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Professional paper

IMMUNOMODULATION AND OXIDATIVE STRESS IN DENIM SANDBLASTING WORKERS: CHANGES CAUSED BY SILICA EXPOSURE

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Workers in denim sandblasting are at a high risk of developing silicosis, an occupational lung disease caused by inhaling crystalline silica dust. The development and progress of silicosis is associated with the activation of the immune system and oxidative stress. In the former, interferon-gamma induces both neopterin release and the enzyme indoleamine [2, 3]-dioxygenase (IDO) in various cells. The determination of the kynurenine-to-tryptophan ratio and neopterin concentration has proven to be an efficient method to monitor the activation status of IDO and cellular immunity. The present study aimed to investigate whether occupational silica exposure leads to any alterations in neopterin levels, tryptophan degradation, and activities of superoxide dismutase (SOD) and catalase (CAT), agents in the antioxidant defense system. Fifty-five male denim sandblasting workers and twenty-two healthy men as controls were included. Mean neopterin and kynurenine levels, kynurenine-to-tryptophan ratio, and SOD activity were higher in subjects with silicosis compared to non-exposed controls (all, $p<0.05$). Neopterin levels and kynurenine-to-tryptophan ratios were positively correlated ($p<0.05$); however, no correlation was observed between length of employment and the measured parameters. Some of the measured parameters were significantly affected by the severity of the pathology. Our results suggest that silica exposure activates the cellular immune response. The increased neopterin levels and tryptophan degradation confirm the possibility of their use as an indicator of cellular immune response.

KEY WORDS: *catalase, neopterin, silica, silicosis, superoxide dismutase, tryptophan degradation*

Silicon dioxide or silica is the most abundant mineral in the world. Crystalline silica is ubiquitous and occurs naturally in rock, stone and sand, and is used in the production of concrete, ceramics, bricks, tiles, etc. Occupational exposure to respirable-size silica dust occurs mainly in mining, quarrying, drilling, foundry working, ceramics manufacturing, and sandblasting (1). In 1997, the International Agency for Research on Cancer (IARC) classified crystalline silica as a human carcinogen (2). The US National Institute for Occupational Safety and Health and National Toxicology Program also subsequently classified crystalline silica as carcinogenic to humans (3, 4). Silica sandblasting carries a high risk of excessive exposure to silica even though respiratory protection is used. Although prevention efforts have been made, silicosis is still a health problem among workers worldwide (1).

Denim sandblasting developed as a result of changes in fashion trends that caused a greater demand for jeans that appear worn (5, 6). Workers are exposed to crystalline silica because they blast silica-containing

sand as an abrasive onto denim to give it a "worn-out" appearance. Due to long working hours and poor hygiene conditions without any efficient respiratory protection, denim sandblasting appears to be more hazardous than most known occupational exposures (5). Although access to sandblasting factories is restricted, illegal production sites have caused a high number of silicosis cases in Turkey during the past two decades (7)

Pneumoconioses are lung disorders caused by inhaling mineral dusts which lead to pulmonary fibrosis and other changes in the lung parenchyma (8). The most common pneumoconioses are coal worker's pneumoconiosis, silicosis, and asbestosis (1, 9). Silicosis is one of the most common occupational lung diseases caused by inhaling crystalline silica (1, 10). Its course can be summarized as a chronic inflammation in which immune cells activate and release toxic mediators, damage the pulmonary architecture, and transform normal lung cells to tumour cells. The rate of its progression appears to depend upon both the rate of silica deposition in the lungs and the total amount of crystalline silica actually retained in the lungs (9, 11). Lymphocytes are one of the potential participants in the cellular network involved in pneumoconiosis (12). Patients with silicosis endure a significant activation of their immune system accompanied by a diminished functional immune response (12-14). Data from animal studies suggest that the lymphocyte-derived interferon-gamma (IFN-γ) is involved in the production of fibroblast growth factors by macrophages (15). Neopterin is a low-molecular-mass compound that can be used as a marker of modulation in cellular immunity. It is released by monocytes/macrophages upon activation by IFN-γ secreted from T-lymphocytes (16). IFN-γ also induces indoleamine 2,3-dioxygenase (IDO), the rate limiting enzyme in the kynurenine (Kyn) pathway, where tryptophan (Trp) is mainly degraded (17). Hence, in the cellular immune response, IFN-γ stimulates monocyte/macrophages and neopterin production increases. Meanwhile, the kynurenine pathway is also induced by IFN-γ resulting in increased tryptophan degradation. Therefore, the increase in neopterin levels correlates well with increased tryptophan degradation products, whereas immune-modulated changes in IDO activity are generally supported by altered neopterin levels (18, 19).

The aims of the present paper were to evaluate the immune changes caused by occupational silica exposure by determining urinary neopterin levels, to support the obtained results by detecting kynurenine pathway-related parameters, and to investigate the possible effect of oxidative stress by measuring the levels of two main antioxidant enzymes, superoxide dismutase (SOD) and catalase (CAT).

SUBJECTS AND METHODS

Participants

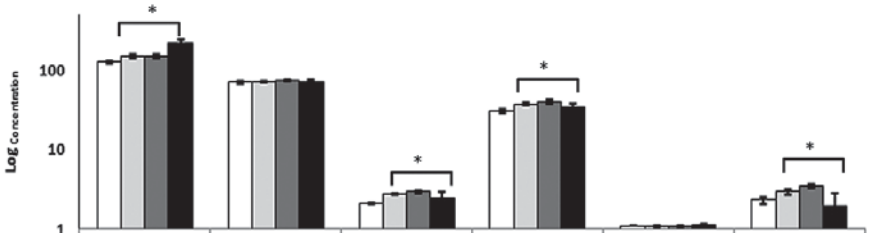
Fifty-five male silicosis patients [mean age: (30±1) years, range: (21 to 48) years], hospitalized in the Occupational Diseases Hospital, were included. Each patient had experience in denim sandblasting, but none were active workers during the investigation. Occupational anamnesis and pulmonary function test results are given in Table 1.

The International Labour Organization (ILO) set four main categories and subcategories in order to indicate the severity of silicosis. These categories

Table 1 *Occupational history and pulmonary function test results of the patients*

Data	Mean±SD (range)
Age of first exposure to sandblasting / year	18±6 (10 to 39)
Total exposure duration / month	33.6±23.8 (2 to 120)
Number of work positions	1 (1 to 4)
Smokers / n (%)	32 (60.3)
FEV_1 / L	3.78±0.35
FEV_1 / % predicted	60.84±26.18
FVC / L	4.45±0.41
FVC / % predicted	66.26±24.35
FEV_1 / FVC %	84.88±1.09

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity



	Neopterin	Tryptophan	Kynurenine	Kyn/Trp	Catalase	Superoxide dismutase
Control	127.2±6.1	70.9±2.8	2.09±0.1	30.5±1.7	1.10±0.02	2.31±0.23
ILO-1	151.1±8.9	73.1±1.9	2.76±0.1	37.8±1.1	1.07±0.03	2.95±0.23
ILO-2	151.7±9.4	74.4±1.6	2.93±0.1	40.1±2.1	1.07±0.03	3.45±0.23
ILO-3	226.2±24.8	72.3±4.1	2.49±0.4	34.2±3.9	1.12±0.03	1.96±0.82

Figure 1 *Comparison of measured parameters in study groups. The Y-axis is a logarithmic scale. The parameters in the* X*-axis are as follows: neopterin (µmol mol^{-1} creatinine); tryptophan and kynurenine (µmol L^{-1}); Kyn/Trp (mmol mmol^{-1}); catalase and superoxide dismutase (IU mg^{-1} protein).*
*p<*0.05* vs. *controls.*

range from 0 to 3, reflecting the severity of silicosis (20). In this paper, the control group was classified as ILO-0, while the patients included 17 workers classified as ILO-1, 34 as ILO-2, and 4 as ILO-3.

The control group consisted of twenty-two healthy men [mean age: (36±10) years; range: (18 to 52) years]. All of the controls were questioned in detail about chronic diseases, the presence of active infections, and possible medication during the sample collection period.

The principles of the University Ethics Committee according to the Helsinki Declaration were followed during the entire study.

Samples

All of the samples were collected early in the morning. Venous blood samples were drawn into vaccutainer tubes. A small volume of each blood sample was heparinized in order to obtain plasma and erythrocyte portions, while the rest was used to separate the sera. The samples were kept away from direct light and stored at -20 °C until analysis.

Measurements

Urinary neopterin and serum tryptophan and kynurenine levels were determined by high performance liquid chromatography (HPLC), as described in another work (21, 22). The neopterin levels were calculated as micromoles of neopterin per mole of creatinine. The tryptophan and kynurenine concentrations were both expressed in µmol L^{-1}. The kynurenine-to-tryptophan ratio (Kyn/Trp) was calculated to estimate IDO activity as the degree of tryptophan degradation (23).

Enzyme Assays

Erythrocyte haemolysates were prepared by adding cold deionized water, centrifuged and the supernatants were used for the enzyme assays. CAT enzyme activity was measured according to Aebi (24) and the determination of SOD activity was performed as described by Marklund and Marklund (25). In order to present specific enzyme activities, the protein content of the samples was also determined (26).

Statistical analysis

Comparisons between two independent groups were investigated using the Mann-Whitney U-test and the correlations of the parameters were detected by a Spearman non-parametric correlation test (p<0.05 was considered significant).

RESULTS

Urinary neopterin levels in the silicosis patients were (155.3±7.2) µmol mol^{-1} creatinine, while the control group exhibited (127.2±6.1) µmol mol^{-1} creatinine. This elevation in neopterin levels in silicosis patients versus controls (22 %) was statistically significant ($p<0.05$). Since two of the patients had excessive neopterin levels [741 µmol mol^{-1} creatinine (classified as ILO-2) and 769 µmol mol^{-1} creatinine (classified as ILO-1)], but had no abnormal changes in physical conditions and other measured parameters, they were excluded and the study continued with 53 workers.

Tryptophan, kynurenine, and Kyn/Trp levels were (70.9±2.75) μmol L^{-1}, (2.08±0.06) μmol L^{-1}, and (30.52±1.67) μmol $mmol^{-1}$ in the control group and (73.96±1.19) μmol L^{-1}, (2.86±0.07) μmol L^{-1}, and (39.23±1.45) μmol $mmol^{-1}$ in the workers, respectively. IDO activity was found to be increased by 28 % in silicosis patients and the difference between the groups was statistically significant ($p<0.05$). Kyn levels were significantly higher in the silicosis group than in the controls ($p<0.05$), while tryptophan levels did not differ compared to controls.

The kynurenine-to-tryptophan ratio representing tryptophan degradation was found to be positively correlated with the neopterin levels (Rs=0.289, $p<0.05$).

Specific catalase activities were measured in the study groups as (1.1±0.02) IU mg^{-1} protein in controls and (1.08±0.02) IU mg^{-1} protein in silica workers, while SOD activity was found to be (2.31±0.22) IU mg^{-1} and (3.22±0.17) IU mg^{-1} protein for controls and workers, respectively. There was no significant difference in terms of CAT activity between controls and patients. A significant difference in specific SOD activity between control and patient groups was found ($p<0.05$). Furthermore, neither CAT nor SOD activities were in correlation with the other measured parameters.

In order to demonstrate the link between the measured parameters and silicosis severity, changes in each finding, accompanied by ILO classification and comparison with controls, are given in Figure 1. All of the workers with silicosis showed significantly higher neopterin results and tryptophan degradation compared to controls. It was also observed that the tendency of increase in the parameters was associated with ILO category. Neopterin levels continuously elevated with ILO category, while Kyn/Trp displayed a different pattern. Kyn/Trp levels showed a slight increase in the first two ILO categories and a decrease in the ILO-3 group. The difference between or among the ILO groups and the correlation of the measured parameters were analysed by Mann Whitney-U Test, Kruskal Wallis Test, and Pearson Analysis.

DISCUSSION

Sandblasting is generally performed within small illegal production facilities that operate as subcontractors for larger companies. It is still used in many applications where the abrasive cleaning of surfaces is required. Although the use of silica for sandblasting has been restricted for some time, the major reasons for its current use are its availability and low price. Many sandblasting facilities use sifted sea sand and have no ventilation whatsoever (27). Silicosis is a preventable occupational disease, but without adequate protection it can be a risk for pulmonary toxicity (9). Silicosis has a latency of approximately 10 to 30 years, although disease can develop earlier in workers exposed to higher quantities of silica dust over a relatively short period of time (10). In this paper, the effect of employment length on the measured parameters was investigated. However, the weak correlation between this length and neopterin as an indicator of T-cell activation or Kyn/Trp representing tryptophan degradation was statistically insignificant.

Silica affects humoral and cellular immune responses and may have systemic effects while in the lungs and regional lymph nodes. Several lines of evidence support the view that the pathogenesis of silicosis involves uncontrolled immune processes (13, 28). It is widely believed that the pathogenesis of fibrotic responses evoked by particulates involves the generation of macrophage-derived growth factor(s) that stimulate proliferation and collagen synthesis by fibroblastic cells in the lungs (15). Crystalline silica is known to cause dysregulation and/or disturbance of the human immune system, particularly autoimmunity (14). Saito et al. (29) used neopterin as a marker of activated alveolar macrophages in patients suffering from interstitial pulmonary diseases. In this paper, neopterin concentrations were increased not only in silicosis patients compared to controls, as in previous papers (28, 30), but also in workers with a classified progression of the pathology (Figure 1). Our results confirm that silica exposure activates cellular immunity as well as that the progression of this immune reaction is positively correlated with the progression of disease severity as mentioned before.

To monitor the activation status of IDO and cellular immunity, the determination of kynurenine and tryptophan concentrations in parallel with neopterin has proven to be a sensitive measure (31-33). In this paper, despite the unchanged tryptophan levels, increased tryptophan degradation in terms of kynurenine concentrations and Kyn/Trp as well as elevated neopterin were observed in silicosis patients compared to controls. The decrease of Kyn/Trp versus the increase in neopterin levels in ILO-3 group seemed to indicate a degradation independent from the Th-1

type immune induction. These results were also indirectly confirmed with the comparison among ILO classification groups, as neopterin levels displayed an elevation with increased ILO class indicating disease severity. The significance of this elevation was confirmed by individual and group statistics. However, the small number of ILO-3 patients limits discussion with regard to this matter. The induction of tryptophan degradation most probably led to an increase in the metabolites of the kynurenine pathway. Actually, it may be speculated that the overproduction of these metabolites may have triggered cellular damage.

Reactive oxidative species (ROS) are known mediators of chronic tissue damage and fibrosis. In the lungs, alveolar macrophages generate reactive species when activated. A relationship between the level of oxidants produced by pulmonary phagocytes and lung damage and severity of pneumoconiosis has been reported by Wallaert et al. (34). They observed that, in alveolar inflammatory cells from patients with single pneumoconiosis, spontaneous superoxide anion generation was three to four folds higher than controls. With the release of polymorphonuclear leukocytes, the oxidant burden in the lung increases and results in lung injury and scarring (11). Superoxide dismutase is an antioxidant enzyme working against oxidative stress by reducing superoxide anion to hydrogen peroxide, which is then converted to water by catalase and glutathione peroxidase (35). SOD activity in the patient group was 1.4 fold higher than in the non-exposed group. The enhanced SOD activity may be considered to be an early indicator of the effect of silica and can be interpreted as a compensatory mechanism in response to the increased ROS generation caused by silicosis. The second measured antioxidant enzyme, catalase, exerts its antioxidant function by reducing hydrogen peroxide to water. However, there is controversial data about the real involvement of this enzyme in oxidative lung damage (33). Moreover, CAT activity did not change with silica exposure. This may be due to the possibility that CAT can sometimes be induced later than SOD.

CONCLUSION

The available literature has clearly identified that oxidative stress is strongly related to the severity of silicosis; however, there are few studies on the changes in neopterin levels caused by silica exposure. So far, there has been no study about tryptophan degradation in denim sandblasting. Our results suggest that the cellular immune response is activated with silica exposure. The increased neopterin levels and tryptophan degradation in denim sandblasters exposed to silica confirm the possibility of their use as indicators of cellular immune response and the participation of macrophages in the pathogenesis of silicosis. Neopterin levels in particular, together with the typical radio-morphological changes, can be used in the diagnosis of environmental and occupational exposure even in the absence of typical symptoms. Neopterin levels and the Kyn/Trp ratio estimating Trp degradation can further be introduced as early markers in the identification of disease progression. However, as the number of our subjects was too small, especially in the ILO-3 group, we can only speculate. This claim should be supported with more detailed studies on a larger number of subjects.

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Conflict of Interest

The authors declare no conflict of interest.

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Sažetak

IMUNOMODULACIJA I OKSIDATIVNI STRES U RADNIKA U PJESKARENJU TRAPER PLATNA: PROMJENE UZROKOVANE IZLOŽENOSTI SILICI

Radnici u pjeskarenju traper platna izloženi su visokom riziku od silikoze, profesionalne plućne bolesti uzrokovane udisanjem čestica silikatne prašine. Razvoj i progresija silikoze povezani su s aktivacijom imunosnog sustava i oksidativnim stresom. Pri aktivaciji imunosnoga sustava, interferon-gama potiče otpuštanje neopterina i enzima indoleamina [2, 3]-dioksigenaze (IDO) u različitim vrstama stanica. Određivanje omjera kinurenina i triptofana te koncentracije neopterina pokazale su se učinkovitim metodama praćenja aktivacijskoga statusa IDO-a i staničnog imuniteta. Ovaj rad istražuje uzrokuje li profesionalna izloženost silici promjene u razinama neopterina, degradaciji triptofana i aktivnosti superoksid dismutaze (SOD) i katalaze (CAT), agenata u antioksidativnom obrambenom sustavu. U istraživanju je sudjelovalo 55 muških radnika u pjeskarenju traper platna i 22 zdrava muškarca u kontrolnoj skupini. Srednje vrijednosti razina neopterina i kinurenina, omjera kinurenina i triptofana, te aktivnosti SOD-a bile su više u radnika oboljelih od silikoze nego u kontrolnoj skupini (p<0,05). Razina neopterina i omjer kinurenina i triptofana bile su u pozitivnoj korelaciji (p<0,05). Međutim, korelacija nije uočena između mjerenih vrijednosti i radnog staža. Neke od mjerenih vrijednosti bitno su ovisile o težini patologije. Dobiveni rezultati daju naslutiti da izloženost silici uzrokuje aktivaciju staničnog imunosnog odgovora. Povećane razine neopterina i degradacije triptofana potvrđuju mogućnost njihova korištenja kao pokazatelja staničnog imunosnog odgovora.

KLJUČNE RIJEČI: *degradacija triptofana, katalaza, neopterin, silika, silikoza, superoksid dismutaza*

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