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Investigation of the Relationship between Genetic Polymorphisms in GSTM1 and GSTT1 Genes and Susceptibility to Lung Functional Abnormalities in Workers Exposed to Air Pollutants at Isfahan Steel Plant

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ABSTRACT

Introduction: Gaseous air pollutants can cause oxidative stress, which can lead to lung damage by inducing inflammation. Polymorphisms in the glutathione S-transferase (GST) gene are involved in the pathogenesis of many diseases, including lung disease. Two glutathione S-transferase Mu 1 (GSTM1) and glutathione S-transferase theta 1 (GSTT1) genes belong to this family, in which deletions occur and the resulting alleles are unable to produce active enzymes.

Materials and Methods: In this study, 41 steel plant workers with impaired lung function were selected. Multiplex PCR technique was used to identify the genotyping of GST M1 and T1.

Results: The results of the frequency of gene deletion among 41 patients showed that there were 10 individuals (17.2%) with deletion of GSTM1 gene, 4 individuals (11.8%) with deletion of GSTT1 gene. The results of the frequency of gene deletion among 50 healthy individuals (control group) also showed that there were 8 individuals (8.5%) with deletion of GSTM1 gene, and 12 individuals (8.3%) with deletion of GSTT1 gene. There were 7 individuals (14%) without deletion of GSTM1 and GSTT1 removal. The results of Chi-square test between healthy and sick groups showed no significance at the level of $p < 0.05$.

Conclusion: According to the results, it can be concluded that the sensitivity to lung function abnormalities in steel workers is directly related to the duration of employment.

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Introduction

Air pollutants may have direct effects on people that can increase the response to allergens, such as causing damage to the epithelium that can increase oxidative stress and inflammation and diverting the immune system to an allergic reaction[1, 2]. Exposure to smoke and particulate matter ($PM_{2.5}$) is associated with various respiratory and cardiovascular diseases as well as mortality[3-5]. Exposure to allergens and air pollution causes DNA methylation, enhances cellular and inflammatory immune responses to allergens, alters protein expression in the lungs, and impairs lung function. Air quality management programs are essential tools of environmental management to

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protect the health and well-being of the population and improve the quality of life[5, 6]. Given the need to evaluate ongoing air pollution control programs, it is strategic to adopt air quality standards as a complementary measure and refer to the maximum emission limits of the pollutants generated. Continuous exposure to air pollution is one of the most important factors affecting the side effects of aging, especially cardiovascular and respiratory diseases[7, 8] .The workplace could be an important factor in determining health issue. On average, adults spends one-third of their life at work. Lung is the most susceptible organ affected by environmental factors in the workplace[9, 10]. Toxic pollutants create free radicals, which results in the production of oxidative stress. Antioxidants could be harmful molecules in the presence of absorbed air pollution through the lungs. Oxidative stress and chronic inflammation are important factors in lung disease. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are released by stimulation of environmental H_2O_2[11, 12]. Antioxidants counteract the harmful effects of free radicals in the workplace. Detoxification enzymes include phase I enzymes (as cytochrome P450) and Phase II enzymes as glutathione S-transferases (GSTs). Glutathione (GSH) is the main antioxidant in the body with important role in the fight against harmful pathogens, free radicals, toxins, pollutants, and other undesirable agents. To this end, GSTs act the same[13, 14] . Among GST polymorphisms, various polymorphisms have been reported, including glutathione S-transferase alpha (GSTA), glutathione S-transferase Mu (GSTM), glutathione S-transferase theta (GSTT), and glutathione S-transferase Pi (GSTP), in which GSTM and GSTT are the most important ones. Thus, polymorphism in GST gene has a great effect on the development of such disease states[15-18] . Contaminants in the workplace can lead to a variety of lung diseases. The pollutants of the steel plant include the main pollutants of PM, carbon monoxide (CO), sulfur dioxide (SO_2), nitrogen oxides (NOX), and the special hazardous pollutant arsenic (AS). Considering the importance of this issue and risks of these pollutants in terms of coking blast, the present study aimed to investigate the relationship between genetic polymorphisms of GSTM1 and GSTT1 and sensitivity to abnormal lung function in workers of the Steel Plant. Studies have shown the presence or absence of a significant relationship between polymorphisms of the studied genes and lung disease. However, the relationship between the polymorphism of these genes and chronic lung disease in people working in highly polluted environments has not been investigated. Therefore, considering the possible role of polymorphism GST in lung diseases in employees working in the steel plant, the polymorphism of GSTM1 and GSTT1 genes was studied in two groups of employees of Isfahan Steel Plant.

In this study, 91 workers of Isfahan Steel Plant were included due to the high level of toxic contaminants. After a deep breath by a healthy person and a person with airway obstruction, they were asked to exhale immediately. The forced vital capacity (FVC) test in both was almost identical, but the healthy person about exhaled 80% of air and the person with airway obstruction exhaled 47% of the air. The air exhaled in the first second is an important criterion for distinguishing lungs with airway obstruction from normal lungs.

Materials and Methods

Sample selection

The present study case-control study was conducted on workers working in the coking department of Isfahan Steel Plant due to its high level of toxic pollutants. The study population was selected based on clinical criteria. Impaired lung function was observed in 80% of workers through the FVC test, 71 workers of whom working in the coking department were impaired. It was due to the high level of toxic pollutants in workers working in the coking plant of Isfahan Steel Plant. At the time of referral, sufficient explanations were given to justify and acquaint the workers with the objectives of the study. People without lung dysfunction working in the coking department were considered for the control group.

In this study, having lung disease and lung

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dysfunction in people working in the Steel Plant in the case group was the inclusion criterion, and not having lung disease and lung dysfunction in people working in the Steel Plant in the control group was the exclusion criterion.

Forced Vital Capacity

The FVC is one of the important factors to evaluate lung function. It is the volume of air that a person exhales vigorously and is used to assess lung function.

In the lungs of a healthy person, about 80% of the air is expelled in the first second of exhalation, but in the lungs of a person with airway obstruction, 47% of the exhaled air is expelled in the first second. In fact, the percentage of air output per second of exhalation is an important diagnostic criterion for distinguishing lungs with airway obstruction from normal lungs[19].

After a deep breath, the normal person and the person with airway obstruction were asked to exhale quickly. The FVC was about the same in both, but in the normal person's lungs about 80% of the air was expelled in the first second of exhalation, and the person with airway obstruction only exhaled 47% of the air in the first second. In fact, the percentage of air exhalation per second is an important criterion for distinguishing lungs with airway obstruction from normal lungs.

In this study, 5 ml blood containing EDTA anticoagulant was taken from the participants. DNA was extracted from peripheral blood using the PLUS- DNG ^ TM kit (Cinnagen). After extraction, DNA was evaluated in terms of quantity and quality (1% agarose gel was used to check the quality of the genome). Then from primers F: 5/GAACTCCCTGAAAAGCTAAAGC 3/R: 5/ GTTGGGCTCAAATATACGGTGG 3/Gene GSTM and GSTT1 genes were used for amplification R: 5/ TCACCGATCATGGCCAGCA 3/ from proprietary primers.

In this study, PCR was used to determine the sequence of primers and bases) 19 base pairs between exons of 5 and 6). These primers can also amplify a 480-nucleotide nucleotide sequence from the GSTT1 gene, located in the exon region between exons 2-3.

A pair of β-Globin primer was used as the control gene (Houskeeping gene) to confirm PCR and detect the genotype of GSTT1 and GSTM1 genes. Pairs of β-Globin primers were designed based on the following sequence:

F: 5/CAACTTCATCCACGTTCACC3/

R: 5/GAAGAGCCAAGGACAGGTAC3/

These primers can be amplified about 268 base pairs with 1 cycle in 94˚ and 5 min, 2 cycles in 94˚ and 30 Sec, 3 cycles in 55˚ and 30 Sec, 4 cycles in 72˚ and 45 Sec, and 5 cycles 5 in 72˚ and 5 min. The data were analyzed by t-test and chi-square tests through SPSS 17 (Version.12.1.4.0) software.

Occupational and industrial pollutants in terms of coking blasts lead to development of various pulmonary diseases. Considering the importance of this issue and the risks of these pollutants were the main aims of the study. Moreover, the relationship between genetic polymorphisms of GSTM1 and GSTT1 and their sensitivity to abnormal lung function in workers of the Steel Plant were considered.

Results

In this study, 91 workers of Isfahan Steel Plant were included due to the high level of toxic pollutants. They were divided into control and control groups.

In this study, 41 workers with impaired lung function and 50 healthy workers as the control group were studied. Table 1 shows the mean age and duration of employment (years) in the coking department of Isfahan Steel Plant in two groups.

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Table 1: Mean age and duration of employment (by year) of the experimental and control groups

Mean	Experimental group (FVC 80 %)	Control group (FVC normal)
Number	41	50
Age	38.5 ± 7.4	31.9 ± 1.7
Duration of employment (year)	13.35 ± 3.7	12.4 ± 4.5

Figure 1 shows the relationship between employment duration and lung disease between the healthy and sick groups. In all cases, the duration of employment in the experimental group is longer than in the control group.

After blood sample preparation, genomic DNA was extracted from peripheral blood leukocytes by DNG-PLUS kit. Horizontal electrophoresis method was selected to evaluate the quality of the extracted DNA. The samples were electrophoresed on 1% agars gel and then photographed by GEL-DOC.

Figure 2 shows the transparent strips of the optimal quality of the extracted DNA and its suitability for PCR testing.

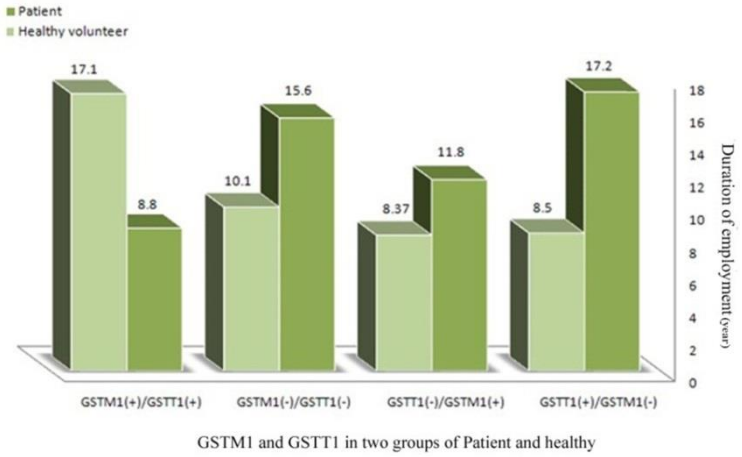

Figure 1: Employment duration in healthy and patient groups

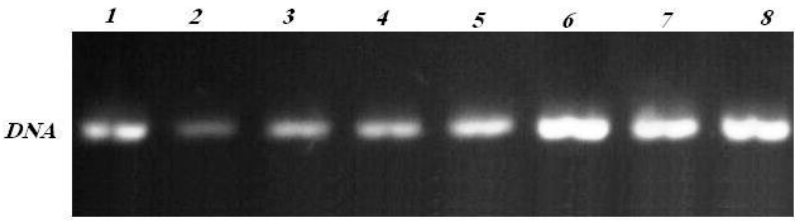

Figure 2: Genomic DNA extracted from blood (using 1% agar gel). Rows 1-8 are DNA extracted from the control and experimental groups

In this study, Multiplex PCR was used to detect the removal of homozygotes in GSTT1 and GSTM1 genes. In order to evaluate the quality of PCR products, 1.5% agars gel was used and these gels were photographed. As shown in Figure 3, the light bands indicate the amplification of the target genes by the primers.

In this method, the absence of a band related to each of the two genes GSTM1 and GSTT1 indicates the deletion of the homozygote of that gene.

Figure 4 shows the final product of Multiplex PCR from GSTM1, GSTT1, and β-globin genes. PCR was performed for the experimental and control groups and the presence or absence of bands in both genes was examined.

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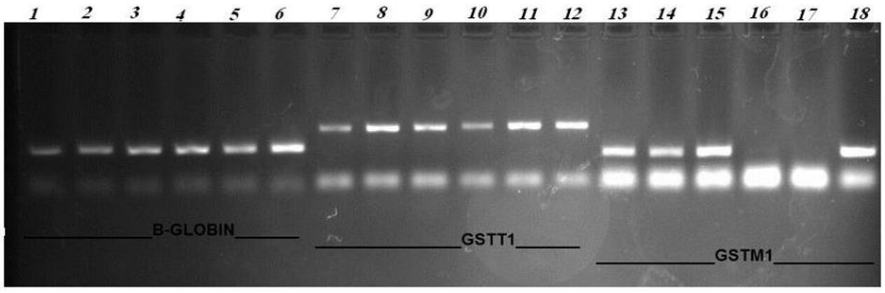

Figure 3: PCR products of GSTM1, GSTT1, and B-Globin genes with agars 1.5%. Rows 1-6 with 268 bp indicate β-Globin gene. Rows 7-12 with 480 bp indicate GSTT1 gene. Rows 13-18 with 219 bp indicate GSTM1 gene.

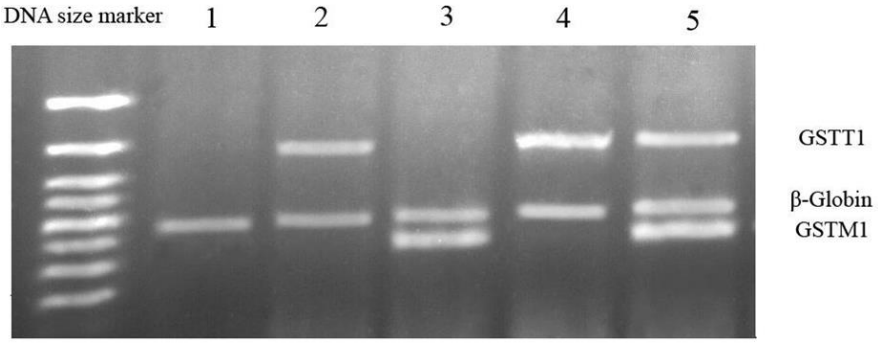

Figure 4: Results of Multiplex PCR (GSTM1, GSTT1, and B-Globin)

No bands are observed in rows 1 and 2 of GSTM1 and GSTT1 genes, so both homozygous genes were deleted. In rows 2 and 4, only GSTM1 gene had homozygous deletion. In row 3, only GSTT1 gene had homozygous deletion. According to the figure in rows 5 and 3 of each band, no gene deletion occurred.

Statistical analysis of the results of the Multiplex PCR of GSTM1 and GSTT1 genes:

In this test, there were 41 patients with homozygous GSTM1 deletion, 4 patients with homozygous deletion of GSTT1, 22 patients with homozygous deletion combined GSTM1 and GSTT1, 5 patients without any homozygous deletion, 8 people with GSTM1 homozygous deletion from 80 healthy subjects (control group). Moreover, there were 12 patients with homozygous GSTT1 deletion, 23 patients with homozygous deletion combined GSTM1 and GSTT1, and 7 subjects without any homozygous deletion. There was no significant difference between the two groups. In 41 patients, there were 32 patients with GSTM1 homozygous deletion, 26 patients with GSTT1 homozygous deletion, and 5 people without any homozygous deletion. There was no significant difference between the two groups. In 41 patients, deletion of GSTM1 gene and deletion of GSTT1 gene were reported 17.2% and 11.8%, respectively. In 50 healthy individuals with mean duration of employment, GSTM1 and GSTT1 gene deletions were reported 8.5% and 8.3%, respectively. To determine if there is a significant difference, t-test was used, except in patients with two homozygous deletions $P < 0.05$.

Discussion

The relationship between the polymorphism of these genes and chronic lung disease in people working in highly polluted environments has not been investigated. Therefore, considering the possible role of GST polymorphism in lung diseases in employees of Zobahan factory, in this study polymorphism of GSTM1 and GSTT1genes was investigated using Multiplex PCR method in the experimental and control groups of Isfahan Zobahan workers. Epidemiological studies have shown that increasing the concentration of toxic gases and PM that can be inhaled in the air

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increases the number of hospital admissions and causes acute respiratory complications, decreased respiratory capacity and increased mortality. Therefore, there is a direct relationship between respiratory diseases and air pollution, according to data, annually about 800,000 people worldwide die due to air pollution-related diseases[20]. Recent studies have shown that one of the main mechanisms of toxicity of occupational pollutants is to increase the production of free radicals and thus oxidative stress[9]. GST gene polymorphisms have been studied in the pathogenesis of many diseases, including lung diseases[21], autoimmune hepatitis[22], diabetes atherosclerosis[23], men with varicocele[24], as well as cancers, such as colon[25], bladder, larynx[26], stomach[27], breast[28] and acute lymphocytic leukemia cancers[29] . Previous studies have shown that polymorphisms in the GST gene may impair their ability to defend against oxidative stress, leading to the development of pulmonary abnormalities[30]. The presence of GST enzyme in lung tissue, especially bronchi, mucus-secreting cells, and alveolar cells was confirmed. After studying GST polymorphisms, it was found that the highest amount of this protein is present in bronchial ciliated epithelial cells, which is GSTP1[31]. The other GST polymorphism also plays a role in lung disease. The examination of GSTO (omega) protein using Western blotting technique in alveolar macrophages obtained from pulmonary secretions of patients with COPD compared to those with healthy lungs showed a decrease in the presence of this protein[32]. Many other studies have also examined GSTM1 and GSTT1 genes in different populations and their association with chronic obstructive pulmonary disease (North India population)[33, 34], chronic pneumonia in children[35], and the possibility of obstructive pulmonary disease[25] and its role in asthma[36]. The relationship between GST gene family polymorphism in smokers and its role in lung damage has been investigated[37]. Fourteen studies confirmed that cigarette smoke carriers of empty GSTM1/T1 genotypes may increase the risk of allergic disease and lung dysfunction[3,38]. MacNeeW et al. concluded that people who are not protected against certain antioxidant genes may have less antioxidant defense capacity and be more susceptible to environmental toxins. This may increase the risk of asthma or lung dysfunction when exposed to oxidative stress[39]. The study by Palmer CAN et al. showed that the presence of GSTP1 in people exposed to tobacco smoke increased the risk of decreased lung function[40]. Imboden M et al. reported significant interactions between GSTT1 genotype and lung time and function in smokers[41].

Conclusion

According to the results, there was no significant relationship between GSTM1 and GSTT1 gene polymorphisms and susceptibility to lung function abnormalities in the Steel Plant workers. However, given that there was a significant difference between the employment duration of the two groups, it can be concluded that the sensitivity to lung function abnormalities in steel workers is directly related to employment duration.

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Conflict of interest

The authors have no conflict of interest.

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