fibrosis of different organs. The occurrence of endothelial dysfunction together with fibrosis indicates that endothelial cell-derived factors, such as endothelin-1 (ET-1), may have an important role in the pathogenesis of SSc. The upregulation of ET-1 activates inflammatory cells and leads to nitric oxide synthase inhibition associated with arterial stiffness.

Objectives: The purpose of this study was to evaluate ET-1 serum levels in women with systemic sclerosis (SSc) compared with healthy controls and to examine possible associations between ET-1 and markers of arterial stiffness.

Methods: This cross-sectional study was performed in San Cecilio Hospital, Granada (Spain) from November 2017 to May 2019. Sixty-two women with SSc and 62 age and sex matched healthy controls were enrolled in this study. Pulse Wave Velocity (PWV) was measured non-invasively along the carotid-femoral arterial segment. Serum ET-1 was analysed using indirect enzyme-linked immunosorbent assay (ELISA).

Results: A total of 62 female patients were included in our study, with a mean (SD) age of 53 ± 10 years. The majority were Caucasian (90.5%). The mean disease duration was 8.8 ± 6.9 years. Forty-four (70.9%) patients had a limited form of the disease and 18 (29.1%) had a diffuse form.

There was a significant difference in ET-1 serum levels between SSc female patients and healthy controls (28.4 ± 10.6 vs. 21.1 ± 11.7 pg/ml, $p = 0.001$). Serum levels of ET-1 were positively associated with PWV ($r = 0.26$, $p < 0.05$), within the study group. In addition, in the linear regression model, higher ET-1 concentrations were associated with higher PWV [$\beta = 0.03$ 95% CI (0.001, 0.060); $p < 0.05$].

Conclusion: This study shows that ET-1 serum levels are associated with PWV in women with SSc. Therefore, drugs that block ET-1 may be effective in reducing large artery stiffness in women with SSc, and thus cardiovascular risk.

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AB0407

CARDIOVASCULAR BURDEN IN SYSTEMIC SCLEROSIS: QRISK3 VERSUS FRAMINGHAM FOR RISK ESTIMATION

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Background: Cardiovascular (CV) diseases, namely myocardial infarction and stroke, are not among the most known and frequent complications of systemic sclerosis (SSc), but there is growing evidence that SSc patients have a higher prevalence of CV diseases than the general population [1].

Objectives: To compare two algorithms for CV risk estimation in a cohort of patients with SSc, finding any correlation with clinical characteristics of the disease.

Methods: SSc patients without previous myocardial infarction or stroke were enrolled. Traditional CV risk factors, SSc-specific characteristics and ongoing therapies were assessed. Framingham and QRISK3 algorithms were then used to estimate the risk of develop a CV disease over the next 10 years.

Results: Fifty-six SSc patients were enrolled. Framingham reported a median risk score of 9.6% (IQR 8.5), classifying 24 (42.9%) subjects at high risk, with a two-fold increase of the mean relative risk in comparison to general population. QRISK3 showed a median risk score of 15.8% (IQR 19.4), with 36 (64.3%) patients considered at high-risk. Both algorithms revealed a significant role of some traditional risk factors and a noteworthy potential protective role of endothelin receptor antagonists ($p=0.003$). QRISK3 was also significantly influenced by some SSc-specific characteristics, as limited cutaneous subset ($p=0.01$), interstitial lung disease ($p=0.04$) and non-ischemic heart involvement ($p=0.03$), with the first two that maintain statistically significance in the multivariate analysis ($p=0.02$ for both).

Conclusion: QRISK3 classifies more SSc patients at high-risk to develop CV diseases than Framingham, and it seems to be influenced by some SSc-specific characteristics. If its predictive accuracy were prospectively verified, the use of QRISK3 as a tool in the early detection of SSc patients at high CV risk should be recommended.

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AB0408

SYSTEMIC SCLERODERMA AND ENVIRONMENTAL RISK FACTORS: IDENTIFYING ASSOCIATIONS MINING THE BIOMEDICAL LITERATURE

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Background: A debate still exists concerning the role of occupational and environmental factors in the pathogenesis of systemic scleroderma (SSc).

Objective: Our aim was to explore associations between SSc and environmental factors utilizing an automatic semantic interpretation of PubMed results.

Methods: The literature search string: ("systemic sclerosis" OR "scleroderma") AND ("occupational exposure" OR "environmental" OR "risk factor") was used to retrieve abstracts from the entire PubMed database, using Semantic MEDLINE 2, on 6/14/2020. This application represents a network of semantic predications (triples of the form subject-predicate (or relation) -object, e.g. Occupational Exposure causes Systemic Scleroderma) on a knowledge graph. Subject and object arguments of each predication are concepts from the Unified Medical Language System (UMLS) Metathesaurus and the relation is taken from the UMLS Semantic Network. The system allows for choosing the central topic ("Systemic Scleroderma"), the length of the network (3 nodes), and automatic summarization, eliminating the less informative predications.

Results: The search string retrieved 864 citations and identified 6,397 predications by using 34 types of relations. Initially, we focused our attention on the 'CAUSES' type of relation (Figure 1), displaying a network with 59 nodes and 57 edges.

The central concepts of this network, identified as having causal relationship with SSc are autoimmune diseases/autoimmunity, chemicals such as bleomycin, occupational and environmental exposure, especially silica, vinyl chloride and trichloroethylene, genes, including HLA and non-HLA genes, genetic polymorphisms, transcription factors (TFs) such as Flt1 and KLF5, and fibrosis. Eosinophilia-myalgia syndrome, toxic oil syndrome and infection were all causally linked to autoimmune diseases. Minerals were associated with occupational exposure and with autoimmune diseases. Concepts causally linked to fibrosis were rare diseases, HLA genes, other non-HLA genes, such as STAT4, IR4, IR5, TLR4, TLR7 and Rho-associated Kinase, and vinyl chloride monomer. Pathogenic factors associated with SSc were endothelial dysfunction and extracellular matrix proteins. Many of the papers in the network also suggested that hormonal factors are involved.

Conclusion: Inspection on the knowledge graphs reveals concepts central to research on the etiopathogenesis of SSc. The relations in which these concepts participate, provide more specific information. The Semantic MEDLINE graph supports the kind of patterns that underpin literature-based discovery.

Although the pathogenesis of SSc remains elusive, it is accepted that initial vascular damage driven by autoimmunity and environmental factors causes abnormalities in the vasculature resulting in the activation of fibroblasts in various organs. Silica and solvents such as trichloroethylene seem to be the most consistently suspected environmental agents in SSc.

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Figure 1. Semantic Network of Casual Relationships of Systemic Scleroderma.

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AB0409

INTRAVENOUS ILOPROST: A REGION WIDE SURVEY OF CURRENT PRESCRIBING AMONGST HOSPITALS IN THE WESSEX MULTI-DISCIPLINARY CONNECTIVE TISSUE DISEASE NETWORK

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Background: Digital ulceration in systemic sclerosis is a severe and disabling aspect of this complex, multi-system disease. Traditionally, intravenous (IV) iloprost has been prescribed to treat the problem. Alternative oral medications including sildenafil and bosentan are now readily available, although NHS clinical commissioning policy is yet to be updated to reflect changes in drug costs. Use of IV iloprost across Wessex was audited to review current practice across the region.

Objectives: To compare use of IV iloprost across 7 different hospital rheumatology departments

Methods: Data was collected across 7 different NHS hospital sites using rheumatology specific pharmacy records for high cost drug prescribing and a single uniform data collection proforma, which was then analysed by 1 person to ensure uniformity of results. Case notes were reviewed retrospectively to determine diagnosis, frequency and duration of iloprost treatment, if patients had been considered for sildenafil treatment (including if sildenafil was prescribed, any cautions or contra-indications to treatment, dose and any reason for discontinuation of treatment) and if patients had been considered for bosentan treatment and if it was prescribed.

Results: 45 patients were identified currently receiving IV iloprost. 32/45 (71%) had a diagnosis of systemic sclerosis, mixed connective tissue disease (CTD) or undifferentiated CTD (to be called scleroderma group). 13/45 had other miscellaneous diagnoses which had resulted in digital ulceration. These 13 patients were excluded from further analysis relating to sildenafil or bosentan prescribing as these medications were not indicated for other causes of digital ulceration. In the scleroderma group, 27/32 (84%) had been considered for sildenafil treatment. Of these, 8/27 started and discontinued due to intolerance and 17/27 remained on sildenafil. In the scleroderma group, 9/32 had been considered for bosentan treatment, and of these 7/9 remained on bosentan.

Conclusion: The authors have identified that IV iloprost is still widely used for management of digital ulceration in rheumatology departments across seven different hospitals in Wessex. Most of this group of patients would likely be eligible for treatment with sildenafil or bosentan. Sildenafil intolerance is a challenge to management. Consideration of bosentan as a treatment option was limited in this group, and may be a cost-effective alternative to IV iloprost which would also eliminate the risk of infection associated with IV access in a potentially immunosuppressed group of patients.

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AB0410

S100A4 PLASMA LEVELS CORRELATE WITH DISEASE ACTIVITY, SKIN FIBROSIS AND INTERSTITIAL LUNG DISEASE IN SYSTEMIC SCLEROSIS PATIENTS

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Background: In our previous study we demonstrated that S100A4 is overexpressed in scleroderma (SSc) skin, SSc fibroblasts and preclinical models of SSc in a TGF- β dependent manner. We showed that S100A4 is a new regulator of TGF- β signalling and its inhibition prevents the pro-fibrotic effects of TGF- β . Inactivation of S100A4 prevented dermal fibrosis induced by bleomycin and in Tsk-1 mice

Objectives: The aim of this study was to evaluate S100A4 in the peripheral blood of SSc patients and characterize its potential association with SSc-related features.

Methods: A total of 33 patients (29 females; mean age 52.8; disease duration 4.2 years; dcSSc/lcSSc = 8/25) who met the 2013 EULAR/ACR classification criteria for SSc and 20 healthy age- and sex-matched individuals were included in this study. Plasma levels of S100A4 were measured using ELISA (CUSABIO, Houston, USA). Data are presented as median (IQR).

Results: S100A4 plasma levels were significantly increased in SSc patients compared to healthy controls (78.6(32.3-146.5) vs. 43.4(32.3-53.4)ng/mL, $p=0.011$). Patients with diffuse cutaneous (dc)SSc had significantly higher levels of S100A4 than patients with limited cutaneous (lc)SSc or healthy controls (168.5(81.5-347.5) vs. 63.4(30.9-130.6), $p=0.017$, $p=0.001$, respectively). Plasma levels of S100A4 positively correlated with mRSS ($r=0.556$, $p=0.001$). Furthermore, S100A4 negatively correlated with forced vital capacity (FVC) and peripheral oxygen saturation (SpO₂) ($r=-0.362$, $p=0.038$; $r=-0.414$, $p=0.029$, respectively). S100A4 levels positively correlated with ESSG activity score ($r=0.750$, $p<0.001$). However, only correlations between S100A4 and mRSS, and ESSG activity score were approved at corrected level of statistical significance after Bonferroni's correction ($p<0.01$). In a prospective analysis of patients ($n=40$) with progressive SSc-ILD treated with 6 ($n=24$) or 12 ($n=16$) monthly i.v. pulses of cyclophosphamide (CPA, 500mg/m²), we observed a significant decrease in plasma S100A4 levels between the baseline samples (month 0) and blood drawn after 6 months of CPA treatment (76.3(52.9-98.6) vs. 73.2(44.4-98.6)ng/mL, $p=0.013$). Furthermore, baseline S100A4 levels predicted the change (m0-m6) in CRP and ESR levels after 6 months of CPA therapy ($r=0.472$, $p=0.004$; $r=0.528$, $p=0.003$, respectively).

Conclusion: We demonstrate that plasma S100A4 levels are significantly increased in SSc patients compared with healthy controls. Increased S100A4 is associated with the dcSSc subset, skin involvement, deteriorated parameters of interstitial lung disease and higher disease activity. In patients with progressive SSc-ILD, S100A4 declines after 6 months of cyclophosphamide therapy and predicts the systemic inflammatory response. These data further support our previous findings on the role of S100A4 as a regulator of TGF- β induced fibrosis in SSc.

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AB0411

CHALLENGES IN THE MANAGEMENT OF MIXED CONNECTIVE TISSUE DISEASE: A RETROSPECTIVE ANALYSIS OF THE MCTD COHORT IN A TERTIARY REFERRAL CENTRE

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Background: As a rare, complex, and heterogeneous disease, mixed connective tissue disease (MCTD) represents a challenge for clinical practice.

Objectives: We aimed to unravel potential pitfalls including correct referral diagnosis, fulfilment of diagnostic criteria, distinction from other CTDs, disease course and activity, and treatment modalities.

Methods: We analysed the prospectively collected MCTD cohort at our tertiary referral centre. The patients' medical histories were investigated for fulfilment of Sharp's (1), Kasukawa's (2), and Alarcón-Segovia's (3) diagnostic MCTD criteria. We defined overlap syndromes as simultaneous fulfilment of clinical as well as immunological criteria of two defined rheumatic diseases. Disease conversion was defined as emergence of new symptoms and autoantibodies consistent with another rheumatic disease. Remission was defined by simultaneous systemic lupus erythematosus disease activity index 2000 (SLEDAI-2 K) of 0 and European League Against Rheumatism scleroderma trial and research (EUSTAR) activity index <2.5. Disease phenotype and disease activity were monitored over time and all patients were evaluated for fulfilment of classification criteria of various connective tissue diseases.

Results: Out of 85 patients initially referred as MCTD, only one third fulfilled the diagnostic MCTD criteria. Most of the remaining patients had undifferentiated CTD (29%) or overlap syndromes (20%). In our final cohort of 33 MCTD patients, 6 (48%) also met the classification criteria of systemic sclerosis, 13 (39%) those of systemic lupus erythematosus (SLE), 6 (18%) those of rheumatoid arthritis, and 3 (9%) those of primary myositis. Over the median observation period of 4.6 (1.6, 9.9) years, only two patients (6%) underwent disease conversion from MCTD to SLE and no patient converted towards other diseases. The number of patients in remission increased from 6 (18%) to 15 (45%) due to introduction of immune modulatory treatment. Combination therapy was favoured in most cases (17 patients, 52%), whereas monotherapy was less frequent (12 patients, 36%), and only 4 (12%) patients remained without immune modulators until the end of the follow-up period. Hydroxychloroquine, prednisone, and methotrexate were the most frequently used medications in our cohort.