Research Square

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Serum Nickel Levels Compromise the Oxidative Status and Lung Functions in Ceramic Workers.

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Abstract

Background

Nickel, in the form of various alloys and compounds, has been in widespread commercial use for over 100 years. Several million workers worldwide are exposed to airborne fumes, dust, and mist containing nickel and its compounds. Further, exposures by inhalation, ingestion, or skin contact occur in nickel-producing industries, like mining, milling, melting, and refining, and in nickel-using industries, like electroplating, welding, and grinding. Insoluble nickel is the predominant exposure in nickel-producing industries, whereas soluble nickel is the predominant exposure in nickel-using industries like the ceramics industry. This study was designed to extrapolate the levels of serum nickel, antioxidant compounds, and stress markers and correlate them with lung function status in craft workers in the ceramics industry

Methods

The study included 50 fiber craft workers from the ceramics industry who met the inclusion criteria. The control group consisted of subjects from the general population with no disease. Blood samples from the workers were collected by a phlebotomist. The levels of nickel and biological antioxidants, i.e. serum glutathione (GSH) and stress marker malondialdehye (MDA), were determined. Estimation of oxidants and haptoglobin (Hp) levels were assessed. The level of nickel was measured by atomic absorption spectrophotometry. A spirometer was used to measure lung functions. The calculated levels of these parameters were compared with those in the control subjects.

Result

An overall increase in nickel and MDA levels and a decrease in GSH level were observed. When these workers were classified into groups, it was observed that prolonged employment in the ceramics industry was associated with an increased nickel concentration in the serum, which in turn increased oxidative stress biomarkers and thus decreased the antioxidant levels to the lower limit. The decrease in GSH level compromises lung function. Our findings of an increase the Hp level is noteworthy, as it increased by 89% in the group with over 10 years of service in the industry compared with the group working for less than 5 years.

Conclusion

Daily exposure to nickel for prolonged periods could result in fatal respiratory disease. Precautionary measures should be made mandatory in all industries.

Introduction

The health hazards associated with manmade fibers have been documented. For example, fiberglass and asbestos fibers may cause respiratory problems like asthma, pneumonia, and lung cancer [1, 2].

Nickel is a strong, lustrous, silvery-white metal that is a staple in our daily lives and can be found in a plethora of products, from the batteries that power television remotes to the stainless steel used to make kitchen sinks. This already wide range of nickel applications is increasing on a daily basis. Nickel is a suitable element that can be combined with other elements to form alloys of various types, conferring them with heat and corrosion resistance and, above all, increasing their strength [3, 4].

Nickel salts are used in electroplating, coinage, electrical components, ceramics, pigments, intermediates like sinter nickel oxide, and also as nickel catalysts in the ceramics industry. Continuous exposure to nickel could result in a fatal outcome in individuals working in such environments [5].

The general population is exposed to low levels of nickel in the ambient air, water, food, and tobacco. Exposure may also occur via inhalation of ambient air and through percutaneous absorption [3, 6, 7]. The daily intake of nickel from food and beverages varies by foodstuff, country, age, and gender [6, 8]. Data from a study in the US gave estimates of daily dietary intakes in the range of 101–162 μg/day for adults. Cohort studies have revealed that nickel (sulfidic oroxidic nickel) exposure increases the risk of lung cancer [8].

It has been proposed that the carcinogenicity induced by nickel may be due to the reduction of bioreactive products, resulting in the production of reactive oxygen species (ROS) [9–11]. These ROS may cause DNA damage, causing breaks in the DNA strands and oxidative DNA lesions. The cell membrane is most susceptible to free radicals, as it is prone to lipid peroxidation and can lead to the generation of mutagenic MDA [12].

The human body buffers the ROS produced to minimum and non-toxic levels. Reduced glutathione (GSH) plays a critical role as an antioxidant, and hence its serum levels are used as inverse markers of oxidative stress [13]. ROS-induced MDA formation another stress marker, the level of which directly correlates with stress. These biomarkers are important in the maintenance of homeostasis and functions of the cell, as well as for activating the body's immune system for scavenging ROS. Antioxidants, on the other hand, help stabilize oxidative stress and abolish the toxic effects of heavy metals via synergic actions [14, 15].

Haptoglobin (Hp) has been classified as an acute-phase protein and is mainly attributed to decreased hemolysis. An increased level of Hp has also been implicated in some conditions like amyotrophic lateral sclerosis [16]. Increased expression of this acute-phase protein has also been validated in human lung cancer [17], and hence Hp (or more specifically its β chain) has been confirmed as a serological biomarker in lung adenocarcinoma [18, 19]. Similarly, its binding with nickel has been identified in the serum of various animals, including humans [20, 21]. A simultaneous increase in the levels of Hp and nickel was observed by Taruna Ikrar *et al.*

Oxidative stress occurs when the excessive formation of ROS overwhelms the antioxidant defense system, which is maintained in fine balance by antioxidants such as ascorbic acid, alpha-tocopherol, glutathione, carotenoids, flavonoids, and antioxidant enzymes including SOD, catalase, and glutathione

peroxidase [12]. SOD scavenges toxic superoxide ions and converts them into hydrogen peroxide, which is maintained by the glutathione system, thus preventing the peroxidation of the cell membrane [22].

Occupational and Non-occupational exposure to Nickel have been studied in different industries and in different region. [23–25]. However, insufficient data is available for the ceramic industry workers and above all limited information is seen, of the direct impact of nickel on the oxidant status of the worker and their lung functions. This study was designed to extrapolate the levels of serum nickel, antioxidant compounds, and stress markers and correlate them with lung function status in craft workers in the ceramics industry.

Materials And Methods

The study included 50 craft workers of the ceramics industry. The workers received an explanation about their participation in the study, signed an informed consent, and completed a questionnaire with demographic data, and information related to other habits (like diet and smoking frequency), number of family members, education level, duration of employment in the ceramics industry, and most importantly the use of precautionary measures in the workplace. The study was carried out according to the tenets of the Declaration of Helsinki for human experimentation and was endorsed by the ethics committee of the University of Lahore, Pakistan, under the reference No. IMBB/UOL/191323.

Workers who were on prolonged treatment with corticosteroids or non-steroidal drugs were excluded from the study. Thirty controls with no history of working in any industry and with no disease were recruited as controls. A phlebotomist collected the random blood samples from all participants. Samples were directly collected in tubes with no additive, and were labeled with specific codes matching the worker's name in order to ensure anonymity. Blood is allowed to clot at room temperature and after 10–15 minutes, sample are centrifuging at 2000 g for 5 minutes. The resulting supernatant; serum is separated from the top, labeled and stored in refrigerator for further analysis.

Measurements:

The levels of nickel in the serum of occupationally exposed workers were measured by flame atomic absorption spectrophotometry as described previously [26]. Antioxidant molecules GSH was measured by observing Tietze preparations [27] protocol of enzymatic recycling method. The stress marker MDA was assessed following the procedure used by Ohkawa et al. [28], and haptoglobin levels were determined using the Human Haptoglobin ELISA Kit (Abcam-ab108856).

A spirometer was used to assess lung function by measuring the forced vital capacity (FVC) and forced expiratory volume in 1 min (FEV1). The ratio of these two parameters was compared with the normal ratio obtained in the control subjects.

Statistical analysis:

Data were analyzed using SPSS 21. Comparison of variables between the workers and the control subjects (normal values) was carried out using Student's *t* tests. The comparison between the levels of serum nickel and oxidative stress markers (GSH and MDA) were explored. A value of $P < 0.05$ was considered significant.

Results

Table 1
Demographic variables of workers

Characteristic of variable		Number of participants
Number of workers between the age of 15 to 20		21
Number of workers between the age of 21 to 30		18
Number of workers between the age of 31 to 50		19
Duration of work	1 to 5 Year	16
	6 to 10 Year	18
	> 10 Year	24
Smoker – 10 Cigarette/day		17
Healthy Habits – (Regular Walk, Exercise, Sports)		12
Number of workers with ≤ 4 dependent family members		24
Number of workers with ≥ 6 dependent family members		21
Number of workers with ≥ 8 dependent family members		13
Chronic Symptoms	Cough (No Sputum)	21
	Frequent Running Nose	09
	Breath lessness end of the day	7
	Headache	10
	No Symptoms	11

Demographic data in Table 1 shows, majority of the peoples engaged themselves at the work before the age of 20. Out of the total 58 participant majority of them continue to work beyond 10 years. Seventeen workers smoke 10 cigarettes per day and invariably number of workers engaged in healthy habit is far less. Worker with chronic symptoms, like cough, headache is proportionally low, however, alarming symptoms in most worker was cough which clearly implicates the inhalation of toxic substance in the ceramic industry.

Table 2.

Table 2
Mean levels of serum MDA, GSH, and nickel in a group of craft workers of the ceramics industry compared with the normal level (control). * $P = < 0.05$, ** $P = < 0.04$ and *** $P = < 0.05$

Analyte	Control	Sample
MDA – nmol/ml	* 2.48 ± 0.21	* 3.87 ± 0.28
GSH – mg/dl	** 4.79 ± 0.73	** 1.42 ± 0.18
Nickel – µg/dl	*** 1.88 ± 0.13	*** 2.82 ± 0.10

There was a moderate increase in the MDA and nickel levels in the workers (56% and 53%, respectively), in relation to the control subjects. However, there were decreased levels (30%) of GSH in these workers compared with the control subjects. These findings suggest an increase in oxidative stress that led to a substantial decrease in the level of antioxidants in the serum of these workers.

Table 3

Table 3
Mean levels of antioxidant compounds and nickel in the serum of factory workers employed in the ceramics industry. * $P = < 0.04$, ** $P = < 0.05$,

Analyte	Sample		
	1 to 5 Year	6 to 10 Year	> 10 Year
GSH – mg/dl	* 3.97 ± 0.16	2.53 ± 0.14	* 1.64 ± 0.13
Nickel – µg/dl	** 1.94 ± 0.11	2.84 ± 0.7	** 2.98 ± 0.8

The antioxidant level was shown to decrease, with a concomitant increase in nickel concentration, as the duration of the employment increased. After 10 years of service in the industry, subjects showed a critically depleted level of antioxidants, with levels at 41%, compared to that in workers with less than 5 years of service. There was a 54% increase in the levels of nickel in subjects with a length of service greater than 10 years. These subjects also showed depletion of GSH levels, which is clearly indicative of oxidative stress.

Table 4.

Table 4
Mean levels of serum MDA and nickel in a group of workers employed at the ceramics industry in relation to the duration of employment. * $P = < 0.04$, * $P = < 0.05$,

Analyte	Sample		
	1 to 5 Year	6 to 10 Year	> 10 Year
MDA – nmol/ml	* 2.95 ± 0.17	3.96 ± 0.18	* 4.68 ± 0.17
Nickel – µg/dl	** 1.94 ± 0.11	2.84 ± 0.7	** 2.98 ± 0.8

An increase in the duration of employment led to a 54% increase in nickel levels, which in turn led to the production of MDA from lipid peroxidation of polyunsaturated fatty acids. As soon as the inhaled nickel particles reach the lungs, they induce damage to the cell membrane of the lung parenchyma; however, the molecular mechanism of this toxic event causing cellular injury remains to be elucidated.

Table 5.

Table 5
Lung functions in factory workers employed in the ceramics industry. Mean value. * $P = < 0.05$.

Lung functions	Normal adult male	1 to 5 year duration of employment	6 to 10 year duration of employment	> 10 year duration of employment
FVC—Liters	**5** ± 0.5	**4.6** ± 0.2	**4.4** ± 0.4	**4.3** ± 0.7
FEV_1—Liters	**4** ± 0.4	**3.5** ± 0.3	**3.1** ± 0.4	**2.8** ± 0.6
FEV_1/FVC	*** 80%** ± 7%	**76%** ± 5%	**70%** ± 8%	*** 65%** ± 5%

Table 1 illustrates the lung functions of the factory workers. It was imperative to demonstrate whether factory workers exposed to toxic levels of nickel could have their lung function compromised. We therefore measured the FVC and FEV_1. The FEV_1/FVC ratio was compared with that in normal adults, and it was found that as the duration of employment in the factory increased, this ratio progressively decreased, and it was found to be 65% in workers who had been working for over 10 years. This suggests compromised lung function following such chronic exposure to the metal. Thus, all individuals with 10 or more years of employment in the factory complained of frequent irritating cough and frequent visits to the doctor (data not shown). Workers with a history of smoking were excluded from this experiment to avoid confounding bias. However, they were included in all other measurements conducted in the study.

Table 6.

Table 6
Mean level of antioxidant compounds and the ratio of forced expiration volume in 1 min/forced vital capacity (FEV_1/FVC) ratio. * $P = < 0.04$, * $P = < 0.05$

Analyte	Control	Sample		
		1 to 5 Year	6 to 10 Year	> 10 Year
GSH – mg/dl	* 4.79 ± 0.73	3.97 ± 0.16	2.53 ± 0.14	* 1.64 ± 0.13
FEV/FVC – Percentage	** 80 ± 7	76 ± 5	70 ± 8	** 65 ± 5

The antioxidant level decreased with decreased performance in the lung function tests, associated with an increase in the duration of employment. After 10 years of working, there was a critical depletion of the antioxidant level to 41%, and lung function decreased to 20% of the normal ratio and to 11% in relation to the level of subjects working for 5 years in the factory.

Figure 1. **Mean increase in haptoglobin levels as the duration of employment of factory workers increases. *** P **= < 0.05.**

As documented earlier, nickel binds to a diverse repertoire of proteins, and most importantly to haptoglobins [20]. In our study, we observed a concomitant increase in the level of haptoglobin in factory workers as their exposure to nickel and duration of employment increased (Fig. 1).

Discussion

In this study, we have demonstrated the increase of serum nickel level in the ceramic industry worker, as their work duration increases, serum level of nickel has already been reported earlier [29–30]. This increased level contemplates the changes in the MDA and glutathione level in the serum and at the molecular level haptoglobin levels increase as the work duration of the worker increases. These impeccable findings clearly had its effect on the pulmonary function of the workers, which was demonstrated with the lung function test. In our study work duration is clearly associated with increased nickel and MDA level with decreased GSH. This finding concomitantly impairs the lung functions of workers.

Inhalation of toxic fibers by factory workers has been a critical issue in third-world countries, especially in those where protective measures have not been taken. In Pakistan, these issues have been addressed; however, authorities have failed to implement efficient measures throughout the industrial sector. Craft workers in the ceramics industry are exposed to high levels of hazardous toxic substances such as silica and SiO_2, which cause a restrictive lung disease known as silicosis [31].

Occupational exposure results in elevated levels of nickel in blood and urine, and inhalation is the main route of uptake [3, 32]. The same results have been observed in our study in which craft workers in the ceramics industry were progressively exposed to soluble nickel. Furthermore, as the duration of employment increased, the levels of nickel in the blood increased as well, eliciting a stress response that

leads to decreased levels of antioxidants (Table 2). Work intensity and stress lead to oxidative stress [33]. We have obtained similar results in this study as well. As the length of service of a worker in the ceramics industry increases, the body becomes more vulnerable to oxidative stress (Tables 3 and 4).

It has been proposed that the imbalance between the generation of free radicals and the activity of antioxidants causes oxidative stress. Mild oxidative stress can be tolerated, but a higher level of imbalance may result in a number of diseases [33]. The increased concentration of soluble metals can be the cause for the development of oxidative stress and the generation of free radicals that can directly bind with the thiol groups of antioxidant enzymes. Furthermore, it can generate DNA lesions, leading to cancer. Nonetheless, increased risk for lung cancer was found in studies conducted in different European countries [34]. We observed an increased MDA level and decreased antioxidant level with continuous exposure to soluble nickel particles in our study as well.

Further, we illustrated how the exposure of fiber craft workers to nickel and the stress induced by excessive nickel inhalation reduce the level of antioxidants in serum, eventually compromising the respiratory system. Furthermore, continuous exposure can increase the Hp level to toxic proportions, thereby causing lung cancer, as reported earlier by a group of researchers [35].

One of the imperative associations of Nickel in our study was its effect on the haptoglobin, which changes as the duration of work increase. The other positive finding we had was the changes in the functional capacities of the lungs measured, using spirometer. Regardless to these finding, the limitations of this study include the small number of subjects from only one factory. Further studies with larger samples are needed to determine the effects of other metal ions on the health status of workers.

Conclusion

We conclude that the high nickel levels in workers of a fiberglass factory are responsible for increased antioxidants levels in their body, which in the long run may potentiate the development of diseases, especially of the respiratory tract. There is a need for national and international help to frame appropriate guidelines for workers working in such hazardous environments. Precautionary measures like wearing gloves and masks, hand washing, and the use of hand sanitizers may protect them from the effects of these chemicals. Failure to control exposure to heavy metals may result in severe complications in the future because of their adverse effects.

Declarations

Ethics approval and consent to participate

Approved by the Ethics committee of the IMBB, of The University of Lahore (UOL) on 28/05/2019 under the reference number; IMB/UOL/19/323.

Consent for publication

All co-authors have read the text and approved the publication.

Availability of data and materials

The original data are available on request to Dr. Uzma Jabbar

Competing interests

The authors declare no conflict of interest.

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Authors' contributions

Uzma Jabbar: Designed the study and carried out the field and laboratory work.

Mazhar Mushtaq: Conducted the analysis of the results and wrote the manuscript.

Javed Anver Qureshi. Supervised the work and guided the data analysis and the writing of the manuscript.

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Figures

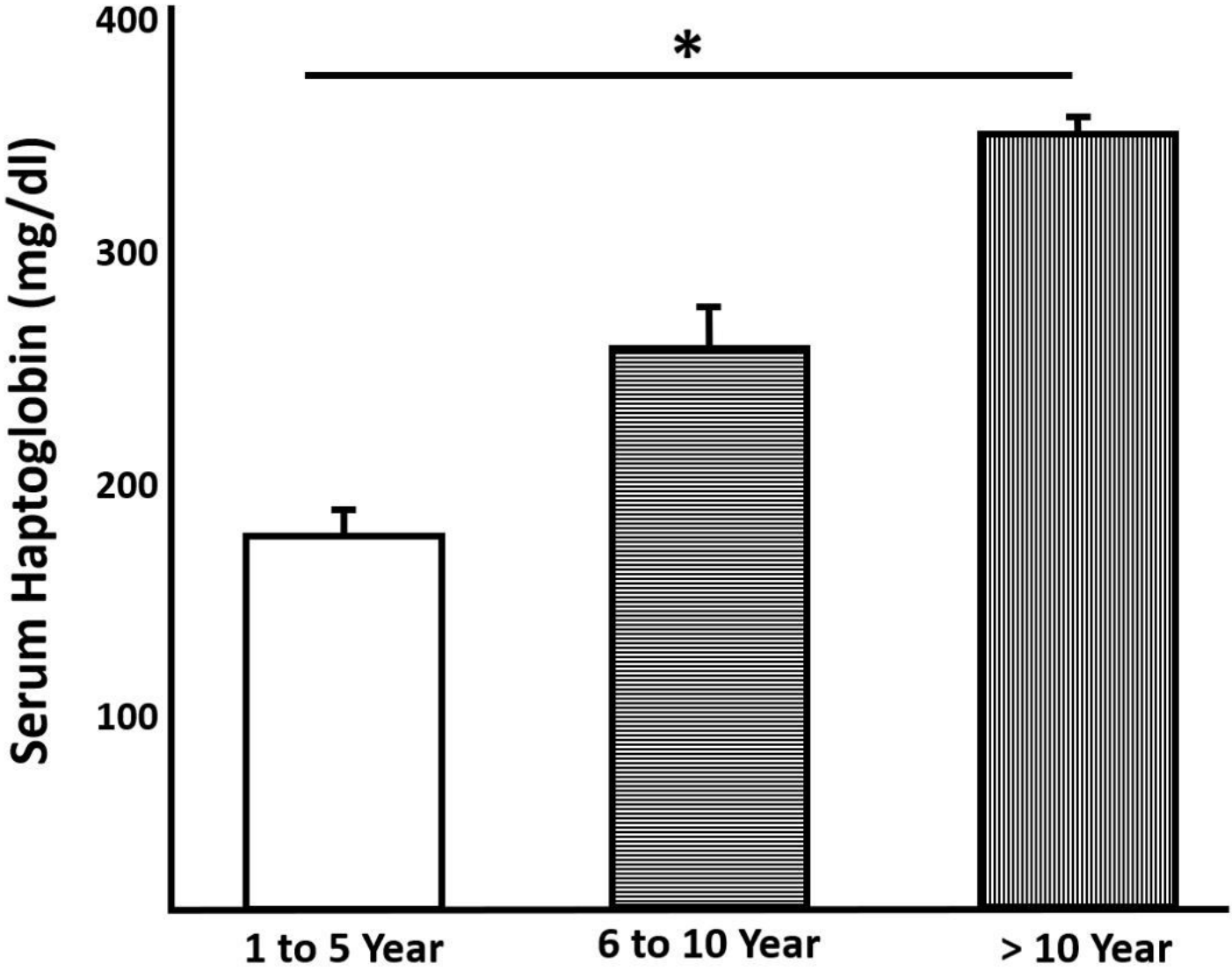

Figure 1

Mean increase in haptoglobin levels as the duration of employment of factory workers increases. * P= <0.05.