Review

Systemic sclerosis and environment: an intriguing and still debated association

G. Lepri, S. Bellando Randone, A. Damiani, J. Blagojevic, S. Guiducci

Division of Rheumatology, Department of Experimental and Clinical Medicine, AOU Careggi, University of Florence, Italy.

Gemma Lepri, MD
Silvia Bellando Randone, MD, PhD
Arianna Damiani, MD
Jelena Blagojevic, MD
Serena Guiducci, MD, PhD

Please address correspondence to:
Gemma Lepri
U.O. di Reumatologia,
Dipartimento di Medicina Clinica e Sperimentale,
Azienda Ospedaliero-Universitaria Careggi,
50139 Firenze, Italy
Università di Firenze,
50139 Firenze, Italy.
E-mail: lepri.gemma@gmail.com

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ABSTRACT

Systemic sclerosis (SSc) is characterised by a heterogeneous clinical expression probably reflecting the different genetic background of each patient. Progress has been made in the definition of the principal pathogenetic events of the disease that can be summarised in endothelial damage and dysfunction, inflammation with activation of immune system and fibrosis. The aetiology of the disease still remains to be clarified and probably the first events are attributable to the repeated action of environmental stimuli in genetically predisposed subjects.

The aim of the present manuscript is to review the most recent and relevant data regarding the association of SSc with environmental factors.

Introduction

Systemic sclerosis (SSc) is a rare connective tissue disease clinically characterised by functional and structural micro-angiopathy and by fibrosis of skin and internal organs (1). Vasculopathy and fibrosis may express heterogeneously in SSc patients making the disease extremely varied from a phenotypic and prognostic point of view. However, almost all patients present specific serum antibodies (anticentromere, anti-topoisomerase I and anti-RNA polymerase III) together with antinuclear antibodies (ANA) (2). The clinical and laboratory disease features reflect the main SSc pathogenetic events, characterised by an early vascular damage, a dysregulation of innate and adaptive immunity and fibrosis due to fibroblasts proliferation and differentiation and to collagen and other extracellular matrix proteins production (3).

In the last few years, important steps have been made in understanding the more significant pathogenetic events of the disease (3, 4). However, the explanation of disease aetiology remains elusive, although it has been hypothesised that it involves environmental trigger factors acting in genetically predisposed subjects (3, 5). In fact, a greater disease incidence has been observed among family members rather than in the general population, therefore a genetic SSc susceptibility could represent a risk factor for the development of the diseases (6, 7). Although the exact mechanisms of interaction between endogenous and exogenous trigger factors and genetic background are unknown, environmental stimuli are recognised to have a significant role in the aetiology of the disease (8).

In this review we report the most relevant data on environmental factors associated to SSc, especially focusing on the debated relationship between the disease and occupational risk factors, silicone breast implants, infectious triggers, with particular reference to the recent scientific interest regarding the potential role of SARS-CoV-2, and microbiome.

Occupational risk factors

Among environmental factors, chemical agents, such as organic solvents, silica dust, particulate matter and epoxy resins, have long been considered possible trigger factors for the disease (9, 10). In 2017, a systematic review confirmed the suspected relationship between SSc pathogenesis and chemical agents as silica and solvents (9).

Blanco-Pérez *et al*. recently reported the presence of systemic autoimmune rheumatic disease in 54/489 (11%) patients with silicosis; in particular, the authors described 10 cases of SSc (2%). In this Spanish cohort, the presence of an autoimmune rheumatic

disease was associated with a higher number of emergency department visits and with a radiological progression of silicosis (11).

A previous study on 100 SSc patients reported that occupational exposure to toxic products may have a role in the development of the disease, in fact authors showed increased odds ratio (ORs) for SSc for crystalline silica, white spirit, chlorinated solvents, trichlorethylene and welding fumes (12).

In 2020, an observational study explored the association of lifetime exposure to silica and lung involvement in SSc patients, reporting an association between silica exposure and oesophageal involvement, hilar and mediastinal lymphadenopathy, male gender and lower total lung capacity (% predicted) at diagnosis. The univariate analysis showed a correlation between a worsened pulmonary performance and high silica exposure score and hilar and mediastinal lymphadenopathy. The multivariable analysis confirmed the association between a worsening of lung involvement and the combination of hilar and mediastinal lymphadenopathy. These data seem to suggest a possible role of silica in altering the function of lung macrophages and promoting lung inflammation (13).

A recent study compared two population of SSc patients (72 with silicosis and 238 without silicosis), reporting an increased prevalence of male gender and a lower age at SSc onset in the first group. In addition, patients with silicosis presented a higher disease severity with a more frequent cardiopulmonary involvement and an increased overall mortality rate (14).

Ferri *et al*. showed high levels of serum silica levels in SSc patients with history of occupational exposure. In addition, this study reported a correlation between serum silica levels and a diffuse cutaneous subset, the presence of inflammatory muscle involvement and lung fibrosis (15).

Erasmus syndrome (ES) is defined as the association between silica and the subsequent development of SSc and several case series supported this association (16-18). Evaluating 947 SSc patients, Rocha *et al*. reported a prevalence of ES of 0.9% (9/947 patients) and confirmed the association of ES with male gender, severe cutaneous involvement, anti-topoisomerase I antibodies and bad prognosis. However, the multivariate analysis did not confirm silicosis as an independent risk factor for SSc patients (19).

Another previous study reported a correlation between the exposure to occupational toxic substances and SSc phenotype and severity. Magnant *et al*. investigated the exposure to occupational risk factors (silica dust, welding fumes, solvents, epoxy resins) in 105 patients. 39/105 subjects were exposed to these toxic substances and in this population a higher prevalence of male gender was described. In addition, an association between the exposure to toxic products and lung involvement, diffuse cutaneous subset and anticentromere negativity was shown (20).

A more recent retrospective study evaluated environmental factors exposure (silica, solvents, pesticides, breast implants and medications) in 662 SSc subjects, reporting a prevalence of 10.6% (70/662 patients). Among these, 36 patients reported exposure to solvents, 14 to silica, 9 to silicone and 8 to pesticides. Also, this study showed a higher prevalence of male gender in the exposed population. In addition, in these patients, a higher frequency of myopathy (particularly in those exposed to silica), alterations in skin pigmentation and a more severe lung fibrosis were detected (21).

The evaluation of 96 patients included in the Belgian SSc cohort revealed a probable exposure to toxic substances in 55 patients (57.3%): 11 subjects (11.5%) presented a probable exposure to solvents, 2 (2.1%) to asbestos and 2 (2.1%) to silica and solvents. The authors showed that occupational exposure was increased in SSc male patients. In addition, exposed patients, particularly those to solvents, presented a higher prevalence of smoking status. Although not significant, patients with a history of occupational exposure to silica or solvents had a higher disease activity score and an increased prevalence of diastolic dysfunction (22).

Bobeica *et al*. investigated the role of aetiological factors in 37 SSc patients in the southeast of Romania evaluating smoking status, occupational exposure to toxic products and history of psychological events before the development of the disease. The authors suggested a combination of different factors in the aetiology of the disease, reporting occupational exposure to toxic substances and industrial pollutants in 24.3% patients, smoking status in about half of the subjects and a history of major traumatic psychological events before the onset of the rheumatic disease in the majority of patients (81.1%) (23).

In another study the evaluation of hair samples revealed higher levels of some metals (antimony, cadmium, leas, mercury, molybdenum, palladium and zinc) in SSc patients compared to controls suggesting an association between SSc and exposure to heavy metal (24). In this context, other data suggested a certain role of heavy metals exposure influencing the risk for SSc (25).

Environmental air pollution has been associated with the development of SSc and the exposure to particulate (PM10) and benzene seems to correlate with SSc features. Borgini *et al*. reported an association between the concentration of benzene and disease severity, particularly a higher skin involvement and a decreased diffusion lung carbon monoxide (26). Another recent study revealed a certain correlation between the exposure to air ozone and severe fibrotic pulmonary involvement and disease progression (27). Interestingly, it has been suggested that air pollution also worsens Raynaud's phenomenon (RP) severity in SSc patients. However, given the correlation between environmental temperature and air pollution and the strong influence of temperature on RP, further studies are required to confirm the possible effect of environmental pollution on the severity of RP (28).

Previous data suggested an association of smoking with gastrointestinal and respiratory symptoms in SSc, although not confirmed by other studies. Comparing two SSc populations (208 ever-smokers and 153 never-smokers), a correlation between the presence of

anti-topoisomerase I antibodies and being never-smokers was described (29). A recent study investigated the relationship between smoking and disease features in the EUSTAR cohort. The authors reported a correlation between smoking and mortality in SSc men and a greater risk of skin progression in ever-smoking women. In addition, smoking was associated with a reduced frequency of anti-topoisomerase I antibodies in female patients and with an increased risk of mortality, skin progression and "any organ progression", regardless of positivity for anticentromere or topoisomerase I antibodies (30).

Breast implants

The suspected correlation of SSc and breast implants still represent a debated topic in scientific literature (31, 32). Already in 1989, Varga *et al*. reported an association of SSc onset and cosmetic mammoplasty with silicone-gel implants in four patients (31). However, several years later, the review by Lipworth *et al*. did not confirm a consistent association between cosmetic breast implants and connective tissue disease (CTDs) (32).

More recently, the cross-sectional study by Watad *et al*. reported a strong association of silicone breast implant and SSc, regardless of the reason for the implant (reconstructive or cosmetic indications) (33).

In 2021, Lazzaroni *et al*. reported a history of silicone breast implants in 12/742 (1.6%) SSc women. Evaluating the 11/12 patients in which the onset of SSc occurred after the breast implant, the authors reported an association of anti-RNA polymerase III antibodies and silicone breast implants, particularly in cases with rupture of the implant (34). These data were in line with results from another study showing a higher frequency of silicone breast implants in SSc patients with anti-RNA polymerase III antibodies than in those with anti-topoisomerase I or anticentromere antibodies, suggesting a possible association of silicone breast implant and the development of a specific subset of SSc characterised by anti-RNA polymerase III antibodies (35).

However, all these studies remark the need for future analyses on larger populations. In addition, the mechanisms underlying the increased risk of SSc in patients with silicone breast implants needs to be clarified also investigating possible interaction between bacterial biofilm on the implant and host microenvironment (36).

Infectious agents

The trigger action of many infectious agents has been largely proposed in the early aetiopathological events of SSc. In this context, previous studies suggested a link of cytomegalovirus (CMV) infection and SSc vasculopathy as the virus seems both to directly damage endothelial cells in SSc patients and to decrease the number of progenitor cells useful for the vasculogenesis through the involvement of bone marrow (10, 37-39).

In the past, the possible involvement of Parvovirus B19 infection in SSc aetiopathogenesis was suggested by studies reporting that SSc patients present higher levels of serum B19 antibodies and of viral DNA in skin and bone marrow samples (10, 40-42).

Ebstein-Barr virus (EBV) DNA, mRNAs and proteins have been found in the skin of SSc patients and data showed that EBV infecting human fibroblast may induce a myofibroblast phenotype typical of SSc (43). In addition, the evaluation of skin biopsies from SSc patients suggested that EBV infection could directly damage endothelial cells and EBV lytic antigens have been detected in dermal vassel. Furthermore, in SSc patients, the levels of EBV loads seem to correlate with the presence of digital ulcers and with an advanced pattern at the nailfold videocapillaroscopy (active or late pattern) suggesting a certain correlation of EBV infection with SSc vasculopathy (44).

In addition to CMV, EBV and ParvovirusB19, the prevalence of other infectious agents such as Helicobacter pylori has been found to be higher in SSc patients than in control subjects (45, 46). In this context, evaluating 2431 SSc patients and 12710 controls, Tiosano *et al*. and reported a higher prevalence of chronic hepatitis B virus and hepatitis C virus in the first group of patients (47).

In the last few years, many scientific efforts have been made to investigate the possible role of SARS-CoV-2 infection in the aetiology of autoimmune diseases.

Already one year after the first cases of SARS-CoV-2 infection, a wide number of case reports described patients with autoimmune-like phenomena in COVID-19 (48). In fact, the presence of autoantibodies, such as antiphospholipid, anti-neutrophil cytoplasmic antibody (ANCA), anti-MDA5 and anti-SSA/Ro antibodies have been described in SARS-CoV-2 infected subjects (48-51). In addition, different skin manifestations, among which chilblain-like lesions, have been reported in COVID-19 patients (52).

In 2023, comparing SARS-CoV-2 infected patients and negative patients Chang *et al*. confirmed a higher risk of some autoimmune rheumatic diseases, including SSc (aHR:2.58, 95% CI:2.02–3.28), in the first population (53).

In recent years, some case reports described the onset of SSc after COVID-19 infection (54-58).

In 2021, the case of a 47-year-old man diagnosed with an overlap syndrome [SSc and polymyositis (PM)] after COVID-19 was reported. The patient presented RP, heliotrope rash, periorbital oedema and muscular weakness with dysphagia associated with ANA, anti-PM/Scl75 and anti-PM/Scl100 positivity after the SARS-CoV-2 infection. Lung high-resolution CT (HRCT) also revealed early signs of interstitial lung disease (55). In 2022 Chandra *et al*. described the case of a woman complaining of RP, and other symptoms such as fatigue, xerostomia, dysphagia, weakness and diffuse skin hyperpigmentation after a SARS-CoV-2 infectious pneumonia. She also presented puffy fingers with sclerodactyly, abnormal nailfold videocapillaroscopy, ANA positivity and signs of non-specific interstitial pneumonia at the HRCT, satisfying the 2013 ACR/EULAR classification criteria for SSc (57). More recently, the case of a woman developing SSc after SARS-CoV-2 infection has been reported. This patient was treated with corticosteroid therapy for polyarthralgia and later she clinically worsened, presenting recurrent scleroderma renal crisis (SRC) (58).

Beyond the possible action of SARS-CoV-2 infection as suspected trigger factor for the onset of SSc, other studies also investigated the influence of SARS-CoV-2 infection on patients with established SSc. In this context, Rimar *et al*. recently reported a case of a man with limited cutaneous SSc presenting SRC after 3 weeks from an asymptomatic COVID-19 infection. He started to complain of headaches after 3 weeks from the onset of the infection. The clinical evaluation revealed an increase in blood pressure, mild haematuria on urine test and new onset anaemia with schistocytes (59). The case of a female with a diagnosis of limited cutaneous SSc and overlap syndrome SSc-PM and with a rapid progression of cutaneous, cardiac and lung involvement after a repeated SARS-CoV-2 infection was recently reported (60). Similarly, a case of a 14-year-old girl with overlap syndrome (SSc-PM) who experienced a progression of disease, especially in its vascular, muscle and lung involvement, after COVID-19 has been described (61). These reports suggest the possible role of infections, in this case COVID-19, as triggers of disease flares. The action of SARS-CoV-2 spike protein has also been studied in bleomycin-induced SSc mouse model demonstrating a higher dermis thickness and lung fibrosis. In addition, the authors confirmed an increased immune system activation with production of antiphospholipid antibodies in infected mice (62).

All together, these reports may suggest that SARS-CoV-2 as well as other viruses could induce autoimmunity phenomena (63, 64).

Furthermore, the risk of Sars-COV2 infection is reported to be higher in patients with autoimmune diseases when compared to controls (65), as also shown by an Italian observational multicentre study including more than 1600 patients with autoimmune diseases (66). These results have been confirmed by another Italian study reporting a more frequent definite COVID-19 in SSc patients with pulmonary fibrosis compared to those without lung involvement (67), and data from another SSc population showed a more severe infection in SSc patients with interstitial lung disease (68). In this context, Güler et al. recently suggested that SSc patients with lung involvement, severe disease activity, more than one comorbidity and treatment with mycophenolate were at major risk of COVID-19 adverse outcomes (69).

All these data suggest a possible role of COVD-19 as a trigger factor in SSc, highlighting once again that the disease can be considered the result of a combined action of multiple endogenous and exogenous factors in predisposed subjects. The scientific enthusiasm of the last years regarding COVID-19 and SSc suggest also including SARS-CoV-2 among the suspected infectious triggers.

Microbiome

In the last years, there has been growing interest in the analysis of skin and intestinal microbiome in SSc. In fact, recent studies have highlighted the possible presence of gastrointestinal (GI) microbial dysbiosis from the earliest phases of SSc, suggesting its potential role in the pathogenesis of GI involvement. In addition, alterations in microbiome seem to correlate with the severity of GI symptoms (70-72). Furthermore, changes in gut microbiome are reported to correlate also with extra-intestinal disease features. In this regard, Russo *et al*. described different composition in GI microbiome comparing SSc patients with anti-topoisomerase I antibodies and those with anticentromere positivity (73). Andréasson *et al*. reported an association between dysbiosis and extra-GI manifestations, such as telangiectasias, pitting scars and pulmonary fibrosis (72). However, to understand whether changes in microbiome cause the disease or are the results of SSc still remains to be clarified and studies on animal models are mandatory to better understand the role of gut microbiome in the pathogenesis of SSc. In this regard, Tang *et al*. detected similar changes in gut microbiome in SSc patients and bleomycin-induced mice model (74).

Recent studies have also reported changes in skin microbiome in SSc patients, as described by Johnson *et al*., evaluating SSc and controls skin biopsies. Furthermore, the authors described a correlation of skin dysbiosis with disease duration and inflammatory gene expressions signatures, suggesting the possible role of microbiome changes in the pathogenesis of the disease (75).

To note that the skin as well as the GI tract represent one of the main targets of the disease and the changes in microbiome composition may be a consequence of the anatomical structural alterations due to SSc (76).

Conclusion

SSc is a complex chronic autoimmune disease, and its aetiology still remains to be clarified. Although the main pathogenetic processes are partially known, the first aetiological events of the disease are undetermined. The most accredited hypothesis suggests a close connection between environmental triggers and genetic susceptibility in the aetiopathogenesis of SSc. When discussing environmental stimuli as potential disease triggers, we are referring to numerous possible exogenous factors also including the exposure to pollution, chemical or physical agents, climatic factors, working activities, infectious stimuli, environmental temperature, diet, geographic area. Essentially, we refer to all non-endogenous factors that may cause an immune system dysregulation in genetically predisposed subjects.

However, to understand the link between exogen stimuli and the onset of the disease remains a challenge due to the phenotypic heterogeneity of SSc patients and the difficulty in quantifying exposure to environmental stimuli. In addition, it is likely that in each SSc patient different triggers may sequentially act also showing a gender preference.

In the present review, we reported the most recent studies focussing on the association between SSc and environmental factors, with reference to occupational risk factors, smoking status, breast implants, infections and microbiome. The possible SSc onset after exposure to specific toxic substances such as silica, epoxy resins or solvents or after infections has led to a growing

interest in a probable environmental aetiology of SSc. In recent years, a number of cases of SSc onset after SARS-CoV-2 infection have been described, highlighting the possible action of infectious stimuli in the aetiopathogenesis of SSc. In addition, recent studies have focussed on the complex relationship between SSc pathogenesis and changes in skin and or gut microbiome. Furthermore, the intriguing connection between SSc and environmental factors seems to be related not only to the development of the disease, in fact it has been reported that exogen stimuli also influence the disease phenotype.

In conclusion, the available data seem to confirm a certain role of exogenous stimuli both in the development of the disease and in influencing its clinical characteristics or exacerbations, however further high-quality research aimed at better clarifying the relationship between environmental stimuli and SSc is needed and must be encouraged.

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