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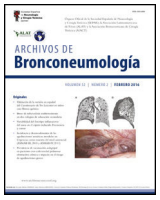

Editorial

# The Polyhedric Reality of Silicosis


The prevalence of silicosis is falling but it is still far from eradicated and remains a major cause of morbidity and mortality in both developed and developing countries.[1,2]

In 1995, the WHO and the International Labour Organization launched a prevention and public awareness campaign with the goal of eliminating silicosis from the world by 2030, but this initiative does not appear to have maintained momentum, and no follow-up studies have been performed.[2]

The extraction and manipulation of granite and slate continues to be the most important source of silica exposure in Spain. However, in the 1990s, a new profile of especially severe silicosis associated with artificial silica conglomerates emerged. These materials, composed of crystalline silica, mainly quartz and cristobalite, dyes and acrylic resin, are widely used in the manufacture of countertops for kitchens and bathrooms.[3,4]

The damage produced by silica has some special characteristics that prompt us to call it a polyhedric disease.

The fact that it is a slowly progressing disease that is rare in terms of the overall population makes randomized trials difficult, and the reduced "market" limits the interest of the pharmaceutical industry. In contrast to other fibrotic lung diseases and common lung diseases such as asthma, very little use has been made of modern research techniques to understand this ancient disease or identify new therapeutic options.[4]

However, our knowledge of the pathogenic mechanisms of damage caused by silica inhalation is steadily growing. Firstly, silica-induced lung injury presumably results from the combined action of several interacting pathogenic mechanisms, including the direct cytotoxic effect of silica on macrophages, activation of macrophage surface receptors, lysosomal rupture, generation of reactive oxygen species (ROS), activation of inflammasome, cytokine and chemokine production, cell apoptosis/pyroptosis, and pulmonary fibrosis.[5] Then there is the accompanying immune dysfunction. Silica inhalation causes the activation and apoptosis of macrophages, while the excess antigen generated is ingested by other activated macrophages. These can migrate to lymph nodes, eventually leading to the activation of T and B lymphocytes. Alterations in Fas/CD95, one of the most important molecules in lymphocyte apoptosis, cause sensitive T cells to survive longer, in contrast to regulatory T cells with increased Fas/CD95 expression that undergo apoptosis and consequently decrease. The imbalance between high levels of responsive T cells and low levels of regulatory T cells increases susceptibility to autoimmune disease.[6]

Given that individual susceptibility is an important factor in the development of the disease, a biomarker for early diagnosis and/or progression of silicosis would be extremely useful.[7]

The likelihood of developing connective tissue disease is enhanced in subjects with exposure to silica and silicosis.[8] Furthermore, there is strong evidence for a very high risk of tuberculosis in the presence of radiological silicosis, but evidence is more tenuous in the case of silica exposure without radiological silicosis.[9] The rates of environmental mycobacteria (EM) or non-tuberculous mycobacteria (NTM) identified in patients with silicosis are increasing steadily.[10]

Silica inhalation is also associated with other adverse effects that occur at lower doses than those needed to cause silicosis, including chronic bronchitis, chronic obstructive pulmonary disease (COPD), and an increased risk of lung cancer.[1]

Several factors associated with an increased risk of progression or mortality have been identified, including a higher cumulative silica dose level, radiographic extension or initial category, tuberculosis, or the presence of autoimmune disease.[11,12]

Biomarkers could replace clinical endpoints in a disease such as silicosis where clinical endpoints are impractical.[4] Some biomarkers, such as IL-8, α1AT, ferritin, CRP, LDH, IL-6, CRP, and angiotensin-converting enzyme, appear to be associated with an increased risk of silicosis, faster disease progression, and higher mortality.[13–15] Chu et al., in line with previous studies on scleroderma-related interstitial lung disease, identified lower levels of miRNA-4508 in workers with silicosis. Although the function of miRNA-4508 is currently unknown, reduced levels appear to be strongly associated with pulmonary fibrosis. Unraveling the molecular and cellular functions controlled by miRNA-4508 could pave the way to discovering new pharmacological treatments.[16]

The 6-minute walk test appears to predict hospitalization and mortality; therefore, in combination with other factors, such as the presence of severe or moderate emphysema, it could play a major role in a tool for predicting silicosis and identifying which patients need closer follow-up.[17]

A better understanding of disease pathogenesis at the cellular and molecular level could also facilitate the search for drugs to treat silicosis. A laboratory model of induced silicosis has been used in the development of new antifibrotics.[18]

The effect of ramatroban, a PGD2/TXA2 receptor antagonist, has recently been studied in the treatment of silicosis in a mouse model. Results showed that ramatroban significantly relieved

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silica-induced lung inflammation, fibrosis, and cardiopulmonary dysfunction compared to the control group.[19]

A specific treatment in this field has emerged only recently. The INBUILD study[20] suggested that nintedanib reduces the rate of progression of interstitial lung disease (ILD) and slows the decline in FVC in patients with chronic fibrotic ILD and a progressive phenotype, regardless of their underlying ILD diagnosis. Following these results, the drug has been used for compassionate use to slow the progression of silicosis in selected patients.

Finally, creating a national register of silicosis will drive the continuous improvement of care programs for this disease and help reduce the prevalence of silicosis, a preventable respiratory disease. There is also an urgent need to promote research and implement clinical trials that can pave the way toward new therapies to prevent silicosis with progressive massive fibrosis in high-risk individuals and to treat it once it occurs.

## Conflict of interests

The authors state that they have no conflict of interests.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2023.05.020.

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José-Jesús Blanco-Pérez[a,*], Laura Fernández-González-Cuevas[b], Juan Cala-García[c], Ivan Rosas[c]

[a] *Servicio de Neumología-Hospital Alvaro Cunqueiro-Vigo, Spain*

[b] *Servicio de Neumología-Hospital Clínico Universitario de Santiago de Compostela, Spain*

[c] *Baylor College of Medicine, Houston, TX 77030, USA*

[*] Corresponding author.

*E-mail address:* Jose.jesus.blanco.perez@sergas.es (J.-J. Blanco-Pérez).