Mini Review

A Threat to Public Health in the Past and the Future: Silicosis

Özlem Şengören Dikiş* and Tekin Yıldız
Department of Pulmonology, University Bursa Yuksek, Turkey

Abstract

Silicosis is a disease caused by inhaling respirable silica particles primarily composed of quartz dust and has been recognised, since the 2000’s, as a human carcinogen. Chronic, accelerated and acute types of silicosis have been described. The most commonly diagnosed chronic silicosis develops after 10 or more years of exposure to relatively low dust concentrations. Silicosis leads to fibrosis and impairment of lung function. It is a preventable disease that is not easily treatable. Despite political and industrial debates, many workers worldwide are still exposed to silica dust. This review emphasizes that silicosis will continue to threaten public health in the future, if adequate preventive measures and widespread case studies of occupational silicosis are not carried out.

INTRODUCTION

Silicosis, documented from the times of the ancient Egypt and Hippocrates, is one of the oldest known occupational lung diseases. Silicon dioxide (SiO₂) or “silica” is one of the most abundant minerals on earth, found in nature in crystalline (as in quartz, cristobalite and tridymite) and cryptocrystalline (e.g., chalcedony) forms or in amorphous form (as with fused silica-opal). Inhalation of silica crystals with 0.5 - 5 µ aerodynamic diameter leads to ‘chronic silicosis’, the most frequently seen form of the disease, the other presentations being ‘accelerated silicosis’ and ‘acute silicosis’. Cristobalite and tridymite microcrystals incur more effective fibrogenic lung reaction as compared to quartz, which constitutes large parts of rock formations.

Epidemiology

Silicosis is a disease with a high prevalence of mortality. Despite having been eradicated nearly completely in many countries with primary preventive measures, it continues to be a serious health concern in some countries, such as in Turkey, with occupational exposure to silica in the glass industry, quarries, quartz mills, cement-brick-tile-crockery production, casting foundries, tunnel excavations and construction.

Other types of occupations, such as dental prosthesis production [1] or denim cloth sand blasting [2] in which serious silica exposure had not been suspected, have also been associated with silicosis in the recent years. Occupations involving sanding which increase exposure to dense microparticulate atmospheres are the most dangerous work forms. Metin Akgün et al.(2005) of Ataturk University Medical School were the first to report silicosis in employees of denim cloth sanding in Turkey [2]. This work form was outlawed in 2009 in Turkey, but the inhalable silica level is still above the acceptable limits in small workshops, a situation also seen in other countries [3]. It has been estimated that at least 100,000 workers in Turkey, 1.7 million workers in the USA, 2 million workers in Europe and 23 million workers in the Peoples Republic of China are occupationally exposed to silica dust [4]. Although the World Health Organisation (WHO) and the International Labour Organisation (ILO) have been preoccupied with silicosis eradication programs in the last 15-20 years, it appears that silicosis will continue to be a serious cause of morbidity and mortality in the foreseeable years of the 21st century.

Classification

Three types of silicosis have been described on the basis of the duration and the density of the inhaled silica crystals:

1. Chronic (classical) form that develops after ≥10 years of exposure to low concentrations of silica dust. Larger than 10mm-size conglomerated nodules can be demonstrated radiologically.
2. Accelerated form resembles the pathological features of the chronic form but develops within 5-10 years. It progresses despite the prevention of exposure to silica dust.
3. Acute form develops in less than 5 years after exposure to high density of silica dust. Generally the numerous nodules formed are smaller that 10 mm in size.

Pathogenesis and the underlying mechanisms

Pathological changes observed in silicosis are attributed to toxic interactions between the alveolar macrophages (AM) and the accumulated silica crystals. Disease causing properties of...
minerals like silica contribute to particulate-induced cell injury as well as cellular and molecular defense mechanisms in response to exposure to these minerals. Hence, exposure to silica dust results in the appearance of chemotactic factors and the release of inflammatory mediators, leading to the accumulation of AM, fibroblasts and the formation of lesions described as "silicotic nodules". These developments are typical of most chronic and accelerated silicosis cases, but they progress faster and on a wider scale in "accelerated silicosis" associated with exposure to dense silicate presence in the inhaled atmosphere. In some cases the apparent adherence of the nodules creates larger nodules or masses indicating the initiation of progressive massive fibrosis. In cases of acute silicosis, the nodules are filled with eosinophilic exudate while the AM are loaded with silica crystals and this appearance is described as "silicoproteinosis".

Polarised microscopy reveals the presence of silica crystals in the nodular lesions. Early lesions are characterized by nodular to stellate aggregates of dust-laden macrophages arranged around a collagenous central region. With time, the central collagen becomes distinctly whorled and the inflammatory cells around the periphery decreases. In diseases caused by a combination of silica plus another dust such as iron oxide, or asilicate, the nodules tend to retain their stellate contour and the central collagen shows less of the whorled arrangement seen in ordinary silicosis. Dynamic and complex surfaces of minerals may be modified in the lung after adsorption of proteins and other macromolecules or following uptake by cells. Magnesium leached from chrysotile fibers changes the surface charge from positive to negative, reducing their toxic potential. Surface chemistry may contribute to the pathogenicity of silica dusts, since freshly fractured silica, generated during abrasive blasting, is more toxic to AMs than aged silica, presumably because of its increased redox potential, as its fresh surface is highly reactive with hydrogen, oxygen, carbon, and sometimes nitrogen. Silica and Silicate radicals on the deavage planes of this mineral also react with water to produce the damaging hydroxyl radical (·OH) [5].

Pathogenicity of silica increases as the atomic packing density of the surface structure decreases. Surface characteristics and composition of silica are linked to bioreactivity as well as to biopersistence in lung. Relationship of pulmonary silica burden and silicosis is complicated by a variety of factors, including type of silica particle involved and coexposures to other types of minerals. Increasing weight of silica retained in the lung increases the pathologic grade of silicosis, but presence or absence of other minerals is important in determining whether or not the patient develops silicosis [6], and has important implications for the prevention of silicosis.

Persistent inflammatory response in animal models of silicosis may be linked to the development of cell injury, cell proliferation, apoptosis, and fibrogenesis. Free radical species may mediate in these events. Oxidants generated by fibrogenic dusts may induce uptake of a variety of particle types [7] and lipid peroxidation [8]. Silica fibers may adsorb iron extracellularly in the lung or pleura [9]. Driven by iron, hydrogen peroxide and superoxide react via a Fenton-like reaction to form the potent hydroxyl radical in vitro and, these reactions also occur in rodent lungs after intratracheal instillation of silica [10]. Free radical generation by silica also occurs via an oxidative burst when fibers are phagocytosed by AMs or other cell types, including alveolar epithelial cells and fibroblasts [7].

Injury to the alveolar type I epithelial cell is seen as an early event in fibrogenesis followed by hyperplasia and hypertrophy of type II epithelial cells [11] which initially may be crucial to repair and regeneration, but progresses to fibrogenesis, if unchecked. Cell proliferation may either start at sites of accumulation of inhaled minerals and spread with the translocation to distal sites of the mineral particles; or, mitogenic cytokines may mediate signaling events, leading to cell replication at physically remote sites [12]. Initiation of proliferation in epithelial cells and fibroblasts by silica may occur after upregulation of the early response protooncogenes, c-fos, c-jun, and c-myc [13, 14] resulting in the promotion of a number of intermediate genes governing inflammation, proliferation, and apoptosis [15]. Increased expression of early response genes and protein products is also linked to the development of apoptosis in AMs by silica [16]. Apoptosis may be a major pathway for the removal of proliferating alveolar type II epithelial cells in acute lung injury [17].

A significant increase in lactate dehydrogenase activity and albumin content in bronchoalveolar lavage fluid (BALF) in rats exposed to silica has been attributed to silica toxicity. Also, the increase in the number of alveolar macrophages and infiltrating neutrophils in the lungs and the elevation in monocyte chemoattractant protein-1 (MCP-1) in BALF together with the histological changes including granuloma formation, type II pneumocyte hyperplasia, thickening of alveolar septa and positive response to Masson's trichrome stain suggested the induction of pulmonary inflammation in the silica exposed rat. Microarray analysis of global gene expression detected 94 and 225 significantly differentially expressed genes in the lungs and BAL cells, respectively. Bioinformatic analysis of the gene expression data indicated diverse types of pulmonary toxicity and especially inflammation, suggesting that chronic inflammation is the mechanism underlying the progression of the pulmonary response to silica [18].

The AM is viewed as a pivotal cell type in fibrogenesis in both lung defense and elaboration of growth factors and oxidants. AM aggregation at sites of mineral deposition is thought to play a role in proliferation of alveolar type II epithelial cells, phagocytosis and clearance of particles, and fibrogenesis [19]. Silica causes increased steady-state mRNA levels of inducible nitric oxide synthase (iNOS) in AMs in vitro and in lung homogenates after intratracheal injection of particles, respectively, suggesting that this enzyme is induced in AMs and possibly other cell types in lung after exposure to fibrogenic dusts [20]. Immune system cells, including neutrophils, T-lymphocytes and mast cells which accumulate in BAL and/or interstitial regions in rodents exposed to silica, are implicated in the development of fibrosis. Silica instillation induces less severe lung lesions in mast-cell-deficient mice when compared with mast-cell-intact mice [21].

Oxidants may induce the release of cytokines such as tumor necrosis factor-alpha (TNF-α) [22]. Early increases in TNF and IL-1 in animal models of silicosis precede frank inflammation and fibrosis that is preventable by receptor blockage or specific
Antibodies to these inflammatory mediators [23]. Silica-induced hydrolysis of phosphoinositides and activation of the arachidonic acid cascade are implicated in regulation of TNF [24]. Silica also directly increases TNF gene transcripion and production in macrophagelike cells partly by upregulating the TNF promoter [25].

Proinflammatory cytokines known as chemokines, including IL-8, macrophage inflammatory protein 2 (MIP-2), and monocyte chemoattractants proteins 1, 2, and 3 (MCP-1,2,3) exhibit chemotactic activity for neutrophils, monocytes, lymphocytes, and eosinophils and have been implicated as key contributors to the inflammatory response in silicosis [26]. Silica increases the steady-state mRNA levels of MIP-2 and TNF mediates the MIP-1α [27] and MIP-2 pathways [28]. Bronchiolar and alveolar epithelial cells, in addition to AMs, synthesize MIP-2, which is upregulated by TNF or silica in rat alveolar type II epithelial cells in vitro, indicating pulmonary epithelial cells are mediators as well as targets of inflammation [26].

Isomers of transforming growth factor-beta (TGF-β) are increased at sites of developing silica-induced granulomas [29]. This growth factor may have multiple roles in fibrogenesis as it is a potent chemoattractant for monocytes and neutrophils and upregulates genes involved in collagen and fibronectin biosynthesis. Its production by AMs and alveolar epithelial cells may serve as a mitogenic stimulus for fibroblasts. Interaction between TGF-β and platelet-derived growth factor (PDGF) may be important in chemotaxis and fibroblast proliferation [30]. Insulin-like growth factor (IGF-1), a possible stimulus for fibroblast proliferation, is also produced by AMs exposed to silica [31]. Upregulation of epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-α), which binds to the EGF-receptor, at sites of silica deposition [32] may also be key to mitogenesis of pulmonary epithelial cells and fibroblasts.

Thus, interaction of chemokines or cytokines with epithelial cells and fibroblasts may govern the eventual outcomes of cell injury and proliferation in response to silica burden in the lung.

Clinical features

In most cases diagnosis of silicosis is made when the patient is asymptomatic. Therefore, early phase symptoms or clinical findings cannot be generalised. When diagnosed disease becomes clinically symptomatic, the earliest and the most general observation is dyspnea appearing with exercise. As the disease progresses, dyspnea persists at rest. Weight loss is another initial symptom in the silicosis patient. Akgun et al., (2008) reported dyspnea to be the most frequent complaint of silicosis, with chest pain (46 %; n:72) being the second most observed symptom [33]. Our study in 2011 on the levels of anxiety and depression and their effects on the life quality in silicosis has shown that, despite normal spirometric parameters, incidence of these psychiatric disorders had increased with adverse effects on the life quality of the patient [34]. Hypoxaemia during exercise or at rest, pulmonary hypertension, right heart failure and cor pulmonale can develop with the progress of the disease [35]. Proneness to tuberculosis and nocardia infections in silicosis has been ascribed to the toxic effects of silica on the alveolar macrophages [36].

Radiological findings

In uncomplicated silicosis, the earliest radiological signs are small round nodular opacities concentrating mainly on the upper lobes and the posterior areas. According to the the ILO typing, these opacities, starting at the apex and covering the upper-middle zones, are predominantly of the maximally 1.5 mm sized "p"-type, 1.5-3 mm sized "r"-type and in less numbers, of the 3-10 mm sized "q"-type (Figure 1). Hilar lymphadenopathy can be observed. The "eggshell" calcification of the lymph nodes is a rare observation useful for diagnosing silicosis.

Progressive massive silicosis is characterised with large opacities. On the basis of ILO classification, category A opacities have a dimension or sum of dimensions in the 10-50 mm range and should be more than one; category B opacities, numbering one or more, with a combined dimension above 50 mm are restricted to an area equivalent to the right upper zone; and the category C opacities, numbering one or more, and having a combined dimension exceeding that of the upper right lobe zone [37] (Figure 2). The fibrotic lesions tend to contract with the compensating emphysema at the edges of the lesions and the lower lobes. Localised pleural thickening neighbouring the conglomerated lesions can be observed with CT, but pleural effusion is rare. Two patients, with a history of occupational exposure to silica, consulting our clinic, whose radiological imaging data are shown in Figures 1,2, were diagnosed with silicosis only after exclusion of all possible lung infections, including tuberculosis and malignancy. Laboratory parameters and sputum samples had to be evaluated with the radiological data. In our study conducted in 2010, centrally located mild bronchiectasis was detected in %13.6 and traction bronchiectasis was present in %6.8 of our patients [38] (Figure 3).

Spirometry

There are not spirometric anomalies specific to silicosis. Data can be completely normal. When pathological, however, an obstructive, restrictive or mixed pattern can be observed. As exposure to silica restricts the flow, the obstructive pattern is more often observed (11[39]). Functional alterations appear earlier in accelerated and acute silicosis and their progression is faster. In accelerated silicosis, particularly, fast impairment of respiratory function and hypoxaemia not responding to treatment can develop.

Figure 1 Micronudular opacities in the lung X-ray imaging of a case with silicosis due to employment in denim cloth sanding.
Silicosis is a preventable disease. What is important is taking the required preventive measures for risky occupations, such as reducing dust formation and its spread and escalation above the permitted level in the work area. The inhalable quartz level permitted in Turkey in 2003 was 0.25 mg/m³ in comparison to 0.05 mg/m³ permitted by the National Institute for Occupational Safety and Health (NIOSH) in the USA. Rapid development in the numbers of silicosis patients employed in denim cloth sanding forced the Turkish Ministry of Health to ban the sanding process using silica containing materials as of March 2009. Since most workers employed in these jobs were not covered by health insurance, alterations in the Health Law allowed these individuals to benefit from national healthcare services as of January 2010. Also, decisions were made to allocate a monthly salary to the uninsured workers who lost capacity to work by developing occupational silicosis [3].

Treatment

There is not a specifically effective treatment method for silicosis. The first measure is to terminate the exposure to silicates when the diagnosis is made and to advise the patient against smoking tobacco products. Total lung lavage can be implemented in the patient with acute silicosis when alveolar proteinosis develops. Heart/lung transplant has been recommended for the young and terminal stage silicosis patients [44,45].

CONCLUSION

Since the establishment of ‘working life’, humans have worked in risky occupations facing injuries, morbidity and mortality. Development of preventive measures have reduced or completely ended the adverse outcomes. The right to live is the primary right allowing the claiming of all other rights and has to be protected. Today, as in the distant past, exposure to silica dust in diverse types of occupations is still threatening public health, indicating the need for informing the public and organisation of effective measures for closer supervision of the work place by the WHO and the health ministries of all the involved countries.

REFERENCES

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