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ORIGINAL RESEARCH

Autoimmune findings in patients with silicosis in Spain

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Abstract

Background: Occupational exposure to silica is related to autoimmune diseases and features of autoimmunity, mainly autoantibodies. The study objectives were to estimate the prevalence of silicosis with associated autoimmune findings or diagnosed autoimmune diseases in Spain, and to assess the clinical and functional characteristics of affected patients.

Methods: This is a multicentre prospective study in patients diagnosed with silicosis. Autoantibodies analysed were antinuclear antibodies, isotypes IgA, IgM and IgG, rheumatoid factor, anticyclic citrullinated peptide, anti-Scl70, anti-Ro, and anti-LA. Pulmonary function tests were performed.

Results: Autoimmunity was assessed in 105 patients. Autoimmune findings were recorded in 29 (27%) patients, including antinuclear antibodies (*n*=21), anti-Ro (*n*=7), rheumatoid factor (*n*=5) and anti-Scl70 (*n*=3). Autoimmune disease was diagnosed in 16 (15%) patients, mainly rheumatoid arthritis (*n*=7) and systemic lupus erythematosus (*n*=4). Patients with silicosis and autoimmune findings had a lower mean time of exposure to silica and showed a trend toward lower values in pulmonary function tests.

Conclusions: Autoimmune findings and diagnosis of autoimmune diseases were frequent in patients with silicosis in Spain.

Keywords: autoimmune diseases, autoimmunity, silicosis.

Citation

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Introduction

Silicosis is an irreversible occupational respiratory disease caused by inhalation of crystalline silica dust (CSD), which induces a fibrotic pulmonary response. Clinical expression varies from asymptomatic disease to chronic respiratory failure with diffuse interstitial pulmonary fibrosis (DIPF).[1] According to the Spanish Institute of Silicosis, in 2021, there were 234 new registered cases of silicosis, of which 186 (80%) were simple and 48 (21%) were complicated, with no cases of DIPF. This incidence was higher than in 2018–2020, with an increasing trend in recent years.[2] Silicosis was traditionally related to mining, yet the use of new materials, such as artificial quartz conglomerate, without personal protection measures has increased occupational exposure,[3,4] and silicosis has re-emerged as an occupational disease in Spain[5] and worldwide.[4] Indeed, silicosis caused 12,900 deaths and led to 655,700 disability-adjusted life years worldwide in 2019.[6] Moreover, this disease could be more common than reported in many countries.[4]

Occupational exposure to silica is linked to autoimmune diseases as well as to features of autoimmunity, especially autoantibodies, without overt disease.[7] Related diseases include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), primary systemic vasculitis, Wegener granulomatosis, and other diseases with positivity for antineutrophil cytoplasmic antibodies.[8] The prevalence of autoimmune diseases is higher in workers with occupational exposure to CSD than in the general population.[7] In addition, data from animal models indicate that combined exposure to silica and viruses could promote systemic autoimmunity, even in cases of low genetic predisposition.[9] A recent study in patients with silicosis from Australia, Israel, Spain and the USA found the most common autoimmune diseases to be RA, SSc and psoriasis/psoriatic arthritis. The authors also reported abnormal autoimmune serology

with no diagnosis of autoimmune disease. Other autoimmune diseases included SLE, Sjögren's syndrome, antineutrophil cytoplasmic antibody-associated vasculitis, mixed connective tissue disease, ocular cicatricial pemphigoid and palindromic rheumatism.[10]

Nevertheless, the mechanisms of development of autoimmune diseases in patients with silicosis are not fully understood. After inhalation, the silica particles reach the alveolar space and are phagocytosed by alveolar macrophages — the cells responsible for their elimination. Occasionally, these cells may fail to remove silica particles, thus activating cellular pattern-recognition receptors and triggering an inflammatory response that eventually leads to fibrosis.[11] Moreover, according to a systematic review, development of autoimmune diseases in rodents, even subclinical disease, was also related to the genetic background and synergism with exposures such as to CSD and asbestos.[12] In addition, it has been suggested that there is significant genetic involvement and gene–environment interactions in silica-induced autoimmunity.[11] However, more studies on the mechanisms of the relationship between silicosis and autoimmune diseases are needed.

Epidemiological studies on autoimmunity in patients with silicosis could provide data to help to enhance the prevention and diagnosis of autoimmune diseases. Therefore, the study objectives were to estimate the prevalence of silicosis with associated autoimmune findings in Spain and to assess the clinical and functional characteristics of affected patients.

Methods

A prospective, multicentre and cross-sectional study was performed in Spain from January 2018 to December 2021. Patients diagnosed with silicosis within the previous 5 years or with a recent diagnosis were invited to participate by their physicians at medical consultations. Silicosis was diagnosed according to the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) guidelines.[1] Exclusion criteria were a diagnosis of silicosis older than 5 years, failure to meet the criteria for silicosis diagnosis, suspicion of associated interstitial lung disease, uncertain differential diagnosis, a diagnosis of acute silicosis, a diagnosis of silico-sarcoidosis, age below 18 years and pregnancy.

The study was performed at the following hospitals in Spain: Ourense University Hospital Complex (CHUO), Ourense; Clinical University Hospital Virgen de la Arrixaca, Murcia; University Hospital of Bellvitge, Barcelona; University Hospital Ramón y Cajal, Madrid; and Hospital of Valdeorras, Ourense.

Demographic, clinical and pulmonary function data

Demographic and clinical data were recorded, including sex, age, smoking status, source of dust, time of exposure, use of personal protective measures, dyspnoea, Charlson comorbidity index and respiratory comorbidities. The presence of fissures, skin ulcers, telangiectasias, Raynaud phenomenon, oedema and Gottron papules was also recorded.

Silicosis was classified as simple, complicated, DIPF, and accelerated according to the SEPAR guidelines.[1] Complicated silicosis was classified as type A, B or C of the International Labour Office (ILO) International Classification of Radiographs of Pneumoconioses.[13]

Pulmonary function was assessed based on arterial oxygen saturation (SaO_2) and spirometry: forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and the FEV_1-to-FVC ratio. Other pulmonary function tests included the diffusing capacity of the lungs for carbon monoxide and pulmonary arterial systolic pressure. Tolerance to exercise was evaluated using the 6-minute walk test.

Assessment of autoimmunity

Patients with autoimmune diseases were diagnosed by the rheumatology departments of the participating hospitals, always with prior evaluation and follow-up at specialized clinics and according to the clinical and serological criteria for specific autoimmune diseases published in rheumatology guidelines.

The autoantibodies analysed were as follows: antinuclear antibodies (ANA); isotypes IgA, IgM and IgG; rheumatoid factor (RF); anticyclic citrullinated peptide (anti-CCP); anti-scleroderma and a 70-kD extractable immunoreactive fragment from topoisomerase I (anti-Scl70, also called antitopoisomerase I); anti-Ro; and anti-LA. Anti-Ro and anti-LA are also known as SSA and SSB, respectively (abbreviations of anti-Sjögren's syndrome related antigens A and B). Tests were performed using the DYNEX DS2 Automated ELISA System (DYNEX Technologies, Chantilly, VA, USA) and the QUANTA Lyser 160 (Inova Diagnostics, San Diego, CA, USA).

According to the autoimmunity findings and the clinical presentation, three groups were defined: patients with silicosis and an autoimmune disease (at least one autoimmune disease, group 1); patients with silicosis and autoimmune findings (no disease and at least one autoimmune finding, group 2); and patients with silicosis but without autoimmune findings or disease (group 3).

Statistical analysis

We performed a descriptive analysis of all the variables, with measures of central tendency for continuous variables and frequency and percentage for categorical variables. Furthermore, we used the Kruskal–Wallis test to compare continuous variables and the χ^2 test to compare categorical variables. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0.

Ethics

The Ethics Committees of all the participating hospitals approved the study. The study was conducted according to the Declaration of Helsinki and to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine signed in Oviedo (Spain) in 1997 and its updates. Furthermore, the study fulfilled the requirements set by the Spanish Data Protection Directive regarding biomedical research, data protection and bioethics. Patients provided a signed and dated informed consent document before entering the study and data collection. Data were anonymized according to current Spanish data protection laws.

Results

The study population comprised 108 patients with silicosis, almost all men (94%), with a mean age of 60.8 years. Most patients (60%) were from the Ourense hospitals. The most frequent type of dust was slate (51%), although there were differences by hospitals: slate exposure was higher in the two Ourense hospitals, whilst exposure to artificial quartz conglomerate was more common in the Barcelona and Murcia hospitals. The mean exposure time was 21 years or more, and only 12% of patients had used personal protection measures. Most patients had level 1 dyspnoea (57%). The Charlson comorbidity index score was assessed in 80 patients, of whom 45 (56%) had 0–2 points (low), 26 (33%) had 3–4 points (moderate) and 9 (11%) had ≥5 points (severe). The most common respiratory comorbidity was chronic obstructive pulmonary disease, diagnosed in 21/90 patients (23%) (Table 1).

Almost half of the patients had simple silicosis, and less than 10% had diffuse pulmonary fibrosis (Table 1). The ILO classification was determined in only 26 of the 46 patients with complicated silicosis and yielded the following results: ILO A, *n*=10; ILO B, *n*=12; and ILO C, *n*=4.

Autoimmunity

Autoimmunity was assessed in 105 patients; autoimmune findings were reported for 29 (28%) and autoimmune disease for 16 (15%). The most common autoimmune find-

Table 1. Demographic and clinical characteristics of the study population (*n*=108).

Variable	Value *n* (%) or mean ± SD; range	*n*
Sex		105
Men	101 (94)	
Women	4 (6)	
Age, years		
Mean ± SD	60.8 ± 13.0	104
Range	32-88	
Smoking		106
Never	40 (37)	
Ex-smokers	60 (56)	
Current active smokers	6 (6)	
Study centre		108
CHUO, Orense	62 (57)	
HCU Virgen de la Arrixaca, Murcia	24 (22)	
HU Bellvitge, Barcelona	14 (13)	
HU Ramón y Cajal, Madrid	5 (5)	
HC Valdeorras, Orense	3 (3)	
Type of dust		107
Slate	55 (51)	
Granite	17 (16)	
Artificial quartz conglomerate	18 (17)	
Coal plus silica	15 (14)	
Others	3 (2)	
Exposure time, years	21.7±10.3; 3–51	102
No personal protection measures	95 (88)	108
Dyspnoea level		84
0	12 (14)	
1	48 (57)	
2	16 (19)	
3	8 (10)	

(*Continued*)

Table 1. (Continued)

Variable	Value *n* (%) or mean ± SD; range	*n*
CCI	2.45±1.9	80
Respiratory comorbidities		90
COPD	21 (23)	
OSAHS	1 (1)	
Tuberculosis	9 (10)	
RB-ILD	1 (1)	
Bronchiectasis[a]	2 (2)	
None	56 (62)	
Type of silicosis		108
Simple	51 (47)	
Complicated	46 (43)	
DIPF	10 (9)	
Accelerated	1 (1)	
Pulmonary function tests		
SaO_2, %	96.2±2.2	80
FEV_1, L	2.3±1.1	104
FVC, L	3.2±1.4	104
FEV_1/FVC	70.3±13.2	103
DLCO, L	75.7±21.4	95
PASP, mmHg	31.2±9.6	37
Tolerance to exercise (6MWT)	368.5±104.4	61

[a]Bronchiectasis and other unspecific findings in the high-resolution computed tomography scan, although not clinically evident.
6MWT, 6-minute walk test; CCI, Charlson comorbidity index; CHUO, Ourense University Hospital Complex; COPD, chronic obstructive pulmonary disease; DIPF, diffuse interstitial pulmonary fibrosis; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FEV_1/FVC, forced expiratory volume in 1 second/forced vital capacity; FVC, forced vital capacity; HCU, Clinical University Hospital; HU, University Hospital; OSAHS, obstructive sleep apnoea/hypopnoea syndrome; PASP, pulmonary arterial systolic pressure; RB-ILD, respiratory bronchiolitis-associated interstitial lung disease; SaO_2, arterial oxygen saturation.

ings were ANA (*n*=21), anti-Ro (*n*=7) and RF (*n*=5) (Figure 1), whilst the more frequent autoimmune diseases were RA (*n*=7) and SLE (*n*=4) (Figure 2).

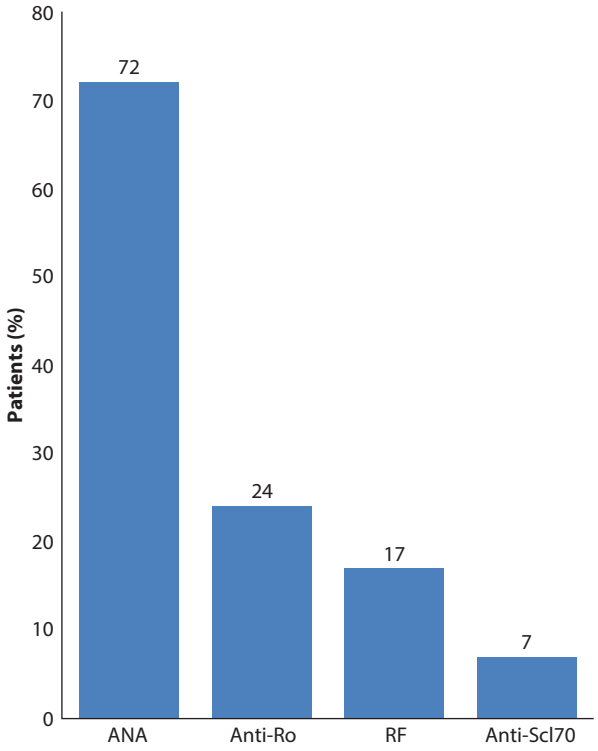
The mean duration of exposure was 20.0±10.3 years in patients with autoimmune findings and 19.6±9.3 in patients with autoimmune disease. There was a trend toward lower values for FEV_1 (2.4±1.0 L), FVC (3.3±1.3 L) and diffusing capacity of the lungs for carbon monoxide (70.0±23.8 L). No statistically significant differences were found for age, sex, smoking habit, type of dust, dyspnoea severity, fissures, skin ulcers, telangiectasias, Raynaud disease, oedema, Gottron papules or comorbidities.

Discussion

We assessed autoimmune findings and diseases associated with silicosis in patients from several regions of Spain where this disease is reported.[2] We also characterized this population with silicosis. Interestingly, there were differences in the type of inhaled CSD by hospital locations. Classical exposure to CSD is from slate, and was higher in Ourense, which is a mining area with large slate mines, compared with the other areas included in the study. In turn, exposure to artificial quartz conglomerate was higher in the Barcelona and Murcia areas, reflecting a change in the causes of silicosis. Jobs other than mining involve new sources of CSD. For example, installation of quartz conglomerate for kitchen and bathroom countertops. It is noteworthy that patients with silicosis by exposure to dust from artificial quartz conglomerate are younger and have been exposed to the dust for shorter periods.[14-17] These differences could be due to the higher toxicity of this material compared with classical products, such as slate, or to inadequate or inexistent personal protection measures.[15] In a case–control study with a 10-year follow-up, the risk of complicated silicosis was higher in workers exposed to quartz conglomerates than in those exposed to ornamental rock (granite and marble),[18] suggesting differences in the effects of quartz and those of granite/marble. Sources of exposure and exposed workers have changed over the years,[19] and a careful occupational history is needed to avoid underdiagnosis.[14] In addition, use of adequate preventive measures in all sectors related to CSD exposure should be encouraged given that, as found in the present study, roughly one in ten workers is currently protected. Furthermore, diagnostic procedures should be standardized, including high-resolution computed tomography scans, and diagnosis of latent tuberculosis should be improved.[19]

Research on the use of antifibrotic drugs already approved for the treatment of idiopathic and non-idiopathic

Figure 1. Autoimmune findings in 29 out of 108 patients with silicosis. Isotype IgA, isotype IgM, isotype IgG, anticyclic citrullinated peptide antibodies (anti-CCP) and anti-LA (anti Sjögren's syndrome related antigen B) were assessed, but there was no positive sample.



ANA, antinuclear antibodies; RF, rheumatoid factor.

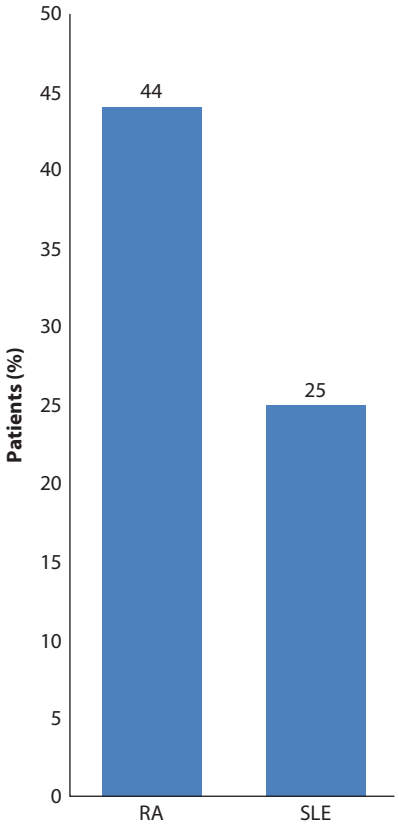
pulmonary fibrosis for the treatment of silicosis is ongoing.[19] Two current examples are the Nintedanib in Progressive Pneumoconiosis Study (NiPPS) (NCT04161014) and a Spanish trial evaluating pirfenidone in patients with silicosis due to artificial stone and progressive massive fibrosis (NCT05118256).

With regard to autoimmune findings and diseases, the association between silica exposure and autoimmune disease has been shown in epidemiological studies,[7] and this seems especially remarkable for quartz products.[20] However, we did not find statistically significant differences according to the type of dust. Furthermore, not only are autoimmune diseases more common in patients with silicosis, but the frequency of specific diseases is also different.[21] The reason for this discrepancy is unknown; however, as silica can trigger the development of an autoimmune cascade,[21] it could affect the prevalence of different autoimmune diseases.

The prevalence of immune rheumatic diseases in adults in Spain[22] is lower than that observed in the present study. In the EPISER study (n=4,916), the prevalence of RA and SLE were both <1%.[23,24] In the present study of 108 patients with silicosis, autoimmune disease was recorded in 16 patients (15%), of whom 7 (7% of the study population) had RA and 4 (4% of the study population) had SLE. Although the number of patients is not substantial, the percentages illustrate the differences in the prevalence of autoimmune diseases between patients with silicosis and the general population.

Results of other studies in Spain partially agree with the present study. From 489 patients with silicosis, 54 (11%) patients also had systemic autoimmune rheumatic diseases, mainly RA (12 patients, 2%), SLE (10 patients, 2%) and SSc (also 2%), with a lower incidence for other autoimmune diseases.[25] These values were lower than in the present study, but still higher than in the general population.[22] Furthermore, patients with silicosis and autoimmune diseases had a higher frequency of Raynaud phenomenon (p<0.001) and comorbidities (p<0.001) than patients with silicosis only[23] whilst, in the present study, we did not find these differences. In another study of 72 patients with silicosis, autoimmune findings were recorded in 18 (27%) patients and autoimmune disease in 11 (16%), mainly RA and SLE. As in the present study, occupational exposure time was lower in patients with autoimmune findings. Most positive antibody results were for antinuclear antibodies (89%). No statistically significant

Figure 2. Autoimmune diseases in 16 out of 108 patients with silicosis. No patient had undifferentiated disease, vasculitis (microscopic polyangiitis), inflammatory myopathy or arthritis secondary to ulcerative colitis.



RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

differences in respiratory test results were recorded.[26] However, in the present study, we found a trend toward lower values in patients with silicosis and autoimmune findings or diseases. Finally, in a multinational registry of 154 quartz conglomerate workers with silicosis, 33 (21%) patients had autoimmune findings or diseases, including in 22 patients from 110 (20%) in Israel and in one patient from 20 (5%) in Spain; RA and SSc were the most frequent diagnoses.[10]

The main strength of this study is that it provides information on autoimmune findings and diseases in patients from different areas (mining regions, industrial zones) and exposure to different types of dust (slate, artificial quartz conglomerate, granite). Moreover, by excluding patients diagnosed more than 5 years ago, we were able to analyse the severity and features associated with autoimmunity without the potential effects of time or disease progression. In addition, we excluded patients diagnosed with silico-sarcoidosis because this would have been a confounding factor when analysing the relationship between silicosis and autoimmunity. A final limitation was the possibility of selection bias, because not all patients with silicosis were invited to participate and not all of those invited finally participated.

Conclusions

Autoimmune findings and diagnoses of autoimmune diseases are common in patients with silicosis in Spain. The results of this study could help to design preventive strategies and enhance early diagnosis of autoimmune diseases. Moreover, a simple approach could be to encourage the use of personal protection measures to minimize exposure to CSD given the currently low uptake of these measures.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Contributions: All authors contributed extensively to the work presented in this paper. HE and VT contributed to conception, design, interpretation of the data, drafting, reviewing the manuscript and supervising the experiments. CB performed the experiments and contributed to data acquisition and analysis. All authors approved manuscript submission. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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