



Blood Oxidative Stress Levels in Workers Exposed to Respirable Crystalline Silica in the West of Iran

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Abstract

Background: Occupational exposure to crystalline silica is still an important health problem, especially in developing countries. Exposure to silica may be associated with the induction of toxic oxidative stress.

Objectives: This study was conducted to assess oxidative stress biomarkers in workers exposed to respirable crystalline silica (RCS) in Hamadan city, the west of Iran.

Methods: This descriptive-analytical study was conducted on two groups of exposed workers selected from four industries and unexposed office workers in 2017. The analysis of RCS in air samples was done by NIOSH method No. 7602. Malondialdehyde (MDA), total antioxidant capacity (TAC), and catalase (CAT) activity were measured in serum samples.

Results: In this study, 48 healthy workers exposed to silica and 47 unexposed workers as controls were selected. The mean MDA levels (26.91 ± 14.26 nmol/mL) and CAT activity (10.83 ± 5.06 U/mL) were higher in the exposed group than in the unexposed group ($P < 0.001$). However, no statistically significant difference was observed in the TAC levels between the groups and no correlation was observed between exposure to RCS and oxidative stress biomarker levels in exposed subjects.

Conclusions: Although there was a significant difference in the oxidative stress levels between the groups, according to other results of our study, it is not possible to claim that oxidative stress biomarkers are appropriate biological indices for silica exposure monitoring in occupational settings. Therefore, we still require a comprehensive study of other aspects of this research field.

Keywords: Crystalline Silica, Occupational Exposure, Oxidative Stress, MDA, CAT, TAC

1. Background

Silica is the most abundant mineral in the earth's crust with various industrial applications (1). Many workers are exposed to crystalline silica in industries such as silica-containing rocks processing, clay, brick, ceramic, porcelain, cement manufacturing, and foundries (2). Exposure to crystalline silica can lead to the formation of fibrotic nodules in the lungs, chronic obstructive pulmonary disease (COPD), and lung cancer in many workers (2-5). Exposure to silica is a global concern because a large number of workers all over the world are exposed to silica and are damaged (6). According to recent reports, 1.7 million workers in the USA, 2 million workers in Europe, and 23 million workers in China are exposed to silica (7). Despite many efforts of the International Labor Organization (ILO) to con-

trol the exposure of workers to silica (4), occupational exposure to crystalline silica in the workplace is still an important health problem (8).

The International Agency for Research on Cancer (IARC) has classified crystalline silica as a known human carcinogen (9). The National Institute for Occupational Safety and Health (NIOSH) and the National Toxicology Program (NTP) also define crystalline silica as carcinogenic to humans (3, 10). Some studies have shown that the exposure of workers to silica in some cases is higher than the TLV (threshold limit value)-TWA (time weighted average). However, so far, no valid and known biomarker has been introduced for early diagnosis of silicosis and measurement of its progress (11). Thus, there is a vital need for reliable biomarkers to predict the likelihood of silicosis and lung cancer development (8).

Recently, the role of oxidative stress biomarkers has been considered by researchers in the mechanism of silicosis to find a biochemical marker. The research findings suggest that crystalline silica can be phagocytized by lung macrophages and activate the generation of reactive oxygen species (ROS) (12). Further, the carcinogenicity of inhalable silica was considered to be associated with the induction of oxidative stress and the generation of ROS (8). Thus, it seems, oxidative stress is an important event in silicosis, which may be caused by the production of free radicals, the imbalance between ROS and the ability of biological systems to detoxify ROS, or inefficient antioxidant defense systems (13).

2. Objectives

The objective of this study was to investigate the effects of occupational exposure to respirable crystalline silica (RCS) on oxidative stress biomarkers such as serum Malondialdehyde (MDA) levels, the activity of catalase (CAT), and total antioxidant capacity (TAC). To the best of our knowledge and based on the literature, there was no previous report of the simultaneous investigation of these three biomarkers of oxidative stress in four industrial fields with different RCS occupational exposure levels. Since limited studies are available in this study field, our findings might be useful to find sensitive biomarkers for identifying and predicting oxidative injury caused by RCS in workers.

3. Methods

3.1. Subject Selection

This descriptive-analytical study was implemented in the west of Iran in 2017. According to the expected correlation between silica concentration and biomarker levels found in previous studies, we estimated the sample size for each of the exposed and unexposed groups. The exposed group consisted of 48 healthy male workers exposed to RCS in crushing, ceramics, foundry, and cement manufacturing industries. The unexposed group comprised 47 office male workers with no exposure to crystalline silica. According to the inclusion criteria, individuals who had at least two years of work experience and had no specific illness for at least one year were selected for the study. Subjects were selected from the same region; thus, they were similar in socioeconomic and nutritional status that might affect the study results. We explained the purpose of the study to workers and those who were unwilling to continue the study were excluded. Each participant completed a questionnaire designed for recording working conditions such as working history, daily working

hours, utilization of protective device and dietary habits, the history of any diseases, and complementary antioxidants consumption. Written informed consent was obtained from all participants in the study, as approved by the Ethics Committee of Hamadan University of Medical Sciences (UMSHA.REC.1395.530).

3.2. Exposure Measurements

Sampling and analysis of RCS at all workplaces were performed based on NIOSH method No. 7602 (14). Then, the obtained results were compared with the TLV. The exposed subjects in this study mostly worked more than eight hours a day during the six working days of a week. Therefore, TLV was adjusted according to the Brief and Scala recommended model (15).

Air sampling was done in non-rainy days and personal respirable air samples were collected from the breathing zone of all workers exposed to crystalline silica during a work shift. According to the recommended method, before sampling, personal sampling pumps (SKC-2224-44 MTX) were calibrated at 2.5 L/min for use in an aluminum cyclone (SKC-UK) and using a polyvinyl chloride (PVC) filter (37 mm, 5- μ m pore size). The prepared filters were placed in the cassettes connected to the pump using flexible tubes. According to the recommended method Also, the number of samples as the blank were taken in any sampling period to assessing any possible interferences.

To prepare the calibration curve, working standards of quartz were prepared by mixing the pre-determined amounts of quartz with intact PVC filters and burning in a muffle furnace at 600°C. Ash samples were mixed with dried potassium bromide (KBr) and were transferred to a pellet die to prepare pellets. Then, for the determination of quartz, the pellets were placed into the fourier-transform infrared spectroscopy (FTIR) (Spectrum Tow/Perkin Elmer). The validity of the analytical method was tested using the coefficient of variation in triplicate reading of standard quartz samples. Finally, for maximum sensitivity, the concentration of quartz was quantified in each sample at 800 cm^{-1} wavelength according to the absorbance of standard samples.

3.3. Biochemical Measurements

Blood samples were taken from all participants in exposed and unexposed groups at the end of the working shift. Each sample was prepared by a laboratory specialist in each industry. Venous blood samples were drawn into tubes to obtain Serum. Then, the samples were centrifuged immediately at 3,000 rpm for 10 min. After serum separation, the samples were kept away from direct light and stored at -20°C until analysis.

3.4. MDA Measurement

Serum MDA levels were determined using a method developed by Ohkawa et al. (16). According to this method, thiobarbituric acid (TBA) reacts with malondialdehyde and is formed from thiobarbituric acid-reactive substances (TBARS). Briefly, we added 0.2 mL of 8.1% SDS and 1.5 mL of 20% acetic acid to 50 μ L of the sample and mixed gently. Then, 4 mL of distilled water and 1.5 mL of 0.8% TBA aqueous solution were added. The mixture was heated in a boiling water bath at 95°C for 60 min. Then, 3 mL of n-butanol was added and centrifuged for 10 min at 3000 rpm. After centrifugation, the supernatant was taken and its absorbance was measured using an ELISA reader (BioTek Synergy HTX) at the excitation wavelength of 515 nm and the emission wavelength of 553 nm.

3.5. CAT Measurement

CAT enzyme activity was measured according to the method developed by Aebi (17). According to the method, CAT activity was assessed in samples by measuring the decrease in the absorbance at 240 nm by the ELISA reader (BioTek Synergy HTX) in a reaction medium containing hydrogen peroxide (H_2O_2 ; 10 mM) and sodium phosphate buffer (50 mM, pH 7.4). One unit of the enzyme was defined as 1 mol of H_2O_2 as substrate consumed per minute, and the specific activity was reported as units per milliliter serum.

3.6. TAC Measurement

TAC was measured using the ferric reducing ability of serum (FRAP) method developed by Benzie and Strain (18). Briefly, the FRAP reagent was prepared, containing 25 mL of acetate buffer (300 mM, pH 3.6) with 16 mL of acetic acid for one portion of buffer solution, 2.5 mL of 2,4,6-tripyridylS-triazine (TPTZ) solution obtained from TPTZ (10 mM) in HCl (40 mM), and 2.5 mL of $FeCl_3 \cdot 6H_2O$. Then, 10 μ L of sample diluted in distilled water was added to 300 μ L of the freshly prepared reagent and incubated at 37°C for 10 min. When the complex between Fe^{2+} and TPTZ was formed, the maximum absorption of the produced bluish complex was measured at a wavelength of 593 nm by the ELISA reader (BioTek Synergy HTX).

3.7. Statistical Analysis

Data analysis was performed using SPSS 21. The normality of data was checked using the Kolmogorov-Smirnov test. Data were expressed as means \pm standard deviation for numeric variables. The differences between the groups were evaluated by Student's *t*-test. As there was a significant difference between the groups in age and working years, for comparisons between the two groups, covariance analysis was used to adjust for the effect of age and

work experience. Relationships between exposure to silica and the levels of oxidative stress biomarkers were evaluated using Pearson's correlation coefficient. The *P* values of < 0.05 were considered statistically significant.

4. Results

The demographic characteristics of participants are shown in Table 1. As can be seen, the exposed group comprised of silica crushing workers (33%), ceramic workers (19%), foundry workers (27%), and cement workers (21%). All workers used protective masks, but some workers did not use masks properly. The smoking duration was not considered because some of the subjects did not remember it correctly.

As shown in Table 2, a significant difference was found in the time-weighted average (TWA) concentrations of RCS between four industrial fields of study ($P = 0.028$). The highest mean RCS concentration (2.01 mg/m^3) was related to silica crushing workers and the lowest mean RCS concentration (0.27 mg/m^3) was obtained for the workers of the cement industry. The results showed that in 98% of the cases, the workers were exposed to RCS higher than TLV-TWA recommended by the ACGIH in 2017 (0.025 mg/m^3).

In this study, the mean MDA and CAT serum levels were higher in exposed workers than in unexposed workers and there were significant differences in MDA and CAT levels between the groups ($P < 0.001$). However, no statistically significant difference was observed in the TAC level between the groups. These results are presented in Table 3.

As shown in Table 4, the highest serum levels of MDA and CAT (31.35 nm/mL and 14.90 U/mL, respectively) were related to silica crushing workers and the lowest ones (20.88 nm/mL and 6.32 U/mL, respectively) were obtained for ceramic workers. According to the findings, there was a significant difference in MDA and CAT levels between workers from different industrial fields of study ($P < 0.001$), but no significant difference was observed in terms of the TAC level. In the present study, there were significant differences between smokers and non-smokers in the TAC level in the unexposed group ($P = 0.02$), in the MDA level in the exposed group ($P = 0.01$), and in the MDA level in total subjects ($P = 0.038$). These results are presented in Table 5. The present study showed that there was no significant relationship between exposure to RCS, age, and working duration, and any of the oxidative stress biomarkers in exposed workers.

5. Discussion

The findings of this study showed that the TWA concentrations of RCS for 98% of the workers were higher than

Table 1. Demographic Characteristics of Subjects in Exposed and Unexposed Groups

| Subject Group | Smoking, No. (%) | | Working Duration, y | | | Age, y | | |
|--------------------|--------------------|---------|---------------------|-----|-----|--------------------|-----|-----|
| | Yes | No | Mean \pm SD | Min | Max | Mean \pm SD | Min | Max |
| Exposed (N = 48) | 14 (29) | 34 (71) | 10.08 \pm 4.1 | 4 | 22 | 38.75 \pm 7.09 | 27 | 62 |
| Unexposed (N = 47) | 9 (19) | 38 (81) | 7.63 \pm 4.7 | 2 | 20 | 35.04 \pm 5.1 | 24 | 50 |
| P value | 0.254 ^a | | 0.009 ^b | | | 0.005 ^b | | |

^aChi-square test^bt-test**Table 2.** TWA Concentrations of RCS in Studied Industrial Fields

| Industrial Fields | Samples, No. (%) | Mean, mg/m ³ | SD, mg/m ³ | Min, mg/m ³ | Max, mg/m ³ | P Value ^a |
|-------------------|------------------|-------------------------|-----------------------|------------------------|------------------------|----------------------|
| Silica crushing | 16 (33) | 2.01 | 2.61 | 0.8 | 9.39 | 0.028 |
| Ceramic | 9 (19) | 0.70 | 0.87 | 0.01 | 9.39 | |
| Foundry | 13 (27) | 0.28 | 0.25 | 0.02 | 1.05 | |
| Cement | 10 (21) | 0.27 | 0.30 | 0.07 | 0.75 | |

^aANCOVA (adjusted for age and working duration).**Table 3.** Mean Levels of Oxidative Stress Biomarkers in Serum Samples

| Oxidative Stress Levels | Subject, Mean \pm SD | | P Value ^a |
|-------------------------|------------------------|--------------------|----------------------|
| | Exposed (N = 48) | Unexposed (N = 47) | |
| MDA, nmol/mL | 26.91 \pm 14.26 | 8.02 \pm 2.99 | < 0.001 |
| CAT, U/mL | 10.83 \pm 5.06 | 5.17 \pm 1.75 | < 0.001 |
| TAC, μ mol/mL | 0.15 \pm 0.038 | 0.15 \pm 0.015 | 0.524 |

^aANCOVA

the TLV-TWA (0.025 mg/m³) recommended by ACGIH in 2017. These findings are similar to other studies in Iran and other countries (19-23). Golbabaee et al. (2005) conducted a study to assess occupational exposure to crystalline silica in cement manufacturing in Iran. The results showed that occupational exposure of workers to crystalline silica in 57% of cases exceeded the REL recommended by the NIOSH (0.05 mg/m³) (24). Chen et al. (2012) found that the mean concentration of respirable silica ranged from 0.12 to 0.3 mg/m³ in the pottery industry in China (25). The difference in RCS concentrations reported in these studies can be attributed to the type of industrial fields, the industry longevity, failure to repair and maintenance, the use of engineering control approaches, and cleaning mechanisms that are factors affecting the worker's exposure to silica at the mentioned workplaces.

Our study established that the mean MDA and CAT serum levels were higher in the exposed group than in the unexposed group. According to recent findings, after arriving at the alveoli, silica is ingested by alveolar macrophages and releases inflammatory mediators. The

activation of ROS can lead to oxidative stress, lipid peroxidation, and direct damage to the lung tissue and can lead to MDA production as one of the lipid peroxidation products (26-28). Therefore, the significant increase in MDA in this study could be due to the increased production of activated oxygen species due to exposure to silica. The presence of oxidative stress-causing agents including chemicals in the environment leads to the production of free radicals such as superoxide. Superoxide is transformed into hydrogen peroxide in the presence of a substrate such as superoxide dismutase; then, the catalase enzyme decomposes hydrogen peroxide into water and oxygen (29). The increased catalase level in the exposed group in this study can be attributed to the increase in free radicals due to hydrogen peroxide that may cause oxidative stress.

We found no significant difference in the TAC levels between the two groups. It is important to consider that pollutants can indirectly affect TAC, including enzymatic and non-enzymatic antioxidants (30). Therefore, the reduced TAC levels may be due to reductions in the antioxidant capacity of the body after exposure to silica. Consistent with our study, Aydin et al. (2004) found that plasma MDA levels were determined to be much higher in cement-exposed workers (26). In addition, Keshvari et al. (2015) showed significant increments in blood LPO levels and CAT activity and concomitantly, lower TAC levels were observed in ceramic-exposed workers than in the referent group (31). The increases in MDA, LPO, and CAT levels in the above-mentioned studies can be attributed to the mentioned reasons. On the other hand, in the survey of the effects of occupational silica exposure on oxidative stress and im-

Table 4. Oxidative Stress Levels in Studies Industrial Fields

| Oxidative Stress Levels | Industrial Fields, Mean \pm SD | | | | P Value ^a |
|-------------------------|----------------------------------|------------------|-------------------|-------------------|----------------------|
| | Silica Crushing | Ceramic | Foundry | Cement | |
| MDA, nmol/mL | 31.35 \pm 17.36 | 20.88 \pm 5.89 | 27.12 \pm 16.27 | 25.90 \pm 11.09 | < 0.001 |
| CAT, U/mL | 14.90 \pm 4.06 | 6.32 \pm 1.77 | 10.83 \pm 4.98 | 8.30 \pm 3.49 | < 0.001 |
| TAC, μ mol/mL | 0.15 \pm 0.04 | 0.15 \pm 0.03 | 0.15 \pm 0.03 | 0.15 \pm 0.03 | 0.978 |

^aANCOVA**Table 5.** Oxidative Stress Levels in Smoking and Non-Smoking Groups

| Subject | MDA, nmol/mL (Mean \pm SD) | P Value ^a | CAT, U/mL (Mean \pm SD) | P Value ^a | TAC, μ mol/mL (Mean \pm SD) | P Value ^a |
|-----------------------|------------------------------|----------------------|---------------------------|----------------------|-----------------------------------|----------------------|
| Exposed | | 0.01 | | 0.74 | | 0.86 |
| Smoking (N = 14) | 34.45 \pm 18.31 | | 11.21 \pm 5.7 | | 0.15 \pm 0.01 | |
| Non-smoking (N = 34) | 23.71 \pm 10.99 | | 10.66 \pm 4.8 | | 0.15 \pm 0.04 | |
| Unexposed | | 0.42 | | 0.18 | | 0.02 |
| Smoking (N = 9) | 8.74 \pm 3.7 | | 4.47 \pm 1.1 | | 0.14 \pm 0.01 | |
| Non-smoking (N = 38) | 7.84 \pm 2.8 | | 5.34 \pm 1.8 | | 0.16 \pm 0.016 | |
| Total Subjects | | 0.038 | | 0.50 | | 0.30 |
| Smoking (N = 23) | 24.39 \pm 19.18 | | 8.57 \pm 5.5 | | 0.15 \pm 0.01 | |
| Non-smoking (N = 72) | 15.22 \pm 11.09 | | 7.81 \pm 4.4 | | 0.15 \pm 0.03 | |

^aANCOVA

immune system parameters in ceramic workers, data demonstrated a significant increase in the MDA levels and the activity of glutathione reductase (GR) and a significant decrease in the levels of total glutathione (GSH) and activities of CAT, superoxide dismutase (SOD), and glutathione peroxidase (GPx) in all workers (8). Meanwhile, Abdelatty et al. (2014) reported a reduction in the activities of SOD, CAT, and GSH in silica-exposed participants (8). Reductions in the CAT levels in these studies may be due to the fact that chronic exposure to contaminants can have a negative effect on CAT by reducing this enzyme instead of its increase. In another study, silicosis was associated with increased plasma MDA and reduced erythrocyte glutathione levels, providing an oxidative link (32). Differences in some values obtained from various studies may be due to the fact that the studies focused on various industries and their workers were exposed to different types and sizes of silica particles. According to studies, features such as size, surface area, and surface properties play important roles in inducing toxicity (33). Moreover, in the present study, the oxidative stress biomarker levels were different between workers from various industries. It seems differences in the body's defense system, weather conditions, and diets between different countries can be another reason for the difference in oxidative stress biomarker levels in the mentioned studies.

In the present study, a significant difference was found between smokers and nonsmokers in the TAC level in the unexposed group, the MDA level in the exposed group, and the MDA level in total subjects. Anlar et al. (2017) showed no significant correlation between GSH levels, CAT, and SOD, and smoking in ceramic workers (8). On the other hand, Nielsen et al. (1997) showed daily smokers had a slightly higher average concentration of plasma MDA than nonsmokers ($P = 0.05$) and plasma MDA was correlated with daily exposure to the cigarette smoke ($r = 0.162$; $P = 0.03$) (34). As can be seen, the results are different in various studies. It is important to consider, although non-smokers do not smoke, they may be exposed to pollution caused by smokers. Also, It should be mentioned that, when smokers consume cigarettes together with other smokers, it may expose them to pollution levels more than when they consume cigarettes alone. The reason for this discrepancy in the results of different studies can be attributed to the uncontrolled conditions. We need more studies to examine the simultaneous effects of smoking and exposure to RCS on oxidative stress biomarker levels in workers.

The results of the present study also indicated no significant relationship of the age and duration of working with serum MDA, CAT, and TAC levels in workers exposed to RCS compared to the unexposed group. Kamal et al. (1989) reported that neither age nor the duration of exposure was

related to the MDA levels among workers exposed to silica dust (35). Furthermore, in the study of ceramic workers, there was no significant correlation between GSH levels, activities of GR, CAT, and SOD, and age and duration of working (8). As can be seen, the results of other studies confirm our results.

Many attempts have been made to determine the relationship between crystalline silica exposure and oxidative stress levels to select an appropriate biomarker in occupational exposures. Although, in the present study, MDA and CAT levels were higher in the exposed group than in the unexposed group, no significant relationship was observed between silica exposure and oxidative stress in both groups. The present finding is in line with Orman et al. (2005) that showed no significant relationship between crystalline silica concentration and plasma MDA levels in spite of a positive correlation between the variables ($r = 0.305$, $P > 0.05$) (32). Contrary, a study performed by Parsaseresht et al. (2017) in sand washing workers demonstrated a positive correlation between the exposure of workers to silica and serum MDA in the exposed group ($P < 0.0001$, $r = 0.881$) (36). Therefore, according to the literature, the reason for discrepancy may be attributed primarily to the determination of RCS just in one day without considering the variations in workload, engineering control performance, and the use personal protective equipment in different days. In some aspects, measuring exposure to RCS in one day as a short survey cannot represent oxidative stress occurring over a long time. This deficiency is the most important limitation of the present study and some other studies, which may lead to discrepancy in the results of similar studies.

5.1. Conclusions

The results of this study showed despite a significant difference in the oxidative stress biomarkers between the exposed and unexposed groups and a significant difference in the levels of biomarkers between the workers of various industries, there was no significant relationship between the levels of oxidative stress biomarkers and the mean exposure to silica. Therefore, according to the results, it is not possible to claim that oxidative stress biomarkers are appropriate biological indices for the monitoring of silica exposure in occupational settings. Thus, this hypothesis still requires a comprehensive study of other aspects in this research field.

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Footnotes

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