A study of silica nephrotoxicity in exposed silicotic and non-silicotic workers

Tze Pin Ng, Yuen Ling Ng, Hock Siang Lee, Kee Seng Chia, Her Yam Ong

Abstract
The possible human nephrotoxicity of silica has often been suggested by previous anecdotal reports and uncontrolled clinical studies of silicotic patients. Urinary excretions of albumin, α-1-microglobulin (AMG), and β-N-acetyl-glucosaminidase (NAG) were measured in 33 male workers exposed to silica (mean duration of employment 16 years) and 19 male age matched non-exposed subjects with no history of primary or secondary renal diseases. Significantly higher urinary excretions of albumin and AMG were found in the workers exposed to silica. Silicotic subjects (n = 7) also had significantly high excretions of albumin, AMG, and NAG. All but one of the silicotic patients had ceased exposure from three to 17 years before the study. Our findings suggest that prolonged exposure to silica is associated with chronic irreversible nephrotoxicity in exposed workers.

Silica has long been suspected of being related to kidney disease. Animal studies suggest that silica is nephrotoxic, causing degenerative changes in the tubular epithelium, interstitial inflammation, and fibrosis and glomerulosclerosis. In a series of 20 patients with chronic silicosis, proteinuria was present in 20%, renal insufficiency in 40%, and concentration defect in 45%. In another series of 15 patients, however, none showed evidence of renal disease by urinalysis, creatinine clearance, or changes in concentrating ability. Distinct renal morphological alterations in the glomeruli and proximal tubules were described in 23 of 45 patients who died from advanced silicosis. More recently, case reports have highlighted similar morphological changes in the glomeruli and proximal tubules, including deposition of IgM and complement C₃ in the glomerular basement membrane, and raised content of elemental silicon in kidney tissue in workers with high exposure to silica, some with acute silicosis.

Evidence as such based on uncontrolled studies of clinical case series and anecdotal reports are suggestive, but they are not sufficient for establishing a causal relation between silica and nephropathy in human subjects. It is also surprising that no controlled studies of the prevalence of renal disorders in workers exposed to silica appear to have been carried out. Most conventional tests of renal function in routine clinical use are either too insensitive or too inconvenient for use in field studies. Many studies, however, suggest that quantified urinary excretions of specific high and low molecular weight proteins and enzymes are useful markers of early glomerular and tubular disturbances, and are highly sensitive tools in screening for industrial nephrotoxicity. We report the results of a preliminary study to investigate the nephrotoxicity of exposure to silica by measuring urinary excretions of albumin, α-1-microglobulin (AMG), and β-N-acetyl-glucosaminidase (NAG) in a group of exposed granite workers and age matched non-exposed persons.

Materials and methods
Subjects with high exposure to silica were selected from a total of 45 male currently working drillers and crushers in three granite quarries. Silicotic patients with similar quarry job exposures in the past were also chosen. The exclusion criteria were a history of glomerulonephritis, urinary calculi or other renal diseases, diabetes, hypertension, or regular ingestion of analgesics. Of the 33 eligible subjects after exclusion, 26 were non-silicotic workers and one silicotic worker currently employed in the quarries, and the remaining six were silicotic workers who had ceased exposure from three to 17 years before the study. The duration of exposure ranged from one to 33 years (mean 16 years). Five of the silicotic subjects had radiological small rounded opacities of profusion category 1 and the other two had category 2 opacities. An age matched non-exposed group of subjects...
Table 1  Urinary values by exposure group

<table>
<thead>
<tr>
<th>Urinary parameters</th>
<th>Exposed subjects (n = 33)</th>
<th>Non-exposed subjects (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y; AM (SD))</td>
<td>49.2 (10.9)</td>
<td>48.7 (11.8)</td>
</tr>
<tr>
<td>Current smokers (No (%))</td>
<td>16 (48%)</td>
<td>10 (53%)</td>
</tr>
<tr>
<td>Past smokers (No (%))</td>
<td>7 (21%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Creatinine (g/l; AM (SD))</td>
<td>1.58 (0.69)</td>
<td>1.72 (0.73)</td>
</tr>
<tr>
<td>Albumin (mg/g creatinine):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM (SD)</td>
<td>9.3 (2.6)*</td>
<td>5.5 (2.0)</td>
</tr>
<tr>
<td>Range</td>
<td>1.6-71.6</td>
<td>1.0-13.0</td>
</tr>
<tr>
<td>AMG (mg/g creatinine):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM (SD)</td>
<td>7.5 (3.2)**</td>
<td>4.6 (2.7)</td>
</tr>
<tr>
<td>Range</td>
<td>1.6-17.1</td>
<td>1.7-12.0</td>
</tr>
<tr>
<td>NAG (U/g creatinine):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM (SD)</td>
<td>2.6 (1.6)</td>
<td>2.4 (1.1)</td>
</tr>
<tr>
<td>Range</td>
<td>0.8-6.9</td>
<td>0.9-4.9</td>
</tr>
</tbody>
</table>

AM: Arithmetic mean; GM: geometric mean.  
*p = 0.03 (t test); **p = 0.002 (t test).  
†No values were below 0.35 g/l.

was selected from among 43 male hospital ancillary workers and community retirees, using the same exclusion criteria. Age matching to within five years was successfully accomplished for 19 subjects.

Urine samples were collected from the subjects in the morning from 10.00 am to 12.00 noon, stored frozen, and analysed within one month of collection. Urinary albumin concentration was measured with an immunoprecipitation assay kit (Orion Diagnostica, Finland), AMG concentration was determined using enzyme immunoassay kits (Fujirebio Inc, Japan), and NAG activity was analysed using a colorimetric assay (Boehringer-Mannheim, Germany). Urinary concentrations of these substances were corrected for urinary creatinine.

Variables with skewed distributions were transformed to give approximate normal distributions, and Student's t test and χ² tests were used as appropriate.

Results

The distribution of the urinary values of albumin showed significantly more raised values in silica exposed workers (table 1; figure). In 13 (39%) silica exposed workers, urinary albumin was raised above the 95th percentile of the non-exposed subjects compared with one (5%) in the non-exposed group (p < 0.001 by χ² test). In silica exposed workers, the mean value for AMG concentration was significantly higher compared with non-exposed subjects (p < 0.002 by t test). No statistically significant differences were found for values of urinary NAG activity between the two groups.

Subjects with silicosis were also compared with non-silicotic exposed workers and non-exposed subjects. Higher albumin (p = 0.05) and AMG concentrations (p = 0.002) and NAG activity (p = 0.02) were found in silicotic subjects. Because silicotic workers were an older group, the analysis was also restricted to those aged 40 years and older (table 2). Similar results in respect of higher urinary albumin concentration (p = 0.06), AMG concentration (p = 0.002), and NAG activity (p = 0.04) were found in silicotic patients.

Discussion

An increasing number of urinary indicators of glomerular and tubular functions are being employed to study the effects of industrial nephrotoxins in
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