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Kidney Disease and Silicosis

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Key Words

Creatinine · Kidney disease · Silicosis · Wegener's granulomatosis

Abstract

Aim: To determine the prevalence of kidney disease in a cohort of individuals with silicosis. ***Methods:*** Review of medical records and questionnaires from patients reported to a state surveillance system for silicosis. Reporting of individuals with silicosis is required by state law. All individuals with silicosis reported as required by law to the State of Michigan. Individuals included in this article were reported from 1987 to 1995. Cases were reported by hospitals, physicians, the state workers' compensation bureau, or from death certificates. Only individuals who met the criteria for silicosis developed by the National Institute for Occupational Safety and Health (NIOSH) were included. ***Results:*** Medical records were reviewed of 583 individuals with confirmed silicosis. This was mainly a population of elderly men. Ten percent of the 583 silicotics were found to have some mention of chronic kidney disease, and 33% of the 283 silicotics who we had laboratory tests on had a serum creatinine level >1.5 mg/dl. An association between kidney disease and age and between kidney disease and race was found among this cohort of 583 silicotics. Individuals with silicosis were more likely to have a serum creatinine level >1.5 mg/dl than age- and race-matched controls. However, no relationship between duration of exposure to silica or profusion of scarring on chest X-ray and prevalence of kidney disease or elevated creatinine levels was found. ***Conclusions:*** This study confirms previous case reports and epidemiologic studies of end-stage renal disease that found an association between kidney disease and exposure to silica. The epidemiologic data are conflicting on the mechanism by which silica causes kidney disease and are compatible with silica being able to cause kidney disease by both an autoimmune and direct nephrotoxic effect. Chronic kidney disease should be considered as a complication of silicosis.

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Introduction

Silica exposure has been associated with both glomerular and tubular kidney dysfunction [1–18]. Data supporting the association include case reports [1, 4, 10, 14–16], cross-sectional studies of tubular function [2, 9, 11, 12],

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pathological studies [8, 17], positive tests for antineutrophil cytoplasmic antibody (ANCA) [6], epidemiological studies of end-stage renal disease [3, 18], and case-control studies of ANCA-positive Wegener's granulomatosis [5, 13]. We reviewed the medical records of individuals reported to a state surveillance system for silicosis to determine the prevalence of kidney disease among individuals with silicosis in Michigan.

Patients and Methods

As part of the Sentinel Event Notification System for Occupational Risks, the State of Michigan, with financial assistance from the National Institute for Occupational Safety and Health (NIOSH), instituted a surveillance/investigation program for silicosis in 1987 [19]. The sources used to identify persons with silicosis were: (1) reports from hospitals; (2) reports from physicians; (3) death certificates, and (4) claims awarded by the Michigan Silicosis, Dust Disease and Logging Industry Compensation Fund.

Reports from hospitals were requested once per year. Hospital discharge summaries for individuals with a primary or a secondary diagnosis of silicosis (ICD 502) or pneumoconiosis not otherwise specified (ICD 505) were obtained from all acute-care hospitals in Michigan, including Veteran's Administration hospitals. Reporting by both Michigan practitioners and hospitals was required under part 56 of Public Act 368 of 1978 which requires the reporting of patients with any known or suspected occupational disease. Physicians reported known or suspected cases as they were identified. Death certificates and workers' compensation data were reviewed on a yearly basis. At the time a report was received, most individuals were no longer exposed to silica.

When a report was received, the individual or, if decreased, the next of kin was administered a standard telephone questionnaire by a trained interviewer. The interview took approximately 30–45 min and consisted of a lifetime work history, cigarette smoking history, medical care history, medication history, and medical and symptom history limited to respiratory conditions.

Medical records including pulmonary function testing and a recent chest X-ray on the reported patients were also collected. A 4th-year medical student reviewed the medical records for any mention of kidney disease and abstracted all creatinine values. No attempt was made to abstract urinalysis or ANCA serologic data. When medical records were available, they were typically the discharge summary from hospitalization, X-ray reports, and assorted laboratory data. Any of the charts with mention of kidney disease identified by the student were reviewed by a physician who is board certified both in internal medicine and occupational medicine.

Due to delays in receiving reports and the availability of databases, the most complete data available were for 1987–1993. Only preliminary data were available for 1994 and 1995. Partial data were also available for the years 1985 and 1986. Individuals may have had silicosis prior to these years, but these were the dates the individuals were first reported to the surveillance system. Receipt of final data for a year increases the number of reports, but does not qualitatively change the preliminary data.

A person is considered to have silicosis if there is: (1) a history of exposure to silica and (2) a chest X-ray interpretation showing rounded opacities of 1/0 or greater profusion per the International Labor Organization's (ILO) classification system for pneumoconiosis or a biopsy report of lung tissue showing the characteristic silicotic nodule. All chest X-rays are reviewed by a physician who is a NIOSH-certified 'B' reader and, therefore, has special training and accreditation to interpret chest X-rays for all pneumoconioses, including silicosis. A person was considered to have kidney disease, if the discharge summary mentioned chronic kidney disease either in the narrative or list of admitting or discharge diagnoses. No attempt was made to obtain additional records to further elucidate the diagnosis. A serum creatinine level >1.5 mg/dl was considered elevated.

Chi-square test for trend and the Mantel-Haenszel χ^2 test were performed to evaluate the statistical significance. This study was approved by the Michigan State University Committee on Research Involving Human Subjects.

Results

We reviewed 583 confirmed cases of silicosis reported to the state from 1985 to 1995. During this same period we received 355 additional reports that did not meet the NIOSH criteria for a confirmed case of silicosis. The majority of the individuals not confirmed had another type of pneumoconiosis (asbestosis or coal worker's pneumoconiosis). The population consisted of 571 men (98%) and 12 women. The average year of birth was 1919. Three hundred and one (52%) were white, 260 (45%) were African-American, 16 (3%) were another race, and race was missing in 5 (1%) of the individuals. Seventy-nine percent had had their exposure to silica in a foundry. One hundred and sixty-four (29%) had progressive massive fibrosis (see table 3). Four hundred and twenty-two (74%) had had more than 20 years of exposure to silica (see table 4).

For 300 of the reports there were no laboratory results in the medical records that were available for review. Among the 283 individuals with creatinine levels reported, 45 (16%) were <1 mg/dl, 88 (31%) were 1–1.2 mg/dl, 58 (20%) were 1.3–1.5 mg/dl, 52 (18%) were >1.5–2.00 mg/dl, 22 (8%) were >2.00–3.00 mg/dl, 8 (3%) were >3.00–4.00 mg/dl, and 10 (4%) were >4.00 mg/dl. The range was 0.4–8 mg/dl.

Subsequent to the review of the medical records, an individual with silicosis and ANCA-positive Wegener's granulomatosis was reported:

Case Report

A 60-year-old white male worked 28 years, from 1965 to 1993, in a foundry. He had symptoms of chronic productive cough, dyspnea, and fatigue. He had done multiple jobs, including making molds,

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chipping, and sandblasting, in the foundry. He never smoked cigarettes. He had a negative skin test for tuberculosis. He did not apply for workers' compensation. His chest X-ray showed r/u-type opacities in the upper and mid zones with a profusion of 3/3 per the ILO criteria. His FVC was 1.46 liters, 29% of predicted, and his FEV_1 was 1.10 liters, 28% of predicted. His FEV_1/FVC ratio was 75%. In 1993 he was diagnosed with antineutrophil cytoplasmic antibody positive vasculitis and nephritis. A kidney biopsy specimen showed two portions of tissue containing a total of 2–4 glomeruli. The glomeruli exhibited varying histologic features. In some instances in some of the sections, the glomeruli appeared essentially unremarkable. In other instances, there appeared to be an increase in mesangial matrix and possibly an increase in mesangial cellularity. In addition, some glomeruli contained wrinkled basement membranes. An occasional glomerulus revealed partial or complete sclerosis. No vasculitis was noted. There were some vascular structures demonstrating at least a mild degree of arteriosclerosis. With the trichrome stain, there was evidence of at least a mild degree of interstitial fibrosis with tubular dropout. In addition, there were some sites of mild, predominantly chronic interstitial inflammation. Some of the tubules were dilated, containing inspissated materials. There was no vasculitis. The final interpretation was interstitial fibrosis, mild interstitial chronic inflammation, and varying sclerosing features. Immunofluorescence histology was negative for IgG, IgA, IgM, C1q, C4, albumin, fibrinogen, and kappa and lambda light chains. There was 1+ diffuse coarse granular staining of walls of globally sclerotic glomeruli for C3. Electron microscopy showed mesangial expansions, primarily with matrix. Large numbers of degradation granules were present. Electron-dense deposits were present beneath the mesangial basement membrane reflections. In addition, some paramesangial locations of deposits were noted, several of which were quite large. An occasional intramembraneous dense deposit was also noted. No peripheral subepithelial, subendothelial, or intramembranous deposits were identified. One capillary lumen showed a reduction in diameter secondary to the mesangial expansion as well as some folding and wrinkling of the basement membrane. Several capillary loops showed increased amounts of new basement membrane formation internal to the original lamina densa. This material has the characteristics of endothelial cell splits rather than circumferential mesangial interposition. Fibrin tactoids and platelet aggregates were not present. The subendothelial space did not appear to be expanded. No tubuloreticular structures were present within the cytoplasm of endothelial cells. No disruptive basement membrane changes were seen. Foot process effacement was diffuse, but incomplete. Microvillous changes were noted. No extracapillary proliferative changes were seen. A globally sclerotic glomerulus exhibited considerable hyalinotic subendothelial deposits, and large numbers of degradation granules were present. Tubular basement membranes were thickened, and degradation granules were present. The interstitium was expanded with connective tissue and some lymphocytes. Tubular epithelial cells contained prominent lipid vacuoles, and cholesterol clefts were present. The wall of an arteriole showed marked hyaline sclerotic changes. Large numbers of red cells were present within the tubular lumina. The final interpretation was ischemic nephropathy associated with hyaline arteriolar sclerosis (moderate to focal marked), focal immune complex mesangiopathic changes of uncertain etiology (an IgA nephropathy cannot be excluded), and tubulointerstitial inflammation and scarring. His blood urea nitrogen level was 50 mg/dl, creatinine 2.4 mg/dl. He took prednisone daily.

Table 1. Prevalence of kidney disease and/or serum creatinine (CR) level >1.5 mg/dl by age

Age years	Total number	Kidney disease		CR >1.5 mg/dl	
		n	%	n	%
<50	16	0	0	2	50.0
50–59	45	1	2.2	1	9.1
60–69	125	8	6.4	13	26.0
70–79	185	19	10.3	27	30.3
≥80	212	28	13.2	49	38.0
Total	583	56	9.6	92	32.5
		$\chi^2 = 0.78$ p = 0.377		$\chi^2 = 3.22$ p = 0.073	

Table 1 shows a statistically not significant increasing prevalence of kidney disease and serum creatinine levels >1.5 mg/dl with increasing age. We compared the prevalence of serum creatinine values >1.5 mg/dl within age and race strata to results in the general population based on the third National Health and Nutrition Examination Survey data [20]. The individuals with silicosis were significantly more likely to have an elevated serum creatinine level (table 2).

Table 3 shows the prevalence of kidney disease and serum creatinine levels >1.5 mg/dl by X-ray profusion. There was no association between increased profusion of scarring on the chest X-ray and evidence of kidney disease. This analysis was repeated within age- and race-specific strata. There continued to be no association between profusion and kidney disease or an elevated serum creatinine level.

Similarly, no association was found between increased duration of exposure to silica and prevalence of kidney disease and serum creatinine >1.5 mg/dl (table 4). This analysis was repeated within age- and race-specific strata. Again, there continued to be no association between duration of exposure to silica and kidney disease or an elevated serum creatinine level.

Information collected on the interview which may relate to the severity of disease was a history of sandblasting and whether the individual had applied for workers' compensation. Individuals with chronic kidney disease and/or serum creatinine levels >1.5 mg/dl were less likely to have performed sandblasting (OR = 0.49, 95% CL 0.25–0.93) but equally likely to have applied for workers' compensation (OR = 1.07, 95% CL 0.65–1.76) as individuals who did not have mention of kidney disease or whose serum creatinine was not >1.5 mg/dl.

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Table 2. Proportion of individuals with silicosis (1987–1995) and serum creatinine level >1.5 mg/dl compared to NHANES III (1988–1994) [20] by race and age

	Age, years									
	<50		50–59		60–69		70–79		≥80	
	n	%	n	%	n	%	n	%	n	%
Whites	1		7		19		32		41	
Silicosis	1	100.0	0	0.0	5	20.8	14	30.4	23	35.9
Controls		0.6		2.3		5.1		13.4		22.7
African-Americans	3		4		25		42		63	
Silicosis	1	33.3	1	25.0	7	28.0	13	31.0	25	39.7
Controls		2.2		9.2		19.8		23.4		27.7

Mantel-Haenstzel age-adjusted relative risk; whites 2.49 (95% CL 1.72–361), African-Americans 1.68 (95% CL 1.18–2.40).

Table 3. Prevalence of kidney disease and/or serum creatinine (CR) level >1.5 mg/dl by X-ray findings

X-Ray findings	Total number	Kidney disease		CR >1.5 mg/dl	
		n	%	n	%
Category[a]					
0 (biopsy evidence only)	20	3	15.0	3	42.9
1	196	13	6.6	23	31.1
2	135	15	11.1	25	35.7
3	49	6	12.2	11	50.0
Progressive massive fibrosis	164	18	11.0	29	27.1
Total	564[b]	55	9.8	91	32.5
		$\chi^2 = 0.78$ p = 0.377		$\chi^2 = 1.282$ p = 0.258	

[a] Categories 0–3 represent the ILO categorization system for grading pneumoconiosis: 0 = 0/–, 0/0, 0/1; 1 = 1/0, 1/1, 1/2; 2 = 2/1, 2/2, 2/3; 3 = 3/2, 3/3, 3/+.
[b] No X-ray, only an X-ray report consistent with silicosis was available in 19 individuals.

Discussion

There are multiple reports in the medical literature of an association between silica exposure and kidney disease. We found that chronic kidney disease was mentioned in approximately 10% of the medical records and that 33% of the individuals from whom laboratory reports were available had serum creatinine levels >1.5 mg/dl. The individuals with confirmed silicosis had a significant increase in the prevalence of elevated serum creatinine as compared with age-, race-, and gender-matched controls from the general population (table 2). However, we did not find any association between our two surrogate measures of silica exposure (profusion of scarring on chest X-ray and duration of exposure to silica) and prevalence of

Table 4. Prevalence of kidney disease and/or serum creatinine (CR) level >1.5 mg/dl by duration of exposure to silica

Time exposed to silica, years	Total number	Kidney disease		CR >1.5 mg/dl	
		n	%	n	%
<10	41	1	2.4	5	26.3
10–20	110	9	8.2	17	27.9
21–30	191	22	11.5	31	36.5
>30	231	24	10.4	36	32.1
Total	573[a]	56	9.8	89	32.1
		$\chi^2 = 1.09$ p = 0.168		$\chi^2 = 0.428$ p = 0.513	

[a] Duration of work was missing in 10 individuals.

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elevated serum creatinine and/or presence of kidney disease. Additionally, individuals with kidney disease or elevated serum creatinine level were less likely to have sandblasted (OR = 0.49, 95% CL 0.25–0.93), a work practice which causes particularly high levels of exposure, and no more likely to have applied for workers' compensation (OR = 1.07, 95% CL 0.65–1.76), a possible marker of severity of silicosis.

Similarly, in a study of 116 workers with silicosis who had elevated albumin, retinol-binding protein, and β-N-acetyl-*D*-glucosaminidase levels as compared with age-matched controls [2], no association was found between renal abnormalities and duration exposure to silica or severity of disease. This absence of a dose-response relationship contrasts with findings of a relationship between duration of exposure to silica or an estimate of cumulative silica exposure from a cross-sectional study of tubular function [12], a cohort study of end-stage renal disease among gold miners [3], and a case-control study of end-stage renal disease [18]. However, among the many case reports of kidney disease in silica-exposed workers, many only had short-term exposure (2–3 years) and normal chest radiographic findings [14]. In our cohort over 95% had X-ray abnormalities from silica exposure, and over 70% had at least 20 years of exposure to silica.

Two possible mechanisms have been proposed for silica's effect on the kidney: (1) a direct nephrotoxic effect and (2) an adjuvant effect to the immune system which evolves into an autoimmune renal disease [21]. The absence of an association in our data between surrogates of exposure (i.e., duration and X-ray severity) does not support a direct dose-related nephrotoxic effect of silica. The lack of an association with exposure, the known increased prevalence of positive tests for antinuclear antibodies and rheumatoid factor in individuals with silicosis as well as the increased prevalence of clinical connective disease among silicotics, a case report with positive immunofluorescence studies showing diffuse IgA and C3 mesangial deposits [22], and the studies associating Wegener's granulamatosis with silica exposure, all support the autoimmune hypothesis. In a previous study of this same cohort [23], we found an increase in connective tissue disease which again was not associated with duration of exposure or severity of disease. On the other hand, our case report and another report [15] revealed negative immunofluorescence findings on kidney biopsy. These findings coupled with the presence of a dose-response effect in some studies [3, 12, 18] and the presence of acute renal failure after massive exposure [4] support a direct nephrotoxic effect of silica. There is no reason why silica cannot be capable of causing kidney disease by both mechanisms.

Limitations of our study include the lack of availability of complete medical records and the inability to adequately characterize the attending physicians' reference to kidney disease. The attending physicians' patient evaluations were not standardized for the purpose of this study, and we did not specifically request medical records for kidney disease related test results for each patient. For this group of silicotics, we only had serum creatinine levels on 283 (49%) of the cohort. We are not aware of any biases related to who we had and did not have laboratory results for.

A second limitation is that the state's surveillance system for silicosis relies on reports from hospitals. It is known that the system does not receive all reports of silicosis in the state and is more likely to receive reports on individuals with more advanced silicosis [19]. If more advanced silicotics had more kidney disease or the presence of two diseases is more likely to lead to hospitalization, then the prevalence of silicotics with kidney disease we found among our cohort is an overestimate of the prevalence of chronic kidney disease in individuals with silicosis.

In summary, we found a higher prevalence of elevated serum creatinine levels as compared with age-, gender-, and race-matched controls. Unlike some previous investigators, we found no association between duration of exposure and severity of fibrosis on a chest X-ray. However, a review of all the studies on this subject suggests that silica may be capable of causing kidney disease by both an autoimmune and a nephrotoxic mechanism. Similar to connective tissue disease, chronic kidney disease should be considered a potential complication in patients with silicosis.

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