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KIDNEY AFFECTION AMONG WORKERS EXPOSED TO SILICA IN AN IRON AND STEEL FOUNDRY

BY

Hussein AM[1], Attia DI[1], Zayed BM[2], Rashed LA[3] and El-Sherif GH[1]

[1]Department of Occupational and Environmental Medicine,[2]Department of Internal Medicine,[3]Department of Biochemistry, Faculty of Medicine, Cairo University

Corresponding author: *El-Sherif GH*. ***Email:*** *ghadaelsherief@kasralainy.edu.eg*

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Abstract

I**ntroduction:** Silica is used in many industries such as foundries, glass production, cement, concrete, ceramic, porcelain, pottery, bricks, sandblasting, abrasives and construction activities. Several studies have linked long term silica exposure to renal diseases, especially glomerulonephritis. **Aim of Work:** To study the effect of silica exposure on the renal functions among iron and steel foundry workers. **Materials and Methods:** Seventy workers exposed to silica in an iron and steel foundry in Helwan, Egypt, were compared to 40 non-exposed individuals as regards full medical and occupational histories, full clinical examination and laboratory investigations including measurement of serum creatinine, serum cystatin C, serum urea, urinary silica, urinary albumin and urinary α1-microglobulin. Albumin creatinine ratio (ACR) and estimated glomerular filtration rate (e-GFR) were also calculated. **Results:** A statistically significant higher values of urinary silica, urinary albumin, urinary α1-microglobulin, serum creatinine, serum cystatin C and ACR were detected among the exposed group compared to the control. A statistically significant lower value of e-GFR was found among the exposed group. Statistically significant positive correlations were present between duration of employment and each of urinary silica, serum cystatin C, serum creatinine, serum urea, urinary α1-microglobulin, urinary albumin and ACR levels among the exposed group. Statistically significant positive correlations were also detected between urinary silica level and each of serum cystatin C, serum creatinine, serum urea, urinary α1-microglobulin, urinary albumin and ACR among the exposed group. Whereas, the e-GFR showed statistically significant negative correlations with both duration of employment and the urinary silica level among the exposed group. **Conclusion and Recommendations:** Silica exposure was associated with altered kidney function tests and decreased level of the e-GFR. Pre-employment and periodic medical examinations for silica-exposed workers should include clinical examination

and determination of kidney functions, e-GFR, urinary α1-microglobulin and serum .cystatin C for early detection of kidney affection
Key words: Silica, Chronic kidney disease (CKD), Cystatin C, α1-microglobulin and Estimated glomerular filtration rate (e-GFR).

Introduction

Silica is a widely abundant mineral that represents the core component of sand, soil and rocks (Hoy and Chambers, 2020). Quartz is the most common and biologically active form of crystalline silica (CS) (Sierra-Calderon et al, 2018). Silica is used in many industries such as foundries, glass production, cement, concrete, ceramic, porcelain, pottery, bricks, sandblasting, abrasives and construction activities (Omidianidost et al, 2016).

The main route for silica entry to the human body is through inhalation of silica particles. Exposure through dermal and oral routes is negligible (Mourad and Ashour, 2020). Silica particles reach the circulation through penetration of the blood-gas exchange barrier in the alveoli. Additionally, some phagocytosed particles are transported to the lymph nodes before being carried to the kidneys via the blood. These particles pass through the glomeruli into the urine with possible reabsorption into renal tubular cells (Schaeffer et al., 2020).

Silica exposure has been associated with 55% risk for chronic kidney disease (CKD) and about 22% mortality due to the subsequent renal failure (Sponholtz et al., 2016). Renal affection induced by CS exposure is related to two distinct mechanistic pathways: direct toxic effect of excessive CS deposition in the kidney, and indirect toxic effects secondary to autoimmune process (Rao et al., 2020).

CKD is defined as any abnormality in the kidney functions or structure that lasts more than three months with associated health impacts (Gaitonde et al., 2017). A more recent definition was addressed by the "Kidney Disease Outcomes Quality Initiative" (KDOQI) guidelines, based on the presence of either: a declined glomerular filtration rate (GFR) <60 ml/min./1.73 m^2 or kidney damage (presence of proteinuria, abnormal renal biopsy or abnormal renal imaging) that lasts for more than three months (Vassalotti, 2020).

Renal failure is the most serious outcome of CKD and its symptoms are caused by complications of reduced

kidney functions. It is diagnosed by GFR <15 ml/min./1.73 m². (Hu et al., 2018).

Serum creatinine level is a simple and inexpensive tool to determine renal functions. However, in some clinical conditions (e.g: ascites, generalized edema, liver cirrhosis and malnutrition) serum creatinine may not indicate the real condition of the kidney function. Also, serum creatinine level may be affected by age, gender, ethnicity, muscle mass, diet and some drugs such as trimethoprim (Lopez-Giacoman and Madero, 2015).

Cystatin C is a low molecular weight cysteine protease inhibitor generated by almost all nucleated cells. It is superior to serum creatinine in evaluating renal function as it is not influenced by age, gender, muscle mass, inflammation or malignancy (Dsa et al., 2017). Also, cystatin C is strongly correlated with CKD outcomes and mortality (Kar et al., 2018).

Diagnosis of CKD based on e-GFR is a more accurate assessment of renal functions than serum creatinine alone. Two equations are widely used in practice to estimate GFR: "the Chronic Kidney Disease–Epidemiology Collaboration" (CKD-EPI) equation and the older "Modification of Diet in Renal Disease Study" equation (MDRD), with the first being more accurate and more popular (Inker et al., 2012 and Inker et al., 2014).

Albumin creatinine ratio (ACR) was recommended by recent guidelines for CKD staging, rather than total urine protein level or urinary protein-to-creatinine ratio, due to its sensitivity and specificity in diagnosing glomerular injury. If tubular proteinuria is suspected, determination of urinary proteins such as α1-microglobulin and β2-microglobulin is recommended. It is better measured in 24-hour collection sample; however, spot urine samples (corrected by urinary creatinine level) are also acceptable because they correlate with 24-hour urinary excretion (Chen et al., 2019, Mourad and Ashour, 2020).

Aim of Work

To study the effect of silica exposure on renal functions among iron and steel foundry workers.

Materials and Methods

- **Study design**: It is a cross-sectional comparative study.

- **Place and duration of the study:** The study was performed in a

national iron and steel foundry located in Helwan, Egypt. Data collection was performed during the period from December 2015 to February 2016.

- **Study sample:** The study included an exposed group and a non-exposed control group. The exposed group consisted of 70 non-smoker silica-exposed male workers which represented all the workers of the morning shift of one iron foundry, who met the inclusion criteria. A comparison non-exposed group of 40 non-smoking male subjects, who had never been occupationally exposed to silica, was randomly selected from the outpatient clinic in Cairo University Hospital. The control population was matched with the exposed group regarding the age, sex, socioeconomic status and special habits of medical importance. Inclusion criteria: Exposed workers should have been working in the iron and steel foundry for at least five years. Exclusion criteria: Exposed workers with work duration less than 5 years, smokers, workers exposed to silica in other jobs outside the foundry, those who had pre-existing kidney disease, those with pre-existing history of hypertension, diabetes mellitus, obstructive uropathy, and autoimmune diseases including rheumatoid arthritis and systemic lupus erythematosus, as well as those taking nephrotoxic drugs.

- **Study methods:** The whole studied population were subjected to the following:

➢ A **self administrated questionnaire** including detailed personnel, medical and occupational histories with special emphasis on manifestations of renal affection.

➢ **General and systemic examinations**

➢ **Laboratory investigations:**

1-Determination of the levels of **serum cystatin C, serum creatinine and serum urea**: A blood sample of 5 cc was obtained from each subject through venipuncture from the arm using a disposable plastic syringe under complete aseptic conditions. Each sample was left to clot then centrifuged to separate the serum for evaluation of cystatin C (ELISA method using Dade Behring diagnostics kit, Marburg, Germany), serum creatinine, and serum urea.

2-Urinary level of silica was estimated as a biomarker for silica exposure.

3-Urinary albumin, creatinine and α1-microglobulin levels were estimated. Urine samples were collected post-shift (after 8 hours of work) from the exposed workers in dry sterile containers to assess urinary silica, creatinine, albumin and α1-microglobulin levels (ELISA method).

4-Albumin creatinine ratio (ACR) was calculated by the following equation:

ACR (mg/g creatinine) = urinary albumin (mg/dl) x 1000 / urinary creatinine (mg/dl)

Chronic kidney disease (CKD) was defined as ACR ≥ 30 mg/g and was categorized as: **stage A1:** ACR ≤ 30 mg/g (normal to mildly elevated); **stage A2:** 30 < ACR< 300 mg/g (moderately elevated), and **stage A3:** ACR >300 mg/g (severely elevated) ***(Sumida et al., 2020).***

5-Estimated glomerular filtration rate (e-GFR) was calculated by CKD-EPI Creatinine-Cystatin equation (Delgado et al., 2022), using the e-GFR calculator made by the National Kidney Foundation based on the following equation:

eGFRcr-cys = 135 × min(Scr/κ, 1) α ×max(Scr/κ,1)-0.544 ×min(Scys/0.8, 1)-0.323 × max(Scys/0.8, 1)-0.778 × 0.9961Age × 0.963, where:

Scr = serum creatinine in mg/dL, κ = 0.9, α = -0.144, min(Scr/κ, 1) is the

minimum of Scr/κ or 1.0, max(Scr/κ, 1) is the maximum of Scr/κ or 1.0,Scys = serum

cystatin C in mg/L and Age = years.

According to e-GFR, chronic kidney disease (CKD) was classified as: **stage 1** (GFR >90 ml/min./1.73 m^2), **stage 2** (GFR= 60-89 ml/min./1.73 m^2), **stage 3a** (GFR= 45-59 ml/min./ 1.73m^2), **stage 3b** (GFR= 30-44 ml/min./1.73 m^2), **stage 4** (GFR= 15-29 ml/min./1.73 m^2) and **stage 5** (Renal failure; GFR<15 ml/min./1.73 m^2) (Vassalotti, 2020).

Consent

A written consent was taken from workers who agreed to participate in the research, to give both blood and urine samples, and to be clinically examined.

Ethical Approval

Prior to the study, approval of the Ethical Committee of the Department of the Occupational and Environmental Medicine, Faculty of Medicine, Cairo University was obtained.

The aim of the study was explained to the manager and the workers of the

iron and steel foundry and the approval of the administrative authority in the factory was obtained. The study was performed during the annual periodic medical examination in collaboration with the Egyptian General Organization for Health Insurance. This work has been carried out in accordance with the code of ethics of the world medical association (Declaration of Helsinki) for studies involving humans.

Data Management

Data were processed and analyzed using the Statistical Package for Social Sciences (SPSS) program version 26. Data was summarized using mean, standard deviation (SD), median, minimum and maximum for quantitative variables, and frequencies (number of cases) and relative frequencies (percentages) for qualitative variables. Comparison between two normally distributed quantitative variables was done using independent t-test. Mann-Whitney test was used for comparison between two quantitative variables not-normally distributed. Kruskal-Wallis test followed by Post Hoc test were used for comparison between more than two quantitative variables not-normally distributed. Chi square ($\chi 2$) test was used for comparison between qualitative variables. Fisher's Exact test was used for comparison between qualitative variables when the expected frequency is less than 5.Correlation coefficient "r" test was used to study the correlation between two quantitative variables not-normally distributed. The statistical significance was defined as $p < 0.05$.

Results

The exposed group consisted of 70 silica-exposed workers, whose ages ranged from 30-59 years with mean of 46.53 ± 7.65 years, that showed no statistically significant difference when compared with the control group, who was composed of 40 personnel; their age range from 29-56 years, with mean of 24.26 ± 8.10 years. As for the exposed group, the work duration ranged from 9-38 years with a mean of 24.26 ± 8.10 years, and the percent use of personal protective equipment (PPE) was 32.9 % (23 workers).

Table (1): Frequency distribution of renal and general clinical manifestations among the studied groups.

Clinical manifestations	Exposed group No=70		Non-exposed group No=40		p-value #
	No.	%	No.	%	
Renal manifestations					
Loin pain	17	24.3 %	5	12.5 %	0.215
Dysuria	3	4.3 %	1	2.5 %	1
Edema	15	21.4 %	2	5.0 %	**0.027***
General manifestations					
Anemia	1	1.4 %	0	0.0 %	1
Clubbing	1	1.4 %	0	0.0 %	1

#: Fisher's Exact test *: Statistically significant

Table (1) showed that although the number of workers complaining of loin pain, dysuria, wheezes, hemoptysis and clubbing was higher among the exposed group compared to the non-exposed, yet, it was of no statistically significant difference. Edema on the other hand was statistically significantly higher among exposed workers compared to controls.

Table (2): Comparison between the studied groups as regards the laboratory findings.

		Exposed group	Non-exposed group	Mann-Whitney test	p-value
		No = 40	No = 70		
Urinary silica (ng/ml)	Mean ± SD Median Range	3.73 ± 2.11 3.32 0.53 – 7.1	0.91 ± 0.29 0.82 0.52 – 1.65	7.588	**0.000***
Serum cystatin C (ng/ml)	Mean ± SD Median Range	0.83 ± 0.37 0.76 0.21 – 2.01	0.33 ± 0.14 0.28 0.13 – 0.57	7.416	**0.000***
Serum creatinine (mg/dl)	Mean ± SD Median Range	2.59 ± 1.34 2.3 1.01 – 6.8	1.09 ± 0.22 1.02 0.84 – 1.8	7.513	**0.000***
Serum urea (mg/dl)	Mean ± SD Median Range	47.7 ± 9.49 50 28 – 64	26.25 ± 7.07 26.5 15 – 38	7.923	**0.000***
Urinary α1-microglobulin (mg/g creatinine)	Mean ± SD Median Range	7.84 ± 3.89 7.97 2.03 – 15.2	3.51 ± 0.77 3.4 1.9 – 5.1	5.992	**0.000***
Urinary albumin (mg/dl)	Mean ± SD Median Range	21.91 ± 18.4 12.5 3.4 – 67.3	5.13 ± 1.46 4.9 2.01 – 8.5	5.541	**0.000***
ACR (mg/g)	Mean ± SD Median Range	129.97 ± 116.54 70.95 17.6 – 427.1	21.91 ± 6.21 20.45 8.3 – 37.2	7.227	**0.000***
e-GFR (ml/min.)	Mean ± SD Median Range	65.60 ± 34.31 58 16 – 174	142.37 ± 26.54 140.5 100 – 207	-7.939	**0.000***

*: Statistically significant ACR : Albumin/Creatinine ratio e-GFR: Estimated glomerular filtration rate.

Table (2) showed that there were statistically significant higher mean values of urinary silica, serum cystatin C, serum creatinine, serum urea, urinary α1-microglobulin, urinary albumin and ACR; and a statistically significant lower mean value of the e-GFR among silica-exposed group compared to the non-exposed.

Table (3): Comparison between the studied groups regarding the prevalence of different stages of both albumin/creatinine ratio (ACR) and the estimated glomerular filtration rate (e-GFR).

		Exposed group No=70		Non-exposed group No=40		p-value #
		%	No.	%	No.	
ACR stages	A1 (Normal)	25	35.7 %	36	90.0 %	0.000*
	A2 (Moderate)	38	54.3 %	4	10.0 %	
	A3 (Severe)	7	10.0 %	0	0.0 %	
e-GFR stages	G1	20	28.6 %	39	97.5 %	0.000*
	G2	12	17.1 %	1	2.5 %	
	G3a	15	21.4 %	0	0.0 %	
	G3b	13	18.6 %	0	0.0 %	
	G4	10	14.3 %	0	0.0 %	

#: Fisher's Exact test * : Statistically significant

Table (3) showed that statistically high significant differences were found between the exposed and the non-exposed groups as regards the prevalence of different stages of both ACR and the e-GFR.

Table (4): Analysis of variance for urinary silica level (ng/ml) among different stages of the Albumin/Creatinine ratio (ACR) and Estimated glomerular filtration rate (e-GFR) among the exposed group.

Exposed group (No=70)		Urinary silica (ng/ml)		Kruskal-Wallis test	p-value
		Range	Mean ± SD		
ACR stages	A1	2.71 ± 2.04	0.91 – 7.1	12.153	0.002*
	A2	4.08 ± 1.93	0.53 – 6.86		
	A3	5.51 ± 1.65	2.97 – 6.92		
e-GFR stages	G1	2.29 ± 1.81	0.91 – 7.1	22.847	0.000*
	G2	2.84 ± 1.79	0.53 – 6.07		
	G3A	4.37 ± 1.96	0.57 – 6.99		
	G3B	4.86 ± 1.70	1.6 – 6.86		
	G4	5.27 ± 1.61	2.71 – 6.92		

*: Statistically significant

Table (4) showed that there were statistically significant differences between the different stages of ACR as well as between the different stages of the e-GFR among the exposed group.

Table (5): Correlation coefficient between duration of employment and urinary silica level and different laboratory investigations among the exposed group (No =70).

	Duration of employment (years)		Urinary silica (ng/ml)	
	r	p-value	r	p-value
Urinary silica (ng/ml)	0.709	**0.000***	-----	-----
Serum cystatin C (ng/ml)	0.534	**0.000***	0.651	**0.000***
Serum creatinine (mg/dl)	0.407	**0.000***	0.369	**0.002***
Serum urea (mg/dl)	0.363	**0.002***	0.365	**0.002***
α-١ microglobulin (mg/g)	0.418	**0.000***	0.480	**0.000***
Urinary albumin (mg/dl)	0.518	**0.000***	0.496	**0.000***
ACR (mg/g)	0.496	**0.000***	0.480	**0.000***
e-GFR (ml/min.)	-0.607	**0.000***	-0.562	**0.000***

r: Spearman correlation coefficient ACR :Albumin/Creatinine ratio

e-GFR: Estimated glomerular filtration rate. *: Statistically significant

Table (5) showed statistically significant positive correlations between duration of employment and each of urinary silica, serum cystatin C, serum creatinine, serum urea, urinary α1-microglobulin, urinary albumin and ACR levels. Statistically significant positive correlations are also detected between urinary silica level and each of serum cystatin C, serum creatinine, serum urea, urinary α1-microglobulin, urinary albumin and ACR. The e-GFR showed statistically significant negative correlations with both duration of employment and the urinary silica level.

Discussion

Exposure to silica occurs in various industries including mining, foundry, cement, glass, concrete, ceramic, brick, pottery, sandblasting and construction (Carrieri et al., 2020). Several studies have reported that foundry work is associated with high levels of silica exposure, as sand is the major component used in the core and mold production process in foundry industry (Kuo et al., 2018).Also they linked long term silica exposure to renal diseases. Renal affection induced by silica exposure is represented by glomerular and tubulointerstitial nephropathies (Altınöz et al., 2018).

The current study aimed to study the effect of silica exposure on renal functions among workers of an iron and steel foundry in Egypt.

When comparing between the exposed and control groups as regards their mean age, no statistically significant difference could be detected. Also, smoking has no effect on the studied parameters, as all selected subjects were non-smokers.

Concerning renal manifestations, the present study revealed that the prevalence of loin pain, edema and dysuria was higher among the exposed group compared to the non-exposed group. However, only edema showed a statistically significant difference (Table 1).This was in agreement with those reported in a study done in Egypt which investigated renal effects among silica-exposed workers. The study showed that the prevalence of renal symptoms was significantly higher among the exposed group in comparison to the controls (Ibrahim et al., 2011).

There was a statistically significant increase in the mean value of urinary silica level among the exposed group compared to the non-exposed (Table 2). This was in accordance with another study which reported statistically significant difference in the mean value of urinary silica level between the exposed and the control groups (Liu et al., 2016).

There were high statistically significant differences between the exposed and the non-exposed groups regarding the increase in the mean values of serum cystatin C, serum creatinine, serum urea, urinary α1-microglobulin and urinary albumin (Table2).These findings was in concordance with an Egyptian study which investigated subclinical signs

of nephrotoxicity among silica-exposed workers. The study showed highly significant differences between the exposed group and the controls regarding serum creatinine, blood urea, urinary creatinine, urinary albumin and urinary α1-microglobulin in urine (Arafaa et al., 2012). Also, the results were in harmony with those of another study done in Egypt which explored renal affection among silica-exposed workers in a ceramic factory and reported a significant increase in the urinary albumin level, α1-microglobulin, creatinine and urinary levels of silica among the exposed group in comparison to the controls (Ahmed et al., 2013).

The results were also in accordance with those reported by Sameen, 2013, in his study in Al-Ramadi City, Iraq; which showed increased serum urea and creatinine levels among silica-exposed workers in comparison to the controls.

There were high statistically significant differences between the two studied groups as regards both ACR and the e-GFR (Table 2), as well as the prevalence of their stages of affection (Table 3). On comparing the urinary silica level between the different stages of the e-GFR and the different ACR grades among the exposed group, statistically significant differences were detected (Table 4). This was in agreement with the results of a case-study done by Ricco et al., 2016, which revealed impaired renal functions in the form of proteinuria, elevated serum creatinine and reduced GFR in a case of mild chronic silicosis.

Similarly, another case study of a 56 years old worker with history of occupational silica exposure for 30 years revealed that serum creatinine and urea levels were elevated and the value of e-GFR was decreased. Also the routine urine analysis revealed proteinuria (Lee et al., 2016).

The duration of exposure is one of the most important key factors that determine the development and severity of silica-induced health effects. This was supported by the presence of statistically significant positive correlations between the work duration and each of urinary silica, serum cystatin C, serum creatinine, serum urea, urinary α1-microglobulin, urinary albumin and ACR levels. Statistically significant negative correlations were detected between the duration of employment and the e-GFR levels (Table 5).

In accordance with the present

findings, previous studies reported a positive correlation between work duration and the urinary silica level, and that urinary silica was rapidly increasing with the years of exposure reaching the peak at 1-5 years (Mourad and Ashour, 2020) and (Liu et al., 2016). The findings of the present study also agreed with those obtained in previous Egyptian studies, in which statistically significant positive correlations were found between the work duration and urinary albumin, serum creatinine and urinary α1-microglobulin among the exposed group (Fahmy et al., 2011) and (Arafaa et al., 2012).

Conclusion and Recommendations

The present study showed that long-term silica exposure is a major cause for developing CKD. This suggestion is supported by albuminuria, increased urinary α1-microglobulin, serum cystatin C, serum creatinine and decreased e-GFR levels among silica-exposed workers.

Pre-employment and periodic medical examinations for silica-exposed workers should include clinical examination and determination of kidney functions, e-GFR, urinary α1-microglobulin and serum cystatin C for early detection of kidney affection. Biological monitoring of exposure is a part of occupational health assessment aiming at early detection and elimination of potential hazards, so determination of urinary silica can be used as indicator of cumulative silica exposure among workers.

Engineering controls should be implemented, with the use of isolated automated machines to control any source of silica dust and to keep workers apart from exposures. Additionally, workers should be encouraged to use personal protective equipment and apply hygienic measures.

Limitations of the study:

The present study is cross-sectional and it does not allow full assessment of CKD, as by definition CKD is an alteration of the renal function or the presence of markers of renal dysfunction or lesions for 3 months. Therefore, further prospective cohort studies involving larger number of workers for extended period would be needed to confirm this inference.

Conflict of Interest

The authors declared that there was no conflict of interest.

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