], N. Yoshinari[1] and J. F. Marques-Neto[2]
[1]*Division of Rheumatology, University of São Paulo, São Paulo and* [2]*Unit of Rheumatology, University of Campinas, Campinas, Brazil*

Background/Purpose. Although some previous studies have demonstrated an increased prevalence of malignancies in SSc, this association is still inconclusive. The present study analyses the frequency of malignancy in a large cohort of SSc patients.
Methods. Nine hundred and one SSc patients attended at the Scleroderma Outpatient Clinic at two referral university centres in Brazil were retrospectively studied. All the patients fulfilled the diagnosis of SSc according to the ACR criteria. Demographics, clinical and laboratory data, as well as the occurrence and site of malignancies, were obtained from medical records. Comparison of covariates by presence or not of malignancies were made by Pearson chi-square; $P < 0.05$ was considered statistically significant.
Results. At least one diagnosis of malignancy was referred by 40 (4.4%) of the 901 SSc patients. They were predominantly females (92.5%), Caucasians (92.5%) and had limited SSc (62.5%). The most frequent sites of malignancies were skin (25%; five basal cell carcinoma and five melanoma), breast (17.5%) and oesophagus (12.5%; two adenocarcinoma associated to Barret's oesophagus, two squamous cell and one Abrikossoff tumour). Other organs were affected although with lower frequency of malignancies: uterine cervix, lymphoma, lung, colon, ovary, thyroid, multiple myeloma, larynx, stomach, liver, kidney, vulva and ear. Patients with malignancies presented a significant association with the Caucasian race ($P = 0.008$) when compared with the SSc patients without malignancy.
Conclusion. In this large series of SSc patients, we found a low frequency of malignancies, predominantly affecting skin, breast and oesophagus. The Caucasian race was significantly associated with SSc-related malignancies.

PS114. ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES IS FREQUENT IN A COHORT OF 901 BRAZILIAN PATIENTS WITH SSc

P. Sampaio-Barros[1], R. Marangoni[1], L. Rocha[1], A. P. Del Rio[2], N. Yoshinari[1] and J.F. Marques-Neto[2]
[1]*Division of Rheumatology, University of São Paulo, São Paulo and* [2]*Unit of Rheumatology, University of Campinas, Campinas, Brazil*

Background/Purpose. Recent studies have pointed out the increased prevalence of autoimmune disorders associated with SSc. The present study describes the prevalence of autoimmune disorders in a large Brazilian cohort of SSc patients.
Methods. Nine hundred and one SSc patients attended at the Scleroderma Outpatient Clinic at two referral university centres in Brazil were retrospectively studied. All the patients fulfilled the diagnosis of SSc according to the ACR criteria. Demographics, clinical and laboratory data were obtained by extent chart review. Comparison of covariates by presence or not of associated autoimmune disease were made by Pearson chi-square; $P < 0.05$ was considered statistically significant.
Results. The association with other autoimmune diseases (AIDs) was present in 27.4% of the SSc patients; 23% presented one AID, 4% two AIDs and 0.4% three AIDs. Thyroiditis (14.7%, predominantly hypothyroidism) and SS (10%) were the most frequent associated AID. Overlap syndromes were diagnosed in 2.3% of the cases (inflammatory myopathy, SLE and RA), and spondyloarthritis was referred by 0.7% patients (four PsA, one AS and one ReA). The frequency of autoimmune liver disorder, ITP, IBD, autoimmune glomerulonephritis, psoriasis and vitilligo was low (<2%). Patients with associated AID had higher frequencies of female gender, lcSSc and ACA than those without associated AID ($P < 0.001$).
Conclusion. In this large series of SSc patients, we found a high frequency of associated autoimmune disorders, especially hypothyroidism and SS. An extended diagnostic screening for associated autoimmune diseases seems reasonable in SSc patients, especially women presenting the lcSSc and ACA.

PS115. CYCLOPHOSPHAMIDE FOR THE TREATMENT OF SKIN INVOLVEMENT IN DIFFUSE SSc

P. Sampaio-Barros[1], A. Bortoluzzo[2], A. P. Del Rio[3], A. Samara[3] and J. F. Marques-Neto[3]
[1]*Division of Rheumatology, University of São Paulo,* [2]*Insper Institute of Education and Research, São Paulo and* [3]*Unit of Rheumatology, University of Campinas, Campinas, Brazil*

Objective. The authors studied the use of CYC for the treatment of skin involvement in patients with early diffuse SSc with no lung, heart or kidney involvement.
Methods. This open, prospective study (1998–2009) analysed the follow-up of 26 adult patients with diffuse SSc, modified Rodnan skin score (mRSS) > 20, <4-year disease duration, and no visceral involvement (lung, heart and/or kidney), who were prescribed monthly i.v. CYC for a period of 12 months. There was predominance of female (73.1%) and Caucasian (57.7%) patients; 34.6% had positive anti-Scl70. The patients were followed during 2 years after the use of CYC.

Results. All the patients completed the 12-month treatment. There was statistical improvement in the mRSS (from $27.2 + 5.8$ to $21.7 + 8.2$; $P < 0.001$). There were no alterations in the mean values of forced vital capacity (FVC) during the treatment. No patients had the diagnosis of severe lung, heart or kidney involvement during the treatment. In the 2-year follow-up, one patient presented a fatal scleroderma renal crisis, and none presented interstitial lung disease or severe heart involvement. Multiple linear regression analysis showed that disease duration was associated with better skin improvement ($P = 0.035$).
Conclusion. These results showed that patients with early diffuse SSc can have benefits with the use of i.v. monthly doses of CYC.

PS116. SURVIVAL, CAUSES OF DEATH AND PROGNOSTIC FACTORS IN SSc: ANALYSIS OF 947 PATIENTS

P. Sampaio-Barros[1], A. Bortoluzzo[2], R. Marangoni[1], L. Rocha[1], A. P. Del Rio[3], A. Samara[3], N. Yoshinari[1] and J. F. Marques-Neto[3]
[1]*Division of Rheumatology, University of São Paulo,* [2]*Insper Institute of Education and Research, São Paulo and* [3]*Unit of Rheumatology, University of Campinas, Campinas, Brazil*

Objective. To analyse survival, prognostic factors and causes of death in a large cohort of patients with SSc.
Methods. During the period 1991–2010, 947 SSc patients were attended at two referral university centres in Brazil. Causes of death were considered SSc-related and non-SSc-related. Survival at 5 and 10 years were estimated using Kaplan–Meier method. Pearson chi-square test, *t*-test and log-rank test were used to identify the prognostic factors.
Results. One hundred and sixty-eight patients died during the follow-up. Among the 110 deaths considered related to SSc, there was predominance of lung (48.1%), heart (24.5%) and kidney (10.9%) involvement. Most of the 58 deaths not related to SSc were caused by infection, cardiovascular or cerebrovascular disease, and cancer. Death was associated with epidemiological [male gender ($P = 0.003$) and diffuse SSc ($P = 0.017$)], clinic [mRSS > 20 ($P = 0.016$), osteoarticular involvement ($P < 0.001$), lung involvement ($P < 0.001$), renal crisis ($P < 0.0001$)] and laboratory [positive anti-Scl70 antibody ($P = 0.087$, trend)] variables. Overall survival rate was 90% for 5 years and 84% for 10 years. Patients with diffuse SSc (85 *vs* 92% at 5 years and 77 *vs* 87% at 10 years, compared with limited SSc), male gender (77 *vs* 90% at 5 years and 64 *vs* 86% at 10 years, compared with female gender), and mRSS > 20 (83 *vs* 90% at 5 years and 66 *vs* 86% at 10 years, compared with mRSS < 20) presented worse prognosis. Caucasian patients presented no significant statistical differences in survival when compared with the African-Brazilians (90 *vs* 89% at 5 years and 84 *vs* 81% at 10 years) ($P = 0.786$).
Conclusions. Survival was worse in male patients with diffuse SSc. Lung and heart involvement were the main causes of death in this series of SSc patients.

PS117. IN SSc PATIENTS THE RECOVERY OF DIGITAL ARTERIES PULSATILITY IS REDUCED AND DYSHOMOGENEOUS AFTER COLD STIMULATION

I. Molinaro[1], E. Rosato[1], S. Pisarri[1] and **F. Salsano**[1]
[1]*Department of Clinical Medicine, Clinical Immunology Unit, Sapienza University of Rome, Scleroderma Center, Rome, Italy*

SSc is typically associated with RP. Microvascular involvement is a hallmark of SSc. Macrovascular involvement is not well documented in SSc. Aim of the study is to evaluate in patients with primary RP (PRP) and SSc digital arteries pulsatility at baseline and after cold stimulation (CS).
Seventy-six SSc patients [72 females and 4 males; mean age 51 (11) years], 72 PRP patients [68 females and 4 males; mean age 42 (16) years] and 68 healthy controls [63 females and 5 males; mean age 48 (10) years] were enrolled in this study. In all patients and healthy controls, photoplethysmography (PPG) was made at baseline and after CS by Termoflow machine (Microlab Elettronica Sas, Pordenone, Italy). The CS was performed using a box, cooled and ventilated, at temperature of 4°C. Participants underwent CS by placing their hands in box (4°C) for 5 min. PPG curves were recorded for 10 min after CS. The acquired photoplethysmographic curves are evaluated for morphology and amplitude of sphygmic wave. A homogeneous pattern was defined as a pattern showing uniformity of morphology and amplitude of sphygmic wave in all then fingers. A dyshomogeneous pattern was characterized by morphology different in two or more fingers of each hand with mean variation of sphygmic wave

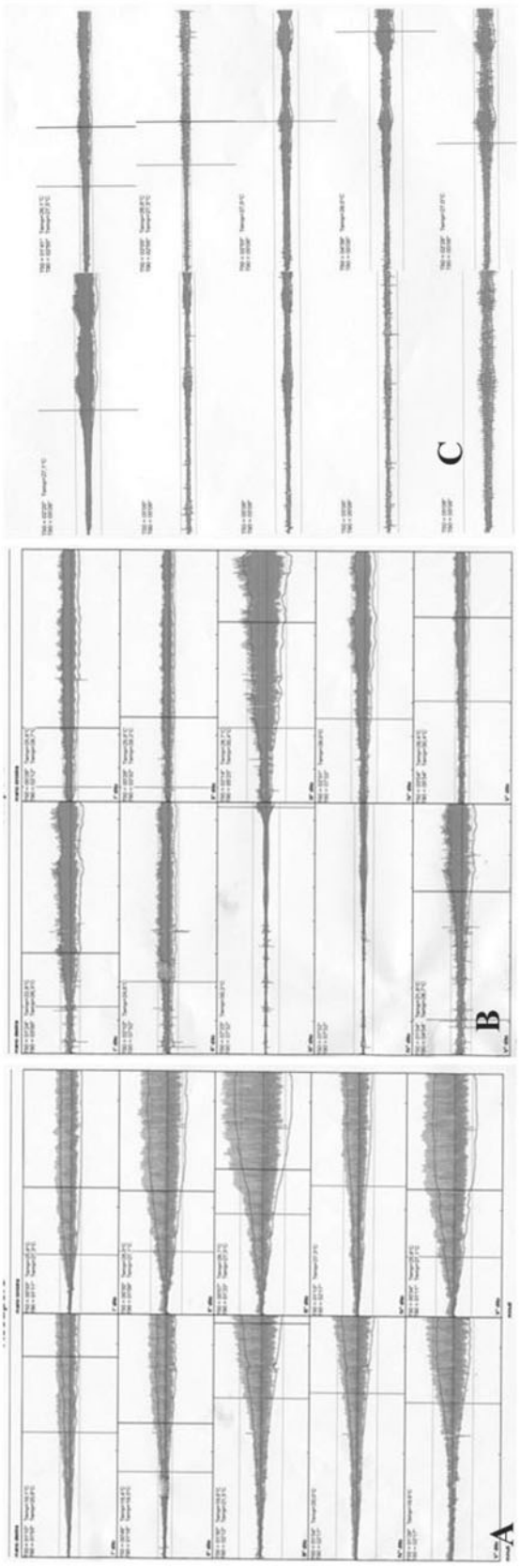


Fig. 1 Photoplethysmographic curves. (**A**) Healthy controls; (**B**) SSc patients; (**C**) primary RP patients.

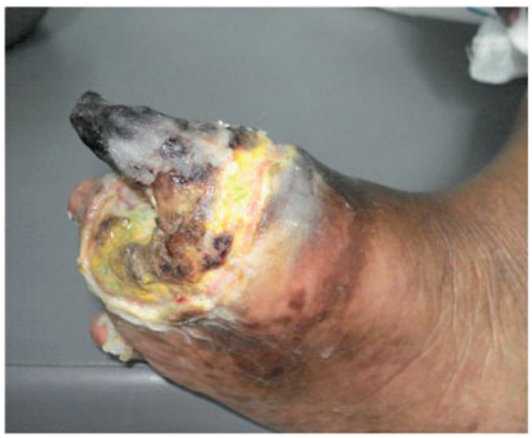
amplitude > 15% in two or more fingers of each hand. The magnitude of sphygmic wave was expressed as percentage of maximum value of sphygmic wave amplitude.
Mean value of sphygmic wave amplitude is lower ($P < 0.0001$) in the PRP group than in SSc group [10 (11) *vs* 23 (19)]. Mean value of sphygmic wave amplitude is lower ($P < 0.0001$) in the SSc group than in healthy controls [23 (19) *vs* 58 (17)]. PPG showed a homogeneous pattern in the 97% of healthy controls, 95% of PRP and 24% of SSc patients. In healthy controls, recovery of digital arteries pulsatility is complete (no significant difference from baseline value of sphygmic wave amplitude) and homogeneous (same morphology in all then fingers) after CS. In PRP patient recovery is absent and homogenous. In all SSc patients the recovery is incomplete and dyshomogeneous (Fig. 1).
We can conclude that digital arteries pulsatility is reduced both for variable degree of vasospasm both structural segmental lesions in the distal vessels.

PS118. SSc WITH EXTENT NECROSIS AND LOST OF PART OF THE FOOT—A CASE REPORT

M. Salgado[1], F. Brandão[1], L. Theilacker[1], G. Aredes[1], F. Freire[1], J. Vaz[1], R. Oliveira[1] and A. Silva[1]
[1]*Federal University of Rio de Janeiro State, Rio de Janeiro, Brazil*

Introduction. The vascular involvement in 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, RP, 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 loss 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 SSc since 1998. Clinical findings were: RP, digital ulcers, claw-like hands, acrosteolisis of fingers and toes. During February 2009 she developed an enormous ulceration with gangrene of the first, second and third right toe, covering the distal extremity of the right foot. We referred her to surgery for debridement. She was taking the follow medicaments: captopril, cilostazol, low-dose prednisone (5 mg/day), pentoxifylline, nifedipine and aspirin 100 mg/day. Sildenafil 50 mg/day and bosentan was added to it, but irregularly and for short time. Since September 2010 she had regular use of bosentan, initially at a dose of 62.25 mg 12/12 h for 4 weeks, increasing to 125 mg 12/12 h, with gradual improvement, but maintaining open sore, with smaller diameter and granulation tissue.
Discussion. Digital ulcers are more frequentely described in hands than feet. It is not common that so large a lesion like this is observed in the patient. New forms of treatment such as phosphodiesterase-V inhibitors and endothelin receptor blockers have proven effective in patients with ischaemia of the extremities as a manifestation of SSc.
Conclusion. Ischaemic 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.

Fig. 1



PS119. PREVALENCE OF PULMONARY HYPERTENSION IN SSc: CORRELATION WITH CLINICAL FORM

M. Salgado[1], L. Madeira[1], L. Theilacker[1], F. Brandão[1], J. Vaz[1] and F. Freire[1]
[1]*Federal University of Rio de Janeiro State, Rio de Janeiro, Brazil*

This study analysed the prevalence of pulmonary arterial hypertension (PAH) in a cohort of patients with 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. Forty-four patients were included during 2 years. The diagnosis of PAH was considered when measurement of pulmonary artery systolic pressure (PASP) was >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 no 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 did not observe significant difference in prevalence and symptoms between limited and diffuse form of SSc.

PS120. LIVING WITH CONNECTIVE TISSUE RELATED INTERSTITIAL LUNG DISEASE: PATIENT EXPERIENCES OF THE DISEASE PROCESS OVER TIME

S. Mittoo[1], **L. Saketkoo**[2], J. Swigris[3], D. LeSage[4], A. Fischer[3] and S. Frankel[5]
[1]*Department of Rheumatology, University of Toronto, Toronto, Canada,* [2]*Louisiana State University Scleroderma and Sarcoidosis Patient Care and Research Center, New Orleans,* [3]*National Jewish Health, Interstitial Lung Disease Program, Denver,* [4]*New Orleans Office of Public Health, New Orleans, USA and* [5]*University of Manitoba, Winnipeg, Canada*

Background. Very limited information is available about the patient experience of CTD-related interstitial lung disease (CTD-ILD), in terms of global effects on functioning in psychological and social spheres or of the patients' approaches to coping with the disease and secondary problems related to it. Such information from the patients' perspective would be useful in informing clinical practice and in developing patient reported outcome measures.
Methods. Data were collected through a focus group interview, involving nine patients. After IRB approval, a purposeful sample was recruited from a tertiary-referral hospital in Manitoba, Canada. Inclusion criteria involved English-speaking adults with a diagnosis of ILD based on at least one of: histology, chest imaging, presence of shortness of breath or cough, restrictive pulmonary physiology and/or impaired DL_{CO}, resting or exertion-related peripheral oxygen desaturation. Patients with pulmonary hypertension or hypersensitivity pneumonitis were excluded. The interview schedule included two questions ('How have you experienced your disease since the diagnosis of ILD?', 'How has the disease changed?'), and the moderator used the WHO-100 domains to develop prompts to insure comprehensiveness. Data were analysed through inductive development of analyst-constructed themes. Thematic structures of two independent analysts were triangulated.
Results. Of the nine participants, eight were females and eight were Caucasian. Mean age was 53.56 (S.D. = 16.02); four out of eight were smokers. CTD sub-types were: idiopathic inflammatory myositis, RA, scleroderma and UCTD; one had an overlap of scleroderma and lupus. Five were SSc or SSc overlap.
Three main themes emerged:

(i) Living with uncertainty in a marginal situation. Uncertainty flowed from areas of confusion between patients and physicians related to diagnosis, evaluation, prognosis and therapeutic plan. Communication seemed to stagnate after diagnosis. Future disease course and origin of current symptoms were not easily delineated.
(ii) Struggle over the new self, maintaining an autonomous voice and resisting social/family pressures to relinquish normal roles.

Parenting and grand-parenting roles were especially important to participants.
(iii) Development of resilience through coping skills. These skills allowed patients to manage their situation and were empowering.

Conclusion. This is the first known effort to report qualify of life-related outcomes (patient experience) in this population. These findings hold important implications for physicians related to enhancing and continuing communication, supporting competence and reinforcing coping. Communication protocols might be developed, and advice given on how patients might maintain as many normal roles as possible. Patients developed coping skills might be studied to identify their effectiveness.

PS121. IN SSc PATIENTS WITH ERECTILE DYSFUNCTION THE ARTERIAL INFLOW OF CAVERNOUS ARTERIES CORRELATES WITH SKIN PERFUSION AND DIGITAL ARTERIES PULSATILITY OF HANDS

E. Rosato[1], I. Molinaro[1], A. Aversa[2], S. Pisarri[1] and F. Salsano[1]
[1]*Department of Clinical Medicine, Clinical Immunology Unit and* [2]*Dipartimento Fisiopatologia Medica, Cattedra di Medicina Interna, Sapienza University of Rome, Rome, Italy*

The prevalence of erectile dysfunction (ED) in men with SSc can be considered a manifestation of endothelium damage. Aim of the study is to evaluate in SSc patients with ED Doppler ultrasound parameters with mean perfusion of hands and digital arteries pulsatility, evaluated, respectively, by laser Doppler perfusion imaging (LDPI) and photoplethysmography (PPG).
In 11 males, SSc patients [median age 48.7 (range 34–68) years] ED was evaluated by Sexual Health Inventory for Men (SHIM). Blood flow velocity in the cavernous artery was determined with Duplex ultrasonography. Arteriogenic ED was defined by the presence of a reduced peak systolic velocity (PSV), while diastolic velocity (EDV) and the resistive index (RI) were estimated to evaluate venocclusive dysfunction. A baseline skin blood flow determination of the dorsum of the subject's hands was acquired through a low-energy 670-nm Lisca Laser Doppler Perfusion Imager. A baseline PPG was recorded simultaneously in all 10 fingers of the hands.
In all SSc patients, a reduction of SHIM is present [median 13.5 (6.3)]. Nine SSc patients showed a reduction of PSV (normal values >30 cm/s) and four patients showed an increase of EDV (normal values <5 cm/s). In all SSc patients, the median value of PSV and EDV were, respectively, 19 (range 9–30) and 5 (range 0–8). A significant correlation ($P = 0.01$) was observed between PSV and skin perfusion (Spearman's rank order correlation $= 0.711$). No significant correlation was observed between venocclusive dysfunction (EDV and IR) and skin perfusion. A significant correlation ($P = 0.01$) was observed between PSV and digital arteries pulsatility (Spearman's rank order correlation $= 0.721$). No significant correlation was observed between venocclusive dysfunction (EDV and IR) and digital arteries pulsatility.
We can suppose that there is a relationship between arterial inflow of cavernous arteries and digital arteries pulsatility and skin perfusion of hands.

PS122. CARDIAC ARREST AS THE FIRST NON-CUTANEOUS MANIFESTATION OF SSc

A. Rodrigues[1], J. Mouta[2], J. Silva[1], M. J. Oliveira[1], B. Lima[3], A. Grilo[1], N. Riso[1] and M. V. Riscado[1]
[1]*Department of Internal Medicine, Hospital Curry Cabral,* [2]*Department of Oncology, Instituto Portugues de Oncologia Francisco Gentil and* [3]*Department of Infectious Diseases, Hospital Curry Cabral, Lisbon, Portugal*

Introduction. SSc is characterized by vascular lesions and fibrosis of the skin and major organ systems including the cardiac system. Heart involvement in SSc can be primary or secondary to systemic or pulmonary hypertension and predicts a poor prognosis. We report a case of SSc in female that had a cardiac arrest as primary manifestation of her heart disease.
Case Report. A 21-year-old female is admitted to a cardiology ward after cardiac arrest during physical exertion in the gym. She was assisted at the site where basic life support was initiated. She was then taken to the nearest emergency department where cardiac monitoring showed ventricular fibrillation. Electric cardioversion was performed and she converted to normal sinus rhythm. Electrophysiological study showed induction of ventricular tachycardia with haemodynamic instability. Coronariography was normal and left ventriculography showed good systolic function with apical hypokynesia. Given these results, a cardioverter defibrillator VVI was placed. Two years before this event, a diagnosis of SSc was made based on severe RP with critical finger ischaemia needing IV iloprost, proximal skin fibrosis and positivity for anti-topo-I antibody. She had no other symptoms to date and previous complementary evaluation was negative for heart, lung, kidney or gut involvement. She was medicated with prednisolone, penicillamine and nifedipine for this condition.
Discussion. Primary cardiac involvement is SSc can manifest as myocardial or pericardial disease, conduction abnormalities or arrhythmias. Although very common at autopsy, heart involvement can be clinically silent. Pathogenesis is multifactorial and seems to be secondary to inflammation, fibrosis and vasculopathy. Fibrosis can lead to re-entrant circuits, which can be the substrate for tachyarrhythmias (supraventricular or ventricular, as in the case presented). Cardioverter-defibrillator is of major importance in this setting, helping to prevent further events of ventricular tachycardia or ventricular fibrillation, which are believed to be a major cause of sudden death in SSc. We assumed in the case presented that the ventricular arrhythmia was secondary to heart involvement by SSc, although it was not confirmed by biopsy. Although cardiac involvement is a common complication of SSc, ventricular arrhythmia as the first manifestation other than skin fibrosis or Raynaud is infrequent, which makes this case of particular interest.

PS123. NAIL-FOLD VIDEOCAPILLAROSCOPY SURVEY ON THE EFFICACY OF DIFFERENT PHARMACOLOGICAL TREATMENTS IN PATIENTS WITH SECONDARY RP

V. Riccieri[1], I. Sciarra[1], K. Stefanantoni[1], N. Iannace[1], D. D'Aluisio[1], M. Vasile[1] and G. Valesini[1]
[1]*Department of Internal Medicine and Medical Specialities, University Sapienza of Rome, Rome, Italy*

Aim of the study: Nail-fold videocapillaroscopy (NVC) is a non-invasive technique able to evaluate microvascular abnormalities in different diseases. The early detection of these abnormalities as well as their early treatment may allow a regression of the vascular damage.
Thus we present three patients with secondary RP, all showing significant NVC changes during the course of different pharmacological therapies.
Case no. 1: B.S., 56-year-old woman, complaining for RP since 15 years. On clinical examination: sclerodactily, oesophageal reflux, telangiectasias. ANA positivity with an anti-centromere pattern. Diagnosis: CREST syndrome.
She performed NVC showing an 'early' scleroderma pattern, with rare megacapillaries, microhaemorrages, an irregular distribution but still a normal number of the capillary loops.
On December 2006 she started therapy with i.v. prostacycline (0.5–2 ng/kg/min for 6 h) for 3 days a month and nifedipine 20 mg daily.
On June 2007 RP improved and her NVC too, presenting minimal aspecific changes with no megacapillary, no microhaemorrages and a regular distribution of the capillary array.
Case no. 2: P.L., 58-year-old woman, RP since 6 years before. On clinical examination: 'puffy fingers', oesophageal reflux. ANA positivity with anti-centromere pattern.
On NVC evident non-specific changes were found, with microhaemorragies, tortuous and ectasic capillary loops, with a reduced capillary density.
On March 2008 she started oral therapy with nifedipine, 30 mg daily.
On March 2009 there was an improvement of RP while her NVC was within normal range with no microhaemorrages, regular distribution and normal number of the capillary loops.
Case no. 3: P.G., 22-year-old woman, RP since few months before. A familial history of autoimmune diseases (grandmother affected by SSc) and ANA positivity with a homogeneous pattern were observed.
She showed an 'active' scleroderma pattern on NVC with frequent megacapillaries, microhaemorrages, reduced number and irregular distribution of the capillary loops (Fig. 1a).
On March 2009 she started oral therapy with pentoxifilline 400 mg twice a day.
On September 2009 her RP was under full control and the NVC showed aspecific evident abnormalities such as microhaemorrages, diffuse ectasias, irregular distribution but no megacapillaries and a normal number of capillary loops (Fig. 1b).
Conclusion. Our three cases demonstrated that, even in those patients assuming vasodilator therapies only, the good clinical effect matches a NVC improvement of the undergoing microangiopathy, independently from the diagnosis. Thus, NVC should be considered a

Fig. 1 (**a**) Patient no. 3: NVC of the 4° finger right hand at the first visit (basal). (**b**) Patient no. 3: NVC of the 4° finger right hand after 6-month therapy.

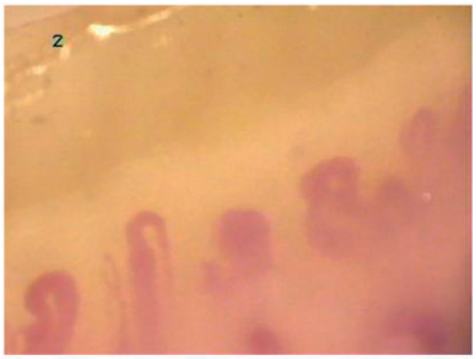


Fig.1a: pts. N°3 – NVC of the 4° finger right hand at the first visit (basal)

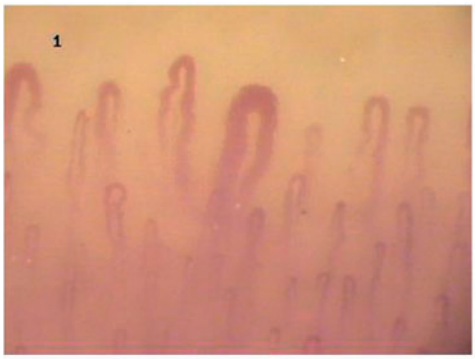


Fig.1b: pts. N°3 – NVC of the 4° finger right hand after six month therapy

sensible instrument not only for the diagnosis but also for the evaluation and follow-up of patients during treatment.

PS124. COLOUR DOPPLER ULTRASONOGRAPHY OF FINGER ARTERIES IN RP

N. Rednic[1], C. Pamfil[2], A. Petcu[2] and S. Rednic[2]
[1]*Medical Clinic IV and* [2]*Department of Rheumatology, University of Medicine and Pharmacy Iuliu Hatieganu, Cluj, Romania*

RP is usually classified either as primary, generally benign, occurring in patients without any underlying disease or as secondary, occurring in patients with arterial occlusions or with CTDs such as SSc, or SLE.
In the last decade, many studies proved the success of colour Doppler ultrasonography in revealing small vessels in fingers. Indeed, the new high-frequency probes allow the rheumatologist to visualize hand and finger arteries: the ulnar and radial artery, the superficial and the deep palmar arch, the common and the proper digital arteries and the nailbed and fingertip arteries.
Looking at patients with primary Raynaud's, secondary Raynaud's and healthy controls the value of colour Doppler US method can be evaluated for the positive and differential diagnosis of RP.
At room temperature, healthy subjects and primary Raynaud's patients present normal arteries, but secondary Raynaud's patients express a reduction of the vascular density into the nail bed and fingertip and narrowing of the digital arteries, chronic or acute occlusions. Cold provocation test and recovery after cold exposure offers useful information. The measurements of the diameter, resistivity index and flow volume of the digital arteries, before and after cold provocation, are different in healthy controls, primary and secondary Raynaud's patients. Analysing dynamic changes during recovery after cold exposure allows further differentiation. The flow starting time in the digital artery and the flow normalizing time are different in these patients
The colour Doppler ultrasound, gains increasing recognition as a method for visualization and quantification of digital artery disease. It is a simple non-invasive technique that quickly provides useful information to discriminate normal subjects, primary and secondary Raynaud's patients.

PS125. SUCCESSFUL TREATMENT OF SEVERE DIFFUSE CUTANEOUS SSc USING RITUXIMAB: A CASE REPORT

D. Martinovic Kaliterna[1], M. Radic[1], D. Perkovic[1] and D. Krstulovic Marasovic[1]
[1]*Department of Rheumatology and Clinical Immunology, University Hospital Split, Split, Croatia*

Rituximab has been successfully used in the treatment of several rheumatic diseases with an acceptable safety profile. Recent pre-clinical and clinical studies lend support to the notion that B-cell depletion is a promising therapeutic target in patients with dcSSc.
We present herein the dSSc patient associated with severe PM who exhibited significant improvement of his muscle function and skin fibrosis following rituximab administration.

Our patient, a 50-year old woman with severe dSSc-associated PM, received two courses of RTX. She was diagnosed as dSSc according to ACR criteria associated with severe PM. PM was diagnosed on the basis of proximal muscle weakness, elevated creatinine kinase (CK) levels of >14 000 U/l, electromyography features and characteristic histological findings on muscle biopsy. Prior to rituximab therapy she was receiving CS combined with MTX or i.v. immunoglobulins without any clinical or laboratory improvement. Since no improvement of the CK levels was observed after CSs with several immunosuppressants, we administered rituximab (1 g 2 weeks apart). She had a good symptomatic improvement, her CK levels fell dramatically from 4000 U/l to 1160 U/l. Skin thickening assessed clinically improved as well. The patient's total skin score improved; modified Rodnan skin score was 14, respectively, compared with 21 of pre-treatment value.
In this case report, we report the successful use of anti-CD20 therapy in patient with refractory dSSc-associated PM who did not respond to conventional therapy.
Several lines of evidence suggest that B-cells may have a pathogenic role in dSSc. B-cells from tight skin mice, an animal model of SSc, exhibit chronic hyperactivity; likewise, B-cells from patients with dSSc overexpress CD19 and are chronically activated. Furthermore, studies have revealed that B-cell genes were specifically transcribed in dSSc skin and that B-cell infiltration was a prominent feature of SSc-associated PM. The potential clinical efficacy of rituximab in dSSc has been explored in a limited number of patients with encouraging results. Preliminary data suggest that rituximab may favourably affect skin as well as PM in dSSc. The clinical improvement of both skin changes and PM after rituximab may indirectly confirm the role of B-cells in the pathogenesis of dSSc, although the mechanisms of action of this drug in immunological disorders remain to be elucidated.

PS126. DEPRESSION AND ANXIETY IN SSc *VS* SYSTEMIC LUPUS ERYTHEMATOSUS: A CROSS-SECTIONAL STUDY

D. Martinovic Kaliterna[1], M. Radic[1], D. Britvic[2] and J. Morovic Vergles[3]
[1]*Department of Rheumatology and Clinical Immnulogy,* [2]*Department of Psychiatry, University Hospital Split, Split and* [3]*Department of Rheumatology and Clinical Immunology, Dubrava University Hospital, Zagreb, Zagreb, Croatia*

Objective. To examine the frequency and reliability of depression and anxiety in patients with SSc and SLE. Symptoms of depression are common among patients with SSc. The current and lifetime prevalence of major depression and anxiety disorders is high in SSc patients, especially during hospitalization. The cause of psychiatric syndromes in SLE patients is mutifactorial and includes primary immunopathogenic mechanisms, non-specific sequelae of chronic disease and concurrent illnesses. The high rates of depression and anxiety reported across studies with SSc or SLE patients suggest that routine screening is recommended. Depression and anxiety are common in SSc and SLE patients.
Methods. We conducted a cross-sectional study of 43 SSc and SLE patients. Forty-three patients with SSc were matched by age and sex to 43 patients with SLE attending ambulatory clinics in a single

academic medical centre. All fulfilled the ACR classification criteria for either SSc or SLE. Anxiety and depression levels were assessed with the Beck Depression Inventory and Beck Anxiety Inventory. Health-related quality of life (HRQOL) was evaluated by the SF-36.
Results. The patients were well matched with regard to age, sex and disease duration. There were no significant differences in self-reported HRQOL, anxiety and depression symptoms between these two groups. In linear regression depression was correlated to disease duration ($P < 0.05$) and to disease activity ($P < 0.01$).
Conclusion. Psychiatric syndromes such as depression and anxiety regardless of aetiology are common in both SSc and SLE patients. In our study, there were significant correlations between scores of depression and disease severity and disease activity in SSc patients. Depression and anxiety in SLE patients may represent global changes in the central nervous system that require ongoing evaluation and treatment. Screening for depression among patients with SSc or SLE is recommended and it should be assessed for routinely.

PS127. IS *HELICOBACTER PYLORI* INFECTION A RISK FACTOR FOR DISEASE SEVERITY IN SSc?

M. Radic[1], D. MartinovicKaliterna[1], D. Bonacin[2], J. Morovic Vergles[3], J. Radic[4], D. Fabijanic[5] and V. Kovacic[4]
[1]*Department of Rheumatology and Clinical Immnulogy,* [2]*Department of Gastroenterology, University Hospital Split, Split,* [3]*Department of Rheumatology and Clinical Immunology, Dubrava University Hospital, Zagreb,* [4]*Department of Nephrology and* [5]*Department of Cardiology, University Hospital Split, Split, Croatia*

Background. *Helicobacter pylori* is suspected to be one of the factors triggering SSc. Data on the possible role of *H. pylori* are lacking.
Objective. The aim of this study was to assess the effect of *H. pylori* eradication in SSc patients.
Methods. Forty-two SSc patients without dyspeptic symptoms were recruited—26 were *H. pylori* positive and 16 were *H. pylori* negative on the basis of invasive test. We evaluated the disease severity using clinical and laboratory parameters according to the Medsger severity scale. The level of SSc activity was evaluated according to Valentini activity score.
Results. The prevalence of *H. pylori* infection in population of SSc patients is 62%. Severity of skin, gastrointestinal and joint/tendon involvement were different between *H. pylori*-positive and -negative SSc patients ($P < 0.001$ for skin involvement, $P = 0.002$ and $P = 0.03$ for gasterointestinal and joint/tendon involvement, respectively) as well as ESR ($P = 0.002$). Severity score according to Medsger was higher in the *H. pylori*-positive than in the *H. pylori*-negative SSc patients ($P < 0.001$).
Conclusion. Our data suggest that *H. pylori* infection correlates with severity of skin, gastrointestinal and joint/tendon involvement in SSc patients. *H. pylori*-positive SSc patients showed higher severity score compared with *H. pylori* negative. Therefore, *H. pylori* infection may play a role in the pathogenesis of SSc and also can provide some prognostic information.

PS128. EFFECTS OF CILOSTAZOL ON RP IN SCLERODERMA PATIENTS

S. Negrini[1], F. Spano'[1], G. Filaci[1] and **F. Puppo**[1]
[1]*Department of Internal Medicine, University of Genoa, Genoa, Italy*

Introduction. SSc is a complex systemic disease characterized by immune dysregulation, wide-spread fibrosis and extensive vascular damage. RP, the earliest manifestation of the vascular involvement, is due to an excessive vasospasm secondary to an altered blood flow response to cold challenge or other stimuli. Management of RP focuses on avoiding triggers (i.e. cold, smoke, emotional stress, drugs causing vasoconstriction) and on medications that dilate the blood vessels, such as calcium channel blockers, angiotensin II receptor antagonists, α-1 adrenergic blockers, nitroglycerin and synthetic analogues of prostacyclin. Nonetheless, available therapies are often modestly effective and associated with frequent side effects. In addition, many of the agents used in the treatment of RP are used off-label and no guidelines have been published for the therapy of RP. Cilostazol is a selective phosphodiesterase 3 (PDE3) inhibitor approved worldwide for the treatment of intermittent claudication. Cilostazol inhibits PDE3 and increases the concentration of cyclic AMP in several cells and causes pleiotropic actions such as inhibition of platelet activation, vasodilation, anti-proliferation of vascular smooth muscle cells and improvement of endothelial cell functions.
Methods. Twenty patients with SSc and moderate-to-severe RP were enrolled in this study to evaluate the efficacy of cilostazol to decrease the duration and number of RF episodes. The prescribed dose was 100 mg of cilostazol twice a day. Patients were asked to complete: (i) a specific daily diary for the frequency and duration of RP attacks; (ii) HAQ; (iii) three different scleroderma-specific visual analogue scales (VAS) for RP, disease activity, digital ulcers (DUs). The study length was 1 year.
Results. Cilostazol significantly reduced the duration (total weekly length and daily mean length, Wilcoxon test $P = 0.0284$ and $P = 0.0283$, respectively) and the number (total weekly number and daily mean number, Wilcoxon test $P = 0.0380$ and $P = 0.0380$, respectively) of RP attacks. The difficulty that patients experienced with RP was reduced by the treatment (Wilcoxon test $P = 0.0422$). Disability evaluated by the HAQ was generally modest (mean 6/60) and was not influenced by the treatment. Cilostazol significantly improved the VAS score related to RP (Wilcoxon test $P = 0.0422$), while disease activity was not influenced. None of the patients presented DU at enrolment or developed DU during the study. Side effects were relatively common but not severe; among these headache and palpitations were the most common.
Conclusions. This study shows that there is clear evidence in favour of cilostazol to treat RP secondary to SSc.

PS129. ULTRASOUND EXAMINATION OF MEDIAN NERVE IN SSc PATIENTS

S. Prodanovic[1], G. R. [1], N. P. [1], N. D. [1], M. Z. [1], K. S.P. [1], D. M. [1] and N. G. [1]
[1]*Institute of Rheumatology, Belgrade, Serbia*

Objectives. to assess median nerve (MN) dimension in SSc patients using US of hand.
Methods. Thirty-six in-SSc patients [35 females and 1 male, mean age 55 (10.6) years, mean duration of SSc 60 (12.7) month] and 20 healthy controls (19 females and 1 male, mean age 52 (5.3) years] were included. US examination was performed using GE 9 machine with 14 MHz linear probe. Circumference of MN (CMN) as it enters carpal canal was assessed of both hands. Dimension of each MN was assessed three times and mean value was further analysed. Values >13 mm were considered pathological. Thickening of skin around wrists was estimated by an independent examiner and assessed as normal and sclerodermal type. A presence of wrist arthritis and tenosynovitis (estimated by US) as well as numbness in hand fingers was also noted. The results were statistically processed in the SPSS system.
Results. The mean value of CMN on the right hand was 19.99 mm and on the left 19.19 mm in SSc patients. Pathological values of MN was found in all patients on both hands. The mean value CMN on the right hand was 11.7 mm and on the left 11.5 mm in healthy controls. Twenty-one patients (58.3%) had diffuse SSc. Thickening of the skin around the wrists, were observed in 33.3% of the patients. Using US arthritis was found in three and tenosynovitis of hand flexors in one patient. Feeling of numbness in either right or left hand had 36.1% of patients. There was statistically significant difference in MN dimensions between SSc patients and healthy controls ($P < 0.05$). There was no statistically significant difference in MN dimensions between patients with feeling of numbness and without it ($P > 0.05$).
Conclusion. In all analysed SSc patients, dimensions of MN estimated by US examination, were pathological and significantly higher than in healthy controls.The findings were asymptomatic, but most of them had severe form of disease.
The further study, with higher number of patients, are needed to show importance of our results.

PS130. CORRELATION BETWEEN MEDIAN NERVE DIMENSION BY ECHOSONOGRAPHY AND CAPILLAROSCOPY IN PATIENTS WITH SSc

S. Prodanovic[1], G. R. [1], N. P. [1], N. D. [1], M. Z. [1], K. S.P. [1], D. M. [1] and N. G. [1]
[1]*Institute of Rheumatology, Belgrade, Serbia*

Objective. To perform ultrasonographyc assessment of median nerve (MN) dimension as it enters carpal canal in SSc patients and to correlate its dimensions with capillaroscopy finding.
Method. Thirty-six in-SSc patients, [35 women, mean age 55 (10.66) years] and 20 healthy controls [19 females, mean age 52 (5.3) years] were included. US examination was performed using GE machine with 14 MHz linear probe. Circumference of median nerve (CMN) as it

enters carpal canal was assessed of both hands. Dimension of each MN was assessed three times and mean value was further analysed. Values >13 mm were considered pathological. Capillaroscopy was done using optical microscope and findings have been described according to Maricq and Cutolo. The results were statistically processed in the SPSS system.
Results. The mean value of CMN on the right hand was 19.99 mm and on the left 19.19 mm in SSc patients. Pathological values of MN had all the patients on both hands in this group. The mean value CMN on the right hand was 11.7 mm and on the left 11.5 mm in healthy controls. Sixteen SSc patients had type IV on capillaroscopy, 12 had type III, 6 had type II and 2 patients had type I on capillaroscopy. There was statistically significant difference in dimensions of MN between SSc patients and healthy controls ($P < 0.05$) There was statistically significant positive correlation between dimensions of MN and severity of capillary distraction in group of examined SSc patients ($r = 0.571$, $P < 0.001$).
Conclusion. In our study, dimensions of MN estimated by echosonography were pathological in all SSc and significantly higher patients compared with controls. Patients with greater dimensions of MN by ultrasonography had more severe microangiopathy changes. The further study with higher number of patients is needed to confirm these results.

PS131. CYTOKINES PANEL IN EXHALED BREATH CONDENSATE IN SSc

M. Mantero[1], S. Aliberti[1], G. Erba[2], E. Allevi[2], M. Ricci[2], S. Galbiati[3], B. Dallari[3], N. Sverzellati[4], A. Pesci[1] and **M. Pozzi**[2]
[1]*Clinica Pneumologica,* [2]*Clinica Medica – SS Reumatologia, AO San Gerardo, Università Milano Bicocca, Monza,* [3]*Dipartimento Malattie Apparato Respiratorio, IRCCS Ospedale Maggiore Policlinico, Università Statale, Milan and* [4]*Dipartimento Scienze Cliniche, Parma, Università di Parma, Italy*

Rationale: The leading causes of mortality in SSc are pulmonary hypertension and pulmonary fibrosis, the latter diagnosed on pulmonary function tests (PFTs) and high-resolution CT (HRCT). Outcome is heterogeneous and few patients develop rapidly progressive lung damage. There are no surrogate biomarkers of alveolitis activity for prognosis and monitoring the therapy efficacy. Dosage of cytokines in bronchoalveolar lavage requires an invasive technique, not suitable in everyday clinical practice. Measurement of inflammatory markers in EBC, a non-invasive technique, could overcome this problem.
Methods. Thirty-two subjects (27 females, 5 males) with SSc, fulfilling ACR criteria, 20 dSSC and 12 lSSc, were enrolled. Mean age was 62.5 (59–73) years, mean disease duration 11.9 (10.43) years, mean skin score (mRSS) 15.06 (8.81). Group A pulmonary fibrosis (16 patients), Group B no lung fibrosis (16 patients). PFT, HRCT, echocardiogram and collection of EBC were performed. An expert radiologist scored extension of lung fibrosis on HRCT. Cytokines IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, INF-γ, EGF, MCP1, TNF-α were measured in EBC using the biochip Kit RANDOX cytokine high-sensivity array (CTK-HS) in patients and in a control group (10 healthy people).
Results. In Group A, 12 patients had NSIP, 4 UIP pattern at HRCT. Association of lung fibrosis with Scl70 is confirmed (69% of Group A, 19% of Group B).We found worst skin involvement in lung fibrosis (mRSS 18 Group A, 11.5 Group B, $P = 0.04$), lower DL_{CO} in patients Scl70+, 56% (IQR 32–77%) *vs* 70% (IQR 60–86%), $P = 0.06$. FVC values had an inverse correlation with lung damage extension ($r = -0.77$, $P < 0.0001$). We did not find different levels of any cytokines between the two groups, neither with respect to controls. No single cytokine correlated with lung functional test or fibrosis extension. Nevertheless, Th1/Th2 cytokine ratio was significantly different in SSc patients *vs* controls but there was no difference between Group A and Group B. Both INF-γ/IL-4 and TNF-α/IL-4 ratios were higher in controls *vs* Group A ($P = 0.04$,-$P = 0.03$, respectively) and Group B ($P = 0.04$, $P = 0.05$, respectively). IL-2/IL-10 value correlated with FVC in Group A ($r^2 = 0.438$; $P = 0.02$) and Group A plus Group B ($r^2 = 0.418$, $P = 0.03$).
Conclusion. We confirmed the relevance of prognostic factors for interstitial lung involvement in SSc (Scl70, mRSS) and the correlation between PFT and extension of radiological lesions. We did not find any distinctive cytokine pattern in SSc patients with ILD, maybe due to the small number of patients and to immunosuppressive therapy. Different cytokine ratios between controls and patients, but not between the two groups, seem to suggest the presence of subclinical imbalance of inflammatory cascade in the lungs of SSc patients without ILD. The prospective dosage of a panel of cytokines in EBC at diagnosis and in the follow-up could clarify the real role of this non-invasive technique in the prediction of respiratory complication in SSc.

PS132. PHOSPHODIESTERASE INHIBITORS IN THE TREATMENT OF VASCULAR DYSFUNCTION IN PATIENTS WITH COLLAGEN VASCULAR DISEASES

M. Popescu[1], C. Tanaseanu[1], S. Tanaseanu[2], A. Dumitrascu[1], I. Tiglea[1], E. Moldoveanu[3] and D. Marta[3]
[1]*Umf Carol Davila, Sf Pantelimon Emergency Hospital,* [2]*N Gh Lupu Hospital, Bucharest, Romania and* [3]*Victor Babes Institute, Bucharest, Romania*

Background. Phosphodiesterase (PDE) inhibitors are enzymes that degrade cellular cAMP and cGMP and are essential for regulating the cyclic nucleotides. Several reports support a role of cAMP in atherogenesis (vascular inflammations) by modulating endothelial functions, productions of reactive oxygen species, controlling the expression of pro-inflammatory molecules, expression of metalloproteinases. Progressive widespread vascular dysfunction is mentioned as one important initiating step in pathogenesis and evolution of collagen vascular disease, some of these diseases being associated with accelerated atherosclerosis.
Aim: The aim was to asses the clinical and biological improvement in vascular function due to PDE inhibition, in patients with SLE and SSc, optimally treated for their diseases.
Material and methods. The study patients were 10 patients with SSc (ARA criteria) without pulmonary hypertension, 10 patients with SLE (ARA criteria) and 5 healthy subjects.They were optimally treated for each disease according to European guidelines and also they received pentoxifilin 1000–1500 mg (i.v. 7 days and oral 1 month).
The established parameters to be measured were: intima–media thickness (IMT) by vascular ultrasonography, diastolic dysfunction of left ventricle assessed by ecocardiography, flow-mediated dilatation (FMD), brachial artery, inflammatory usual tests, attested markers for vascular risk and serum antioxidant capacity: lipoprotein-associated phospholipase A2 (Lp-PLA2), ET-1 and paraoxonase (PON).
Results. Patients with SSc display a more pronounced inflammatory vascular disease than SLE patients having higher levels of Lp-PLA2, ET-1 and lower levels of PON. Moderately but sustained decreased serum levels are observed after pentoxifilin treatment in these patients (SSc, SLE).
The vascular involvement includes microvascular and macrovascular changes with progressive formation of thickened neointima. Mean IMT in SSc patients is thicker than in SLE and FMD is severely depressed in SSc patients.
Conclusions. (i) Collagen vascular disease represent an increased risk of premature atherosclerosis. (ii) Inhibition of PDE activity by a non-selective molecule (pentoxifilin) is associated with reduction of inflammation-related molecules (iii) PDE inhibitors exibit remarkable haemodynamic and inotropic properties, and cytoprotective effects. (iv) PDE inhibitors may be a valuable adjacent therapy in patients with collagen vascular diseases.

PS133. SSc: DEMOGRAPHIC, CLINICAL AND SEROLOGICAL FEATURES IN 100 IRANIAN PATIENTS

H. Poormoghim[1], A. Salek-Moghaddam[2], M. Moradi-Lakeh[3], M. Jafarzadeh[2], B. Asadifar[2] and M. Ghelman[2]
[1]*Rheumatology Research Center,* [2]*Immunology Research Center and* [3]*Department of Community Medicine, Tehran University of Medical Sciences, Tehran, Iran*

Objectives. To describe the demographic, clinical and laboratory features associated with the scleroderma-specific auto-antibodies.
Methods. Sera of 100 patients with SSc were analysed by an IIF technique with HEp-2 cells as a substra, and patterns reported. Specific ANAs such as ACAs, anti-topo, anti-RNA polymerase III (Pol 3), anti-U3-RNP (U3-RNP), anti-Th/To (Th/To) and anti-Pm/Scl (Pm/Scl) were determined by immunoblot, anti-U1-RNP (U1-RNP) determined by ELISA technique. The data of the scleroderma patients were extracted from the data bank.
The frequency of clinical features, organ system outcomes, within a specific antibody group, was cumulative over the follow-up period. The frequency of a specific clinical feature was compared across scleroderma subtype and antibody groups to identify significant differences.
Results. Some demographic, clinical and organ system findings were associated with the specific antibody, and other features with the scleroderma subtype (limited cutaneous or diffuse cutaneous scleroderma). ANA was positive in 94% of the patients, and was seen with significant higher skin score, Raynaud's and digital ulcer/gangrene. Anti-topo was detected in 71% of all patients, and, in diffuse and limited subtypes, it was 90.5% and 65.8%, respectively. Anti- topo

were significantly associated with dcSSc subtype, higher skin score, digital ulcer/gangrene, pulmonary fibrosis, DL_{CO}<70%. U1-RNP antibody was associated with lower fibrosis in lung. ACA was positive in 7% of the sera of all patients, the whole of which was found only in limited patients.
Conclusions. Differences in prevalence of autoantibodies in this study should be suggestive of further genetic study.

TABLE1. Autoantibody differences in terms of clinical or paraclinical features

Antibody	Missing data	ANA+	ACA+	Topo+
Antibody status in 100 patients	*0*	***93***	*7*	***71***
Age at the time of entry, mean (S.D.), years	*0*	***42.5 (14.1)***	*45.7 (18.1)*	***42.1 (13.6)***
Female: Male	*0*	***80:13***	*6:1*	***61:10***
dcSSc :lcSSc	*0*	***20:73***	0:6	**19:52**
Skin score, mean (S.D.)	0	**12.4 (8.0)**	*8.4 (7.2)*	**13.5 (8.3)**
RP, *n* (%)	0	**90 (96.8)**	*6 (85.7)*	68 (95.8)
Digital pitting ulcer	0	53 (57.0)	*3 (42.9)*	**44 (62.0)**
Digital ulcer/gangrene	0	**39 (41.9)**	*3 (42.9)*	31 (43.7)
Oesophageal reflux	*0*	***78 (83.9)***	*6 (85.7)*	***58 (81.7)***
Diarrhoea	*0*	12 (12.9)	*0*	10 (14.1)
Tendon friction rub	*0*	***10 (10.8)***	*0*	***8 (11.3)***
Arthritis > 1 joint	*2*	***7 (7.5)***	*0*	***5 (7.1)***
Muscle weakness	*0*	***6 (6.5)***	*0*	***5 (7.0)***
CPK elevation >2× normal	*17*	***7 (8.9)***	*0*	***5 (8.8)***
Fibrosis in HRCT	23	32 (43.2)	*1 (20.0)*	**28 (49.1)**
PAH without fibrosis	*28*	***2 (2.9)***	*0*	**0**
FEV1 <70% normal	*15*	***7 (8.6)***	*1 (20.0)*	**6 (9.4)**
DL_{CO} <70% normal	*19*	***39 (50.0)***	*2 (33.3)*	**33 (55.0)**
Pericarditis	*26*	***9 (12.7)***	*0*	***6 (12.2)***
CHF	*26*	***2 (2.8)***	*0*	***1 (2.0)***
Hypertension	*6*	***15 (17)***	*2 (33.3)*	***10 (15.2)***

CHF: congestive heart failure.

PS134. THE USE OF NAIL-FOLD CAPILLAROSCOPY IN OUR CLINICAL PRACTICE

C. Ponte[1], A. Castro[1], C. Resende[1] and J. A. Pereira Da Silva[1]
[1]*Serviço de Reumatologia e Doenças Ósseas Metabólicas, Hospital de Santa Maria, Centro Hospitalar de Lisboa Norte, Lisboa, Portugal*

Background. Nail-fold capillaroscopy is the most reliable method to distinguish between primary and secondary RP. A specific capillaroscopic pattern, so-called scleroderma pattern, is typically found in SSc and in other CTDs and inherits high positive predictive value for the development of these diseases.
Objectives. To describe our single-centre experience in the use of nail-fold capillaroscopy.
Methods. Review of all the nail-fold capillaroscopies done between January 2004 and September 2011 in the Rheumatology Department of Santa Maria Hospital, Lisbon, Portugal.
Results. Four hundred and fifty-five nail-fold capillaroscopies were made in patients who had RP (87% females and 13% males). The mean age of these patients was 46.6 (range 5–79) years and twenty-one of them did more than one nail-fold capillaroscopy (19 patients did two exams and 2 patients did three). In 62 exams (13.6%) was found the scleroderma pattern: 25 (40.3%) could be classified as having early pattern (presence of giant capillaries and microhaemorrhages), 30 (48.3%) as active pattern (the addition of capillaries loss) and only 7 (11.2%) as late pattern (neo-angiogenesis, fibrosis and desertification). Only 33 patients (53.2%) with scleroderma pattern had the previous diagnose of SSc. The others had SLE (3 patients), SS (3 patients), RA (3 patients), MCTD (3 patients), UCTD (3 patients) and RP without yet fitting the classification of a specific rheumatic disease (17 patients). In these last group, seven patients (41.6%) had positive ANAs and four (23.5%) had positive antibodies for ACA or anti-SCL70. In 119 exams (26.1%) were found some changes, but without a typical scleroderma pattern (haemorrhages and dilated or winding capillaries). Twelve (10.0%) of those exams corresponded to patients with the previous diagnoses of SSc. In the rest of the exams, considered normal (274 nail-fold capillaroscopies), only 3 (1.1%) corresponded to patients with SSc and 202 (73.7%) corresponded to patients that did not have any diagnosed disease (primary RP). The 21 patients that repeated the exam maintained the same results, with no different changes found.
Conclusion. In conclusion, nail-fold capillaroscopy is of crucial importance for the differentiation of primary and secondary RP and a very useful method in the early diagnoses of some CTDs, especially SSc.

PS135. CORRELATION OF THE ANTIBODIES PROFILE, SEEN IN PATIENTS WITH SSc, AND THE SYSTOLIC PULMONARY ARTERY PRESSURE MEASURED BY ECHOCARDIOGRAM

C. Ponte[1], A. Castro[1], C. Resende[1], M. Ferreira[2], S. Martins[2], A. Almeida[2] and J. A. Pereira Da Silva[1]
[1]*Serviço de Reumatologia e Doenças Ósseas Metabólicas and* [2]*Serviço de Cardiologia, Hospital de Santa Maria, Centro Hospitalar de Lisboa Norte, Lisboa, Portugal*

Background. Pulmonary arterial hypertension (PAH) is a common and fatal complication of CTDs, particularly SSc. Patient with positive ACAs, usually seen in the limited form of SSc, are more likely to develop PAH. Echocardiography is known to be a useful non-invasive method to asses PAH, especially with the measurement of the systolic pulmonary artery pressure (PAPs).
Objective. To correlate the values of PAPs, measured by echocardiogram, with the presence of the different antibodies usually seen in patients with SSc.
Methods. Review of all the echocardiograms with PAPs measurements made in patients with SSc between January 2007 and September 2011, in Santa Maria Hospital, Portugal. Review of all the positive serological antibodies found in those patients.
Results. Forty-seven patients (2 males and 45 females), with a mean age of 54.9 (range 18–81) years were evaluated: 22 patients had diffuse SSc, 20 patients had limited SSc and 5 patients had overlap syndrome (3 with SLE and 2 with DM). Forty-four patients were positive for ANAs and their mean PAPs was 40.8 (range 93–23) mmHg, 19 patients had positive ACA and their mean PAPs was 40.3 (range 25–93) mmHg and 18 patients had positive anti-Scl70 antibodies and their mean PAPs was 40.4 (range 23–56) mmHg.
Discussion/Conclusions. The measurement of PAPs in these patients with SSc, using echocardiographic methods, did not show a positive correlation with the different antibody profiles. Patients with ACA or anti-Scl70 antibodies had almost the same mean PAPs. Due to the low sensitivity of echocardiogram in the assessment of PAH, right-heart catheterization should be preferred for this measure. Nevertheless, this study was made with a small number of patients. More studies should be undertaken.

PS136. BOSENTAN IN CLINICAL PRACTICE FOR TREATING DIGITAL ULCERS IN PORTUGUESE PATIENTS WITH SSc AND OTHER CONNECTIVE TISSUE DISEASES: SINGLE-CENTRE EXPERIENCE

C. Ponte[1], C. Resende[1] and J. A. Pereira Da Silva[1]
[1]*Serviço de Reumatologia e Doenças Ósseas Metabólicas, Hospital de Santa Maria, Centro Hospitalar de Lisboa Norte, Lisboa, Portugal*

Background. In SSc, and in other CTD, the occurrence of digital ulcers (DUs) is a painful, debilitating and recurrent complication. Bosentan is approved for the reduction in the occurence of new DUs in patients with SSc.
Objectives. To describe treatment outcomes and safety experience with bosentan in DUs of patients with SSc and other CTDs in the rheumatology outpatient clinic of Santa Maria Hospital, Portugal.
Methods. Chart review of patients with SSc and other CTDs, with or without pulmonary arterial hypertension (PAH), who initiated bosentan therapy for DUs. Relevant measures included number of DUs, occurrence of new DUs, healing time, functional assesment and adverse events.
Results. Eighteen patients (3 males and 15 females) with a mean age of 49.8 (14–79) years and a mean BMI of 22.5 (15.6–31.1) kg/m^2 were treated with bosentan: nine patients had diffuse SSc, six patients had limited SSc, one patient had SLE, one patient had an overlap syndrome (SLE + SSc) and one patient had pansclerotic morphoea. They had a mean disease duration of 10.9 (1–51) years and five patients also had PAH. Fourteen patients were previously submitted to e.v. prostacyclins. Bosentan was taken for a period of 17.3 (2–41) months in a mean daily dose of 196 (32–-250) mg. The patients were evaluated prior to treatment initiation, 1 month after its beginning and later with a quarterly basis. In the first evaluation, the patients had a mean of 3.9 DUs (range 1–14) and a medium VAS of 7.3 (range 2–10) concerning the performance of daily activities. In the follow-up evaluations, there were three patients that reported diarrhoea but without the need of drug withdrawal. After 2 months of treatment, the patient with pansclerotic morphoea stopped bosentan because of liver toxicity. After 3 months of treatment, another patient stopped the therapy because of lower limb oedema. After 10 months of treatment, the patient with SLE had an episode of diffuse skin erythema that led to bosentan withdrawal. In the last follow-up visit, the patients had a

mean of 1.2 DUs (0–6) and a medium VAS of 6.2 (1–9). During this treatment period, 27.8% of the patients did not develop new DUs. There were no benefits observed in the healing time of DUs.
Conclusion. Bosentan appeared to be effective and safe in reducing the occurrence of new DUs in patients with SSc and other CTDs. It also showed improvement in the performance of daily activities.

PS137. SSc AND NON-HODGKIN'S LYMPHOMA: A CASE REPORT

S. Pimenta[1], G. Terroso[1], J. Abelha[1], A. Bernardo[1] and J. M. Bernardes[1]
[1]*Rheumatology Department, C.H. São João, E.P.E., Oporto, Portugal*

Introduction. SSc and scleroderma-like syndromes are characterized by complex immune disorders, vascular damage and overproduction of the extracellular matrix by activated fibroblasts. The most common malignancies associated with SSc include lung and breast cancers. The association of scleroderma and non-Hodgkin's lymphoma is an uncommon event.
Case report. A 71-year-old woman was hospitalized for the first time in October 2009 with polyarthralgia, weight loss and fatigue. She had RP for several years. Physical examination revealed sclerodactyly, perioral sclerosis and telangiectasia of the face, which began 2 years ago and no evidence of arthritis. Chest X-ray did not reveal pulmonary involvement. Oesophageal manometry detected aperistalis in the distal oesophagus. Electrocardiographic and echocardiographic examinations as well as respiratory functional tests were normal. Levels of serum RFs were positive (233 UI/ml; $n<30$), ANAs were positive ($>1/1000$, with a nucleolar staining pattern), ACAs and anti-topo-I antibodies were negative. Polyclonal hypergammaglobulinaemia was present. The CREST syndrome was diagnosed. Pentoxifylline, proton pump inhibitors, NSAI's and low dose of CS were administered and the patient improved. In May 2011, the patient developed significant fatigue and dyspnoea associated with a cervical mass. CT scan revealed multiple cervical, axillary, mediastinic, retroperitoneal and mesenteric lymphadenopathy. Lymph node biopsy revealed a Grade 2 follicular lymphoma with nodular growth pattern. Cytogenetic examination revealed a translocation t(14;18).
The R-CHOP regimen was recently initiated.
Conclusion. Although rare, the association of SSc and non-Hodgkin's lymphoma may not be coincidental and this connection suggests an increased vigilance of the risk for lymphoproliferative disorders in scleroderma patients.

PS138. THE COEXISTENCE OF SSc WITH OTHER AUTOIMMUNE DISEASES—A SINGLE-CENTRE EXPERIENCE

A. Petcu[1], C. Pamfil[1], I. Filipescu[1], B. Dumitru[1], M. M Tamas[1], H. Popov[1], D. Leucuta[2] and S. Rednic[1]
[1]*Department of Rheumatology and* [2]*Medical Informatics and Biostatistics Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania*

Objective. To assess the prevalence of other autoimmune diseases in a retrospective series of SSc patients.
Background. SSc is a rare, multisystemic autoimmune disease involving overlapping process. Recent studies have pointed out the increased prevalence of autoimmune disorders associated with SSc.
Methods. We retrospectively analysed 126 patients with SSc fulfilling the ACR criteria (they were grouped as dcSSc, lcSSC and other—most of it overlap syndrome). Demographic, clinical and laboratory data were obtained from previous database and clinical charts. Patients were included in the study if they have certain diagnosis of other autoimmune diseases, such as RA, PM, DM, primary billiary chirosis, sclerositis colangitis, Hashimoto thyroiditis, psoriasis. The associated autoimmune diseases were defined in accordance with international classification criteria.
Results. We analysed 126 SSc patients (84.9% women). The limited subset was present in 57 patients (45.2%), similar to the diffuse subset. Twelve had other disease (overlap syndrome, scleroderma sine scleroderma). Twenty-nine patients (23.1%) of the SSc patients studied have developed additional autoimmune diseases. Overlap syndromes were diagnosed in 6.3% of the cases. Patients with associated autoimmune disorders were predominantly women (93.1%).
Patients with lcSSC has a higher prevalence of primary billiary chirosis, while the dcSSc presented with higher prevalence of thyroid disease. We noticed that primary billiary chirosis was present only in the lcSSc subgroup. In the overlap subgroup, the main associations was with PM, followed by DM and RA cases. Other correlations regarding the presence of autoimmune disease and the manifestation of the disease were made.
Conclusions. Primary biliary cirrhosis and thyroiditis were the most frequent associations. We found no cases of association with SS unlike literature reports that places this association on the first place (despite the fact that several patients had sicca sydrome). Only in cases of lcSSc, association with CBP have been identified. The prevalence of autoimmune thyroiditis was similar in both subtypes of SSc. Our results suggest that both forms of SSc could exhibit a tendency to be associated with other autoimmune diseases. Therefore, an extended diagnostic screening for associated autoimmune diseases seems reasonable in SSc patients, especially female gender.

PS139. CAUSES FOR DEATH IN SSc—A SINGLE-CENTRE EXPERIENCE

A. Petcu[1], C. Pamfil[1], I. Nicoara[1], L. Damian[1], L. Muntean[1], S.-P. Simon[1], H. Popov[1] and S. Rednic[1]
[1]*Department of Rheumatology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania*

Objective. To study survival and causes of death in a cohort of patients with SSc between January 1988 and June 2011.
Background. SSc has the highest case-specific mortality among the rheumatic diseases.
Methods. Patients with SSc fulfilling the ACR criteria followed up between January 1988 and June 2011 were included. Clinical and laboratory data of 126 patients with SSc were retrieved from medical charts.
Results. We report 11 patients who died in the last 5 years. Six patients were women (54.5%). Of male patients, 26.3% included in the database died compared with 5.6% of female patients. Seven patients were from rural space (63.6%). Among the total of 11 dead patients, 81.8% had dcSSc and 18.2% had lcSSc. Of the deaths, 72.8% were attributed directly to SSc and 27.2% to non-SSc causes. Four cases were attributed to pulmonary arterial hypertension, one case to pulmonary fibrosis, one case to malabsorbtion, two cases to cardiac-related scleroderma causes, two cases to malignancy and one case to accident. Renal crisis was present in five of the 126 patients (present in 2 of the 11 dead patients), but no fatal event was described. Other correlations were made regarding mean age at death, mean duration of follow-up, proteinuria, skin score and the presence of other comorbidities.
Conclusion. Death among the patients with SSc is still in favour of SSc-related causes and even those has changed over years. Our data indicates an increased per cent of deaths among men affected by SSc. Renal crisis was not causing death among our patients, the majority of the cases being attributed to pulmonary arterial hypertension. Our report is limited by the number of the patients and the presence of comorbidities.

PS140. MEMBRANE DIFFUSION AND CAPILLARY BLOOD VOLUME MEASUREMENTS IN PATIENTS WITH SSc

F. Perrin[1], A. Chambellan[2], J. B. Hardouin[3], E. Mourrain Langlois[4], A. Néel[1], A. Masseau[1], B. Planchon[1], M. Hamidou[1] and **C. Agard**[1]
[1]*Department of Internal Medecine,* [2]*Department of Pulmonary Function Laboratory,* [3]*Departement of Biostatistics and* [4]*Department of Radiology, University Hospital Hôtel Dieu, Nantes, France*

Introduction. Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) represent the first cause of mortality in SSc.
The diagnosis and monitoring of these complications are based on transthoracic echocardiography (TTE), right-heart catheterization, thoracic computed tomodensitometric scan (CT scan) and pulmonary function tests (PFTs) with measurement of transfer factor of the lung for carbon monoxide (TL_{CO}). The partition of TL_{CO} determines two parameters: membrane diffusion (Dm) and capillary volume (Vc). The measures of Dm and Vc enables to distinguish alveolocapillary wall (Dm) or capillary involvements (Vc). The value of these parameters for the diagnosis and monitoring of lung involvements in SSc remains to be defined.
Patients and methods. In this monocentric retrospective study, 72 patients with SSc were evaluated with PFT which included measurements of DL_{CO}, Dm and Vc.
Demographic, clinical and biological characteristics, PFT parameters, TTE estimate of systolic pulmonary artery pressure (sPAP) and CT scan findings were retrospectively analysed. The severity of ILD

extension was assessed by a radiological score from 0 to 3 (0: no ILD, 1: ground glass, 2: moderate fibrosis, 3; severe fibrosis).
Results. The study included 72 patients with SSc: 54 with limited cutaneous form and 18 with diffuse form of SSc. ILD was present in 42.5% and PAH in 8.5%.
In univariate analysis, TL_{CO}, Dm and Vc correlated with extent of ILD. TL_{CO} correlated with sPAP, whereas Dm correlated with dyspnoea.
Expectedly patients with ILD+/PAH− ($n = 27$) had significantly lower TL_{CO} than patients ILD−/PAH− ($n = 40$) ($P < 0.05$). This was also the case for Vc and Dm ($P < 0.05$).
However, mean TL_{CO}, Vc and Dm were similar in ILD+/PAH− ($n = 27$) and ILD−/PAH+ ($n = 6$) patients.
In one-way ANOVA analysis, variance analysis was too weak to differentiate the three groups ILD+/PAH−, ILD−/PAH+, and ILD−/PAH−.
ROC curve analysis showed that Dm had a slightly higher predictive value for PAH (AUC = 0.6502) as compared with TL_{CO} (0.6306). Vc and Dm were slighty similar to TL_{CO} for the prediction of ILD (0.68 and 0.69 *vs* 0.67). However, overall diagnostic accuracy of diffusion remained weak.
Conclusion. In this cross-sectional study, the use of the partitioned diffusion with measures of Vc and Dm had little if any interest as compared with TL_{CO}. Overall diagnostic accuracy of Dm and Vc are weak in our experience. Whether these parameters could have a prognostic value in patients without any lung involvement remains to be determined. The longitudinal analysis of a cohort of patients with unexplained decreased TL_{CO} may clarify this point.

PS141. MHC ANTIGENS IN PATIENTS WITH OR WITHOUT RP

C. Peralta-Ginés[1], V. Cuellar-Cruz[1] and C. Delgado-Beltrán[1]
[1]*Department of Rheumatology, Lozano Blesa Clinic Hospital, Zaragoza, Spain*

Background. Major histocompatibility complex (MHC) is composed by antigens found on cellular surfaces, with genes located in chromosome 6. Approximately 100 diseases are associated with the classic genes of Classes I and II MHC (i.e. HLA-DR4 and RA). RP is the consequence of an exaggerated response to cold or to emotional stress being primary or secondary, among others, to autoimmune disorders. In addition, 13% of patients initially diagnosed of primary RP can develop later a connective disease [2, 3].
Objective. To analyse the autoimmune profile and HLA alleles in patients with RP.
Methods. Prospective longitudinal study of outpatients with RP from Hospital Clínico in Zaragoza. Adult patients with or without an autoimmune disease diagnosis were included. Capillaroscopy and blood analyses including autoantibodies and HLA were performed. The data of 72 of 98 patients who met inclusion criteria was used due to unknown analytical results of those excluded.
Results. Most of our patients with RP are women with a total of 65 *vs* 7 males, mean age 46 years (range 19–87 years). Twenty-eight of them are smokers and five are on β-blocking treatment. Autoantibodies profile is described in Table 1. Of the patients, 23% have negative autoantibodies. The most common allele of HLA system is HLA-DR52, found in 73% ($n = 53$) of cases, followed by HLA-DR53 in 58% ($n = 42$) and DQ2 in 53% ($n = 39$). Other alleles are described in Fig 1.
This HLA-DR52 was present in 15 of 17 patients with RP and negative autoantibodies, followed by 12 patients with cryoglobulinaemia, two of four cases of pre-scleroderma and the rest in CTDs. After reviewing literature we found that SSc, in which 95% of patients have RP, has been linked to HLA-DR52 [4]. In another study, the frequency of HLA-DR52 genes was greater in primary SS patients [5]. However, we found no studies that related HLA-DR52 to the presence of primary RP.
Conclusion. HLA-DR52 allele may confer susceptibility to RP, both primary and secondary, in our population participating, with other factors, in the vascular dysfunction pathogenesis and increased vascular activity.

Fig. 1 HLA allele frequency (%) in patients with RP.

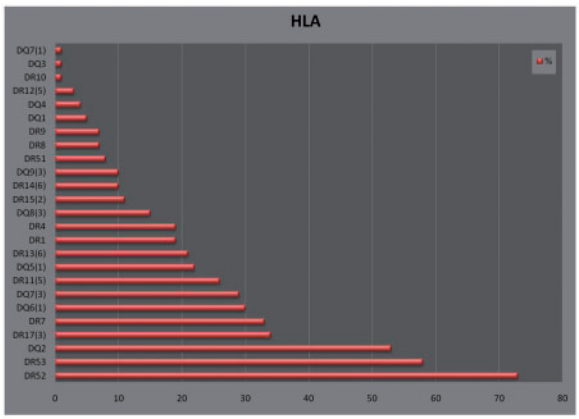


Table 1. Autoantibodies in patients with RP

Autoantibodies	Frequency (%)
ANA	36 (50)
Mixed policlonal cryoglobulinaemia	14 (19)
Anti-thyroid	8 (11)
Anti-smooth muscle	7 (10)
Anti-parietal cell	7 (10)
ACA	6 (8)
Anti-Ro60	5 (7)
RF	5 (7)
Anti-citrullinated protein	4 (6)
Anti-Ro 52	4 (6)
Anti-coagulant lupic	4 (6)
Anti-cardiolipin	3 (4)
Anti-histone	3 (4)
Anti-ribosomal P	3 (4)
Anti-DNA	3 (4)
Anti-RNP	2 (3)
Anti-nucleosome	1 (1)
Anti-mitocondrial	1 (1)
c-ANCA	1 (1)

PS142. ANALYSIS OF THE DATA OF MOLINETTE PAH REGISTRY—SCLERODERMIA-ASSOCIATED PAH: CLASS 1 SUBGROUP OR DISTINCT ENTITY?

S. Sturnia[1], W. Grosso Marra[1], F. Gaita[1], D. Libertucci[3], P. Omede'[1], M. Cannillo[1], **S. Parisi**[2], C. L. Peroni[2], F. Ambrogio[2], M. Bruzzone[2], M. Scarati[2] and E. Fusaro[2]
[1]*S.C. Cardiology,* [2]*S.C. Rheumatology and* [3]*S.C. Pneumology, San Giovanni Battista Hospital - Molinette, Turin, Italy*

Background. Pulmonary arterial hypertension (PAH) complicates ~15% of scleroderma patients. Even though PAH associated with sclerodermia (SS) represents a Class 1 subgroup of Dana Point classification, clinic and prognostic features are different from scleroderma patients to other PAH patients, so that this disease can represent a distinct nosographic entity.
Methods. We collect clinical and instrumental data from 50 patients with PAH (Group 1) visited and treated by our study group. Seventeen of them suffering from PAH associated with SS were compared with the other 33 patients.
Results. Age at diagnosis was significantly higher for SS group [63.8 (11.2) *vs* 50.9 (17); *P* 0.011]. There were significant differences signs of right ventricular failure were more common in scleroderma patients (48 *vs* 35%; $P = 0.018$). NYHA-WHO functional class distribution was, for scleroderma group, 0% Class 1, 12% Class 2, 59% Class 3 and 29% Class 4. Between other patients 3% was in WHO Class 1, 21% in Class 2, 51% in Class 3 and 24% in Class 4.
At right heart catheterization systolic and mean pulmonary arterial pressure (PAPs and PAPm) resulted significantly lower in scleroderma patients [PAPs: 49.8 (15) *vs* 79.8 (22.9); $P < 0.01$; PAPm 35.25 (11.25) *vs* 51.6 (15.8); $P < 0.01$]. About echocardiographic data there were no significant differences regarding weather TAPSE [18.1 (3.3) *vs* 17.8 (4.8); $P = 0.49$] or pericardial effusion (17 *vs* 9%; $P = 0.15$), even though the last one, that is an important negative prognostic factor, was more frequent in scleroderma patients.
Among scleroderma-associated PAH patients 41% was not able to perform 6MWT due to ipossia at rest, *vs* 22% of other patients ($P = 0.03$); among those who perform the test there were no differences as for metres walked [355 (94) *vs* 367 (116); $P = 0.9$]. There were no set differences in NTproBNP amount between the groups ($P = 0.43$).Patients were divided according to guidelines risk class. Among scleroderma patients anyone was at low risk, 58% was in an intermediate risk class and 41% was at high risk. Risk class

were so distributed among the other group: 6% al low risk, 60% at intermediate risk and 33% at high risk.
Conclusions. Even though some instrumental data (RHC, Echocardiogram, 6MWT, NTproBNP) could notice no significant differences or even show to be better compared with others patients in Class 1, patients with sclerodermia-associated PAH develop clinical features (functional WHO class, ipossia at rest that make them unable to perfrm 6MWT) that place them among patients at high risk. This represents an important reason for the early diagnosis of PAH in scleroderma population.

PS143. FIVE-YEAR SURVIVAL IN PATIENTS WITH SSc: PROGNOSTIC FACTORS

I. Filipescu[1], A. Petcu[1], C. Pamfil[1], L. Ghib[1], D. Leucuta[2] and **S. Rednic**[1]
[1]*Department of Rheumatology and* [2]*Department of Medical Informatics and Biostatistics, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania*

Background. SSc is a multisystemic disease of connective tissue with reduced survival compared with other autoimmune disease. This is due to causes related to scleroderma and/or independent factors.
Objectives. The aim of this article was to evaluate some clinical features at first presentation that would predict the 5-year survival in our SSc patients.
Methods. This single-centre retrospective, longitudinal study included 46 patients with SSc according to ACR classification criteria followed for at least 5 years or shorter if they died. We evaluate if some parameters present at onset are predicted for 5-year survival. The baseline variables collected are: age, sex, type of SSC, Rodnan skin score, digital ulceration, force vital capacity (FVC), diffusing capacity for carbon monoxide (DLco), a right ventricular systolic pressure (RVSP), EKG aspect, blood pressure, gastro-esophageal reflux, malabsorbtion, ESR, haemoglobin levels, serum urea and creatinine levels, urine protein, ANAs, ACAs and anti-topo antibodies (Scl 70).
Results. We evaluated 26 patients with diffuse SSc, 16 with limited disease SSc and 4 with overlap scleroderma. At 5 years, 4 (9.75%) of 41 women and 4 (80%) of 5 men had died. Data were missing for six patients. All patients who died had diffuse SSc and were aged >45 years at first presentation. Using multivariate statistic test hazard rate is 4.0 (95% CI 2.6, 90.9) for malabsorbtion ($P < 0.08$), 1.1 (95% CI 1.0, 1.2) for ESR ($P < 0.008$) and 15.3 (95% CI 2.6, 90.8) for urea ($P < 0.002$). These parameters are significantly associated with low survival at 5 years.
Conclusions. Our results confirm that age, diffuse SSc, renal failure, systemic inflammation and malabsorbtion at presentation are important prognostic factors for survival. These parameters easily collected initially can be the useful tools in predicting mortality. The main study limitation is a consequence of the small number of patients.

PS144. SSc IN MEN: A DISTINCT DISEASE SUBSET RELATED OF SILICA EXPOSURE

C. Pamfil[1], H. Popov[1], I. Filipescu[1], I. Oancea[2], L. Ghib[1] and S. Rednic[1]
[1]*Department of Rheumatology, Iuliu Hatieganu University of Medicine and Pharmacy and* [2]*Phoenix Diagnostic Clinic, Cluj-Napoca, Romania*

Background. SSc has many faces, many subsets, with differences regarding the autoantibody profile, organ involvement and outcome. Gender is another important prognostic key factor.
Objective. To assess gender differences between clinical features, organ involvement and outcome in patients with SSc.
Patients and method. We performed a retrospective study on 128 patients registered in our centre. The analysed data was obtained from clinical records. Statistical interpretation was performed with the chi-square test.
Results. We identified 19 (14.9%) men with SSc with a predominance of diffuse SSc (73.6%). Organ involvement was more frequent and severe in man than in women. There were statistically significant differences in the frequency of pulmonary hypertension ($P < 0.001$), renal crisis ($P = 0.025$) and heart involvement (regarding extrasystoles, diastolic dysfunction and heart failure, but not pericarditis). Pulmonary fibrosis was frequent, but lacked signs of exudative alveolitis in most male patients. Of note, nine patients had been miners and most of them had long-term silica exposure. Men required more frequent aggressive therapy with CYC ($P < 0.001$). Death occurred in six (31.5%) patients; in 66% cases due to scleroderma-related complications (pulmonary hypertension, cardiac fibrosis and malabsorbtion) and in 33% of patients due to silica-related cardio-pulmonary complications.
Conclusions. Scleroderma in men is associated with significantly greater morbidity and mortality than in women. Exposure to silica may be a significant risk factor for developing SSc and as comorbidity, may aggravate the course of disease.

PS145. REYNOLD'S SYNDROME: A FEATURE OF BOTH LIMITED AND DIFFUSE SSC

B. Dumitru[1], **C. Pamfil**[1], I. Felea[1], I. Filipescu[1], I. Oancea[2], C. Nemes[1] and S. Rednic[1]
[1]*Department of Rheumatology, Iuliu Hatieganu University of Medicine and Pharmacy and* [2]*Phoenix Diagnostic Clinic, Cluj-Napoca, Romania*

Introduction. SSc associated to primary biliary cirrhosis (PBC) is an overlap syndrome described predominantly in association with limited SSc and ACAs.
Objective. To analyse the outcome, clinical and biological features, as well as organ involvement in patients with SSc-PBC overlap syndrome registered in the EUSTAR database at our centre.
Results. Out of 128 patients with SSc, 3 (2.34%) patients presented overlap with PBC. All patients were female, one of them had limited and two had diffuse SSc. The diagnosis of SSc followed the diagnosis of PBC in all cases and the mean duration between the two diagnoses was 1 year. Relevant immunological features include positive anti-mitochondrial antibodies in all cases, ACAs in the limited subtype and anti Scl-70 in the diffuse subtypes. Regarding organ involvement, none of the patients had cardiac or renal involvement, nor pulmonary hypertension. All three patients had mild gastro-oesophageal dismotility and one patient had severe interstitial lung disease. Interestingly, one patient had associated SS. Treatment consisted in AZA and/or MTX with the normalization of the cholestatic syndrome and control of disease.
Conclusions. SSc-PBC overlap syndrome is a feature of both limited and diffuse SSc. PBC associated with SSc seems to have a good prognosis under immunosuppressive therapy and the association of PBC did not seem to alter the course of SSc. Yet, the association of two autoimmune diseases can be a path to a wider mosaic of autoimmunity.

PS146. SOLUBLE LEPTIN RECEPTOR IN PATIENTS WITH SSc

Y. Oyoshi[1], M. Jinnin[1], T. Makino[1] and H. Ihn[1]
[1]*Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan*

Microvascular damage is one of the primary pathological components of SSc. Serological abnormalities of the angiogenic and angiostatic factors in SSc had been previously described. Similarly in these factors, the plasma levels of leptin were significantly increased in patients with SSc with respect to normal control. However, leptin receptor has not been examined in patients with SSc. In this study, we evaluated the serum levels of leptin receptor by a sandwich ELISA.
Serum samples were obtained from 36 patients with SSc. Twelve healthy control subjects, and 10 SSD patients, who did not fulfil the criteria of SSc but were thought to develop SSc in the future, were also included in this study. Mean serum leptin receptor levels were significantly higher in SSD patients than SSc patients (255.7 ng/ml *vs* 184.6 ng/ml, $P < 0.05$ by a Mann–Whitney test). There was no statistically significant difference between healthy control subjects and SSc patients. Moreover, we evaluated the clinical parameters, and the frequency of oesophageal reflux was significantly higher prevalence in patients with decreased serum leptin receptor levels than in those with elevated levels (35.3 *vs* 6.3%, $P < 0.05$).
In summary, these results suggested that the serum levels of leptin receptor are useful markers of SSD, and the serial time-course measurements of serum leptin receptor in SSD patients may lead to early detection of developing SSc. Additionally, serum leptin recetor levels may also become useful marker of the oesophageal reflex in SSc patients. However, we could not explain the role of leptin receptor in the pathogenesis of oesophageal reflex.

PS147. PREVALENCE, SEVERITY AND RISK FACTORS FOR DEVELOPMENT OF RENAL INSUFFICIENCY IN PATIENTS WITH SSc

P. Ostojic[1], T. Jovic[1], S. Zivojinovic[1], N. Pilipovic[1], K. Gosic[1] and N. Damjanov[1]

[1]*Institute of Rheumatology, Belgrade, Serbia*

Objective. This study aims to assess the prevalence and severity of renal insufficiency (RI) in patients with SSc and to identify possible risk factors for development of RI.
Patients and methods. Forty-three patients with SSc (mean age 54 years and 10 months, mean disease duration 7 years and 8 months) were included in this study. Twenty-nine (67.4%) patients had limited and 14 (32.6%) patients diffuse form of the disease. ACAs were positive in 19 (44.2%), while anti-topo antibodies (ATA) were present in 24 (55.8%) patients. Renal function was assessed by calculating creatinine clearance (CCr) in each patient. RI was defined as CCr<90 ml/min. According to the calculated CCr value, one can differentiate four stages of RI: mild (60–89 ml/min), moderate (30–59 ml/min), severe (15–29 ml/min) and end-stage RI (<15 ml/min). We assessed the prevalence and severity of RI in our patients with SSc, and estimated the relationship among RI, age, disease duration, form of the disease, antibodies, earlier diagnosed arterial hypertension and use of medications, which may have impact on renal function.
Results. RI was diagnosed in 33/43 (76.7%) patients with SSc. Mild RI was present in 16/43 (37.2%), moderate in 16/43 (37.2%) and severe RI in 1/43 (2.3%) patients. We have noticed a statistically significant correlation between CCr and age of patients ($P = 0.008$), and disease duration ($P = 0.05$). There was no difference ($P = 0.81$) between CCr in patients with ACA [69.2 (22.7) ml/min] and ATA [70.4 (27.6) ml/min]. Mean value of CCr was significantly lower in patients with limited SSc, than in patients with diffuse SSc (lSSc: dSSc = 61.9 : 86.4 ml/min, $P = 0.002$). Patients who were treated with NSAID's had lower CCr than patient who did not take these drugs (57.4 *vs* 76.7 ml/min, $P = 0.01$), as well as patients who were treated with CSs (56.1 *vs* 76.8 ml/min, $P = 0.012$). Mean value of CCr did not differ between patients taking and not taking cytostatic drugs, ACE inhibitors or calcium channel blockers. No difference in CCr was noticed in patients with or without previously diagnosed arterial hypertension (66.5 *vs* 69.9, $P = 0.61$).
Conclusion. RI is offten present in patients with SSc. RI is more severe in older patients with longer disease duration and limited form of the disease, as well as in patients treated with CSs and NSAIDs.

PS148. CARDIAC MAGNETIC RESONANCE ASSESSMENT OF MYOCARDIAL INVOLVMENT IN SSc

I. Oancea[1], C. Pamfil[2] and S. Rednic[2]
[1]*Phoenix Diagnosis Clinic, University of Medicine Iuliu Hatieganu and* [2]*University of Medicine Iuliu Hatieganu, Cluj-Napoca, Romania*

Purpose. The purpose of the study is to detect and evaluate the myocardial changes in patients with SSc on cardiac MRI, highlighting the frequency and importance of cardiac involvement in these patients.
Materials and method. Nine consecutive patients with SSc were investigated by cardiac MRI in our department. All MRI examinations were performed using a 1.5 T machine (Siemens Avanto), and the protocol of examination included trueFISP sequences for cine images, STIR images in short-axis view and an inversion recovery turboFLASH sequence for late enhancement (LE) study acquired at 10 mins after contrast administration. All the patients were prospectively included in the study, undergoing the complete MR protocol (8 women, 1 man with mean age 50.4 years, age range 37–62 years). The disease duration varied between 3 and 26 years from the moment of diagnosis. One radiologist assessed the cardiac MR images and noted the myocardial motion abnormalities; evaluated the presence of LE areas within the myocardium, their location (with respect to AHA segmentation) and pattern of LE lesions and calculated the left ventricular function and the myocardial mass. Other associated findings like pericardic fluid and valvulopathies were noted.
Results. Myocardial changes were found in seven patients (77%) on LE sequences and in two patients (22%) on STIR sequences. The myocardial lesions had focal distribution in two patients (22%), multifocal distribution in four patients (44%) and diffuse distribution in one patient (11%). In six patients (66.6%), late enhancement sequences showed lesions with non-ischaemic pattern as follows: two patients had subendocardic lesions involving 3 segments; five patients had mid-wall lesions involving 16 segments and one patient had subepicardic lesions involving 2 segments; probably corresponding to fibrotic myocardial changes. One patient presented diffuse hyperintense lesions on LE sequences, some of them involving the subendocardic region with transmural extension with kinetic abnormalities and thinning of the wall, most probably corresponding to a myocardial infarction intricate with fibrotic diffuse changes. The evaluation of cardiac function showed moderate and severe heart failure in two patients: one with dilatative cardiomyopathy, other with left ventricular systolic dysfunction due to pulmonary hypertension. The average myocardial mass was 56.66 g/m^2.
Conclusion. Cardiac MRI is a useful imagistic method that can provide an accurate evaluation of cardiac structural and functional changes in SSc. The LE study could detect the wall lesions offering an insight characterization of myocardial involvement in these patients.

PS149. HIGH LEVELS OF INFLAMMATORY BIOMARKERS IN PATIENTS WITH SSc

A. Nordin[1], L. Björnådal[1], A. Larsson[2] and E. Svenungsson[1]
[1]*Department of Medicine, Rheumatology Unit, Karolinska Institute, Stockholm* [2]*Department of Clinical Chemistry and Pharmacology, Akademiska Hospital, Uppsala, Sweden*

Background. SSc is a systemic autoimmune disease with female predominance. Fibrosis of multiple organs and small-vessel vasculopathy are characteristics of the disease. Systemic inflammation is generally not considered to be a prominent clinical feature of SSc; however, increased sedimentation rate is associated with a bad prognosis. To elucidate the role of systemic inflammation in SSc we investigated a large number of inflammatory biomarkers in SSc patients and controls.
Methods. A population-based cohort encompassing 75% of the SSc patients in Stockholm county, Sweden, 111 patients, fulfilling the ACR criteria for SSc, and 105 individually age- and gender-matched population controls were investigated.
All underwent a thorough medical examination. Fasting blood samples were collected. Biomarkers of systemic inflammation and autoantibody patterns were tabulated.
Results. Mean age was 61.8 (12.4) *vs* 61.4 (12.3) years among patients and controls, respectively. In the patient group, 32% were ACA positive and 23% had antibodies to Scl70. The disease duration was 9.5 (7.6–17.3) years. Of the patients, 78% had an lcSSc and 22% a dcSSc. Of the patients, 46% had pulmonary fibrosis, 39% had a history of digital ulcers and 5% had pulmonary arterial hypertension (PAH). High-sensitivity (hs) CRP, haptoglobin, orosomucoid, α1-antitrypsine, fibrinogen, sedimentation rate (SR) and TNF Receptor(R)-2 were higher among patients than controls. The levels of serum amyloid A (SAA), IL-6, pentraxin-3 and TNFR1 did not differ between patients and controls. Notably TNF-α levels were lower in the patient group. Investigated biomarkers did not differ between the subtypes (dcSSc and lcSSc), but a higher SR was associated with Scl70 antibodies. Pulmonary fibrosis was associated with high SR and high levels of orosomucoid, pentraxin-3 and TNFR1 ($P < 0.05$) and skin score was positively associated with orosomucoid, TNFR-1, haptoglobin and α1-anti-trysine ($P < 0.05$). There was no association between inflammatory markers and digital ulcers or pulmonary hypertension.

Inflammation	Patients ($n = 111$)	Controls ($n = 105$)	*P*-value
hsCRP, mg/l	2.2 (1.0–4.3)	1.75 (0.76–3.2)	**0.05**
Haptoglobin, mean (SD), g/l	1.35 (0.78)	1.12 (0.45)	**0.09**
Orosomucoid, mean (SD), g/l	0.86 (0.23)	0.77 (0.17)	**0.0009**
α1-anti-trypsine, g/l	1.5 (1.4–1.6)	1.4 (1.2–1.5)	**<0.0001**
Fibrinogen, g/l	3.77 (3.3–4.34)	3.53 (2.80–4.25)	**0.03**
SR, mm	14 (9–26)	10 (7–16.5)	**0.002**
SAA, mg/l	5.6 (2.7– 9.6)	4.3 (2.6–6.8)	0.09
IL-6, pg/ml	29.9 (21.4–40.9)	27.1 (21.2–32.5)	0.08
Pentraxin-3, pg/ml	2622 (1920–4371)	2728 (1674–4063)	0.27
TNF-α, pg/ml	37.1 (30.4–50.7)	61.2 (30.6–91.9)	**0.036**
TNFR1, pg/ml	2940 (2573–3693)	3589 (2420–4698)	0.11
TNFR2, pg/ml	4762 (3980–6166)	4412 (3243–5401)	**0.0002**

Conclusion. Levels of inflammatory biomarkers were higher in SSc patients as compared with controls. Patients with signs of fibrosis, affecting lungs and/or skin, had higher levels of several inflammatory biomarkers than SSc patients with other symptoms. This was not the case in patients with more vascular damage such as digital ulcers or pulmonary hypertension.

PS150. VITAMIN D STATUS IN PATIENTS WITH SSc

L. Groseanu[1,2], A. Necula[1], I. Saulescu[1,2], M. Negru[1,2], C. Constantinescu[1,2], M. Abobului[1,2], D. Predeteanu[1,2], A. Balanescu[1,2] and R. Ionescu[1,2]
[1]*UMF Carol Davila, Faculty of Medicine and* [2]*Santa Maria Hospital, Bucharest, Romania*

The lack of precise correlations between scleroderma and vitamin D levels brought afloat the need for further investigations upon this subject.
The purpose of the study at hand is to evaluate the vitamin D levels in patients with SSc as well as to define the correlations existing between these levels and the bio-clinical manifestations, the subtype of disease and the registered scores.
This is a descriptive cross-sectional study realized between July 2010 and June 2011 in the Internal Medicine and Rheumatology Department of the 'Sfanta Maria' Hospital, on a batch consisting of 17 patients. The batch was made up entirely out of Caucasian women with a mean age of 52.17 years, a mean age at the beginning of the disease of 39.8 years and a mean evolution time of the disease of 12.36 years. Fourteen patients had oesophageal manifestations, 10 patients had pulmonary interstitial fibrosis, 8 patients had pulmonary hypertension and 9 patients had cardiac manifestations. The mean of Rodnan's score was 13.88 and eight patients had active disease according to EUSTAR SSc activity score.
The evaluation of clinical and paraclinical manifestations was achieved through clinical examination, use of questionnaires and other specific investigations (upper gastrointestinal barium study and endoscopy, CT). The measurement of 25(OH)D levels was done using the radioimmunoassay method. In order to analyse the data, the Mann–Whitney/Wilcoxon two-sample test was applied within EpiInfo programme.
Alongside the main findings are: the mean level of vitamin D was 17 ng/ml, considered insufficient level, as well as the existence of correlations between low vitamin D levels and diffuse cutaneus scleroderma type, the presence of: oesophageal manifestations, distal joint contracture, muscular weakness/myalgia, ejection fraction $<60\%$, TL_{CO} value $<80\%$ and pulmonary interstitial fibrosis, out of which the last one has also been cited in other studies.

PS151. CLINICAL, FUNCTIONAL AND HEALTH-RELATED QUALITY OF LIFE CORRELATES OF ANXIETY AND DEPRESSION IN PATIENTS WITH SSc: A CROSS-SECTIONAL SURVEY

L. Mouthon[1], T Baubet[2], B. Ranque[3], A. Berezne[1], C. Mestre-Stanislas[1], F. Rannou[4], A. Papelard[4], S. Morel-Dubois[5], M. Revel[4], M. R. Moro[5], L. Guillevin[1], S. Poiraudeau[4] and C. Nguyen[1]
[1]*Internal Medicine, Cochin Hospital, Paris Descartes University, Paris,* [2]*Psychiatry Department, Bobigny,* [3]*Internal Medicine Department, Hôpital Européen Georges Pompidou, Paris,* [4]*Rehabilitation Department, Hôpital Cochin, Paris Descartes University, Paris and* [5]*Internal Medicine Department, CHRU Lille, Lille, France*

Objectives. To identify clinical, functional and health-related quality of life (HRQoL) correlates of anxiety and depression in patients with SSc.
Methods. Three hundred and eighty-one patients fulfilling the ACR and/or the LeRoy and Medsger criteria for SSc were assessed for visceral involvement, disability and HRQoL. Anxiety and depression were evaluated with the Hospital Anxiety Depression Scale (HAD) (defined cut-off > 8).
Results. Thirty-four (9.2%) patients had limited SSc, 187 (50.7lcSSc, and 149 (40.4%) dcSSc. Overall, 40.4 and 58.8% of patients had depression and anxiety, respectively. Compared with patients without depression, patients with depression had poorer health status and HRQoL mental component and greater global disability, hand disability and aesthetic impairment. On multivariate analysis, variables independently associated with depression were age, global disability, SF-36 mental health area and HRQoL mental component. Compared with patients without anxiety, patients with anxiety had poorer SF-36 emotional role and mental health areas, and HRQol mental component. On multivariate analysis, the only variable independently associated with anxiety was SF-36 mental health area. Remarkably, patients with and without psychiatric symptoms were comparable for all disease-related clinical features assessed.
Conclusion. High levels of anxiety and depression are observed among SSc patients. Psychiatric symptoms are rather associated with increased disability and altered HRQoL, than with disease-specific organ manifestations.

PS152. PATIENTS', RELATIVES' AND PRACTITIONERS' VIEWS CONCERNING SSc AND ITS MANAGEMENT: A QUALITATIVE INTERVIEW STUDY

L. Mouthon[1], S. Alami[2], D. Desjeux[3], E. Hachulla[4] and S. Poiraudeau[5]
[1]*Internal Medicine, Cochin Hospital, Paris Descartes University,* [2]*Université Paris Descartes and Cerlis, Interlis,* [3]*Université Paris Descartes, Faculté des Sciences Humaines et Sociales, Cerlis, Paris,* [4]*Internal Medicine Department, Université Lille 2, Lille and* [5]*Rehabilitation-Cochin Hospital, Paris Descartes University, Paris, France*

Background. The views of patients, relatives and practitioners concerning SSc and its management have seldom been studied.
Objective. To survey views of patients and care providers regarding the management of SSc and to reveal potential hurdles to improving health-care strategies.
Methods. A qualitative study was performed combining four complementary methods: semi-structured interview, life story interview, focus group and participant observation. Twenty-five patients, 10 practitioners and 4 patients' relatives were included.
Results. The relationship with care providers, especially doctors is commonly cited as a priority by patients. Expectations regarding this relationship are numerous, complex and sometimes ambivalent. Patients expect doctors to be human, attentive but also implicated in research in the field and to provide psychological and affective supports to help them accepting the uncertainty of disease evolution and the absence of curative treatments. They also expect more individualized managements, improvements in diagnosis and follow-up organization, more efforts in education and information, comprehensive behaviours and supports from working colleagues and from relatives, and increased funding from the health-care system. Care providers expectations differ from those of patients. They are more focused on treatment improvements, optimization of the health-care system, education of general practitioners and other health-care providers and expect increased funding for research.
Conclusions. Our results suggest several potential improvements to optimize patients' management: more attention and time should be devoted to patient/practitioner relationship. Patients' profiles should be more precisely defined regarding coping strategies and treatment preferences to propose more adapted and specific options.

PS153. VEGF SERUM LEVELS AS AN INDICATOR OF A VISCERAL INVOLVEMENT IN SSc

E. Morgiel[1], G. Wiland[2], P. Piesiak[3], B. Bogut[4] and **P. Wiland**[1]
[1]*Department and Clinic of Rheumatology and Internal Medicine, Wroclaw Medical University,* [2]*Ophthalmology Outpatient Clinic,* [3]*Department and Clinic of Pulmonology and Lung Cancers and* [4]*Department of Physiotherapy, Wroclaw Medical University - Wroclaw, Poland*

Background. SSc is a chronic, inflammatory CTD. The main manifestation of this disorder is excessive fibrosis which causes skin thickening and visceral organ dysfunction. The early symptom of SSc is vascular damage. The mechanisms that link vascular alteration and fibrosis remain unknown. Elevated plasma concentrations of VEGF have been reported in many autoimmune disorders and they correlated with diseases activity. VEGF increases vascular permeability and migration of cellular inflammation. The aim of this study was to assess VEGF serum concentration in SSC patients in comparison with healthy controls and to investigate the relationship of serum VEGF concentration with vascular and organ involvement.
Material and methods. Thirty patients (26 women, 4 men) who fulfilled the criteria of ARA for SSc were involved in the study. Nineteen had limited and 11 had diffuse SSc. The mean age of SSc patients was 54 (range 31–73). Twenty subjects matched by age and sex were enrolled in the study as a control group. In both groups, the concentration of VEGF was measured using ELISA. In all SSc patients, nail-fold capillaroscopy was performed and other standard diagnostic tests in order to assess organ lesion.
Results. The serum concentrations of VEGF in dSSc patients were significantly higher than in healthy controls [566 (443) *vs* 250 (143); $P = 0.004$] and in dSSc group it was higher in comparison with lSSc group [566 (443) *vs* 254 (153); $P = 0.012$]. There were not significant differences between VEGF concentration among SSc subsets. Higher concentrations of VEGF were detected in patients with higher ESR level. VEGF concentrations were correlated with the presence of pulmonary hypertension, pulmonary fibrosis on chest radiographs and reduction of DL_{CO} and FVC. Patients with more severe changes in nail-fold capillaroscopy tended to have higher VEGF serum concentration.
Conclusion. These results suggested that VEGF may play an important role in pathogenesis of Ssc. Moreover, VEGF concentration reflects visceral organ involvement in SSc patient. The further studies in a larger group are needed.

PS154. ANALYSIS OF SINGLE NUCLEOTIDE POLYMORPHISMS IN THE IL-7R AND IL-7 GENE IN SSc PATIENTS

P. Moinzadeh[1,2], C. Fonseca[1], D. J. Abraham[1], V. H. Ong[1] and C. P. Denton[1]
[1]*Centre for Rheumatology, Royal Free Hospital, Medical School, UCL, London, UK and* [2]*Department of Dermatology and Venerology, University of Cologne, Cologne, Germany*

Background. SSc is characterized by vascular damage, autoimmunity and fibrosis. The interplay between these processes is likely to be pivotal to pathogenesis of SSc. Clinical heterogeneity is a hallmark of SSc and it is likely that this is determined at least in part by genetic factors. In particular differences in expression and signalling through IL-7 receptor (IL7R) have been identified as factors determining clinical activity in other autoimmune rheumatic diseases such as SLE and systemic vasculitis but no detailed studies of genetic alterations of IL-7 and (IL-7R) in SSc have been undertaken. SSc represents a prototypic, chronic, non-relapsing, progressive autoimmune disease; we investigate whether genetic alterations also exist in SSc patients that may associate with clinical phenotypes.
Patients and methods. Patients with SSc ($n = 728$) and healthy controls ($n = 260$) were genotyped for 15 SNPs in the gene region of IL-7R and 7 polymorphisms in the region of IL-7. All patients and controls were UK Caucasian and we grouped our SSc patients according the autoantibody status and organ involvement. Genotyping was performed by the KASPar system (allele specific PCR, KBiosciences, UK).
The statistical analysis was performed using logistic regression analysis to compare the distribution of IL7R/IL7 polymorphisms.
Results. No significant differences in the genotype distribution were observed between the patient group and healthy controls, all of which were in Hardy–Weinberg equilibrium. However, there was a significant difference between SSc patients being positive *vs* negative for anti-topo I antibodies (ATA) in four SNPs located in the IL-7R region, rs11567685 [$P = 0.0075$, odds ratio (OR) for CC genotype 1.469, 95% CI 1.11, 1.95], rs11567751 ($P = 0.007$, OR for TT 1.467, 95% CI 1.11, 1.94), rs987107 ($P = 0.0081$, OR for TT 1.456, 95% CI 1.10, 1.92) and rs3194051 ($P = 0.0072$, OR for GG 1.466, 95% CI 1.11, 1.94).
Conclusion. Here we report that homozygous carriers of the minor allele in four SNPs of the IL-7R gene region were significantly stronger associated with a positive ATA status in SSc patients. This gene has been described to be associated with immune regulation in other autoimmune diseases opening a possibility of a common autoimmune genetic pathway. This is the first study which reports a potential association of Il-7R gene in SSc susceptibility. Additional independent cohorts should be analysed to confirm our findings. In addition it is possible that IL-7 expression of signaling may prove a useful candidate biomarker in disease assessment.

PS155. INVESTIGATION OF PARAMETERS OF ORAL APERTURE IN 131 PATIENTS WITH SSc IN A 3-YEAR SINGLE-CENTRE PROSPECTIVE LONGITUDINAL STUDY

Z. Bálint[1], H. Farkas[1], K. Horváth[1], C. Varjú[1], G. Kumánovics[1], L. Czirják[1] and **T. Minier**[1]
[1]*Department of Rheumatology and Immunology, University of Pécs, Pécs, Hungary*

Background. Decreased ability of mouth opening has a remarkable impact on oral hygiene, nutrition and quality of life in SSc.
Objectives. To evaluate different parameters of oral aperture in a large consecutive SSc patient cohort, and to examine their relationships with clinical parameters, disability indicators and the SF-36 Health Survey.
Methods. A total of 131 consecutive SSc patients (91 with lcSSc and 40 with dcSSc) were enrolled with a mean (S.D.) disease duration of 8.1 (7.2) years. Patients were re-evaluated 12 and 36 months later. Vertical interincisial distance at maximally opened mouth (VIID), vertical interlabial distance at maximally opened mouth (VILD), horizontal width at closed mouth (HWCM) and horizontal width at maximally opened mouth (HWOM) were measured. The area and circumference of the mouth was also estimated by considering it as an ellipse. Detailed physical examination included the modified Rodnan skin score, number of joint contractures, hand anatomic index (HAI) and presence of ulcers on the whole body surface. The European Scleroderma Study Group Activity Index was calculated. Patients filled the HAQ and the SF-36. Enrolled patients learned the physiotherapeutic protocol generally taught in our tertiary centre (including extensive orofacial exercises).
Results. The VIID, VILD, mouth area and circumference correlated negatively with the HAQ-DI, number of contractures and DASH, and positively with the HAI at all three evaluations. In addition, VIID correlated positively with the body weight and VILD with the ulcer score and the area with both of these latter clinical parameters. Changes in the area and circumference correlated with the HAQ disability index at all three evaluations.
VIID decreased significantly from a mean (S.D.) 33.2 (8.3) to 31.6 (7.2) mm after 12 months, but showed significant improvement (34.9 (7.3) mm) at 36 months. The VILD, HWOM, area and circumference showed also significant worsening after 12 months, and did not improve back to the original value. The HWCM showed a progressive significant worsening (from 51.3 (7.5) to 48.7(5.8) mm).
Conclusions. Estimated mouth area and circumference, and furthermore the interincisial and interlabial distances were related to disability parameters, including the HAQ-DI and the number of contractures. The mouth area and circumference proved to be also sensitive to change, as their changes correlated to the changes in HAQ-DI. The everyday routine physiotherapy may have a favourable effect on the temporomandibular joint movements (reflected by interincisial distance), but its effect on late-stage skin atrophy may be questionable and needs further clarification.

PS156. SCREENING FOR VERY EARLY SSc: THE VEDOSS APPROACH IN ONE EUSTAR CENTRE

C. Mihai[1], A. M. Gherghe[1], M. Bojinca[1], R. Dobrota[1], R. Sfrent-Cornateanu[1], I. Ancuta[1], M. Milicescu[1], L. Macovei[1], E. Giurescu[1], R. Jurcut[2], T. Constantinescu[3] and V. Stoica[1]
[1]*Cantacuzino Hospital,* [2]*CC Iliescu Institute of Cardiology and* [3]*M Nasta Institute of Pneumology, Carol Davila University, Bucharest, Romania*

Background. VEDOSS is a EUSTAR-endorsed multicentric, prospective, observational study and its primary goal is to develop a screening algorythm for the very early diagnosis of SSc in a population at risk: patients with RP, SSc-specific capillaroscopic changes and SSc-specific autoantibodies. This article reports on the VEDOSS screening experience in our centre.
Objectives. to assess the efficiency of the VEDOSS method—and especially the contribution of nail-fold capillaroscopy (NFC)—to identify patients at risk for SSc (as described above) in the larger population of patients with RP of unknown aetiology.
Patients and methods. our EUSTAR centre advertized the VEDOSS study to primary-care physicians and doctors of various specialties (internal medicine, rheumatology and other). Patients aged >14 years with RP of unknown aetiology were referred to the centre, where history, physical examination and NFC were performed at the first visit. Patients who presented NFC abnormalities were tested for SSc-specific serology. All patients were investigated for the clarification of RP aetiology and a classification of primary or secondary RP was made by a rheumatologist with experience in SSc. We analysed the association of various clinical and NFC features with the diagnosis of secondary RP using logistic regression.
Results. Forty-nine RP patients, among which 41 (83.7%) women, aged 18–71 [mean (S.D.) 41.5 (15.0)] years were referred to our centre between 1 February 2010 and 1 July 2011. Most patients (83.7%) were referred by a rheumatologist. After NFC and other investigations, 11 patients were diagnosed with primary RP (I RP), 29 with secondary RP (II RP) and 9 were not classified because of insufficient data. Classification of II RP patients was: 7—very early SSc (14.3%), 10—various overlap syndromes (20.4%), 5— UCTD (10.2%), 2—SLE and 2—RA (each 4.1%) and 1 (each 2%) of the following: DM, SS, systemic vasculitis. Abnormal NFC, megacapillaries and microhaemorrhages were significantly associated with II RP (odds ratios 5.75, 8.0 and 8.0, respectively, compared with I RP patients). Overall sensitivity and specificity of NFC for identifying II RP were 79.3 and 63.6%, with a positive predictive value of 69.7%.
Conclusion. Despite the predominance of referrals by rheumatologists, our approach identified a rather small number of patients at risk for SSc. The majority of II RP patients had various forms of mild CTDs. Inexpensive and non-invasive, NFC is a valuable tool in identifying II RP patients.

PS157. FREQUENCIES AND CLINICAL ASSOCIATIONS OF NON-ORGAN-SPECIFIC AUTOANTIBODIES IN A LARGE PATIENT COHORT OF THE GERMAN SCLERODERMA NETWORK

R. Mierau[1], E. Genth[2], T. Krieg[3] and N. Hunzelmann[3] for the DNSS centres[3]

[1]*Laboratory at Rheumaklinik Aachen,* [2]*Rheumaklinik Aachen and* [3]*Department of Dermatology and Venerology, University of Cologne, Cologne, Germany*

Sera of 863 SSc patients of the German Network for Systemic Scleroderma were analysed in detail for non-organ-specific autoantibodies and their clinical associations. We used a standardized protocol performed in a single laboratory by a single group of technologists, at least including IF, immunoprecipitation, line immunoassay and immunodiffusion. In addition, antibodies to cyclic citrullinated peptide (CCP) were determined in 733 of these patients.
ANAs were detected in 94.2% of patients. In 81.6%, at least one of the autoantibodies highly associated with SSc or with overlap syndromes with scleroderma features was detected, i.e. ACA (35.9%) or anti-topo I (30.1%), followed by antibodies to PM-Scl (4.9%), U1-RNP (4.8%), RNA polymerases (3.8%), fibrillarin (1.4%), Ku (1.2%), aminoacyl–tRNA synthetases (0.5%), To (0.2%) and U11-RNP (0.1%). Simultaneous presence of these autoantibodies was rare (1.6%).
SSc-associated autoantibodies disclosed characteristic associations with clinical features of patients, some of which were previously not acknowledged. Patients with ACA were less often male, older at disease onset, had a limited extension of cutaneous involvement and less involvement of internal organs except pulmonary hypertension. dcSSc was mainly associated with anti-topo I, -RNA polymerases and -fibrillarin. Patients with anti-PM-Scl frequently had muscular involvement but a low ESR and more often were devoid of any internal organ involvement.
Furthermore, additional autoantibodies were detected in 55.4% of the patients with SSc, of which anti-Ro(/-La), anti-mitochondrial and anti-p25/23 ('anti-chromo') antibodies were most frequent. Coexistence of SSc-associated and other autoantibodies was common (43% of patients). Anti-Ro and/or -La antibodies showed a high correlation with elevated ESR. Anti-p25/23 was exclusively detected in conjunction with ACA and particularly associated with sicca syndrome. Antibodies to CCP were found in 6.1% of the patients and were significantly associated with synovitis as well as with antibodies to U1-RNP.
The five autoantigens centromere, topo I, PM-Scl, U1-RNP and RNA polymerase were detected by >95% of the known SSc-associated antibody responses in ANA-positive SSc patients and characterize ~79% of all SSc patients in a central European cohort. These data confirm and extend previous data on the role of non-organ-specific autoantibodies in defining the diagnosis, subset allocation and prognosis of SSc patients.

PS158. ULTRASONOGRAPHY IS HELPFUL IN THE EVALUATION OF ARTICULAR MODIFICATIONS OF THE TEMPOROMANDIBULAR JOINT IN SSc

D. Melchiorre[1,2,3,4], M. Maresca[1,2,3,4], F. Bandinelli[1,2,3,4], A. Del Rosso[1,2,3,4], G. Salvadorini[1,2,3,4], Y. Blagojevic[1,2,3,4] and M. Matucci-Cerinic[1,2,3,4]
[1]*Department of Rheumatology AVC,* [2]*Department of Biomedicine,* [3]*Department of Medicine and* [4]*Denothe Center, University of Florence, Florence, Italy*

Background. The inflammatory involvement of TM joint (TMJ) in rheumatic diseases may induce the damage of the TMJ provoking a severe impairment of mouth opening and affecting patient's quality of life. TMJ may be also involved in SSc.
The aim of the present investigation was to evaluate the usefulness of US imaging for the detection of disc displacement, condylar alterations and IA effusion in SSc patients compared with MRI.
Methods. Twenty SSc patients (females with mean age 66.9 years) with TMJ involvement were consecutively examined. US examination was performed on both TMJ, in static and dynamic phases, by means of My Lab70 US 7-18 MHz (Esaote, Genoa, Italy). The probe was placed along the axis of the mandibular branch. The following TMJ characteristics were evaluated in each joint: (i) joint space; (ii) presence of joint effusion; (iii) condylar profile; (iv) position of the articular disc at open and closed mouth. MRI on both TMJ was performed in all patients.
Results. All SSc patients had reduced mouth opening with monolateral or bilateral TMJ pain. Not correlation with disease duration was found.
MRI: in the patients, joint effusion was depicted by a thin line or area of high signal intensity within the joint space. It was detected in 6/25 SSc patients (24%). Condylar alterations were detected by MRI in 13/25 SSc patients (52%). MRI revealed also disc displacement in 7/25 SSc patients (28%). In 7 SSc patients erosions were present.
US: in 7/25 SSc patients (28%) US showed joint effusion. Condylar alterations were observed in 15/25 SSc patients (60%). Disc displacement was evident in 8/25 SSc patients (32%). Erosions were detected in nine SSc patients.
Concordance MRI-US: the concordance between US and MRI was evaluated. For joint effusion, concordance was 86%. In US assessment of disc displacement, a concordance with MRI was 87.5%. A concordance for condylar alterations was detected 79.3%.
Conclusions. Our data show that TMJ modifications may be detected by US examination in SSc patients.
It is important to note that pain in SSc patients is not usually related to the occurrence of joint effusion but more often to disc displacement or remodelling of the condyle and the presence of condylar alterations in SSc is an interesting finding observed by US.

PS159. NAIL-FOLD VIDEOCAPILLAROSCOPY IN PULMONARY HYPERTENSION: A VALUABLE DIAGNOSTIC TOOL?

F. Meier[1], M. Geyer[1], U. Müller-Ladner[1], R. Dinser[1] and W. Hermann[1]
[1]*Department of Internal Medicine and Rheumatology, JLU Gießen, Kerckhoff-Klinik, Bad Nauheim, Germany*

Background. Pulmonary hypertension (PH) is characterized by elevated pulmonary arterial pressure, untreated resulting in right ventricular heart failure. PH can be based on idiopathic pulmonary arterial hypertension (iPAH), chronic thromboembolic events (CTEPH), left heart disease (PV-PH) or it can be associated with other diseases such as chronic obstructive pulmonary disease (COPD-PH) or SSc (SSc-PAH). In this study, analysis of microvascular patterns of microangiopathy of patients with PH have been performed using nail-fold videocapillaroscopy (NVC).The benefit of this easy to handle diagnostic tool in PH was evaluated with a distinct focus on SSc patients.
Method. NVC was performed in 90 patients, of whom 63 had PH due to different disease entities. 27 had SSc without PAH. Second to fifth fingers were bilaterally analysed. Three pictures of adequate quality for evaluation, at least one from each hand, were scored for capillary density (CD, capillaries per millimetre), afferent, efferent, apex and total width. Parameters such as haemorrhages, neoangiogenesis and oedema or capillary alterations such as ectasia (>20 μm), irregular shape, tortuousity or giant shape (>50 μm) were qualitatively assessed. For SSc patients, the respective pattern of microangiopathy ('early', 'active' or 'late') was determined.
Result: Of the patients, 6.7% had COPD-PH, 15.6% CTEPH, 13.3% iPAH, 13.3% PV-PH, 41.1% SSc, of whom 11.1% had PAH. Of them, 10% had other causes of PH. In SSc, 32% showed the 'early' [CD 6.5 (1.6)], 41% the 'active' [CD 4.2 (1.2)] and 27% the 'late' pattern [CD 3.5 (0.9)]. The CD in SSc-PAH was significantly lower compared with all other PH forms (<0.0001), but did not differ compared with SSc non-PAH ($P = 0.73$, Table 1). In general, afferent, efferent, apex and total width of capillaries were larger in SSc-PAH (Table 1). Ectasia was very

TABLE 1. Capillary dimensions in pulmonary hypertension

					SSc		
	COPD-PH	CTEPH	iPAH	PV-PH	PAH	Non-PAH	Total
n	6	14	12	12	10	27	37
Age, years	61 (8)	68 (13)	68 (14)	70 (7)	63 (10)	55 (13)	57 (12)
Sex, female:male	1:1	1.8:1	3:1	1:1.4	9:1	3.5:1	4.3:1
CD, capillaries/mm	11.7 (1.7)	9.47 (1.9)	10.2 (1.0)	10.0 (1.7)	4.7 (1.6)	4.9 (2.2)	4.8 (1.8)
Width, afferent, μm	11.9 (2.9)	13.0 (2.6)	13.2 (3.9)	12.4 (2.2)	40.7 (23.8)	41.3 (22.3)	40.8 (23.1)
width, efferent, μm	14.6 (2.6)	17.0 (3.3)	16.2 (4.5)	15.6 (2.9)	56.2 (32.0)	54.1 (28.7)	55.7 (30.7)
width, apex, μm	19.2 (5.5)	21.3 (5.2)	19.9 (4.1)	18.4 (3.8)	59.4 (28.9)	57.9 (33.8)	59.0 (29.8)
width, total, μm	39.5 (6.9)	42.0 (5.7)	39.8 (7.9)	38.8 (4.6)	124.5 (62.3)	128.7 (56.0)	125.6 (59.9)

Data expressed as arithmetic means, 95% confidence interval or standard deviation in brackets.

common in SSc-PAH (90%), but to some extent also present in other forms, most frequently in COPD-PH (66.7%). Giant capillaries and oedema were generally only present in SSc (81 and 73%, respectively). Haemorrhages occurred in all disease forms of this study; however, mostly in SSc (86%) and COPD-PH (83%).
Conclusion. Assessing capillary density in PH is a powerful tool to discriminate between SSc-PAH and other forms of PH. In this respect, qualitative parameters such as giant shape and oedema can support the elucidation of the underlying disease. Therefore, NVC should be considered if the underlying cause of PH is unclear.

PS160. DETERMINANTS OF MAIN PULMONARY ARTERY DIAMETER IN SCLERODERMA PATIENTS WITH AND WITHOUT PULMONARY INVOLVEMENT

R. McCall[1], P. Nietert[1], J. Ravenel[2], R. Silver[1] and M. Bolster[1]
[1]*Department of Medicine and* [2]*Department of Radiology, Medical University of South Carolina, Charleston, USA*

Purpose. To explore findings by pulmonary function testing (PFT) and right heart catheterization (RHC), which may contribute to the main pulmonary artery diameter (MPAD) in scleroderma patients with possible interstitial lung disease (ILD) and/or pulmonary hypertension (PH).
Materials and methods. Medical record review and CT image analysis were performed on 57 patients with suspected scleroderma who were identified as having undergone a chest CT scan at the Medical University of South Carolina between 28 November 2003 and 28 November 2008. Patients were required to have undergone PFTs and RHC within 6 months of the chest CT scan for inclusion into the study. Correlations were examined between MPAD and several potential predictors of pulmonary artery diameter including forced vital capacity (FVC), diffusion capacity for carbon monoxide (DL_{CO}) and CT-based measures of pulmonary involvement. Multivariable linear regression was used to evaluate the contribution of additional covariates to a nested model of MPAD that controlled for both mean pulmonary arterial pressure (mPAP) and aortic diameter (AD). Patients were then divided into the following groups: Group A (FVC values $>70\%$ predicted), Group B (FVC values $<70\%$ predicted), Group C ($DL_{CO}>40\%$ predicted) and Group D ($DL_{CO}<40\%$ predicted). Correlations between MPAD and mPAP were subsequently determined for each group.
Results. Following chart review and after excluding those patients with poor vascular delineation or insufficient CT evaluation of the chest, 33 patients remained for whom both RHC and PFT data were available. The strongest unadjusted correlation between MPAD and the candidate predictors was with mPAP ($r^2=33.6\%$, $P=0.0004$). When controlling for both mPAP and AD, five additional variables were found to be potential contributors to the MPAD model: FVC, DL_{CO}, BSA, age and the presence of fibrosis on chest CT scan. The unadjusted correlation between MPAD and mPAP in Group A ($r^2=47.3\%$) was different from Group B ($r^2=17.6\%$), although this difference did not reach statistical significance ($P=0.30$). Similarly, variation in the correlation between MPAD and mPAP was seen as Group C ($r^2=38.8\%$) trended towards a stronger correlation than Group D ($r^2=22.6\%$).
Conclusion. As expected, MPAD is largely associated with mPAP. However, diminished pulmonary function as represented by a decrease in FVC and/or impaired DL_{CO} may explain a significant amount of the variability in MPAD when considering the scleroderma population.

PS161. TREATMENT OF DIGITAL ULCERS IN SSc: A REVIEW OF EIGHT PATIENTS FROM A SINGLE CENTRE AND DISCUSSION ON OUTCOME

J. Matos Costa[1], I. Aguiar Camara[1], J. P. Andrade[1], A. R. Paulos[1], H. V. Dias[1], Y. Abuowda[1] and C. Santos[1]
[1]*Hospital Distrital DE Santarém, Santarém, Portugal*

Introduction. In SSc, digital ulcers (DUs) are debilitating and sometimes recurrent complications. Treatment of DU is not dissociable from that of RP, both being clinical expressions of the same underlying microvascular disfunction, although of different gravity. Our goal is clinical characterization of a population of SSC patients with DU, its treatment, complications and outcome.
Patients and methods. Retrospective study of 38 patients, with SSc meeting ACR or LeRoy classification criteria, from our outpatient clinic in a Portuguese hospital serving ~200 000 inhabitants. Clinical data were obtained from patient files.
Results. During follow-up of 38 patients from 1999 to 2011, DUs were diagnosed in 8 patients. Three males (37.5%), and 5 females (62.5%), aged between 38 and 76 years (mean age 56.1). All eight patients had limited-type SSc/CREST syndrome, ACAs were positive in seven. Healing of DU was made with i.v. prostanoid in seven patients, every patient was previously treated with calcium channel blockers (CCBs) for RP. Seven patients were later treated with bosentan and there was no recurrence of DU in six. Two patients had digital loss. One of these patients presented with pulmonary arterial hypertension (PAH) and DU, and the diagnosis of SSc was made; PAH normalized after treatment with bosentan. Two patients are dead: one died of liver failure and the other with massive digestive bleeding. Three patients are still professionally active.
Conclusion. DUs are serious manifestations of vasculopathy, a sign of target-organ damage; they are associated with increased morbidity (hand disability, reduced quality of life) and mortality. Treatment of DU comprises: (i) detection of complications, (ii) promoting healing, (iii) preventing recurrence. Patients with SSc and DU have a worse prognosis, but there is sufficient evidence to support recommendations on standard of care and the most effective drugs available. The i.v. prostanoids and CCB have the highest level of evidence. Bosentan is recommended to prevent recurrence of DU, improving outcome. In this small series, patients with worse outcome were older, had longer follow-up and late diagnosis, already with organ damage. Younger and more recent patients have better results, probably mirroring improvement in quality of care.

PS162. DIGITAL ULCERS IN SSc: TREATMENT OF THREE CASES WITH BOSENTAN

S. Martins[1], C. Gil[1] and M. Carvalho[1]
[1]*Internal Medicine Department, Rainha Santa Isabel Hospital, Torres Novas, Portugal*

The authors describe three clinical cases of patients with SSc and digital ulcers treated with bosentan.
The first case is of a 57-year-old male patient, diagnosed with SSc in October 2008. At the time of diagnosis, he presented digital ulcers of both hands, for which he was treated with bosentan. Despite improvement at this level, there was progression of his underlying illness, and he died in December 2009.
The second case describes an 81-year-old female patient diagnosed with SSc in March 2010. Two months later she developed digital ulcers of both feet, achieving good clinical response to therapy with bosentan. Not unexpectedly, this patient also demised 1 year after initial diagnosis due to natural disease progression.
The third case reports a 63-year-old female patient, diagnosed with SSc in May 2010. At the time of diagnosis, she presented painful digital ulcers of both hands which interfered with the realization of her daily activities. She initiated treatment with bosentan with complete ulcer regression.
These three cases reflect the experience of our Hospital's Auto-immunity Consult in the use of bosentan, an ET-1 receptor antagonist, for effective treatment of digital ulcers in the context of underlying SSc.

PS163. RP AND DIGITAL ULCERS IN SSc: EXPERIENCE OF AN INTERNAL MEDICINE DEPARTMENT

A. Martins[1], G. Guerreiro[1], A. Baptista[1], F. Alves[1], D. Nunez[1], H. Brito[1], I. Mendonça[1] and P. Silva[1]
[1]*E.P.E. – Internal Medicine Department, Hospital of Faro, Faro, Portugal*

SSc is a complex multisystemic autoimmune disease of unknown aetiology characterized by cutaneous and visceral fibrosis and widespread vascular pathology. In SSc there is an exaggerated generalized vasospastic tendency clinically represented by RP, an abnormal reactivity of blood vessels to cold and other stimuli. Excessive vasoconstrictive responses lead to pallor and cyanosis of distal extremities, with complications such as digital ulceration and infarction. Ulcers on the fingertips and over the interphalangeal joints are extremely painful and limit function; they heal with scarring and digital resorption, and, when infected, can lead to osteomyelitis and serious soft tissue infections. Therapeutic management of RP and digital ulcers include non-pharmacological measures (tobacco abstinence, avoid cold exposure, minimize emotional stress), calcium channel blockers, phosphodiestrase type 5 inhibitors, prostacyclin analogues and endothelin receptor antagonist. Although many of these pharmacological agents have shown to be effective in treating RP, digital ulcerations remains a serious complication for many patients

and its treatment is still a clinical challenge. The authors propose to retrospectively analyse the prevalence, treatment strategies and outcome of vascular complications in patients with SSc who are followed in the department. This evaluation will be based on patient's demographic data, SSc history and type, presence of autoantibodies, prevalence of RP and digital ulcers, previously and ongoing treatment and its outcomes.

PS164. DIGITAL ULCERS EVOLUTION WITH BOSENTAN

C. Brito[1], M. Magalhães[1], A. Araújo[1], D. Fernandes[1], P. Soares[1], L. Teixeira[1], N. Sousa[1], M. Goja[1], A. Ponte[1], A. Ferrão[1] and R. Saraiva[1]
[1]*Centro hospitalar Leiria – Pombal, Leiria, Portugal*

Digital ulcers, defined as necrotic lesions located in the distal portion of the fingers or in the osseous prominences, are a manifestation of vascular dysfunction that can occur in SSc (until 50% of patients) as well as in other diseases, as in MCTD.
His pathogenesis is related with tissue ischaemia consequent to vasospasm secondary to RP, fibro-proliferation of the intima and digital arteries thrombosis.
These are, in many cases, very debilitating, making it difficult the diary activities, assuming a great impact in the patient well-being.
Currently there are many pharmaceutical options in the treatment of the digital ulcers, being important the pain relief and the local care to avoid infections.
The authors present two clinical cases, of two patients, one with the diagnosis of SSc, and the other with MCTD, with debilitating digital ulcers, without improvement with first-line therapy, which healed after treatment with bosentan.

PS165. MULTISYSTEMIC ENVOLVEMENT AFTER 25 YEARS OF NON-TREATED SSc: CASE REPORT

V. Machado[1], A. Cabral[1], C. C. Vaz[2], F. Maçoas[3], F. Cabral[4], A. Sousa[1] and R. Pereira[1]
[1]*Internal Medicine Service,* [2]*Rheumatology,* [3]*Gastroenterology Service and* [4]*Dermatology Service, Hospital Sousa Martins – ULS Guarda EPE, Guarda, Portugal*

Introduction. SSc is a chronic autoimmune disease characterized by fibrosis of the skin and internal organs as well as small-vessel vasculopathy. It has a wide range of clinical manifestations and one of the highest case-fatality among the CTDs.
Objectives. The authors present a clinical case of advanced SSc with potentially fatal complications.
Materials and methods. Review of a patient's clinical file.
Clinical Case: A 46-year-old woman with a personal history of SSc (25 years of evolution) who had always refused immunosuppressive therapy, was admitted to our Emergency Service with a sudden onset of dyspnoea, gurgling sounds with breathing and atypical chest pain. The initial physical examination revealed central and peripheral cyanosis, cold skin, chest retractions, tachypnoea, low oxygen saturation with a high-flow mask, tachycardia, jugular vein engorgement, pulmonary auscultation with fine bilateral crepitant rales and lower limb oedemas. The diagnosis of acute pulmonary oedema was established and it was necessary to apply intensive medical therapy and noninvasive ventilation. She was admitted to the Intensive Care Unit for 2 days and then transferred to the Internal Medicine Service. She had already undergone seven oesophageal stricture dilatations and on clinical examination presented with fatigue, skin induration associated with tightening and thickening, pigmentary changes, facial telangiectasias and paucity of wrinkles, microstomia, severe deformities and bilateral sclerodactyly with loss of digital tissue of the fingers. The serum levels of ANAs (1:640) and anti-Scl-70 (144 U/ml) were increased. The X-rays of the hands showed calcinosis, severe acro-osteolysis and deformities of both hands. Echocardiography revealed a moderate pericardial effusion with pre-colapse of the right atrium and pulmonary hypertension (PASP: 50 mmHg). The respiratory function test showed moderate restrictive respiratory syndrome. The chest CT images revealed pulmonary fibrosis, peribronchovascular and pleural thickening, small pleural effusion, large pericardial effusion and osteolytic lesions of two thoracic vertebrae. New distal ischaemic lesions of the fingers appeared during hospitalization. The patient remained clinically and analytically stable and was later transferred to a Rheumatology Service of a Central Hospital in order to initiate specific treatments for the identified complications.
Conclusions. This patient had a significant long-term evolution of SSc without specific treatment which allowed the development of dermatological, osteoarticular, gastroenterological, pulmonary and cardiovascular complications, some of them life-threatening. This clinical case alerts to the importance of an early accurate diagnosis, the need to initiate adequate treatment as soon as possible and apply measures to enhance the patient's compliance.

PS166. KIENBÖCK DISEASE IN A PATIENT WITH SSc: A CASE REPORT

F. Lumetti[1], A. Manfredi[1], **D. Giuggioli**[1], M. T. Mascia[2], A. Marcuzzi[3] and C. Ferri[1]
[1]*Rheumatology Unit,* [2]*Department of Pathology of Locomotor System and* [3]*Hand Surgery Unit, University of Modena and Reggio Emilia, Modena, Italy*

Kienböck's disease (KD) is a rare disease characterized by osteonecrosis of the carpal lunate bone. The dominant hand of males in adulthood is predominantly affected, with peak of incidence between the second and fourth decade. The KD is rarely bilateral; early diagnosis is based on MRI or CT findings.
The aetiology of KD is uncertain, but the theory of repeated traumatism/microtraumatism associated with vascular changes is considered to be a reliable hypothesis.
We describe the rare case of a patient followed in our Rheumatology Unit affected by SSc since 1996 and recently complicated by KD.
Case report. Woman, 45 year old, clerk, affected by dcSSc, anti-Scl-70 antibody positive.
The patient's clinical history was characterized by recurrent digital ulcers, mild interstitial lung disease with normal respiratory function tests and DL_{CO}, mild gastro-oesophageal reflux and xerostomia.
No other comorbidities or risk factors for osteonecrosis were detectable. In the past, she was treated with low-dose steroids; more recently long-term treatment with prostanoids and bosentan was administered. In October 2010, the patient reported swelling and pain in his left wrist (VAS pain, 80/100), worsened with movements and refractory to both NSAID and analgesics.
X-ray examination of the wrist showed the presence of dense lunate. The diagnosis of KD, stage II, was successively confirmed by MRI.
Blood tests reported normal coagulation tests and absence of other immunological alterations, namely LAC, anti-cardiolipin, -B2GP1 and -DNA antibodies.
The resection of the first chain of the wrist was suggested by the hand surgeon, refused by the patient. Local treatment with magnetotherapy and shock waves slightly improved the local pain (VAS 50/100).
A radiological re-evaluation of the lesion has been planned to decide the next treatment.
Discussion. Nonetheless the low prevalence of both SSc and KD, some other patients with such association have been described since 1987.
The alterations in the microcirculation, which represent one of the main pathogenetic features of SSc, are considered to be possible causes of osteonecrosis. These common vascular abnormalities may explain at least in part the association between SSc and KD; other unknown pathogenetic co-factors are probably decisive for the appearance of this rare association.
From a practical point of view, patients with SSc suddenly developing deep pain of the wrist, unresponsive to analgesic and anti-inflammatory therapy, should undergo X-ray examination, and if indicated MRI or CT scan, in order to exclude the typical osteonecrosis of the lunate.

PS167. PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH CONNECTIVE TISSUE DISEASE: A SINGLE-CENTRE EXPERIENCE

M. Luknar[1], P. Lesny[1], I. Varga[1], P. Solik[1], J. Lukac[2], J. Rovensky[2] and E. Goncalvesova[1]
[1]*National Cardiovascular Institute, Bratislava and* [2]*National Institute of Rheumatic Diseases, Piestany, Slovak Republic*

Background. Pulmonary arterial hypertension (PAH) can be associated with several CTD and is a strong negative prognostic factor. Patients with CTD associated PAH have been proven to benefit from specific treatment. Right heart catheterization is essential for the correct diagnosis.
Aim: To describe the prevalence of PAH among patients with CTD referred to a single centre due to clinical and/or echocardiographic suspicion of PAH.
Patients and methods. Eighty-seven patients were presented to PAH centre by rheumatologists due to either clinical or echocardiographic suspicion of PAH from May 2007 to August 2011. The patients had preserved left ventricular ejection fraction and no significant left heart

valvular disease. Scleroderma spectrum of disease (mostly limited form) was the underlying CTD in 65 patients, systemic lupus in 6 patients, DM and PM in 3 patients, RA in 3 patients, primary SS in 2, overlap syndrome in 3 and other CTD in 5 patients. PAH suspicion was discarded in 38 patients due to a lack of clinical and echocardiographic signs or for obvious other reasons for PH such as marked lung disease. Catheterization was considered in 49 patients and finally performed in 38 patients (11 patients refused the invasive procedure). A comprehensive diagnostic algorithm was used to rule out or confirm other classes of PH.

Results. Sixteen patients had no PH according to current criteria. From among 22 patients with pulmonary hypertension, 4 had class II PH due to left vetricular diastolic dysfunction. Class III PH due to hypoxia was confirmed in three patients. Eventually, 15 patients were diagnosed with PAH. In 11 patients, the underlying CTD was scleroderma, 2 patients had RA, 1 SS, and 1 patient lupus. These patients were treated by specific PAH treatment.

Conclusion. PAH was confirmed in 17.2% of CTD patients referred due to clinical and/or echocardiographic suspicion. In the scleroderma subgroup, the prevalence was 16.9%. This does not reflect the actual prevalence of CTD associated PAH due to group characteristics and other factors. Catheterization is warranted in symptomatic patients even in the absence of marked echocardiographic signs of PH.

PS168. RELATIONSHIP BETWEEN QUANTITATIVE NAIL-FOLD CAPILLAROSCOPIC MEASUREMENTS AND ECHOCARDIOGRAPHIC PULMONARY ARTERIAL SYSTOLIC PRESSURE IN SSc

A. H. L. Low[1,2,3], Y. S. Tan[1], J. Yoong[1,2,3], L. C. Chew[1,2,3], N. L. Lui[1,2], K. Y. Y. Leung[1,2,3], K. Y. Fong[1,2,3] and J. Thumboo[1,2,3]
[1]*Department of Rheumatology and Immunology, Singapore General Hospital, Singapore,* [2]*Yong Loo Lin School of Medicine, National University of Singapore and* [3]*Duke-National University of Singapore, Graduate School of Medicine, Singapore, Singapore*

Aims: In order to investigate whether nail-fold capillaroscopy (NFC) may be useful as a complementary tool to echocardiography in screening for pulmonary hypertension (PH) in patients with SSc, we sought to determine the relationship between quantitative measurements on nail-fold capillaroscopy (NFC) and echocardiographic pulmonary arterial systolic pressure (PASP).

Methods. Capillary density (CD, defined by number of capillary loops per 1 mm length) and loop diameter (LD, expressed as the mean LD of up to five consecutive visible loops per finger) were studied in 21 patients with SSc. NFC measurements were made within 6 months of echocardiography in all patients. Spearman's correlation (r) and Mann–Whitney U-test were used to investigate the relationship between PASP and NFC measurements.

Results. Of 21 patients with SSc, 5 had echocardiographic PASP $\geq$ 40 mmHg. There was no statistically significant correlation between PASP and either CD ($r = -0.06$, $P = 0.8$) or LD ($r = 0.3$, $P = 0.2$). Comparing patients with and without PH defined by echocardiographic PASP $\geq$ 40 mmHg, CD (5.0 *vs* 5.4 per mm) and LD (52.8 *vs* 54.2 μm) were not significantly different between the two groups.

Conclusion. In this pilot study, NFC does not appear to be useful in the evaluation of PH in SSc.

PS169. VALIDATION OF THE SCLERODERMA HEALTH ASSESSMENT QUESTIONNAIRE AND QUALITY OF LIFE IN ENGLISH- AND CHINESE-SPEAKING PATIENTS WITH SSc

A. H. L. Low[1,2,3], M. E. Png[1], H. H. Li[2,4] and J. Thumboo[1,2,3]
[1]*Department of Rheumatology and Immunology, Singapore General Hospital,* [2]*Duke-National University of Singapore, Graduate Medical School,* [3]*Yong Loo Lin School of Medicine and* [4]*Department of Clinical Research, Singapore General Hospital, Singapore, Singapore*

Aims: Conceptual differences between quality of life concepts and attitudinal differences towards data collection are known to exist between Asian and Western cultures. In this era of multicentre international trials, it is important to assess the cross-cultural validity of these instruments. Our aims were to perform cross-cultural adaptation and validation of the Scleroderma Health Assessment Questionnaire (SHAQ, comprising the HAQ-DI and additional five Visual Analogue Scales) and Systemic Sclerosis Quality of Life scale (SSc-QoL) in English- and Chinese-speaking patients with SSc.

Methods. In this Institutional Review Board-approved study, patients with SSc seen at the rheumatology outpatient clinics were consecutively recruited over 11 months. We used the Chinese translation of the HAQ-DI previously validated for patients with RA in Singapore, and adopted the guidelines by Beaton in the Chinese translation of the five SHAQ VASs and the SSc-QOL. We evaluated (i) test re-test reliability using the Intraclass Correlation Coefficient (ICC), (ii) known-groups construct validity by stratifying patients according to organ involvement and symptom severity and (iii) convergent validity with short-form 36 version 2 (SF-36v2). Spearman's correlation, Kruskal–Wallis and Mann–Whitney U-tests were used as appropriate to evaluate construct and convergent validity.

Results. Fifty-five SSc patients completed the questionnaires (31 in Chinese, 24 in English), of whom 39 responded to the re-test (21 in Chinese, 18 in English). The SSc-QoL, HAQ-DI, Breathing, Finger Ulcer and Overall Disease Severity Visual Analogue Scales (VASs) demonstrated high reliability (ICCs 0.70–0.91). The Intestinal, Breathing, Raynaud's, Finger Ulcer and Breathing VASs were able to differentiate patients according to their respective organ involvement (all $P < 0.05$). HAQ-DI was significantly worse in patients with severe peripheral vasculopathy (1.12) compared with those without (0.38, $P = 0.015$). Overall disease severity VAS was significantly worse in patients with increasing New York Heart Association functional class ($P = 0.006$). As hypothesized, the SHAQ correlated better with the physical summary component than the mental summary component scores of the SF-36v2. The SSc-QoL also demonstrated good convergent validity with the SF-36v2 scales.

Conclusion. In this pilot study, we demonstrated good test–retest reliability and reasonable construct and convergent validity of S-HAQ and SSc-QoL for use in English- and Chinese-speaking SSc patients. This forms the basis for future studies to assess their psychometric properties more extensively.

PS170. ASSOCIATION OF PULMONARY HYPERTENSION BY ECHOCARDIOGRAPHY WITH CLINICAL PARAMETERS IN ASIAN PATIENTS WITH SSc

A. Low[1,2,3], G. G. Teng[4], W. G. Law[5,2], A. Y. N. Lim[4], E. T. Koh[5,2], K. Y. Fong[1,2,3], G. Chan[5,2], A. Santosa[4], J. L. Tan[6], J. Yip[7] and J. Thumboo[1,2,3]
[1]*Department of Rheumatology and Immunology, Singapore General Hospital,* [2]*Yong Loo Lin School of Medicine, National University of Singapore,* [3]*Duke-National University of Singapore, Graduate School of Medicine,* [4]*Division of Rheumatology, University Medicine Cluster, National University Health System,* [5]*Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital,* [6]*Department of Cardiology, National Heart Centre and* [7]*National University Heart Centre, Singapore, Singapore*

Aims: Pulmonary hypertension (PH) is a major cause of mortality in SSc. Screening is necessary to identify patients early for treatment. In Asian patients with SSc, we investigated the relationship between PH by echocardiography and clinical parameters, to better identify patients at risk of PH.

Methods. In this cross-sectional pilot study, patients with SSc were consecutively recruited during their annual screening for PH with Doppler echocardiography. Exclusion criteria were serum creatinine >150 μmol/l or left ventricular systolic function <40%. NT-proBNP and clinical assessment using standardized protocol were determined within 2 and 6 weeks of echocardiography, respectively. PH was defined by pulmonary arterial systolic pressure (PASP) >40 mmHg on echocardiography. Univariate analysis was performed.

Results. Sixty-two patients (92% female; 79% Chinese, 11% Malay, 7% Indian and 3% other ethnicity) were diagnosed with SSc fulfilling ACR classification criteria (90%) or EULAR criteria for early SSc (10%) (44% diffuse, 53% limited cutaneous disease, 3% sine scleroderma), at a median age of 45 years. Median age and disease duration at the time of echocardiography were 54 and 4.5 years, respectively. Pulmonary function test (PFT) within 1 year of echocardiography was available in 49 patients. Prevalence of PH was 24% ($n = 15$), of whom 11 had concomitant interstitial lung disease (ILD) diagnosed by high-resolution CT.

Patients with PH were significantly older (57 years) compared with those without PH (44 years) ($P = 0.03$) with no difference in disease duration (4 *vs* 5 years, respectively) ($P = 0.5$) at the time of echocardiography. Increasing New York Heart Association functional class was associated with PH ($P = 0.01$). Reduced DL_{CO}% predicted [at thresholds <50% ($P = 0.03$); <60% ($P = 0.001$)] and increased FVC/DL_{CO} ratio [at thresholds >1.4 ($P = 0.006$); >1.6 ($P < 0.006$); >1.8 ($P < 0.001$)] were associated with PH. There was significant difference between median NT-pro-BNP levels (213 *vs* 67 pg/ml, $P < 0.001$) in patients with and without PH.

Conclusion. Age at SSc diagnosis, NYHA class, PFT parameters and NT-proBNP were associated with PH by echocardiography. Limitation of this study was the use of PASP as a surrogate marker of PH.

This pilot study provides the basis for confirmation of the relationship between the above parameters (individually or in combination) with right heart catheter confirmed pre-capillary PH in Asian patients with SSc.

PS171. HLA-DRB1 ALLELES AND AUTOANTIBODY PRODUCTION IN A PORTUGUESE SCLERODERMA COHORT

A. Lopes[1], M. Fonseca[1], I. Almeida[1], F. Perneta[1], A. Bettencourt[2], C. Carvalho[2], A. Marinho[1], P. P. Costa[3], B. Martins[2] and C. Vasconcelos[1]
[1]*Unidade de Imunologia Clinica, Hospital de Santo Antonio, Centro Hospitalar do Porto,* [2]*UMIB, Instituto de Ciencias Biomedicas Abel Salazar, Universidade do Porto and* [3]*Instituto Nacional de Saude Dr Ricardo Jorge, Insa Porto, Porto, Portugal*

Introduction. SSc is a complex autoimmune multisystemic disease. There is increasing evidence of a genetic component in its pathogenesis, clinical manifestations and serological phenotype. Previous studies have suggested a link between specific organ involvement (lung fibrosis and renal crisis) and HLA genotypes.
Objective. To evaluate possible associations between disease subphenotypes, clinical subsets, autoantibody production and HLA-DRB1 genotypes in a Portuguese SSc patient's cohort.
Patients and methods. A total of 64 patients, all white, were enrolled and characterized for demographics, disease duration and pattern of skin disease (diffuse *vs* limited). Organ involvement was evaluated using the Medsger severity scale. SSc-specific autoantibodies—including ACA, anti-topo I (ATA), anti RNA polymerase III (ARA) were recorded. HLA-DRB1 alleles were genotyped by PCR-SSP. The chi-square or Fisher's exact test were applied to analyse the data.
Results. An association between HLA-DRB1* 01 and ACA positivity [$P = 0.001$, OR = 3.6 (1.5, 8.3)] was found. HLA-DRB1*11 and DRB1*15 alleles were also correlated with ATA positivity [$P = 0.006$ OR = 4.0 (1.60, 9.97)]. The remaining serological results and clinical parameters such as disease pattern and severity showed no significant HLA associations.
Conclusion. This study demonstrates that autoantibody production in SSc is associated with the presence of certain HLA Class II alleles. These results are consistent with previous reports observed in larger cohorts and confirm this correlation in a Portuguese population. Further studies should be undertaken in order to find additional associations between disease subphenotypes and genetic background.

PS172. INTERPLAY BETWEEN BODY MASS INDEX AND BRAIN NATRIURETIC PEPTIDE IN SCREENING FOR PULMONARY ARTERIAL HYPERTENSION IN SSc

S. Lee[1], S. Lee[1] and W. Chung[1]
[1]*Dong - A University, Pusan, South Korea*

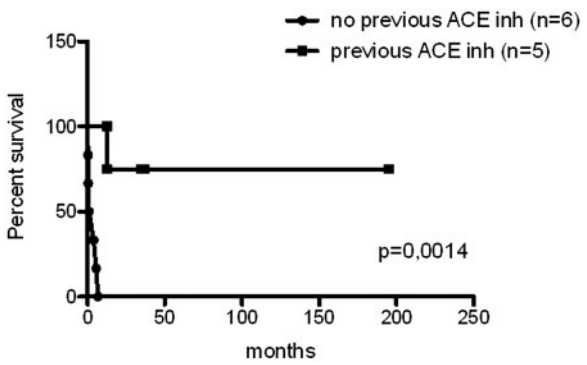
Objective. To analysed affection of the BMI in level of brain natriuretic peptide (BNP) in screening for pulmonary arterial hypertension (PAH) in SSc.
Methods. Between January 2010 and September 2011, outpatients referred to our unit and satisfying LeRoy criteria for SSc were assessed for PAH. Doppler echocardiography, BNP measurement and BMI measurement were done concomitantly for a complete clinical, instrumental and biochemical evaluation. Right-heart catheterization was carried out in cases of suspected PAH [estimated pulmonary arterial pressure (PAP) >40 mmHg; diffusion capacity for carbon monoxide (DL_{CO}) <40% of predicted value; 1-year DL_{CO} decline >20% in absence of pulmonary fibrosis; unexplained dyspnoea].
Results. Twenty-nine patients were enrolled (23 women, 6 men; 4 limited SSc, 25 diffuse SSc); precapillary PAH was found in two patients (0 limited SSc, 2 diffuse SSc). All subjects were divided into three groups: Group A, BMI<25 ($n = 25$); Group B, BMI 25–30 ($n = 3$) and Group C, BMI>30 ($n = 1$). Group A: significantly increased with BNP, CRP and troponin I. As BMI increased, BNP, and malnutrition state significantly decreased, while BNP decreased in Group C. The estimated PAP correlated with BNP ($r = 0.3$; 95% CI 0.14, 0.44) but not with BMI ($r = 0.7$, 95% CI 0.14, 1.45). BNP ($P = 0.032$) and creatinine ($P = 0.049$) were independent predictors of PAH, while BMI was not ($P = 0.50$).
Conclusion. In our single-centre study, low BMI was correlation with high BNP but not PAH in SSC. So BMI affected the level of BNP in PAH of SSC. We observed that impaired renal function is associated with an increased risk of PAH in SSc. Further multicentre studies are needed to confirm our results.

PS173. INFLUENCE OF PRIOR TREATMENT WITH ACE INHIBITORS AND CORTICOSTEROIDS ON THE PROGNOSIS OF SCLERODERMA RENAL CRISIS

D. Launay[1], T. Sy[1], L. Mouthon[2], A. Mahr[2], A. Berezne[2], C. Agard[3], M. Mehrenberger[4], L. H. Noel[4], P. Trolliet[5], C. Frances[6], J. Cabane[7], P. Y. Hatron[1], E. Hachulla[1] and L. Guillevin[2]
[1]*Université Lille 2, Service de Médecine Interne, Lille,* [2]*Université Paris Descartes, Service de Médecine Interne, Paris,* [3]*CHU Service de Médecine Interne, Nantes,* [4]*Université Paris Descartes, Service d'Anatomo-Pathologie, Paris,* [5]*Centre Hospitalier Lyon-Sud, Service de Néphrologie, Lyon,* [6]*Hopital Tenon, Service de Dermatologie and* [7]*Faculté de Médecine Pierre-et-Marie-Curie-Paris 6, Service de Médecine Interne, Paris, France*

Objectives. Scleroderma renal crisis (SRC) is is characterized by malignant hypertension, oliguric/anuric acute renal failure and important mortality. Several retrospective studies have found high-dose CS therapy to be associated with increased risk of SRC in SSc. Treatment relies on the early control of blood pressure with increasing doses of angiotensin-converting enzyme inhibitors (ACEi). The role of ACEi in preventing SRC is still a matter of debate and some authors suggest that it could be not only inefficient but also harmful by increasing the risk of normotensive CRS which are associated with a worse prognosis.
Patients and methods. In a retrospective study, we collected the treatment administered before the occurrence of a SRC in 91 patients with ScS, with a focus on ACEi and CSs. Overall survival was compared between patients with normotensive and hypertensive SRC according to the prior treatment with ACEi and/or CSs.
Results. Seventy-eight patients had a hypertensive SRC and 13 had a normontensive SRC. In the whole population of 91 patients, previous use of CSs or ACEi before the SRC onset was not associated with a different prognosis when compared with patients not previously treated by these drugs. The same results were observed in the subgroup of patients with a hypertensive SRC ($n = 78$). Conversely, in the subgroup of patients with a normotensive SRC ($n = 13$), the prior treatment by ACEi was associated with a better prognosis when compared with patients without prior use of ACEi (Fig 1). The overall survival of patients with a normotensive SRC occurring in the setting of prior treatment by ACEi ($n = 5$) was 100% at 1 years *vs* 0% for patients with a normotensive SRC occurring in the setting of no prior treatment by ACEi ($n = 6$).
Conclusion. This study was not designated to assess the usefulness of ACEi in preventing SRC in SSc. However, this study suggests that prior use of ACEi is not associated with a worse prognosis in SSc-related SRC and is associated with a better prognosis in normotensive SRC. One hypothesis could be that there are different types of normotensive SRC and that normotensive SRC occurring without previous use of ACEi are associated with a dreadful prognosis, whereas normotensive SRC occurring in the setting of previous use of ACEi have a much better prognosis. However, these results are preliminary in a small number of patients and have to be confirmed in prospective trials.

Fig. 1 Survival of normotensive SRC with or without prior treatment with ACE inhibitor.



PS174. LUNG TRANSPLANTATION IN SSc: A MONOCENTRIC EXPERIENCE OF 9 PATIENTS

D. Launay[1], L. Savale[2], A. Berezne[3], M. Humbert[2], L. Mouthon[3], O. Mercier[4], E. Hachulla[1], O. Sitbon[2], L. Guillevin[3], P. Dartevelle[4], G. Simonneau[2] and S. Mussot[4]
[1]*Université Lille 2, Service de Médecine Interne, Lille,* [2]*Université Paris Sud, Service de Pneumologie, Clamart,* [3]*Université Paris Descartes, Service de Médecine Interne, Paris and* [4]*Centre Chirurgical Marie-Lannelongue, Le Plessis Robinson, France*

Introduction. Interstitial lung disease (ILD) and pulmonary hypertension (PH) are the two leading causes of death in SSc. Lung transplantation (LT) for respiratory insufficiency secondary to SSc remains controversial, mainly because of the systemic nature of SSc and the risks of complications after LT. We aimed to comprehensively report our single-centre experience of LT in SSc.
Patients and methods. All SSc patients who underwent LT in Marie-Lannelongue Centre were retrospectively assessed. Early and late mortality, infections, rejection and other complications were collected.
Results. Nine patients were included (eight females, eight lcSSc). Four patients underwent a bilateral LT (indication: pulmonary veno-occlusive disease in the four cases), one patient had a single lung transplantation for ILD and four underwent heart-LT for PH. The mean time on the waiting list was 8 (6) months. Four LTs were performed in a context of high emergency. No patients died during the LT procedure. After LT, complications were lung oedema ($n=3$), bronchial dehiscences ($n=4$), digital necrosis ($n=3$ with one amputation), acute renal failure ($n=5$), and infections ($n=7$). One patient died with the first 30 days. Five additional patients died during the follow-up with a median survival of 72 months. Causes of death were one infection, one SSc-related acute renal crisis, two bronchiolitis obliterans syndromes (BOS) and one complication of the LT.
Conclusion. This study suggests that, whereas LT is an option in SSc, complications are not infrequent including acute renal failure, digital necrosis or bronchial dehiscences where SSc is playing a role. Indeed, these latter, together with a BOS, are probably favoured by the SSc-related gastro-oesophageal reflux. A comprehensive patient assessement prior LT and a specific management of SSc patient during and after LT appears of utmost importance to improve the prognosis of LT in SSc.

PS175. EVALUATION OF THE COMBINED CARBON MONOXIDE AND NITRIC OXIDE SINGLE-BREATH METHOD IN SSc LUNG INVOLVEMENT

N. Sivova[1], **D. Launay**[1], G. Denis[1], S. Morell-Dubois[1], P. De Groote[2], M. Remy-Jardin[3], P. Y. Hatron[1], E. Hachulla[1] and T. Perez[4]
[1]*Service de Médecine Interne,* [2]*Service de Cardiologie,* [3]*Service de Radiologie Thoracique and* [4]*Service d'Explorations Fonctionnelles Respiratoires, Université Lille 2, Lille, France*

Objectives. Lung diffusing capacity for carbon monoxide (DL_{CO}) is recognized as a useful tool to screen SSc patients for the presence of interstitial lung disease (ILD) and pulmonary hypertension (PH). DL_{CO} has been correlated with pulmonary artery pressure level, dyspnoea score and mortality in SSc and in SSc-related ILD. However, its interpretation is sometimes difficult as DL_{CO} lacks of specificity. Moreover, in the presence of ILD, a low DL_{CO} can be explained not only by the extension of the disease but also by the presence of an ILD-related PH. DL_{CO} may be schematically separate into two components: the conductance of the alveolocapillary membrane (DM) and the lung capillary blood volume (Vc). It is possible to determine DM and Vc using a single-breath method with concomitant inhalation of CO and nitric oxide (NO) and thus, theoretically, to better interpret a low DL_{CO}. The aim of this study was to assess the utility of determining DM and Vc in patients with SSc and lung complications.
Patients and methods. Sixty-four consecutive patients with SSc [mean age 56 (13) years] were evaluated using the single-breath method with concomitant inhalation of CO and NO. Twenty-five patients had neither ILD nor PH (control group). Eight patients had an isolated pre-capillary PAH without any ILD (PAH group), 19 patients had an isolated ILD without evidence of PH (ILD group) and 12 patients had both PH and ILD (PH-ILD group).
Results. DL_{CO}, DM and Vc differed statistically between the four groups of patients. PH-ILD patients had a significantly lower DL_{CO}, DM and Vc than the other groups. ILD patients had a significantly lower DL_{CO}, DM and Vc than the control group. Conversely, there were no statistically significant differences between ILD patients and PH patients. DL_{CO} <29% and Vc<30% had a sensitivity of 72% and a specificity of 100% to identify among patients with ILD the presence of an associated PH.
Conclusions. This study shows that both DM and Vc are lowered in SSc-related ILD, especially if there is an associated PH. However, determination of Vc did not allow a better prediction of the presence of PH in ILD patients than DL_{CO}.

PS176. PROGNOSIS FACTORS FOR SURVIVAL AND PROGRESSION-FREE SURVIVAL IN SSc-ASSOCIATED INTERSTITIAL LUNG DISEASE

N. Le Gouellec[1], J. B. Faivre[2], A. L. Hachulla[2], E. Hachulla[1], T. Perez[3], S. Morell-dubois[1], M. Lambert[1], G. Lefevre[1], H. Maillard[1], P. Y. Hatron[1], M. Rémy-Jardin[2] and **D. Launay**[1]
[1]*Service de Médecine Interne,* [2]*Service de Radiologie Thoracique and* [3]*Service d'Exploration Fonctionnelle Respiratoire, Université Lille2, Lille, France*

Objectives. SSc-associated interstitial lung disease (SSc-ILD) is one of the leading cause of morbi-mortality in SSc. Progression of ILD is variable among patients and some prognosis factors of mortality and progression have been suggested such as the extension of ILD on HRCT or the cutaneous extension of the disease. However, to our knowledge, there is no available study which assessed the prognostic information provided both by the HRCT/pulmonary function tests (PFT) at baseline and the clinical/biological characteristics of SSc
Patients and methods. We restrospectively collected data of 75 consecutive SSc patients with ILD on HRCT and with a regular follow-up with PFT. Progression of ILD was defined by a decrease of FVC≥10% and/or DL_{CO}≥15% or the introduction of an immunosuppressive treatment. Each baseline HRCT was reviewed by two independent radiologists in order to assess the extension of disease and the proportion of ground-glass opacities and reticular pattern.
Results. Overall survival was 97, 94, 90 and 85% at 1, 3, 5 and 10 years, respectively. Significant prognosis factors were FVC, DL_{CO}, age at ILD diagnosis, left ventricular ejection fraction, CRP, haemoglobin level and presence of ACAs. Conversely, neither the subtypes of SSc, nor the sex, 6-min walk test or the extension of ILD on the HRCT were significant prognosis factors for survival. Progression-free survival was 78, 50, 43 and 24% at 1, 3, 5 and 10 years, respectively. Significant prognosis factors of progression-free survival were only NYHA functional class and the extension of ILD on the baseline HRCT whatever the proportion of ground-glass opacities or reticular pattern.
Conclusion. This study shows a good long-term survival of patients with SSc-ILD in our centre. However, the progression-free survival is much worse. The two prognosis factors of progression-free survival were the NYHA functional class and the extension of ILD on the baseline HRCT. Neither the subtypes of SSc nor the subtype of autoantibodies were prognosis factor for progression-free survival.

PS177. HIGH SERUM TGF-α LEVELS IN SSc PATIENTS WITH SIGNIFICANT OESOPHAGEAL DYSMOTILITY: IMPLICATIONS FOR IMPROVED TREATMENT

M. Lalovac[1], D. Martinovic Kaliterna[2], S. Mejic Krstulovic[1], I. Salamunic[3], D. Perkovic[2], M. Radic[2] and V. Markovic[4]
[1]*Department of Internal Medicine, County Hospital Dubrovnik, Dubrovnik,* [2]*Department of Immunology and Rheumatology,* [3]*Department of Laboratory Diagnostics and* [4]*Department of Nuclear Medicine, Clinical University Hospital Split, Split, Croatia*

We report a comparison of serum TGF-α levels and the index of retention (RI) from oesophageal scintigraphy in patients with SSc to the patients with overlap syndrome. We also report a correlation between the value of serum TGF-α and the index of retention from oesophageal scintigraphy in all our patients, and then separately for each group (i.e. SSc patients and overlap syndrome patients). Serum samples and oesophageal scintigraphy results were analysed for 14 patients with SSc and for 19 patients with overlap syndrome. Although levels of serum TGF-α varied widely in both groups, the results show that levels of serum TGF-α were significantly higher in patients with SSc. Also, we found that oesophageal hypomotility was of higher significance in patients with SSc. A correlation was found between the level of serum TGF-α and the RI from oesophageal scintigraphy when comparing these two values in all our patients (i.e. from both groups), although when analysed separately, there was no definitive, significant, statistical correlation between these two parameters in any of the patient groups. Based on this data, serum TGF-α may have a significant role as a target in the therapy of patients with SSc in the future.

Results. The mean level of serum TGF-α in the SSc group was 35.89 (20.87) pg/ml and the RI from oesophageal scintigraphy was 78.56 (28.23)%. In the group of patients with overlap syndrome, the mean level of serum TGF-α was 8.56 (4.7) pg/ml and the RI from oesophageal scintigraphy was 38.42 (25.68)%. There were significant differences in serum TGF-α levels between patients with SSc and patients with overlap syndrome ($Z = 4{,}627$, $P < 0.001$), as well as with the RI from oesophageal scintigraphy between the two groups of patients ($Z = 3{,}344$, $P < 0.001$).
We did not find a significant statistical correlation between the level of serum TGF-α and the RI from oesophageal scintigraphy in the group of patients with SSc ($\rho = -0{,}011$, $P = 0{,}970$), nor in the group of patients with overlap syndrome ($\rho = 0{,}207$, $P = 0{,}395$). However, when analysing patients from both groups together, we found a correlation between the value of serum TGF- α and the RI from oesophageal scintigraphy ($\rho = 0.537$, $P = 0.001$).
Conclusion. Serum TGF-α levels are significantly higher in patients with SSc and may be new serum marker important for the diagnosis and staging of this disease. Consequently, novel approach to the treatment of this disease may arise in the future.

PS178. MEASURING FEAR OF PROGRESSION IN PATIENTS WITH SSc

L. Kwakkenbos[1], F. H. J. van den Hoogen[1], J. Custers[2], J. Prins[3], M. C. Vonk[4], W. G. J. M. van Lankveld[1], E. S. Becker[2] and C. H. M. van den Ende[1]
[1]*Department of Rheumatology, Sint Maartenskliniek Nijmegen,* [2]*Radboud University Nijmegen, Behavioural Science Institute, Clinical Psychology,* [3]*Department of Medical Psychology and* [4]*Department of Rheumatology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands*

Objective. Although concerns about the future are often expressed by patients with SSc [1], as yet no valid quantitative measure is available to assess the extent to which patients with SSc are troubled by those concerns. The purpose of the present study was to validate the Dutch translation of the Fear of Progression-Questionnaire Short Form (FoP-Q-SF)[2] for patients with SSc.
Methods. Measurement properties of the FoP-Q-SF were assessed using a cross-sectional design in which 215 patients with SSc were included. Patients completed the FoP-Q-SF as well as questionnaires on physical and psychological functioning. Psychometric properties of the FoP-Q-SF were assessed using the COSMIN checklist [3].
Results. In total, 69 men and 146 women completed the questionnaires. Most patients (74.1%) were married or living as married. One-third of the patients were employed at time of the study, and 42% received higher education. Mean time since onset of non-Raynaud symptoms was 9.2 years (s.d.7.9). Mean FoP-Q-SF score in patients with SSc was 30.05 (s.d. 8.97). There were no indications of floor or ceiling effects. Confirmative factor analysis supported the single-factor structure of the questionnaire [χ^2 (52) = 96.84, $P < 0.001$, RMSEA = 0.064, CMIN/DF = 1.86). Cronbach's α was .86 for the questionnaire. Most of our a priori-determined hypotheses (11 out of 12, 92%, Table 1) were confirmed in the data, supporting the construct validity of the questionnaire.

Table 1. Hypotheses and correlations of variables with FoP-Q-SF

Hypotheses	Correlation	*P*	Confirmed
Moderate to large positive correlation with			
Anxiety (IRGL[a])	0.59	<0.001	Yes
Depressive symptoms (CES-D[b])	0.58	<0.001	Yes
Active problem-oriented coping (CISS[c])	−0.01	0.862	No
Moderate to large negative correlation with			
Social functioning (subscale SF-36[d])	−0.39	<0.001	Yes
Role emotional (subscale SF-36)	−0.47	<0.001	Yes
Mental health (subscale SF-36)	−0.58	<0.001	Yes
Small to moderate negative correlation with			
Physical functioning (subscale SF-36)	−0.25	<0.001	Yes
Role physical (subscale SF-36)	−0.37	<0.001	Yes
Bodily pain (subscale SF-36)	−0.34	<0.001	Yes
General health (subscale SF-36)	−0.42	<0.001	Yes
Vitality (subscale SF-36)	−0.45	<0.001	Yes
Age, years	−0.15	0.031	Yes

[a]Impact of rheumatic diseases on general health and lifestyle. [b]Centre for Epidemiologic Studies – Depression. [c]Coping Inventory Stressful Situations. [d]Medical Outcomes Trust Short-Form-36.

Conclusion. The present study demonstrates that the Dutch FoP-Q-SF is a useful and valid instrument for the measurement of fear of disease progression in patients with SSc. This is important since fear of progression is one of the most important stressors in these patients.

PS179. SOCIODEMOGRAPHIC, DISEASE AND PSYCHOSOCIAL CORRELATES OF DEPRESSIVE SYMPTOMS IN PATIENTS WITH SSc, INCLUDING FEAR OF PROGRESSION AND APPEARANCE SELF-ESTEEM

L. Kwakkenbos[1], W. G. J. M. van Lankveld[1], M. C. Vonk[2], E. S. Becker[3], F. H. J. van den Hoogen[1] and C. H. M. van den Ende[1]
[1]*Department of Rheumatology, Sint Maartenskliniek Nijmegen,* [2]*Department of Rheumatology and* [3]*Behavioural Science Institute, Clinical Psychology, Radboud University Nijmegen, Nijmegen, The Netherlands*

Objective. The prevalence of depressive symptoms is high in patients with SSc (scleroderma). This study was conducted to determine which disease-related and psychosocial factors, including fear of progression and appearance self esteem, are associated with depressive symptoms, independent of sociodemographic factors.
Methods. In total, 215 patients with SSc completed questionnaires on sociodemographics, physical functioning (HAQ-DI), pain (VAS), fatigue (CIS), psychosocial characteristics (CISS, ICQ, PRQ, ASE, FoP-Q-SF) and depressive symptoms (CES-D). Disease characteristics (disease duration, subtype, mRSS) were collected by the attending rheumatologist. Hierarchical linear regression analysis was conducted to assess associations with depressive symptoms.
Results. In total, 69 men and 146 women completed the questionnaires. Mean time since onset of non-Raynaud's symptoms was 9.2 years (s.d. 7.9). The mean CES-D score was 12.9 (s.d. 9.7) and the prevalences of patients scoring ≥16 and ≥19 were 32.1 and 25.1%, respectively. The variance explained by sociodemographics and disease characteristics was negligible (R^2 =<0.09). By adding fatigue, pain and HAQ-DI, variance explained increased remarkably (R^2 change = 0.35), although HAQ-DI was not independently associated with depressive symptoms. After adding psychological factors (Table 1), lower satisfaction with social support, emotion-focused coping, helplessness and higher fear of progression were also significantly associated with depressive symptoms (total $R^2 = 0.65$).

Table 1. Hierarchical regression analysis of demographics, disease status and psychological variables associated with depressive symptoms (CES-D, range 0–60)

Variable	*B*[a] (95% CI)	P	β[a]	Total R^2
Demographics				
Age	−0.04 (−0.12, 0.05)	0.371	−0.05	
Sex	−0.86 (−3.00, 1.28)	0.427	−0.04	0.03
Socioeconomic status				
Higher education	−0.37 (−2.42, 1.69)	0.725	−0.02	
Married/cohabitating	−2.0 (−4.41, 0.43)	0.106	−0.09	0.07
Disease characteristics				
Limited disease	−0.04 (−2.38, 2.31)	0.975	0.00	
Disease duration	0.02 (−0.10, 0.14)	0.738	0.02	
mRSS	0.08 (−0.10, 0.26)	0.409	0.05	0.09
Physical functioning				
HAQ score	−1.16 (−2.95, 0.62)	0.200	−0.09	
Pain	0.05 (0.00, 0.09)	0.054	0.11	
Fatigue	0.23 (0.13, 0.33)	<0.001	0.31	0.44
Psychosocial factors				
Social support	−0.03 (−0.12, −0.01)	0.014	−0.14	
Helplessness	0.39 (0.04, 0.75)	0.030	0.17	
Acceptance	0.06 (−0.26, 0.37)	0.693	0.03	
Problem-focused coping	−0.03 (−0.12, 0.07)	0.618	−0.03	
Emotion-focused coping	0.18 (0.08, 0.28)	<0.001	0.23	
Avoidance coping	0.06 (−0.05, 0.16)	0.298	0.06	
Appearance self-esteem	−0.23 (−0.49, 0.03)	0.083	−0.10	
Fear of progression	0.20 (0.05, 0.34)	0.007	0.18	0.65

[a]Final model.

Conclusion. Depressive symptoms were common in the present study of patients with SSc and were independently associated with pain, fatigue, social support, emotion-focused coping, helplessness and fear of progression. Results suggest that, in addition to assessment of disease characteristics, attention should be given to psychological factors to identify patients at risk for depressive symptoms. For the development and trialling of psychological interventions, fear of progression could be an important target.

PS180. NATURAL HISTORY OF PULMONARY FUNCTION IN PATIENTS WITH SSc AND INTERSTITIAL LUNG DISEASE

M. Kuwana[1] and J. Kaburaki[2]
[1]*Keio University and* [2]*Shin-Akasaka Clinic, Tokyo, Japan*

Background. Interstitial lung disease (ILD) is the leading cause of mortality in patients with SSc. Rates of decline in pulmonary function

are heterogeneous among SSc patients, and only a small subset develops end-stage lung disease (ESLD). In our institution, ILD-SSc was not a treatment target before 2000. Therefore, our cohorts of untreated patients are useful in assessing the natural history of pulmonary function in SSc patients with ILD. We also evaluated initial factors that predict development to ESLD.

Methods. We enrolled 50 patients with SSc, who were diagnosed as having SSc between 1980 and 1995. These patients were selected from our database based on the following criteria: they had ILD as determined by chest radiographs at diagnosis, had disease duration <3 years at diagnosis, were followed for >10 years unless death due to ILD-related causes, had at least four serial pulmonary function tests, and had never received immunosuppressants, >10 mg daily prednisolone, or other potential disease-modifying drugs. ESLD was defined as having at least one of the following: $<50\%$ FVC, required oxygen supplementation or death due to ILD-related causes. We performed statistical analyses stratified by development to ESLD and multivariate analysis to assess factors that predict the ESLD development.

Results. At study entry, disease duration and %FVC were 14.2 (7.2) months and 83.7 (14.2)%, respectively. The patients were followed for 173.5 (64.7) months and 16 patients (32%) developed ESLD. Initial characteristics associated with future development to ESLD included dcSSc, anti-topo I antibody, the absence of ACA, exertional dyspnoea, elevated KL-6, reduced %FVC and reduced $\%DL_{CO}$. Multivariate analysis revealed that dyspnoea and elevated KL-6 were the parameters independently associated with the ESLD development. The decline in %FVC during the 12-month period was 4.6 (2.4)% in patients who developed ESLD and 0.5 (0.8)% in patients who did not ($P < 0.0001$). The rate of %FVC decline was similar between 0 and 3, 3 and 6 and >6 years after diagnosis [5.0 (3.6)%, 3.7 (2.9)%, and 3.9 (3.2)%, respectively]. Finally, the rate of %FVC decline was negatively correlated with KL-6 at diagnosis ($r = 0.71$, $P < 0.0001$).

Conclusion. Only 32% of SSc patients with ILD at diagnosis developed ESLD. Exertional dyspnoea and elevated KL-6 at baseline are predictors of future %FVC decline in SSc patients with ILD.

PS181. CLUSTERING OF CONNECTIVE TISSUE DISEASES AND AUTOIMMUNE THYROID DISEASE IN SSc RELATIVES: RESULTS OF A FRENCH CASE–CONTROL STUDY

E. Koumakis[1], P. Dieude[2], J. Avouac[1], A. Kahan[1] and Y. Allanore[1]
[1]*Rheumatology A Department, Cochin Hospital, Paris Descartes University, APHP and* [2]*Rheumatology Department, Université Paris Diderot, Hôpital Bichat Claude-Bernard, Paris, France*

Introduction. Clustering of multiple AIDs within families has been recognized in a number of autoimmune disorders. In SSc, the coexistence of multiple AIDs within SSc patients (polyautoimmunity) is well established. However, scarce data are available on the clustering of specific autoimmune phenotypes in SSc families.

Objective. To assess the prevalence of autoimmune diseases (AIDs) in first-degree relatives of patients with SSc, and to compare these results with control families in order to identify patterns of AIDs in relatives.

Methods. A retrospective case–control postal questionnaire survey was performed in France to recruit SSc patients belonging to SSc patients' association and unrelated age- and gender-matched controls. Each participant was asked to self-report on the existence of AIDs in their first degree relatives. The prevalence of AIDs in SSc patients' families was compared with the corresponding prevalence in controls' families.

Results. A total of 121 SSc families out of 373 (32.4%) reported at least one AID in one or more first-degree relatives. Autoimmune thyroid disease (AITD) (4.9%), RA (4.1%), psoriasis (3.9%), and type 1 diabetes mellitus (2.9%) were the most frequent AIDs in SSc families when adjusted for family size. Compared with controls' families, AITD and CTDs (SSc or SLE or SS) were more likely to occur in SSc families ($P = 0.01$ and $P = 0.01$, respectively), with odds ratios (OR) of 3.20 (95% CI 1.25, 8.18) and 5.20 (95% CI 1.22, 21.8). In contrast, IBD was less likely to occur within SSc families ($P = 0.02$; OR $= 0.29$; 95% CI 0.11, 0.80). In addition, the coexistence of more than one AID in the index SSc case was associated with familial aggregation of AIDs.

Conclusion. Our results show that AIDs cluster within families of patients with SSc. This supports that these diseases might arise on a shared genetic basis underlying several autoimmune phenotypes.

PS182. THE STABILIZATION OF LUNG FUNCTION IN PATIENTS WITH SCLERODERMA-ASSOCIATED INTERSTITIAL LUNG DISEASE DURING MYCOPHENOLATE MOFETIL THERAPY

O. Koneva[1], L. Ananjeva[1], L. Korzeneva[1], R. Alekperov[1], O. Desinova1, M. Starovoytova[1], T. Nevskaja[1] and O. Ovsjannikova[1]
[1]*Institute of Rheumatology, Moscow, Russia*

Background. Pulmonary disease in SSc is associated with significant morbidity and mortality. At least one-third of patients with SSc have clinically significant interstitial lung disease (ILD). The principal factor influencing survival in patients with dSSc is pulmonary involvement. Recent literature support MMF to be as effective in current therapy in ILD in SSc. MMF may exert direct effects on fibroblast extracellular matrix remodeling, inhibits endothelial cell proliferation and should be studied as a possible treatment for SSc-ILD.

Objective. This pilot study was aimed at evaluating the efficacy and safety of the therapy with MMF in SSc patients suffering from active (clinically significant) ILD.

Patients and methods. Seventeen patients (13 dSSc, 4 lSSc; 15 females, 2 males) were enrolled and treated with MMF [for 11.5 (1.2) months] and oral low-dose [mean 10 (4.9) mg/day] of glucocorticoids in this open-label prospective trial. All patients according high-resolution CT had radiographic abnormalities consistent with ILD. Initially, patients were treated with MMF, 1000 mg/day for a month, thereafter 2000 mg/day. Clinical assessment, modified Rodnan total skin score (TSS), pulmonary function tests (carbon monoxide diffusing capacity (DL_{CO}) and forced vital capacity (FVC), were performed before and after MMF therapy.

Results. MMF therapy was well tolerated. Of 17 patients, 2 experienced adverse reactions with gastrointestinal tract disturbances, 3 had infections, 2 reversible effusion pericarditis, but these patients did not discontinue treatment with MMF. TSS in patients with dSSc decreased during the study from 14 (9.6) at baseline to 4.8 (3) ($P = 0.0003$). Since starting MMF the average percentage of FVC [75.6 (21.7) *vs* 77.2 (19.6)%] and DL_{CO} [49.2 (21.6) *vs* 45.9 (23.3)%] for the cohort did not change significantly. From the time of MMF initiation FVC% in one patient increased by $\geq 10\%$. Over the same time interval, the FVC% in three patients, and $DL_{CO}\%$ in another four patients decreased by $\geq 10\%$.

Conclusion. The apparent stability of pulmonary function and the improvement in skin score during the study period suggest, that treatment with MMF and small doses of CSs may represent an effective, well-tolerated therapy in patients with SSc-ILD.

PS183. CORRELATION BETWEEN ENDOTHELIN-1 AND MORPHOLOGICAL DIFFERENCE OF NAIL-FOLD CAPILLARY IN PATIENT WITH SSc

E. J. Kim[1], Y. S. Kim[1], H.-S. Kim[1] and H. J. Lee[1]
[1]*Chosun University Hospital, Gwangju, South Korea*

Endothelial and vascular damage are the main leading disability in SSc. RP is the early symptom that present vascular damage. Nail-fold capillaroscopy (NFC) is an easily accessible diagnostic tool in secondary RP. Considering the endothelial damage, clinical manifestations and plasma cytokines was compared with traditionally used NFC parameter for, which to observe the number of capillaries, deletions in 3 mm, apical limb width and the capillary width itself. We hypothesize that a computer-based NFC system can generate a new powerful parameter that predicts the capillary dimension. We investigated the relationship among the plasma ET-1, clinical manifestations and quantitative analysis of computerized NFC, and to assess the optimal method in SSc.

The level of ET-1 in 60 SSc patients, 30 healthy and 23 disease controls were measured by ELISA kit. We present a significant differences in all parameters of NFC between SSc patients and control groups. ET-1 level was increased in patients with SSc. In SSc group, capillary dimension and capillary deletion score were strongly associated with digital ulceration ($P < 0.01$) and pulmonary hypertension ($P < 0.05$). Capillary dimension and ET-1 level was in correlation with skin hardening grade, and was higher in SSc patients with pulmonary hypertension or digital ulcer. Capillary dimension showed strong correlation with the endothelin-1 in SSc, healthy and disease control groups ($R = 0.31$, $P < 0.05$; $R = 0.82$, $P < 0.001$; $R = 0.83$, $P < 0.001$). The results suggest that computer-based microscopic analysis of NFC is a useful method that potentially provides information on organ involvement and plasma ET-1. Capillary dimension maybe a powerful parameter possibly applicable in outpatient clinic for assessing SSc patients.

PS184. ANXIETY AND DEPRESSION IN PATIENTS WITH PROGRESSIVE SSc

V. Cosentino[1,2], R. Lopez Martinez[1,2], K. Mendoza[1,2], S. F. Montoya[1,2], N. L. Bustos Cavilla[3] and E. Kerzberg[1,2]
[1]*Rheumatology Department, J. M. Ramos Mejía Hospital,* [2]*Osteoarticular Diseases and Osteoporosis Center, School of Medicine, University of Buenos Aires and* [3]*A.A.D.E.Y.R. (Argentinean Association of Systemic Sclerosis and Raynaud), Buenos Aires, Argentina*

Introduction. Progressive SSc (PSS) is an autoimmune disease characterized by immune dysfunction and vascular damage that ultimately lead to abnormal fibrotic processes that affect the skin and other organs. These conditions have an emotional and social impact on patients and may lead to anxiety disorders or depression.
Objective. To assess anxiety and depression in patients with PSS in comparison to patients with RA and a control group.
Materials and methods. Forty-five female patients with PSS diagnosis, according to the ACR criteria, were assessed. Of them, 60% had limited PSS while the other 40% showed diffuse affection. The Spanish version of the Hospital Anxiety and Depression Scale (HADS) was elected as screening tool. The mean values for anxiety and depression were analysed and a cut-off value of >8 for established anxiety and depression. This group was compared with 45 patients with RA of the same time of evolution of the disease, and was also compared with 45 patients with no associated diseases, all groups had the same age and sex. In order to analyse the data, descriptive statistics, chi-square, *t*-test and ANOVA of a factor (with *post hoc* analysis) as well as Software SPSS for Microsoft Windows were used. $P < 0.05$ was considered to be significant.
Results. The mean age of PSS patients was 52.82, for RA patients was 53.49 and 50.40 for the control group ($P = 0.4$). Patients with PSS had 8.69 years of evolution of their disease and patients with RA had 6.71 years of evolution their disease. The mean score for HAQ among PSS patients was 0.53 while the mean score for RA patients was 0.88 ($P = 0.003$)

A *post hoc* analysis showed that the group of patients with PSS had a statistically significant difference if compared with the control group, with regards to anxiety levels (Tukey HSD test $P = 0.013$) and depression (Tukey HSD test $P = 0.009$). There were no significant differences between PSS and RA patients. Considering a cut-off value >8, it was described that 46.7% of PSS patients had established anxiety *vs* 31.1% of RA and control group ($P = 0.2$). Moreover, 31.1% of PSS patients had established depression *vs* 20.0% of RA patients and 17.8% of the control group ($P = 0.27$).

TABLE 1. Anxiety and depression in patients with progressive SSc

	PSS	RA	Control	*P*
Anxiety	8.13	6.42	5.73	0.014*
Depression	6.36	5.07	3.91	0.013*

Conclusion. Patients with PSS show a greater level of anxiety and depression if compared with same sex and similar age RA patients with higher level of functional disablity.

PS185. QUALITY OF LIFE RELATED TO HEALTH IN PATIENTS WITH SSc

R. I. López Martínez[1,2], V. Cosentino[1,2], K. Mendoza[1,2], M. V. Sanabria[1,2], S. F. Montoya[1,2], N. Loretta Bustos Cavilla[3] and E. Kerzberg[1,2]
[1]*Rheumatology Department, J.M. Ramos Mejía Hospital,* [2]*Osteoarticular Diseases and Osteoporosis Center, School of Medicine, University of Buenos Aires and* [3]*A.A.D.E.Y.R. (Argentinean Association of Systemic Sclerosis and Raynaud), Buenos Aires, Argentina*

Objective. To assess quality of life related to health (QLRH) in patients with SSc and to determinate if there is a correlation with age, years of evolution and functional capacity.
Patients and methods. Forty-five patients with SSc (ACR criteria 1980) were assessed during three consecutive meetings of the Argentinean Association of Systemic Sclerosis and Raynaud. QLRH was analysed with the self-administrated Short-Form 36 Health Survey (SF-36), whereas the functional capacity was measured with the HAQ Disability Index (HAQ-DI). In order to obtain clinical and demographic data, a created ad hoc self-administrated questionnaire was used. The results were compared with 45 subjects with no associated diseases, of the same sex and ages. With regard to the analysis of the data, we used descriptive statistics, *t*-test and linear correlation (Pearson coefficient) and Microsoft Excel for Windows. $P < 0.05$ was considered as significant.
Results. All the assessed patients were females, with a mean age of 52.82 (11.46) (range 35–71 years). Findings: Diffuse SSc (DSSc) $n = 18$ (40%), limited SSc (LSSc) $n = 27$ (60%), years of evolution of the disease 8.69 (7.64), HAQ-DI 0.53 (0.27). There was no difference in age with regard to the control group ($P = 0.11$).

TABLE 1. Quality of life related to health in patients with SSc

	SSc, mean (S.D.)	Control group, mean (SS)	*P*
Physical comp.	56.68 (22.66)	88.57 (27.45)	0.0000
Mental comp.	54.81 (21.75)	84.98 (18.49)	0.0000
Physical functioning	61.22 (25.97)	95.29 (31.42)	0.0000
Role physical	64.44 (35.38)	92.91 (27.20)	0.0001
Bodily pain	56.64 (27.95)	92.53 (23.52)	0.0000
General health	50.76 (18.99)	90.78 (25.33)	0.0000
Vitality	50.33 (23.19)	71.33 (22.93)	0.0000
Social functioning	66.67 (26.11)	92.50 (19.38)	0.0000
Role emotional	51.11 (34.15)	94.55 (28.12)	0.0000
Mental health	55.20 (23.40)	75.73 (20.93)	0.0000

Correlation SF-36

Pearson	Physical Pearson	*P*	Mental	*P*
Age	0.0201	0.9766	−0.0194	0.8571
Evol.	−0.0405	0.7916	−0.0314	0.8377
HAQ-DI	−0.4532	0.0018	−0.2434	0.1072

Conclusions. According to our findings, QLRH assessed by SF-36 in patients with SS is significantly affected in all its domains in comparison with the control group, independently of age and years of evolution of the disease. We found an inverse correlation between functional capacity measured by HAQ-DI and the physical component of SF-36. There were no significant differences in SF-36 values for DSS and LSS. We recommend the assessment of QLRH as part of the integral care of patients with SS in clinical practice, exploring the possibility of validating briefer generic alternatives to the SF-36.

PS186. EVALUATION OF NUTRITIONAL STATUS AND DIETARY INTAKE IN WOMEN WITH SSc

C. Kayser[1], L. Martini[2], M. Pinheiro[1], V. Szejnfeld[1] and T. F. Marighela[1]
[1]*Rheumatology Division, Universidade Federal de São Paulo and* [2]*Universidade de São Paulo, São Paulo, Brazil*

Purpose. To evaluate nutritional status, body composition and dietary intake in SSc women, as well as to compare these findings according different disease subsets.
Methods. A total of 61 SSc women (31 with limited and 30 with diffuse cutaneous form) and 67 age-matched healthy women were included in this transversal study. Body composition measurements were performed using dual energy X-ray absorptiometry (DXA) in order to evaluate fat mass, lean mass and appendicular lean mass. BMI was measured and a validated 3-day food intake questionnaire was used in all patients and controls. Nutrient intakes were assessed using Nutrition Data System for Research software (University of Minnesota, 2007) and their adequacies according DRI's proposed values. Total energy (kcal/day), and total macronutrients and fibre intake were evaluated. In addition, all data were compared among dcSSc and lcSSc patients, and between patients with and without gastrointestinal involvement (oesophageal dysmotility or intestinal abnormalities). $P < 0.05$ was set as significant.
Results. Women with SSc had significantly lower BMI, total fat mass, total and appendicular lean mass as compared with healthy controls ($P = 0.02$; $P = 0.009$; $P = 0.04$; $P = 0.01$, respectively). Women with lcSSc have no significant changes on body composition when compared with healthy controls. Besides, dcSSc women had significantly lower BMI, total fat mass and total and appendicular lean mass than healthy women (Table 1). In addition, BMI and appendicular lean mass was also significantly lower in dcSSc in comparison with lcSSc women. There was no significant difference in DXA parameters or BMI values between patients with or without gastrointestinal involvement. The total energy and macronutrients intake was similar between SSc and controls, but there was a lower intake of fibres in SSc patients, with no significant difference between dcSSc and lcSSc patients or between patients with and without gastrointestinal involvement.
Conclusions. An abnormal body composition, probably related to more severe disease, was found in dcSSc women, but not in those with lcSSc. Our data suggest some degree of malnutrition and

cachexia in dcSSc patients, regardless of dietary intake or previous gastrointestinal involvement. Thus, a more detailed screening, including medical history, nutritional approach and imaging, should be performed for better clinical management in SSc patients.

TABLE 1. Clinical and body composition data in SSc patients and healthy controls

	dcSSc ($n=30$)	lcSSc ($n=31$)	Healthy controls ($n=67$)	P
Age, years	48.5 (11.49)	53.43 (12.11)	48.28 (14.64)	0.116
BMI, kg/m^2	22.6 (6.2)***	26.3 (5.0)**	26.6 (4.8)*	0.002
Total far mass, kg	19.2 (11.5)*	23.9 (10.5)**	26.3 (9.2)	0.007
Total lean mass, kg	33 (4.5)*	35.4 (6.4)	36.1 (4.9)*	0.03
Appendicular lean mass, kg	13.8 (2.7)***	15.7 (3.4)**	16 (2.6)*	0.002

Tukey's test, with *$P < 0.01$; **$P < 0.05$.

PS187. ARTERIAL STIFFNESS AND ENDOTHELIAL FUNCTION IN PATIENTS WITH SSc AND RA

D. Karpec[1], J. Dadoniene[2], A. Cypiene[3], R. Rugiene[2], S. Stropuviene[2] and A. Laucevicius[3]
[1]*Vilnius University,* [2]*State Research Institute for Innovative Medicine, Vilnius University,* [3]*State Research Institute for Innovative Medicine, Vilnius University Hospital Santariskiu Clinics, Vilnius University, Vilnius, Lithuania*

Background. RA and SSc are associated with increased cardiovascular mortality because of early atherosclerosis. Increased stiffness of conduitive arteries or aorta and endothelial dysfunction are considered as the markers for early atherosclerosis. The development of new non-invasive techniques and diagnostic methods might be useful for determining the initial vascular alterations.
Objectives. The goal of this study was to compare the stiffness of the arteries and endothelial function in RA and SSc groups by using applanation tonometry and peripheral artery tonometry plethysmography techniques.
Methods. One hundred and six patients at age 59.3 (S.D. 8.59), 96 women and 10 men, were enrolled into this study: 73 with established RA and 33 suffering with SSc. Pulse wave velocity (PWV) measured between carotid-radial and carotid-femoral arteries is the index to estimate the stiffness of the arteries [1]. Carotid and radial pulse waves were obtained non-invasively by applanation tonometry using high-fidelity micromanometer. Aortic augmentation index (Aix) as a derived marker of arterial wall dysfunction was calculated from radial pulse waves by using the integrated software. Endothelial function was measured using reactive hyperaemia index (RHI) by peripheral artery tonometry. RHI in a level of ≥ 2 is considered as normal [2].
Results. Carotid-radial/carotid-femoral pulse wave velocity (m/s) were 9.14 (1.2)/9.0 (1.7) and 9.0 (2.0)/8.1 (1.6) in RA and SSc patient groups, respectively. Standardized AIx (%) was 31.8 (7.5) in RA and 28.9 (7.1) in SSc group. So carotid-radial or carotid-femoral PWV and standardized AIx were more increased in RA patients group showing arterial stiffness being more pronounced. But the most visible differences were found in comparing RHI as a parameter of small-vessel endothelial functioning. Patients of SSc group showed RHI significantly lower [1.5 (0.7)] meaning the functioning of small arteries definitely worse than in RA group [2.0 (0.6)].
Conclusions. We conclude that in RA the most pronounced changes occur in conduitive arteries and aorta, consequently AIx is higher in this group showing the decreased elasticity of the arteries. However, in SSc patient group the changes occur in small vessels showing the endothelial functioning being damaged early in this disease.
Acknowledgements. This research was funded by a grant (No. MIP 83/2010) from the Research Council of Lithuania.

PS188. THE DIETARY FLAVONOID APIGENIN IS NOT EFFECTIVE IN PREVENTING DEVELOPMENT OF A BLEOMYCIN-INDUCED MURINE MODEL OF SCLERODERMA

J. Jun[1], J. Kim[2], Y. Na[3], H. Han[4], S. Paik[4], S. Kim[5] and Y. Kim[2]
[1]*Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea,* [2]*Department of Bioengineering, College of Engineering, Hanyang University, Seoul, South Korea,* [3]*Institute of Rheumatism, Hanyang University, Seoul, South Korea,* [4]*Department of Pathology, Hanyang University Medical Center, Seoul, South Korea,* [5]*Department of Internal Medicine, Hanyang University College of Medicine, Seoul, South Korea*

SSc is a CTD characterized by vasculopathy, excessive accumulation of extracellular matrix, and fibrosis of the skin and internal organs. No single agent has been convincingly shown to be an effective treatment, and the pathogenesis of SSc remains unknown. The dietary flavonoid apigenin has been shown to reduce expression of the myofibroblast phenotype and to inhibit contraction of collagen gels. Recently, we successfully induced scleroderma by weekly s.c. injections of bleomycin using a thermo-reversible combination gel composed of low molecular weight methylcellulose. We investigated the effect of apigenin on the prevention and treatment of a modified bleomycin-induced animal model of scleroderma. A weekly s.c. injection of methylcellulose gel loaded with bleomycin-induced focal skin fibrosis on the back skins of mice. However, daily i.p. injection of 1.0 mg/kg or 2.5 mg/kg of apigenin starting a week before the bleomycin injections failed to prevent the development of skin fibrosis and reduce the fibrotic phenotype of skin and lung tissue. In conclusion, we failed to demonstrate that i.p. injection of apigenin was effective in preventing and treating skin and lung fibrosis in the bleomycin-induced mouse model of SSc, although some *in vitro* experiments have supported a potential role of apigenin in the treatment of fibrosis. Further studies in other animal models of SSc and long-term administration of apigenin with follow-up are called for.

PS189. THE ELECTROCARDIOGRAM IN 110 PATIENTS WITH SSc: COMPARISON WITH POPULATION-BASED CONTROLS

K. Jensen-Urstad[1], A. Nordin[2], L. Björnådal[2] and E. Svenungsson[2]
[1]*Department of Clinical Physiology, Södersjukhuset and* [2]*Department of Medicine, Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden*

Purpose. ECG abnormalities such as ventricular conduction abnormalities, septal q (narrow complex), QTC-interval prolongation, signs of left ventricular hypertrophy and right atrial hypertrophy have been described in patients with SSc. The prevalence of abnormal ECG in an epidemilogically based cohort of SSc patients was investigated and compared with population controls. We also investigated if abnormal ECG findings correlated with the occurrence of impaired left ventricular (LV) ejection fraction (EF).
Methods. Of 149, 118 (79%) of identified SSc patients who fulfilled the ACR criteria for SSc in Stockholm county and 110 controls from the general population, individually matched for age, gender and area of living participated. Electrocardiograms and echocardiography were obtained for 110 patients [62 (12) years] and 105 control subjects [61 (12) years]. A subset of 91 participants (49 patients, 42 controls) underwent a 22- to 24-h Holter-ECG recording.
Results. ECG: possibly or definitely abnormal ECGs were found in 41 patients and in 25 controls ($P = 0.03$). Eighteen patients and four controls had AV conduction abnormalities ($P < 0.01$) (also counting two patients with pacemaker due to AV II and one control with pacemaker for unknown reason); left bundle branch block (LBBB) was found in eight patients and one control subject. Seven patients and three control subjects had a low anteroseptal R or septal q wave pattern with narrow QRS complex. Three patients and one control had ECGs indicating left ventricular hypertrophy. Three patients and two control subjects were not in sinus rhythm. Three patients and four controls had ECGs with unspecific ST-T wave abnormalities. All patients and controls with a normal resting ECG had LVEF estimated from echocardiography >50%.
Holter. Thirty-three patients had normal recordings, 16 abnormal. The most common abnormal finding was an increased number of extrasystoles, eight had >1000 VES/24 h. Four patients noted symptoms. Thirty-five controls had normal recordings, seven abnormal. Two controls had pacemakers: one had atrial fibrillation, one had sinus rhythm with frequent ventricular extrasystoles. The other five control subjects had an increased number of extrasystoles (one had >1000 VES/24 h).
Conclusion. AV conduction abnormalities and septal q wave/low R pattern without QRS prolongation are common resting ECG findings found in 16 and 4% of SSc patients, respectively. Arrhythmias were equally common in SSc patients and controls, but appear more severe in the SSc patients. All subjects with normal resting ECGs had normal LVEF estimated by echocardiography.

PS190. HEALTH-RELATED QUALITY OF LIFE AND ITS CORRELATES IN MOROCCAN WOMEN WITH SSc

Y. Ibn Yacoub[1], B. Amine[1], A. Laatiris[1] and N. Hajjaj-Hassouni[1]
[1]*Department of Rheumatology, El Ayachi Hospital, University Hospital of Rabat-Sale, Sale, Morocco*

Objective. We aimed to assess the aspects of health-related quality of life (HRQoL) and its correlations with disease-related parameters in Moroccan women with SSc.
Material and methods. Fifty-four women with SSc were consecutively recruited. The Arabic version of the Medical Outcomes Study Short Form 36 Health Survey: the SF-36 was applied to assess HRQoL. Sociodemographic data (socioeconomic status and educational level) were collected. Age at onset, diagnosis delay, disease duration, treatments, pain intensity (on a visual analogue scale), skin involvement, vascular manifestations, pulmonary involvement, joint and/or muscle involvement and gastrointestinal tract involvement were specified. ESR and immunological status were assessed. Functional disability was measured by using the Scleroderma HAQ (S-HAQ).
Results. In our data, all domains of SF-36 were deteriorated in a significant way. The most altered domains were role limitation, role emotional, vitality and bodily pain. Decreased scores of SF-36 were correlated with diagnosis delay, severity of joint pain, pulmonary involvement (severity of dyspnoea and altered pulmonary function tests), altered functional status (S-HAQ) and treatment with CSs (for all $P < 0.001$). Patients with low educational level had decreased scores of vitality, mental health and social functioning (for all $P = 0.001$).There was significant association between vascular manifestations (Raynaud's syndrome) and the deterioration of bodily pain ($P = 0.003$). There were no correlations between SF-36 scores and skin involvement or other visceral disorders of disease. In regression models the main associated factors with lower scores of SF-36 were: the delay of diagnosis ($R^2 = 1.275$, 95% CI 1.130, 1.768) and the intensity of joint pain ($R^2 = 1.515$, 95% CI 0.314, 0.833) (for all $P < 0.001$).
Conclusion. In our data, Moroccan women with SSc had altered aspects of all domains of HRQoL. The delay in diagnosis and the severity of disease (joint, respiratory and vascular involvement) were the main associated factors with altered quality of life. Optimizing the evaluation of HRQoL in routine clinical assessment of our SSc and recognizing the parameters influencing it should to be highlighted in order to improve patients' management and daily living.

PS191. SPINSTERHOOD AND DISEASE CHARACTERISTICS IN MOROCCAN WOMEN WITH SSc

Y. Ibn Yacoub[1], B. Amine[1], H. Abid[1] and N. Hajjaj-Hassouni[1]
[1]*Department of Rheumatology, El Ayachi Hospital, University Hospital of Rabat-Sale, Sale, Morocco*

Objective. To evaluate the relationships between spinsterhood and disease features and quality of life (QoL) in Moroccan women with SSc.
Methods. Fifty women with SSc were included. Marital status was categorized in three groups: Spinsterhood (never-married woman over 38 years old), married women and divorced or widowed. We also specified the marital adjustment (distressed and no distressed marriage) by a self-report concerning coping and burden caring of husbands. Following data were collected: age, socioeconomic status, educational level, age at onset, diagnosis delay, disease duration, pain intensity and the activity of disease: severity of skin involvement (Rodnan skin score), musculoskeletal manifestations (tender and swollen joints and radiological changes), respiratory involvement [dyspnoea (using a breathing VAS), pulmonary function tests and chest radiograph], vascular symptoms; gastrointestinal involvement and the ESR. Functional status was evaluated by the SSc HAQ (S-HAQ). The other organs involvement, immunological abnormalities and treatment details were assessed. QoL was measured using the generic instrument SF-36. Comparisons were assessed using the analysis of variance.
Results. Nineteen patients (38%) were spinsters, 22 (44%) were married [9 (18%) with no distressed marriage and 13 (26%) with distressed marriage] and 9 (18%) were divorced or widowed. Never-married women had an early age at onset ($P = 0.014$), severe joint involvement [severe arthritis-related pain ($P = 0.001$) and higher number of swollen joints ($P = 0.007$)], severe dyspnoea ($P = 0.011$), high level of ESR ($P = 0.008$), more gastrointestinal infectious complications ($P = 0.01$) and impaired functional status ($P < 0.001$). Also, there was significant association between spinsterhood and lower educational levels ($P = 0.031$) and lower socioeconomic status ($P = 0.001$) compared with the other groups. There were no statistically significant differences in skin involvement, vascular symptoms, immunological status or treatments between the four groups. Never-married women had significantly altered scores of the domains of mental health, vitality and social health of QoL (for all $P < 0.001$) even compared with women with distressed marriage. In logistic regression analysis, spinsterhood was associated with a young age at onset (OR = 1.943, 95% CI 1.101, 1.752), arthritis-related pain (OR = 2.027, 95% CI 1.280, 1.814), altered functional status (OR = 2.853, 95% CI 1.121, 1.780) and impaired social domain of QoL (OR = 1.802, 95% CI 0.258, 0.766).
Conclusion. In our SSc women, spinsterhood seems to be a determinant factor of active disease, severe functional disability and poor QoL. Our results may underscore the importance of considering not only disease-related parameters but also social factors in our patients and may inform clinical interventions of SSc.

PS192. ASSESSING ORGAN INVOLVEMENT AND CURRENT SYMPTOMS AS INDICATORS FOR DISEASE PROGRESSION IN 3047 PATIENTS COHORT

N. Hunzelmann[1], P. Moinzadeh[1], T. Krieg[1], N. Blank[2], E. Genth[3], I. Koetter[4], I. Melchers[5], C. Pfeiffer[6], U. Müller-Ladner[7], G. Riemekasten[8], C. Sunderkoetter[9], G. Fierlbeck[4] and C. Seitz[10]
[1]*Department of Dermatology and Venerology, University Hospital of Cologne, Cologne,* [2]*Department of Internal Medicine, Heidelberg University Hospital, Heidelberg,* [3]*Rheumatology Hospital Aachen, Aachen,* [4]*Department of Internal Medicine, University Hospital of Tübingen, Tübingen,* [5]*University Medical Center Freiburg, Clinical Research Unit for Rheumatology, Freiburg,* [6]*Department of Dermatology, University Hospital of Ulm, Ulm,* [7]*Department of Rheumatology and Clinical Immunology, Kerckhoff Clinic, Bad Nauheim,* [8]*Charité Berlin, Rheumatology and Clinical Immunology, Berlin,* [9]*Department of Dermatology, University of Münster, Münster and* [10]*Department of Dermatology, Venerology and Allergology, University Medicine Goettingen, Göttingen, Germany*

Background. To improve detection and follow-up of patients with SSc, the German Network for Systemic Scleroderma (DNSS) was founded and initiated a registry gathering information on diagnosis, clinical symptoms and therapy of SSc patients.
Methods. Up to date, more than 3000 patients have been grouped into four descriptive disease subsets, i.e. lcSSc, dcSSc, overlap syndrome and UCTD with scleroderma features. Disease progress between initial patient registration (Year 0) and fourth follow-up (Year 4) was measured using organ involvement and present symptoms as indicators.
Results. Recent analyses revealed that 49% of patients suffer from limited SSc (lSSc), 31% from diffuse SSc (dSSc) and 10% of patients were diagnosed with an overlap syndrome. 8% had an undifferentiated form while scleroderma sine scleroderma was present in 0.7% of patients.
Follow-up data are available from 1595 patients after 1 year, from 901 patients followed for 2 years, 573 patients followed for 3 years and 386 followed for at least 4 years. After 4 years a significant increase was detected in the frequency of pulmonary hypertension (PAH) (14.4–24.2%, $P = 0.001$), lung fibrosis (38.8–47.6%, $P = 0.006$), oesophagus involvement (58.5–74.8%, $P = 0.0001$), bowel involvement (13.6–19.9%, $P = 0.03$), Kidney (10.7–15.8%, $P = 0.03$) and heart (13.4–24.0%, $P < 0.0001$) involvement.
Disease subsets were associated with different organs being more frequently involved, i.e. lcSSc with PAH (13.5–25.0%, $P = 0.007$), oesophagus (60.7–77.0%, $P = 0.0001$) and colon involvement (7.3–11.6%, $P = 0.002$); dcSSc with PAH (19.0 *vs* 25.9%, $P = 0.035$), lung fibrosis (63.5 *vs* 71.4%, $P = 0.02$) and heart involvement (19.1 *vs* 27.7%, $P = 0.007$). Interestingly, patients with overlap syndrome showed no significant change in organ involvement over time.
Conclusions. After 4 years of follow-up in a large well-defined SSc cohort, a significant increase in frequency of organ involvement was observed, particularly with respect to the lung, GI-tract and heart. Patients with SSc should be followed at least annually for organ involvement, the frequency of follow-ups being increased depending on the disease activity.

PS193. DOES THE USE OF ACE INHIBITORS PRIOR TO SCLERODERMA RENAL CRISIS AFFECT PROGNOSIS – RESULTS OF THE INTERNATIONAL SCLERODERMA RENAL CRISIS SURVEY

M. Hudson[1], M. Baron[1], S. Tatibouet[2], D. Furst[3] and D. Khanna[4]
[1]*Department of Medicine, McGill University,* [2]*Lady Davis Institute, Division of Clinical Epidemiology, Montreal, Canada,* [3]*University of California, Geffen School of Medicine, Los Angeles and* [4]*University of Michigan, Scleroderma Program, Ann Arbor, USA*

Background. Scleroderma renal crisis (SRC) is an infrequent but life-threatening complication of SSc. The outcome of SRC has improved considerably since the advent of angiotensin-converting

enzyme (ACE) inhibitors. The incidence of SRC has also appeared to have decreasd, perhaps in part due to the more liberal use of ACE inhibitors in SSc. However, recent retrospective data suggests that patients with SRC exposed to ACE inhibitors prior to the onset of SRC may have worse outcomes. We undertook a prospective study to verify whether SSc patients with incident SRC on ACE inhibitors prior to the onset of SRC had worse outcomes compared with those who were not on these drugs.

Methods. We designed a prospective, observational cohort study of incident SRC subjects identified through a web-based survey. Every second week, an e-mail was sent to 589 participating physicians from around the world to identify incident cases of SRC. Data on patient demographic and disease characteristics, as well as exposure to ACE inhibitors was collected. A 1-year follow-up case report form was sent to all the physicians who identified a case. The primary outcome of interest was death or dialysis at 1 year after the onset of SRC, comparing patients exposed and unexposed to ACE inhibitors prior to the onset of SRC.

Results. We identified 94 incident cases of SRC (mean age 53 years, 65% women, 68% diffuse SSc and median disease duration since the onset of the first non-Raynaud's symptom 1.6 years). Of these, 85 (90%) had a hypertensive SRC and 9 (10%) a normotensive SRC. Twenty-two patients (23%) were on an ACE inhibitor immediately prior to the onset of the SRC. To date, we have collected 1-year follow-up data on 70 patients, of which 42 (60%) died or remained on dialysis 1 year after the SRC. The crude odds ratio of death or dialysis at 1 year in those exposed to ACE inhibitors immediately prior to the onset of the SRC compared with the unexposed was 1.30 (95% CI 0.42, 4.05, $P = 0.65$).

Conclusion. SRC is associated with poor 1-year outcomes. However, exposure to an ACE inhibitor immediately prior to the onset of SRC was not associated with an increased risk of death or dialysis at 1 year follow-up. These data may be explained by a lack of association of ACE inhibitors with outcomes in SRC or type II error due to small sample size.

PS194. BIOPSY-PROVEN MYOCARDIAL INVOLVEMENT IN SSc

J. Henes[1], S. Weretka[2], M. Schmalzing[1], M. Horger[3], K. Klingel[4], U. Kramer[3], L. Kanz[1], J Schreieck[2] and I. Koetter[1]
[1]*Department of Internal Medicine II (Oncology, Haematology, Immunology, Rheumatology, Pulmology),* [2]*Department of Cardiology and Cardiovascular Medicine,* [3]*Department of Diagnostic and Interventional Radiology and* [4]*Department of Molecular Pathology, University Hospital, Tübingen, Germany*

Background. Clinical cardiac involvement is predictive of a poorer outcome. Due to our experiences with several fatal arrhythmias in our cohort we intensified our screening for myocardial involvement, especially in patients planned for autologous stem cell transplantation (aSCT).

Method. Systematic review of all patients with SSc in our database who underwent myocardial biopsy. Additional diagnostics (echocardiography, 24-h Holter ECG, stress echocardiography and cardiac MRI) as well as troponin and brain natriuretic peptid (BNP) were analysed. If cardiac MRI was performed, late enhancement was determined as pathological. Additionally, myocardial contractility (ejection fraction) and abnormal (reduced) wall motion were registered. 24-h ECG were evaluated using the Lown-classification with Lown 3 or higher judged suspicious. Echocardiography and stress echocardiography were utilized to detect reduced wall motion and estimate the systolic pulmonary arterial pressure (papSys; $>$ 30 mmHg judged pathological).

Results. Our database includes 266 patients with SSc (lcSSc and dcSSc). Of these, 25 patients (17 males, 8 females, median age 47 years) underwent myocardial biopsy. Seven patients had a limited and 18 a diffuse cutaneous manifestation with a median Rodnan skin score of 15 (4–31) at the time of biopsy. Thirteen patients were tested positive for Scl70 antibodies. Myocardial biopsy revealed a cardiac involvement in 100%. The 24-h ECG found 12 pathological results in 16 patients. Cardiac MRI could detect pathological late enhancement in 5/16 patients. Troponin and BNP were elevated in 14/25 patients for troponin, 11/25 for BNP and in 9 patients for both. Resting echocardiography was assessed in 20 patients and revealed reduced wall motion in 2 and elevated papSys in 8 patients.

Conclusion. All 100% of our patients with pathological findings either in 24-h ECG, cardiac MRI, stress echocardiography or laboratory showed a cardiac involvement by means of histopathology. These findings might be biased by the negative selection in our cohort but emphasizes the need for intensive screening to identify SSc patients at risk for sudden cardiac death. A prospective trial is needed to evaluate the accuracy of the different screening methods. In our patients, the most accurate tools in asymptomatic patients were laboratory tests for troponin and BNP and 24-h ECG for arrhythmias. Cardiac MRI is an elegant tool to assess ventricular function but is less sensitive in diagnosing conductive disorders. As a consequence in 12 of these patients a cardiac defibrillator was implanted before autologous stem cell transplantation.

PS195. IS FATIGUE RELATED TO CYTOKINE IMBALANCE IN PATIENTS WITH SSc?

B. Harper[1], M. Mayes[2], E. Gonzalez[1], H. Draeger[3], D. Nair[2], S. Agarwal[2], F. Tan[2] and S. Assassi[2]
[1]*University of Texas Medical Branch, Galveston,* [2]*University of Texas Health Science Center Houston, Houston and* [3]*University of Texas Health Science Center San Antonio, San Antonio, USA*

Background. Fatigue is a prominent symptom of patients with SSc. SSc patients considered fatigue as their most prevalent symptom that had at least moderate impact on activities of daily living. Fatigue, as measured by the fatigue severity score (FSS) a validated measure of fatigue severity, is associated with presence of gastrointestinal and joint manifestations as well as ineffective pain control and coping skills in SSc. Abnormalities of serum cytokine levels have also been associated with disease subtype and presence of pulmonary fibrosis in SSc. No reports have been published to date of a relationship between fatigue and cytokine levels in SSc. Our goal is to evaluate the relationship between fatigue and Th1, Th2, Th17 and IFN-inducible cytokines.

Methods. Plasma from patients with SSc was obtained at enrolment in the GENISOS cohort, a prospective cohort of early SSc. Demographic and clinical data including FSS were simultaneously obtained. Levels of key cytokines (TNF-α, IL-6, IL-8, IL-5, IL-12, IL-10, IL-13, IL-1β, IL-2, IL-4, IFN-γ, IP-10, MCP-1 and ITAC) were measured in duplicate by electrochemiluminescent multiplex assays. Cytokine levels were log transformed for analysis. Levels of IL-4, IL-2 and IFN-γ were dichotomized into detectable *vs* undetectable for analysis as they were detectable in less than 50% of subjects. Univariable and multivariable regression analyses controlling for age, ethnicity, gender and use of immunosuppressants were performed.

TABLE 1.

Cytokine	Mean value, pg/ml	Univariable regression		Multivariable regression	
		b (95% CI)	*P*		
IFN-γ	0.8468	−0.0661 (−0.3100, 0.1776)	0.593	−0.0601 (−0.3043, 0.1840)	0.628
TNF-α	3.8531	0.0422 (−0.1054, 0.1899)	0.573	0.0435 (−0.1044, 0.1915)	0.562
IL-6	1.8524	−0.0031 (−0.1049, 0.0985)	0.951	−0.0021 (−0.1040, 0.0998)	0.968
IL-8	20.5928	0.0464 (−0.0330, 0.1258)	0.251	0.0413 (−0.0390, 0.1217)	0.312
IL-4	0.289	−0.0161 (−0.2480, 0.2157)	0.891	−0.0082 (-0.2409, 0.2243)	0.944
IL-5	2.0629	0.0715 (−0.0741, 0.0884)	0.862	0.0048 (−0.0766, 0.0864)	0.906
IL-12	23.5521	−0.0042 (−0.0664, 0.0579)	0.893	−0.0054(−0.0677, 0.0569)	0.864
IL-10	7.6172	0.0029 (−0.0729, 0.0788)	0.939	0.0045 (−0.0715, 0.0806)	0.906
IL-2	0.8259	−0.0857 (−0.3177, 0.1425)	0.454	−0.0869 (−0.3177, 0.1438)	0.459
IL-13	8.4412	−0.0067 (−0.0798, 0.0662)	0.855	−0.0083 (−0.0816, 0.0649)	0.822
IL-1β	0.9116	0.0572 (−0.0274, 0.1418)	0.184	0.0557 (−0.0290, 0.1406)	0.196
IL-17	3.2738	−0.0171 (−0.1442,0.1099)	0.791	−0.0127 (−0.1409, 0.1154)	0.845
IP-10	168.5975	−0.0740 (−0.1858,0.0376)	0.193	−0.0646 (−0.1771, 0.0479)	0.259
ITAC	206.2231	−0.0017 (−0.1213, 0.1179)	0.978	0.0061 (−0.1139, 0.1263)	0.92
MCP-1	88.0111	0.1011 (−0.0934, 0.2958)	0.307	0.1149 (−0.0799, 0.3098)	0.246

Results. Plasma from 266 patients with SSc was assessed. Patients were on average 48.6 years old with 83.1% women, diffuse skin involvement was present in 156 (58.7%) patients, and mean disease duration was 2.5 years.

As shown in Table 1, the investigated cytokines including TNF-α and IL-6 did not correlate with perceived fatigue as captured by FSS. Similar results were seen after adjustment for age, ethnicity, gender and exclusion of patients taking immunosuppressants or prednisone doses >7.5 mg/day in the multivariable model (Table 1).

Conclusion. No association was found between levels of the investigated cytokines and patient reported fatigue in a cohort of early SSc. These data suggest fatigue in SSc is determined by specific disease manifestations and psychosocial factors rather than by a cytokine imbalance.

PS196. SSc PROFILE OBSERVED IN INTERNAL MEDICINE DEPARTMENT

D. Hakem[1], R. Yahyaoui[2], S. S. Salah[3], M. C. Abaddi[3], R. Amrane[2], S. Ayat[4], B. Mansouri[4] and A. Berrah[1]
[1]*Internal Medicine Department,* [2]*Pneumology, Dr Mohammad-Lamine Debaghine's Hospital, Bab-El-Oued, Universitary Hospital Center,* [3]*Immunology, Pasteur Algerie Institute and* [4]*Radiology, Dr Mohammad-Lamine Debaghine's Hospital, Bab-El-Oued, Universitary Hospital Center, Algiers, Algeria*

Aim. To review through an Internal Medicine Practice the SSc profile.
Patients and methods. Patients presenting for various symptoms from January 1997 to December 2010 fulfilling the ARA criteria for SSc were included. We have are not included in this study the patients <16 years old, whose clinical and immunological data are insufficient and whose follow-up is <2 years. Investigations including immunological tests (ANAs), haemogram, liver and kidney functions, (thoracic tomodensitometry, barium swallow), pulmonary function test, echo-cardiography, etc.), digestive investigations (oesophageal manometry and others) were done. Others explorations are dictated by the context (cardiac catheterization,cardiac MRI, liver, or kidney biopsy).
Results. Ninety-one women and nine men with the mean age of of 45.7 (11.62) and a mean duration of 7.41 (4.69) years. Most common presenting symptoms were skin binding-down (81%), RP (92%), pigmentary changes morphoea (71%) more than hyperpigmentation, contracture of fingers (67%) and fingertip ulcer (37%). Other symptoms revealing SSc are dyspnoea (50%), joint complaints (31%), muscles weakness (17%), dysphagia (37%), abdominal pains (5%), renal crisis (1%). Various and multiple symptoms are often intricated. The data analysis finds a thyroid (39%) and a hypophyseal achievement (3%). Morbid associations is a type 2 diabetes (9%), a type C hepatitis (3%), a valvular disease (5%), ischaemic stroke (5%), a severe malnutrition by intestinal malabsorption (4%), major oesophageal stenosis (7%). The immunological profile finds positive ANAs (91%), antiScl70 antibody (41%), ACAs (35%), anti-mitochondria (5%) and anti-SSSA (10%). Pulmonary function tests showed restrictive (57%) and obstructive pattern (4%). Diffuse SSc are dominant and CREST syndrome found in meadows of a third of the cases. Pulmonary hypertension (PH) is found in proportions equal in the group anti-Scl70 and anti-centromeres. The liver injury is at the origin of a cirrhosis (3) and the course towards a fibrosis lungwort is in our follow-up badly estimated by 20%.The causes of death (12) are thromboembolic diseases (3), infectious (1), severe PH (4), fibrosis lungwort (2), cirrhosis (1) and scleroderma renal crisis (1).
Conclusion. Correlations' between clinical and immunological SSc remains to specify by the homogenization of immunological tests and algorithm to investigations to be more definite for identifiying the profile of SSc in our country.

PS197. DIGITAL NECROTIC ULCERATIONS REVEALING A RACAND DISEASE

D. Hakem[1], S. Lassouaoui[1], M. A. Boukretaoui[2], A. Zenati[2] and A. Berrah[1]
[1]*Internal Medicine Department and* [2]*Immunology, Dr Mohammad-Lamine Debaghine's Hospital, Bab-El-Oued, Universitary Hospital Center, Algiers, Algeria*

Case report. OH, a 29-year-old woman without pathological history is investigated for Raynaud's syndrome associated with fingertip ulceration. Pulses (humeral, radial) are present and hands do not present any deformation or tumefaction. No slerodactily, or proximal sclerosis, or calcinosis skin, or morphoeas or tendon retractions are observed. The cardiovascular auscultation and the lungworts are normal. The video nail capillaroscopy showed an aspect mega capillaries and haemorrhagic compatible with microangiopathy compatible with active systemic scleroderma 'SSc' (Stage 2 of SSc). The exploration by echo Doppler US method (above aortic trunks, upper limbs) and trans-oesosphageal cardiac echo Doppler did not show abnormalities. The arterial pulmonary hypertension is estimated to be ~25 mmHg. We do not objectives disorders of the oesophageal motility to the manometry. The thoracic CT does not reveal compatible images with damage of fibrosis lungwort and the respiratory function test are in the norms finds. Viral serologies, cryoglobulin, cold agglutinins, anti-phospholipids tests are negative. ACAs are positive in 1/320. Glycaemia, renal function, liver tests, blood cells, lipid profile are normal. The daily proteinuria is negative. The thrombophilia tests are normal (protein C, S, anti-thrombin III, Leiden factor mutation, etc.).
Diagnosis. A RACAND disease (RD) is a very likely diagnosis evoked on the presence of two criteria (necrosis digital, ACA, etc.) and in the absence of criteria being enough for CREST syndrome. Based on this fact, the patient benefits from a monitoring on the cardiovascular plan (systematical annual echocardiography) to detect a pulmonary hypertension (PH) (which occurs usually in this entity) and the other systemic signs to reclassify in a nearby entity (CREST, diffuse systemic scleroderma). A symptomatic treatment is introduced with peripheral vasodilators, calcium canal blockers and local care and of anti-platelet drugs without any improvement. Ilosprost is helpful in curing and amending digital ulcerations in a spectacular and long-lasting way.
Conclusion. Of recent individualization the RD, the entity of which remains to specify, must be evoked in front of any digital necrosis associated with a Raynaud's syndrome, ACAs and PH. The treatment by Ilomudine can be compromised by a severe PH imposing of this fact the recourse to the other therapeutic alternatives (immunosuppressive drugs) whose protocol remains to be validated.

PS198. REYNOLDS' S SYNDROME: REVIEW OF THREE CASES

D. Hakem[1], H. Djerrah[1], S. S. Salah[2], L. Stof[3], S. Ait-Younes[4], N. Ouadahi[1], F. Asselah[4], M. C. Abaddi[2], B. Mansouri[3] and A. Berrah[1]
[1]*Internal Medicine Department, Dr Mohammad-Lamine Debaghine's Hospital, Bab-El-Oued, Universitary Hospital Center,* [2]*Immunology, Pasteur Algiers Institut,* [3]*Radiology, Dr Mohammad-Lamine's Hospital, Bab-El-Oued Universitary Hospital Center and* [4]*Anatomopathology, Mustapha Universitary's Hospital Center, Algiers, Algieria*

Introduction. Reynolds syndrome (RS) is a condition characterized by systemic scleroderma (SSc) (mainly limited to CREST syndrome) with primary biliary cirrhosis (PBC). We report three observations of liver injury during an SSc-related entity with various profiles (clinical, immunological, histopathological and morphological) raising the problem of the nosological borders with RS and the therapeutic impacts.
Case reports. Three patients (two women, one man), middle-aged of 45 years (41–51 years), a main disease duration of 5.7 years (3–7 years) are investigated for hepatic disturbances of fortuitous discovery (1), on the occasion of a wild pruritus (2), associated with a hepatomegaly (1), a thrombopenia (2) and a portal hypertension (PH_) (1). The SSc is characterized by complete CREST syndrome (2), diffuse SSc (1), associated with ACAs (1) and positive antiSclo70 antibodies (2). The liver injury is of type PBC (2) and auto-immune cholangitis (1). The liver tests showed cholestasis syndrome (2), a mixed syndrome associating cholestasis and fluctuating cytolysis (1), hepatocellular insufficiency) (1), cytopenia (2) and anti-mitochondrial antibodies (3). The data of the hepatobiliary MRI are compatible with a sclerosing cholangitis (1) and with a CBP (2) and visualized signs of PH (2). Other associated visceral achievements are a fibrosis Interstitial lung (3), a pulmonary hypertension (2), digestive disorders as a intestinal pseudo-obstruction with severe malnutrition (1), an oesophageal achievement (3) as dyspepsia, hypomotility, stenosis (1) and finally a digital ischaemia (3) with fingertip ulceration (2). A Gougerôt-Sjogreen syndrome is individualized (1). The viral serologies are negative (3). The hepatic biopsy is compatible with PBC (1) and autoimmune cholangitis (1) diagnosis. The disease course is fatal with cirrhotic decompensation (1) and favourable in systemic and hepatic states (2) under conventional medical treatment and sreening.
Discussion. These case reports show that liver diseases during the SSc represent a wide spectrum not answering the definitions established for the syndrome of RP and can be observed in all the clinical forms of the SSc. These forms related must be estimated, in wider series, both on the immunological and histopathological characteristics for a better understanding of their aetiopathogenical mechanisms to definite the nosological diagnostic and to be precise the optional therapeutic.

Conclusion. A prirutus, often attribute wrongly to the skin achievement of SSc has to benefit regularly from liver tests to detect early liver disease integrated into an RS (or a variant of this entity) to treat and to preserve the prognosis of this morbid association (autoimmune liver disease and SSc).

PS199. COMPUTERIZED NAIL-FOLD VIDEO CAPILLAROSCOPY AND SYSTEMIC DISEASES

D. Hakem[1] and A. Berrah[1]
[1]*Dr Mohammad-Lmaine Debaghine's Hospital, Bab-El-Oued Universitary Hospital Centee, Algiers, Algeria*

Introduction. The computerized nail-fold video capillaroscopy (CNVC) is of a tall interest in the exploration of RP. It permits to determine with a tall sensitiveness and a large specificity many autoimmune diseases (AID) not yet identified showing morphological abnormalities of capillaries, rheological disorders orienting to collagen diseases (CD) as SSc, SLE, acute DM and mixed collagen tissue diseases (MCTD).CNVC-aimed diagnostic is a non-invasive examination that must be realized not in all unexplained RP but also in all unidentified arthromyalgias.
Objectives. To appreciate the rentability of CNVC realized to investigate chronic inflammatory diseases not yet identified. To recognize, through CNVC, earlier AID as SSc, SLE particularly in RP and to describe the main abnormalities observed in CNVC: morphological, rheological, capillary distribution, haemorrhagic injuries.
Patients and methods. We bring back the experience of the Internal Medicine Centre on a period of five consecutive years, collect 150 requests for CNVC from many symptoms as arthralgia, myalgia, scleroderma, RP, etc., which are all excluded from these study subjects of $<$16 years and $>$60 years old. The old and all identified CDs as SLE, SSs and the associated diseases are identified as interfering in the interpretation of CVNC study (type 2 diabetes mellitus, hypertension, vasoconstrive drugs myeloproliferative syndrome, etc.).
Results. A 150 requests retrospectively analysed sex ratio: 0:3 with 105 women and 45 men, median age: 35.7 (16–57] years. AID identified by autoantibodies, skin biopsy (SSc, DM and SLE) and CNVC are compatibles with organic diseases: 95 cases (63%), inorganic and functional disturbances in 29 cases (30%). CNVC shows normal aspect or is not contributing in 16 cases (7%). The morphological area aspect studied in 95 inorganic CNVD observed are as follows: a capillary depletion in 29 cases (30%) and an abnormality distribution in 31 cases (32%), whose major expression is anastomosis distribution in 21 cases (22%) and fish bed aspect in 10 cases (21%). The morphological abnormalities: major dystrophy in 79 cases (73.68%), major ecstasies with mega capillaries 45 (47.36%), focal ecstasies (17) and capillary tortuosity (11). The haemorrhage area is observed in 39 (41%); the rheological abnormalities in 25(26.31%) as minor flow disturbances in 19 (sludge type 1) or major in 6 patients (sludge 2 and 3). The other particularities described the venous-capillary stases and microthrombi. On conclusion, main diseases evoked in these CNVD are CD in 71 patients (74.73%), SSc (41), SLE (12), DM (7), RA (8) or MCTD (3); a Raynaud's disease (functional disturbance) is established in 20 cases (22.22%) and are non-contributive in the other cases.
Discussion. Rentability of CVNC to predict or to approach the diagnosis of AID appears less performing in referring to the literature data (63 *vs* 88%).What about false positivity? The absence of expression of systemic diseases in 2 years of follow-up after iterative CVNC showing stigmata of organic abnormalities observed in five cases are supposing arbitrary as false positivity. But it is established that many AIDs appear many years after micro-angeitis is focalized in CVNC. Arthromyalgias and RP without identified disease could expose in missed diagnosis in digital necrotic risks and requires regular CVNC screening for definite longer times. What about false negativity? The non-observance of abnormalities in CVNC in scleroderma constitute a major argument for differential diagnostic in SSc and suggest a Shulman's disease that certitude diagnosis is established in fact by neuromuscular biopsy showing a fascia hypertrophy. Iterative CVNC, through 2 years of follow-up, in RP is usual to determinate the character organic or not of RP particularly if it is associated with arthralgia, myalgias, CD context, etc., to avoid a false negativity. The non-rentability of CVNC could be so linked to the exam conditions (difficulties to explore black skin, nail mycosis, finger retractions, scleroderma, infiltrate hand, micro traumatisms, etc.). But CVNC is also operator-dependent. Classically, only SSc diagnostic is imperatively associated with precocious and constant CVNC abnormalities.
Conclusion. CVNC is a no invasive examination, which must be realized not only in all unexplained RP but also in arthomyalgias and any symptoms suggesting AID. The normality of CVNC did not exclude definitely the eventuality of AID but justify confrontation with clinical and biological context and in many times iterative CVNC in the follow-up particularly in RP. Normality of CVNC in scleroderma investigation conducts the diagnosis of inflammatory fasciitis. Inversely, abnormalities of CVNC determinate a group of patients presenting high risks to develop autoimmune diseases and justify immunological tests and a CVNC screening in the follow-up. Rentability of CVNC is operator-dependent. Precise in formations in requests physician could approve its rentability.

PS200. SEASONAL VARIATION OF ENDOTHELIAL FUNCTION IN SCLERODERMA-RELATED AND IDIOPATHIC RP

F. Hafner[1], C. Fazekas[1], T. Gary[1], H. Froehlich[1] and M. Brodmann[1]
[1]*Department of Internal Medicine, Division of Angiology, Medical University of Graz, Graz, Austria*

Introduction. RP is characterized by a sudden acral pallor and subsequent reddish and/or livid discoloration, especially affecting the fingers. This disease has a broad geographic and seasonal volatile prevalence. RP can occur idiopathic without an underlying disease, this mostly affects young women. As a secondary form, RP can also be related to scleroderma. In early stages of scleroderma, RP may present the first and unique symptom of this CTD, but it has been proven that also endothelial damage and endothelial dysfunction are already present at these early stages. Our aim was to evaluate the presence of a seasonal variation of endothelial function among patients with scleroderma-related and idiopathic RP.
Methods. Fifty-two patients with present RP (25 idiopathic and 27 scleroderma-related RP patients) and 20 healthy subjects were included in the study. Endothelial function was evaluated by flow-mediated dilatation (FMD) of the brachial artery once in the cold season (October until March) and once during summer-time (April until September). All FMD measurements were performed according to the present guidelines by the same trained technician.
Results. The mean FMD between the two measurements was 3.9 (3)% among scleroderma patients, 4.6 (4.6)% among idiopathic RP patients and 5.5 (2.4)% among the control subjects (NS). We observed a trend towards lower FMD values during the cold season: scleroderma summer 4.4 (3.2)% *vs* winter 3.4 (4.4)%, idiopathic RP summer 5.2 (4.2)% *vs* winter 4.0 (6.5)% and control subjects summer 6.5 (3.7)% *vs* 4.5 (6.5)%. This trend of lower FMD values during the cold season was statistically not significant within these groups, but we observed a significant difference between mean summer and winter FMD values of the whole study group with values of 5.3 (3.8)% and 3.9 (4.9)% respectively ($P = 0.029$).
Discussion. Endothelial dysfunction has previously been proven in scleroderma patients. The method of FMD by Celermajer showed a seasonal variation among the whole study group, independent of the underlying disease of RP, in idiopathic and scleroderma-related forms. However, it is not proven, whether this reduction of FMD is also associated with an indeed decrease of endothelial function. If FMD is considered as a parameter of endothelial function in future studies, it seems essential to define the point of time of FMD measurement.

PS201. CASUISTIC STUDY OF ALL THE PATIENTS WITH THE DIAGNOSIS OF SYSTEMIC SCLERORIS FOLLOW-UP IN OUR AMBULATORY CLINIC

G. Guerreiro Mascarenhas[1], A. Baptista[1], A. Martins[1], F. Alves[1], H. Brito[1], D. Nunez[1], G. Sequeira[1] and I. Mendonça[1]
[1]*Hospital de Faro, Faro, Portugal*

SSc is an autoimmune disease, multisystemic and rare. In its initial phase manifests itself with symptoms and/or signs that occur frequently in the general population, such as RP, osteoarticular disease or gastro-oesophageal reflux disease (GERD). It can also compromise, aggressively, organs such as kidney, lung and heart.
Based on all patients followed in our ambulatory clinic of autoimmune diseases with the diagnosis of SSc, the authors purpose to make a clinical review of the clinical manifestations, complications and therapy.
It is noteworthy that although no further treatment capable of modifying the progression of the disease, there are currently several drugs that reduce morbidity and consequently improve the quality of life for patients. Therefore, it is essential to do as early as possible the diagnosis and intervention.

PS202. SSc SINE AUTOANTIBODIES

M. Gomes[1], L. Santos[1], R. Ferreira[1], C. Canha[1], F. Vilão[1], M. Petrova[1] and J. M. N. Costa[1]
[1]*Internal Medicine Department, Coimbra University Hospital, Coimbra, Portugal*

Objectives. To report two cases of patients with limited SSc who had only low titres of ANAs, without conclusive IF findings.
Results. These two patients have, most certainly, clinical SSc, as well as nail-fold capillaroscopy typical findings of limited variant of SSc, but their autoimmunity panel is, persistently, very poor and with only slight deviations from a normal one. Thus, clinical findings do not match everytime with autoimmunity; so, diagnosis must be built on both clinical and laboratory findings.
Conclusion. Not always autoimmunity is consistent with clinical findings, whereas the latter must remain the punctum saliens in SSc.

PS203. SSc SPECTRA—FOUR DIMENSIONS TO RECOGNIZE

M. Gomes[1], L. Santos[1], M. Simões[1], P. Alves[1], H. Esperto[1], A. Chaves[1], S. Ramos[1] and J. M. N. Costa[1]
[1]*Internal Medicine Department, Coimbra University Hospital, Coimbra, Portugal*

Objectives. To show the dissonance between clinical features and complementary diagnostic tests in 14 patients with SSc.
Methods. The authors collected retrospective data from 14 patients with established diagnosis of SSc, whether in its limited or in its diffuse variant. The analysis included clinical features, laboratory tests, autoantibodies and nail-fold capillaroscopy findings. Follow-up time varied, as some patients had recent diagnosis and others had long time known disease.
Results. Fourteen patients were included in the study—11 with limited and 3 with diffuse variant of SSc. Only one patient with limited variant of SSc had no history of RP; on the other hand, only one patient with diffuse variant had a history of RP. Only one patient had pulmonary hypertension (limited variant of SSc) and two patients had pulmonary fibrosis (one with limited, other with diffuse variant of SSc). One patient had SSc sine scleroderma. Eight patients had oesophageal dysmotility and one patient had intestinal sclerosis. Two patients with limited variant had no ACAs but only low titres of ANAs with no conclusive IF. Two patients had anti-nucleolar autoantibodies: one with diffuse, other with limited variant of SSc. The most frequent findings of nail-fold capillaroscopy were giant capillaries. Every patient had, somewhere during follow-up, elevation of inflammatory response biomarkers.
Conclusion. The diagnosis and follow-up of SSc is very challenging, as its clinical features do not always match with the expected findings in complementary diagnostic tests, as suggested by literature. Thus, it requires a multifaceted approach in order to identify every single problem and, in some cases, predict and prevent future ones.

PS204. HEPATIC INVOLVEMENT IN SSc—REPORT OF THREE CASES, TWO DIFFERENT OVERLAP SYNDROMES

M. Gomes[1], L. Santos[1], C. Canha[1], R. Ferreira[1], E. Meira[1], E. Ferreira[1], H. Esperto[1] and J. M. N. Costa[1]
[1]*Internal Medicine Department, Coimbra University Hospital, Coimbra, Portugal*

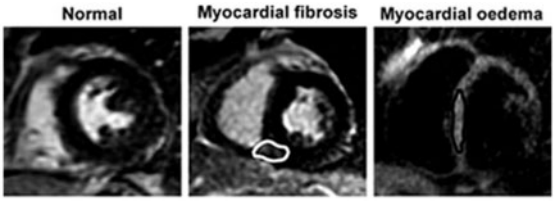
Objectives. The authors report the cases of three patients with SSc in its limited cutaneous form with liver involvement, namely one with autoimmune hepatitis and two with primary biliary cirrhosis.
Results. Both autoimmune hepatitis and primary biliary cirrhosis can be the mirror of hepatic involvement in SSc (the latter resulting in the Reynolds syndrome), although the association between these clinical entities is rare. Thus, the evaluation of liver enzymes and screening for autoantibodies should be performed periodically with the purpose of an early recognition of liver involvement.
Conclusions. These patients are different, tacit examples of rare forms of hepatic involvement associated with SSc, warning us of the possibility of its unusual, but possible occurrence, allowing an early, accurate approach and management.

PS205. CARDIAC INVOLVEMENT IN SSc: THE ADDED VALUE OF MAGNETIC RESONANCE IMAGING

L. Gargani[1], A. Pingitore[1], D. De Marchi[2], S. Guiducci[3], M. Doveri[4], S. Bellando Randone[3], L Bazzichi[4], C. Bruni[3], S. Bombardieri[4], M. Lombardi[2], E. Picano[1] and M. Matucci Cerinic[3]
[1]*Institute of Clinical Physiology,* [2]*Gabriele Monasterio Foundation, National Research Council, Pisa,* [3]*Department of Biomedicine, Division of Rheumatology, AOUC, Excellence Centre for Research, Transfer and High Education D, Florence and* [4]*Department of Internal Medicine, Rheumatology and Immunoallergology Units, Pisa, Italy*

Background. Cardiac involvement in SSc affects the prognosis of the disease. Myocardial fibrosis is the pathological hallmark of this complication and has been reported in 50–80% of cases in necropsy. Echocardiography is the routine imaging tool to easily detect cardiac involvement, but it is not accurate to detect myocardial fibrosis. Delayed gadolinium enhancement (DE) cardiovascular magnetic resonance (CMR) is the gold-standard for myocardial fibrosis assessment.
Aim. To evaluate the added value of DE-CMR to echo colour Doppler in SSc patients.
Methods. After a thorough clinical characterization, 53 SSc patients [age = 52 (14), 95% females, 34% diffuse form] underwent, on the same day, a comprehensive echocardiogram, including tissue Doppler imaging (TDI) and a DE-CMR.
Results. Echocardiography showed normal systolic function [ejection fraction = 64 (6%)] and wall motion score index (1) in 53/53 (100%) patients, whereas DE-CMR showed a pattern of non-ischaemic myocardial fibrosis in 12/53 (23%) patients. In 2/53 patients (4%), T2-weighted CMR showed myocardial oedema, that resolved after steroid therapy. Among clinical (age, duration of disease, limited or cutaneous form, Rodnan skin score, activity score), echocardiographic (indexed left atrium and left ventricular volumes, right atrium and ventricular dimensions, 2D and TDI parameters of left and right ventricular function, and pulmonary arterial systolic pressure) and CMR parameters, only TDI mitral annulus E/E′ was an independent predictor of the presence of myocardial fibrosis at multivariate analysis (hazard ratio 1.8; 95% CI 1.1, 3.1).
Conclusions. Subclinical cardiac involvement is relatively frequent in SSc. CMR can detect different patterns of reversible (by T2-weighted) and irreversible (by DE) cardiac involvement. Elevated E/E′ at echocardiography may raise the suspicion of myocardial fibrosis.

FIG. 1



PS206. PULMONARY HYPERTENSION IN A SERIES OF PATIENTS WITH SSc. PREVALENCE OF DIFFERENT VARIANTS

M. J. Castillo-Palma[1], F. J. García-Hernández[1], R. González-León[1], C. González-Pulido[1], E. Montero-Mateos[1], A. León-Guisado[1], I. Porras-Antras[1], C. Ocaña-Medina[1], M. L. Artero-González[1] and J. Sánchez-Román[1]
[1]*Collagenosis and Pulmonary Hypertension Unit, Internal Medicine Department, University Hospital Virgen del Rocío, Seville, Spain*

Background. Patients diagnosed of SSc are a known risk group for developing PAH. However, pulmonary hypertension (PH) in patients with SSc can respond to different causes: PAH, PH secondary to interstitial pulmonary disease (IPD), PH related to left-sided heart disease (LSHD) or chronic thromboembolic PH (CTEPH). Except in a recent publication (Avouac *et al.,* 2010), studies do not distinguish adequately the relative frequency of these variants.
Objective. To analyse the frequency of the different types of PH in patients with SSc.
Method. A protocolized follow-up for early detection of PAH in a cohort of 180 patients diagnosed of SSc was started in June 2003. Annual assessment included echocardiogram, lung function tests (LFTs) and, optionally, high-resolution CT. sPAP was considered high if it was >35 mm Hg. Patients were monitored if sPAP was <50 mm Hg in the absence of symptoms; if sPAP was ≥50 mmHg or patient was symptomatic, a diagnostic algorithm for PH adjusted to the international guidelines was applied. Patients diagnosed with PH despite the screening programme were also taken into consideration.
Results. Until 31December 2010, 131 of 180 patients (72.8%) were evaluated; sPAP >35 mmHg was detected in 50 (38.1%). PH was judged to be related with structural heart disease in four patients and related with IPD in two (1.5%). sPAP was normal in successive

echocardiograms in other five cases. Right heart catheterization (RHC) was done in 27 patients with high sPAP not related with known or significant LSHD or IPD, including those with IPD but a disproportionate reduction of DL_{CO} ($FVC/DL_{CO} > 1.8$), and PH was confirmed in 23. PH was post-capillar in 2 and pre-capillar in 21: PAH in 20 and CTEPH in 1. Thus, PH not related to IPD was confirmed in 17.5% of patients: PAH in 15.2%, PH related with LSHD in 1.5% (which increased to 4.6% when patients with previous evidence of structural cardiopathy were added) and 0.8% for CTEPH. Twelve patients remain under observation.
Conclusions. (i) After systematic evaluation in our series of patients with SSc, the observed prevalence of PAH was higher than reported in other studies. (ii) This assessment strategy allows a more accurate classification of patients and an earlier diagnosis and treatment of PAH in these patients.

PS207. CARDIOPULMONARY EVALUATION BEFORE AND AFTER 6-MIN WALK IN SSc PATIENTS

J. Fryc[1], S. Sierakowski[1], R. Skiepko[2], A. Lisowska[3], B. Sobkowicz[3], Z. Zietkowski[2], A. Bodzenta-Lukaszyk[2] and W. Musial[3]
[1]*Department of Rheumatology and Internal Diseases,* [2]*Department of Allergology and Internal Diseases and* [3]*Department of Cardiology and Internal Diseases, Medical University of Bialystok, Bialystok, Poland*

Background. Pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD) are the leading cause of mortality in patients with SSc. However, patients are often diagnosed in advanced stage of these complications. The important goal is to find tool for early diagnosis of these diseases. The exercise tests and among them the 6-min walk test (6MWT) are performed to assess functional capacity in SSc. 6MWT evaluates the global and integrated responses of all the systems involved during exercise, but little is known what changes occur in the pulmonary and cardiovascular systems of SSc patients immediately after this test.
Objectives. The purpose of this study was to investigate the influence of 6MWT on changes in cardiopulmonary parameters in patients with SSc.
Methods. The study was conducted in a group of 24 patients with SSc, 22 females and 2 males [mean age 45 (15) years, mean disease duration 4.3 (4.2) years]. Of the patients, 58% had limited SSc (lSSc) and 42% had diffuse SSc (dSSc). Patients with SSc were asked to walk as far as possible during 6 mins in a standardized setting. The 6MWT was performed once for echocardiography and second 6MWT was conducted for pulmonary function tests during 2–3 consecutive days (one test per day). 6MWT distance, oxygen saturation and heart rate were measured and metabolic equivalent of task (MET) was calculated using the following formula: [mean walking speed (km/h) $\times$ $1.667 + 3.5]/3.5$. Before and after 6MWT lung diffusion capacity for carbon monoxide (DL_{CO}), mean pulmonary artery pressure (mPAP), systolic pulmonary artery pressure (sPAP) and ejection fraction (EF) were measured.
Results. The 6MWT distance was 395 (99) and 412 (102) metres and the energy cost was 2.88 (0.47) MET and 2.96 (0.48) MET for each 6MWT, respectively ($P = $ NS). After 6MWT mPAP increased from 24 to 26 mmHg ($P < 0.05$), sPAP increased from 36 to 40 mmHg ($P = 0.001$), DL_{CO} decreased from 56% of predicted value to 53% of predicted value ($P < 0.05$). EF did not change significantly after test. Results are given as mean (S.D.).
Conclusion. The influence of level of exercise should be taken into account in choosing the appropriate test for assessing cardiopulmonary function of SSc patients. Clinical interpretation of DL_{CO} should take into account not only haemoglobin concentration and alveolar lung volume, but also influence of exercise.

PS208. AUTO-ANTIBODY COEXISTENCE IN SSc: INDEPENDENCY, CHANCE OR MEANING?

S. Fritsch[1], V. I. Dal Pizzol[1], E. S. Paiva[1] and **C. S. Muller**[1]
[1]*Reumatologia, Hospital de Clínicas, Universidade Federal do Paraná, Curitiba, PR, Brasil, Brazil*

Autoantibodies influence clinical manifestations of SSc. This clinical–serological correlation, associated with the paucity of autoantibody concomitance, rose the historical paradigm of mutual exclusivity of autoantibodies. However, one can question this assumption. Does autoantibody concomitance mean coexistence of two different entities? On the other hand, if considered a unique disease, is this phenomenon a random event or does it represent a distinct subgroup of patients, with peculiar clinical, pathogenic and immunogenetic characteristics? The auto-antibody prevalence in early SSc is high. However, ACA andanti-topo 1 antibody (ATA) duplicity is a rare event. Similarly, the ACA, ATA and anti-RNAP III (anti-RNA polymerase) coexistence have not yet been described in single patient. In the reported case, with ACA, ATA and anti-RNAP III positivity, we have noted early vascular manifestations and later limited cutaneous involvement. This is, to our knowledge, the first report of three concomitant specific autoantibodies in a patient with SSc. We do believe this coexistence represents a rare serological subgroup of a unique disease, with possible clinical and prognostic value, although this remains to be confirmed.

PS209. PULMONARY HYPERTENSION IN SSc: CONDUCT IN PATIENTS WITH BODERLINE PULMONARY ARTERY PRESSURE

R. R. Travassos Júnior[1], E. Freire[1], C. R. T Burity[1] and L. B. Dantas Júnior[1]
[1]*Multidisciplinary Group of Pulmonary Hypertension, João Pessoa, Brazil*

SSc is an uncommon disease characterized by vascular changes and fibrosis in skin and various organs. Pulmonary arterial hypertension is one of the leading causes of death in this pathology. Pulmonary arterial hypertension is a rare disease and the prognosis that, when associated with progressive SSc, has severe outcome, making it essential for early diagnosis of these patients. Once we diagnose patients with mean pulmonary artery pressure catheter with >30 mmHg, follow-up should be rigorous. International guidelines recommend screening by Doppler echocardiography annually, yet there is no opinion about the routine cardiac catheterization in borderline patients. In cases whose blood pressure is borderline, ie between 25 and 30 mmHg, the procedure is still controversial in the literature. This article aims to report the long-term monitoring of patients with borderline blood pressure levels, as well as the discussion of catheterization as a routine procedure.
Case report. Patient, female, aged 53 years, a native and resident of Campina Grande Joao Pessoa, Brazil, diagnosed 4 years ago with SSc, managed with monthly pulse therapy. For medical advice, underwent an echocardiogram, performed by a professional member of the Multidisciplinary Group of Pulmonary Hypertension, results of which showed mean pulmonary artery pressure of 35 mmHg. Referred to the outpatient Pulmonary Hypertension reference state, indicated to cardiac catheterization, which showed mean arterial pressure of 30 mmHg. As the patient is asymptomatic respiratory, the procedure adopted was to show up with Doppler echocardiography quarterly and contraindicated the standard treatment. It is argued, on this account, the need for new catheterization, even in asymptomatic patients and borderline levels of mean arterial pressure.

PS210. MALIGNANT FIBROUS HISTIOCYTOMA: DIFFERENTIAL DIAGNOSIS OF SSc AS PARANEOPLASTIC SYNDROME

E. Freire[1], L. M. Souto[2], P. C. Gottardo[3], R. I. L. Machado[2], C. M. Camelo[3], A. H. G. Dantas[4], D. C. S. E. de Brito[1] and A. C. P. de Oliveira[3]
[1]*Rheumatology Service of University Hospital Lauro Wanderley/ Federal University of Paraíba,* [2]*Medicine School of Federal University of Paraíba,* [3]*Residence Program of Internal Medicine of University Hospital Lauro Wanderley/Federal University of Paraíba and* [4]*Supervision of Residence Program of Internal Medicine/University Hospital Lauro Wanderley/Federal University of Paraíba, João Pessoa, Brazil*

Introduction. The presence of skin thickening is suggestive of SSc. Differential diagnosis is supported by extracutaneous features and characteristic serum auto-antibodies. The skin biopsy may be necessary to discern from scleroderma-like conditions. Among the differential diagnosis of indurated skin, it may be considered infiltrative disorders, endocrine diseases, among other causes or as a result of exposition to drugs, toxins or harmful environmental factors. Dermal malignant fibrous histiocytoma (MHF) is a soft-tissue sarcoma that usually presents skin changes. We report a case of a paraneoplastic MHF of a breast cancer that simulated scleroderma due to its clinical aspect.
Case report. VF, woman, aged 34 years, white, referred to the Rheumatology Unit of University Hospital Lauro Wanderley/UFPB with hardened maculopapular lesions in the neck, face, chest, abdomen and upper limbs. She also presented alopecia, madarosis and RP.

During hospitalization she presented polyserositis (pleural effusion, pericardial effusion and ascites). Because of these findings, she was under investigation for SSc. The breast physical exam revealed hardened, stony and retracted breasts. Then, anti-topo I, anti-DNA, anti-nRNP and ACAs, VDRL, RF were required and showed negative. The haematological and biochemical analysis were not altered. The capillaroscopy was performed and presented normal capillary loops. Pleural fluid, pericardial effusion and ascites were punctured and showed exudative aspect. The biopsy was performed from skin lesions and breast tissue. The breast biopsy showed lobular breast carcinoma and the skin biopsy revealed MHF, oestrogen and progesterone receptor positives in immunohistochemical analysis. Given the findings, the patient follows completion of chemotherapy and surgical approach was not considered because of the detection of metastasis.

Discussion. Single case reports of paraneoplastic scleroderma-like syndrome have been described in association with stomach, lung, skin, T-cell lymphoma and breast cancer. High concentrations of profibrotic cytokines participating in the pathogenesis of SSc, like TGF-β, are found in some malignancies, like breast, ovary and kidney cancer. The present case demonstrates a typical dermatological change of the SSc, which is often related to breast paraneoplastic findings, which further strengthened this aetiological possibility for these injuries. After the anatomo-pathological findings and biochemical diagnosis were completed, MHF was diagnosed as paraneoplastic feature of a lobular breast cancer, which is not a classical differential diagnosis of SSc. MHF is a pleomorphic sarcoma composed of histiocyte-like and fibroblast-like elements that clinically presents skin features similar to scleroderma, which suggests its inclusion as a differential diagnosis of SSc.

PS211. EARLY ECHOCARDIOGRAPHIC ALTERATIONS IN SSc WITH ANTI-RNA POLYMERASE III ANTIBODIES

M. Fredi[1], E. Vizzardi[2], I. Cavazzana[1], M. Taraborelli[1], P. Airo'[1] and F. Franceschini[1]
[1]*Rheumatology Unit and* [2]*Cardiology Unit, Spedali Civili, University of Brescia, Brescia, Italy*

Background. Anti-RNA polymerase III (RNAP III) antibodies represent a marker of very rapid onset and progression of SSc. This study aimed to define any echocardiographic parameter that could reveal an early myocardiac involvement of the disease.

Patients and methods. From a cohort of 360 Italian patients with a diagnosis of SSc, 16 showed an isolated positivity for anti-RNAP III. All the patients performed routine echocardiography every 6–12 months. Four of them performed additional echocardiography in order to assess early heart diastolic and systolic disfunction indexes, such as myocardial performance index (namely, MPI). MPI, representing a global systolic and diastolic ventricular function, is considered an hallmark of congestive heart failure.

The serum of all patients was analysed by IIF test using commercial HEp-2 slides (BioRad, Hercules, CA, USA) to look for ANA and they were considered positive at titre >1:160. Anti-RNAP III antibodies were evaluated by commercial ELISA kits, with recombinant antigen (MBL, Nagoya, Japan; INOVA, San Diego, USA).

Results. Four patients with isolated positivity for anti-RNAP III showed a mean age at disease onset of 40 years (S.D. 25.8) and mean follow-up of 8 years (S.D. 4.1). At the moment of echocardiographic evaluation, a dcSSc was diagnosed in three cases, active interstitial lung disease (ILD) in two cases, acral ulcers in three cases, while no patients showed pulmonary hypertension, cardiac arrythmias or myositis. Patients globally showed a normal pulmonary function at onset [mean FVC 95.7% (16.3); mean DL_{CO} 72% (3.4)] and at the moment of cardiological evaluation [mean FVC 89.5% (21); mean DL_{CO} 65.5% (19.7)], without any significant differences.

All the patients showed a normal ejection fraction (mean 63.5%, S.D. 2) and a normal left ventricular diastolic function (mean E/A 1.14, S.D. 0.35). Nevertheless, two patients showed a left E/A ratio <1, indicating an altered diastolic relaxation of the left ventricle. The same patients showed an impaired myocardial performance of the right heart. MPI was globally altered [0.42 (0.2)] comparing with normal value (<0.4): these two patients showed an elevation of MPI (0.65 and 0.59, respectively). No cases of pulmonary hypertension were detected at the moment of the echocardiographic study (normal TAPSE and PAPs values). Only one patient developed pulmonary hypertension within 3 years of follow-up.

Conclusion. A more accurate echocardiographic analysis could reveal early alterations of myocardial performance in patients with SSc and anti-RNAPIII antibodies, that could predict any evolution to myocardial failure.

PS212. THE PREVALENCE AND CLINICAL CORRELATES OF AN AUSCULTATORY GAP IN SSc PATIENTS

T. Frech[1], J. Penrod[1], M. Battistone[1], A. Sawitzke[1] and B. Stults[1]
[1]*University of Utah, Salt Lake City, USA*

Introduction. Accurate blood pressure (BP) measurement is essential to the diagnosis and management of hypertension in patients with SSc to help prevent renal and cardiovascular complications. The presence of an auscultatory gap during manual BP measurement—the temporary disappearance of Korotkoff sounds during cuff deflation—leads to a potentially important underestimate of systolic BP if undetected.

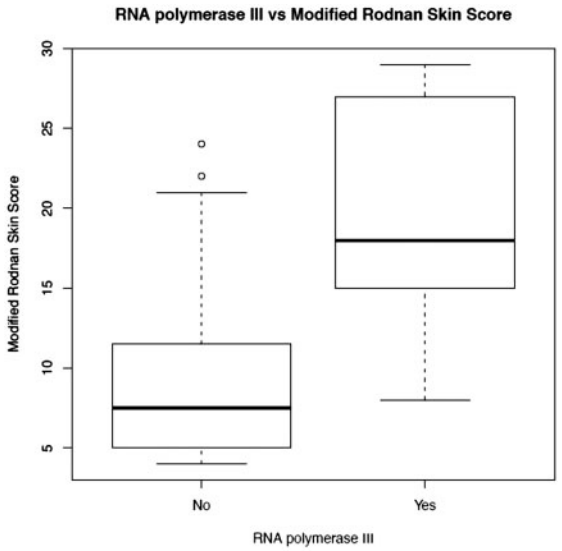
Objectives. Since the presence of an auscultatory gap is frequently associated with increased vascular stiffness, we investigated its presence and correlates in 50 consecutive SSc patients.

Methods. For each patient, BP was measured sequentially using three different approaches performed in the same order. Clinical features of each patient were recorded. For 10 of these SSc patients and 12 Internal Medicine patients, two separate physicians assessed for an auscultatory gap to determine inter-observer agreement.

Results. Sixteen of 50 patients (32%) had an auscultatory gap ranging from 4 to 12 mmHg that if undetected would have resulted in clinically important underestimates of systolic BP in four patients. The presence of an auscultatory gap was statistically associated with the presence of antibodies to RNA polymerase III ($P < 0.0068$) and diagnosis type—limited *vs* diffuse cutaneous disease ($P < 0.01$), both potential markers for more severe SSc vasculopathy.

Conclusions. Our study demonstrates that auscultatory gaps are relatively common in SSc and correlate with markers for SSc vasculopathy. If undetected because of incorrect manual BP measurement technique, auscultatory gaps may result in clinically important underestimation of systolic BP and failure to intervene early in hypertension. Electronic oscillometric BP measurement is not affected by the presence of an ausculatory gap and may be preferred in SSc patients.

FIG. 1



PS213. SPONTANEOUS SKIN REGRESSION AND PREDICTORS OF SKIN REGRESSION IN THAI SCLERODERMA PATIENTS

C. Foocharoen[1], A. Mahakkanukrauh[1], S. Suwannaroj[1] and R. Nanagara[1]
[1]*Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*

Background. Skin tightness is a major clinical manifestation of SSc. Importantly, for both clinicians and patients, spontaneous regression of the fibrosis process has been documented.

Objectives. To identify the incidence and related clinical characteristics of spontaneous regression among Thai SSc patients.

Materials and methods. An historical cohort with 4 years of follow-up was performed among SSc patients over 15 years of age diagnosed with SSc between 1 January 2005 and 31 December 2006 in Khon

Fig. 1 Comparison between KM curves for limited and diffuse subset of SSc.

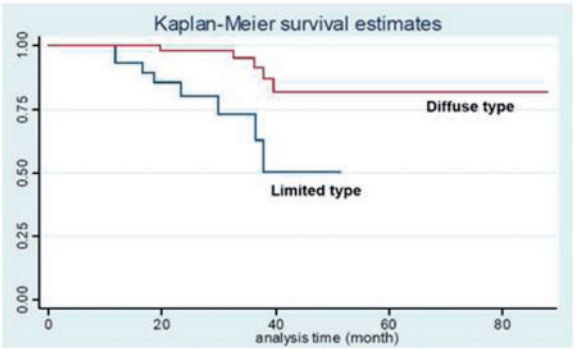
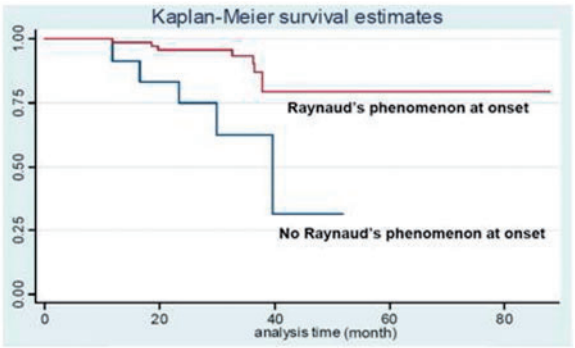


Fig. 2 Comparison between KM curves for non-RP and RP at onset.



Kaen, Thailand. The start date was the date of the first symptom and the end date was the date of the skin score <2. To estimate the respective probability of regression and to assess the associated factors, the Kaplan–Meier method and Cox regression analysis was used.

Results. A total of 117 cases of SSc were included with a female to male ratio of 1.5:1. Thirteen patients (11.1%) experienced regression: the incidence was 0.31 per 100 person-months. The incidence rate of spontaneous skin regression was 0.31 per 100 person-months and the average duration of SSc at the time of regression was 35.9 (15.6) months (range 15.7–60). The factors negatively correlated with regression were (i) diffuse cutaneous type; (ii) RP; (iii) oesophageal dysmotility; and (iv) colchicine treatment at onset with a respective hazard ratio (HR) of 0.19, 0.19, 0.26 and 0.20. By contrast, the factor positively correlated with regression was active alveolitis with CYC therapy at onset with an HR of 4.23 (95% CI 1.23, 14.10). After regression analysis, only RP at onset and diffuse cutaneous type had a significantly negative correlation to regression.

Conclusions. Spontaneous regression of the skin fibrosis process was not uncommon among Thai SSc patients. Factors suggesting a poor predictor for cutaneous manifestation were: RP, diffuse cutaneous type; while early CYC therapy might be related to a better skin outcome.

Table 1. Cox regression model for prediction of skin softening

Variables	Crude HR (95% CI)	Adjusted HR (95% CI)	*P*-value
Diffuse cutaneous type	0.19 (0.06, 0.59)	0.39 (0.09, 1.68)	0.209
RP at onset	0.19 (0.06, 0.58)	0.11 (0.03, 0.43)	0.001*
Oesophageal dysmotility at onset	0.26 (0.07, 0.95)	0.39 (0.09, 1.61)	0.195
Alveolitis at onset	4.23 (1.23, 14.10)	3.15 (0.77, 12.89)	0.110
Colchicine treatment at onset	0.20 (0.05, 0.73)	0.25 (0.52, 1.23)	0.089
Maximum skin score at onset	3.29 (0.01, 0.87)	0.07 (0.07, 0.59)	0.015*

PS214. PATTERN OF SKIN THICKNESS PROGRESSION AND CLINICAL CORRELATION IN THAI SCLERODERMA PATIENTS

C. Foocharoen[1], A. Mahakkanukrauh[1], S. Suwannaroj[1] and R. Nanagara[1]
[1]*Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*

Background. Skin thickness progression in scleroderma (SSc) varies in daily clinical practice observation.

Objectives. To define the pattern of skin thickness in SSc and to ascertain the clinical correlation with each skin pattern.

Materials and methods. An historical cohort with a 3-year follow-up was performed on patients over 15 years of age in Khon Kaen, Thailand, between 1 January 2005 and 31 December 2006. The skin thickness progression rate (STPR) and skin thickness regression rate (STRR) were calculated by the difference in modified Rodnan skin score between the first diagnosis and at the end of follow-up divided by the time of follow-up. 'Rapid skin progression' was defined as STPR >44 points per year, while intermediate and slow progression was 25–44 and <25, respectively. The rapid skin regression rate

Table 1. Clinical characteristics of the disease in each skin pattern

Clinical characteristics	Continuous intermediate progression (*n* = 2)	Continuous slow progression (*n* = 37)	Slow progression to peak then slow regression (*n* = 77)	Slow progression to peak then intermediate regression (*n* = 1)	*P*-value
Female, *n* (%)	0	24 (64.9)	46 (59.7)	0	0.15
Age at onset, median (IQR), years[a]	48.6 (47.5–49.7)	49.1 (28.0–69.2)	48.3 (24.4–75.5)	55.2	0.915
Peak skin score, median (IQR), point[a]	25 (16–34)	21 (5–45)	17 (4–40)	25	0.332
Clinical presentation at onset, *n* (%)					
Subset					
Limited type	0	11 (29.7)	24 (31.2)	0	0.99
Diffuse type	2 (100)	26 (70.3)	53 (68.8)	1 (100)	
RP	2 (100)	34 (97.9)	66 (85.7)	1 (100)	0.690
Digital ulcer	1 (50)	6 (16.2)	10 (13.0)	1 (100)	0.081
Telangiectasia	0	13 (35.1)	5 (6.5)	0	0.001*
Salt and pepper appearance	1 (50)	19 (51.4)	51 (66.2)	1 (100)	0.342
Tendon friction rub	0	3 (8.1)	5 (6.5)	0	0.768
Joints contracture	0	19 (51.4)	23 (29.9)	1 (100)	0.031*
Polyarthritis	0	5 (13.5)	10 (13.0)	0	1.000
Oesophageal dysmotility	1 (50)	21 (56.8)	40 (52.0)	1 (100)	0.916
Pulmonary involvement	1 (50)	16 (43.2)	32 (41.6)	1 (100)	0.837
Renal crisis	0	1 (2.7)	0	0	0.342
Pulmonary hypertension	0	0	0	0	–
Anti Scl-70 positive	0	13 of 14 (13.9)	7 of 9 (77.8)	1 (100)	0.595
New clinical characteristic development during follow-up, *n* (%)					
Digital ulcer	0	16 (43.2)	34 (44.2)	0	0.739
Joints contracture	0	15 (40.5)	15 (19.5)	0	0.062
Gastrointestinal dysmotility	1 (50)	4 (10.8)	10 (13.0)	0	0.431
Pulmonary involvement	0	17 (45.9)	39 (50.6)	1 (100)	0.844
Renal crisis	0	3 (8.1)	4 (5.2)	0	0.735
Pulmonary hypertension	0	2 (5.4)	10 (13.0)	0	0.518

(STRR) was STRR >44 points per year while intermediate and slow regression were 25–44 and <25, respectively. The chi-square or Fisher's exact test and Student's *t*-test or Kruskal–Wallis test were used to analyse the association between the clinical characteristics and pattern of skin progression.

Results. A total of 117 SSc cases were included and the female to male ratio was 70:47. The mean age of onset was 49.8 years (range 24.4–75.5 years). The most common skin pattern was (i) 'slow progression to peak then slow regression' (77 cases; 65.8%) followed by (ii) 'continuous slow progression' (37; 31.6%), (iii) 'continuous intermediate progression' (2; 1.7%) and (iv) 'slow progression to peak then intermediate regression' (1; 0.9%). The respective mean peak skin score and duration of disease at peak skin score was 19.8 points (range 4–45 points) and 20.3 months (range 1–42.2 months). Only telangiectasia at onset and joint contracture were related to 'continuous slow progression' of skin thickness with $P = 0.001$ and $P = 0.042$, respectively. Neither the type of SSc nor internal organ involvement was correlated with the pattern of skin thickness.

Conclusion. The most common skin pattern in Thai SSc was 'slow progression to peak then slow regression'. Telangiectasia at onset and joint(s) contracture were predictive of continuous progressive skin thickness in the first 3 years.

PS215. PROGNOSTIC FACTORS OF MORTALITY AND 2-YEAR SURVIVAL ANALYSIS OF SSc WITH PULMONARY ARTERIAL HYPERTENSION IN THAILAND

C. Foocharoen[1], R. Nanagara[1], S. Kiatchoosakun[1], S. Suwannaroj[1] and A. Mahakkanukrauh[1]
[1]*Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*

Background. Pulmonary arterial hypertension (PAH) is a major complication and cause of death in SSc but natural history of PAH without any treatment has been not identified.

Objectives. To identify the predictive factors of mortality and the 2-year survival rate among Thai sufferers of PAH-SSc.

Materials and methods. An historical cohort study was performed among PAH-SSc patients followed up at Srinagarind Hospital, Thailand, between January 2005 and December 2008. Kaplan–Meier and Cox regression analyses were used to estimate the probability of survival and to assess the significant factors associated with death.

Results. PAH was recognized in 60 patients using echocardiographic criteria, right ventricular systolic pressure (RVSP) >35 mmHg. Two-thirds of the patients were female, >50 years of age, with the diffuse SSc subtype. Twenty patients (33.3%) died: the mortality rate was 15.6% per 100 person-years. The respective 1-, 2-, 3- and 4-year survival rates were 86.1, 71.3, 64.6 and 53.9%, respectively. The majority (85%) died without any specific treatment for PAH. Using univariate analysis, the mortality risk was associated with: the World Health Organization functional class (FC) III [hazard ratio (HR) 27.82, 95% CI 3.17, 244.40], visceral organ involvement (HR 5.14, 95% CI 1.19, 22.22), oesophageal dysmotility (HR 3.08, 95% CI 1.13, 8.77) and pericardial effusion (HR 2.84, 95% CI 1.12, 7.16). Using Cox regression, the only predictor of death was FCIII. The causes of death in PAH-SSc were related to PAH (60%), infection (30%) and acute renal failure (10%).

Conclusions. Up to one-third of Thai sufferers of PAH-SSc died within 2 years of PAH diagnosis, without any specific treatment being given. Increased mortality risk was found in SSc patients who had FCIII and visceral organ involvement.

TABLE 1. Cox regression model for prediction of death

Variables	Crude HR (95% CI)	Adjusted HR (95% CI)	*P*-value
FCIII	27.82 (3.17, 244.40)	41.67 (4.35, 397.90)	0.001*
Every 5% increased in EF	0.67 (0.54, 0.83)	0.78 (0.53, 1.14)	0.195
Every 5-point increased in skin score	1.35 (1.003, 1.78)	1.01 (0.73, 1.39)	0.972
Other internal organ involvements	5.14 (1.19, 22.22)	2.81 (0.21, 38.34)	0.438
Osophageal dysmotility	3.08 (1.11, 8.51)	1.92 (0.36, 10.21)	0.446
Pericarditis	2.84 (1.12, 7.16)	3.35 (0.61, 18.48)	0.165
Myositis	3.14 (1.13, 8.77)	1.63 (0.35, 7.56)	0.534

FIG. 1 Kaplan–Meier survival curve in different FC status.

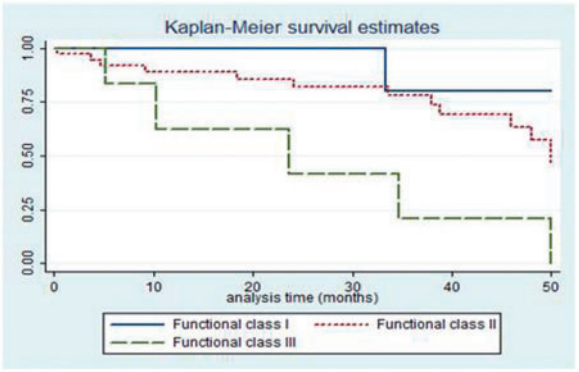
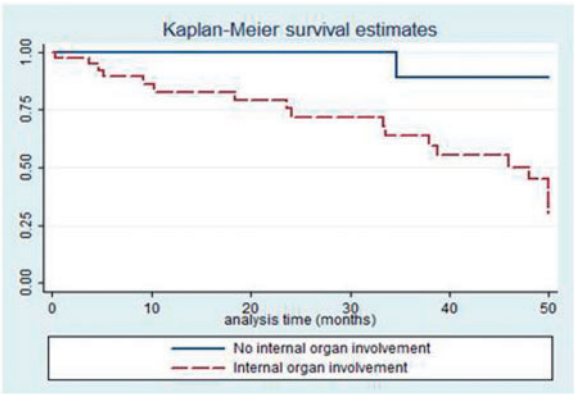


FIG. 2 Kaplan–Meier survival curve comparing patients who developed/did not develop other internal organ involvements.



PS216. INCIDENCE RATE AND CAUSES OF INFECTION IN THAI SSc PATIENTS

C. Foocharoen[1], Y. Siriphanon[1], A. Mahakkanukrauh[1], S. Suwannaroj[1] and R. Nanagara[1]
[1]*Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*

Background. Infection is a cause of death in SSc. The causes of infection could be bacterial, viral, or fungal. Despite of immunosuppressant therapy, there were only few reports of opportunistic infection.

Objectives. To estimate the incidence rate of infection, causes of infection, and risk factor of infection in Thai SSc patients.

Materials and methods. A historical cohort analysis was conducted on SSc patients over 15 years of age, attending the Scleroderma Clinic at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand, between January 1, 2005 and December 31, 2006. The incidence rate with 95% CI was calculated and Odds ratio (OR) was performed to assess the risk of infection and find out the association between type of infection and SSc clinical presentations.

Results. The medical records of 117 SSc patients were reviewed. The female to male ratio was 1.5:1. Of the total 310 person-years under observation, 63 events of infection occurred. The incidence rate of infection was 20.3 per 100 person-years (95% CI 15.6, 26.0) and the incidence rate of major infection was 11.0 per 100 person-years (95% CI 8.4, 16.5). The mean age and mean duration of SSc at the time of infection was 50.1 (11.1) years (range, 25.2-76.6) and 12.9 (10.4) months (range, 0.5-34.6), respectively. Urinary tract infection was the most common infection (23.8%), followed by infected ulcer (17.5%) and strongyloidiasis diarrhoea (12.7%). Opportunistic infection was found in 1 case (oesophageal candidiasis). Oesophageal dysmotility was related to a major infection with statistical significant (OR 3.22).

There was the clinical association between aspiration pneumonia and oesophageal dysmotility (OR 1.23), as well as non-strongyloidiasis diarrhea and gastrointestinal involvement (OR 2.28). However, there was no association between strongyloidiasis diarrhea and gastrointestinal involvement, infected ulcer and RP or digital ulcer, aspiration pneumonia and pulmonary fibrosis, urinary tract infection and renal crisis or female gender, and any infection and immusuppressant therapy or duration of disease. One case was died due to severe bacterial aspiration pneumonia.

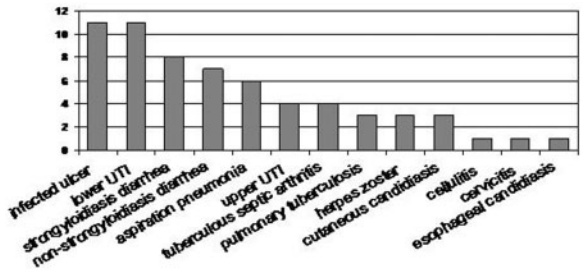
Conclusions. Infection was not uncommon in SSc patients, however; opportunisitic infection was rare despite of immunosuppressant therapy. Oesophageal dysmotility increased risk factor of major infection particular aspiration pneumonia.

TABLE 1. The clinical differences between major and minor infection

Clinical parameter	Minor infection (event = 26)	Major infection (event = 37)	OR (95% CI)	*P*-value
Age at onset of disease				
≤60-year old	76.96	91.9	1	
>60-year old	23.1	8.1	0.29 (0.04, 1.59)	0.09
Sex female	80.8	7.6	0.50 (0.12, 1.85)	0.25
SSc subset				
Limited	26.9	32.4	1	
Diffuse	73.1	67.6	0.77 (0.21, 2.62)	0.64
Rodnan skin score >20	36.4	31.0	0.79 (0.21, 3.01)	0.69
Anti-Scl70 positive	100.0	80.0	NA	NA
RP	100.0	94.6	NA	NA
Digital ulcer	50.0	54.1	1.18 (0.38, 3.62)	0.75
Synovitis	11.5	10.8	0.93 (0.14, 6.96)	0.93
Tendon friction rub	0	13.5	NA	NA
Oesophageal dysmotility	42.3	70.3	3.22 (1.01, 10.51)	0.03*
Gastrointestinal involvement	42.3	54.1	1.60 (0.52, 5.00)	0.36
Pulmonary fibrosis	69.2	46.0	0.38 (0.11, 1.21	0.07
Active alveolitis	50.0	53.2	1.02 (0.52, 3.44)	0.82
Pulmonary arterial hypertension	11.5	10.8	0.92 (0.14, 6.96)	0.93
Renal crisis	11.4	10.6	0.91 (0.16, 6.94)	0.92
Low-dose steroid therapy	41.0	35.0	0.77 (0.42, 1.43)	0.38
Immunosuppressant therapy	91.2	10.8	0.51 (0.11, 2.70)	0.34

Values are represented as percentages, unless otherwise mentioned.

FIG. 2 Causes of infection.



PS217. PRELIMINARY RESULTS FOR 6-MIN WALK VALUES IN HEALTHY GERMAN CHILDREN

I. Foeldvari[1] and G. Himmelmann[1]
[1]*Hamburger Zentrum fuer Kinder- und Jugendrheumatologie, Hamburg, Germany*

Introduction. 6-min walk is a primary outcome measure in therapeutic studies for patients with pulmonary hypertension. Currently we have a two of sets of data [1, 2] regarding test results in the 6-min walk test (6MWT) in healthy children with a large span in the normal values in the different age groups.

Aim of the study. To establish normal values for healthy German children for the 6MWT.

Method. The team of an occupational therapist and a study nurse is visiting schools, where previously the parents agreed on the participation of the students on the test. Always students from just one class are invited to participate in the test. The students are performing the test according to the international guidelines. The demographic data of the students are collected and the parents fill out a short survey regarding the physical activity and the health condition. Children with chronic diseases that decrease the stamina are excluded.

Results. Up till now 354 students participated from the age 7–12 years; 22 in the age group of 6 years; 49 in the age group of 7 years; 61 in the age group of 8 years; 64 in the age group of 9 years; 50 in the age group of 10 years; 51 in the age group of 11 years; and 57 in the age group of 12 years. The mean 6 min walk distance was 449.1 m in the age group of 6 years, 470 m in the age group of 7 years; 484 m in the age group of 8 years; 491.6 m in the age group of 9 years; 471.3 m in the age group of 10 years, 571 m in the age group of 11 years and 502.3 m in the age group of 12 years. BMI correlated with the walked distance.

Conclusion. Our results are in the range of the patients from the UK published by Lammers *et al*. [1] and are in significantly lower range than in the Chinese population collected data by Li *et al.* [2]. This reflects the importance of this study to gain normal values for our patient population.

PS218. PROMPT RECURRENCE OF DIGITAL ULCERS AFTER DISCONTINUATION OF BOSENTAN THERAPY IN A SSP MALE PATIENT

G. Finzi[1]
[1]*Azienda Ospedaliero-Universitaria, Parma, Italy*

A male patient, 59 years old, affected by CREST syndrome, was referred to our hospital for persistent digital ulcers of both hands. Previous treatments with nifedipine, CSs and aspirin, had been uneffective.

The patient received a 4-week cycle of full dose iloprost (2 ng/kg/min for 8 h/day) without results, followed by a 2 months treatment of tadalafil, 5 mg/day, p.o., on an outpatient basis. None of the ulcers showed significant improvement, and treatment with bosentan, a direct antagonost of ETa and ETb receptors, was the final option, at the initial dosage of 62.5 mg twice a day for 4 weeks, and 125 mg twice a day in the following weeks. Before the end of the third month of treatment all the digital ulcers had completely recovered, and the patient was discharged on bosentan therapy. Three months later the patient went for a holiday to the island of Zanzibar, and discontinued the therapy relying on the benefit of hot weather. Fifteen days after discontinuation of bosentan a new painfull digital ulcer appeared on the apex of the third fnger of the right hand, and the patient, few days after the end of his holiday, was newly referred to our centre, where bosentan was administered again, at full dosage. Three weeks later the ulcer appeared significantly diminished in its dimensions, and the patient was free of pain. Before the end of the second month the ulcer was healed. This case report seems to indicate that patients with SSP and digital ulcers, who benefit from bosentan therapy, should not discontinue the treatment, even if they are exposed to hot weather that could contraindicate generic vasodilators.

PS219. ARE ANTI-RO52 ANTIBODIES ASSOCIATED WITH PULMONARY INVOLVEMENT IN SCLERODERMA?

J. Ferreira[1], I. Almeida[1], A. Marinho[1], C. Cerveira[1] and C. Vasconcelos[1]
[1]*Centro Hospitalar do Porto, Porto, Portugal*

Introduction. The presence of anti-Ro52 antibodies has been reported in a wide variety of autoimmune diseases, particularly in myositis, scleroderma and autoimmune liver diseases. Clinical significance of anti-Ro52 antibodies remains controversial. Studies are lacking in clarifying the association of anti-Ro52 with pulmonary involvement in scleroderma.

Objectives. To determine if anti-Ro52 antibodies are associated with pulmonary involvement (interstitial, indirect pulmonary hypertension or both) in scleroderma.

Methods. Single-centre, retrospective study based on immunoblotting panel analysis and patient clinical records. Pulmonary manifestations were sub-grouped in: (i) interstitial (alveolitis and/or fibrosis), (ii) pulmonary artery systolic pressure (PASP) ≥40 mmHg plus interstitial pulmonary disease and (iii) isolated PASP ≥40 mmHg (purely vascular).

Results: Our scleroderma cohort included 200 patients, of which 137 had immunoblotting panels with anti-Ro52 reactivity analysis. The search was conducted between January 2010 and July 2011.

The frequency of pulmonary manifestations in patients with positive anti-Ro52 antibodies was 67.7% ($n = 31$) and 60% ($n = 24$) in the negative anti-Ro52 group, showing no significant differences between groups ($P = 0.621$).

Still no significant differences were found when pulmonary manifestations were evaluated according to the subgroups ($P = 0.525$).

Sensitivity, specificity, positive and negative predictive values of anti-Ro52 reactivity for determining pulmonary involvement in scleroderma were low.
Conclusion. Anti-Ro52 antibodies are neither good nor independent in predicting pulmonary involvement in scleroderma.

PS220. CARDIAC INVOLVEMENT IN SSc: DIFFERENCES IN THE PRESENTATION AND SURVIVAL BETWEEN PATIENTS WITH LIMITED, DIFFUSE AND SINE SCLERODERMA SSc

A. Fernandez Codina[1], C. P. Simeon-Aznar[1], F. J. Prado-Galbarro[2], C. Tolosa-Vilella[3], A. Fernandez-Luque[1], A. Sarria-Santamera[2], J. Candell-Riera[4], V. Fonollosa-Pla[1] and M. Vilardell-Tarres[1]
[1]*Internal Medicine Department, Hospital Universitari Vall d'Hebron, Autoinmune Disease Unit, Barcelona,* [2]*Agencia de Evaluación de Tecnologías Sanitarias, Instituto de Salud Carlos III, Madrid,* [3]*Internal Medicine Department, Corporació Sanitaria Parc Taulí and* [4]*Cardiology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain*

Objectives. To describe the clinical characteristics and survival of a cohort of patients with SSc and cardiac involvement (CI) and compare them between the three main SSc subsets (lcSSc, dcSSc and sine ssSSc).
Methods. Patients with CI and SSc were selected from a third-level reference teaching hospital's database that consists of an overall of 413 patients diagnosed **of** SSc from April1980 to July 2011, according to the ACR and LeRoy's classification. We compared the following items: demography, organ involvement, immunological parameters, nail fold capillary pattern, treatment and the overall survival between the three SSc subsets.

One hundred and eighty-seven patients with CI were included. CI was defined by: clinical manifestations, alterations in echocardiography, stress myocardial perfusion SPECT, cold-induced myocardial perfusion SPECT, coronary arteries catheterization, chest X-ray and ECG.
Results. Statistically significant cardiac-related variable comparisons between the three SSc subtypes regarding to epidemiological data were the following: time between SSc onset and cardiac disease diagnosis in dcSSc(13.68 years) differ from ssSSc (8.91years, $P = 0.026$); age at the moment of death in dcSSc (57.9 years) differs from lcSSc (68.48 years, $P = 0.002$)and ssSSc (78.5 years, $P = 0.04$), age when ACEI/ARAII were started in dcSSc (54 years) differs from lcSSc (62.81 years, $P = 0.012$) and ssSSc (68.88 years, $P = 0.004$) and age when calcium channel inhibitors were started in dcSSc (48.93 years) differs from lcSSc (58.92 years, $P = 0.000$) and ssSSc (59.18 years, $P = 0.010$).

Regarding epidemiological statistically significant non-cardiac-related variable comparisons between the three SSc subtypes, age at the SSc diagnosis in dcSSc (48.46 years) differs from lcSSc (56.5 years, $P = 0.02$) and ssSSc (57.8 years, $P = 0.015$).

No statistically significant differences were found in comparing pericarditis, ischaemic cardiopathy, conduction alterations, coronary arteries alterations, cold and stress SPECT, left ventricle hypertrophy, diastolic dysfunction and pacemaker bearing between SSc subsets.

Average survival at 10, 15, 20 and 25 years were 94, 87.1, 79 and 76.5, respectively, in lcSSc; 75.6, 73, 53.3 and 49.8, respectively, in dcSSc; 89.9% for the first three periods in ssSSc. Log-Rank test showed significant differences in survival between lcSSc and dcSSc (18.777, $P = 0.000$), dcSSc and ssSSc (14.831, $P = 0.000$) and lcSSc and ssSSc (4.063, $P = 0.044$).
Conclusion. There were no significant differences between CI variables compared by the three SSc subsets. Time lapse between SSc onset and CI diagnosis in ssSSc is significantly shorter than in dcSSc. Epidemiological and demographical characteristics of the series agree with the previously published literature. There are significant differences in survival rates, compared by SSc subset. ssSSc has shown a better survival rate than lcSSc, in contrast with other previous studies.

PS221. SCLERODERMA-RELATED PULMONARY HYPERTENSION: COMPARISON OF BASELINE CHARACTERISTICS AND PROGNOSIS BETWEEN PATIENTS WITH LCSSc *VS* dcSSc

A. Fernández[1], C. P. Simeón[2], V. Fonollosa[2], A. Fernandez Codina[2], F. J. Prado[3], A. Sarria[3] and M. Vilardell[2]
[1]*Mollet Hospital, Internal Medicine,* [2]*Vall D'H'ebron Hospital, Internal Medicine, Barcelona and* [3]*Department of Statistics, Carlos III Institut, Madrid, Spain*

Introduction and objectives. Pulmonary arterial hypertension (PAH) is a major cause of morbidity and mortality in patients with scleroderma (SSc). This report analyses the differences at baseline between patients with lcSSc *vs* dcSSc who develop PAH.
Methods. We performed a retrospective cohort study of patients with scleroderma-related PAH (SSc-PAH): 6 with dSSc and 26 with lSSc. Demographic, clinical, haemodynamic characteristics and pulmonary function test at the moment of diagnosis were compared between the two groups.
Results. There were no differences regarding sex and age at the moment of diagnosis of SSc or PAH between both groups. Time from diagnosis of SSc to diagnosis of PAH was 172.7 and 239 months for dSSC and lSSc, respectively, with no statistical significance.

Most patients also had interstitial lung disease (ILD): 100% in dSSc and 80.8% in lSSc. In the dSSc group PAH was associated with other vascular complications of the SSc more often than in the lSSc group: 100% in dSSc group *vs* 46% in lSSc showed digital ulcers ($P = 0.024$) and 33% of dSSc *vs* 0% of lSSc ($P = 0.03$) developed sclerodermic renal crisis (SRC). In the same way, all patients with dSSc who had undergone capillaroscopy had an active pattern. The capillaroscopy pattern in lSSc group was active only in 7.7%, slow in 57.7% and normal in 11.5%.

Values of TLCO/VA were 57.7 and 46.3 for dSSc and lSSC ($P = 0.17$), and FVC/TLCO values were 0.96 and 1.70, respectively ($P = 0.06$).

The haemodynamic parameters were as follows: mPAP was 35.3 *vs* 42.5 mmHg for dSSC and lSSc, respectively ($P = 0.24$), and cardiac index 2.38 *vs* 2.20 ($P = 0.78$).

In dSSc group 50% showed pericardial effusion in echocardiography *vs* 26.9 in lSSc ($P = 0.34$), and the percentages of right ventricle dysfunction were 50 and 65%, respectively ($P = 0.66$).

The prognosis in both groups was similar: 66.7% in dSSc group died (75% due to PAH) compared with 46.2% of patients with lSSC (83.3% for PAH). No differences were found in time between diagnosis of PAH and exitus (12.3 *vs* 16.3 months in dSSc and lSSc, respectively, $P = 0.7$). There were also no differences between both groups in time from first TLCO <80% to diagnosis of PAH (60.5 *vs* 65.2, $P = 0.83$).
Conclusions. Patients with SSc-related PAH and dSSc have higher incidence of other SSc-related vascular complications (ulcers, SRC) than patients with lSSc and PAH. We found no other differences between both groups in survival, pulmonary function and haemodynamic severity.

PS222. CLINICAL, EPIDEMIOLOGICAL AND HAEMODYNAMIC DIFFERENCES BETWEEN IDIOPATHIC AND SCLERODERMA-RELATED PULMONARY ARTERIAL HYPERTENSION

A. Fernández[1], C. P. Simeón[2], V. Fonollosa[2], M. López-Meseguer[2], A. Román[2] and M. Vilardell[2]
[1]*Mollet Hospital and* [2]*Vall D'Hebron Hospital, Barcelona, Spain*

Objective. Scleroderma-related Pulmonary Arterial Hypertension (S-PAH) has a different behaviour and a worse prognosis than idiopathic PAH (IPAH). We describe clinical, epidemiological and haemodynamic differences between both conditions in a population of patients of a single centre.
Methods. Retrospective cohort study comparing baseline data from 105 patients (36 with S-PAH and 69 with IPAH). Clinical, epidemiological and haemodynamic features were analysed.
Results. All clinical, epidemiological and haemodynamic findings are showed in Table 1.

At diagnosis, S-PAH patients were older than IPAH patients and in both groups women were predominant.

In both groups, most of the patients were in NYHA class III when diagnosed. Functional capacity measured by the 6-min walking test showed better outcomes for IPAH patients. Left ventricular dysfunction was not observed in any patient.

Regarding pulmonary function tests, the S-PAH group had lower mean forced vital capacity and lower mean diffusing capacity for carbon monoxide than IPAH. This finding may probably be related to the fact that ~50% of patients in S-PAH group had, besides, interstitial lung disease.

Regarding haemodynamics, pulmonary artery pressures (PAPs) were lower in the S-PAH group but no differences for cardiac indexes (CIs) were found.

Survival at 3 and 5 years was clearly lower in the S-PAH group as shown in Table 1. The percentages of patients diagnosed in each decade were similar for both groups, eliminating the possible bias due to the emergence of the specific vasodilator therapies from the year 2002.

Conclusions. S-PAH appears in a latter age of life than IPAH and has a more aggressive behaviour, with worse functional capacity and prognostic than IPAH despite having lower PAP and similar CI. The age at diagnosis, co-morbidity and possible myocardial disease itself may influence in this fact.

TABLE 1.

	S-PAH	IPAH
Age[a]		
Gender	57.2	43
Female	35	50
Male	1	19
NYHA FC (%)[a]		
I	11	5
II	14	11
III	69	71
IV	2	11
FVC (%)[a]	69.8	81
TLCO (%)[a]	50	62.5
6MWT (m)[a]	242	325
HT[a]	9	6
LV dysfunction[a]	0	0
sPAP (mmHg)[a]	68.6	82.7
mPAP (mmHg)[a]	43.7	54
CWP (mmHg)[a]	9.7	9
CI (l/min/m^2)[a]	2.25	2.3
3- to 5-year survival (%)		
Year of diagnosis *n* (%)	61.2, 58.4	89.9, 87
1981–90	2 (5)	3 (4)
1991–2000	10 (27)	26 (37)
2001–10	23 (63)	40 (57)

[a]At the time of diagnosis, FVC: forced vital capacity; TLCO: transfer factor of the lung for carbon monoxide, 6MWT: 6-min walk distance; HT: arterial hypertension; LV dysfunction: left ventricular dysfunction; sPAP: systolic pulmonary artery pressure in cardiac; mPAP: mean pulmonary artery pressure; CWP: pulmonary capillary wedge pressure; CI: cardiac index.

PS223. TREATMENT WITH BOSENTAN IN AUTOIMMUNE DISEASES: A CENTRE EXPERIENCE

N. Fernandes[1], A. Serafim[1], A. Cardoso[1], S. Rodrigues[1], C. Esteves[1] and V. Silva[1]
[1]*Autoimmune Diseases Centre, Centro Hospitalar Barreiro Montijo, Barreiro, Portugal*

Introduction. Bosentan is an oral dual endothelin receptor antagonist, which has been demonstrated to be efficient for prevent new digital ulcers (DUs) in patients with SSc and improving pulmonary artery hypertension (PAH).
Objective. To evaluate the efficacy of bosentan on patients with autoimmune diseases.
Methods. We evaluated five patients on bosentan, with digital ulcers, RP and PAH, followed in autoimmune diseases clinic.
Results. Three patients with SSc, one with SLE and another one with secondary RP were evaluated. The median age was 17 years. At the start of bosentan treatment, RP was present in four patients and two (50%) had digital ulcers. PAH was present in one patient (20%). The two patients with DU did not develop new ones. The five patients (100%) improved with bosentan. The median treatment duration was 6 months. The main adverse event, as increase of aminotransferase, did not occur in any patient.
Conclusion. Bosentan treatment was well tolerated and no adverse effects occurred. Good results were verified in all patients, stopping ulcers progression, improving PAH and avoided emergence of new ulcers.

PS224. BOSENTAN IN AUTOIMMUNE DISORDERS

N. Fernandes[1], N. Fernandes[2] and V. Silva[2]
[1]*Autoimmunes Diseases Centre, Hospital Litoral Alentejano and* [2]*Autoimmune Diseases Centre, Centro Hospitalar Barreiro Montijo, Barreiro, Portugal*

Introduction. Bosentan is a dual endothelin receptor antagonist used in the treatment of pulmonary artery hypertension (PAH). It has been show to be capable for prevent new digital ulcers (DUs) in patients with SSc.
Objective. To evaluate the effect of bosentan on patients with autoimmune diseases.
Methods. This retrospective study assesses patients on bosentan, with PAH, DUs and RP, followed in autoimmune diseases clinic.
Results. We included five patients (80% women, median age 54 years), two with SSc, one patient with connective mixed tissue disease, one with severe primary RP and another one with undifferentiated connective tissue disease. When bosentan treatment was initiated RP was present in all patients and two (40%) had digital ulcers. PAH was present in two patients (40%). The five patients (100%) improved with bosentan. One patient died due to co-morbidities of the disease. All the patients experienced no adverse events.
Conclusion. The bosentan appears to be a good therapeutic option when there is severe RP, even in the absence of digital ulcers. When started early could possibly prevent its onset. However, extensive studies are needed for this purpose.

PS225. INTERFACE BETWEEN GENERAL PRACTITIONERS AND SPECIALISTS IN SSc MANAGEMENT

A. Fauchais[1], K. Demaziere[1], K. Ly[1], G. Gondran[1], H. Bezanahary[1], E. Liozon[1], C. Martel[1], S. Palat[1] and E. Vidal[1]
[1]*Internal Medicine Department, Limoges, France*

Introduction. Relationship between specialists and family physicians is fundamental in the optimization of early diagnosis and management of orphan diseases. We report the experience of a French regional competence centre (RCC) for SSc.
Method. A questionnaire was sent anonymously to general practitioners (GPs, $n = 107$) of 112 SSc patients followed in a RCC.
Results. The response rate was 39% ($n = 42$). Thirty-nine (93%) GPs performed clinical and immunological screening for autoimmune diseases. The diagnosis of SSc was establish ($n = 11$) or suspected ($n = 25$) by GP before the RCC consultation that was motivated by RP ($n = 38$), skin appearance ($n = 27$), inflammatory arthralgia (n=23) or asthenia ($n = 21$). Diagnosis delay [22 (19) months] is directly related to their lack of knowledge of SSc for 29% of GPs. However, only 62% ($n = 26$) upgraded their own SSc expertise after diagnosis and only eight (19%) know the National Protocol for Diagnosis and Treatment of SSc.

GP considered that information regarding SSc (67%), diagnosis (74%) and treatment (74%) are globally satisfying for the management of SSc patients after hospital discharge. However, the necessity of annual screening for PAH and others systemic complications is not clearly understand by GP (54 and 56% of satisfied GP, respectively).

Although information on SSc related disability is considered as adequate for 63% of GPs, information concerning SSc impact on professional activity is considered sufficient for 44% of GPs only. The management of intercurrent disease remains a problem for 19% of GPs. The creation of a specific 'SSc specialist interaction book' resuming clinical SSc-related complications and specific treatment appears to be the solution to improve hospital/GPs interface for SSc management for 90% of GPs.
Conclusion. The GP remains the primary care physician of SSc patients. It seems necessary to optimize interface between GP/competence centre with specific interactive book resuming SSc management.

PS226. SSc NAILS ABNORMALITIES: RESULTS OF A PROSPECTIVE CASE-CONTROLS STUDY

A. Sparsa[1], J. Fayol[1], V. Doffoel-Hanz[1], K. Ly[2], C. Martel[2], G. Gondran[2], S. Palat[2], J. M. Bonnetblanc[1], E. Liozon[2], E. Vidal[2] and **A. L. Fauchais**[2]
[1]*Dermatology Department and* [2]*Internal Medicine Department, Limoges, France*

Introduction. Studies concerning SSc nail changes (NCs) are sparse and the physiopathological mechanisms of such nail modifications still non-elucidated. RP intensity, microcirculation modifications and cutaneous fibrosis are probably involved in NC mechanisms.
Patients and methods. Fifty-seven SSc patients (dcSSc $n = 10$) and 23 age- and sex-matched healthy volunteers have been prospectively included. Demographic (age, gender, RP duration), clinical [modified Rodnan score, systemic involvement, previous and evolutive digital ulcerations (DUs), treatment] have been collected. NCs have been analysed independently and comparatively by three dermatologists including one with a nail pathologies specialization. Periungual tissues involvement, nail plates modification (form, surface and colour alterations) have been described.
Results. Comparing to healthy volunteers, SSc NC are characterized by cuticle [7.9 (5.5) fingers abnormalities *vs* 2.3 (4.2), $P < 0.001$] and nail fold alterations [telangiectasia, ulceration, paronychia 2.7 (2.9) *vs* 0.04 (0.02), $P < 0.001$) without nail plates modification (NS).

NCs are correlated to cutaneous fibrosis intensity ($P = 0.02$) but seem to be independent of RP duration. By contrast, pulmonary

fibrosis and pulmonary hypertension are correlated to the modification of the nail plate form (hippocratism) and nail fold, respectively ($P < 0.05$). Patients with DU are characterized by an increased frequency of periungual tissue abnormalities (i.e. cuticle, nail fold and hyponychium alterations, $P < 0.05$).
Conclusion. SSc-related NCs are characterized by important periungual tissues modifications, worsening with modified Rodnan score and digital ischaemia.

PS227. SSc IN EGYPT

N. Fathi Awad[1] and E. H. Choy[2]
[1]*Rheumatology and Rehabilitation Department, Assiut University Hospital, Assiut, Egypt and* [2]*Department of Medicine, Cardiff University School of Medicine, Cardiff, UK*

Introduction. SSc or scleroderma is a rare connective tissue disease. The precise pathogenesis of scleroderma remains unknown although both environmental and genetic factors have been implicated. There are limited data on the characteristics of patients with scleroderma in Egypt. The purpose of this study is to describe the clinical features of scleroderma in a University Hospital in Egypt.
Method. Patients with SSc were identified through a retrospective analysis of medical records held at the chronic rheumatic illnesses outpatient clinic of a University Hospital in Assiut Egypt in 2010. All patients who fulfilled the ACR criteria for classification of SSc were approached to participate in the study. Written informed consent was obtained. Twenty-eight individuals with SSc were examined clinically as well as modified Rodent scale, pulmonary function test, echocardiography and barium meal.
Results. In total, 28 female patients were recruited. The average age of the patients was 41.6 (12.2)-years. Fourteen patients have acute onset while the other 14 had insidious onset. Thirteen patients have diffuse disease, 12 patients have limited scleroderma, 3 patients have morphea only. Nine patients have progressive disease, 12 patients have stable disease and in 7 patients, the disease was regressing. Comparing patients with progressive, stable and regressive disease, several features were statistically significant $P < 0.05$ by ANOVA (Table 1). No statistically significant difference was found in cardiovascular (CV) and gastrointestinal manifestation on echocardiogram and barium meal. Comparing which group I think you can compare diffuse type against limited time or put the per cent of GIT and CV affection in diffuse and limited.
Conclusion. Patients with progressive scleroderma in Egypt are older. Attacks of RP are more frequency and severe in those with progressive disease. In addition, tender joint count and acute phase reactants are higher in patients with progressive disease.

TABLE 1.

	Regressive	Stable	Progressive	*P*-value
Age (years)	38.4 (12.3)	37.2 (11)	50 (9.6)	0.036
Duration of RP (min)	6.4 (3.2)	8.3 (5.6)	13.3 (3.8)	0.013
Frequency of RP (per day)	1.5 (1)	2.8 (1.7)	3.4 (1.2)	0.042
RP (Visual Analogue Scale)	2 (1.3)	4.4 (2.7)	5.4 (1.4)	0.01
Tender joint count	0.9 (1.1)	3.2 (2.5)	5.8 (1.6)	<0.0001
Digital ulcer	0.3 (0.8)	3 (2.1)	4 (2)	0.002
Hand closure	0.43 (0.79)	0.92 (0.7)	1.7 (0.71)	0.007
ESR	22 (9)	30 (21)	45 (17)	0.03
CRP	0 (0)	4 (5.9)	12.9 (9.5)	0.002

PS228. CORONARY MICROVASCULAR DYSFUNCTION IN PATIENTS WITH SSc: A NON-INVASIVE STUDY

S. Franchini[1], A. Faccini[1], E. Agricola[1], M. Oppizzi[1], M. G. Sabbadini[1] and P. G. Camici[1]
[1]*Vita-Salute San Raffaele University and San Raffaele Scientific Institute, Milan, Italy*

Introduction. SSc is a connective tissue disease characterized by vascular dysfunction and excessive fibrosis. The cardiac involvement is often subclinical during the first stages of the disease due to the coronary microvascular dysfunction (CMD), but when clinically evident it confers a mortality rate of 70% within 5 years.
Objectives. Aim of this study was to evaluate the prevalence and severity of CMD in asymptomatic SSc patients, by dipyridamole stress echocardiography.
Methods. We enrolled 14 consecutive patients (12 females and 2 males), with the dcSSc ($n = 6$) and lcSSc ($n = 8$). None had history of atherosclerotic coronary disease nor cardiac symptoms. All underwent coronary microvascular function examination, combining the analysis of abnormal segmental motion during dipyridamole (0.84 mg/kg/6 min) stress echocardiography with the evaluation of coronary flow reserve (CFR) by means of transthoracic pulsed Doppler on the left anterior descending coronary artery.
Results. Mean age of the SSc patients was 50.36 (13.25) years and mean time from the onset of RP was 10.57 (9.57) years. Seven (50%) had a reduced CFR value (<2.0, lowest value 1.4; two with lcSSc and five with dcSSc); the remaining seven (six with lcSSc and one with dcSSc) all had normal values (>2.0, highest value 2.94). The dcSSc subgroup was characterized by a higher prevalence of reduced CFR than the lcSSc subgroup (5/6 *vs* 2/8, $P = 0{,}031$). Among patients with lSSc, an inverse relationship between the time since the onset of RP and CFR values was observed (correlation coefficient −0.623; $P = 0.05$).
Conclusions. This study demonstrates the presence of cardiac involvement in half of our asymptomatic patients, with a higher prevalence in those patients affected by the diffuse form of the disease. These data highlight the importance of an exhaustive cardiac evaluation in all SSc patients, even at an early stage, including non-invasive evaluation of the CFR.

PS229. TRENDS IN MORTALITY IN PATIENTS WITH SSc FOR OVER 40 YEARS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF CASE-CONTROL AND COHORT STUDIES

M. Elhai[1], C. Meune[2], J. Avouac[1], A. Kahan[1] and Y. Allanore[1]
[1]*Rheumatology A Department and* [2]*Cardiology Department, Paris Descartes University, Cochin Hospital, APHP, Paris, France*

Background. Among the many different immune-mediated rheumatic diseases, SSc stands out as a severely incapacitating and life-threatening disease, the pathogenesis of which is largely unknown and for which therapeutic options are few and insufficient. Nevertheless, a recent cohort study has suggested a decrease in mortality with 10-year survival rates of 60% in the subgroup of patients included before 1985 as compared with 77% in the subgroup included later one. Thus, we set out to determine whether mortality rate in SSc patients has decreased over the past 40 years.
Materials and methods. We performed a systematic review and a meta-analysis of literature in MEDLINE and EMBASE databases from January 1960 to June 2010. All cohort studies reporting SSc mortality risk were included. Articles had to report enough data to compute a standardized mortality ratio (SMR). We calculated pooled SMRs of SSc mortality and determined their evolution with time using meta-regression analysis. We also conducted adjusted meta-regression analyses, for the methodology of the studies and for relevant covariates, respectively.
Results. Among a total of 721 identified references, 637 were excluded on the basis of their title or abstract resulting in 84 articles examined for full text. There were finally nine independent studies in which SMR was available. They were analysed corresponding to a total of 2691 patients: mean age; 50.1 years, 2230 (83%) were women; 713 (26%) had dcSSc. Mid-cohort year ranged from 1977 to 1995 (<1980: two studies; 1980–90: five studies; >1990: two studies). Seven hundred and thirty-two deaths occurred during a mean follow-up of 7.3 years. The overall pooled SMR was 3.53 (95% CI 3.03, 4.11). Among 732 deaths, 389/612 deaths (64%) were considered as related or possibly related to SSc whereas 223/612 deaths (36%) were defined as not related to SSc. Cardiac deaths were the most frequent causes of deaths (29%) followed by lung involvement (23%). All adjusted meta-regression analyses did not show any significant change in SMR over time ($P = 0.523$). Exclusion of the studies before 1980 revealed a trend for a decrease in SMR but not significant ($P = 0.112$).
Conclusion. Our results confirmed that SSc is a devastating condition associated with a high risk of mortality reflected by a pooled SMR of 3.5. Despite some data suggesting a decrease in the mortality risk in SSc, SMR has not significantly changed over the last 40 years. Further studies are needed to assess the effect of recent available therapies on mortality in SSc.

PS230. ADVERSE EFFECTS OF BOSENTAN IN PATIENT WITH SSc-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION

S. Egashira[1], T. Makino[1], M. Jinnin[1] and H. Ihn[1]
[1]*Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kkumamoto, Japan*

Bosentan hydrate, a dual endothelin receptor (ETA and ETB) antagonist, has been used as a primary drug for pulmonary arterial

hypertension (PAH). There are many reports that bosentan is an effective treatment for the digital ulcers and pulmonary fibrosis of SSc. Seventeen patients with PAH or digital ulcers associated with SSc were included in this study. All patients were treated by bosentan and eight cases of them had side effects (five cases of liver dysfunction, two of haematocytopenia, one of blood pressure reductions), and eight cases abandoned bosentan immediately, then all cases recovered from side effects. In this study, we evaluated the risk factor of liver dysfunction, and the incidence of liver dysfunction caused by bosentan was statistically higher in patients with a past history of liver dysfunction than without (80.0 *vs* 16.7%, $P = 0.012$). And it tended to be higher in patients with anti-U1 RNP antibody than without, but there was no statistically significant (60.0 *vs* 16.7%, $P = 0.074$). All cases with liver dysfunction had taken a number of concurrent medications. However, only a case was administered a calcium antagonist that was reported interaction with bosentan, all cases had taken the other drugs metabolized by cytochrome P450 and competed with bosentan.

PS231. THE AORTIC COMPLIANCE—POSSIBLE USEFUL PARAMETER IN PATIENTS WITH SSc

A. Dumitrascu[1], I. Mantu[1], R. Sarov[1], C. Margarit[1], E. Gjermeni[1], C. Dumitrascu[1], M. Popescu[1], S. T. Tanaseanu[1] and C. M. Tanaseanu[1]
[1]*Sf Pantelimon Emergency Hospital, Bucharest, Romania*

Accelerated atherosclerosis and impaired flow-mediated vasodilatation have been described in SSc. SSc is characterized by alterations of the microvasculature, disturbances of the immune system and by massive deposition of collagen. Arterial stiffness increases in accelerated atherosclerosis due to inflammation. Large artery stiffness is recognized as a modifiable, independent predictor of cardiovascular risk.

Aim of the study. To assess the utility of the aortic compliance, as new parameter in the evaluation of vascular involvement in patients with SSc.

Methods. Sixteen patients with SSc [mean age, 46 (15) years] and 16 healthy, age-matched control subjects were studied. The patients underwent clinical exam, routine lab tests, determination of anti-SCL and ACAs, echocardiographic studies. M mode was performed in ascending thoracic aorta with measurement of the difference between systolic and diastolic diametres and with measurement of brachial pressure pulse to calculate aortic distensibility (AD). The endothelium-dependent flow-mediated dilatation (FMD) test in a brachial artery was performed by the ultrasound system.

Results. Compared with control subjects, the value of aortic distensibility was significantly lower than in controls ($P < 0.0001$). Also aortic distensibility was significantly lower in patients with localized SSc [8.39 (1.87) m/s] compared with those with diffuse SSc [10.04 (2.01) m/s] ($P = 0.034$). There was a significant, positive linear correlation between AD and FMD ($r = 0.32$, $P = 0.045$). We also observed significant correlations between AD and age ($r = -0.31$, $P = -0.048$), and AD and disease duration ($r = -0.40$, $P = -0.011$) in SSc patients.

Conclusion. Decreased aortic compliance in comparison to age- and sex-matched healthy controls indicate increased large-vessel stiffness in patients with SSc. FMD and AD are reproducible indicators of the presence and degree of arterial stiffening. Because arterial stiffness may correlate with disease duration and age in patients with SSc, aortic distensibility may be a useful diagnostic test in the assessment of arterial function.

PS232. BOSENTAN AS AN EFFECTIVE TREATMENT FOR DIGITAL ULCERS OF DIFFERENT AETIOLOGIES

C. Dias[1], **G. Dias**[1], T. Faria[1], J. Martins[1] and M. L. Brazão[1]
[1]*Internal Medicine Department, Autoimmune Diseases Clinic – Central Hospital in Funchal, Madeira Island, Portugal*

Introduction. Recurrent digital ulcers (DUs) can be a complication on a wide range of autoimmune diseases (AIDs) with a vasculitic component. In SSc, for example, they have an estimated frequency of 30-50% and its aetiology is multifactorial. It has been proposed that ET-1 is a key mediator in regulation of vascular tone and its enhanced production in SSc is believed to lead to vasoconstriction, vessel remodelling, local ischaemia and ulcers of fingertips. Treatment with the endothelin receptor antagonist, bosentan, has proven to be effective in both treating and preventing new digital ulcers although one study showed that it had no effect on their healing.

Objective. To describe the effect of bosentan in DU with different aetiologies in six patients.

Methods. The authors present summarized case reports of six patients with DU with different aetiologies (SLE, vasculitis, SSc, aPL syndrome, RA and secondary SS). Clinical files were consulted and analysed demographical data, characteristics of the ulcers and their aetiology. All were submitted to bosentan in the same dosage (62.5 mg b.i.d. in the first 4 weeks and then 125 mg bid). Follow-up was performed at the end of the 1st and 3rd months after initiating treatment.

Results. All patients had a complete resolution of the DU with no recurrences reported (median time of improvement: 4 weeks). By the first follow-up appointment, all patients had significant improvement in their lesions and one had complete resolution. By the 3rd month follow-up appointment all patients had complete healing and the number of events of RP had decreased. No side effects were reported.

Discussion and conclusions. These results strengthen the evidence that ET-1 plays an important role not only in the vascular manifestations of SSc, as previously reported, but also in DU of other aetiologies. Therefore, bosentan can be an effective therapy in these patients. In contrast with one study, we found bosentan to be very effective in healing of DU. The fact that the number of RP events decreased cannot be solely attributed to the therapy with bosentan therapy since all patients but one had their DU in late winter and had their follow-up performed in Spring/Summer times. More studies are needed to clarify the indications and effectiveness of bosentan and in DU of other aetiologies apart from SSc in clinical practice.

PS233. APPLICATION EXPERIENCE OF RITUXIMAB IN PATIENTS WITH SSc

O. Desinova[1], M. Starovoytova[1], O. Koneva[1], O. Ovsyannikova[1] and L. Ananieva[1]
[1]*Institute of Rheumatology of RAMS, Moscow, Russia*

Introduction. Interstitial lung disease (ILD) is a common manifestation of SSc. ILD develops in up to 80% of patients with SSc overall and may be life threatening and require aggressive therapy. We assessed a possible effect of anti-human CD20 antibody [rituximab (RTX)] therapy on skin fibrosis and lung involvement in SSc patients.

Objectives. Objective of this study was to analyse the effects and safety of RTX in SSc patients.

Methods. There were nine SSc patients in the study. The female : male ratio was 7 : 2. The mean (S.D.) age of the patients was 50.6 (9.7 years) years. The duration of disease from the first non-RP was 5.2 (4.7 years) years. A total of eight (89%) patients had dcSSc, one (11%) had lcSSc. All patients had SSc-associated ILD, more of them were treated previously with immunosuppressive agent ($n = 7$). Application scheme RTX in four patients was 2×500 mg given 2 weeks apart; four patients was 4×500 mg given 4 weeks apart; one patient was 1×500 mg given 1 week apart. All patients were treated by prednisolone 10–15 mg/day. One patient had co-treatment with CYC during 6 months after RTX. We evaluated the modified Rodnan skin score (mRSS), forced vital capacity (FVC), diffusing capacity of carbon monoxide (DL_{CO}), the Valentini Disease Activity index, levels of B-cells in peripheral blood before and 1 year after completed RTX.

Results. After 1 year patients presented a median decrease of the skin score and the Valentini Disease Activity index compared with baseline is shown on Table 1. The median percentage of improvement of FVC in a year was 9%, however, this results was not significant. The median percentage of DL_{CO} in a year increased insignificantly only 1%. Complete depletion of peripheral blood B-cells was observed in all patients and persistence during year.

TABLE 1.

Parameters	Base line, mean (S.D.)	Over 1 year, mean (S.D.)	*P*-value
mRSS	19.2 (7.9)	10 (5.0)	0.01
FVC (%)	76.6 (9.6)	85.6 (13.3)	0.08
DL_{CO} (%)	48.5 (9.5)	49.1 (11.1)	0.7
Activity index	2.9 (1.7)	1.2 (0.43)	0.01

During RTX treatment, infections occurred in 2 patients, one of them had herpes zoster after 2 weeks, and another one had acute bronchitis after 2 months. These infections were successfully treated and did not have complications. Two patients had ST instability on ECG 10 days after RTX infusion without consequences.

Conclusion. Our results indicate possible beneficial effect of RTX therapy on skin fibrosis and lung involvement in SSc patients. This study reported also the safety of RTX in SSc patients. It's possible to discuss a smaller RTX doses, considering duration of B-cells depletion.

PS234. IS NT-PROBNP A MARKER OF VASCULAR BURDEN IN SSc?

A. Della Rossa[1], S. Casigliani[1], A. D'Ascanio[1], M. Doveri[1], A. Tavoni[2], L. Bazzichi[1] and S. Bombardieri[1]
[1]*Department of Internal Medicine, Unit of Rheumatology and* [2]*Unit of Immunoallergology, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy*

The aim of the present study was to retrospectively evaluate the risk factors and response to therapy of ischaemic digital ulcers in a cohort of 75 patients affected by SSc cyclically treated for long time with intravenous Iloprost for peripheral vascular involvement [mean: 50.41 (38.43) months].
Seventy-five SSc patients were enrolled. Data were collected by chart review and by phone or direct interview. Patients underwent a thorough physical examination with Allen test and questionnaires for quality of life, hand function, ulcer count and routine work up at the end of follow-up. The incidence of severe vascular manifestations during the follow-up was also assessed. Statistical analysis was performed by Wilcoxon signed rank test and descriptive statistics, using Stat View software. Patients underwent Iloprost treatment at regular intervals [mean number of circles/months of follow up: 0.46 (0.2)].
Of 75, 55 (73%) patients had a history of ischaemic digital ulcers And 29 patients (38.6%) had active digital ulcerations. Skin ulcers completely healed in Of 29, 26 patients (90%) at the end of the first treatment. Of 55, 41 patients (74%) relapsed after a mean of 24 months. A non-significant reduction of the number of ulcers was observed at the end of the follow-up. Pain and RP visual analogue scale and global health assessment significantly improved. Relapse rate was significantly correlated with the diffuse subset and abnormal Allen test. Higher number of ulcers at the end of follow-up was correlated with a worse hand function. Patients with an increase of NT-proBNP had a higher number of ulcers than patients whose values were within the normal range. The variation of NT-proBNP during the follow-up was correlated to the number of ulcers at the end of follow-up. The annual incidence of pulmonary arterial hypertension (PAH) was 2.42/100 patient-year, the rate of gangrene was 4% and no cases of scleroderma renal crisis were recorded.
These data suggest that our patients treated with Iloprost have a higher vascular burden than the rest of SSc population as mirrored by a higher rate of digital ulcer history, gangrene and PAH annual incidence. NT-proBNP is substantially increased in patients with digital ulcers and the variation of this marker during follow-up correlates with the load of ulcers. This finding suggests that such patients, even though asymptomatic, might be at risk of myocardial dysfunction, and thus warrant further investigation.

PS235. NAILFOLD CAPILLARY MICROSCOPY IN INFLAMMATORY MYOPATHY: A NON-INVASIVE TOOL TO MONITOR DISEASE ACTIVITY?

A. Della Rossa[1], S. Barsotti[1], M. Cazzato[1], V. Iacopetti[1], R. Neri[1], S. Casigliani[1], E. Vesprini[1] and S. Bombardieri[1]
[1]*Department of Internal Medicine, Rheumatology Unit, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy*

Nailfold capillary microscopy is a useful non-invasive tool to evaluate microvascular involvement in connective tissue diseases, particularly in scleroderma spectrum disorders. The microarchitecture of skin vessels correlates with systemic involvement and a number of studies have demonstrated the capability of this technique to furnish a number of prognostic indications, both for cutaneous and visceral involvement. The studies on inflammatory myopathies point to a significant role of capillaroscopy also in these disorders, although the role of this technique in monitoring disease activity is still controversial. The aim of the present study was to evaluate the role of capillaroscopy in discriminating between active and inactive disease in PM and DM. Thirty-eight patients underwent a total of 44 capillaroscopies. According to Bohan and Peter criteria, 18 patients were affected by DM, 20 by PM. Table 1 shows clinical features of the case series. A semiquantitative rating of capillaroscopy was divided in four classes according to the severity of the pattern, basing on authoritative sources. Disease activity of muscle and cutaneous involvement was defined on clinical grounds on four semiquantitative classes from inactive disease (0) to very active disease (3). Comparison between capillaroscopic score and activity of the disease was made by means of Spearman rank correlation. A scleroderma pattern was unveiled in 15/18 DM (83%) *vs* 2/20 PM patients (10%) ($P < 0.0001$). No correlation was found between muscle activity and capillaroscopic score, on the other hand a strong correlation was demonstrated between cutaneous activity and capillaroscopy in DM patients (ρ: 0.7, $p = 0{,}005$). Capillaroscopic score was also significantly higher in subjects with gottron's papules and heliotrope rash (Table 2, Fig. 1). Capillaroscopy might contribute to a better characterization and an earlier diagnosis of inflammatory myopathies, particularly DM.

Table 1. Clinical features of the case series

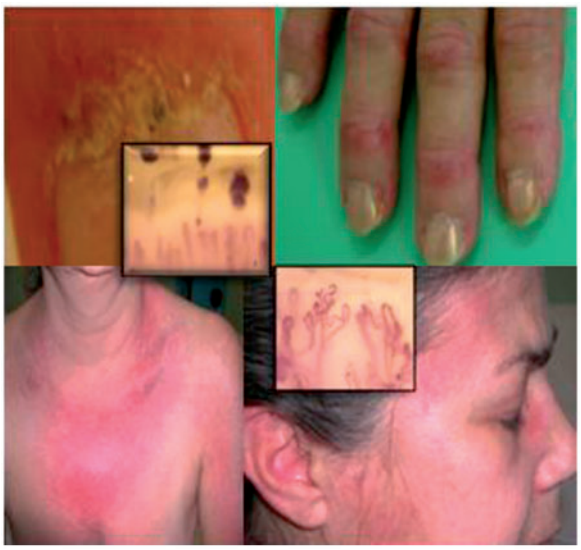
		RP	SSc pattern
Patients, *n* (%)	38		17/38 (44)
Female/Male, *n*	6.6		
Age, mean (s.d.), years	56.7 (16.9)		
Disease duration	49.5 (174)		
PM, *n* (%)	20	2/20 (10)	2/20 (10)
DM, *n* (%)	18	6/18 (30)	15/18 (83)
Heliotrope rash	14/18 (78)		
Gottron's papules	13/18 (72)		

Mean (s.d.), years

Table 2. Capillaroscopic score and clinical correlation

	Capillaroscopic score
Activity score	$\rho = 0.7$ $P = 0.005$
Gottron's papules	$P = 0.0025$
Heliotrope rash	$P = 0.0006$

Fig. 1 Cutaneous involvement and capillaroscopic patterns.



PS236. ROLE OF LASER DOPPLER IMAGING IN THE DIFFERENTIAL DIAGNOSIS OF RP

A. Della Rossa[1], S. Casigliani[1], M. Doveri[1], M. Cazzato[1], A. D'Ascanio[1], A. Tavoni[2] and S. Bombardieri[1]
[1]*Rheumatology Unit, Department of Internal Medicine and* [2]*Immunoallergology Unit, Department of Internal Medicine, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy*

SSc is a chronic disorder with a peculiar affection of vascular system and an early loss of angiogenic potential; RP and vascular complications are frequent and severe in this condition. The involvement of vascular system is exploited for the differential diagnosis of RP and in fact capillaroscopic abnormalities are now a pivotal benchmark for the early recognition of SSc. The role of laser flowmetry is less well defined in this context.
The purpose of the study was to evaluate the pattern of flow distribution in the dorsum of the hand and the dynamic response to physical stimuli in a population of consecutive Raynaud's patient in comparison with healthy people.
To this aim laser speckle perfusion imaging (Pericam PSI, Perimed, Jarfalla) was performed in 17 normal subjects and 37 RP patients divided into 9 primary RP (PRP), 15 RP secondary to CTD of scleroderma spectrum (RP-CTD), 13 RP suspicion, but not clearly secondary to CTD (susp RP).

Parameters recorded were: basal flux in perfusion units, homogeneity of distribution and proximal distal gradient; cold challenge and ischaemia: per cent variation from the basal value, time of rescue of the initial flux (after cold test and ischaemia), area under the curve (AUC) flux, peak flow (after ischaemia). Statistical analysis: non parametric tests (Wilcoxon signed-rank test) and contingency tables for cathegorical variables (Stat-View, SAS). In view of the high number of comparisons inolved, only $P \leq 0.01$ was considered significant.
We observed the following differences: (i) higher rate of patchy pattern of flux distribution in CTD-RP (85%) in comparison with Susp-RP (23%) and healthy and PRP subjects (0%) ($P < 0.0001$). (ii) Per cent variation after cold test between healthy subjects (22%) and RP-CTD (52%) ($P = 0.0022$) and between PRP (21%) and CTD-RP ($P = 0.01$). (iii) Peak flow after ischaemia between healthy subjects (249%) and CTD-RP (106.9%) ($P = 0.0026$) and between PRP (390%) and CTD-RP ($P = 0.01$). (iv) AUC between healthy subjects (103%) and RP-CTD (56%) ($P = 0.01$). (v) Strong correlation between capillary density and peak flow and AUC ($\rho = 0.773$; $P < 0.0001$ for peak flow, $\rho = 0.625$, $P = 0.0002$ for AUC).
The present study outlines a number of differences between healthy subjects and RP patients. The abnormalities are most striking in CTD-RP both in the pattern of distribution and in microvascular reactivity.

PS237. DISTRICT DISABILITY DIFFERENTLY IMPACTS ON SSc SUBSETS AND AFFECTS GLOBAL DISABILITY AND QUALITY OF LIFE IN PATIENTS WITH SSc

A. Del Rosso[1], S. Maddali-Bongi[1], B. Francini[1], A. Branchi[1], M. Del Nero[1], F. Braschi[1], L. Amanzi[1], L. Rasero[2] and M. Matucci-Cerinic[1]
[1]*Division of Rheumatology, Department of BioMedicine and* [2]*Department of Public Health, AOUC, University of Florence, Florence, Italy*

Background. In SSc, the involvement of hands and face is common and leads to disability and reduced functionality in these districts.
Objectives. To assess hand and face disability in a cohort of SSc patients and their correlation with global disability and quality of life (QoL).
Methods. Ninety-nine SSc patients [89 women and 10 men; age and disease duration 57.93 (13.86) and 10.31 (6.0) years; 71 with lcSSc and 28 with dcSSc], were assessed by Hand Mobility in Scleroderma test (HAMIS), Cochin Hand Function Disability Scale (CHFDS), finger to palm (FTP) distance, hand opening; Mouth Handicap in SSc scale (MHISS), mouth opening. Global disability and QoL were assessed by HAQ and Summary Mental and Physical indexes (SPI and SMI) of SF-36.
Results. dcSSc patients present higher FTP distance at both hands, lower mouth opening and higher scores in HAMIS and lower SF36-SPI than lcSSc patients (Table 1).

HAMIS is correlated with CHFDS ($r = 0.58$; $P < 0.0001$), FTP distance of right and left hand ($r = 0.47$ and $r = 0.61$; $P < 0.0001$) and to right and left hand opening ($r = -0.35$ and -0.26; $P < 0.05$). Correlation with MHISS ($r = 0.30$; $P = 0.01$), mouth opening ($r -0.27$; $P < 0.05$), HAQ ($r = 0.47$; $P < 0.0001$) and SF-36-SPI ($r = -0.29$; $P < 0.05$) were also found.

CHFDS is correlated with HAMIS ($r = 0.58$; $P < 0.0001$), right and left FTP distance, ($r = 0.39$ and 0.46; $P < 0.001$) and right and left hand opening ($r = -0.30$ and -0.29; $P < 0.05$). It is also correlated with MHISS ($r = 0.46$; $P < 0.0001$), mouth opening ($r = -0.33$; $P < 0.05$), HAQ ($r = 0.75$; $P < 0.0001$) and SF-36-SMI ($r = -0.47$; $P < 0.0001$).

MHISS is correlated with mouth opening ($r = -0.38$; $P < 0.001$), HAMIS ($r = 0.30$; $P < 0.05$), CHFDS ($r = 0.46$; $P < 0.0001$), right and left FTP ($r = 0.23$; $P < 0.05$ for both). Correlations with HAQ ($r = 0.43$; $P < 0.0001$), SF-36-SPI ($r = -0.49$; $P < 0.0001$) and SF-36-SMI ($r = -0.24$; $P < 0.05$) were also shown.

Table 1. District and global disability in SSc patients (pts)

	SSc (99 pts)	lcSSc (71 pts)	dcSSc (28 pts)	*P* (lcSSc *vs* dcSSc)
HAMIS	4.80 (5.76)	3.90 (4.56)	7.64 (6.72)	0.015
CHFDS	10.30 (13.47)	9.77 (14.43)	13.13 (11.44)	NS
Opening of right hand, cm	3.19 (1.34)	3.29 (1.35)	2.68 (0.78)	NS
Opening of left hand, cm	3.07 (1.38)	3.17 (1.44)	2.74 (0.99)	NS
Right FTP distance, cm	0.98 (1.47)	0.61 (1.08)	2.05 (1.85)	0.0002
Left FTP distance, cm	1.12 (1.66)	0.80 (1.54)	1.98 (1.73)	0.005
Total MHISS	17.40 (11.11)	16.86 (10.94)	20.81 (10.53)	NS
Mouth opening, cm	3.76 (1.02)	4.0 (0.88)	3.06 (0.97)	0.0001
HAQ	0.65 (0.69)	0.60 (0.73)	0.75 (0.58)	NS
SF-36- SPI	39.41 (10.24)	40.43 (10.12)	35.77 (9.25)	<0.05
SF-36- SMI	44.17 (11.17)	44.08 (10.46)	42.65 (12.73)	NS

Conclusions. Our SSc patients present a prominent disability at hand and face, higher in dcSSc than in lcSSc. Hand and face disabilities are correlated and also affect global disability and QoL. Thus, the evaluation of distinct disability should be included in the assessment of SSc patients.

PS238. CLASS I HLA AND CLINICAL FEATURES OF SSc

A. Del Rio[1], Z. Sachetto[1], A. C. Londe[1] and M. B. Bértolo[1]
[1]*University of Campinas Faculty of Medical Sciences, Campinas, Brazil*

Introduction. SSc is known as a clinically heterogeneous disease. Several studies have looked into association between particularly Class II HLA alleles and disease expression. The number of previous studies including Class I alleles is limited. The objective of this study was to determine if there is an association between Class I HLA alleles and some of the most frequent clinical manifestations.
Methods. Patients followed from 2000 to 2011 in State University of Campinas, Brazil, were selected. Clinical data were obtained through chart review. Molecular HLA typing was performed through PCR/sequence-specific oligonucleotides. Statistical analysis included Fisher's exact test and multivariate analysis.
Results. One hundred and eight patients with SSc, 91 women (84.3%) and 17 men (15.7%) were included and Class I HLA typed. The clinical variables tested were the degree of skin involvement (diffuse, limited or uninvolved, sine scleroderma), presence of positive ANAs and its main patterns, gastrointestinal involvement, presence of interstitial lung disease and pulmonary arterial hypertension. Thirty-four per cent of the patients were classified as diffuse SSc, 59% as limited disease and 5% as sine scleroderma. Approximately 80% had gastrointestinal involvement, 40% had interstitial lung disease and 9% had pulmonary hypertension. An association between Class I HLA alleles was found through statistical analysis only for the gastrointestinal involvement, when considering 10% level of significance: A*29 ($P = 0.117$), B*39 ($P = 0.118$), B*51 ($P = 0.118$) e B*08 ($P = 0.117$). There was no significaney when analysing the other features.
Conclusion. This study demonstrated poor association between Class I HLA alleles and SSc expression.

PS239. CARDIAC MAGNETIC RESONANCE IMAGING IN SSc: FIRST 10 REPORTED CASES FROM URUGUAY, LATIN AMERICA

N. Danese Larriera[1], M. Rebella Fischer[1], G. Parma[2], V. Garra Cerviño[1], N. Lluberas Gonzalez[2], A. Pazos[1], V. Braggio[3] and E. Cairoli Morossini[1]
[1]*Systemic Autoimmune Disease Unit, Clínica Médica C,* [2]*Cardiology Department and* [3]*Imagenology Department, Hospital de Clínicas, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay*

Objectives. To assess the clinical and cardiovascular features detected by cardiac MRI (CMRI) in SSc patients.
Methods. A prospective, descriptive study was performed. Ten consecutive patients with SSc assisted at the Systemic Autoimmune Disease Unit from the Hospital de Clinicas, Montevideo, Uruguay, were assessed to determine clinical, echocardiography and CMRI patterns. Patients with overlap syndrome, diffuse interstitial lung disease, previous diagnosis of pulmonary hypertension and/or structural heart disease were excluded. CMRI was performed using Magnetom Avanto 1.5T Resonator-Siemens, with Argus software.

Comparisons between two groups were performed using non-parametric *t*-test and correlation studies were made with Pearson index. Statistically significant *P*-values were considered <0.05.
Results. Nine women with limited and one with diffuse SSc were included. The mean age was 58 (15) years with an evolution average of 71 (47) months. All patients had ANA positives. Eight patients showed a sclerodermiform pattern at the digital capillaroscopy. Application of the EUSTAR score demonstrates activity in four patients.

Right and left atrial enlargement was founded by echocardiography in four and five patients, respectively. Atrial enlargement was detected in all cases by CMRI. Pericardial effusion was founded in half of patients. Increased pulmonary artery diameter was detected in three patients.

One patient reported an increase in T2 intensity (equivalent to the presence of oedema). No fibrosis was detected with the delayed enhancement sequence. A positive correlation between right atrial diameter and pulmonary artery diameter ($r = 0.777$, 95% CI 0.289, 0.945, $P = 0.008$) was evidenced. The detection of right atrial

enlargement was higher for CMRI than echocardiography ($P = 0.032$) as well as to detection of pericardial effusion.
Discussion. The CMRI was able to demonstrate the existence of cardiovascular abnormalities in all patients, especially in the detection of atrial enlargement and pericardial effusion. The correlation between right atrial enlargement and increase of the pulmonary artery diameter could suggest (as an indirect sign) the presence of pulmonary hypertension. The non-detection of fibrosis could be related to small sample size, the greater proportion of limited SSc patients and/or the software performance. CMRI is an important complementary method in the early detection of cardiovascular abnormalities in SSc. Future studies are needed to confirm these results.

PS240. SERUM MARKERS OF FIBROBLAST ACTIVATION ARE ALTERED IN EARLY SSc

S. Vettori[1], V. D'Abrosca[2], E. D'Aiuto[3], G. Cuomo[2] and G. Valentini[2]
[1]*Department of Internal Medicine, Cardiology and Immunology, Federico II University,* [2]*Department of Clinical and Experimental Medicine, Rheumatology Section and* [3]*Department of Clinical and Experimental Medicine, Immunology Section, Second University of Naples, Naples, Italy*

Background. Since fibroblast activation and fibroblast/T-cell interplay are crucial mechanisms of SSc pathogenesis, we aimed to investigate whether these events already occur in early SSc patients.
Materials and methods. Serum levels of collagen metabolites, and profibrotic chemokines and cytokines were measured in 132 patients with RP and 25 healthy controls (HCs). Basing on a complete screening for SSc, patients were divided into four groups: early SSc (eSSc), i.e. positivity for marker autoantibodies and typical capillaroscopic findings; probably definite SSc (pSSc), i.e. eSSc features plus digital ulcers/scars, puffy fingers, arthritis, telangiectasia, dysphagia, heartburn, shortness of breath; definite SSc; UCTD. Collagen metabolites were measured by competitive radioimmunoassay. Chemokines (CCL2 and CXCL8) and cytokines (TGF-β, IL-13, IL-33, sIL-2r, sCD30) were measured by a multiplexed suspension fluorescence-based immunoassay.
Results. Nineteen patients received diagnosis of eSSc, 44 of pSSc, 54 of SSc, and 15 of UCTD. Elevation of carboxyterminal cross-linked telopeptide of type I collagen (ICTP) and of CCL2 was statistically significant ($P < 0.05$) in eSSc, pSSc and SSc, but not in UCTD and HC group, showing a progressive increase according to the subset (lowest in eSSc, highest SSc; $P < 0.05$). Aminoterminal propeptide of type III procollagen (PIIINP) showed a statistically significant increase ($P < 0.05$) in pSSc and SSc, but not in eSSc *vs* UCTD and HC group, being higher in SSc than in pSSc ($P < 0.001$). In addition, CXCL8, TGF-β, IL-13, IL-33, sCD30 (all $P < 0.05$) and sIL-2r ($P < 0.0001$), were elevated in pSSc *vs* HC. sIL-2r was elevated in pSSc *vs* eSSc as well ($P < 0.001$). CXCL8 was elevated in eSSc *vs* HC ($P < 0.001$). As expected, ICTP and PIIINP correlated with the extent of skin sclerosis in definite SSc patients ($P < 0.01$), and with ACAs in pSSc patients ($P < 0.01$).
Conclusions. Our data show that fibroblast activation is an early, preclinical, event in the pathogenesis of SSc, as shown by the increase in serum levels of ICTP and CXCL8 in eSSc patients. ICTP also discriminated eSSc from UCTD patients, suggesting it might be a sensitive and specific marker for SSc even in early stages. In addition, ICTP, as well as PIIINP, serum increase parallelled to clinical progression. Finally, elevation of cytokines serum levels in pSSc but not in eSSc patients suggests that T-cell activation might be subsequent to fibroblast activation.

PS241. PREVALENCE OF THE METABOLIC SYNDROME IN PATIENTS WITH SSc

R. Irace[1], G. Cuomo[1], M. E. Frongillo[1], M. Iudici[1], V. D'Abrosca[1], G. Abignano[1] and G. Valentini[1]
[1]*Rheumatology Unit, Second University of Naples, Naples, Italy*

Background. The metabolic syndrome is an independent risk factor for ischaemic heart disease. Patients with SLE have an increased prevalence of the metabolic syndrome [1]. There are no controlled studies of the metabolic syndrome in patients with SSc.
Objective. To compare the prevalence of the metabolic syndrome in patients with SSc and controls and to evaluate its relationship to activity and severity of disease.
Methods. A total of 130 consecutive patients with SSc (118 females, median age 49 years; range 18–85 years) and 50 controls (patients with FM) (48 females, median age 45 years; range 27–72 years) were studied. The prevalence of the metabolic syndrome was compared in patients and controls using the National Cholesterol Education Program Adult.
Treatment. Panel III (NCEP-ATPIII): central obesity: waist 102 cm in men and 88 cm in women;

hypertriglyceridaemia: >150 mg/dl [2]; low HDL: 40 mg/dl in men and, 50 mg/dl in women [3]; high blood pressure: >130/85 mmHg or use of drugs for high blood pressure [4]; and high fasting glucose >110 mg/dl, and associations with activity and severity of the disease were examined [5].
Results. The metabolic syndrome was present in 13% of patients and in 18% of controls subjects ($P > 0.05$). Among patients with SSc, the metabolic syndrome was significantly associated with higher value of ESR (ESR > 30) (7/17 *vs* 12/113; $P = 0.0037$) and was significantly associated with higher prevalence of pulmonary hypertension evaluated by echocardiography (PHA > 40 evaluated by echocardiography) (4/17 *vs* 3/113; $P = 0.0057$). Neither disease activity nor severity scores were associated with the metabolic syndrome.
Conclusions. Patients with SSc have a lower prevalence of the NCEP-ATPIII-defined metabolic syndrome than controls. This result may help to justify the coronary prevalence in SSc patients similar to that of the general population [2, 3].

PS242. RELATIONSHIP OF THE 6-MIN WALKING TEST AND QUALITY OF LIFE

G. Cuomo[1], R. Irace[1], M. E. Frongillo[1], G. Abignano[1], M. Iudici[1] and G. Valentini[1]
[1]*Rheumatology Unit, Second University of Naples, Naples, Italy*

Background. The 6-min walking test (6MWT) is a standardized measure of submaximal exercise capacity. It is a surrogate measure of heart and lung involvement. There are no studies on relationship between 6MWT and quality of life evaluated by short-form 36 (SF-36).
Objective. To evaluate the relationships between of the 6-min walking distance (6MWD) and each items of SF-36.
Methods. Sixty-five consecutive SSc patients were investigated. They underwent 6MWT and complete the SF-36 [assessed the eight domains of the questionnaire as well as the physical component score (PCS) and mental component score (MCS)].
Results. 6MWD ranged from 255 to 580 (median 420); Table 1 list the correlations from 6MWT and only the statistically significant features of SSc and the items of SF-36.
Conclusion. Our study first demonstrates that 6MWT is correlated with some aspects of quality of life as measured by SF-36 in the SSc patients. This results must been considered when assessing 6MWT in SSc.

TABLE 1.

	Median (range)	ρ	P
Age, years	56 (19–81)	−0.51	<0.0001
EScSG activity index	0.5 (0–5)	−0.33	0.009
HAQ-DI	0.375 (0–2.275)	−0.26	0.048
mRSS	2 (0–17)	−0.35	0.007
Pulmonary hypertension (echocardiography)	30 (13–80)	−0.26	0.048
SF-36			
PCS	43 (20–65)	0.41	0.0016
PF	75 (0–100)	0.40	0.002
GH	50 (10–92)	0.43	0.0007

PS243. DIFFUSE SSc WITH SEVERE MULTIORGAN INVOLVEMENT

F. Salvador[1], J. Cunha[1], A. Lima[1], C. Pinto[1], E. Pinelo[1], P. Carrola[1], E. Serradeiro[1], A. Morais[1] and A. Faria[1]
[1]*Centro Hospitalar de Trás-os-Montes e Alto Douro, Unidade de Doenças Autoimunes, Vila Real, Portugal*

Systemic sclerosis is a chronic autoimmune multisystemic disease that has a severe impact on daily activities of affected patients. The prognosis depends on the severity of organ damage and can often be inferred by the magnitude of cutaneous involvement. Early diagnosis and aggressive treatment early in the evolution of the disease are the key to improving the quality of life and reduce mortality.
We describe the case of a woman with 39 years of age diagnosed with diffuse SSc with multi-organic involvement.
The patient was referred to the Autoimmune Diseases's Consultation at age of 34 years by polyarthralgia with synovitis of large joints, enthesitis and myositis. She had severe skin disease with diffuse skin thickening and loss of folding of the skin and RP. Laboratory tests

showed ANAs and anti-Scl70 positive antibodies. The nail-fold capillaroscopy revealed late phase of scleroderma pattern.
Despite optimal therapy there was progression of organ involvement with severe digestive and breathing problems. Oesophageal manometry showed the existence of hypotonia of the oesophageal body and lower oesophageal sphincter. A CT scan of the chest showed diffuse pattern of pulmonary alveolitis and fibrosis in bilateral lower lobes. The bronchoalveolar lavage showed fields compatible with alveolitis. Pulmonary hypertension was excluded by echocardiography and cardiac catheterization.
There has been worsening over time although increased immunosuppression. There was progression of skin thickening and enthesitis with claw hands and functional disability; maintenance of digital ulcers with progression to digital amputation despite treatment with nifedipine, iloprost and bosentan; worsening of lung disease under treatment with CYC and MMF with fibrosis progression, significant reduction of DLCO and chronic respiratory failure.
The severity of lung involvement justified referral for lung transplantation.
This case demonstrates the severity that the SSc can take and the speed of inexorable organic and functional damages despite optimal immunosuppressive therapy.

PS244. NITRIC OXIDE DIFFUSION IN PATIENTS WITH SSc

E. Zanatta[1], G. Guarnieri[2], E. Pigatto[1], M. Rizzo[1], C. Campana[1], L. Riato[1], P. Maestrelli[2] and **F. Cozzi**[1]
[1]*Department of Clinical and Experimental Medicine and* [2]*Department of Environmental Medicine and Public Health, University of Padua, Padua, Italy*

Background. Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are common causes of death in patients with SSc. The diagnosis of these complications is based on non-invasive diagnostic methods such as HRCT for ILD, echocardio Doppler for PAH and carbon monoxide diffusing capacity test (DL_{CO}) for both. A DL_{CO} reduction has been detected in early phases of both ILD and PAH.
Objectives. The aim of this study was to evaluate the feasibility and utility of nitric oxide diffusing capacity test (DL_{NO}), compared with DL_{CO}, in order to investigate if DL_{NO} is able to distinguish in SSc patients the alveolar capillary membrane damage characteristic of ILD and the pulmonary microcirculation alterations typical of PAH. Other studies have evaluated DL_{NO} in some pulmonary diseases, but not in SSc [1, 2].
Methods. The work was performed in 37 consecutive patients affected with SSc, 31 females and 6 males, mean age 53.81 (13.61) years and with mean disease duration of 10 (7) years. Eighteen patients were affected by dcSSc and 19 by lcSSc. ANAs were positive in all patients, with anti-topo I pattern in 17 cases, ACA in 12, nucleolar in 5 and anti-RNA polymerase III in 3. SSc patients were divided into three groups: 12 with ILD (HRCT score >4), 8 with PAH (PAPs >40 mmHg), 17 without pulmonary complications (HRCT score <4 and PAPs <40 mmHg). Twenty healthy subjects, sex and age matched, were considered as controls.

Patients were submitted to single-breath CO and NO diffusion. DL_{CO}, DL_{NO} and ratio of DL_{NO}/DL_{CO} were calculated. Statistical analysis was performed by Mann–Whitney test.
Results. DL_{CO} and DL_{NO} were significantly reduced in SSc patients in comparison with control subjects ($P < 0.01$). DL_{CO} and DL_{NO} were significantly lower both in the group with ILD ($P < 0.05$ and $P < 0.001$, respectively) and in the group with PAH ($P < 0.005$ and $P < 0.001$ respectively), in comparison with patients without pulmonary complications. DL_{NO}/DL_{CO} was higher in the group with PAH (4.52), when compared with the group with ILD (4.29) and to the third group (4.40), but the differences were not significant.
Conclusion. These data suggest that DL_{NO} is a further diffusion test able to detect complications as ILD or PAH in SSc patients. The ratio DL_{NO}/DL_{CO} is useful to identify SSc patients with different pulmonary impairment.

PS245. CAPILLARY BLOOD VOLUME MEASUREMENT IN SCLERODERMA PATIENTS SUBMITTED TO NITRIC OXIDE DIFFUSION TEST

F. Cozzi[1], G. Guarnieri[2], E. Zanatta[1], E. Pigatto[1], M. Favaro[1], S. Cardarelli[1], P. Maestrelli[2] and L. Punzi[1]
[1]*Department of Clinical and Experimental Medicine and* [2]*Department of Environmental Medicine and Public Health, University of Padua, Padua, Italy*

Background. Pulmonary microvascular damage is part of a more generalized involvement of the microcirculation in SSc and could play a relevant role in the pathophysiological mechanisms of interstitial lung disease (ILD) and of pulmonary arterial hypertension (PAH), which are severe complications and leading causes of death in SSc.
Objectives. The aim of this study was to evaluate the changes of the capillary blood volume, a method to investigate pulmonary microcirculation calculated by NO and CO diffusion tests, in SSc patients with ILD, with PAH or without pulmonary complications.
Methods. The study was performed in 37 consecutive patients affected with SSc, 31 females and 6 males, mean age 53.86 (13.61) years and with mean disease duration of 10 (7) years. Eighteen patients were affected by dcSSc and 19 by lcSSc. ANA were positive in all patients, with anti-topo I pattern in 17 cases, ACA in 12, nucleolar in 5 and anti-RNA polymerase III in 3. SSc patients were divided into three groups: 12 with ILD (HRCT score >4), 8 with PAH (PAPs >40 mmHg), 17 without pulmonary complications (HRCT score <4 and PAPs <40 mmHg). Twenty healthy subjects, sex and age matched, were considered as controls.

Patients were submitted to single-breath NO and CO diffusion tests, evaluating DL_{NO} and DL_{CO}; alveolar-capillary membrane diffusion (DM) and capillary blood volume (VC) were also calculated, according to the Roughton–Foster equation [1, 2]. Statistical analysis was performed by Mann–Whitney test.
Results. DM values were in the normal range in SSc patients without pulmonary complications, while they were significantly reduced in both groups with ILD ($P < 0.01$) and with PAH ($P < 0.001$). VC values were significantly reduced not only in the group with ILD ($P < 0.005$) and in that with PAH ($P < 0.001$), but also in patients without pulmonary complications ($P < 0.01$).
Conclusions. These data suggest that a lung microvascular damage is present in all SSc patients, even in those without evidence of pulmonary complications (ILD and PAH).

PS246. CARDIAC INVOLVEMENT IN SSc

I. Cordeiro[1], A. Cordeiro[1], M. J. Loureiro[2], L. Lopes[2], M. J. Santos[1] and J. Canas Da Silva[1]
[1]*Rheumatology Department and* [2]*Cardiology Department, Hospital Garcia de Orta, Almada, Portugal*

Background. Cardiac disease is one of the major causes of mortality in SSc patients.
Objectives. We aimed to assess cardiac involvement in a cohort of Portuguese SSc patients followed up at our rheumatology department.
Patients and methods. Thirty patients were included (18 limited SSc, 9 diffuse, 1 SSc sine scleroderma, 2 SSc overlap syndromes SSc/PM), including 27 females and 3 males, with a mean age of 56 (14) years and a mean disease duration of 6 (7) years. Patients were assessed for cardiac complaints according to the World Health Organization (WHO) functional class, electrocardiogram (EKG) abnormalities, echocardiogram (EchoCG) abnormalities [including right ventricular dysfunction (RVD), dilatation of cardiac chambers, pulmonary artery systolic pressure (PASP) estimation] and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, if available. Patients with elevated PASP were submitted to right heart catheterization (RHC).
Results. Only 9.6% of patients presented with functional class 3–4 according to the WHO classification. EKG abnormalities at rest were rare. EchoCG abnormalities were present in 55% of patients. The most common finding was left atrial enlargement (37.5%). Left heart dysfunction was frequent (12.5%), valve abnormities were present in 13% of patients, mostly tricuspid regurgitation (41%). No statistically significant difference was found in cardiac involvement between disease subsets. PASP was elevated in 23% of patients. RHC was performed in six patients. Two of these patients were classified as having pulmonary arterial hypertension (Group I of the DanaPoint Meeting 2008 classification). The other patients confirmed to have pulmonary hypertension came under the pulmonary disease and/or left heart involvement categories. Elevated NT-proBNP was present in 35% of patients. Anticentromere positivity was associated with lower NT-proBNP values ($P = 0.003$). NT-proBNP showed no correlation to PASP ($P = 0.084$).
Conclusion. Despite the mild clinical complaints, cardiac abnormalities in EchoCG could be found in approximately half of the patients, not necessarily related to pulmonary vascular involvement. These findings reinforce the need to increase awareness of cardiac involvement in order to implement adequate prophylactic and therapeutic measures.

PS247. FINANCIAL BURDEN OF VASOREACTIVITY TEST IN THE TREATMENT OF PATIENTS WITH SSc -RELATED PULMONARY ARTERIAL HYPERTENSION

J. S. Cardona[1], **P. Coral-Alvarado**[2,3], P. Mendez-Patarroyo[2,3] and G. Quintana[4]
[1]*Fundacion Santa Fe de Bogota,* [2]*Universidad de Los Andes-Fundacion Santa Fe de Bogota,* [3]*Reumavance-Pharmacoeconomics Study Group and* [4]*Universidad Nacional de Colombia, Bogota, Colombia*

Introduction. SSc-related pulmonary hypertension (PH) has great impact on morbidity and mortality of patients with this entity. New treatment options have improved survival a quality of life, but costs of these new alternatives can greatly impact the health system.
Materials and methods. We model the costs of screening and treatment for 5 years. Medical fees, diagnostic tests (e.g. right heart catheterization with or without vasoreactivity test) were included. Number of patients was determined according to the 2010 Colombian population census.
Results. There are 1620 patients with SSc-related PH. One hundred and sixty-two patients initially have a positive vasoreactivity test; and each year 10% lose response to calcium-channel blockers (CCBs).

Differences of U$ 697.762 and U$ 1.494. 150 were found when vasoreactivity test was avoided, respectively, with epoprostenol and adenosine in 1620 patients with SS-related PH in Colombia.
Conclusions. Vasoreactivity test can be considered unnecessary given the low positivity and loss of response to CCB. Saving with this conduct could cover 1-year treatment for 1105 patients in Colombia with phosphodiesterase inhibitors (Sildenafil).

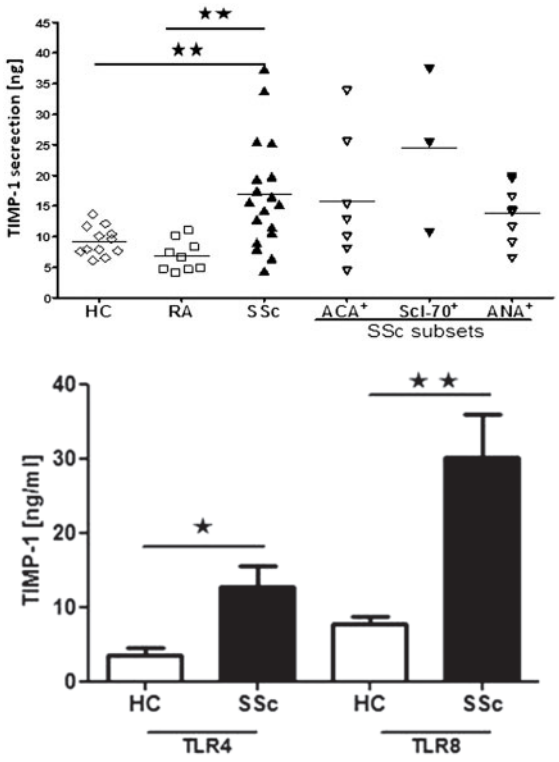
This study shows that practicing VT should be reassessed because of its great impact in health system. Besides, these resources could be directed to a therapeutic or diagnostic use in these patients.

PS248. A NOVEL ROLE OF MONOCYTES IN THE INDUCTION OF PROFIBROTIC TISSUE-INHIBITOR OF METALLOPROTEINASE-1 MEDIATED BY TOLL-LIKE RECEPTORS STIMULATION IN SSc

M. Ciechomska[1], C. A. Huigens[1], T. Hügle[1], A. Gessner[1], S. O'Reilly[1] and J. M. Laar[1]
[1]*Newcastle University, Institute of Cellular Medicine, Newcastle, UK*

Background. SSc is an autoimmune disease characterized by fibrosis, vascular dysfunction and abnormal activation of immune cells including monocytes. For example, substantial evidence indicates that SSc monocytes overexpress type I IFN-regulated genes in response to certain toll-like receptors (TLRs) stimulation. We postulated that circulating monocytes from SSc patients produce tissue inhibitor of metalloproteinase-1 (TIMP-1) that could contribute to excessive matrix deposition and consequently disease progression.
Objectives. To examine TIMP-1 production by SSc monocytes when compared with healthy controls (HCs) and RA patients, and to investigate whether TLR triggering of monocytes isolated from SSc patients or HC induces TIMP-1 secretion.
Methods. Twenty-three patients with SSc, 16 HCs and 11 RA patients were included in this study. Monocytes were isolated from PBMC and further separated by CD14+ microbeads. The production of TIMP-1 by monocytes was determined by ELISA and qRT–PCR, in response to either SSc sera or TLR agonist stimulation.
Results. TIMP-1 produced by monocytes was elevated in SSc patients compared with HC as measured by qRT–PCR (fold increase 3.1, $P = 0.03$). Also, TIMP-1 expression was significantly stronger (Fig. 1.) when healthy monocytes were co-cultured with sera from SSc patients compare with sera from both HC and RA (fold increase 16.8, 9.1, 6.9 and $P = 0.01$, $P = 0.04$, respectively). SSc monocytes and HC monocytes stimulated with TLR4 (LPS) and TLR8 (ss-RNA) agonists secreted robust levels of TIMP-1 (Fig. 2.), but the response was more pronounced in SSc monocytes [mean (S.D.)] 12.76 (2.86) ng/ml, $P = 0.016$, and 30.21 (5.80) ng/ml, $P = 0.0051$, respectively). Agonists against other TLRs were not effective in inducing TIMP-1 in monocytes. Pre-treatment with Myd88 inhibitors attenuated TIMP-1 production, confirming the specificity of the agonists.
Conclusion. This study indicates a potential link between TLR signalling and excessive TIMP-1 secretion in circulating monocytes from SSc patients, supporting an important role of monocytes in production of profibrotic factors. Therefore, blockade of TLR signalling may represent a new therapeutic target for patients with SSc.

FIG. 1



PS249. THE ROLE OF N-TPROBNP IN SCLERODERMA RENAL CRISIS

C. Chighizola[1], H. Penn[2], P. L. Meroni[1], C. P. Denton[3] and V. Ong[3]
[1]*Istituto Auxologico Italiano, Immunorheumatology Research Laboratory, Milan, Italy,* [2]*Rheumatology Department, Northwick Park Hospital, Harrow and* [3]*Royal Free Hospital, Centre for Rheumatology and Connective Tissue Diseases, London, UK*

Background. Scleroderma renal crisis (SRC) is a serious complication of SSc. Although outcome has greatly improved, there remains significant mortality and morbidity with frequent requirement for renal replacement therapy. Therefore, novel biomarkers to identify patients at risk of poor renal outcome would be invaluable. The N-terminal fragment of brain natriuretic peptide (N-TproBNP) has a role as biomarker in heart failure and pulmonary arterial hypertension. In addition, it reflects haemodynamic status in renal failure.
Objectives. To assess the role of N-TproBNP in a retrospective cohort of SRC patients.
Methods. Nineteen SRC patients were enrolled in this study. SRC was defined by new-onset systemic hypertension >150/85 mmHg with a decrease in estimated glomerular filtration rate (eGFR) >30%. All patients had normal pulmonary artery systolic pressure. Serum N-TproBNP levels were measured by Roche E-170 assay. Three patient subgroups were identified based on renal outcomes (no dialysis, temporary and permanent dialysis). Kruskal–Wallis test was used to compare N-TproBNP levels among the subgroups. ROC curves were generated to identify N-TproBNP levels that gave optimal sensitivity and specificity to predict requirement for renal replacement therapy. Logistic regression analysis was performed to investigate the relation between N-TproBNP levels and renal outcome. N-TproBNP levels were compared at SRC presentation and at follow-up using a Wilcoxon matched-pair test. Associations between N-TproBNP and continuous clinical variables were determined by the Spearman's coefficient.
Results. There was a significant difference in N-TproBNP levels among three subgroups of patients based on renal outcome (median in the subgroups: 'no dialysis' 119, 'temporary dialysis' 1729.5 and 'permanent dialysis' 3373 pg/ml; $P = 0.003$). The ROC curves of

N-TproBNP to predict requirement for dialysis provided a sensitivity of 87.5% at an N-TproBNP level of 1494 pmol/l with a specificity of 90.9% (95% CI 0.73, 0.99, area under ROC curve 0.9545). In the logistic regression model adjusted for creatinine, N-TproBNP levels >360 pmol/l significantly predicted renal outcome ($P = 0.019$).

Among 11 patients (57.9%) who had N-TproBNP levels repeated at 6 months, there was a significant reduction in N-TproBNP values ($P = 0.0029$). N-TproBNP is well correlated with Cr ($r = 0.6105$, $P = 0.0055$) and eGFR ($r = -0.7446$, $P = 0.0009$). N-TproBNP levels were negatively correlated with Hb levels ($r = -0.7123$, $P = 0.0006$) and disease duration ($r = -0.7083$, $P = 0.0007$). Correlation between N-TproBNP levels and LVEF but this did not meet significance ($r = -0.4594$, $P = 0.0734$).

Conclusions. These data suggest that N-TproBNP may be a useful biomarker in risk stratification of renal outcome among SRC patients, selectively identifying those likely to require renal replacement therapy.

PS250. N-TERMINAL PROBNP: A BIOMARKER OF CARDIAC INVOLVEMENT IN SSc PATIENTS?

C. Chighizola[1], P. L. Meroni[1], G. Coghlan[2], B. Schreiber[2], G. Coghlan[2], C. Denton[2] and V. Ong[2]
[1]*Istituto Auxologico Italiano, Immunorheumatology Research Laboratory, Milan, Italy and* [2]*Royal Free Hospital, Centre for Rheumatology and Connective Tissue Diseases, London, UK*

Background. Cardiac involvement is common in SSc and is often clinically occult. It is recognized as a poor prognostic factor contributing significantly. Early detection of cardiac disease with non-invasive tools is therefore critical.

Aim. To assess the role of N-TproBNP in SSc-related cardiac involvement in a retrospective cohort of patients.

Methods. Twenty-one SSc patients (14 dcSSc) with cardiac involvement were enrolled in this study. Cardiac involvement was defined as haemodynamically significant arrhythmias, pericardial effusion or congestive heart failure, requiring specific treatment. All patients had normal pulmonary artery systolic pressure and none had serum creatinine >140 μmol/l. This group was compared with 42 SSc patients without evidence of cardiac involvement or pulmonary arterial hypertension. N-TproBNP levels were measured with the Roche E-170 immunoassay. Normal N-TproBNP levels were <20 pmol/l. Mann–Whitney test was used to compare N-TproBNP values between subgroups based upon presence of organ involvements. ROC curves were drawn; logistic regression analysis was performed to investigate the relationship between N-TproBNP and heart involvement. Serial N-TproBNP levels were compared using Wilcoxon matched-pair test. Univariate mortality analysis was performed with Kaplan–Meier method. Associations between N-TproBNP and continuous clinical variables were determined by Spearman's coefficient.

Results. Compared with those without cardiac involvement, N-TproBNP was significantly increased in SSc patients with heart involvement (median 11 and 219 pmol/l respectively, $P < 0.0001$; 136-445). ROC curves of N-TproBNP to predict the presence of cardiac involvement in SSc were drawn: a sensitivity of 86% was achieved at a level of 51 pg/ml with a specificity of 98% (area under curve 0.9870, 95-1). N-TproBNP levels >50 pmol/l were shown to be strong predictor of heart involvement (OR 78, $P < 0.001$, 14-424). A significant progressive reduction in N-TproBNP after the acute phase of cardiac involvement was observed during 6 months follow-up ($P = 0.0231$). Within the group with cardiac involvement, N-TproBNP levels were categorized as high if above the median value of 219 pmol/l: higher levels of N-TproBNP did not predict survival ($P = 0.895$ by log-rank).

N-TproBNP levels strongly correlated with LVEF ($\rho = -0.7384$, $P = 0.0002$); there was no correlation between N-TproBNP and age, troponin-I, mRSS, FVC, DL_{CO}, systolic and diastolic BP.

N-TproBNP levels did not show any difference between subgroups of patients with and without DU, PF, GI involvement and myositis.

Conclusions. These data suggest that N-TproBNP may be a surrogate marker for cardiac involvement in SSc. Further studies are required to evaluate the utility of N-TproBNP levels for cardiac assessment.

PS251. CLINICAL PROFILE OF SSc PATIENTS SEEN AT A UNIVERSITY HOSPITAL IN ARGENTINA

L. Catoggio[1], M. Sabelli[1,2], Z. Bedran[1,2], E. Lancioni[1,2], J. Marin[1,2], C. Saucedo[1,2], M. Scolnik[1,2] and E. Soriano[1,2]
[1]*Seccion Reumatologia, Hospital Italiano de Buenos Aires, Instituto Universitario Escuela de Medicina, Hospital Italiano and* [2]*Fundacion Dr Pedro M. Catoggio para el Progreso de la Reumatologia, Buenos Aires, Argentina*

Background. Clinical characteristics of patients seen at different institutions vary among other things according to level of care (primary, secondary and tertiary) and referral patterns.

Our objective was to examine the characteristics of patients seen at our institution over the past decade, a university hospital that combines primary, secondary and tertiary care.

Methods. Population: patients registered in the hospital's electronic databases. Case ascertainment: (i) patients included in Rheumatology databases; (ii) patients with the problem scleroderma, SSc or CREST in the computer-based Patient Record System; (iv) patients with ICD 9 code 710.1 (SSc) on admission to hospital; and (v) patients with anti-Scl-70, ACAs or ANAs in the laboratory database. Medical records of all patients found were reviewed and only cases fulfilling ACR 1980 criteria (or considered to be SSc by authors in spite of incomplete criteria) were included. They were classified as dcSSc or lcSSc according to LeRoy's criteria with limited being separated into sclerodactyly and acrosclerosis.

Results. Since the year 2000, 230 patients (194 females) were seen at our institution as out-/ in-patients. Sixty-three (27%) had dcSSc and 167 (73%) lcSSc (138 sclerodactyly and 29 acro). One hundred and nine (47%) were followed for >3 years; 17 of these have died under our care and 120 are being currently followed. Ten-year survival rate was 82% for lcSSc and 55% for dcSSc 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 dcSSc. ACAs were detected in 51% of patients overall and 70% of lcSSc. Ten of 29 patients with acrosclerosis (34%) had anti-Scl-70 antibodies and 5 (17%) had ACAs.

Digital ulcers occurred similarly in dcSSc (28%) and lcSSc (34%) ($P = 0.6431$), GI involvement in 36% of dcSSc *vs* 41% of lcSSc ($P = 0.5603$), interstitial lung disease in 63% of dcSSc, 41% of acro ($P = 0.0468$) and 19% of sclerodactyly ($p < 0.001$ *vs* dcSSc). Renal crisis was only seen in one patient with dcSSc (0.4%). Pulmonary hypertension (Echo > 35 mm Hg) was detected in 11% of dcSSc and 13% of lcSSc ($P = 0.6743$).

Conclusion. Data appears to be similar to that from other centres in different parts of the world. Patients with acrosclerosis had more anti-Scl-70 antibodies and interstitial lung disease than those with just sclerodactyly, supporting an intermediate form as suggested by Barnett.

PS252. LATE-ONSET SSc: CASE REPORTS AND LITERATURE REVIEW

M. Casal Moura[1], J. Rema[1], V. Araújo[1] and C. Dias[1,2]
[1]*Serviço de Medicina Interna, Hospital de São João, E.P.E. and* [2]*Faculdade de Medicina da Universidade do Porto, Porto, Portugal*

Background. SSc is a heterogeneous disease and its clinical presentation depends on age. Scleroderma has a median age of onset in the fifth decade of life; however, many individuals develop scleroderma later. Patients with juvenile-onset SSc have less skin involvement and lower mortality but suffer more frequently from overlap syndromes. In contrast, patients with a late-onset SSc, after 75 years, suffer more from lcSSc and have higher rates of ACAs. Despite the higher prevalence of lcSSc, they usually have fewer digital ulcers. This suggests a milder disease course in late-onset SSc patients, but might be biased by a shift of patients with mild disease into the late-onset group. Pulmonary hypertension is more prevalent in late-onset SSc. In elderly, SSc has a more stable course. ACR criteria are fulfilled in fewer patients in the late-onset group. This might indicate a more atypical disease course.

Methods. The authors found two patients with a late-onset SSc diagnosis in a retrospective analysis of a population of patients observed over a 10-year period to an autoimmunity unit of a general hospital and describe them based on age of the diagnosis, gender, smoking habits, first manifestations, organ involvement, auto-antibodies profile, overlap characteristics, treatment and mortality.

Case reports. Both patients were female and diagnosed at the ninth decade (80 and 81 years) with a late-onset lcSSc. They presented at least two criteria of diagnosis according to the ACR. None was a smoker. The first manifestation was skin discolouration with cutaneous sclerosis and exuberant RP associated to Stage 4 digital ulcers. The nailfold videocapillaroscopy was positive and pulmonary hypertension was present in one patient. Other extracutaneous presentations were excluded. They showed ANAs with a centromeric pattern (titres 1/1000 in both) and ACAs. Overlap characteristics were absent. They were treated with pentoxifylline and calcium-channel blockers and remained asymptomatic.

Conclusions. Our data corroborate those reported in recent systematic reviews. However, our patients presented with digital ulcer that is an uncommon presentation in late-onset SSc. Although a benign disease course was showed in both patients, older patients are at greater risk for pulmonary hypertension, renal impairment, cardiac disease and muscle weakness. Awareness of the risk for specific organ manifestations should guide the care of these patients.

PS253. SYSTEMIC SCLERODERMA CASE SERIES OF AN AUTOIMMUNITY UNIT: CLINICAL FEATURES AND LITERATURE REVIEW

M. Casal Moura[1], J. Rema[1], V. Araújo[1] and C. Dias[1,2]
[1]*Serviço de Medicina Interna, Hospital de São João, E.P.E. and* [2]*Faculdade de Medicina da Universidade do Porto, Porto, Portugal*

Background. The prevalence of scleroderma-like conditions range from 4 to 489 cases/million individuals. Incidence figures for systemic scleroderma (SSc) are 0.6–122/million persons-year. The general manifestations like malaise, fatigue, arthralgias and myalgias are common symptoms but their prevalence is unclear. Skin involvement is a nearly universal feature, however, ~10% of the patients in whom a diagnosis of SSc is made do not have obvious skin induration (sine scleroderma). The most characteristic clinical manifestation of vascular dysfunction is RP with digital ulcers. Extracutaneous organ involvement is very frequent. Serologic tests are helpful in confirming, but not in excluding the diagnosis. Certain autoantibodies found in SSc are associated with subsets of the disease. Treatment of these conditions is difficult, incomplete and not curative. The organ-based treatment is the best strategy. Immunomodulatory and anti-fibrotic approaches to the treatment, while theoretically appealing, did not prove to be more beneficial than harmful.
Methods. The authors made a retrospective analysis of a population observed over a 10-year period (2002–11) to the autoimmunity unit of a general hospital and select those with an SSc diagnosis. We describe this subpopulation based on age of the diagnosis, gender, smoking habits, first manifestations, organ involvement, auto-antibodies profile, overlap characteristics, treatment and mortality.
Results. In 370 patients observed 12 were diagnosed with SSc (3.2%). Only one patient presented dcSSc. The majority were females (83.3%) and the median age for the diagnosis was 51 years (ages between 24 and 81 years). Only two patients were smokers. The most frequent first manifestation was the skin discolouration presented for seven patients (58,3%). There was skin involvement in 11 patients (91.7%). The most frequent extracutaneous involvement was oesophageal dysmotility (41.7%). The RP was present in 11 patients (91.7%) and three patients (25%) presented digital ulcers. At least two criteria for the diagnosis were confirmed in 10 patients (83.3%). About 55% of the patients with lcSSc showed ACAs. Overlap characteristics were seen in half of the patients. All the patients were treated with pentoxifylline and only four (41.7%) were treated with corticosteroids. All the patients are alive.
Conclusions. The prevalence of SSc was ~3%. The lcSSc was more frequent than the dcSSc form associated with ACA in 55%. About 17% presented 'sine scleroderma'. All the patients presented with extracutaneous manifestations. The overlap syndromes were frequent. The organ-based treatment was the strategy of choice.

TABLE 1.

SSc patients (n= 12)	
Gender, female	10 (83.3)
Median age of diagnosis	51 years
Pattern of SSc	11 lcSSc (91.7)
Clinical presentation	
Skin discolouration	5 (41.7)
Arthralgia	3 (25)
Digital ulcers	3 (25)
Cutaneous sclerosis	1 (8.3)
RP	11 (91.7)
Cutaneous involvement	10 (83.3)
Organ involvement	
Gastrointestinal	5 (41.7)
Pulmonary	3 (25)
Cardiac	0 patients
Musculoskeletal	4 (33.3)
Neuromuscular	1 (8.3)
ACR criteria	
1 (cutaneous)	2 (16.7)
2 (cutaneous + vascular)	7 (58.3)
3 (cutaneous + vascular + extracutaneous)	3 (25)
Antibodies	11 (91.7)
anti-ScL 70	0 patients
anti-centromere	6 (54.5)
Other antibodies	11 (90.9)
ANAs	9 (81.8)
Beta2-GP IgM	3 (27.3)
RF	3 (27.3)
anti-dsDNA	2 (18.2)
Overlap characteristics	5 (45.5)
SLE	3 (60)
CTD	2 (40)
APS	1 (20)
RA	1 (20)
Treatment	
Organ based	12 (100%)
CSs	4 (33.3%)
Mortality	0 patients

Values are represented as n (%).

PS254. NEARLY HALF OF THE PATIENTS WITH SEVERE PRIMARY PULMONARY ARTERIAL HYPERTENSION ASSOCIATED TO SSc DO NOT FULFIL THE 1980 ACR CLASSIFICATION CRITERIA FOR THE DISEASE

B. Joven[1], M. J. Ruiz-Cano[2], L. Carmona[3], P. Escribano[2], M. A. Gomez-Sanchez[2] and **P. E. Carreira**[1]
[1]*Rheumatology Department,* [2]*Pulmonary Hypertension Unit, Cardiology Department, Hospital Universitario 12 de Octubre and* [3]*Fundacion Española de Reumatologia, Madrid, Spain*

Objective. To investigate the fulfilment of ACR 1980 Preliminary Classification Criteria for SSc in patients with severe pulmonary arterial hypertension (PAH) associated to SSc.
Patients and methods. All SSc patients, fulfilling the 1980 SSc-ACR criteria or the proposed 2001 criteria for early SSc were included in a database containing demographic and clinical information. Severe PAH was defined by a mean pulmonary arterial pressure (mPAP) >40 mmHg in right heart catheterization, in the absence of lung fibrosis and LV dysfunction. Severe PAH patients were selected. Clinical characteristics, haemodynamics and survival were compared between patients with or without 1980 SSc-ACR criteria, using Chi-Square, t-test and Kaplan–Meyer analysis.
Results. From 356 patients, 33 [9%, 2 males/31 females, age 56 (16) years] presented severe PAH as previously defined. Time from RP onset to HAP diagnosis was 16 (11) years. Two had diffuse and 31 lcSSc. ANA were positive in 31 (94%), ACA in 22/31 (71%) and aRNP in 5/31 (16%). Mean mPAP was 56 (10) mmHg, wedge pressure was 10 (3) mmHg, and pulmonary arteriolar resistance (PAR) was 13 (7) UW. Only 17 (52%) fulfilled 1980 SSc-ACR criteria. All patients not fulfilling ACR criteria presented RP. Capillaroscopy showed scleroderma pattern in 14/15 (93%), sclerodactyly was present in 15 (94%), telangiectasia in 13/15 (87%), dysphagia and gastro-oesophageal reflux in 6 (38%), calcinosis in 3/13 (23%), hand oedema in 9 (56%), low DL_{CO} in 12/14 (86%), low FVC in 4/15 (26%), ANA in 14 (87%), ACA in 9/15 (60%) and aRNP in 3/15 (20%). One patient had renal crisis. None had joint contractures or ischaemic lesions. Acroosteolysis ($P = 0.04$), ischaemic lesions ($P > 0.0001$) and calcinosis ($P < 0.0001$) were more frequent in patients fulfilling ACR criteria, who also had lower FVC% at PAH diagnosis (82 *vs* 95; $P = 0.04$). In haemodynamics, patients not fulfilling ACR criteria presented higher PAR (16 *vs* 11; $P = 0.04$). Median survival was 5.2 years (95% CI 2.4, 8), similar in both groups. After 6 (6) years of follow-up, 20 patients died (19 of PAH) including 10 without ACR criteria.
Conclusions. Nearly half of the patients with severe SSc-PAH do not fulfil 1980 ACR criteria for the disease, but develop clinical SSc characteristics (sclerodactyly, capillaroscopic changes, telangiectasia, calcinosis, dysphagia, low DL_{CO}, ANA/ACA), and have the same poor survival as those fulfilling ACR criteria. Our study points out the importance of: (i) performing capillaroscopy and ANA to every patient with RP; and (ii) screening all SSc patients, even those with very mild limited disease, to detect HAP as early as possible.

PS255. A CASE OF SSc COMPLICATED BY TAKAYASU'S ARTERITIS

M. Caronni[1], A. Severino[1], L. Beretta[1] and R. Scorza[1]
[1]*Fondazione IRCCS Ca' Granda Policlinico di Milano, Milan, Italy*

Background. SSc is a CTD characterized by activation of the immune system, vasculopathy and deposition of collagen and extracellular matrix in the skin and internal organs. Takayasu's arteritis is a rare necrotizing and obliterative giant cell arteritis that involves the aorta and its main branches, coronary and pulmonary arteries. Associations between Takayasu's arteritis and SSc have seldom been described so far, with the description of three cases in the medical literature.

Methods. We report a case of SSc complicated by Takayasu's arteritis. A 59-year-old woman with a 14-year history of lcSSc was regularly followed in our outpatients' clinic since the diagnosis. The disease was characterised by RP, sclerodactyly, oesophagopathy, telangiectasia, presence of ANAs and ANCs; the patient had been treated with calcium-channel blocker, low-dose aspirin, proton-pump inhibitors and cyclic iloprost infusions but she had never been given steroids or immunosuppressive agents. At a follow-up visit in 2004, physical examination showed the presence of asymmetrical blood pressure and completed absence of left radial pulse and bruits over right subclavian artery. Doppler ultrasonographic investigation showed a 85% narrowing of the left internal carotid and subclavian arteries and a 50% narrowing of the right carotide and subclavian artery. The patient then underwent arteriography that showed a 45% narrowing of the common left carotid, just after the origin and a 75% narrowing of the common right carotid just after the origin; the left subclavian artery was obliterated with revascularization by occipital artery. Laboratory blood tests showed an increased CRP to 10.9 mg/l (unl $<$ 0.5), an increased erythrocyte sedimentation rate to 63 mm/h; the other parameters were remarkably normal, including the complete blood count, the renal and the liver function, immunoglobulin levels, the lipid profile and the thrombophilic screening (homocysteine, antithrombin III, protein C and S, Leyden's factor, aPLs). Pulmonary function testings, echocardiography and high-resolution CT were within the normal limits as well.

The patients was diagnosed as having SSc overlap Takayasu's arteritis and she was prescribed MTX 20 mg/week, yet therapy was soon interrupted due to the occurrence of recurrent pulmonary infections. AZA 100 mg/day + cilostazole was then introduced with a progressive normalization of the CRP and ESR. Radiological controls performed in the last 5 years showed no progression of artery disease.
Conclusion. Here, we report the rare association between SSc and Takayasu's arteritis.

PS256. RP AND THE ROLE OF NAILFOLD VIDEOCAPILLAROSCOPY

M. C. Amaral[1], I. Ferreira[1], S. Oliveira[1], F. Paula[1], M. Neves[1] and J. Delgado Alves[1]
[1]*Department of Medicine IV, Immune-Mediated Systemic Diseases Unit – Fernando Fonseca Hospital, Amadora, Portugal*

Background. RP is a common clinical condition which can be primary (Raynaud's disease) or secondary to other entities, including immune-mediated systemic diseases (ISDs). Nailfold videocapillaroscopy is able to detect early microvascular changes in patients with RP, particularly if the 'capillaroscopic scleroderma pattern' is found. Previously, our group had suggested as criteria to distinguish primary from secondary RP the following: major capillary abnormalities, enlarged/giant capillaries, number of capillaries per milimetre, type and velocity of circulation. Later on, microhaemorrhages have also been considered.
Aim. This present work aims to determine sensitivity, specificity and predictive values of our modified methodology to evaluate RP.
Methods. Patients with RP were recruited consecutively from our outpatient clinic. Each subject stayed in a temperature controlled room (20–22°C) for 20 min before the nailfolds of his/her eight fingers were examined. Patients were classified as secondary RP if they had at least three of the following characteristics: $>$5% of capillaries with major abnormalities, presence of enlarged/giant capillaries, $<$8 capillaries/mm, presence of local microhaemorrhages, reduced red blood cell velocity, intermittent flux with 'sludge'. Relation between this data and patients' diagnosis was then analysed.
Results. Four hundred and sixteen patients, 368 women (88.5%) and 48 men (11.5%), had a mean age of 43.3 years. Capillaroscopic data: 235 (56.5%) patients had $>$5% of capillaries with major abnormalities, 217 (52.2%) had enlarged/giant capillaries, 179 (43%) had $<$8 capillaries per mm, 117 (28.1%) had microhaemorrhages, 233 (56%) had reduced red blood cell velocity, 248 (59.6%) had intermittent flux with 'sludge'. Clinical data: 137 (32.9%) patients had non-ISD associated RP, 89 (21.4%) had SSc, 140 (33.7%) had another immune-mediated systemic disease (SLE, RA, vasculitis) and 50 (12%) had an undifferentiated ISD. According to our criteria 151 (36.3%) patients were classified as primary RP and 265 (63.7%) as secondary RP. The relation between our results and patients' diagnosis had a sensitivity of 72.7%, a specificity of 79.9%, a positive predictive value of 61.6% and a negative predictive value of 86.8%, with a significant P value $<$ 0.0001.
Conclusion. Our criteria showed a strong negative predictive value for the presence of ISD, which emphasises the ability to identify primary RP. The addition of microhaemorrhages as a useful parameter appears to increase the specificity of our methodology.

PS257. BONE MASS DENSITY AND BODY COMPOSITION IN PATIENTS AFFECTED BY SSc—PRELIMINARY RESULTS

G. Barausse[1], P. Caramaschi[1], S. Pieropan[1], D. Gatti[1], S. Tonetta[1], D. Sabbagh[1], D. Biasi[1] and S. Adami
[1]*Rheumatology Unit, Verona, Italy*

Background. Contrasting data have been published about bone mass density (BMD) in SSc. We analysed BMD, body mass composition and markers of bone turnover in a group of SSc patients.
Methods. Eighty-four SSc patients underwent the following investigations: calcium urinary excretion, calcium serum levels, phosphates, PTH, 25-OH-vitamin D, bone-ALP, CTX; moreover BMD and body mass composition were analysed by DEXA.
Results. In SSc patients hip neck, total hip and lumbar spine BMDs (Z-score $<$ or $= -1$) were lower than in healthy, age- and sex-matched subjects (28.0, 25.6 and 24.7, respectively, of the cases). Comparison between SSc and healthy controls showed that Z-score is significantly lower at hip neck [−0.42 (0.84), $P = 0.00$] and total hip [−0.24 (0.96), $P = 0.027$), but not at the level of lumbar spine. These data were confirmed when SSc patients were divided into different subgroups concerning disease duration, corticosteroid therapy in women and menopause condition. Z-score was normal in SSc males.

A significant reduction in total lean mass in SSc subjects with a disease duration $>$5 years was found compared to those with a more recent disease onset [38844 (6655) *vs* 42807 (7296) g, $P = 0.043$]. No other associations were found between both BMD or body mass composition and the following features: disease duration, disease activity, disease pattern, cutaneous involvement severity, autoantibody profile, nailfold videocapillaroscopic pattern, presence of pulmonary fibrosis or pulmonary arterial hypertension. Vitamin D serum concentration resulted under normal values in 40 subjects (47.6%). Furthermore, CTX value resulted significantly higher in subjects with moderate *vs* mild cutaneous involvement as assessed by modified Rodnan skin score [0.51 (0.28) *vs* 0.38 (0.17) ng/ml, $P = 0.021$]. PTH value was high in almost half of the patients (41.5%), particularly with dcSSc pattern in comparison with lcSSc [74.34 (31.94) *vs* 59.80 (23.82) pg/ml, $P = 0.021$].
Conclusion. BMD in SSc patients was low at level of the cortical bone, but not at the site of trabecular bone. This may be due to reduced physical activity in relation to pulmonary, cardiac and muscle-skeletal involvement. Our observation does not agree with previous Italian studies, in which a low BMD had been found also at lumbar spine. Such a difference can be explained by a very moderate use of CSs in our patients. Other factors that negatively influence both cortical and trabecular bone are high incidence in hypovitaminosis D, low solar exposition, persistence of a chronic inflammatory state with consequent development of local oxidative stress.

PS258. DIGITAL AMPUTATION IN SSc: INCIDENCE AND CLINICAL ASSOCIATIONS. A RETROSPECTIVE LONGITUDINAL STUDY

P. Caramaschi[1], D. Biasi[1], C. Caimmi[1], G. Barausse[1], D. Sabbagh[1], I. Tinazzi[1], S. Tonetta[1] and S. Adami[1]
[1]*Rheumatology Unit, Verona, Italy*

Objective. To evaluate the incidence of digital necrosis requiring surgical amputation in a monocentric group of SSc patients.
Methods. We reviewed the record-charts of 188 SSc patients (26 men, mean age 59.2 years, mean disease duration 8.0 years, mean time from RP onset 11.7 years, median follow-up duration 92 months) who had been seen at Rheumatology Unit of Verona since 2004.
Results. Nine patients (4.8%) underwent partial or total digital amputation due to necrotic process; all but one had a long history of multiple and persistent digital ulcers. Six patients had multiple digit amputation events and three patients a single episode. In two patients after multiple toe loss both legs were amputated.

All nine patients had a concomitant large-vessel involvement. In eight cases, lower limb eco colour Doppler evaluation evidence of atherosclerotic plaques with multiple arterial stenosis and/or occlusions was observed. All these patients showed one or more cardiovascular risk factors: hypercholesterolaemia was observed in all the cases, while high blood pressure, smoking history and obesity were detected in 5, 1 and 1 case, respectively. None of these patients suffered from diabetes. In one of the patients, who lost three fingers of right hand but without cardiovascular risk factors, angiography showed the occlusion of ulnar artery and the stenosis of radial artery at the same side, but no evidence of atherosclerotic plaques.

The comparison between patients with and without digital amputations showed that the patients who developed this severe

complication were older [70.0 (1.0) *vs* 58.7 (1.2), $P = 0.040$ by ANOVA], had a longer duration from RP onset [29.2 (1.5) *vs* 11.2 (2.1), $P = 0.000$ by ANOVA] and a longer disease duration [18.9 (1.6) *vs* 7.6 (2.5), $P = 0.002$ by ANOVA]. Digital amputations were significantly associated with peripheral artery diseases ($P = 0.000$ by Fisher's exact test) and with hypercholesterolaemia ($P = 0.014$ by Fisher's exact test).

Concerning autoantibody profile the positivity for ACA was significantly associated with digit amputation ($P = 0.038$ by Fisher's exact test).

Discussion. With the limits of a retrospective analysis, our study suggests that concomitant peripheral artery disease is strongly associated with digit amputation. It appears that in SSc the preventive strategy for digital ulcers and amputation should include an extensive diagnostic and preventive work-up for peripheral atherosclerosis.

PS259. LIPOPROTEIN LEVELS IN PATIENTS WITH SSc: SIMILARITIES WITH THE DYSLIPIDAEMIA PRESENT IN SYSTEMIC LUPUS ERYTHEMATOSUS

E. Cairoli[1], **M. Rebella**[1], N. Danese[1], V. Garra[1], P. Chalart[1] and J. Tafuri[1]
[1]*Systemic Autoimmune Disease Unit, Clínica Médica C, Hospital de Clínicas, Universidad de la República, Montevideo, Uruguay*

Objectives. To assess the levels of lipoprotein in SSc patients.
Methods. A prospective, descriptive study was performed. Twenty-five consecutive patients with SSc assisted at the Systemic Autoimmune Disease Unit from the Hospital de Clínicas, Montevideo, Uruguay, were assessed to determine clinical features, pharmacological treatment, TSH level and levels of lipoproteins, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL). Patients with known dyslipidaemia and/or lipid-lowering therapy were excluded. As a control group, 40 patients with SLE were included (sex and age matched ± 5 years). Comparisons between 2 or 3 groups were performed using non-parametric *t*-test and ANOVA, respectively. Association studies were performed using chi-square test (Yates correction). $P < 0.005$ were considered significant.
Results. The mean age of SSc group and SLE group was 55.1 (10) years and 50.5 (12.2) (9) years, respectively. There were no significant differences in gender, age and BMI. In the SSc-group, five patients receiving lipid-lowering therapy must be excluded from the analysis. In seven patients, thyroid dysfunction was detected. The mean dose of prednisone (PDN) in SLE group was 7.6 (12) mg/day.

The levels of TC, TG, HDL and LDL were 204.1 (39), 138.4 (53), 57.3 (17) and 119 (31) in the SSc group and 188.5 (45), 132.9 (60) 52.9 (16) and 110.8 (36) in SLE group, respectively, and there were no significant differences in the respective comparisons. A comparative sub-analysis was performed, subdividing the SLE group according to the current HCQ therapy in: HCQ users + SLE group ($n = 20$) and HCQ-SLE non-users group ($n = 20$). There were no differences between the SSc group and HCQ-SLE group. Conversely, the HCQ + SLE group showed lower levels in all lipoproteins [TC 173.5 (45), TG 118.2 (47), HDL 51.4 (17), LDL 98 (32)] with significant differences because of an increase in TC and LDL ($P = 0.020$ and $P = 0.015$, respectively) in the SSc group patients. The association analysis showed no significant differences between the increased values of TC and LDL and the presence of thyroid dysfunction ($P =$ NS) in the SSc group.
Conclusions. SSc patients have comparable levels of lipoproteins to patients with SLE, even when compared with those receiving HCQ, where we demonstrated a significant increase in TC and LDL, regardless of the presence of thyroid dysfunction.

PS260. LOW FECAL ELASTASE IS ASSOCIATED WITH HIGHER MORTALITY IN SSc PATIENTS

Y. Braun-Moscovici[1], M. Braun[2], D. Markovits[1] and A. Balbir-Gurman[1]
[1]*Rambam Health Care Campus, Rappaport Faculty of Medicine, Technion, B.Shine Rheumatology Unit, Haifa and* [2]*Beilinson Campus, Sackler School of Medicine, Tel Aviv University, Liver Institute, Petach Tikva, Israel*

Fecal pancreatic elastase-1 is considered to be a sensitive and specific non-invasive exocrine pancreatic function test. Exocrine pancreatic dysfunction had been previously reported in patients with SSc, but the clinical implications are unclear. The aim of this study was to assess fecal elastase-1 in SSc patients and to look for correlation with clinical and laboratory features.

Methods. Thirty-eight Caucasian SSc patients [31 female patients; 24 limited and 14 diffuse disease; mean age 53.6 (15) years; disease duration 6.6 (5.8) years] underwent clinical assessment and laboratory evaluation including fecal elastase-1 and fecal trypsin activity, serum albumin, PTINR and vitamin 25(OH)D. Fecal elastase was measured by ELISA (normal>200 mcgg, moderate pancreatic insufficiency 100–200 mcgg, severe insufficiency <100 mcgg).
Analysis. Spearman's correlation was utilized to find possible correlation between fecal elastase-1 levels and diarrhoea, weight loss, age, disease duration and type, vitamin D, albumin and INR. Multiple linear regression was used to predict the value of one variable from another. The *t*-test and Mann–Whitney rank sum were used to compare the groups with low and normal fecal elastase.
Results. Low levels of fecal elastase-1 were measured in seven patients (18.4%) (moderately reduced in five patients, and severely reduced in two patients). Malignancy was diagnosed in three patients with reduced fecal elastase-1 (bronchio-alveolar carcinoma and gastric carcinoma, respectively, in two patients with moderate insufficiency, pancreatic carcinoma in another patient with severe insufficiency). Another patient with moderately reduced fecal elastase was a past alcoholic. Seventeen patients suffered of recurrent diarrhoea. All patients had normal PTINR, serum albumin and fecal trypsin activity. Vitamin D deficiency was found in 14 patients (41.1%). No statistical significant correlation was observed between low fecal elastase and diarrhoea, weight loss, vitamin D deficiency or the other above parameters. Five-year mortality rate was significantly increased in patients with low fecal elastase, compared with those with normal levels (42.8 and 12.9%, respectively).
Conclusions. We suggest that fecal pancreatic elastase has no role as a screening tool for malabsorption in SSc patients. The high mortality rate and the occurrence of malignancy in patients with low fecal elastase need further investigation.

PS261. SILDENAFIL AND RP IN SSc: RESULTS FROM A RETROSPECTIVE STUDY

S. Bellando Randone[1], S. Guiducci[1], M. L. Conforti[1], J. Blagojevic[1], G. Salvadorini[1], G. Fiori[1], F. Bartoli[1], F. Nacci[1], A. Candelieri[2], C. Bruni[1], A. Moggi Pignone[3] and M. Matucci Cerinic[1]
[1]*Department of BioMedicine, Division of Rheumatology, University of Florence, Florence,* [2]*Department of Information Systems and Comunication, University of Milan Bicocca, Milan and* [3]*Department of Medicine, Division of Medicine, University of Florence, Florence, Italy*

Background. RP is an early sign of SSc. Sildenafil is a selective inhibitor of cGMP-specific phosphodiesterase type 5 and promotes vasodilation effects by enhancing intracellular cGMP levels. For this reason it has been previously used in the treatment of RP.
Objective. Retrospective analysis of the effect of sildenafil (comparing monotherapy, combination therapy and PGE i.v.) on RP after 3 and 6 months of treatment and of the safety profile of this drug.
Methods. The chart of 45 patients with RP secondary to SSc were reviewed and divided into three groups: 15 treated with sildenafil (20 mg three times daily), 15 with combination therapy (sildenafil 20 mg three times daily and PGE i.v. 60 mcg once a week) and 15 with PGE i.v. only (60 mcg once a week). Symptoms were assessed by diary cards including a 10-point Raynaud's condition score (RCS), Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), Scleroderma HAQ (S-HAQ) and videocapillaroscopy (NVC) were performed in all patients at baseline and every 3 months. Results were analysed with the Wilcoxon Mann–Whitney test.
Results. After 6 months of treatment the comparison between the three groups did not show any significant difference in almost all parameters examined. Decrease of RCS was greater in PGE group than in sildenafil group ($P < 0.005$). After 6 months RCS was significantly lower in the combination therapy ($P = 0.008$) and PGE group ($P = 0.008$). Combination therapy was effective immediately in the first 3 months of treatment ($P = 0.005$), while in PGE group only at the 3rd month of treatment ($P = 0.025$). NVC pattern was unmodified in all patients and HAQ was reduced in combination therapy group only ($P = 0.027$). Four patients reported side effects leading to discontinuation of the sildenafil.
Conclusions. This retrospective study indicates that sildenafil is a well-tolerated treatment for RP in SSc patients. Even if our data show that sildenafil monotherapy (20 mg three times daily) does not seem to have a significant effect on RP in SSc, they suggest that combination therapy overlapping sildenafil and PGE may achieve satisfactory results. Long-term study are mandatory to eventually confirm these results, to investigate sildenafil effect on other outcome measures and to determine the optimal efficacious doses.

PS262. THE MODIFIED RODNAN SKIN SCORE AND ITS CLINICAL ASSOCIATIONS IN A MULTINATIONAL PATIENT COHORT—A EUSTAR/EULAR STUDY

M. Becker[1], D. Huscher[2], U. Mueller-Ladner[3], L. Czirjak[4], C. Denton[5], G. Valentini[6], O. Distler[7], Y. Allanore[8], G. The Eustar Centres and [1,2]
[1]*Department of Rheumatology and Clinical Immunology, University Hospital Charite,* [2]*German Rheumatism Research Centre, Leibniz Institute, Berlin,* [3]*University Hospital Giessen, Kerckhoff Clinic, Bad Nauheim, Germany,* [4]*Department of Immunology and Rheumatology, University of Pecs, Pecs, Hungary,* [5]*Royal Free Hospital and University College London, London, UK,* [6]*Clinica Reumatologica, Universita di Napoli, Napoli, Italy,* [7]*Department of Rheumatology and Institute of Physical Medicine, University Hospital Zurich, Zurich, Switzerland and* [8]*Department of Rheumatology A, Cochin Hospital, Paris, France*

Purpose. SSc is characterized by abnormal fibrosis of the skin and other organs as well as autoantibody production indicating autoimmunity. The degree and location of skin involvement reflected by the modified Rodnan skin score (mRSS) determines the subtype of SSc, i.e. diffuse or limited SSc. Preliminary data from a German registry for SSc indicated that some forms of severe organ involvement are equally distributed within the patient population, independently of the skin thickness. The purpose of this study was to validate these data and their implications within the large multinational EUSTAR/EULAR patient cohort.
Methods. We analysed data from over 7300 SSc patients from the EUSTAR/EULAR registry for the distribution of skin thickness as reflected by the mRSS and its clinical associations. In addition, we calculated survival curves according to the mRSS and determined risk factors associated with the mRSS status by multivariate analysis.
Results. The analysis of the EUSTAR patient cohort reveals that skin thickness is not equally distributed within the population and changes over time. Overall, the first 6 years of the disease show the greatest changes in the mRSS. Accordingly, and in contrast to previous reports, various degrees of skin thickness are associated with severe clinical complications such as cardiopulmonary involvement or even death. In addition, the degree of skin thickness determined (SSc-specific and overall) survival and the SSc-specific survival was different of patients with or without a significant increase of the mRSS >6/52 points. A higher mRSS, ACA positivity, an active disease and joint contractures were statistically linked to a further increase in mRSS (more than 6 points) or death by SSc.
Conclusion. Clinical associations and complications change with the mRSS and disease duration in this SSc patient cohort and the development of skin thickness may be important for the risk stratification of patients.

PS263. PRE-SCLERODERMA: PROFILE AND LONG-TERM OUTCOME

B. Rodríguez-Lozano[1], E. Delgado[1], V. M. Flores[1], V. Hernández[1], M. Gantes[1] and S. Bustabad[1]
[1]*Department of Rheumatology, Hospital Universitario de Canarias, La Laguna, Prov. S/C de Tenerife, Spain*

Introduction. Factors that condition evolution of pre-scleroderma (preSSc) to SSc are not well established. Otherwise there are few descriptive epidemiological studies in this time of the disease.
Objective. (i) To describe the pattern of evolution and identify possible predictive risk factors in the preSSc. (ii) To estimate the prevalence of preSSc in patients referred for capillaroscopy during 1999–2010.
Patients and methods. Retrospective study of patients diagnosed with preSSc based on the presence of RP and positive autoantibodies (nucleolar pattern ANA/Scl-70/ACA) and/or capillaroscopic findings of scleroderma pattern. These patients were referred to our Rheumatolgy Department for capillaroscopy during1999–2010. Cutaneous involvement was performed using modified Rodnan score, capillaroscopy by the same observer, ECG, chest X-ray, respiratory function tests, echocardiogram, oesophageal manometry at baseline and end of study. At baseline, none of the patients met the 1980 ACR nor LeRoy and Medsger criteria.
Results. Of 878 patients, 55 patients (6.3%) referred for capillaroscopy were diagnosed as preSSC. Of 320 patients, 19 patients undergoing capilloroscopy during 1999–2002, mean age 52 years (15–62 years) were diagnosed as preSSc and 1 patient with dSSc after first evaluation. Reasons for performing capillaroscopy in the selected population: RP (67%), puffy swollen digits/sclerodactily (12%) and RP with positive Scl-70/ACAa (18%). Baseline capillaroscopic patterns (Maricq): slow scleroderma (36%), active scleroderma (15%), non-specific pattern of connective tissue disorders (31%) and normal (21%). Clinical data: puffy fingers (13%), dysphagia (11. 6%), pathological oesophageal manometry (47%), chest X-ray with interstitial pattern (4.24%) and DL_{CO}/VA alteration in two patients. At baseline, no patients presented sclerodactyly-type skin involvement associated with lung involvement. Follow-up during 9–10 years was performed in 16 patients (two were lost to follow-up and one died after 3 years of diagnosis). Evolution to defined SSc five patients: four dSSc and one lSSc. All these patients at baseline had presented: RP, positive Scl-70 or ACAs, cutaneous involvement as puffy fingers or asymptomatic visceral (oesophageal) type and slow capillaroscopic pattern of scleroderma.
Conclusions: (i) Of all patients referred for capillaroscopy in a 10-year period, 6.3% were diagnosed as preSSc . (ii) In this exploratory study, evolution to defined SSc was observed in 26% of those patients followed up for a 10-year period. (iii) Given the infrequency of this disease, multicentre studies are required to be able to draw conclusions with statistical power. However, all those patients who envolved to SSc presented at baseline: RP, anti-Scl-70 or anti-centromere, puffy fingers or visceral (oesophageal) involvement and slow capillaroscopic pattern of scleroderma.

PS264. EFFICACY AND SAFETY OF INTRAVENOUS CYCLOPHOSPHAMIDE IN SCLERODERMA LUNG DISEASE: 7-YEAR FOLLOW-UP, ONE-CENTRE EXPERIENCE

A. Balbir-Gurman[1], M. Yigla[2], L. Guralnik[3], A. Rozin[1], D. Markovits[1], K. Toledano[1], M. A. Nahir[1] and Y. Braun-Moscovici[1]
[1]*B. Shine Rheumatology Unit,* [2]*Division of Pulmonary Medicine and* [3]*Department of Diagnostic Imaging, Rambam Health Care Campus, The Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel*

Background. Three RCTs demonstrated various efficacy of CYC for treatment of scleroderma (SSc)-associated interstitial lung disease (ILD) with follow-up for 2 years.
Aim. We analysed changes in FVC, DL_{CO}, pulmonary artery pressure (PAP) estimated by ECHO and skin score assessed by modified Rodnan skin score (mRSS) at 4 and 7 years after IV CYC monthly treatment of SSc-ILD.
Methods. Diagnosis of active ILD was based on the presence of ground glass and/or fibrosis on chest HRCT and reduction in FVC and/or DL_{CO} for >10% during two consecutive visits. Patient's data was completed from EUSTAR database at our site. Student's paired *t*-test, Mann–Whitney U-test and Wilcoxon signed-ranks tests were used for statistical analysis.
Results. Among 207 SSc patients registered at our site 42 patients had active ILD. Data of 28 patients (female 78.6%) started CYC before 2007 and 17 patients started before 2004 were eligible. Mean age, disease duration and follow-up period were 50.7 years, 16.3 (17.9) months, 6.5 (6) years. Eight patients died, two patients during first 4 years. Mean cumulative CYC dose was 8.96 (3.8) g. At the end of the first year, FVC and DL_{CO} changed: 78.3 and 75.4% ($P = $ NS); 65.6 and 54.7% ($P < 0.005$). More than 20% FVC, DL_{CO} and mRSS reduction and PAP elevation during 4 and 7 years was registered in 34%/7%; 68%/24%; 80%/7% and 25%/6%, respectively. The rate of annual reduction in FVC, DL_{CO} and mRSS different significantly in the first 4 years and next 4–7 years: 3.2 (2.9) and 0.4 (1.0) ($P < 0.004$); 4.6 (2.9) and 0.9 (1.6) ($P < 0.001$); 1.8 (1.9) and 0.2 (0.2) ($P < 0.002$), respectively. Reduction in mRSS was significant ($P = 0.023$) at both total CYC doses (6 and 12 g). Adverse events were pneumonia, HBV reactivation, Kaposi sarcoma and premature menopause.
Conclusions. IV CYC treatment stabilized FVC up to 1-year follow-up but did not prevent reduction in FVC and DL_{CO} in the next 4 and 7 years. CYC improved mRSS. Treatment with more than 6 g CYC had no additive contribution on lung functions or mRSS. Treatment with CYC was relatively safe. Treatment with CYC is effective for induction of SSc-ILD remission but should be followed by less toxic disease-modifying drugs for maintenance of achieved FVC stability. We suggest that > 24 months of follow-up should be considered in judgement of therapeutic efficacy in RCTs in SSc-ILD.

PS265. MEDIUM AND LARGE VESSEL INVOLVEMENTS CONTRIBUTE TO DIGITAL ULCERS IN SSc

C. Meune[1], M. Meunier[2], **J. Avouac**[2], A. Kahan[2] and Y. Allanore[2]
[1]*Cardiology Department and* [2]*Rheumatology A Department, Paris Descartes University, Cochin Hospital, AP-HP, Paris, France*

Background. Digital ulcers (DUs) are a burden in SSc. Microangiopathy is a cardinal feature of SSc that has a critical role in the development of DU. However, whether injury of the medium or

large vessels also contributes to DU in SSc has been poorly investigated. The importance of large artery stiffening has been highlighted by the observation that aortic pulse wave velocity (PWV), which is inversely related to distensibility, and central augmentation index (AIx), a composite measure that depends on the site and degree of wave reflection, are independent predictors of cardiovascular and total mortality in selected patient groups. In addition, previous reports suggested that AIx is a more sensitive marker of arterial stiffening and risk in younger individuals.
Objectives. To measure PWV and AIx in SSc patients stratified according to the presence of DUs.
Methods. Reflected waves assessed by radial applanation tonometry and PWV were measured and compared in a prospective cohort of consecutive SSc patients with and without active DUs, recruited during a 6-month period.
Results. Sixty-three consecutive SSc patients were included (male 14, age 57 (12) years, diffuse cutaneous form 10, disease duration 9.7 (7.1) years. Among these, 10 SSc patients (15.9%) had active DU. Systolic, diastolic aortic pressure, as well as aortic pulse pressure, were similar in patients with *vs* without active ulcers ($P = 0.104$, 0.531 and 0.143, respectively). Regarding our primary criteria, when compared with patients without ulcer, SSc patients with active DU had increased AIx_75 [35 (28–38) *vs* 29 (21–34)%, $P = 0.048$] without any significance difference in PWV [7.3 (6.7–10.1) *vs* 7.6 (6.7–8.6) m/s, $P = 0.913$]. By univariate analysis, age ($P = 0.002$), the existence of active ulcer ($P = 0.048$) and ESR ($P = 0.010$) are the only associated factors with AIx_75. In bivariate analysis, after adjustment for age, the presence of active ulcer remained a strong determinant of AIx_75 ($P = 0.038$). In addition, the AIx_75 of the reflected wave correlated with age ($r = 0.76$, $P = 0.035$) and NT-proBNP concentration ($r = 0.388$, $P = 0.004$), whereas PWV correlated only with age ($r = 0.520$, $P = 0.001$).
Conclusion. SSc patients with active ulcer have increased AIx_75 but similar PWV when compared with patients without active ulcer. These data suggest that patients with active ulcer have a different arteriolar site of reflection, possibly due to increased peripheral arteries vasoconstrictor tone. If confirmed this could suggest that this vascular component should be targeted by the drug regimen in SSc patients with active DU.

PS266. ULTRA SENSITIVE TROPONIN IN SSc

C. Meune[1], **J. Avouac**[2], C. Gobeaux[3], M. Meunier[2], A. Kahan[2] and Y. Allanore[2]
[1]*Cardiology Department,* [2]*Rheumatology A Department and* [3]*Biochemistry A Department, Paris Descartes University, Cochin Hospital, AP-HP, Paris, France*

Background. Microangiopathy is a cardinal feature of SSc that has a critical role in the development of primary myocardial involvement and possibly pulmonary hypertension. Cardiac troponin (cTn) is the recommended biomarker to detect myocardial injury. The recently developed high-sensitive assays of cTn (hs-cTn) allow the measurement of concentration 20-fold lower than previously. Numerous studies have reported the high prognostic significance of these new assays; moreover some studies reported that hs-cTnT may be elevated in other condition than acute myocardial infarction, including acute and chronic myocardial ischaemia.
Objectives. Our aim was to measure hs-cTn in SSc patients and to examine associated factors with elevated hs-cTn concentrations (99th percentile).
Methods. The plasma HScTnT concentrations were measured using an electrochemiluminescence immunoassay (Roche Diagnostic, Meylan, France) in consecutive stable SSc patients. The 99th percentile, with a CV<10% is achieved for 14 ng/l.
Results. Ninety consecutive SSc patients were included [19 males, age 59 (13) years, diffuse cutaneous form 30, disease duration 10.3 (8.9) years]. A single patient had LEVF <55%; reduced LV/RV contractility, as assessed by Tissue-Doppler echocardiography was detected in 18 patients (36.7%).

Hs-cTnT concentration ranged between 3 ng/l (the limit of detection) and 53 ng/l, with 17 patients (19.5%) having elevated hs-cTnT concentration >14 ng/l (99th percentile). Hs-cTnT correlated with NT-proBNP ($r = 0.52$, $P < 0.001$). By univariate analysis, the following parameters were associated with increased hs-cTnT; age ($P = 0.046$), systolic pulmonary aterial pressure ($P = 0.012$), the presence of ACA ($P = 0.03$), CRP ($P = 0.037$), previous treatment with prednisone ($P = 0.046$) and untreated hypertension ($P = 0.050$). By bivariate analysis, after adjustment for age, the presence of elevated pulmonary artery pressure (sPAP>40 mmHg) remained strongly associated with elevated *vs* normal hs-cTnT concentration ($P = 0.031$).
Conclusion. Hs-cTnT, a strong prognosticator, might be elevated in SSc patient. It correlates with NT-proBNP, a marker of global myocardial involvement. The major determinants of SSc elevation were age, sPAP, ACA and past prednisone treatment that may reflect the severity of the disease. Elevated pulmonary artery pressure remained the main associated factor with elevated *vs* normal hs-cTnT after adjustment for age. The capacity of hs-cTnT to predict pulmonary hypertension occurrence, as well as its prognostic significance, in the context of SSc remained to be established.

PS267. INCOMPLETE THYMIC INVOLUTION IN SSc AND RA

M. Meunier[1], R. Bazeli[2], **J. Avouac**[1], A. Feydy[2], J. L. Drape[2], A. Kahan[1] and Y. Allanore[1]
[1]*Rheumatology A Department and* [2]*Radiology Department B, Paris Descartes University, Cochin Hospital, AP-HP, Paris, France*

Background. The thymus is a central lymphatic organ responsible for many immunological functions, including the production of mature functional T cells and the induction of self-tolerance. Several reports have suggested a potential association between thymus alterations and some immune-mediated rheumatic diseases, with radiological thymic alterations, such as incomplete thymic involution, thymic hyperplasia or thymoma., However, data regarding thymus alterations and SSc or RA are sparse.
Objective. The aim of this study was to evaluate by chest CT scans the frequency and characteristics of incomplete thymic involution, in patients with SSc and RA, together with a non-autoimmune group of controls.
Methods. We performed a retrospective observational study including 161 patients who were at least 40 years old, between 2006 and 2009. These patients comprised 96 SSc patients (median age 59 years, 80% women) and 65 RA patients (median age 57 years, 88% women). All patients had a systematic chest CTscan performed during the usual follow-up of their disease. SSc and RA patients were compared with 32 healthy controls (median age 63 years, 62% women) free of autoimmune disease. For the purpose of our study, complete involution of the thymus was defined as the absence of a residual thymus or a gland thickness, corresponding to the short axis on the axial slice of <7 mm. We defined incomplete involution of the thymus as a residual thymic tissue >7 mm thick.
Results. The frequency of incomplete thymus involution was significantly higher in SSc and RA patients (respectively, 15 and 14%) than in the control group (0%; $P < 0.05$). SSc patients with incomplete thymic involution were younger than SSc patients with complete thymic involution [47 (39–80) years *vs* 59 (39–87) years; $P = 0.002$] and more likely to have pulmonary fibrosis with restrictive syndrome (24 *vs* 0%, $P = 0.03$). There was no correlation between incomplete thymic involution and other SSc-related disease characteristics, especially specific autoantibodies. In RA patients, incomplete thymic involution was more frequently associated with treatment with biologics (100 *vs* 62%; $P = 0.02$) and an absence of ANAs (0 *vs* 32%, $P = 0.05$).
Conclusion. The prevalence of incomplete thymic involution to be higher in SSc and RA patients than in the control group. Our results suggest that incomplete thymic involution is linked to disease severity. Further larger studies are required to confirm this association and clarify the pathological significance of incomplete thymic involution in autoimmune diseases.

PS268. INCREASED RISK OF OSTEOPOROSIS AND FRACTURE IN PATIENTS WITH SSc. A COMPARISON TO RA

J. Avouac[1], E. Koumakis[1], E. Toth[1], M. Meunier[1], E. Maury[1], C. Cormier[1], A. Kahan[1] and Y. Allanore
[1]*Rheumatology A Department, Paris Descartes University, Sorbonne Paris Cité, Cochin Hospital, Paris, France*

Purpose. To investigate whether patients with SSc have increased risk of osteoporosis (OP) and fractures compared with a 'high-risk' population with RA.
Method. Cross-sectional study with successive inclusion of SSc and RA patients matched for age and sex on an 18-month period. Risk factors for OP and fractures were collected for all patients. BMD was assessed at lumbar spine (L1–L4) and total hip region. We included 75 successive patients with SSc (70 women, 93%) and 147 (139 women, 94%) with RA. The mean (S.D.), age of SSc and RA patients was 62 (12) and 61(11) years, respectively; the mean (S.D.) disease duration of SSc and RA patients was 10 (9) years and 18 (13) years, respectively ($P < 0.0001$). RA patients were more likely to receive CSs than SSc

patients [137 (93%) *vs* 45 (60%), $P < 0.0001$]. Cumulative dose of CSs and CRP were significantly higher in patients with RA than SSc [39 554 (29 661) *vs* 19 392 (19 333) mg, $P < 0.0001$ and 12 (16) *vs* 7 (7.9) mg/l, $P = 0.01$].

Result. The prevalence of OP (*t*-score less than −2.5) was 28 and 32% in SSc and RA, respectively ($P =$ NS). BMD (lumbar spine and total hip) was not different between SSc and RA patients. The point prevalence of fractures was 33 and 32% in SSc and RA, respectively ($P =$ NS). In multivariate analysis, patients with SSc and OP ($n = 21$) were more likely to have longer disease duration than patients without OP [odds ratio (OR) 1.11, 95% CI 1.03, 1.21]. There was no association between OP and treatment with CS, systemic inflammation or any SSc feature. In comparison, patients with RA and OP ($n = 47$) were more likely to be older (OR 1.04, 95% CI 1.01, 1.09) and treated with CSs than patients without OP (OR 3.30, 95% CI 1.02, 10.70). Cumulative dose of CSs negatively correlated with BMD measured at lumbar spine ($r = -0.38$, $P = 0.01$) and total hip ($r = -0.49$, $P = 0.008$) in RA patients. In multivariate analysis, SSc and RA patients with fractures ($n = 25$) were more likely to be older (OR 1.10, 95% CI 1.03, 1.18 and OR 1.07, 95% CI 1.02, 1.12, respectively) and to have vitamin D deficiency (OR 5.04, 95% CI 1.27, 20.02 and OR 4.97, 95% CI 1.53, 16.13, respectively).

Conclusion. The prevalence of OP and fracture in SSc patients was comparable with those with RA, highlighting an increased risk of OP and fracture. Age and vitamin D deficiency were found to be important risk factors of fracture. Increasing the awareness to perform BMD measurements and supply vitamin D in patients with SSc may be warranted based on our results.

PS269. B-CELL DEPLETION THERAPY IN LIMITED SSc. A CASE OF RITUXIMAB-INDUCED REGRESSION OF SKIN CALCINOSIS

I. Antonopoulos[1], D. Daoussis[1], S. N. Liossis[1], A. Kazantzi[2], G. Giannopoulos[1] and A. P. Andonopoulos[1]
[1]*Division of Rheumatology, Department of Internal Medicine and* [2]*Department of Radiology, Patras University Hospital, Patras, Greece*

Background. Evidence suggests that B cells may be actively involved in the fibrotic process. Moreover, clinical trials of rituximab (RTX) in diffuse SSc have reported encouraging preliminary results but so far, there are no data on the potential clinical efficacy of RTX in limited SSc. We report herein a patient with CREST syndrome who received RTX treatment.

Case presentation. Our patient, a 53-year-old female, was diagnosed as having CREST syndrome in 1996. The main clinical manifestation was extensive calcinosis at her right knee, right elbow and right thumb; in these areas lesions were sizeable, persistent, frequently ulcerating. The calcinosis at her thumb reduced her grip strength thus causing functional impairment. Her treatment consisted of HCQ, low-dose steroids and diltiazem. She had no symptoms suggestive of interstitial lung disease, pulmonary function tests (PFTs) were normal and did not have pulmonary hypertension. In early 2008, she developed dry cough and her chest high-resolution CT (HRCT) revealed ground glass lesions. She had an FVC and DL_{CO} of 81 and 67% of predicted values, respectively, mild skin thickening with an MRSS score of 8 and an HAQ score of 0.625. In March 2008, she was treated with RTX (4 weekly infusions, 375 mg/m^2 each). In September 2008, her cough improved; PFTs remained stable, MRSS was 6, HAQ score declined to 0.375 and no new calcinosis developed. In March 2009, 1 year from RTX administration, her cough disappeared; FVC and DL_{CO} values were 76 and 66%, respectively. Surprisingly, the calcifications at her knee and elbow had significantly diminished. The thumb lesions had modestly improved but pain was significantly reduced. Again, no ulceration had been noted and the patient did not report draining of calcified material from the affected areas. Based on these, she was retreated with RTX in September 2009. In March 2010, FVC and DL_{CO} reached values of 86 and 78%, respectively, chest HRCT did not show any changes, MRSS was 4, HAQ score further declined to 0.125. Skin calcinosis substantially improved at all sites. She had maintained this stable improved condition at her last visit to the clinic in August 2011 and had not developed any new calcific lesions.

Conclusions. RTX appeared to have a beneficial effect as indicated by the improvement of PFTs, skin thickening and functional status. The effect of RTX on skin calcinosis is noteworthy, because so far there is no effective therapy for this commonly devastating manifestation.

PS270. COMPARISON OF THREE MEASURING SYSTEMS FOR SCORING THE SEVERITY AND CHANGES IN HRCT EXTENT OF INTERSTITIAL LUNG DISEASE IN SSc

L. Ananyeva[1], V. Lesnyak[2], O. Ovsyannikova[1], O. Koneva[1] and D. Goryachev[1]
[1]*Institute of Rheumatology RAMS and* [2]*Clinical Hospital N83, Moscow, Russia*

High-resolution CT (HRCT) is well-established as a sensitive method of detecting and characterizing interstitial lung disease in SSc (ILD-SSc). No agreement has yet been reached on how ILD should be scored, especially on serial CT.

Objectives. To compare three different scales of assessing radiological involvement of lung on HRCT in ILD-SSc and to use these indexes for the assessment of lung damage on serial CT

Methods. We compared three radiological indexes developed by Kazerooni et al., Wells et al. and Warrick et al. Interstitial and alveolar scores of Kazerooni were summed into overall index. Inter-rater reliability was determined for measures of three radiological indexes separately. The agreement of radiological indexes was evaluated for assessment of ILD progression using Cohen's κ. During 2006–08 we prospectively followed 110 patients with ILD-SS. In all of them, HRCT was performed twice over 1 year by one expert (L.V.N). This expert recruited CT scans of six patients with definite improvement and six patients with indubitable progression of ILD. The final cohort consisted of 12 patients, mean age 42 (13.2) years, 11 females, diffuse form 7, limited 5. Overall 24 scans were respectively evaluated by means of three scoring systems by the expert and by three thoracic radiologists, who were blinded to clinical data and the dates of HRCT research.

Results. Intraclass correlation coefficient (ICC) for measures of three radiological indexes (two-way random single measure, type consistency, 95% CI) were the following: Kazerooni—0.56 (0.37, 0.75); Wells—0.76 (0.61, 0.87) and Warrick—0.66 (0,48, 0.81). From a statistical point of view, Well's index was better, so we used it for evaluating Cohen's κ. Agreement in detection of progression of ILD was not satisfactory. The strength of agreement was poor (κ 0, 5), slight (κ 0, 12) or fair (κ 0, 25). The first and the second assessments of the scans did not show any changes of Well's index value. When the dates of HRCT investigations were opened and radiologists independently compared the first and the second scans of all patients, there were no disagreements about the improvement or worsening of CT features of ILD in each case.

Conclusion. The radiological indexes applied with 1-year interval did not reveal the improvements or worsening of CT features of ILD. Our experiments displayed that applied score systems failed to detect evident changes on serial CT scans.

PS271. KIR AND SCLERODERMA IN A PORTUGUESE POPULATION

A. Alves Bandeira Leitão Da[1], **D. Lopes**[1], I. Almeida[1], F. Perneta[1], A. Marinho[1], J. Pestana[1], A. Bettencourt[2], C. Carvalho[2], B. Martins[2] and C. Vasconcelos[1]
[1]*Unidade de Imunologia Clínica – Centro Hospitalar do Porto and* [2]*UMIB – ICBAS – UP, Porto, Portugal*

Background. Scleroderma is an autoimmune disorder of unknown aetiology. A genetic contribution to disease susceptibility has been demonstrated, and genes influencing activation of the immune system have been potentially identified in this process. Activation of T cells is mediated and modulated through T-cell receptors, including killer immunoglobulin-like receptors (KIRs). A positive association between KIR2DS2 and SSc has been reported, in the absence of the corresponding inhibitory KIR2DL2; the presence of these two alleles confers protection to the development of SSc. Because there are still only few studies supporting the role for KIR in disease susceptibility, we sought to determine whether KIR genotypes are associated with SSc in this population, and if they correlate with type of autoantibodies present and SSc phenotypes.

Methods. Sixty-one patients with SSc and 177 healthy individuals were typed for 10 KIR genes using PCR with sequence-specific primers; clinical data were assessed using the Medsger et al. severity scale, performed for each patient at first appointment; ACA, anti-topo (ATA) anti-RNA polymerase III and anti-U3 RNP autoantibodies were included in this study. Comparisons were statistically evaluated using the chi-square or Fisher's exact test.

Results. All KIR2DS2-positive patients were also KIR2DL2 positive. A lower frequency of KIR2DS2 (37.7 *vs* 55.4%; $P = 0.017$) was found in SSc patients compared with controls. No significant associations between KIR genotypes, type of autoantibodies present and SSc phenotypes were observed.

Conclusions. This study confirms the protective role of the KIR2DS2 phenotype, in the presence of KIR2DL2, as previously described by Salim et al., and suggests significant role of the KIR system in SSc. The complexity of this gene system, with its concomitant variety of

phenotype profiles, makes the corroboration of these results in a larger cohort and/or in an independent population mandatory.

PS272. ORAL SUBMUCOSAL FIBROSIS: FIRST CASE REPORT FROM RUSSIA

R. Alekperov[1]
[1]*Institute of Rheumatology, Moscow, Russia*

Background. Oral submucosal fibrosis (OSF) is a chronic disease characterized by inflammation and progressive fibrosis of submucosal tissues of oral cavity. OSF is observed predominantly in South-Asian population.
Objectives. We report the rare case of OSF in female of European origin.
Results. Russian female of age 37 years referred with complain of impossibility of opening her mouth due to adherence of lips and cheeks to gingiva, and as consequences of this, inability to take food and speech abnormalities. Her disease began in 2007 with appearance of reddish spots and small painful aphthae on tongue and gingiva. The aphthous stomatitis reappeared every 1–2 m and was accompanied by low-grade fever. In 2009, the painful oedema and tightening of lips and limitation in the mouth opening appeared. At the same time there were a lot of erosions and herpetiform aphthous ulcers with purulent covering on the labial mucosa and soft palate, the papillomatous outgrowth on the buccal mucosa. A burning sensation and increased salivation appeared. Lesions heal with scarring within 1–1.5 m followed by impaired mouth movements. Her voice got nasal tonality. During 2010 the rapidly progressed inability to open the mouth was observed. Examination showed the high-grade deformity and incomplete closing of lips, sialorrhoea. The dense bands were palpable in the labial thickness and in the area of nasolabial folds. Oral cavity was inaccessible for examination. The laboratory investigations revealed decrease in Hb, protein levels and increase in ESR.
Conclusion. OSF is a devastating disease with high malignant potential. The timely diagnosis is important because the treatment started early may help prevent further damage.

PS273. SSc AND MUCOEPIDERMOID CARCINOMA—A CASE REPORT

A. Aleixo[1], G. Terroso[1], A. Bernardo[1], S. Pimenta[1] and M. Bernardes[1]
[1]*Hospital S. João (Rheumatology Department), Porto, Portugal*

SSc, as other CTDs, is known to increase the risk of malignancy, lung and breast cancer being the most prevalent.
We present the case of a 75-year-old non-smoker female with long-term SSc (skin sclerosis, dysphagia, arthritis, Raynaud with recurrent digital ulcers and pulmonary hypertension, with positive ANAs and anti-Scl70). The patient complained about exertional dyspnoea and weight loss. She had left pleural effusion with haematic fluid compatible with exsudate, without evidence of infection.
The bronchoalveolar lavage cytology was normal. Pleural biopsy by thoracoscopy diagnosed mucoepidermoid carcinoma. Extrapulmonary malignancies were excluded. Bone, left kidney and coeliac lymph node metastasis were found.
Chemotherapy was started, initially complicated by febrile neutropenia. Afterwards she developed a scleroderma flare with marked Raynaud and digital ulcers. The patient maintained high titres of tumoural markers without clinical improvement, so the treatment was stopped at the fourth cycle. Palliative care was provided and the patient died 9 months after the diagnosis.
Pulmonary involvement is the second most frequent organ involvement of SSc and the first cause of mortality. Interstitial lung disease and pulmonary arterial hypertension are the most frequent types of lung involvement. Lung cancer, although rare, causes clinically significant disease to warrant assessment in the SSc patient presenting with respiratory symptoms.
General risk factors are: late-onset disease, marked skin sclerosis, organ fibrosis and male gender. Autoantibodies such as ACAs and anti-topo I are inconsistent in their risk for developing malignancy. Lung cancer usually develops in patients with a prolonged history of SSc and pulmonary fibrosis with female prevalence.
This case stresses the importance of close surveillance. These patients tend to have worst prognosis, especially if they had previous fibrosis.

PS274. USE OF BOSENTAN FOR THE PREVENTION OF DIGITAL ULCERS RELATED TO SSc. RETROSPECTIVE FRENCH STUDY OF 89 PATIENTS TREATED SINCE 2007

C. Agard[1], P. Carpentier[2], L. Mouthon[3], P. Clerson[4], V. Gressin[5], A. Berezne[3], E. Diot[6], P. Jego[7], C. Lok[8], E. Chatelus[9], A. Sparsa[10], A. Khau Van Kien[11], I. Quere[11], J. Sibilia[9] and E. Hachulla[12]
[1]*Internal Medicine, Nantes,* [2]*Vascular Medicine Unit, Grenoble,* [3]*Internal Medicine, Cochin Hospital, Paris,* [4]*Orgamétrie, Roubaix,* [5]*Actelion Pharmaceuticals France, Paris,* [6]*Internal Medicine, Tours,* [7]*Internal Medicine, Rennes,* [8]*Dermatology, Amiens,* [9]*Rheumatology, Strasbourg,* [10]*Dermatology, Limoges, France,* [11]*Vascular Medicine, CHU Montpellier, Montpellier and* [12]*Internal Medicine, Chru, Lille*

Introduction. Bosentan, an ET-1 receptor antagonist, is indicated since 2007 for the prevention of new digital ulcers (DUs) in SSc. The objectives of this study were to identify modalities of bosentan use and the profile of patients receiving such preventive treatment at any time since 2007 in current practice.
Methods. This retrospective observational study was conducted in 2011 in 10 French specialist centres. Patients included were adults with SSc (ACR or LeRoy–Medsger criteria), starting bosentan for prevention of DU between 2007 and 2010. Patients treated with bosentan in clinical trials and patients deceased since the start of bosentan were excluded. From the complete list of eligible patients of each centre, 10 patients were randomly selected.
Results. From 130 eligible patients, 89 patients (mean age 52 years) were drawn. Male-to-female ratio was 1:2.2. SSc was diffuse in 44% of patients; 26% had continuous corticoid therapy; one out of four was active smoker. At start of bosentan, RP was present for 14.7 (12) years. Time since first DU episode was 6.2 (7) years, but 43% of patients had recent ulcerative disease (<3 years). Prior to start of bosentan, ulcerative disease was complicated by autoamputation (8%), surgical amputation (5.6%), osteitis (5.6%) and gangrene (4.5%). Reasons for bosentan prescription were recurring (81%), severe (64%), complicated DU (30%) and failure of other preventive measures including calcium blockers (49%). Initial bosentan dosing was 125 mg/day ($n = 86$); 79 patients received long-term treatment with 250 mg/day. Prescription was seasonal in six patients. During bosentan treatment (mean duration 19 months), 19 patients developed no new DUs. Frequencies of complications were: autoamputation 2.3%, surgical amputation 1.1%, osteitis 1.1% and gangrene 0%. In 18 patients, bosentan was definitively stopped; in 6 of them for hepatic cytolysis (6.7%).
Discussion. Patients treated with bosentan have severe ulcerative disease, which is often resistant to other preventive measures. Among these, male patients and those with diffuse disease forms appear overrepresented. One-quarter of patients present the potentially aggravating factors corticoid therapy and active smoking. In the large majority of cases, target dosing of bosentan was respected; tolerance was satisfactory and comparable with results of previous studies.
Conclusion. This study has created the first national cohort of patients treated with bosentan for prevention of DU in SSc. Ulcerative disease is severe when bosentan is started; reduction of severity is observed during treatment. Male gender and active smoking are suspected to play a role in the severity of ulcerative disease.

PS275. COMORBIDITIES IN PATIENTS WITH SYSTEMIC SCLERODERMA

S. Agachi[1] and L. Groppa[1]
[1]*State Medical and Pharmaceutical University, Kishinau, Moldova*

Background. Both the prognosis and the quality of life in patients with systemic scleroderma (SSc) undoubtfully depend on the comorbidities.
Objectives. To study the prevalence of some comorbidities in patients with SSc and depict correlations with the patients' age and disease duration.
Material and methods. Our study included 75 patients with SSc, out of them only 3 were males. The mean age of the included patients was 43.5 years. Mean disease duration was 16.1 years. Out of them 65 (86.7%) presented with limited SSc, and 10 (13.3%) with diffuse SSc. The average activity was estimated to 4.3 (according to EUSTAR scoring). The diagnosis was established according to the ACR proposed in 1980. The patients were examined comprehensively clinically and paraclinically.
Results. Conditions with mechanisms different from SSc that were not included as complications of the disease or the applied treatment were considered as comorbidities.

The following conditions were registered: urinary infections in 34 (45.3%) patients, nephrolithiasis in 12 (16%) patients, nephroptosis in 8 (10.7%) patients, altered glucose tolerance in 4 (5.3%) patients, 1st type diabetes mellitus in 3 (4%) patients, OA in 11 (14.7%) patients, vertebrogenous radiculopathies in 10 (13.3%) patients, uterine myoma in 5 (6.7%) patients, atherosclerotic discirculatory encephalopathy in

8 (10.7%) patients, ischaemic heart disease in 3 (4%) patients and cataract in 5 (6.7%) patients.

We have depicted a series of correlations in the development of some of comorbidities and, first of all, the age of patients at onset of SSc. In patients, with SSc onset before 30 years of age, the dominant comorbidities were renal disease and disorders of the glucid metabolism, while in those with SSc onset after the age of 30 degenerative disorders of joints and atherosclerotic vasculopathies prevailed.

There was also seen a correlation between SSc duration and onset of comorbidities i.e. such comorbidities as degenerative joint disease and atherosclerotic vasculopathies developed in patients with SSc duration up to 10 years, suggesting possible implication of SSc-specific pathogenic mechanisms in their development and not just belonging to a specific age group.

Conclusions.

(i) In patients, with SSc onset before 30 years of age, the dominant comorbidities were renal disease and disorders of the glucid metabolism, while in those with SSc onset after the age of 30 years degenerative disorders of joints and atherosclerotic vasculopathies prevailed.
(ii) Such comorbidities as degenerative joint disease and atherosclerotic vasculopathies developed in patients with SSc duration up to 10 years, suggesting possible implication of SSc-specific pathogenic mechanisms in their development and not just belonging to a specific age group.

PS276. OPTICAL COHERENCE TOMOGRAPHY VALIDATION: A NEW QUANTITATIVE IMAGING BIOMARKER FOR AFFECTED SKIN IN SCLERODERMA

G. Abignano[1,2], S. Aydin[3], C. Castillo-Gallego[4], A. Meekings[5], D. Woods[5], D. Mcgoonagle[1], P. Emery[1] and F. Del Galdo[1]
[1]*Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK,* [2]*Rheumatology Unit, Second University of Naples, Naples, Italy,* [3]*Goztepe Training and Research Hospital, Istanbul, Turkey,* [4]*Hospital Universitario La Paz, Madrid, Spain and* [5]*Michelson Diagnostics Ltd, Kent, UK*

Background. Skin involvement in SSc is often primary outcome in clinical trials but it is still orphan of a quantitative imaging technique. Optical coherence tomography (OCT) is an emerging imaging technology for clinical examination employing a low-intensity infrared laser beam and providing high-contrast 2-mm deep skin images with a 4 micron resolution. The purpose of this study was to evaluate face validity of OCT in scleroderma.
Methods. Dorsal aspect of forearms was assessed in this study employing topical probe 'VivoSight' (Michelson Diagnostics) and optics of Swept-source Fourier-Domain type with a laser wavelength of 1305 ± 15 nm. A 4-mm area was scanned with 100 scans each of 4 micron thickness. Clinical skin involvement was determined using the modified Rodnan skin score (mRSS). The study included five forearms scored as '3', five scored as '0' and fiev from healthy controls. Matlab software was employed to calculate mean density of the scans. Haematoxylin–eosin (H&E) staining was performed from forearm skin biopsy, within 1 cm of OCT scanned region, in two SSc patients.
Results. OCT images collected in healthy volunteers showed, consistently with published findings, a regular hyper-reflective border of the skin surface (4 micron) and a homogeneous hypo-reflective epidermal layer (60 micron). The papillary dermis was consistently visualized as hyper-reflective area compared with the adjacent epidermis allowing the visualization of the dermal–epidermal junction (EDJ). Mean optical density (OD) data showed that EDJ was an OD nadir region between 60 and 70 micron from the surface, the papillary dermis a high-density region (OD range 0.64–0.72; micron range 60–100) and the reticular dermis had a OD ranging from 0.72 and 0.4. In contrast, SSc-affected tissues (mRSS = 3) showed no EDJ and no increase in OD in the papillary dermis which appeared with a range density of 0.61–0.56. Interestingly, the OD range of this area was almost normal in patients with mRSS = 0 (OD = 0.64–0.67). Validation with H&E staining of two SSc patients with mRSS = 3 in the target region, confirmed the localization of the above-mentioned density areas.
Conclusion. This is a proof of concept validation of face validity of OCT as quantitative imaging technique of scleroderma skin. Sensitivity to change ability of OCT is under evaluation to determine whether the technique could be used as outcome measure of skin involvement in SSc.

PS277. EXTENDED COURSE CYCLOPHOSPHAMIDE AND METHYLPREDNISOLONE PULSE THERAPY CAN STABILIZE INITIALLY REFRACTORY INTERSTITIAL LUNG DISEASE IN PATIENTS WITH SSc: A SINGLE-CENTRE EXPERIENCE

G. Abignano[1,2], F. Del Galdo[1], P. Emery[1] and M. Buch[1]
[1]*Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK and* [2]*Rheumatology Unit, Second University of Naples, Naples, Italy*

Background. Pulmonary arterial hypertension and interstitial lung disease (ILD) are the main causes of scleroderma (SSc)-related deaths [1]. CYC is currently recommended for the treatment of SSc-ILD [2]. The relatively marginal benefit observed [3], however, has questioned the real usefulness.
Objective. The aim of this study was to evaluate the efficacy of a standard protocol of CYC and methylprednisolone (MP) pulse therapy in SSc patients with recently deteriorated ILD. Benefit of additional standard or high-dose pulses in SSc patients with severe ILD was also evaluated.
Methods. The medical records of 55 SSc patients, all fulfilling the ACR classification criteria, treated with CYC/MP pulse therapy for ILD at our centre, were retrospectively reviewed. Patients with overlap syndrome were excluded from the analysis. Complete data were available in 45 patients and included in this study. Patients either had a recent decrease $\geq$10% of the predictive value) of either forced vital capacity (FVC) $\pm$ diffusing lung capacity for CO (DL_{CO}) $\pm$ deterioration of ILD on HRCT chest. All patients received 'standard protocol' i.v. CYC/MP: $\times$6 CYC 15 mg/kg plus MP 10 mg/kg 3- to 4-weekly pulses; 33/45 patients were treated with further pulses (15 mg/kg or 22.5 mg/kg CYC plus MP 10 mg/kg)('extended protocol'). An increase of $>$10% in either FVC or DL_{CO} was considered indicative of improvement in the context of symptoms and chest HRCT findings; a change between 0 and 10% of stable disease; a decrease of $>$10% of worsening. Chest HRCT findings classified patients as improved, stable or worsened compared with ILD-related findings before therapy. Formal scoring is in process.
Results. Of 45 SSc patients, 7 (15.6%) showed improvement in PFT parameters with standard protocol; 20 (44.4%) remained stable; 18 (40%) worsened. In patients requiring extended protocol, 3/33 SSc patients (9%) improved, 8 (24.2%) remained stable; 21 (63%) worsened. PFT at the end of the extended protocol were not available in one case. Chest HRCT showed an improvement in 9 cases and stabilization in 21 cases after six pulses; improvement in 4 cases and stabilization in 18 cases after additional pulses. Overall, 60% of patients had improvement or stabilization of pulmonary function after the standard protocol, 33.2% after the extended protocol.
Conclusion. In this single-centre cohort, CYC/MP pulse therapy stabilized deteriorating ILD (although was not associated with improvement). In refractory disease, additional CYC/MP seemed to minimize continued decline in lung function. Extended course pulse CYC/MP should be considered in initially resistant SSc-ILD.

PS278. CANCER IN SSc: A SINGLE-CENTRE COHORT REPORT

G. Abignano[1,2], H. Lee Hevans[1], P. Emery[1], F. Del Galdo[1] and M. Buch[1]
[1]*Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK and* [2]*Rheumatology Unit, Second University of Naples, Naples, Italy*

Background. Malignancy has been reported in 3.6–10.7% of patients with SSc [1] with lung and breast being the most commonly reported types. The aim of this study was to determine the incidence of cancer in our SSc cohort, describe their demographic and clinical features and any cancer risk factors.
Methods. The medical records of 191 patients admitted to our centre and diagnosed with SSc between 1985 and 2010, all fulfilling the ACR classification criteria, were retrospectively reviewed. The epidemiological and clinical information and any risk factors of the patients with cancer history were compared with those of a gender-matched control group, randomly selected from our scleroderma database. Unpaired two-tailed *t*-test was used to compare groups. Qualitative variables were compared using Fisher's exact test. Data were analysed using GraphPad Prism software.
Results. Of 191 SSc patients, 18 (9.4%) were found to have a history of cancer. Twenty-one primary cancers were identified. Breast cancer was the most frequent (seven cases, 3.6%), followed by non-melanoma skin cancer (four cases, 2.1%; three basal cell carcinoma, one squamous cell carcinoma), lung cancer (three cases,

TABLE 1.

Parameters	Post-SSc cancer ($n=15$)	Pre-SSc cancer ($n=2$)	Post-SSc cancer *vs* pre-SSc cancer (*P*-value)	Pre- and post SSc cancer ($n=1$)	SSc no cancer ($n=18$)	All SSc-cancer ($n=18$) *vs* controls (*P*-value)
Gender, male/female, *n*	2/13	0/2	1	0/1	2/16	–
Subset, L/D, *n*	12/3	2/0	1	1/0	13/5	0.69
ANA $^+$, *n* (%)	14 (93.3)	2 (100)	1	1 (100)	17 (94.4)	1.5
ACA $^+$, *n* (%)	7 (46.6)	0 (0)	0.48	1 (100)	5 (27.7)	0.49
AntiScl-70 $^+$, *n* (%)	3 (20%)	1 (50%)	0.43	0	6 (33.3)	0.71
Age at SSc onset, mean (S.D.), years	52.9 (17)	47.5 (3.5)	0.67	65	37.9 (18.2)	0.0123
Age at cancer dx, mean (S.D.), years	63.4 (11.3)	42 (4.2)	0.02	41	–	–
Family malignancy history, *n* (%)	1 (6.6)	1 (50)	0.23	0	3 (16.7)	1
ILD, *n* (%)	7 (46.6)	0 (0)	0.49	0	5 (27.7)	0.72
Tobacco, *n* (%)	5(33.3)	1 (50)	1	0	4 (22.2)	0.71
Alcohol, *n* (%)	0 (0)	0 (0)	–	0	1 (5.55)	1
CYC, *n* (%)	8 (53.3)	1 (50)	1	0	3 (16.6)	0.075
MMF, *n* (%)	2 (13.3)	1 (50)	0.33	0	2 (11.1)	1
AZA, *n* (%)	0 (0)	0 (0)	–	0	0 (0)	–
MTX, *n* (%)	0 (0)	1 (50)	0.12	0	2 (11.1)	1

1.6%), non-Hodgkin's lymphoma (three cases, 1.6%), melanoma (one case, 0.5%), myeloma (one case, 0.5.%), colon (one case, 0.5%) and parotid cancer (one case, 0.5%). In two patients, cancer preceded the SSc onset (one breast cancer, one non-Hodgkin's lymphoma). One patient had two primary cancers, breast and colon, before and after the SSc onset, respectively. Comparing the two groups with gender-matched controls, we found that cancer diagnosis occurred at a younger age in patients that developed SSc after the malignancy ($P=0.02$). Patients with cancer developed SSc at an older age compared with controls ($P=0.0123$). No difference was found in any risk factors. The risk associated with the CYC therapy in SSc patients with cancer was nearly significant ($P=0.075$) (Table 1).

Conclusion. In line with previous reports, we found breast and lung cancer among the most common types of malignancy in our SSc patients. High incidence of non-Hodgkin's lymphoma cases was also observed. Although not mostly associated in SSc patients, a relatively high incidence of non-melanoma skin cancers was noted in our cohort; the small studied population may underlie these findings. With the limitations of a case–control study, no risk factors were identified, except for the nearly significant risk associated with the CYC therapy.

PS279. PEYRONIE'S DISEASE AND SSc, A CASE REPORT

A. Abdessemed[1], N. Khaldoun[1], N. Brahimi[1] and A. Ladjouze[1]
[1]*Department of Rheumatology, EHS Hopital de Ben Aknoun, Algiers, Algeria*

Background. SSc is a chronic autoimmune disease characterized by microvascular disease and abnormal fibrotic processes that can affect multiple organ systems.

Peyronie's disease is a localized connective tissue disorder that primarily involves the tunica albuginea of the corpora cavernosa of the penis. Francois de La Peyronie first described the condition in a treatise on ejaculatory failure. It usually presents with palpable induration of the penis. The formation of fibrotic plaques in the tunica albuginea and surrounding cavernosal tissue alters anatomy and cause acquired penile deformities during erection with different degrees of bending and narrowing. This condition presents with or without penile pain as well as erectile dysfunction. The cause of this disorder is unknown.

Case report. Male, 56 years old, diagnosed as having a lcSSc since 1993. He had RP, cutaneous telangiectasis, erosive arthropathy and gastro-oesophageal reflux. There was no evidence of pulmonary and cardiovascular involvement. ANA and ACPA were positive in high titres.

Recently the patient complained of penile pain and curvature, erectile dysfunction and sexual disability. Urological evaluation revealed Peyronie's disease. Penile Doppler ultrasonography was normal.

He was treated with vitamin E and colchicine.

Conclusion. Few cases of Peyronie's disease in SSc were described. This disease may cause impotence, although as noticed by other authors the more common cause of impotence in patients with scleroderma is the vascular involvement that limits the blood flow of the arteries of the penis. Treatment of Peyronie's disease seems difficult.

Oral therapies most commonly employed include tocopherol (vitamin E) and para-aminobenzoate, with colchicine. Surgical approaches have also been tried with variable success.

PS280. LOCALIZED SCLERODERMA-ASSOCIATED JUVENILE IDIOPATHIC ARTHRITIS OR MORPHOEA WITH EXTRACUTANEOUS MANIFESTATIONS

A. Abdessemed[1], N. Khaldoun[1], N. Brahimi[1] and A. Ladjouze[1]
[1]*Department of Rheumatology, EHS Hopital de Ben Aknoun, Algiers, Algeria*

Background. Scleroderma is a rare condition in children. As in adults, two main distinctive categories are known: juvenile SSc and juvenile localized scleroderma, which for the most part, is a benign, self-limited condition with manifestations confined to the skin and/or subcutaneous tissues. Some limited case reports have suggested that localized scleroderma is not always a purely cutaneous disease.

Case report. We report the case of a 12-year-old girl, presenting since the age of 10 years arthritis and RP. Cutaneous examination was normal. ESR was elevated, ANA and ACPA were negative, RF was positive. X-ray and ultrasonography of the wrists and the hands were normal. She was diagnosed as having RF-positive polyarticular JIA. The patient was treated with MTX (10 mg/m^2 once per week) and oral steroids. Two months later the girl developed plaque morphoea. Doppler echocardiography, respiratory function test, thoracic high-resolution CT, endoscopy, manometry and nail-fold capillaroscopy were normal. She was negative for relapsing fever. The doses of MTX and steroids were increased. She also benefited from a treatment with HCQ, topical steroids and emollient cream. Six months later, she improved; there was no occurrence of new lesions.

Discussion. Articular manifestations were present before cutaneous lesions, but the patient did not have erosions or deformity. Arthritis was completely unrelated to the site of the skin lesion. Arthritis and arthralgia can occur in 45% of patients with localized scleroderma. RF can be positive in 15% of patients. So the patient was diagnosed as having morphoea with articular involvement.

Conclusion. Patients with juvenile localized scleroderma can have extracutaneous manifestations particularly joint involvement.

PS281. CLINICAL AND RADIOLOGICAL FEATURES OF THE HAND AND THE FOOT IN SSc

A. Abdessemed[1], N. Khaldoun[1], N. Brahimi[1] and A. Ladjouze[1]
[1]*EHS Hopital de Ben Aknoun Department of Rheumatology, Algiers, Algeria*

Objective. To assess clinical and radiological hand and foot features in a retrospective study of SSc patients.

Patients and methods. Clinical records of 101 SSc patients fulfilled the ACR classification criteria and/or LeRoy and Medsger classification criteria, admitted to rheumatology department between 1986 and 2010, were reviewed. All the patients underwent clinical examination and X-ray

Hand disability was assessed by the Cochin Hand Function scale (CHFS)

Results. Among the patients included in the study 89 were women and 12 men with a median age of 40 years and disease duration of 6 years. Of the patients, 25% had a diffuse scleroderma, 75% had a

limited scleroderma. All the patients had RP, 46% had digital ulcers, 65% oesophageal dysmotility and reflux oesophagitus, 22% had an Interstitial lung disease and 16% a PAH.

Hand features were arthritis 47%, arthralgia 36%, Jaccoud's arthropathy3%, flexion contracture 32% and digital amputation 11%.

X-ray of the hand showed: erosive arthropathy 15%, OA 3%, acro-osteolysis 35% and calcinosis11%.

The mean CHFS for the entire group was 24.6. Foot features were arthritis 13%, erosive arthropathy 7%, acro-osteolysis 7% and calcinosis 3%.

Conclusion. Osteoarticular and soft tissue involvement are more frequent in the hand and are a source of disability.

PS282. PROTECTIVE EFFECTS OF ILOPROST INFUSION MAINTENANCE THERAPY FOR PULMONARY HYPERTENSION IN PATIENTS WITH RP ASSOCIATED WITH SCLERODERMA AND OTHER COLLAGEN VASCULAR DISEASES

S. Aamar[1], R. Carmel[1], S. Omar[1] and D. Livovsky[1]
[1]*Hadassah Mount Scopus Hospital, Jerusalem, Israel*

Pulmonary arterial hypertension (PAH) is one of most important complications of SSc (scleroderma) and is associated with high morbidity and mortality rate. Range of physical activity and function limitations are WHO classified I–IV and management is tailored for the different class. i.v. Epoprostenol and i.v. Iloprost have limited use and are reserved for the advanced disease and Class >III and Class IV.

We present our cohort of patients suffering from symptomatic RP with and without digital ulcers, who are treated with i.v. Iloprost vasodilator. The regular regimen is i.v. iloprost at weekly basis titrated to a tolerated dose and body weight. Most RP subjects are middle-aged females and have an underlying collagen vascular disease including scleroderma, CREST syndrome, SLE and MCTD. The range of time period of weekly Iloprost maintenace therapy for RP is between 6 months and 10 years. Patient-years data from the last decade show that Iloprost-treated patients due to RP had no new presentation of PAH complication.

These data strongly suggest the positive effect of i.v. Iloprost use in preventing the manifestation of pulmonary hypertension. Annual screening for pulmonary hypertension in scleroderma (and other CTDs) is highly important but RP-protocol of Iloprost use is a promising recommendation for early prevention and control of pulmonary hypertension.

PS283. LONG-TERM ORAL CYCLOPHOSPHAMIDE THERAPY IN SSc: EXPERIENCE OF A SINGLE CENTRE

S. Calvisi[1], A. Vacca[1], P. Garau[1], M. Piga[1], A. Floris[1] and A. Mathieu[1]
[1]*Unit and Chair of Rheumatology, AOU of Cagliari, Cagliari, Italy*

Introduction. CYC despite its toxicity remains the most widely used drug for SSC-related interstitial lung disease (SSc-ILD). However, a definition of the best treatment available as well as the optimal dosage, duration of therapy and way of administration are still a matter of debate. Some authors suggested that a prolonged CYC regimen might be more effective than a shorter course.

Objectives. To evaluate safety and efficacy of a long-term treatment with monthly oral CYC in combination with low or high doses of prednisone in patients with SSc-ILD.

Methods. Twenty-two patients with SSc who demonstrated active alveolitis were retrospectively included in this study. A complete clinical examination, high-resolution CT (HRCT) scan, pulmonary function tests (PFTs) were performed before therapy, and annually during the follow-up [86.6 (47.4) months]. Patients were treated with oral CYC at the dosage of 50 mg/day, for consecutive 10–15 days per month for 63.8 (34.2) months, in association with oral prednisone at low (<10 mg/day; $n = 9$) or high doses (>10 mg/day; $n = 13$).

Results. The overall CYC dosage reached was 39 (28.7) g. The differences between diffusion lung capacity for carbon monoxide (DL_{CO}) and forced vital capacity (FVC) performed at baseline and every year of follow-up were <15% and 10%, respectively; moreover, they remain stable after CYC discontinuation. In multivariate analysis, an improvement of ≥15% in DL_{CO} after CYC discontinuation significant correlated with limited SSc, early disease, severe ILD, elevated acute-phase serum proteins. On HRCT we observed a regression of ground-glass (GG) pattern in 77% of the patients. Decrease of GG was mostly detected in the first year of therapy ($P < 0.01$) and when the GG was the predominant pattern. Disease activity estimated by European disease activity score, improved significantly after the first year ($P < 0.01$) and then stabilized during the follow-up. Medsger severity scale score remained overall stable. Rodnan skin score remained unchanged. Ten out of 22 patients (45%) developed adverse events that require drug withdrawal just in seven cases. Three patients died for not related drug causes. No side effects were reported after the drug withdrawal.

Conclusions. In our series of patients, oral long-term therapy with CYC appears encouraging in ameliorating and/or stabilizing lung function and HRCT pattern in SSc-ILD, with favourable results lasting up after interruption. Therapy was overall well tolerated with no life-threatening or irreversible adverse reactions. Future controlled investigations are warranted.

PS284. SSc WITH AND WITHOUT PULMONARY ARTERIAL HYPERTENSION COMPARED TO IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION. DIFFERENT BEHAVIOUR OF SOME ANGIOGENETIC BIOMARKERS

K. Stefanantoni[1], I. Sciarra[1], N. Iannace[1], M. Vasile[1], E. Crescenzi[2], S. Papa[2], R. Poscia[2], R. Badagliacca[2], C. D. Vizza[2] and **V. Riccieri**[1]
[1]*Dipartimento di Medicina Interna e Specialità Mediche and*
[2]*Dipartimento di Malattie Cardiovascolari e Respiratorie, Sapienza Università di Roma, Rome, Italy*

Background. The SSc vasculopathy greatly depends on an impairment of different angiogenic and angiostatic factors. Pulmonary arterial hypertension (PAH), a severe complication in 10–15% of the SSc patients, is strictly related to the vascular involvement and is characterized by a remodelling and occlusion of pulmonary arterioles. Compared with the idiopathic form of PAH (iPAH), SSc cases seem to behave differently, especially concerning prognosis or response to treatment.

Thus we decided to measure plasma levels of nine molecules, involved in the endothelial damage, in a group of SSc patients with and without PAH and in iPAH subjects.

Methods. We enrolled 12 SSc patients with PAH, 12 ScS patients without PAH and 13 iPAH cases, all matched for sex, age and disease duration. Pulmonary arterial pressure was evaluated through echocardiography and confirmed by right heart catheterization.

Plasma levels of angiopoietin-2 (Ang-2), follistatin, granulocyte-colony stimulating factor (G-CSF), hepathocyte growth factor (HGF), IL-8, Leptin, platelet derived growth factor-BB (PDGF-BB), platelet endothelial cellular adhesion molecule-1 (PECAM-1) and vascular endothelial growth factor (VEGF) were measured using commercially available multiplex bead-based sandwich immunoassay kits (Human Angiogenesis 9-Plex Panel, Bio-Rad Laboratories).

Results. We detected significantly increased serum levels of Leptin ($P < 0.0001$ and $P < 0.0003$ respectively), PDGF-BB ($P < 0.003$ and $P < 0.0001$, respectively) and PECAM ($P < 0.01$ and $P < 0.0002$, respectively) in SSc patients with or without secondary PAH compared with those with iPAH. Plasma levels of Ang-2 were significantly higher in the two groups of patients with PAH with respect to the group of SSc patients without PAH ($P < 0.04$ in both cases), while SSc patients with PAH had higher levels of IL-8 with respect to iPAH subjects ($P < 0.003$).

SSc patients without PAH had higher serum levels of PDGF-BB ($P < 0.04$) and PECAM-1 ($P < 0.04$) compared with SSc patients with PAH and decreased serum levels of G-CSF ($P < 0.02$) with respect to iPAH cases.

Conclusions. Our findings seem to underline a different behaviour of specific vascular biomarkers in SSc patients, with or without PAH, as well as in iPAH patients. These molecules may have a different role in each group of patients, partly explaining the different behaviour of iPAH respect to secondary PAH, although further studies are needed to define the function of these biomarkers that may lead to better evaluate and treat these patients.

PS285. N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE LEVEL IN SSc

S. Pinto[1], T. Videira[1] and P. Ferreira[1]
[1]*Centro Hospitalar Vila Nova Gaia, Vngaia, Portugal*

We evaluated the clinical significance of serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level in SSc.

We studied 25 SSc patients of mean age 41.1 (10.3) years with a mean duration of disease 7.2 (6.0) years and 25 age- and sex-matched healthy controls.

Patients were subjected to modified Rodnan skin score (mRss). Systolic pulmonary artery pressure was measured by echocardiography. Lung involvement was evaluated by pulmonary function testing and by using high-resolution CT scores. Assay of serum NT-pro BNP was done for all patients and controls.
NT-proBNP levels were significantly higher in patients with SSc compared with healthy controls.
There was a significant positive correlation between serum levels of NT-proBNP in SSc patients and mRss and systolic pulmonary artery pressure (sPAP).
There was no significant correlation in the mean value of serum levels of NT-proBNP and percentage of carbon monoxide diffusion capacity (DL_{CO}) in SSc patients with restrictive pulmonary affection compared with those with normal respiratory function test.
Our small suggests that serum NT-proBNP may be a biologic marker of skin fibrosis and pulmonary vascular involvement in SSc.

PS286. TRENDS IN MONITORING AND MANAGING SSc IN A SINGLE EUSTAR CENTRE

A. M. Gherghe[1], C. Mihai[1], M. Bojinca[1], A. Soare[1], A. Lupu[1], I. Ancuta[1], M. Milicescu[1], L. Macovei[1], R. Sfrent-Cornateanu[1], R. C. Ionitescu[1], R. Jurcut[2], A. Calin[2], T. Constantinescu[3], S. Arama[1] and V. Stoica[1]
[1]*Cantacuzino Hospital,* [2]*CC Iliescu Institute of Cardiology and* [3]*M Nasta Institute of Pneumology, Carol Davila University, Bucharest, Romania*

Background. The management of SSc is still largely perfectible, as relatively few drugs have proven efficacy in clinical trials and even fewer can be regarded as disease-modifying treatment. The 2009 EULAR/EUSTAR recommendations for SSc management support the use of evidence-based drugs.
Objectives. To assess the changes of investigations and treatment of SSc patients visiting our clinic since the publication of the EULAR/EUSTAR treatment recommendations.
Patients and methods. We included all the SSc patients of our EUSTAR centre registered in the MEDS-online database with at least one visit after January 2009 and we assessed the treatment and the investigations performed. We compared them with a cohort including all SSc patients examined in our clinic from 2003 to 2005.
Results. Fifty SSc patients, among which six (12%) men, aged 18–71 [mean (S.D.) 53.1 (12.8)] years were recorded in the MEDS-online database from 1 January 2009 to 31 July 2011 (first visit or follow-up) and 36 SSc patients, among whom 5 (13.9%) men, aged 28–79 [mean (S.D.) 51.4 (12.7)] years were examined in our clinic between 2003 and 2005. ACR criteria for of SSc were fulfilled by 48 (96%) MEDS patients and 36 (100%) comparison cohort (CC) patients. All patients had ECG and chest X-ray done yearly in both groups and 10 patients (20%) in the MEDS group *vs* none in the CC had lung high-resolution CT performed on the first visit. On the last visit recorded in MEDS, 27 (54%) and 28 (56%) patients performed pulmonary function tests + DL_{CO} and cardiac US with power Doppler, respectively, compared with 21 (56.8%) and 7 (18.9%), respectively, in the CC.

Immunosuppresive treatment was prescribed to 19 (38%) MEDS patients and 5 (13.9%) CC patients as follows: CYC in 8 *vs* 8.3%, MTX in 12 *vs* 0 and AZA in 18 *vs* 5.5% cases. Low-dose glucocorticoids were recommended in 12 (24%) MEDS and 19 (51.4%) CC patients. D-penicillamine was received by 1 (2%) *vs* 11 (29.7%), HCQ in 0 *vs* 3 (8.3%) and colchicine in 0 *vs* 6 (16.2%) MEDS and, respectively, CC patients. Proton pump inhibitors were recommended in 46 (92%) *vs* 26 (70.3%) and calcium channel blockers in 36 (72%) *vs* 24 (64.9%) MEDS and CC patients, respectively. Only MEDS cohort patients received IV prostacyclin (two cases, 4%).
Conclusion. Changes in disease monitoring and management have been performed in agreement with the EUSTAR recommendations, but there are still difficulties in the accessibility of some drugs and investigations.

PS287. OUTCOMES OF SSc ASSOCIATED POLYARTHRITIS OR MYOSITIS IN PATIENTS TREATED BY BIOTHERAPIES TOCILIZUMAB OR ABATACEPT: A EUSTAR OBSERVATIONAL STUDY

M. Meunier[1], M. Matucci[2], B. Maurer[3], G. Riemekasten[4], R. Pellerito[5], C. A. Von Mulhen[6], V. Vacca[7], P. Airo[8], F. Bartoli[2], G. Fiori[2], M. Bokarewa[9], O. Disler[3] and Y. Allanore[1]
[1]*Rheumatology A Department, Paris Descartes University, Paris, France,* [2]*Department of Biomedicine, Section of Rheumatology, Florence, Italy,* [3]*University Hospital Zurich, Zurich, Switzerland,* [4]*Department of Rheumatology and Clinical Immunology, Charité University Hospital, Berlin, Germany,* [5]*Division of Rheumatology, Ordine Mauriziano Hospital, Turin, Italy,* [6]*Rheumatology Department, Saint Lucas Hospital, Pontifical Catholic University of Rio Grande do Sul, Porto Allegre, Brazil,* [7]*Chair of Rheumatology II, Department of Medical Sciences, Cagliari,* [8]*Rheumatology and Clinical Immunology Service, Brescia, Italy and* [9]*Institute of Medicine, Gothenburg, Sweden*

Introduction. Musculoskeletal involvement is frequent in SSc. Treatment is not standardized and polyarthritis is not uncommonly refractory to DMARDs. Tocilizumab and abatacept have proven to be effective in RA. The aim of this prospective multicentre observational study was to evaluate the safety and effectiveness of tocilizumab and abatacept in SSc-polyarthritis or SSc-myositis.
Methods. By querying the EUSTAR network, 16 SSc patients with active polyarthritis and insufficient response to DMARDS and seven patients with active myositis and insufficient response to immunosuppressants were included. According to the decision of their physician, 12 patients received tocilizumab (8 mg/kg/month) and 11 patients abatacept (10 mg/kg/month). All patients with myositis received abatacept. Clinical and biological assessments were carried out at treatment initiation and at last infusion.
Results. In SSc patients, mean follow was 9.7 (8) months, mean disease duration 9 (5) years. Of 15 patients, 9 had dcSSc, 6 patients had positive anti-CCP antibodies. Eight of 15 patients received biotherapy in association with DMARDs.

Tocilizumab induced a significant response for joint involvement with a mean decrease of DAS-28 of 2 [2.8 (1) at last infusion *vs* 4.9 (1) at baseline, $P < 0.001$] and swollen joints of 3.9 [0.9 (2) *vs* 4.8 (4)]. Of 12, 8 patients achieved EULAR good response. Rodnan's skin score and HAQ did not significantly change. Treatment was stopped for three patients: two because of treatment failure and one for liver cytolysis.

Abatacept induced a significant response for joint involvement with a mean decrease of DAS-28 of 1.8 [2.6 (1) *vs* 4.4 (1) at baseline, $P = 0.03$] and swollen joints of 3.8 [0.2 (1) *vs* 4 (2)]. Three of four patients fulfilled EULAR good response. Rodnan's skin score did not significantly change, neither did HAQ. Among SSc-myositis patients, five of seven had biopsy-proven myositis, with a 20 (10) months follow-up. Abatacept induced a response for joint involvement and myositis, as DAS-28, VAS activity and CK decreased, respectively, of 1.9 [2.2 (1) *vs* 4.1 (1)], 15/100 [30 (37) *vs* 50 (25)] and 707 ng/l [291 (289) *vs* 998 (1103)]. No safety issue for abatacept use was raised during this trial.
Conclusion. In this preliminary pilot study, tocilizumab and abatacept appeared to be safe and improved joint involvement in refractory SSc-arthritis and SSc-myositis patients. Follow-up is too short to estimate the impact on fibrotic lesions. A larger number of cases is expected to be included with EUSTAR network support. Larger studies with longer follow-up are warranted to further determine the safety and efficacy of these drugs in SSc, and potentially raise the opportunity of developing randomized controlled trials.

PS288. BETTER SURVIVAL IN SSc-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION PATIENTS ENROLLED IN THE PULMONARY HYPERTENSION ASSESSMENT AND RECOGNITION OF OUTCOMES IN SCLERODERMA REGISTRY

L. Chung[1,2], R. Domsic[3], B. Lingala[1] and V. Steen[4] and the PHAROS Investigators
[1]*Stanford University, Stanford,* [2]*Palo Alto VA Health Care System, Palo Alto, CA,* [3]*University of Pittsburgh, Pittsburgh, PA and* [4]*Georgetown University, Washington DC, USA*

Background/purpose. Patients with SSc-associated pulmonary arterial hypertension (SSc-APAH) experience poorer outcomes than patients with idiopathic PAH and other forms of CTD-APAH. We sought to assess cumulative survival rates and identify independent predictors of mortality in patients with incident SSc-APAH from the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) registry.
Method. PHAROS is a multi-centre prospective registry of SSc patients at high risk for PAH or with definite PH diagnosed by right heart catheterization (RHC) within 6 months of enrolment. Only patients with World Health Organization Group I PAH [mean pulmonary artery pressure (mPAP) = 25 mmHg and pulmonary capillary wedge pressure = 15 mmHg without significant interstitial lung disease] were included in these analyses. Kaplan–Meier curves were estimated for survival from the time of the diagnostic RHC. Differences in outcomes between subgroups were assessed by the log-rank test. Univariate and multivariate Cox regression models were used to identify

significant predictors of mortality. Backward selection was used to determine the final model retaining only variables with $P < 0.05$.
Result. A total of 131 patients with incident PAH had a mean age of 60.4 (10.4) years and disease duration from first non-Raynaud symptom of 10.2 (9.4) years. Of the patients, 84% were female, 82% Caucasian, 70% had limited cutaneous disease and 34% were ACA positive. Mean 6-min walk distance (6MWD) was 339 (130) m, diffusing capacity of carbon monoxide (DL_{CO}) 42 (16)% predicted, mPAP 36.7 (10.3), pulmonary vascular resistance (PVR) 5.5 (3.1) WU and creatinine 1.0 (0.6). A 34% had a pericardial effusion; 55% were functional class (FC) I or II and 5.3% were FC IV. Twenty-four (18%) patients died over a mean follow-up of 2.0 (1.4) years. The 1-, 2- and 3-year survival was 93, 88 and 75% in the overall cohort. Four (17%) deaths were known to be unrelated to cardiopulmonary causes (two renal crisis, one cancer, one infection). The following variables were significant predictors of mortality in univariate analyses: FC IV (HR 6.0, 95% CI 2.0, 18.2), $DL_{CO} < 39\%$ predicted (HR 4.3, 95% CI 1.6, 11.9), and PVR > 4.6 WU (HR 3.4, 95% CI 1.3, 8.7). Age >60 years, presence of a pericardial effusion, 6MWD<165 m, mPAP > 35 mmHg, ACA positivity and creatinine did not predict death. On multivariate analysis ($n = 77$), FC IV (HR 4.7, 95% CI 1.4, 15.6, $P = 0.01$) and $DL_{CO} < 39\%$ predicted (HR 8.3, 95% CI 1.7, 40, $P = 0.008$) remained significant predictors of mortality.
Conclusion. The 75% 3-year survival of SSc patients with incident PAH followed at scleroderma centres involved in the PHAROS registry was higher than other recently described cohorts. FC IV status and $DL_{CO} < 39\%$ predicted at the time of diagnosis are strong predictors of death.

PS289. EOSINOPHILIC FASCIITIS

M. Meurer[1]
[1]*University Hospital Dresden, University Allergy Center, Dresden, Germany*

Introduction and objectives. A number of clinical conditions present with pronounced skin fibrosis and may be confused with SSc. Eosinophilic fasciitis (EF) characterized by SSc-like skin changes and painful induration of subcutaneous tissues, first described by Shulman in 1974, occurs spontaneously in adults but rarely in children. New cases are being reported from all over the world making EF one of the more common SSc-like fibrosing disorders.
Materials and methods. Applying a new diagnostic system for the classification of EF, we retrieved from 196 publications 169 cases with definite EF and compared their relevant clinical data with those from 13 patients seen in the Department of Dermatology, University Hospital Dresden.
Results. The meta-analysis showed the mean age of all EF patients being 41.4 years; the male/female ratio was almost equal. Leading clinical symptoms were symmetrical indurations involving the upper ($n = 108$) and the lower extremities ($n = 90$); whereas head and neck were only rarely involved ($n = 11$). Diffuse swelling of affected skin was less frequently reported as were contractures of the upper limbs ($n = 75$) or lower limbs ($n = 36$). The frequently cited peau d'orange was seen only in 20% of EF patients. Morphoea-like plaques were reported in 2.4%, SSc-like microstomia only in 1.2% and Raynaud's syndrome in 5.3%. Only 11.2% were ANA positive, SSc-specific autoantibodies were not detected. Blood eosinophilia was present in 77%. When bone marrow puncture was performed, 38% specimen showed tissue eosinophilia. Skin biopsy results confirmed typical thickening of the fascia with eosinophilic infiltration in >80%.
Conclusions. The comparison of published cases of definite EF with our EF patients showed the strikingly uniform clinical expression and course of this unusual tissue disorder in which the diagnosis relies on a few typical clinical signs and histological changes only. The mechanism triggering tissue eosinophilia and diffuse thickening of fascia mainly involving the limbs remains unknown; there is no overlap between EF and SSc and rare EF cases with morphoea-like lesions can be correctly classified upon our diagnostic criteria.

PS290. NAIL-FOLD CAPILLAROSCOPY IN SYSTEMIC AUTOIMMUNE DISEASES: THE SCLERODERMA PATTERN AND THE 'CONNECTIVE (TISSUE DISEASE)' PATTERN

L. Sáez[1], J. Velilla[1], M. Pérez-Conesa[1], N. Guiral[2], P. Casanova[2], C. Vallejo[2] and O. Gavín[2]
[1]*Unidad de Enfermedades Autoinmunes Sistémicas, Servicio de Medicina Interna and* [2]*Servicio de Medicina Interna, Hospital Universitario Miguel Servet, Zaragoza, Spain*

Objective. To describe the findings of the capillaroscopies performed in our unit in last 3 years.

To analyse capillaroscopic features in the scleroderma and 'connective' (tissue disease) pattern.
Methods. Retrospective study of capillaroscopies performed in our unit since 24 June 2008 to 21 June 2011. Eight fingers of both hands were examined, with the stereomicroscope Zuzi 235. Clinical data analysed were: gender, age, service of origin, RP and its duration. Capillaroscopic data were: médium capillary size, number of megacapillaries, morphological changes, capillary loss and pallor of the bed of capillaries. Each capillaroscopy was classified as non-specific, connective pattern (capillaroscopy changes but not indicative of SSc) and scleroderma pattern (Cutolo's classification). Each pattern was compared with each other using chi-square for univariate analysis and logistic regression for the multivariate analysis. SPSS 15.0 was used for the statistical analysis.
Results. A total of 612 capillaroscopies were done over 3 years, 425 (81.1%) by the same investigator. Eighty-two of them (13.4%) were repeated patients and 530 (86.6%) were 'first' capillaroscopies. Among these 530 first capillaroscopies, 78.5% were women and 21.5% men, with a medium age of 47.5 years (13–88 years). Of the patients, 84.7% reported RP. The service of origin was Internal Medicine in 85.3% patients, Rheumatology in 11.9% patients and 2.9% from other services. Capillaroscopy pattern is showed in Table 1. Of the studies, 74.9% showed morphological changes: sinusoids (71.7%), ramified (59.1%), megacapillaries (46.6%), pallor of the capillary bed (46.6%), microhaemorrhages (42.3%), visible venous plexum (34%), capillary disarrangement (29.4%) and capillary loss (25.2%). In the scleroderma pattern, more megacapillaries, microhaemorrhages, enlargement and capillary loss were observed. In the connective pattern, megacapillaries were observed but not so frequently, ramifications, sinusoids and microhaemorrages. No capillary enlargement nor disarrangement was observed in this connective pattern.
Conclusion. Nail-fold capillaroscopy allows to distinguish between a connective and scleroderma pattern in patients with RP.

TABLE 1. Capillaroscopic patterns

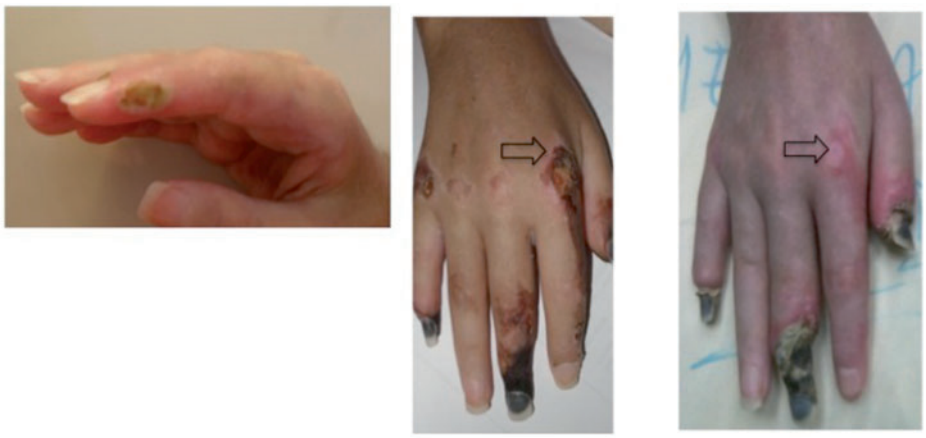
	Capillaroscopies, *n* (%)
Non-specific	225 (42.5)
CTD	160 (30.2)
Scleroderma	131 (24.7)
Total	516 (97.4)

PS291. A CASE OF CATASTROPHIC DIGITAL NECROSIS IN NEW ONSET SSc WITH ANTI-PHOSPHOLIPID SYNDROME: BOSENTAN AS EFFECTIVE RESCUE THERAPY

S. Donnelly[1] and E. McCarthy[1]
[1]*Mater Misericordiae University Hospital, Dublin, Ireland*

We report a case of severe digital ulcerations rapidly progressing to necrosis of multiple digits in a patient with new-onset scleroderma on an APS and therapeutic anti-coagulation background. The patient, a 31-year-old female teacher, complained of increasing RP for 6 months prior to the presenting episode and 3 months earlier had a pulmonary embolus for which she was therapeutically anti-coagulated. She presented with two small fingertip ulcerations and dusky discolouration of one finger pulp and was treated with standard medical therapy including immunosuppression (prednisolone 10 mg), vasodilatation (oral nifedipine, i.v. epoprostenol × 14 days) and aspirin in addition to therapeutic warfarin in a local hospital. Laboratory testing revealed her to be ANA positive in high titre with anti-Ro specificity, positive RF and CRP 90 in the absence of infection. Serology confirmed APS. She twice tested negative for cryoglobulins and ACAs and Scl-70 antibodies. Initial diagnosis was of SLE with secondary APS.
After 14 days of therapy she had deteriorated significantly with development of ischaemic digits, necrotic cutaneous lesions bilaterally over the MCPs and on her left heel and was transferred to our centre for further management including amputations. We noted minor sclerodermatous skin change on her feet and calcinosis at the buttocks and a diagnosis of SSc was made. She was immediately commenced on MTX, increased prednisolone (20 mg) and bosentan 62.5 mg b.i.d. Within 2 days of commencing bosentan we observed a halt in progression of necrotic changes in her hands and feet and almost complete healing of the ulcerated necrotic skin by the end of Week 4. Progressive healing continued such that the plastic surgeons were able to conserve both feet and much more of her hands than was originally expected. Necrotic cutaneous ulceration of her right index

FIG. 1



Right (dominant) hand *changes l to r*

Day 1 : warfarin therapy only
Day 14: progression despite nifedipine, apsirin, prednisolone and iv epoprostenol
Day 42: healing of cutaneous ulceration and necrosis which was observed to commence within days of initiation of bosentan 62.5mg p.o b.i.d. with methotrexate

finger extending from tip to MCP healed remarkably, allowing preservation of the digit and maintenance of pincer grip despite required teminalization of seven digits. Over the next 6 months, the patient developed rapidly progressive diffuse skin involvement SSc without major internal organ involvement to date and MTX was switched to MMf 1g b.i.d. This report provides an impressive example of the effectiveness of bosentan therapy in a patient with catastrophic cutaneous and digital necrosis due to new-onset SSc in the presence of APS, which failed to improve on standard therapy including i.v. epoprostenol and steroid.

PS292. SILENT CARDIOVASCULAR INVOLVEMENT IN PATIENTS WITH DIFFUSE SCLERODERMA: A CASE CONTROL STUDY

F. Atzeni[1,2], L. Gianturco[3], P. Sarzi-Puttini[2], C. Ricci[3], L. Tomasoni[3] and M. Turiel[3]
[1]*Experimental Medicine and Rheumatology, Queen Mary University of London, London, UK,* [2]*Rheumatology Unit, L. Sacco University Hospital and* [3]*IRCCS Galeazzi Orthopedic Institute, University of Milan, Department of Health Technologies, Cardiology Unit, Milan, Italy*

Background. An association between systemic autoimmune diseases (SADs) and atherosclerosis has been described in many CTDs, and leads to increased cardiovascular (CV) morbidity and mortality. SSc is characterized by multi-system organ inflammation, endothelial wall damage and vasculopathy. There are many markers of endothelial dysfunction and/or atherosclerotic risk, such as asymmetric dimethylarginine (ADMA), arterial stiffness parameters, carotid intima–media thickness (cIMT) and coronary flow reserve (CFR) assessed by means of trans-thoracic echocardiography (TTE). The aim of this pilot study was to identify early CV involvement in a group of SSc patients using different endothelial or atherosclerosis markers.
Methods. The study involved 20 patients with diffuse SSc [2 males, 18 females; mean age 52.96 (12.51) years] without any signs or symptoms of CV disease (CVD) and 20 age- and gender-matched controls. They all underwent a dipyridamole echocardiographic stress test with the determination of CFR, and an evaluation of cIMT, arterial stiffness and plasma ADMA levels.
Results. All of the patients were ANA and Scl-70 positive, and they had significantly higher CRP and ESR values than the healthy controls ($P < 0.01$ for both); however, there were no significant differences in heart rate, arterial blood pressure, age or BMI.

At baseline, standardized 2D echocardiography showed no significant alterations in either group.

All measures of arterial wall were significantly different in the diffuse SSc group compared with controls and both right and left cIMT, pulse wave velocity (PWV), stiffness index β.

The patients also had significantly lower CFR ($P = 0.0033$) and significantly higher plasma ADMA levels ($P < 0.0001$) than the healthy controls.

There was no significant correlation between plasma ADMA levels and CFR.
Conclusions. The results of the study showed that the SSc patients without any clinical evidence of CVD had subclinical atherosclerosis, as suggested by the early impairment of the coronary microcirculation and macrovascular involvement.

PS293. THE ROLE OF TRANSIENT ELASTOGRAPHY (FIBROSCAN) IN THE STUDY OF LIVER FIBROSIS IN SSc

S. Salvatore[1], G. Serviddio[2], I. Donatiello[2], F. Bellanti[2], E. Altomare[2], A. Corrado[2], A. Gaudio[2], R. Colia[2], F. Cantatore[2], L. Stoppino[2], R. Bellitti[2], L. Macarini[2], V. Ramoni[1] and A. Brucato[1]
[1]*Ospedali Riuniti di Bergamo, Bergamo and* [2]*Ospedali Riuniti di Foggia, Foggia, Italy*

Objective. SSc is an autoimmune disorder of unknown aetiology characterized by severe and often progressive cutaneous and visceral fibrosis. Liver dysfunction is not rare in patients with collagen disease. Hepatic fibrosis is the main aspect of the damage in the course of chronic liver disease. The aim of this study was to determine the role of Transient Elastography (FibroScan) [1] in the study of liver fibrosis in SSc.
Methods. Thirty-three SSc patients (32 females and 1 male, mean age 54 years) without liver diseases and 33 controls (all females, mean age 54 years) were consecutively studied. All patients underwent Transient Elastography for the evaluation of liver fibrosis; 9 SSc patients (including five without and four with suspected liver disease) underwent double-enhanced magnetic resonance (MR) imaging with superparamagnetic iron oxide (SPIO)-enhanced and double-enhanced spoiled gradient-echo (SPGR) sequences [2–4].
Results. Sixteen SSc patients had a FibroScan Stiffness value of <5.3 kPa, (no liver disease), while in 17 patients stiffness was >5.3 kPa (suspicion of liver disease) [5]. No statistically significant difference was demonstrated by comparing the values of stiffness in patients with active disease and those with inactive disease. The Spearman test showed the presence of a linear regression between the values of stiffness and that of creatinine clearance (Spearman = −0531, $P = 0.034$) and between stiffness and creatininaemia (Spearman = 0,396, $P = 0.022$). The Pearson's correlation index (FibroScan *vs* Diffusion MR) showed a linear regression between the values of stiffness and the diffusion-coefficient (ADC AVG) ($r = -0.83$, $P = 0.0056$) and in agreement with this McNemar's test (FibroScan *vs* diffusion-MR and SPIO-MR) did not show the presence of significant differences between the methods compared.

Conclusion. Transient Elastography (FibroScan) suggested liver fibrosis in 50% of patients with SSc; this finding was confirmed by diffusion-MR [5] and SPIO-MR. Stiffness correlated with creatinine clearance and creatininaemia values. Long-term implications of these findings should be further evaluated.

PS294. ENDOTHELIN RECEPTOR ANTAGONIST IN TREATMENT OF PANSCLEROTIC MORPHOEA IN CHILDREN—CASE REPORT

R. Marques[1], F. Ramos[1], P. Costa[2], H. Canhão[1], J. E. Fonseca[1] and J. A. Pereira Da Silva[1]
[1]*Serviço de Reumatologia e Doenças Ósseas Metabólicas and* [2]*Serviço de Pediatria, Centro Hospitalar Lisboa Norte, Hospital de Santa Maria, Lisbon, Portugal*

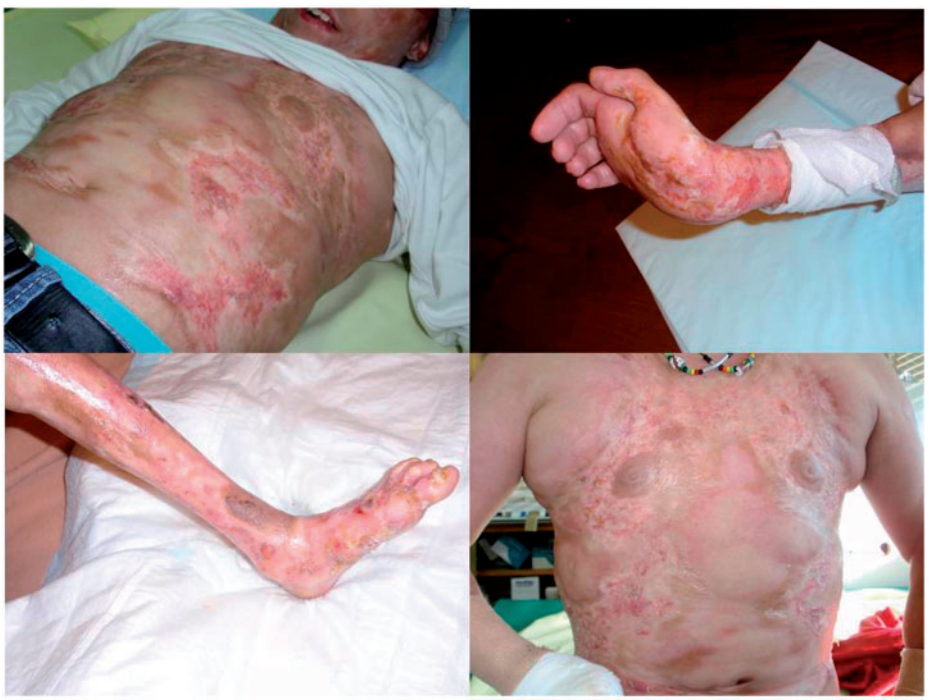
Disabling pansclerotic morphoea (PM) of childhood is a rare and severe variant of localized scleroderma. It is characterized by rapid progression of deep cutaneous fibrosis, severe joint contractures and cutaneous ulcerations. It typically appears in childhood and it is associated with impaired quality of life and poor prognosis.
Bosentan is an orally active dual endothelin receptor antagonist, effective in the treatment of pulmonary arterial hypertension (PAH), including PAH associated with SSc. In several case reports and randomized controlled studies it also shows a beneficial effect on other manifestations of SSc, such as ischaemic digital ulcerations and cutaneous fibrosis.
We describe the case of a boy with an autoimmune hepatitis diagnosed at 4 years old, thereafter under prednisolone and AZA treatment. At the age of 7 years, a depigmented atrophic lesion appeared on his right forearm and was diagnostic of morphoea in an active inflammatory stage. In the following years, the boy had a rapid progression of deep cutaneous fibrosis extending into the muscle fascia with disabling joint contractures of the hips, knees, ankles, fingers, torso, abdomen and face, alopecia and recalcitrant ischaemic ulcerations, typical of PM. He also required four grafts because of eyelid ectropion, but he never showed systemic disease involvement. He was prescribed vitamin D analogues (calcipotriene), D-penicillamine, immunoglobulin, MMF, psoralen–UV-A, MTX and iloprost, but had a worsening skin involvement response.
He was then started on therapy with oral endothelin receptor antagonist bosentan (31.25 mg b.i.d.), and despite mild hepatic cytotoxicity, an improvement in his limb ulcers and a decrease of skin thickness, were noted and remain after 3 months of treatment. The therapeutical findings are similar to the only case report found in the literature.
In the context of scleroderma, bosentan may be a promising option in the treatment of PM, but the obtained results warrant a longer follow-up.

PS295. SCLERODERMA RENAL CRISIS AND OVARIAN HYPERSTIMULATION SYNDROME RELATED TO THE USE OF CLOMIFENE IN A PATIENT WITH SCLERODERMA

S. Kobak[1], S. Hacivelioglu[2] and S. Gungor[3]
[1]*Department of Rheumatology, SIFA University, Izmir,* [2]*Department of Obstetrics and Gynecology, and* [3]*Department of Internal Medicine, Canakkale Onsekiz Mart University, Çanakkale, Turkey*

Introduction. SSc is a chronic inflammatory disease characterized by dermal and visceral fibrosis, often accompanied by obliterative vasculopathy. Scleroderma renal crisis (SRC) is a rare but fatal complication related to a sudden onset of malign hypertension.
Aim. This paper presented a-28-year-old female with SSc who developed SRC and ovarian hyperstimulation syndrome following clomifene administration.
Case report. In April 2011, a-28-year-old woman visited our rheumatology clinic with the complaints of a 2 weeks severe nausea and vomiting, headache and sudden changes in conscious state. The patient who presented with swelling in hands, morning stiffness lasts more than an hour, skin thickness and RP was diagnosed with scleroderma by the rheumatologist in 2007. The patient visited the gynaecology and obstetrics clinic and was given clomifene 100 mg/day for ovarian stimulation in March 2011. Three weeks later, the patient experienced some complaints such as nausea, vomiting and severe headache. However, the patient was referred to our rheumatology clinic in April 2011, when symptomatic relief was not maintained. At the time of admission, laboratory tests revealed newly developed microangiopathic haemolytic anaemia (MAHA), thrombocytopenia and significantly increased creatinine level. Tests for ANAs at a titre of 1 : 1 60 and Scl-70 antibodies were positive. Chest X-ray also revealed minimal pleural effusion in the left side. Echocardiographic examination demonstrated a non-compressive minimal pericardial effusion. The findings of cranial MRI were found to be normal. Abdominal ultrasonography showed increased bilateral renal parenchymal echogenicity that was consistent with type I renal parenchymal disease. Colour Doppler ultrasonography demonstrated bilateral ovarian enlargement including the largest ones with anechoic

Fig. 1



mass with regular contours 33 × 30 mm (right) and 37 × 32 mm (left). The test results of estradiol and β-HCG were evaluated together. When these findings indicated OHSS related to the use of clomifene, supportive care and fluid-electrolyte therapy were given. All clinical and laboratory findings were assessed and a therapy including ACE inhibitors and calcium-channel blockers was also instituted for the management of hypertensive SRC with regular monitoring. At 3 months, the symptoms were completely resolved and acute phase reactants and urinalysis showed normal values. Chest X-ray, abdominal ultrasonography and echocardiography were also repeated and all indicated normal findings.

Conclusion. Our study is one of the important investigations of aetiopathogenesis of SRC seen in the patients with scleroderma; large-scale studies are required to shed light on the nature of the pathogenesis of SRC and possible risk factors.

PS296. PULMONARY HYPERTENSION IN PATIENTS WITH SYSTEMIC SCLERODERMA, MIXED CTD, LOCALIZE SCLERODERMA AND PRIMARY RP

A. Smrzova[1], P. Horak[1], M. Skacelova[1], R. Metelka[1], J. Vymetal[1] and M. Zurek[1]
[1]*Faculty Hospital and University Palacky Olomouoc, Olomouc, Czech Republic*

Pulmonary hypertension (PH) is rare in general population, but is common in connection with some autoimmune disease, especially with SSc. Prevalence of PH in SSc is up to 12%. Patients with SSc-associated PH have 1-year survival rate 87%, 3-year survival rate is only 64%. In last years there is a trend to a decrease mortality of SSc-associated PH due to new options of treatment, particularly ET-1 antagonists. Two-years survival is now 74% compared with 47% in 2002.

From September 2009 to December 2010, we examined 703 patients with RA, systemic CTD; localize scleroderma (LSc), primary RP and primary APS to analyse presence of pulmonary hypertension screened by echocardiography. This group included 53 patients with SSc (10 men, 43 women, age 58.1 and 56.9 years, respectively), three women with LSc (age 58.3 yaers), 25 patients with RP (10 men, 15 women, 43.5 and 39.2 years, respectively) and 55 patients with mixed CTD (12 men, 43 women, 45.5 and 49.7 years, respectively). According to the echocardiographic measurement four zones of pulmonary pressure were defined (20–25 mmHg as a border zone, 26–35 mmHg lower zone and 36–45 mmHg moderate increase and >46 mmHg high increase). Some patients with higher values were indicated for right-sided catheterization. The immunology profile and organ involvement including functional examination of pulmonary function were analysed. Results and relations between parameters will be presented.

PS297. GENERALIZED MORPHEA: A CLINICAL CASE WITH GOOD RESPONSE TO UVA1 PHOTOTHERAPY

T. Santiago[1], **M. Santiago**[1], M. J. Salvador[1] and A. Malcata[1]
[1]*Department of Rheumatology, Coimbra, Portugal*

Morphea, also known as localized scleroderma, is a sclerotic condition limited to the skin characterized by excessive collagen deposition leading to thickening of the dermis, subcutaneous tissues or both. It may progress to large indurated plaques, muscle atrophy, and even, to flexion deformities or poorly healing ulcers. Therapeutic options are numerous, including topical agents, systemic imunosupressors, physiotherapy and more recently phototherapy.

We describe an unusual case of severe generalized morphea in a 49-year-old woman, with an exuberant clinical picture consisting of multiple sclerotic plaques in the trunk and in the left leg. In the leg, the lesions had a deep and linear character. The patient was admitted in the Rheumatology Department for studying organ involvement that was negative. Initially, due to the generalized involvement, the patient started with oral steroids and MTX that were insufficient. Later, she was submitted to UVA1 phototherapy with encouraging results, reduction of disease progression and, even, a moderate reversion of cutaneous fibrosis.

The authors emphasize two peculiarities in this clinical case. First, the generalized and deforming character that a morphea can exhibit, causing difficulties in the differential diagnosis with systemic scleroderma. Secondly, they want to alert to the good results obtained with UVA1 phototherapy, a relatively recent and safe treatment, which can be associated to the systemic conventional options in morphea.

PS298. PHYSICAL, PSYCHOLOGICAL AND SOCIAL IMPACT OF SCLERODERMA IN EUROPE AND BRAZIL

A. Maia[1] and C. Leite[1]
[1]*Minho University, School of Psychology, Braga, Portugal*

Scleroderma involves several physical changes in visible parts of the body, as face and hands, affecting body image and being associated with depressive and anxiety symptoms. Scleroderma symptoms can be painful, such as digital ulcers, RP, skin changes, joint contractures and gastro-oesophageal reflux and the severity of these symptoms is associated with depression and anxiety.

This study aims mainly to characterize the most common symptoms of scleroderma, the impact felt by patients, the satisfaction with medical care and the psychological symptoms.

The participants were 563 patients (mostly woman) belonging to various European countries and Brazil. The instrument used was the Canadian Scleroderma Patient Survey of Health Concerns and Research Priorities.

The five most common symptoms reported by patients were: joint pain, fatigue, RP, muscle pain and hardening/tightening skin. Fatigue was the symptom reported as having the higher impact on the daily lives of participants.

Participants, who reported more symptoms, also reported higher impact of symptoms. Participants with more years of diagnosis revealed to be more satisfied with the medical care they receive, but almost a third of participants reported that they do not have access to all medical care due to its cost and almost half the participants reported that scleroderma affects their ability to work.

Regarding depression, 38% of participants have sensitivity for severe depression, and younger participants reported more depression. Depressive symptoms are associated with the perceived impact of symptoms.

In relation to anxiety, 32% of participants reported symptoms of generalized anxiety and these symptoms are correlated to worse body image and pain.

The symptoms of social phobia are reported by 30% of the participants. More than half of participants reported that they avoid activities where they are the centre of attention. Participants with social phobia reported worse body image and 84% reported concerns with body image due to scleroderma.

Due to gravidity, lack of knowledge, unpredictability and disfigurement of scleroderma, the socials costs and the psychological symptoms in these patients are high and should be routinely addressed.

PS299. CORRELATION BETWEEN SCL-70 AUTOANTIBODY AND CLINICAL MANIFESTATION OF SCLERODERMA IN IRANIAN PATIENTS

B. Nazari[1], M. Gharibdoost[2], B. Nazari[3], M. Mahmoudi[4], A. R. Jamshidi[4] and F. Gharibdoost[4]
[1]*Department of Immunology, School of Medicine,* [2]*Department of Medicine, School of Medicine, Tehran University of Medical Sciences,* [3]*School of Biology, College of Science, University of Tehran and* [4]*Rheumatology Research Centre, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran*

Objective. As many references mentioned, the estimated percentage of positive results for Scl-70 autoantibodies in scleroderma patients would be variable (16–35%). To report the percentage of Scl-70-positive results in Iranian scleroderma patients, we investigated 160 cases. In the next step, we compared clinical manifestation of disease between two groups (which show positive and negative results).

Method. One hundred and sixty cases consist of 88 patients with diffuse form of Scleroderma and 72 limited forms were evaluated. We analysed the level of Scl-70 autoantibodies with ELISA kit and gathered clinical data from the patient's medical files.

Result. Among the patients we studied, 72 cases of 88 cases with diffuse scleroderma show positive results for scl-70 autoantibodies (~82% of cases suffering from diffused form) while among the limited scleroderma patients, 20 cases of 72 cases show positive results (~28% of limited form); Totally positive results were ~57% of all cases. In addition, comparison of organ involvement in two groups showed that the patients with Scl-70 autoantibody-positive results developed pulmonary fibrosis, renal crisis and cardiac involvement more than the negative group.

Conclusion. We suggested that the existence and the level of scl-70 autoantibodies could be a predictive tool to estimate severity and clinical manifestation of the disease.

PS300. VITAMIN D DEFICIENCY IN A COHORT OF PATIENTS WITH SSc: ASSOCIATIONS WITH CLINICAL AND LABORATORIAL ASPECTS

M. G. Santiago[1], S. Serra[1], T. Santiago[1], M. J. Serra[1], R. Ferreira[1], C. Duarte[1], M. J. Salvador[1] and J. A. P. Da Silva[1]
[1]*Serviço de Reumatologia, Hospitais da Universidade de Coimbra, E.P.E., Coimbra, Portugal*

Context. Vitamin D is a steroid hormone with well-known role in calcium phospate homeostasis and bone metabolism. In addition to the traditional known metabolic activities, vitamin D has been shown to modulate the immune system and its deficiency associated with the risk and severity of autoimmune diseases. The overall effect of vitamin D is immunosuppressive, by inhibiting the Th1 profile and B-cell proliferation and by stimulating Th2 dominance. Vitamin D may be acquired from various sources, and its level depends on many variables, such as age, BMI, lifestyle, geography and seasonal factors. To ensure optimal bone health, the serum 25-hydroxyvitamin D (25OHD) level should be at least 30 ng/ml, with the ideal range being estimated at 30–60 ng/ml, but the required level to exert immunomodulatory effects is not known.
Purpose. To analyse the association between 25OHD levels with clinical and laboratorial aspects in a cohort of patients with SSc.
Methods. The levels of 25OHD were determined in 45 patients. The SSc patients fulfilled the ACR criteria for the classification of SSc and were classified according to LeRoy *et al*. They underwent clinical and laboratorial evaluation, which included Rodnan skin score, ESR, CRP, diffusing lung capacity for carbon monoxide (DL_{CO}), sun exposure time, BMI and 25OHD serum level. The 25OHD levels were used to assess the vitamin D status, using the commercial kit LIAISON 25-OH vitamin D assay.
Results. Forty-five patients, 39 women and 6 men, with a mean age of 59.4 (11.5) years and a mean disease duration of 11.2 (7.5) years. lcSSc represented 80% of the patients and dcSSc the remaining 20%. The mean level of 25OHD was 16.6 (8.3) ng/ml and suboptimal levels of 25OHD were observed in 40 patients (88.9%). 25OHD serum levels were lower in patients with shorter sun exposure time ($P < 0.001$). A negative correlation (weak to moderate) between 25OHD serum levels and Rodnan skin score was observed (r's $= -0.458$, $P = 0.002$). No correlation was found between 25OHD serum concentrations and patients' age, disease duration, subsets of SSc (dcSSc or lcSSc), DL_{CO}, ESR, CRP and BMI.
Conclusions. In SSc patients low levels of vitamin D are common. Lower levels are observed in patients with shorter sun exposure time and a negative correlation was observed between vitamin D levels and skin involvement. Moreover, patients' age, disease duration and pulmonary involvement were not related with vitamin D levels.

PS301. PREVALENCE OF VITAMIN D DEFICIENCY IN A COHORT OF PATIENTS WITH SSc

M. G. Santiago[1], S. Serra[1], T. Santiago[1], M. J. Serra[1], R. Ferreira[1], C. Duarte[1], M. J. Salvador[1] and J. A. P. Da Silva[1]
[1]*Serviço de Reumatologia, Hospitais da Universidade de Coimbra, E.P.E., Coimbra, Portugal*

Context. Subclinical vitamin D deficiency and insufficiency are affecting a large fraction of healthy individuals and patients of all age groups. Even an adequate diet may not provide enough vitamin D to reach the serum concentrations currently recommended. This emphasizes the need for adequate sun exposure. Moreover, low vitamin D levels have been reported in various autoimmune diseases and emerging evidences suggest that vitamin D displays immunomodulatory effects.
Purpose. To estimate the prevalence of vitamin D deficiency in patients with SSc as compared with healthy controls.
Methods. The levels of serum 25-hydroxyvitamin D (25OHD) were determined in a cohort of 45 SSc patients and in 27 healthy controls sex-, age- and season matched, not taking vitamin D supplements. The SSc patients fulfilled the ACR criteria for the classification of SSc and were classified according to LeRoy *et al*. The 25OHD levels were used to assess the vitamin D status, using the commercial kit LIAISON 25-OH vitamin D assay.
Results. We studied the serum levels of 25OHD in a cohort of 45 SSc patients [age 59.4 (11.5) years] and 27 healthy control subjects [age 53.7 (11.5) years]. Both groups were mostly female (87.7% in SSc group and 85.2% in the control group). 25OHD levels were classified as deficient (<10 ng/ml), insufficient (≥10 ng/ml and <30 ng/ml) and normal (≥30 ng/ml). In the present study, we registered a statistically significant difference in 25OHD levels between SSc group and control group (median 16.3 *vs* 27 ng/ml, $P < 0.001$). Vitamin D deficiency was found in 13 SSc patients (28.9%) *vs* 2 healthy controls (7.4%) and only 5 SSc patients (11.1%) showed normal values, against 9 healthy controls (33.3%). We registered a statistically significant difference between 25OHD serum levels and sun exposure time in both groups. The difference in 25OHD levels between groups remained statistically significant even after adjusting 25OHD levels for sun exposure time. In logistic regression analysis, disease ($\beta = 0.329$, $P = 0.001$) and sun exposure time ($\beta = 0.483$, $P < 0.001$) were considered predictors of 25OHD levels.
Conclusions. Patients with SSc have significantly lower serum vitamin D concentrations compared with healthy control subjects, and the prevalence of vitamin D deficiency in SSc patients is higher than that founded in healthy controls. Sun exposure time was good predictor of vitamin D values.

PS302. NAILFOLD CAPILLAROSCOPY

M. Reynoso[1], Y. Llahyah[1], G. Rombo[1], S. Grazioso[1] and R. A. Fernandez Busy[1]
[1]*Hospital Centenario de Rosario, Rosario, Argentina*

Primary and secondary RP can be distinguished using nailfold capillaroscopy. It should be indicated in patients presenting RP, puffy fingers and ANA positive for very early diagnosis of SSc (VEDOOS). The possibility of early diagnosis might block disease evolution and prevent tissue damage.
Objectives. The aim of this study is to analyse the different patterns presented in 130 nailfold capillaroscopies performed in Hospital Provincial del Centenario de Rosario, from June 2010 to August 2011.
Methods. We performed a retrospective analysis of the database from our department.
Results. One hundred and thirty capillaroscopies were performed. Seventy-four capillaroscopies (56.9%) showed a normal pattern, 15 (11.5%) an unspecific pattern, 8 (6.1%) a tortuous pattern and33 (25.3%) a scleroderma pattern (SD). Last pattern had 14 early stage, 15 active stage and 4 late stage.
Conclusions. In patients presenting early SD pattern ($n = 14$), RP, puffy fingers, ANA positive very early diagnosis of SSc should be suspected. Complementary studies should be indicated and multidisciplinary patient's management.

PS303. RESIDU: PROSPECTIVE FOLLOW-UP ON EPIDEMIOLOGY AND BURDEN OF DISEASE OF DIGITAL ULCERS IN PATIENTS WITH SSc

M. C. Vonk[1], A. E. Voskuyl[2], M. J. F. Walravens[3], M. Otten[4], P. van Paassen[5] and A. J. M. Schuerwegh[6]
[1]*University Medical Centre st Radboud, Nijmegen,* [2]*VU University Medical Centre, Amsterdam,* [3]*Maasstad hospital, Rotterdam,* [4]*Actelion Pharmaceuticals Nederland B.V., Woerden,* [5]*Maastricht University Medical Centre, Maastricht and* [6]*Leiden University Medical Centre, Leiden, The Netherlands*

Background. Digital ulcers (DUs) are a frequent complication of SSc with a negative impact on quality of life. The Dutch incidence, prevalence and natural history of DU in SSc patients are largely unknown. Furthermore, clinical management varies, as international standardized guidelines for the management of DU are not available.

RESIDU is a national observational registry designed to collect epidemiological data from patients with DU in SSc. RESIDU aims to describe demographics, clinical characteristics and Dutch management practice.
Methods. Known Dutch SSc-treating physicians were invited to participate in RESIDU. METC approval was obtained in participating hospitals. Charts of all registered SSc patients were screened for a history of DU and/or pitting scars (PSs). Upon enrolment into RESIDU, patient data were registered using the international online DUO-registry.
Results. In June 2011, 28 hospitals (31% of all Dutch hospitals) participated in RESIDU. Most of the larger hospitals participated. RESIDU is therefore estimated to represent approximately half of the Dutch SSc population. In total 1304 patient charts were screened; 547 patients (42%) were identified with a history of DU. Until June 2011, data of 439 patients were included in RESIDU. Because of missing data, the actual number of patient is given for each item.

Patient inclusion per site varied between 6 and 301 SSc patients and the incidence of DU varied between 5 and 63%. Smaller sites showed a larger variation in incidence of DU, probably caused by different policies of forwarding patients to specialized sites.

The average age at first RP was 43 (15) years ($n = 378$) and at first DU 49 (15) years ($n = 315$). Time between first RP and DU was 4.4

years ($n = 287$). Other SSc manifestations were gastrointestinal involvement (57.1%, $n = 424$), lung fibrosis (31.4%, $n = 424$), pulmonary hypertension (9.9%, $n = 424$), cardiac involvement (6.4%, $n = 424$) and kidney involvement (4.7%, $n = 424$). The most important DU complications were gangrene (29.2%, $n = 432$), soft tissue infection requiring antibiotics (19.3%, $n = 409$), auto-amputation (6.7%, $n = 406$), and osteomyelitis (3.7%, $n = 432$). Hospitalization was needed in 41.5% of patients ($n = 427$), mainly due to need for parenteral prostanoids (38.2%).
Conclusion. The RESIDU database represents half of the Dutch SSc-DU population and therefore provides good estimates of Dutch DU epidemiology and of the burden of disease in these patients. Forty-two per cent of Dutch SSc patients suffer from DUs during the course of their disease. The current data show that SSc-DU patients suffer from a considerable burden of disease. Furthermore, RESIDU allows for prospective follow-up in enrolled patients and it offers clear opportunities for evaluation of patient management practices.

PS304. EPITHELIAL-TO-MESENCHYMAL TRANSITION AND LUNG FIBROSIS

A. Tam[1], S. Sonnylal[2], A. Leask[3], C. P. Denton[1], B. de Crombrugghe[2], J. Norman[1] and D. J. Abraham[1]
[1]*Division of Medicine, UCL Medical School, Royal Free Campus, London, UK,* [2]*Department of Genetics, MD Anderson Cancer Center, University of Texas, Houston, TX, USA and* [3]*CIHR Group in Skeletal Development and Remodeling, University of Western Ontario, London, ON, Canada*

Background. SSc is a connective tissue disease characterized by inflammation and autoimmunity, vasculopathy and interstitial remodelling, which results in tissue scarring and fibrosis. During fibrosis, normal tissue architecture is gradually replaced by abnormal collagen-rich extracellular matrix (ECM). Epithelial-to-mesenchymal transition is likely to play a role, at least in part, to the generation of interstitial fibroblasts, an important cell type in ECM accumulation during organ fibrosis. We have found that transgenic mice (Col1a2-CTGF) with fibroblast-specific overexpression of connective tissue growth factor (CCN2/CTGF) and mice expressing constitutively-active TGF-β type I receptor (ALK5) develop tissue fibrosis, principally in the skin and lung. Our *in vivo* data suggests that overexpression of CTGF leads to pathological changes in the epithelium adjacent to these fibroblasts including α-smooth muscle actin (α-SMA) expression at the alveolar epithelial lining of the Col1a2-CTGF transgenic mice. This prompted further investigation into EMT in lung epithelial cells and the potential involvement of CTGF as a mediator of this process.
Materials and methods. Rat SV40-immortalised type II (SV40-T2) alveolar epithelial cells were maintained in DMEM supplemented with 10% fetal calf serum (FCS), 100 U/ml penicillin and 100 μg/ml streptomycin at 37°C in a humidified atmosphere of 5% CO_2 until confluent. Cells were quiesced in serum-free DMEM for 24 h and subsequently incubated for 24–48 h after the addition of either TGF-β1 (4 ng/ml) for 24–72 h or with CTGF (10–200 ng/ml) diluted in serum-free media. Immunofluorescence, real-time PCR (qPCR), western blot and ELISA analyses were used to assess the effect of treatment on the expression of the prototypical epithelial cells marker, E-cadherin, and mesenchymal cell markers including CTGF, α-SMA, collagen type I and fibronectin. Data are expressed as mean (S.E.M.) ($n = 3$).
Results. TGF-β1-induced morphological changes in the SV40-T2 cells, causing them to lose their cuboidal shape, typical of type II epithelial cells to become more elongated and spindle-like. Immunofluorescence revealed that TGF-β1 also stimulated expression of α-SMA in the form of stress fibres. qPCR, western blot or ELISA analyses were performed to identify whether treated cells expressed markers of EMT. It was found that TGF-β1- and CTGF-treated cells expressed a number of mesenchymal cell markers including the myofibroblast marker, α-SMA, as well as collagen type I and fibronectin.
Conclusions. These data suggest that rat type II alveolar epithelial cells may undergo EMT-like changes mediated by TGF-β1 and CTGF. This may be relevant in SSc-associated lung fibrosis, as fibroblast overexpression of CTGF may mediate phenotypic switching of lung epithelial cells into mesenchymal-like cells and hence add to the expanding pool of profibrotic, ECM-producing activated fibroblasts.

PS305. COMPARISON OF THE DIAGNOSTIC PERFORMANCES OF TWO DIFFERENT PROTOCOLS FOR HAND PERFUSION SCINTIGRAPHY PERFORMED FOR RP

W. Jeong[1], J. Kim[1] and J. Lee[1]
[1]*Jeju National University Hospital, Jeju, South Korea.*

Background. Hand perfusion scintigraphy using radiopharmaceuticals is helpful for diagnosing RP; however, there is no consensus on an optimal protocol for scintigraphy.
Purpose. The aim of this study was to compare the diagnostic performances of two different protocols of hand perfusion scintigraphy for diagnosing RP.
Methods. A total of 130 patients who underwent hand perfusion scintigraphy for the suspected RP and 40 healthy volunteers were enrolled. Of these, 66 patients (Group A) and 25 volunteers underwent 99mTc-methylene diphosphonate (MDP) hand perfusion scintigraphy without one-hand chilling. The finger-to-palm ratio (FPR) was calculated by drawing regions of interests (ROIs) around the finger and palmar regions. The remaining 64 patients (Group B) and 15 volunteers underwent 99mTc-MDP hand perfusion scintigraphy with one-hand chilling. Three parameters (the chilled to ambient hand ratios of the first peak height, initial slope and blood pool uptake) were calculated by comparing the time–activity curves of blood flow images and ROIs around the finger region on blood pool images.
Results. Forty-eight and 47 patients were clinically diagnosed with RP in Groups A and B, respectively. In Group A, patients with RP had significantly lower FPRs than the ones without RP, and the receiver operating characteristic (ROC) curve analysis showed that FPR of 0.51 was the best cut-off value for diagnosing RP, with a sensitivity of 63% and a specificity of 83%. In Group B, three aforementioned parameters significantly differed (lower or higher) between the patients with RP and those without RP. The ROC curve analysis provided highly sensitive and specific results for all three parameters. The initial slope ratio showed the highest sensitivity of 87% with a specificity of 88% when using cut-off values of 0.78 and 1.25.
Conclusion. Although both protocols used for hand perfusion scintigraphy showed a high specificity for diagnosing RP, the protocol with one-hand chilling showed higher sensitivity and specificity than that without one-hand chilling.

PS306. DOWN-REGULATION OF MICRORNA-196A CONTRIBUTES TO THE CONSTITUTIVE UP-REGULATED TYPE I COLLAGEN EXPRESSION IN SCLERODERMA DERMAL FIBROBLASTS

N. Honda[1], M. Jinnin[1], I. Kajihara[1], T. Makino[1], K. Makino[1], S. Masuguchi[1], S. Fukushima[1], Y. Okamoto[2], M. Hasegawa[2], M. Fujimoto[2] and H. Ihn[1]
[1]*Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University, Kumamoto and* [2]*Department of Dermatology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan.*

The microRNAs (miRNAs), short RNA molecules on average only 22-nt long, are post-transcriptional regulators leading to gene silencing. miRNAs have been implicated in the pathogenesis of various human diseases such as immunological disorders, cancers and metabolic disorders. In this study, we tried to evaluate the possibility that miRNAs play some roles in the type I collagen up-regulation in cultured dermal fibroblasts derived from involved skin of scleroderma patients. Several miRNAs were down-regulated in scleroderma fibroblasts compared with normal fibroblasts by miRNA PCR array. Among them, miR-196a expression was decreased in scleroderma skin both *in vivo* and *in vitro* by real-time PCR or *in situ* hybridization. miR-196a inhibitor leads to the overexpression of Type I collagen in normal fibroblasts, whereas overexpression of the miRNA resulted in the down-regulation of Type I collagen in scleroderma fibroblasts. In addition, miR-196a was detectable in the serum of scleroderma patients. Patients with lower serum miR-196a levels had significantly higher modified Rodnan total skin thickness score than those without. Taken together, miR-196a may play an important role in the pathogenesis of scleroderma. Investigation of the regulatory mechanisms of type I collagen expression by miR-196a may lead to new treatments using miRNA.