Journal of Dermatology and Skin Science

Review Article Open Access

Silica and Connective Tissue Disorders: The Important Role of the Dermatologist

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Article Info

Article Notes
Received: January 04, 2022
Accepted: April 19, 2022

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Keywords
Silica; Autoimmune diseases
Artificial stone
Silicosis
Scleroderma
Mixed connective tissue disease
Raynaud's phenomenon

Abstract

Dermatological manifestations of connective tissue diseases (CTDs) are common and frequently precede other symptoms. Thus, dermatologists may be the first clinicians to diagnose these disorders. Silica exposure is an acknowledged cause of several CTDs, but this is under-appreciated by clinicians, who may also be unaware of the wide range of jobs in which silica exposure can occur. The CTDs associated with silica exposure include systemic sclerosis (SSc), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis and overlap syndromes. Silica-related systemic sclerosis (Si-SSc) is associated with a specific antibody profile and more severe disease. Silicosis has re-emerged worldwide recently due to several new workplace exposures, including a new type of silicosis (artificial stone (AS) silicosis), which is associated with a particularly high rate of auto-antibody formation. Dangerous work practices are still occurring. This article summarises recent literature on the topic of the resurgence of silicosis and silica-induced CTDs and reminds dermatologists of the importance of taking a thorough occupational history in all patients. Early intervention in CTDs and reduction in dust exposure can reduce risk and improve prognosis. Treatment options are rapidly improving.

Introduction

Autoimmune diseases (AID) are complex disorders involving immune responses to self-antigens. Although of unknown etiology, these are currently believed to result from interactions between genetic and environmental factors[1]. Connective tissue disorders (CTDs) are a subset of AID, affecting tissues such as the skin, joints and cartilage. Skin manifestations occur in almost all CTDs, making the dermatologist a key player in the diagnosis and management of these clinically heterogeneous conditions. Cutaneous manifestations may occur before systemic disease and can enable early risk stratification into subtypes, which affect prognosis. Both local and systemic diseases are increasingly treatable using modern therapeutic approaches[2].

There are many different CTDs, and evidence about their origins increasingly suggests an environmental contribution toward their development; collectively these are frequently encountered in clinical practice. Estimates of CTD prevalence in developed countries range between 3-7% of the population[3], and they are generally more common in women. There is now convincing evidence that several CTDs, including scleroderma (SSc), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) are associated with exposure

to crystalline free silica (CFS), and evidence regarding other CTDs is evolving. These are not new findings, the relationship having been suggested over a century ago[4].

Interest in this area has been stimulated by the recent re-emergence of severe silicosis in young workers, with several deaths from this totally preventable disease. The tragedy of denim-associated silicosis in the early 2000s in Turkey showed that a fashion item could literally become something "to die for"[5]. These workers were sandblasting, a practice which has been known to be highly dangerous for centuries. Also, a severe new type of progressive silicosis was described in 2010[6], now known as artificial stone (or engineered stone) silicosis. Existing legislation nominally restricted silica exposure to safe levels. Nonetheless it was late-stage disease which first presented to clinicians[7], highlighting the gap between regulation and actual workplace practice. Engineered stone (or artificial stone, AS) silicosis has subsequently been found in many other countries including Israel, Italy, China, Belgium, the USA and Australia[8-12]. Case finding studies in Australia have demonstrated that this is disturbingly common even in a wealthy, highly regulated country[13].

AS dust exposure is associated with a particularly high rate of autoimmunity[9,13]. Because of the long latency between exposure and disease, the future legacy of these exposures has yet to be revealed. At the same time, there has also been a resurgence of cases of silicosis in the coal mines of the USA, related primarily to higher silica exposures[14], and the association between coal dust exposure and arthritis has been re-visited[15]. These developments have been described at a time when basic knowledge regarding the pathophysiology of adverse effects of silica exposure is improving, revealing that low level silica exposure is probably more dangerous than has previously been believed[16-18].

These events have highlighted the relevance of inhaled exposures in the pathogenesis of CTDs and the need for clinician awareness. Clinicians cannot assume that modern workplace dust exposures are too low to produce significant disease. We need to take a continued interest in the work that our patients do and remember to take a careful history of potential environmental exposures, some of which may have occurred many years ago. Clinicians still play a vital role in identifying and understanding these disorders.

Silicosis: a disease revisited

Silicosis is a disease most dermatologists will probably remember from their medical school days, but hopefully few will encounter in their day-to-day practice. Silica and silicates are ubiquitous minerals which are the basic components of soil, sand and granite. Silicosis is a fibrotic lung disease which only occurs with relatively high silica inhalation and has specific radiological and pathological characteristics[12]. Silicosis is mainly caused by the inhalation of free silica (silicon dioxide (SiO2)), a crystalline form of the element silica. Respirable crystalline silica (RCS) is that fraction of SiO_2 which can be inhaled into the peripheral lung and comprises the "silica" which is regulated and measured in workplaces. RCS is usually found as quartz, which is the major constituent of most soils and rocks. Thus, it is frequently encountered in mining, quarrying, road building and is used in a surprisingly wide variety of industrial processes. Silicosis can also occur after inhalation of amorphous silicates, such as China clay and diatomaceous earth[18]. Silicates are SiO_2 linked with another element, usually a metal oxide, and are also very common in the occupational environment.

Silicosis differs from silica exposure, where no pulmonary fibrosis is present, but where a pathophysiological response to silica exists. The dose required for production of disease is not uniform among humans and no threshold for the fibrotic response has been documented[19-21]. Most silica-related disorders (including CTDs) have been described at levels which are too low to produce pulmonary fibrosis, and the actual dose which is safe for inhalation is debatable[21,22]. Genetic susceptibility and co-exposure to other environmental factors are also very likely to play a role. Nonetheless, it is clear that the more RCS inhaled, the greater the risk of disease. Freshly fractured particulate silica is more toxic than older silica particles[12,21,22], and thus the risks from cutting, grinding and blasting are higher than simply working with weathered rock. Silicone (as used in breast implants), is a totally synthetic product, and does not cause silicosis, although it has been implicated in autoimmune disorders[24].

It has taken many years for the full range of effects of silica dust inhalation to be appreciated. As well as silicosis and CTDs, RCS is now known to cause several other lung disorders, including lung cancer, diffuse interstitial pulmonary fibrosis (or diffuse dust-related fibrosis), chronic obstructive pulmonary disease (COPD, which includes emphysema), and is also implicated in renal disease[23,25]. The development of all these diseases is dose-related. In real life, patients are exposed to a mixture of different dusts, and often also other inhaled substances such as tobacco fumes, vapours and organic dusts, especially over a long working career. Thus, it can be difficult to tease out the different effects of exposures, which is why it is very helpful to have exposures documented contemporaneously.

Prevention of silica-related disease

Silica-related disease is believed to be totally preventable using modern dust control measures ie reduction of dust production, dust suppression (often using water), and ventilation. The use of masks (or personal protective

equipment, PPE), represents a last-ditch control method which should not be relied upon[20]. Early diagnosis (or early documentation of excessive exposure) with reduction or removal from exposure will prevent or slow progression and enable treatment if required. This is the rationale for the periodic surveillance programs which are mandatory in many workplaces[26,27], but which may not actually occur in practice.

The wide range of occupations in which silica exposure may occur

Silica is the most abundant mineral on earth, and clinicians may not appreciate just how many jobs involve exposure to silica and silicates (Table 1). Silica is invisible to the naked eye, so exposure may go unnoticed. Freshly fractured particulate silica (crystalline silica or quartz) is produced in any job which involves drilling or fracturing rock[25]. Silicosis has traditionally been recognized in the so-called dusty trades (mining, particularly coal, gold, shale and granite), polishing (e.g., the knife grinders of Sheffield) and in tunnelling. Exposure commonly occurs nowadays in construction of dams and roads, and in the pottery, ceramics, brick, tile and cement industries[20,28,29]. Silica is widely used in many industrial processes. More recently, silicosis has been described in less obvious trades like jewellery[30] and dentistry[31]. It is estimated that more than 40 million workers are at risk from exposure from RCS[32-34]. These are usually (but not always) manual workers, from lower socio-economic groups.

Several work practices are particularly associated with a high risk of silicosis, such as abrasive blasting using sand (sandblasting)[35] and cutting or polishing artificial stone. Sandblasting involves forcibly propelling a stream of abrasive material against a surface under high pressure – a system ideally suited to produce respirable particles, which may derive not only from the abrasive material but also from the surface blasted. Sandblasting was the practice causing the Turkish denim jean outbreak of silicosis in 2006[5] and was subsequently banned due to popular outcry[36]. Substances other than sand can be substituted e.g., metals, steel grit, coal slag, glass beads, or "softer" ones like crushed nut shells or magnesium sulphate, in which case the lung disease may look atypical. Abrasive blasting is still common in industries involving ship, car and pipe repair and production of monuments or signs.

The introduction of new products can also change risks. Engineered (or artificial) stone is a relatively new building product made by mixing finely crushed rock with polymeric resin. It is available in hundreds of different varieties and is very attractive; the product is cheaper and more durable than traditional stones and sales have increased exponentially over the last 15 years. The content of RCS in AS can be very high (approximately 90 % compared to 3% in natural marble and 30% in granite). AS is factory manufactured then cut to size on site using power tools, producing very high levels of RCS[25]; high levels of silica nanoparticles are generated[37]. Despite excellent knowledge regarding the hazards of use of high silica content-stones and existing regulations requiring dust control measures, control measures have been rarely used in practice[13]. Even dust suppression by using water (wet cutting), a practice which has been known for centuries to significantly suppress silica dust levels, has been neglected, as has been PPE. The silicosis which resulted in these workers has been more rapidly progressive than with other types of silicosis and has been accompanied by a high incidence of positive autoimmune autoantibodies, up to 60% in some studies[9,13]. Lung transplants have been required in several patients and the full spectrum of autoimmune disease which will evolve from this exposure is as yet unknown. Silica nanoparticles may play an important role[37,38], acting via impairment of macrophage efferocytosis[39].

Table 1. Jobs commonly involving exposure to crystalline free silica (CFS).

Stone and brick masonry: paving, surfacing, angle grinding
Artificial stone fabrication and installation: manufacture, cutting, drilling, polishing
Sandblasting: cleaning and priming of surfaces, glass etching, stone washed denim
Concreting: air polishing, jackhammering, chiselling
Construction: plastering, roofing, rendering
Demolition: labouring, plant operating, cleaning
Mining: cutting, blasting, tunnelling, bolting
Quarrying: excavation, earth moving, stone processing
Tunnel construction: drilling, boring
Hydraulic fracking: gas and oil wells
Road construction and maintenance: earthworks, asphalt, concrete and bitumen laying
Foundry work: metal casting, surface cleaning
Pottery work: porcelain, ceramics, clay
Jewellery production: grinding, polishing, sanding
Glass manufacture: handling, mixing and transporting raw materials, sandblasting
Dental technicians: levelling, smoothing and polishing of porcelain prostheses
Agriculture: inorganic dust exposure in the stockyard, ploughing and harvesting

New practices such as hydraulic fracking are also likely to involve significant RCS exposure. Fracking to recover hydrocarbons involves using large volumes of water along with a solid (called a proppant) and sand is often used for this purpose. The US National Institute of Occupational Safety and Health (NIOSH) has recently recommended substitution of sand by non-silica proppants to reduce dust levels, after a study showed that more than 50% of measured exposures in several US states exceeded the permissible exposure limits[40].

Unrecognised silica exposure and that occurring in non-occupational settings

Significant RCS exposure also may occur in non-occupational settings, but this has been much less studied. Non-occupational exposures can occur in ordinary life, for example when using scouring powders, cleaning dusty clothes, and in do-it-yourself hobbies[41]. Silicosis can occur from inhalation of agricultural and desert dusts, particularly dust storms[42]. Silicosis has also been described in animals including horses and camels[43,44]. These types of activities tend to pass unnoticed and respiratory protection is seldom used; questions about these exposures are hardly ever recorded in questionnaires or taken into account in case-control or cohort studies.

Silica and connective tissue disease

There is a now a convincing body of evidence confirming an association between RCS exposure and CTDs[1,45-48]. The evidence for a causative relationship is currently most convincing for SSc and RA. Pre-clinical features of autoimmunity, such as autoantibodies, as well as clinical autoimmune diseases occur in the absence of established silicosis, suggesting that events prior to fibrosis are important for silica-induced autoimmunity. Basic science and animal studies have elucidated potential mechanisms[16,17,38]. These suggest that the ingestion of silica particles by alveolar macrophages activates the innate immune system leading to the production of proinflammatory cytokines and pulmonary inflammation (Figure 1). This leads to activation of adaptive immunity, loss of tolerance and the production of autoantibodies. Fibroblasts are stimulated to proliferate and produce collagen which encases silica particles resulting in fibrosis and silicotic nodules[16]. There are several excellent reviews and meta-analyses available for the interested reader[46,47] as well as comprehensive summaries from government agencies[48-50].

Systemic sclerosis (SSc)

Systemic sclerosis is a rare disease with a widely varying incidence and a female predominance. The incidence of SSc in women reported to be up to 14 times higher than that in men[51]. The low concordance rate reported in twin studies and the unequal geographic distribution of SSc[51-53] suggest that environmental factors are relevant to disease initiation. Thus, when SSc occurs in a man, an occupational or environmental contribution should be suspected.

Knowledge about the link between silica and and SSc is not new. This was first described over 100 years ago by the Scottish physician Bryrom Bramwell[54], who specifically mentioned the importance of dermatologists in diagnosing

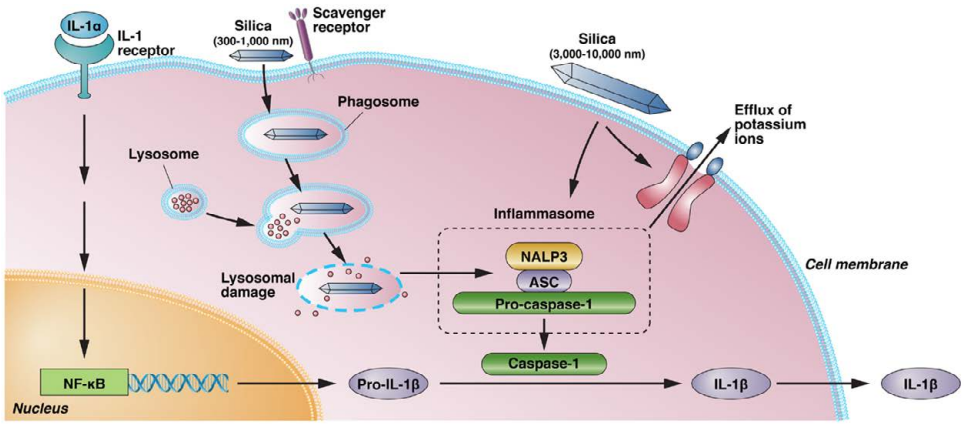

Figure 1: Silica-induced activation of inflammasome and IL-1 production. IL-1α, released from alveolar macrophages following crystalline exposure, results in NF-κB activation and transcription and translation of pro-IL-1β. Phagocytosis of crystalline silica leads to phagosomal damage and release of phagosome contents into the cytoplasm. This results in the activation of NALP3 and its association with the intracellular adapter protein ASC, which combines with and activates pro-caspase-1. The resulting inflammasome cleaves pro-IL-1β to the proinflammatory IL-1β. However, binding of immobilized silica crystals to the cell membrane of macrophages is also sufficient to induce IL-1β without evidence of lysosomal damage. Activation of the NALP3 inflammasome by silica also results in efflux of intracellular potassium ions, suggesting a possible interaction of silica with a membrane-associated protein, but it is unclear if K+ efflux following binding of immobilized silica crystals to the cell membrane results in inflammasome activation. Scavenger receptors have a role in the recognition and uptake of silica. NALP3, NACHT, LRR, and PYD domains-containing protein 3; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; NF-κB, nuclear factor-κB; IL, interleukin.
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Table 2. Meta-analysis of occupational silica exposure as a risk factor for scleroderma

Author	Study years	Study type	Effect size (95% CI)
Rubio-Rivas 2017 (68)	1960-2014	15 case control 4 cohort	overall OR= 2.81 (95%CI 1.86–4.23; $p < 0.001$) overall RR= 17.52 (95%CI 5.98–51.37; $p < 0.001$)
McCormic 2010 (65)	1949-2009	9 case control 3 cohort 4 other	Combined estimator of relative risk (CERR) 2.24 (95% CI, 1.65–3.31) CERR 15.49 (95% CI, 4.54–52.87)

scleroderma. In his paper, Bramwell notes that "*cases of diffuse sclerodermia come at least a frequently under the care of the general physician as under the care of the dermatologist*", and that he was able to tell the occupation of the patient "*as soon as I saw and felt the h*ands". It was not until 1957 that Erasmus from South Africa performed another study in miners, attempting to compare the incidence of SSc in gold miners with that in the general population[55]. Erasmus described 17 cases of SSc in miners who had "gross" sclerodermatous skin changes and had worked underground in gold mining for an average of 9 years. Only 6 had radiological silicosis, and there was an average 18 years from first dust exposure to when skin changes had started. The sites and types of skin lesions are carefully documented in his report. All had "*gross changes in the skin of the fingers, which were thickened, taut and glistening*", and 12 of the 17 had Raynaud's phenomenon despite the warm South African climate. Erasmus' report stimulated several more case series and case-control studies in later years[56-58].

In the 1960s Gerald Rodnan, a rheumatologist at the University of Pittsburgh, USA, became interested in the association and again confirmed "heavy exposure to silaceous dusts" in the men he studied. His patients were mainly coal miners although some worked as enamellers, pottery and foundry workers[59], and again Raynaud's phenomenon was common (10/26). Rodnan later developed the Rodnan skin score, a validated outcome measure for skin thickness in SSc[60] which is still used today.

Since then, many case-control and cohort studies been conducted[61-64] and summarised in reviews and meta-analyses[64-68]. In general, these confirm a significant association between silica exposure and SSc in males, more marked with cumulative exposure[64-66]. The association between SSc and silica appears to be with more severe forms of the disease[69]. A consensus report from National Institute of Environmental Health in 2012[48] listed silica as an environmental exposure that "we are confident contributes to the development of human autoimmune disease". This report summarised the evidence from 16 studies (3 cohort, 9 case control and 3 mortality studies). As would be expected, the different studies had a range of relative risk (RR) estimates, but 11 of the 16 RR estimates were >1.5. The mean RR from all studies was 3.2 (1.89-5.43), without a raised RR in females (1.03; 0.74-1.44). Cohort studies showed a RR of 15.49 (4.54-52.87), possibly due to higher exposures, while case control studies showed a lower RR of 2.24 (1.65-3.31)[47] (Table 2).

These data have been confirmed in many countries throughout the world, including in a recent 2020 Australian study where more than 30% of men in a systemic sclerosis registry of 1670 patients reported a history of silica dust inhalation compared with 3.7% of women[70]. The relationship between silica exposure and scleroderma is now so convincing that an accompanying editorial pointed out that this "could no longer be ignored"[71]. This has also been acknowledged by several international agencies including the UK Industrial Injuries Advisory Council IIAC[49]) and the French Agency for Food, Environmental and Occupational Health and Safety (ANSES)[50]. The latter concluded that the relationship is "certain and strong".

Clinical and autoantibody features

Although the clinical, serological and immunological features of Si-SSc were initially reported as identical to those of idiopathic disease[2,58,60-62], recent studies have suggested otherwise. Improvements in antibody testing, new methods of clinical assessment, and better clinical registry data have allowed better discernment between groups. Si-SSc is associated with more severe, progressive disease, with Raynaud's phenomenon, and progressive fibrosing interstitial lung disease (PF-ILD)[63-68].

Clinical studies contrasting silica-exposed and non-exposed patients have been reported[61,63-65,68], and there have been several meta-analyses[65,68], with a systematic review from 2015 noting 32 published studies and clinical data on 254 patients, the vast majority of whom were men (96%)[67]. Diffuse SSc predominated, with an overall prevalence of interstitial lung disease of 81%, and lower overall survival compared with those unexposed to silica.

More recent data has confirmed that silica exposure is highly associated with systemic disease and there are several clinical features which can be easily clinically assessed and are predictive of survival[63-69]. Raynaud's phenomenon (RP) affects almost all patients (>95%) and is one of the three criteria for early diagnosis of scleroderma, along with puffy fingers and ANA positivity[71], but these features do not predict prognosis. Nail fold capillaroscopy (NFC) can assess severity of microvascular damage and is considered a biological marker of disease progression, and predictive of multi-organ involvement in SSc[72]. Digital ulcers also predict survival and are associated with

pulmonary hypertension[72]. Diffuse disease, interstitial lung disease, digital ulcers, myocardial dysfunction and positive anti-Scl-70 are more closely associated with Si-SSc and indicate a worse prognosis[63,65,70].

These clinical features have been confirmed recently by Patel et al in the Australian SSc cohort[70], where clinical and immunological features of silica related and unrelated SSc were compared. In the silica-exposed group, there was a higher frequency of diffuse disease subtype, anti-Scl 70 antibody positivity, joint contractures and higher modified Rodnan skin score. Although ILD was more common in the silica-exposed group, the difference in prevalence between those exposed and non-exposed did not reach statistical significance (32.5% vs 27.0%, p=NS). All physician and patient-reported outcomes were worse in SSc male patients exposed to silica compared to those unexposed (p=0.02). Thus, simply asking the patient about work exposure to silica predicted worse physical function and higher disease activity.

Autoantibody testing is helpful for diagnosing SSc and also for distinguishing between different disease subtypes[73]. Autoantibodies are detected in > 90% of patients with SSc, usually anti-nuclear antibodies (ANAs), which are positive at a titre of >1:160. Two ANAs are relatively specific: anti-topoisomerase-1 (otherwise known as anti-Scl-70), and an anti-centromere antibody (ACA) called RNA polymerase III (RNApol3). Other anti-centromere antibodies (ACAs) are less specific for SSc, and more likely to be found in the limited cutaneous subset of SSc or CREST syndrome. ACAs are also produced in SLE, Sjögren's syndrome, RA, and primary biliary cholangitis, thus identifying SSc overlap syndromes[71-75].

Anti-topoisomerase antibodies (anti-Scl 70 or ATAs) and anti-RNA polymerase antibodies (ARAs) are highly specific for SSc and rarely detected in other autoimmune diseases[76]. They can be of different immunoglobulin subtypes eg IgG, IgM or IgA. ATAs are up to 99.6% specific although significantly less sensitive (24%) for SSc. ATAs are associated with diffuse SSc and a higher risk of interstitial lung disease (ILD). However, ATAs can also be positive in some cases of limited SSc. A particular ARA called RNA pol 3 or anti-RNA polymerase III is a marker of rapidly progressive skin involvement and an increased risk of renal crisis. ILD is linked to anti-topoisomerase, anti-U11/U12 RNP and anti-Th/To. Also, RNApol3 is topical because its emergence has been shown to coincide with the development of malignancy, suggesting that some SSc can be initiated by autoantigen mutation within the patient's cancer[77] Interestingly, in patients with positive RNApol3 the risk of different cancer types differs according to skin subtype. Thus, patients with SSc had an increased breast cancer risk (SIR 5.14, 95%CI 2.66–8.98), while those with limited scleroderma had a high lung cancer risk (SIR 10.4, 95%CI 1.26–37.7). In contrast, patients with ACAs had a lower risk of cancer (SIR 0.59, 95% CI 0.44–0.76)[76]. Thus, skin subtype combined with autoantibody subtype can be highly relevant to clinical course.

It seems likely that the observed variation in incidence of positive auto-antibodies (between 10% - 60 %) in patients with Si-SSc could reflect the wide range of different doses of silica acting on different genetic susceptibilities[9,76]; more information is needed on this topic. Also, brief exposure to dust with a high silica content could be associated with SSc, but this is seldom recorded. There is a need for further inquiry in this area using a multidisciplinary generalised approach. Hopefully, this will be assisted by a new initiative for SSc which is currently emerging using the 2013 ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) classification which aims to select patients very early in the disease process[78]. This (the **V**ery **E**arly **D**iagnosis **O**f **SS**c or VEDOSS approach) employs NFC and clinical detection of "puffy fingers" as well as ANA testing[78]. Dermatologists would be key contributors to this endeavour[79].

Overall, thus, it is clear that where dermatological and autoantibody features of SSc occur in a man, an additional history of silica exposure can identify a group of patients who are likely to progress and develop complications, and who should probably be followed up closely and treated earlier.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is another CTD with a female predominance. Although it has well described genetic predisposing factors (particularly HLA-DRB1 (the "shared epitope"), heritability only accounts for ~40–50% of seropositive RA, and ~20–30% of seronegative RA[80]. RA has been linked to exposures to many environmental agents, particularly in men[81], and there is now a substantial evidence base regarding RA and silica exposure.

The identification of anti-citrullinated protein antibodies (ACPAs, or anti-CCPs) in 1998 enabled better elucidation of potential mechanisms in the pathogenesis of RA, including the role of environmental triggers. ACPAs are present in the majority of patients with RA and are highly specific (88-96%), allowing early diagnosis even before clinical manifestations occur[82]. Cigarette smoking is an important environmental trigger for RA and is, like silica, associated with ACPA positive disease. The lung is probably an initiating site of injury[83], in bronchus-associated lymphoid tissue (BALT), with an interaction between two or more toxins potentially enabling auto-antibody formation. Although other environmental risk factors have also been described (e.g., mineral oils, farming and pesticide exposure, electrical work, pollution), the strongest association documented to date with occupational agents is with silica.

Table 3. Systematic Review and Meta-analysis on the Association Between Occupational Exposure to Crystalline Silica and the Risk of Developing Rheumatoid Arthritis

Author	Study year	Study design	Effect Size (95%CI)
Morotti 2021 (91)	1986- 2019	7 case control 5 cohort	OR =1.94 (95% CI 1.46–2.58).
Mehri 2020 (92)	1987-2018	8 case control 5 cohort 2 cross sectional	OR = 2.59 (95% CI = 1.73 - 3.45).

The association between RA and silica dust exposure was first reported by clinicians many years ago by both Colinet in Belgium[84] and Anthony Caplan in Wales[85]. Caplan described multiple, rounded opacities on the chest X rays of coal miners which were not pneumoconiosis. Miners either had RA or those later developed this; he noted these were associated with rheumatoid nodules of the skin. He suggested that "*in the majority of cases the association of the two conditions is more than coincidental*". This association was confirmed in later studies and much epidemiological research[86-94].

Collectively, this work has consistently reported a raised RA in individuals exposed to silica (Table 3)[91,92]. A recent meta-analysis[92] found a significant association between occupational exposure to silica with a relative risk of developing RA of 2.59 (95% CI 1.73-3.45), similar to the increased risk produced by smoking (2.49, 95% CI 1.13-3.86). In general, the risk is for ACPA-positive RA, consistent with Caplan's original description. An intriguing interaction with cigarette smoking has also been noted. In one study, the risk for ACPA-positive RA among silica-exposed current smokers was 7.4 times higher than among non-smokers without silica exposure, exceeding the risk expected from the separate effects of silica and smoking[89]. However, the recent Swedish National Registry Case-Control Study, published in 2021, found a statistically significant increase in OR for both seropositive and seronegative RA but in men alone. Relative risks were much lower at 1.22 for seropositive RA and 1.23 for seronegative RA[94].

These studies suggest a causative association between ACPA-positive RA and silica exposure. There is currently insufficient information regarding any particular clinical features which could distinguish between silica-induced and other types of RA: this needs to be examined in the future.

Systemic Lupus Erythematosus, ANCA positive vasculitis, Sjogren's syndrome and overlap syndromes

There is less evidence available on exposure to silica and SLE, anti-neutrophil cytoplasmic autoantibody (ANCA) positive vasculitis, Sjogren's syndrome and overlap syndromes. Because of their rarity, these diseases are difficult to study, and the ANCA-positive vasculitides comprise a number of different diseases which have been reclassified since their initial description. These include granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis), microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (formerly called Churg-Strauss syndrome)[95]. If silica does induce vasculitis, then this could underlie the observed association between renal disease and silica exposure.

Silica exposure has been implicated in the pathogenesis of SLE for years in clinical reports and case-control studies[95-98]. Cases of SLE have been repeatedly identified among workers heavily exposed to silica[95,97-98]. Case control studies from the Americas and Europe support an association between silica exposure and SLE, but not all have shown a risk of biopsy-confirmed SLE nephritis[96,98].

Several case-control studies from Europe and the USA support the association between crystalline silica exposure and increased risk of anti-neutrophil cytoplasmic antibody (ANCA)-related diseases, including ANCA positivity, ANCA-positive small vessel vasculitis[97-101]. The RR associated with silica exposure was greater than 2.0 compared with non-exposed individuals in almost all studies[96-98,100,101], and a dose effect was reported. Nonetheless, a recent large case-control study from Sweden did not find a significant association of Wegener's granulomatosis with 32 occupations evaluated[99]. Another more recent nationwide study from Denmark demonstrated an increased risk of SSc, RA, SLE and small vessel vasculitis in men but less in women[102]. The relative risk was lower for SLE and vasculitis than for SSc and RA but suggestive of a causative effect.

Overall, the results of these studies are inconsistent. The literature has been relatively recently summarized both by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES)[50]. and in two reports from the UK Industrial Injuries Advisory Council[49,97]. These concluded that there was a possible, but not certain, association between silica exposure and ANCA-associated vasculitis. The situation with regard to Sjogren's and overlap syndrome is similarly difficult to confirm with the current evidence base but seems plausible.

Conclusions

Despite silica being one of the best known of occupational exposures, this is still causing significant disease in the 21st century. Knowledge of the spectrum of silica's pathogenic effects has broadened with improved scientific understanding in the 20th and 21st centuries,

and silica-related disorders are now acknowledged to be commoner than previously believed. Clinical suspicion of a causative association between silica and systemic sclerosis can now be regarded as confirmed, and silica exposure has been implicated in a wide variety of CTDs. Silica seems likely to interact with several other environmental agents, notably cigarette smoking, and be affected by genetic predispositions. Where dermatological and autoantibody features of SSc occur in a man, then an additional history of silica exposure can identify a group of patients who are likely to progress and develop complications, and who should probably be treated earlier. All clinicians should be alert to this common exposure and should identify a patient's contact with silica as early as possible. Clinicians are in a position to enable better prevention and early intervention and to offer early treatment to provide better outcomes. Dermatologists are uniquely placed to be at the forefront of these developments and work collaboratively with colleagues from other specialties in this rapidly progressing field.

Conflicts of Interest

Neither of the authors have any conflicts of interest to declare.

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