Silica Nephropathy

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Abstract

Occupational exposure to heavy metals, organic solvents and silica is associated with a variety of renal manifestations. Improved understanding of occupational renal disease provides insight into environmental renal disease, improving knowledge of disease pathogenesis. Silica (SiO₂) is an abundant mineral found in sand, rock, and soil. Workers exposed to silica include sandblasters, miners, quarry workers, masons, ceramic workers and glass manufacturers. New cases of silicosis per year have been estimated in the US to be 3600–7300. Exposure to silica has been associated with tubulointerstitial disease, immune-mediated multisystem disease, chronic kidney disease and end-stage renal disease. A rare syndrome of painful, nodular skin lesions has been described in dialysis patients with excessive levels of silicon. Balkan endemic nephropathy is postulated to be due to chronic intoxication with drinking water polluted by silicates released during soil erosion. The mechanism of silica nephrotoxicity is thought to be through direct nephrotoxicity, as well as silica-induced autoimmune diseases such as scleroderma and systemic lupus erythematosus. The renal histopathology varies from focal to crescentic and necrotizing glomerulonephritis with aneurysm formation suggestive of polyarteritis nodosa. The treatment for silica nephrotoxicity is non-specific and depends on the mechanism and stage of the disease. It is quite clear that further research is needed, particularly to elucidate the pathogenesis of silica nephropathy. Considering the importance of diagnosing exposure-related renal disease at early stages, it is imperative to obtain a thorough occupational history in all patients with renal disease, with particular emphasis on exposure to silica, heavy metals, and solvents.

Keywords: Occupations; Kidney; Silicon dioxide; Silicosis; Kidney diseases; Glomerulonephritis; Nephrotoxicity; Balkan nephropathy

Introduction

Due to their unique circulatory and metabolic characteristics, the kidneys are particularly susceptible to the toxic effects of heavy metals, organic solvents and silica. Occupational and environmental exposure to these compounds is associated with a variety of renal manifestations. It is obviously extremely important to identify occupation-related renal diseases in order to provide ideal preventive protection to exposed workers. Equally important is the fact that enhanced understanding of renal diseases associated with work-related exposure provides insight into environmental renal disease, beyond occupational contact. The identification of an occupational renal disease in a group of exposed workers can potentially lead to improved knowledge of the etiology and pathogenesis of the disease entity. This will direct efforts at superior preventive measures in large populations. The major environmental and occupational renal diseases include those related to lead, cadmium, chromium, mercury, arsenic, organic solvents and silica.' While many of these toxins, such as lead, cadmium and chromium are associated predominantly with tubulointerstitial disease, others, such as mercury, are associated with glomerular disease. A third category of environmental/occupational toxins can lead to a combination of tubulointerstitial and glomerular disease. Regardless of the initial renal manifestation,
the common end-result in many of these exposures is the development of chronic kidney disease (CKD) and progression to end-stage renal disease (ESRD). Silica (SiO$_2$), an abundant mineral found in sand, rock, and soil is an increasingly identified environmental nephrotoxin with fairly unique renal and systemic manifestations. Approximately two million people are occupationally exposed to silica in the US. Of these individuals, 100,000 are at more than twice the recommended exposure limit determined by the National Institute for Occupational Safety and Health (NIOSH). Workers in many occupations, particularly sandblasters, miners, quarry workers, masons, ceramic workers and glass manufacturers are particularly at risk of silica toxicity. In addition to the association between inhalation of silica and disabling lung disease that has been suspected for centuries and very well-recognized for many years, the renal implications of exposure to silica has also been increasingly described over the past two decades. While the incidence and prevalence rates relating to silica nephrotoxicity are not well-known, the new cases of silicosis per year has been estimated in the US to be 3600–7300. The present article will review the association between exposure to silica and various forms of kidney disease.

Clinical Findings

The initial descriptions of silica nephropathy consisted mainly of sporadic case reports. Saldanha, et al, reported a 44-year-old man with history of significant industrial silica exposure who presented with hypertension and proteinuria. Renal biopsy revealed focal glomerulonephritis and renal tissue showed significant silica content. Giles, et al, described a 23-year-old sandblaster who developed acute onset massive proteinuria and fatal renal failure. Case presentations have stimulated population research. The association between kidney disease and exposure to silica was studied in a cohort of 583 individuals who met the criteria for silicosis developed by the NIOSH. Ten percent of these individuals were suspected of CKD by history, and 33% of the individuals for whom laboratory tests were available had a serum creatinine level >1.5 mg/dL. In this study, silicosis was associated with higher likelihood of a serum creatinine level >1.5 mg/dL, independent of age and race. There was no relationship between duration of silica exposure and prevalence of kidney disease or elevated creatinine. In a highly suggestive observation, an increased prevalence of renal disease, particularly glomerulonephritis, in Upper Weardale, UK has been attributed to possible silica exposure secondary to mining. Silica nephropathy occurs following heavy exposure to silica dust over a prolonged period of time. While the initial manifestations might be subtle and consist mainly of low urinary specific gravity, the more advanced manifestations include hypertension and proteinuria. With more prolonged exposure, the glomerular filtration rate (GFR) will progressively decline. Rapidly progressive forms of nephropathy have also been described. Occupational exposure to high-levels of silica is associated with higher rates of autoimmune diseases compared to the general population. Silica nephropathy, mainly in the form of glomerulonephritis, has also been reported to occur in the setting of autoimmune multisystem diseases, such as systemic lupus erythematosus (SLE), scleroderma, Goodpasture’s syndrome, polyarteritis nodosa, systemic vasculitis, and c-ANCA-positive Wegener’s granulomatosis. It is estimated that 25%–50% of patients with pulmonary silicosis might demonstrate an elevated antinuclear antibody...
Finally, a rare but interesting possibly silicon-related syndrome presenting with painful, nodular skin lesions has been described in dialysis patients with excessively high levels of silicon.

The following three sections detail specific types of renal involvement associated with silica exposure.

CKD and ESRD

There is ample epidemiological evidence suggesting that silica exposure is associated with an increased risk of ESRD. In a case-control study of 325 men with ESRD, risk of ESRD was significantly related to regular occupational exposures to silica (OR = 1.67). Occupational exposures with particularly elevated risks were silica exposure in foundries or brick factories (OR = 1.92), and silica exposure during sand-blasting (OR = 3.83). Among a cohort of 4626 silica-exposed workers in the industrial sand industry, an excess of ESRD incidence (standardized incidence ratio = 1.97; 95% CI: 1.25–2.96) was observed. An increasing ESRD incidence was also found with increasing cumulative exposure to silica (standardized rate ratios by quartile of cumulative exposure: 1.00, 3.09, 5.22, and 7.79). In a more recent study, however, the risk of ESRD was not related to cumulative exposure. In a retrospective cohort study of 2412 gold miners in South Dakota, the ESRD incidence among the gold miners was compared with that in the US population. There were 11 cohort members with ESRD with a standardized incidence ratio of 1.37 (95% CI: 0.68–2.46), increasing to 7.70 (95% CI: 1.59–22.48) among workers with 10 or more years of employment. Further evidence of the association between exposure to silica dust, nephrotoxicity and excess incidence of ESRD is obtained from the study of a cohort of 2980 male ceramic workers in Civitacastellana, Lazio, Italy. In this cohort, six patients with ESRD were detected while 1.87 were expected (observed [O]/expected [E] = 3.21; 95% CI: 1.17–6.98). The excess risk was present among non-smokers, smokers, workers without silicosis (O/E = 2.78) and workers with silicosis (O/E = 4.54). Not all studies have shown an increased risk of ESRD associated with exposure to silica. Among 1328 workers with silicosis an ESRD rate ratio of 1.67 (95% CI: 0.76–3.17) suggests that patients with silicosis do not have an excess risk of developing ESRD. Also, in a study of 17644 German porcelain production workers, exposure to crystalline silica was not associated with increased risk of non-malignant renal disease.

Multisystem Disease

Occupational exposure to silica dust and

TAKE-HOME MESSAGE

- Kidneys are particularly susceptible to the toxic effects of heavy metals, organic solvents and silica.
- It is important to identify occupation-related renal diseases in order to provide ideal preventive protection to exposed workers.
- Silica exposure is associated with excess mortality from acute renal disease and can also be associated with an increased risk of end-stage renal disease.
- Silica exposure has been linked to several multisystem autoimmune diseases.
- The main goal at all stages follows the basic principle of removing the source of exposure in order to minimize the disease progression.
actual silicosis have been linked to several multisystem autoimmune diseases. Individuals with silicosis manifest a significantly increased risk for rheumatoid arthritis,\textsuperscript{26} progressive systemic sclerosis,\textsuperscript{27,28} polyarteritis nodosa,\textsuperscript{15} SLE, connective tissue disease,\textsuperscript{29} ANCA-associated small vessel vasculitis\textsuperscript{30} and Wegener’s granulomatosis\textsuperscript{31}. The association between silica exposure and Wegener’s granulomatosis is particularly remarkable. Inhalation of silica and grain dust was associated with a seven-fold risk of development of Wegener’s granulomatosis.\textsuperscript{31} Arnalich, \textit{et al}, have described a 55-year-old man with silicosis who presented with massive proteinuria, microscopic hematuria, moderate renal failure and distal polyneuropathy. Renal angiography showed multiple intraparenchymal saccular aneurysms; renal biopsy showed focal segmental necrotizing glomerulonephritis and arteriolitis—findings consistent with polyarteritis nodosa.\textsuperscript{15} A manifestation consistent with connective tissue disease and silica-related renal disease has been reported by several authors. Among four patients with proteinuria and rapidly progressive renal failure in the setting of silica exposure, three had manifestations of connective tissue disease. Light microscopic findings of renal biopsy showed glomerular hypercellularity and sclerosis, crescents, interstitial cellular infiltrates and tubular necrosis. Electron microscopy revealed foot process effacement, cytoplasmic dense lysosomes, microtubules and dense deposits. Two of the four patients died and one progressed to ESRD, requiring dialysis.\textsuperscript{29} In a study to evaluate the association of lifetime silica exposure with development of ANCA-associated small vessel vasculitis, a population-based case-control study was conducted by Hogan, \textit{et al},\textsuperscript{30} Silica exposure was found in 78 (60%) of 129 case patients and in 49 (45%) of 109 control subjects, with an increased risk with high exposure (OR: 1.9; 95% CI: 1.0–3.5; \( p = 0.05 \)); crop harvesting was associated with elevated risk (OR: 2.5; 95% CI: 1.1–5.4; \( p = 0.03 \)). The impact of silica exposure on exacerbation of systemic autoimmunity was studied in a mouse model susceptible to SLE. Compared to controls, survival in silica-exposed mice was decreased, circulating immune complexes showed a trend towards an increased acceleration in level; ANA levels, and autoantibodies to histone were significantly higher.\textsuperscript{32} There was an increased in the inflammatory infiltrates and fibrosis with excess collagen deposition in the lungs of the silica-exposed mice. These findings confirm the impact of silica exposure on exacerbating the course of SLE.\textsuperscript{32}

**Balkan Endemic Nephropathy**

Among the syndromes possibly associated with silica is Balkan endemic nephropathy. This is a slowly progressive chronic tubulo-interstitial disease which occurs among inhabitants of villages along the Danube River in Croatia, Serbia, Romania and Bulgaria.\textsuperscript{33} It may occur at any age and may affect all members of the same family. The etiology is unknown, but it is postulated to be associated with multifactorial environmental nephrotoxicity. In particular, chronic intoxication with drinking water polluted by silicates released during soil erosion seems to be the most probable cause. Due to subtle manifestations, the diagnosis of the condition in the early stages requires a high index of suspicion, decreased urinary specific gravity and presence of β\textsubscript{2} microglobulin in the urine. The full-blown manifestations include coexistence of renal dysfunction with urethelial carcinoma. Renal biopsy reveals glomerular sclerosis, IgG and IgA deposits in the glomeruli and osmiophilic granulations within the mitochondria of proximal
An interesting autopsy finding has been the substantially enlarged kidneys (180 g) observed in some of the inhabitants of the region who have died due to causes other than renal disease. The increased weight of the kidneys has been attributed to the excessive accumulation of water due to the significant affinity of silica for water.\(^3\)

**Pathogenesis**

The mechanisms underlying silica nephropathy have not yet been fully elucidated. However, most evidence is consistent with the interplay of at least two mechanisms:\(^3\) the direct toxic effect of the deposited crystalline material in the renal parenchyma and an autoimmune process involving interaction of silica particles with the immune system, mainly by activation of macrophages through which the kidneys are affected.\(^3\) The non-degradable nature of silica leads to saturation of the macrophages and it has been demonstrated that macrophages that ingest silica release factors that increase biosynthesis by fibroblasts.\(^2\) A possible explanation for the development of nephritis in the setting of granulomatous pulmonary nodules is the triggering of a mal-adaptive immunological response to a component of the silica-containing nodules.\(^3\) Confirming this response is the serologic evidence for various forms of autoimmune processes in patients with occupational lung disease.\(^2\)

**Renal Pathology**

A rather wide spectrum of renal histopathology, with no single pathognomonic finding, has been described for silica nephropathy. The histopathology from the patient described by Saldanha, *et al.*, revealed focal glomerulonephritis, intraluminal sloughing of the proximal convoluted tubule, cytoplasmic vacuolization and granularity; renal tissue showed significant silica content.\(^3\) Others have reported a variety of lesions ranging from mild proliferative glomerulonephritis with granular IgM and C\(_3\) deposits\(^10\) to crescentic glomerulonephritis with subendothelial immune deposits,\(^4\) crescentic IgA nephropathy,\(^3\) and necrotizing glomerulonephritis with aneurysm formation suggestive of polyarteritis nodosa.\(^5\) Ultrastructural studies by electron microscopy have shown the proximal tubules to be filled with large vacuoles some containing aggregates of dense osmiphilic particles.\(^9\)

**Course and Therapy**

Although the direct data regarding association between silica exposure and non-malignant renal disease-related mortality is conflicting,\(^2\,21\,25\,42\,43\) there is good evidence that occupational exposures to silica is associated with a significantly elevated risk of ESRD.\(^2\,22\,24\,44\) Extrapolating from this evidence and the high mortality associated with ESRD,\(^4\) it is reasonable to extrapolate that silica exposure is associated with above the expected mortality from non-malignant renal disease. Studies have shown exposure to silica to be associated with excess mortality from acute renal disease (standardized mortality ratio [SMR]: 2.61; 95% CIs: 1.49–4.24) and CKD (SMR: 1.61; 95% CI: 1.13–2.22)\(^2\) and the overall excess risk of death from renal disease is estimated at 1.8% (0.8%–9.7%)\(^4\). The treatment for silica nephrotoxicity is non-specific and depends on the mechanism and stage of the disease. It ranges from administration of steroids and cytotoxic agents for the vasculitic and immune-mediated processes to strategies at controlling blood pressure and proteinuria. Once the patients have reached ESRD, the treatment goals are similar to those for other patients with ESRD. The main goal at all stages follows the basic principle of removing the source of exposure in order...
to minimize the disease progression.

**Summary and Discussion**

There is increasing evidence for the nephrotoxicity of silica. While early reports were limited to case description of workers with heavy silica exposure, more recent large-scale epidemiological studies have demonstrated an association between chronic occupational exposure to silica and the development of ESRD. A wide spectrum of clinical renal presentations ranging from very subtle urinary changes to proteinuria and CKD have been described. It is likely that the individual manifestations are determined partially by differences in genetic susceptibility or other environmental exposures.\(^{47}\) The variability in the reported risk of silica-associated kidney disease is possibly related to the type of silica exposure. For example, freshly ground silica dusts and silica ground without water are more cytotoxic and more inflammatory compared with aged silica dusts and silica ground with water.\(^{48,49}\) The mechanism of silica nephrotoxicity is still unclear—in addition to the direct nephrotoxic effect of silica, there is fairly good evidence for renal involvement through silica-induced autoimmune diseases such as scleroderma and SLE. The data on the pathogenesis of silica-induced nephropathy and the mechanisms of CKD progression is inconclusive partially due to the fact that most of the studies have looked at individuals with ESRD, rather than the development of early CKD. It is quite clear that much further research is needed, particularly to elucidate the pathogenesis of silica nephropathy. Reviews of exposure-related renal disease, such as the present article, highlight the importance of a thorough occupational history in all patients with renal disease, with particular emphasis on exposure to silica, heavy metals, and solvents.

**Conflicts of Interest:** None declared.

**References**

Silica Nephropathy


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An Achaemenid king’s tomb craved out of the rock face. The entrance of the tomb is at the center. There are four such tombs in *Nāqš-e Rostām*—an important archeological site in Fars province, Iran. Quarry workers and masons are at risk of silica toxicity (see page 108).