



Demonstration of Subclinical Early Nephrotoxicity Induced by Occupational Exposure to Silica among Workers in Pottery Industry

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Abstract

Background: For many years, several studies drew attention to the possible nephrotoxic effects of silica and distinct renal dysfunction involving glomerular and renal tubules in workers exposed to silica.

Objective: To determine the early signs of subclinical nephrotoxic effects among some Egyptian workers exposed to silica in the pottery industry.

Methods: This study was carried out in El-Fawakhir handicraft pottery area, in Greater Cairo, Egypt. The studied population included 29 non-smoking male workers occupationally exposed to silica in addition to 35 non-smoking administrative male subjects who represented the comparison group in the study. Measured urinary parameters were concentrations of total protein (TP), microalbumin (Malb), activities of alkaline phosphatase (ALP), g-glutamyl transferase (g-GT), lactate dehydrogenase (LDH), kidney injury molecule-1 (KIM-1), and silicon (Si).

Results: Silica-exposed workers showed significantly ($p < 0.05$) increased levels of urinary TP, Malb, ALP, g-GT, LDH, and KIM-1 compared with the comparison group. Among the silica-exposed group, increased urinary Si levels were positively and significantly correlated (Spearman's $\rho > 0.60$, $p < 0.001$ for all variables) with the elevated urinary proteins (including KIM-1) and enzymes levels. All measured urinary parameters were positively and significantly correlated ($\rho > 0.75$, $p < 0.001$ for all variables) with the duration of work among exposed subjects. No significant correlation was observed between the measured variables and the age of workers.

Conclusion: There is associated subclinical glomerular and tubular affection among silica-exposed workers, which is related to the duration and intensity of exposure.

Keywords: Silicon dioxide; Occupational exposure; Kidney diseases; Renal insufficiency; Kidney glomerulus; Kidney tubules; Proteinuria

Introduction

Occupational exposure to crystalline silica has long been known to cause various lung diseases, most

notably silicosis. The main route of entry of silica into the human body is through the respiratory system as dust; the exposure via skin or the gastrointestinal tract is negligible. The most common industries

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and occupations that have the potential for silica exposure include mining, quarrying, foundry work, glass manufacture, ceramic, pottery, and cement production.¹

Silica dust was suspected to affect the human kidney over 90 years ago. The detected pathologic renal changes are similar to those induced by nephrotoxic heavy metals in the form of dose-related nephropathy that causes degenerative changes in tubular epithelium and interstitial inflammation, fibrous nephrosis, glomerulonephritis, and systemic vasculitis. Additionally, it was demonstrated that silica exposed workers can experience distinct renal histologic alterations in glomerular and proximal tubules.^{2,3}

Various urinary biomarkers have been proved to be useful to locate defects in specific parts of the nephron and can detect early renal changes resulted from exposure to nephrotoxins. These biomarkers include high molecular-weight protein, and albumin for evaluating glomerular integrity—low molecular weight protein for assessing tubular protein reabsorption. As a result of tubular epithelial damage and cellular lysis, both cytosolic and lysosomal enzymes are released. Evaluating the urinary concentrations of these enzymes can be considered a perfect non-invasive sensitive method to assess tubular integrity. These significant urinary renal enzymes include alkaline phosphatase (ALP) and γ -glutamyltransferase (γ -GT), which are found on the epithelial cells of the proximal tubule; lactate dehydrogenase (LDH) is located at distal tubular cells. Referring to several recent human studies, these urinary biomarkers have been used to detect early subclinical renal dysfunction.³⁻⁵

Another novel urinary biomarker that has recently been shown to have more sensitivity and specificity in the detection of the initial preclinical renal tubular insult, is the urinary kidney injury molecule-1 (KIM-1). A meta-analysis including 11

studies (2979 patients) estimates the urinary KIM-1 specificity for the diagnosis of acute renal injury at 86% and sensitivity at 74%.⁶ KIM-1 is a type I transmembrane glycoprotein mainly expressed on the surface of T cells. It has two extracellular domains. KIM-1 expression is low in normal kidneys but is significantly increased in proximal tubular cells following kidney injury. Upon kidney injury, the extracellular domains of KIM-1 separate from the cell surface and enter the urine through a metalloproteinase-dependent process.⁷ As the tubular injury appears to precede glomerular damage in the pathophysiology of renal diseases, several recent studies resorted to study the urinary levels of KIM-1 as a reliable evidence for the degree of subclinical tubular affection and hence assessing the extent of preclinical nephrotoxicity.⁸⁻¹⁰

We therefore conducted this study to demonstrate the early signs of subclinical nephrotoxic effects involving renal glomeruli and tubules among some Egyptian workers occupationally exposed to silica in pottery industry.

Materials and Methods

In this cross-sectional study, 29 occupationally silica-exposed subjects were recruited from non-smoking male workers in El-Fawakhir handicraft pottery area, in Greater Cairo, Egypt. A comparison group of non-smoking male population were also selected from the administrative department of Kasr Al-Ainy hospital to include 35 matching subjects with history of usual exposure to silica during their daily life but without occupational exposure.

A questionnaire was used to identify the main demographic and lifestyle characteristics of the studied subjects such as smoking habit, detailed occupational history and medical history with the medication intake to reveal the possible indicators of

nephrotoxicity among the studied population during the time of urine collection.

The whole number of the workers in this factory was 93. The exposed group included those workers in the factory who have been exposed to the manufacturing process. It is worth to mention that 64 workers were excluded before starting the study based on the pre-determined exclusion criteria. Workers were excluded from the study if any was a smoker, had experienced kidney disease or any disease likely to impair renal functions and/or parameters that were to be tested (creatinine, ALP, γ -GT, and LDH). Others excluded from the study were those who had previous or current potential exposure to agents capable of damaging the kidney such as lead, cadmium, and mercury or other nephrotoxics such as organic solvents. The workers might also be excluded if they revealed a history of having consumed drugs with potential nephrotoxicity such as analgesics and anti-inflammatory agents and abuse of aminoglycoside antibiotic therapy. The comparison group subjects were selected with comparable sex, age, socioeconomic standards, and special habits of medical importance (especially in being non-smokers) to the exposed group after applying the previously mentioned exclusion criteria.

Sample Collection

A random single-voided urine sample in a closed container was collected from each participant. The container was labelled with the study number of the participant which is written on the questionnaire form to avoid any risk of mix-ups or incorrect identification of samples. Spot urine was used because urinary protein/creatinine ratio,¹¹ as well as dividing urinary enzyme activity by the urine creatinine concentration in the random sample,¹² correlates with 24-hour urinary excretion and eliminates variations due to changing rates

TAKE-HOME MESSAGE

- Prolonged and intensive occupational exposure to silica could result in subclinical nephrotoxicity. It can thus be associated with an increased risk of future end-stage renal disease.
- Usage of urinary biomarkers to detect signs of preclinical glomerular and tubular affection seems to be a simple and non-invasive screening tool to identify silica-exposed workers who carry a higher risk of future nephropathy.

of urine output and provides a measurement of concentration. The collected urine sample was transported in a closed box at room temperature within two hours after the collection.

Sample Analysis

Each urine sample was analyzed to assess glomerular integrity through measuring urinary levels of total protein (TP) using the semiautomated Technicon Bayer RA 1000[®] analyzer (Ireland Technicon Limited), and microalbumin (Malb) using Hemocue[®] urine albumin system (Hemocue AB, Angelhom, Sweden); proximal and distal tubular structural integrity by determining urinary activities of γ -GT and ALP, which are proximal tubule enzymes, and LDH located at distal tubular cells,¹³ using automated Olympus AU640[®] analyser (Japan Mishima Olympus Optical Company Limited); and urinary silicon levels using the Buck Model 210 VGP Atomic Absorption Spectrophotometer[®] (Bulk Scientific, Inc).³ Urine level of KIM-1 was determined using a commercially available quantitative sandwich immunoassay technique (SunRed Biotechnology Company, Shanghai, China), as per manufacturers' instructions. Urinary KIM-1 level was normalized by dividing by urine creatinine.¹⁰

Internal Quality Control

The internal quality control sample mate-

Table 1: Median (IQR) of studied demographic characteristics, and the levels of urinary proteins, enzymes, KIM-1 and silicon among silica-exposed and the comparison groups

Parameter	Silica-exposed (n=29)	Comparison (n=35)	p value
Age (yrs)	45 (25)	39 (29)	0.096
Work duration (yrs)	25 (19)	17 (21)	0.117
TP/Cr (mg/g Cr)	560.4 (1264.6)	15.4 (137.9)	0.001
Malb/Cr (mg/g Cr)	54.3 (88.7)	1.0 (25.5)	0.03
ALP/Cr (IU/g Cr)	20.0 (25.9)	2.4 (4.6)	0.001
γ-GT/Cr (IU/g Cr)	235.1 (341.3)	20.5 (74.1)	0.001
LDH/Cr (IU/g Cr)	201.4 (236.6)	29.0 (28.4)	0.001
KIM-1/Cr (pg/mg Cr)	210.4 (126.6)	120.1 (100.0)	0.001
Si/Cr (mg/g Cr)	26.4 (15.0)	2.1 (3.3)	0.001

TP: Total protein, Malb: microalbumin, ALP: Alkaline phosphatase, γ-GT: γ-glutamyl transferase, LDH: Lactate dehydrogenase, KIM-1: kidney injury molecule-1, Si: Silicon, Cr: Creatinine

rials were run together with the urine specimen from the study subjects. Values obtained for the internal quality control materials for each of the measured parameters was accepted if it was within ±2 SD from the target value.

Ethics

Ethical approval was sought and granted by the Ethical Committee of the Occupational and Environmental Medicine Department, Kasr Al-Ainy Hospital, Faculty of Medicine, Cairo University, Cairo, Egypt. Approval was taken from the Chief Executive Officer (CEO) of the factory. The participants were reassured of confidentiality in the handling of information and procedures involved in this study. Informed written consent for sharing in the study was voluntarily obtained from each individual after a proper explanation of the objectives of the current study.

Statistical Analysis

Results of all measured parameters were each divided by the levels of urinary concentration of creatinine (in g/L)¹¹ so as to correct for variations in urinary concentration due to hydration.¹⁴ Data generated from the study were entered into MS Excel® software and then exported to SPSS® for Windows® ver 25 for statistical analysis.

Data were tabulated as median (IQR) because most of the measured parameters were not normally distributed. Differences between investigated groups (male referents, male silica-exposed subjects) were assessed by Mann-Whitney U test. Correlation between quantitative variables was done using Spearman's rank correlation coefficient (ρ). Univariate linear regression between quantitative variables was done to test significant predictors for measured urinary proteins and enzymes among the exposed group. A p value <0.05 was considered statistically significant.

Results

Table 1 shows the levels of urinary proteins, enzymes, KIM-1, and silicon among the studied groups. Silica-exposed male workers had significantly increased levels of urinary TP, Malb, ALP, γ-GT, LDH, KIM-1 and Si (p<0.001 for all except Malb, p=0.03), compared to that of the comparison subjects.

A significant positive correlation was observed between the work duration and the urinary Si level *vs* all other measured urinary parameters among the exposed group (Figs 1, 2; Spearman's ρ >0.60, p<0.001 for all variables). There was no significant correlation between the age and the measured urinary parameters among silica-exposed workers.

Work duration in addition to the urinary Si level could be considered signifi-

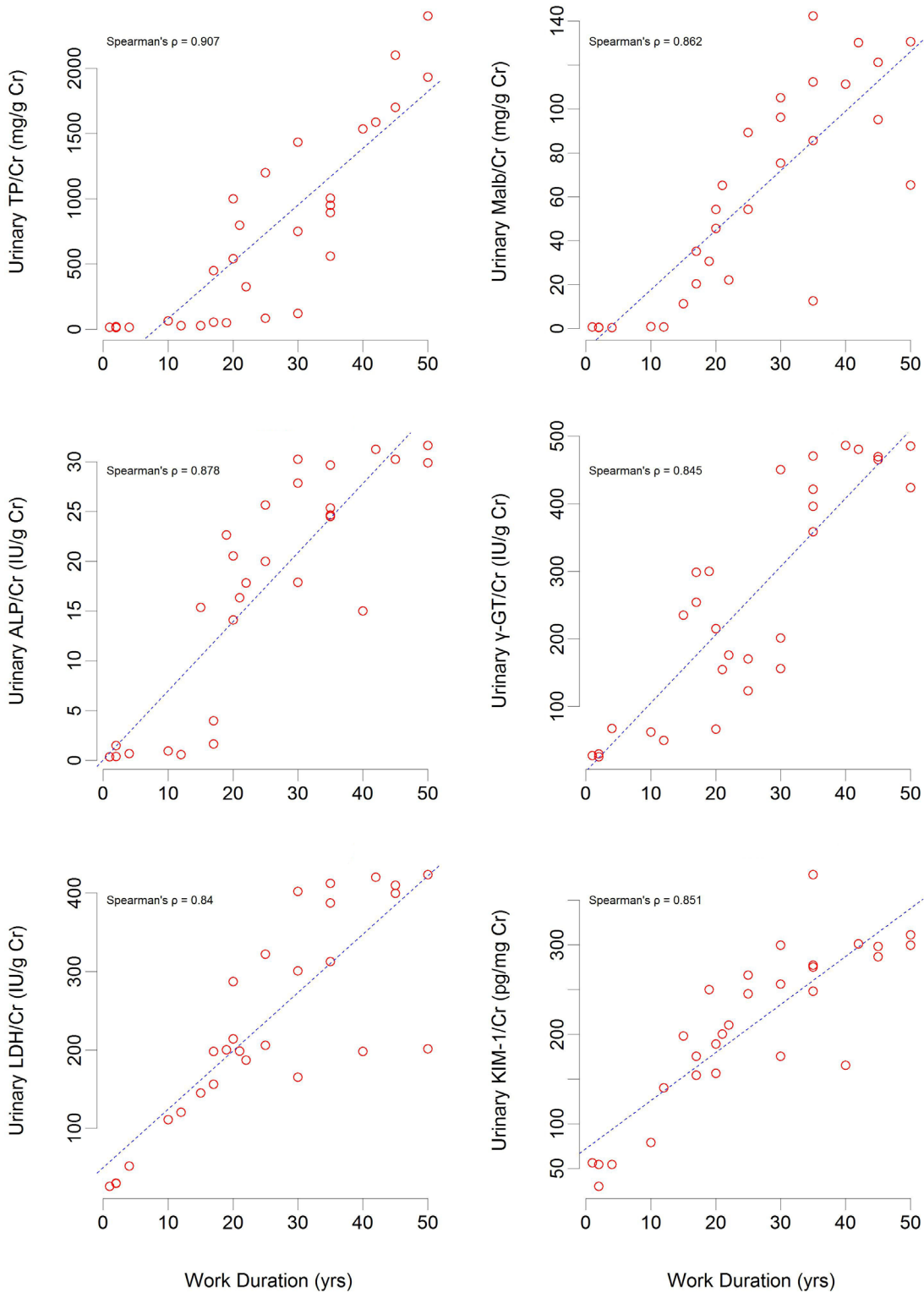


Figure 1: Scatter plots representing linear regression between all measured urinary proteins, enzymes, KIM-1 of silica-exposed workers vs their work duration

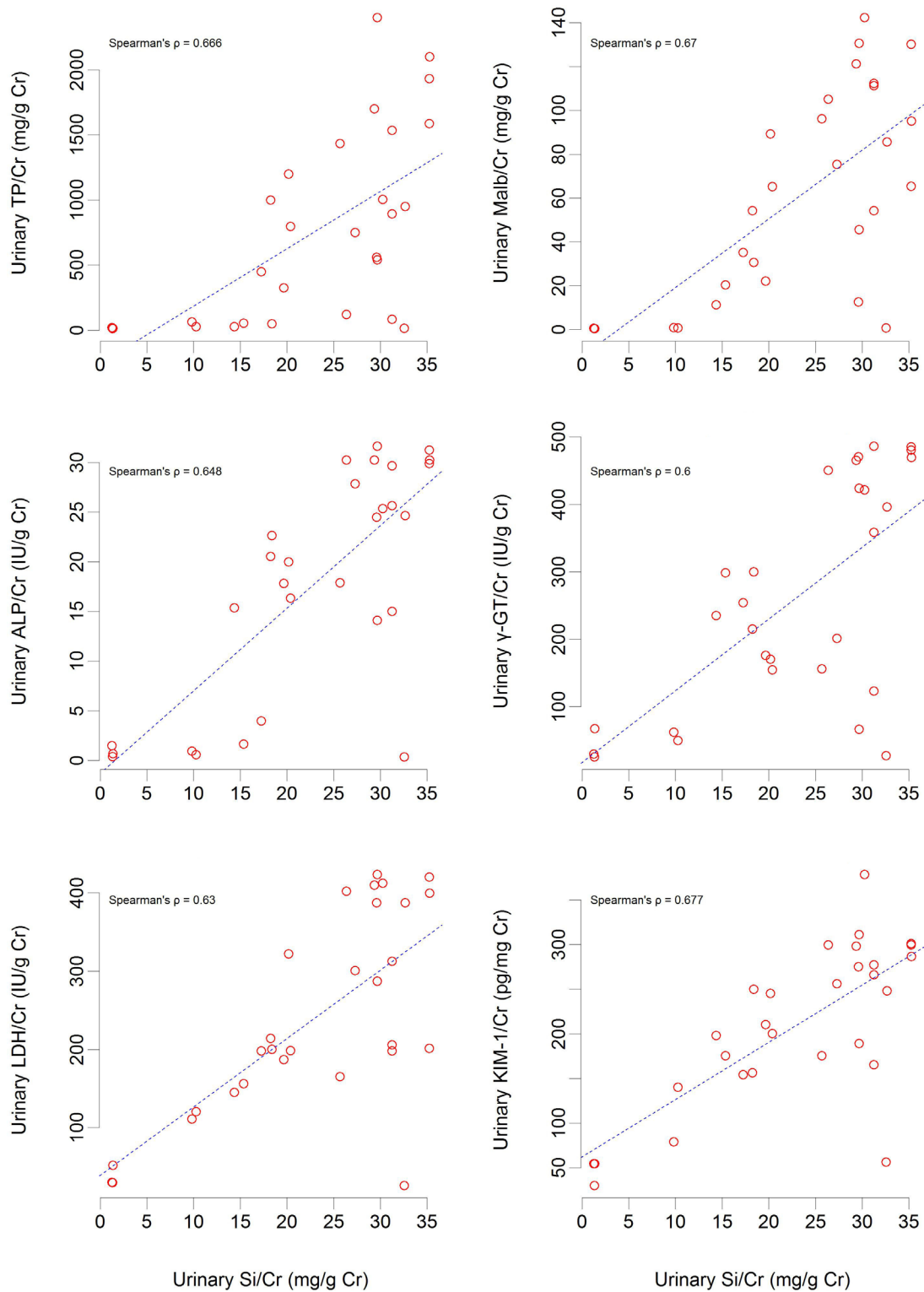


Figure 2: Scatter plots representing linear regression between all measured urinary proteins, enzymes, KIM-1 of silica-exposed workers vs their urinary silicon level

Table 2: Univariate linear regression analysis to detect significant predictors of measured urinary proteins, enzymes and KIM-1 from the age, work duration and urinary silicon levels among silica-exposed workers

Independent variable	Dependent variables	Coefficient (95% CI)
Age (yrs)	TP/Cr (mg/g Cr)	16.75 (-13.52 to 45.97)
	Malb/Cr (mg/g Cr)	1.07 (-1.05 to 3.08)
	ALP/Cr (IU/g Cr)	0.21 (-0.41 to 0.82)
	γ-GT/Cr (IU/g Cr)	3.15 (-4.87 to 11.43)
	LDH/Cr (IU/g Cr)	2.06 (-3.41 to 8.71)
	KIM-1/Cr (pg/mg Cr)	1.07 (-3.57 to 6.58)
Work duration (yrs)	TP/Cr (mg/g Cr)	43.46 (33.37 to 53.56)
	Malb/Cr (mg/g Cr)	2.71 (1.987 to 3.44)
	ALP/Cr (IU/g Cr)	0.69 (0.54 to 0.85)
	γ-GT/Cr (IU/g Cr)	10.09 (7.85 to 12.32)
	LDH/Cr (IU/g Cr)	7.43 (5.43 to 9.43)
	KIM-1/Cr (pg/mg Cr)	5.37 (4.07 to 6.68)
Urinary Si/Cr (mg/g Cr)	TP/Cr (mg/g Cr)	44.00 (22.80 to 65.21)
	Malb/Cr (mg/g Cr)	3.14 (1.86 to 4.42)
	ALP/Cr (IU/g Cr)	0.83 (0.55 to 1.11)
	γ-GT/Cr (IU/g Cr)	10.63 (5.95 to 15.31)
	LDH/Cr (IU/g Cr)	8.74 (5.28 to 12.20)
	KIM-1/Cr (pg/mg Cr)	6.42 (4.11 to 8.73)

TP: Total protein, Malb: microalbumin, ALP: Alkaline phosphatase, γ-GT: γ-glutamyl transferase, LDH: Lactate dehydrogenase, KIM-1: kidney injury molecule-1, Si: Silicon, Cr: Creatinine

cant ($p < 0.001$) predictors for the elevated urinary parameters among silica-exposed workers. There was no significant association between workers' age and elevated urinary parameters among the workers (Table 2).

Discussion

The results of the significantly increased urinary TP, Malb, and Si among the silica-exposed workers compared to the comparison subjects suggested that occupational

silica exposure could result in glomerular injury and would consequently induce glomerular-type proteinuria. Normally, the glomerular capillary epithelial cells are coated with sialoprotein layer that repels and prevents the passage of serum proteins in urine. Maintenance of sialoprotein coat integrity is mainly the function of epithelial cells, so damage to this system could result in proteinuria.¹⁵ These findings were in line with those of other investigators who report that crystalline silica exposure results in an elevation of urinary proteins

among silica-exposed industrial workers.^{2,3,16,17}

The significant elevation of urinary ALP, γ -GT, and LDH among silica-exposed group compared to their controls suggested renal tubular affection and agreed with the results of previous studies that report significantly increased biomarkers for renal proximal tubular dysfunction such as urinary retinol-binding protein (RBP) and urinary N-acetyl- β -D-glucosaminidase (NAG) among silica-exposed industrial workers.^{2,18,19} More recent studies used the same urinary enzymes (ALP, γ -GT, and LDH) to detect early signs of subclinical nephropathic tubular effect among silica-exposed workers³ and among patients with diabetes.^{4,5}

Additionally, the novel urinary biomarker for preclinical nephrotoxicity (KIM-1) showed significantly elevated levels among silica-exposed subjects compared with their comparison group. Urinary KIM-1 is not normally present but is expressed on the proximal tubule apical membrane with renal injury. KIM-1 has proved to be an outstanding indicator of kidney injury, outperforming blood urea nitrogen and serum creatinine as predictors of histopathological changes in the proximal tubule in response to many pathophysiological states or toxicants. Studies in man indicate that tissue expression and urinary excretion of the ectodomain of KIM-1 are sensitive and specific markers for renal injury as well as predictors of outcome.²⁰ Consequently, the observed significantly elevated levels of KIM-1 in addition to the presence of significantly increased levels of urinary silicon detected among the studied exposed group denoted the implications of occupational exposure in inducing this nephrotoxicity. The mechanisms by which silica may damage the kidney could be either through direct (*ie*, renal silica particles) or indirect toxicity.²¹ The indirect toxicity

likely occurs when the lungs, after being exposed to silica particles, start to produce macrophages to attack the particles. This process, in addition to lymph node stimulation, would activate the immune system and can lead to glomerulonephritis.²² More recently, some reports and studies are associating autoimmune renal diseases and silica exposure where autoantibodies against nuclear and other self-antigens deposit in and damage kidneys.^{23,24}

The results revealed that there was a highly significant positive correlation between the duration of occupational exposure to silica and the elevated levels of the measured urinary biomarkers among silica-exposed workers. Additionally, the linear regression analysis showed that the duration of silica exposure could be considered a highly significant predicting factor for the glomerular and tubular subclinical affection. Various recent studies report an increased risk for kidney diseases with the longer duration of silica exposure based upon a dose-response trend.²⁵⁻²⁷

The observed significant positive correlation between the urinary Si level and all other measured urinary biomarkers among silica-exposed workers supported the suggestion that occupational silica exposure might result in disruption of both the glomerular and tubular structural integrity. Also, the results of linear regression analysis revealed that the urinary Si level could be considered a significant predictor for the elevated urinary parameters among the exposed group. Several studies point out that the silica-exposed industrial workers can be exposed to highly toxic fresh crystalline silica generated during the processing of pottery products, ceramics, bricks, and tiles, while the general population could be exposed to amorphous aged silica particles with low toxicity.^{1,3,28} A very recent interdisciplinary research relates the variable toxicity of silica particles to their surface chemistry. New physico-

chemical methods can finely characterize and quantify silanols at the surface of silica particles. A silanol is a functional group in silicon chemistry with the connectivity Si–O–H. Surface silanols are critical determinants of the interaction between silica particles and biomolecules, membranes, and cell systems in animal models.²⁹

The observed lack of a correlation between the workers' age and their urinary levels of biomarkers of renal affection might imply that renal insult due to silica exposure is duration and intensity related, not age-related. Furthermore, it is worth to mention that among the studied silica-exposed group, there were younger workers (aged 20's) with relatively longer work duration (>10 years) and higher levels of urinary biomarkers compared to older workers with relatively shorter work duration and experienced lower levels of urinary biomarkers. This finding was also encountered by another investigator who observed no correlation between age and the studied parameters of kidney function among silica-exposed subjects.³⁰

At the end of the study, individuals found with evidence of nephrotoxicity were referred to Kasr El-Ainy hospital for further nephrologic evaluation and follow up. The industry was also advised to apply rotational schedules for staff working in areas with significant occupational silica dust exposure to minimize the risk of renal affection.

Regarding the limitations of the study, since the used biomarkers were limited to urinary ones, we cannot deduce “definite nephrotoxicity” due to the lack of blood biomarkers and biopsies. However, urinary biomarkers usually provide a simple and non-invasive method of assessment with reliable results to some extent. The use of urinary ALP, γ -GT and LDH represented accompanied changes in urine rather than being biomarkers of kidney injury. These biomarkers, although are

not definite signs of kidney injury, were used as surrogates for kidney injury in this study. Certainly, blood biomarkers and renal biopsies should have been considered for more accurate assessments of nephrotoxicity.

In conclusion, this study could draw attention to the potential subclinical nephrotoxic effects resulted from occupational exposure to silica in pottery industry. The significant elevated levels of urinary biomarkers of glomerular and tubular affection among exposed workers could support the hypothesis that silica might influence the occupationally exposed population and predispose them to expected end-stage renal diseases, depending on their exposure duration and intensity.

Conflicts of Interest: None declared.

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