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Research Article

ASSOCIATION OF DETOXIFYING GENE POLYMORPHISMS WITH CYTOGENETIC DAMAGE IN STEEL INDUSTRY WORKERS

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ABSTRACT

Context: Steel is crucial to the development of any modern economy and is considered to be the backbone of human civilization. Occupational exposure to steel dust might result in adverse health effects. This study aims to investigate the possible association of detoxifying gene polymorphisms with cytogenetic damage in steel industry workers.

Methods: 150 steel industry workers and 146 control subjects with no history of occupational exposure to steel dust or any other chemical were recruited for the study. Cytogenetic damage was evaluated using the simple and reliable procedures like analysis of the chromosomal aberrations and sister chromatid exchanges in peripheral blood lymphocytes of male steel industrial workers. Analysis of GSTM1 and GSTT1 gene polymorphisms was done by multiplex PCR method.

Results: The results showed an increase in the frequency of chromosomal aberrations and sister chromatid exchanges in peripheral blood lymphocytes of the steel industry workers compared to the control subjects. A statistically significant increased frequency of total chromosomal aberrations and sister chromatid exchanges was observed in GSTM1null genotype of the steel industry workers. The results clearly establish the association of null GSTM1 gene polymorphisms with cytogenetic damage in steel industry workers. However, we observed no statistically significant differences in the GSTM1 and GSTT1 genotype frequencies in both exposed and control groups.

Conclusion: Cytogenetic analysis showed that occupational exposure to steel dust significantly increased chromosomal aberration and sister chromatid exchange frequencies. The study also presented evidence for the association of GSTM1null genotype with cytogenetic damage indicating the influence of GSTM1 polymorphisms on these biomarkers.

INTRODUCTION

The steel and iron industry has been one of the world's most important industries ever since it was first founded. The steel dust that is liberated from the industry contains nickel, chromium, iron, manganese, cobalt, molybdenum and vanadium which are carcinogenic and mutagenic (Cornelia 2002). Earlier studies have shown an increase in health problems such as lung tumors, diabetes, rheumatoid arthritis, hypertension and cardiovascular diseases in male steel industry workers (Roberto Cappelletti *et al*., 2016).

Hayes (1997) and Sabine Martin (2009) reported that exposure to metals like cadmium, cobalt, nickel, and chromium compounds are carcinogenic in humans. Workers occupationally exposed to heavy metals were considered to be at an elevated risk for developing cancer (Pool *et al*., 1994, Keshava *et al*., 1999, De Flora *et al*., 2000, Gibb *et al*., 2000). Earlier studies have shown mutagenic effects in workers exposed to welding fumes (Hedenstedt *et al*., 1997). A significant increase in the frequency of chromosomal aberrations was observed with increase in age and years of exposure in welding workers (Elias *et al*., 1989,Knudsen *et al*., 1992). Studies have shown that welding fumes from stainless steel industry are mutagenic (Maxild *et al*., 1978). Biomonitoring through analysis of Cytokinesis-block

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micronucleus (CBMN), chromosomal aberrations (CAs), and sister chromatid exchanges (SCEs) can provide relevant information on the possible cancer risks.It is also shown that polymorphisms of enzymes involved in the metabolism of carcinogens, mutagens, DNA repair may influence the causation of micronuclei, chromosomal aberrations (CAs), and sister chromatid exchanges (SCEs).

Glutathione *S*-transferases (GSTs) are the frequently studied polymorphisms concerning of Xenobiotic compounds. The most important function of GSTs is metabolic activation and protection against electrophilic compounds. In view of its important in detoxification, the possible role of the polymorphisms of these genes on cancer risk (Vural *et al*., 2010, Vidyullatha *et al*., 2016), DNA damage (Giri *et al*., 2012, Massimo moretti *et al*., 2007) and cytogenetic damage (Anna Maria Rossi *et al*., 2008) was studied. Of these genes, GSTM1 and GSTT1 genes because of high prevalence of homozygous deletions resulting in null genotypes were studied extensively.

Studies have shown that GSTT1, and GSTM1 polymorphisms modulate chromosomal damage in workers exposed to genotoxic agents and carcinogenic agents (Iarmacovai *et al*., 2007). Genetic polymorphism in these genes may be responsible for individual susceptibility to cancer by environmental carcinogens(Bolufer *et al*., 2006, Bolt and Thier 2006, Carlsten *et al*., 2008, Hiyama *et al*., 2008, Parl 2005,Shi *et al*., 2008, Vineis *et al*., 2007, White *et al*., 2008).

Recent evidence shows that genetic variation provides a significant association between cytogenetic damage and GSTM1 and GSTT1 gene polymorphisms which are involved in bioactivation and detoxification of environmental toxins (Medeiros *et al*., 2004, Loft and Moller, 2006). The lack of glutathione S-transferase M1 (GSTM1 null genotype) is associated with increased frequency of CAs and SCEs. (Gulgun *et al*., 2004). The aim of our study is to evaluate the cytogenetic damage using chromosomal aberrations (CAs), and sister chromatid exchanges (SCEs) as biomarkers and to assess the association of GSTT1 and GSTM1 gene polymorphisms as effect modifiers with cytogenetic damage in steel industry workers occupationally exposed to the steel dust.

MATERIALS AND METHODS

Study subjects

The study was carried out in 150 workers of steel industry who were occupationally exposed to steel dust and 146 subjects who were not exposed occupationally to industrial chemicals and dust for comparison (control group). Subjects for the present study were selected among the workers at the steel industry situated at Patancheru, Hyderabad, India. All the subjects of steel industrial workers and controls were clinically examined and information on age, literacy, occupation, years of service, socio economic status, habits, hours of work per day, life style, , income, living conditions, marital status, Health problems, family history, medical history, personal safety measures taken were recorded using a standard questionnaire. The study was approved by the Institutional Ethics Committee of the Centre and written informed consent was obtained from all the participants of the study.

Analysis of chromosomal aberrations in peripheral blood lymphocytes

Blood samples from each individual was added into a 5 mL RPMI 1640 medium supplemented with 20 % foetal calf serum and 2 % PHA-L on the day of sampling. The cultures were incubated in the dark at 37 °C for 48 h. Three hours before the harvest, colchicine (0.05 µg mL-1) was added to the culture. The cells were collected by centrifugation, re-suspended in a hypotonic solution (0.075 mmol L-1 of KCl) for 20 min and fixed in acetic acid: methanol (1:3). Slides were prepared by air-drying and stained with a 5 % Giemsa solution.

For each individual 100 well spread metaphases were screened in coded slides for structural aberrations such gaps, breaks, fragments, exchanges, dicentrics and numerical aberrations (polyploids). However, gaps and polyploids were not included in total number of aberrations. Well spread metaphases were micro photographed.

Analysis of sister chromatid exchanges (SCEs) in peripheral blood steel industry workers

Culturing of peripheral blood lymphocytes was carried out in a similar way as the analysis of chromosomal aberrations except that BrdU (3 ug/ml) was added after 24 hours of culturing. The culture vials were then wrapped in dark black paper to avoid photolysis of BrdU substituted DNA and incubated at 37^0C.Colchicine was added to the culture vials at the 70th hour of incubation to arrest the spindle formation and the cultures were harvested for 72 hours. The slides prepared and dried by conventional flame drying method, were stained by using FPG (Fluorescence Plus Giemsa) technique of Perry and Wolff (1974). Three days old slides were kept in Hoechst – 33258 (2 ug/ml) working solution for 20 minutes, then rinsed in distilled water and layered by Sorenson's phosphate buffer. The slides were subjected to ultra violet light for 40 minutes then the slides were thoroughly rinsed in distilled water and were stained in 4% Giemsa dye (2ml Giemsa and 48 ml Sorenson's buffer) for 3 to 5 minutes,50 well spread metaphases from each sample were analyzed under the microscope for SCE frequencies.

Analysis of GSTM1 and GSTT1 gene polymorphisms by multiplex PCR

GSTM1 and GSTT1 genotyping: Genomic DNA was isolated from 200 µL of whole blood by Spin column kit (Bangalore Genei, India). Multiplex PCR assay was used for analyzing the GSTM1 and GSTT1 gene polymorphisms. To detect the GSTM1 polymorphisms, the primers used were F (5′ GAA CTC CCT GAA AAG CTA AAGC 3′) and R (5′ GTT GGG CTC AAA TAT ACG GTG G-3′). For GSTT1, the primers used were F (5′-TTC CTT ACT GGT CCT CAC ATCTC- 3′) and R (5′-TCACCGGATCATGGCCAGCA-3′).The PCR amplicons were electrophoresed on a 4% agarose gel, stained with ethidium bromide, and the results were documented using a gel documentation system. The presence of GSTM1 and that of GSTT1 genes were indicated by the resulting 215 and 480 bp PCR amplicons, respectively. A DNA sample with GSTM1 and GSTT1 alleles present was run as a positive control in each run. As an internal control, human albumin gene (HAB) was amplified (350bp) using the primers F (5′-CAACTTCATCCACGTTCACC-3′) and R (5′-

GAAGAGCCAAGGACAGGTAC-3′) for the authentication of multiplex PCR. The PCR protocol included an initial denaturation temperature of 94 °C (5 min) followed by 35 cycles of amplification (denaturation at 94 °C for 1 min, annealing at 59 °C for 1 min and extension at 72 °C for 1 min). A final 10 min extension step (72 °C) terminated the process. The final PCR products were visualized on an ethidium bromide stained with 2.0% agarose gel. The size of the GSTM1 was visualized as 215bps, GSTT1 as 480 bps and the HAB internal control as 350 bps fragment.

Statistical analysis: The results were analyzed statistically using Student's t-test to find the significance in the differences between the two groups for the association of detoxifying gene polymorphisms with cytogenetic damage. Mean values and standard deviations were computed for the statistical significance ($P < 0.05$). The differences for the distribution of genotype frequencies in CAs and SCEs between the groups were calculated using the $\chi 2$-test. Genotype frequencies were checked for deviation from Hardy–Weinberg equilibrium and were not significantly different from those predicted. Odds ratios and 95% confidence interval (95% CI) were calculated to assess the relationship between GSTM1 and GSTT1 gene polymorphisms.

RESULTS

The results on the percentage of chromosomal aberrations and sister chromatid exchanges in peripheral blood lymphocytes of steel industry workers are presented in Table 1-2

Table-1 shows an increase in the percentage of chromosomal aberrations in peripheral blood lymphocytes of steel industry workers compared to controls. The percentage of total number of chromosomal aberrations in steel industry workers was 3.57% as against 1.14% in controls.

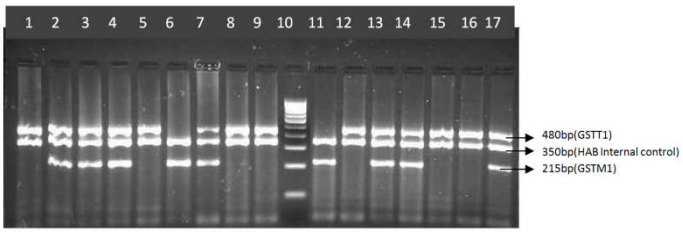

Fig 1 Gel Picture showing GSTM1 and GSTT1 bands

GSTM1 and GSTT1 polymorphisms: The GSTM1 and GSTT1 gene deletions were analyzed simultaneously by multiplex PCR. Amplicons of 215 bp and 480 bp indicate, respectively GSTM1 and GSTT1.LANE -1,2,3,4,5,7,8,9,12,13,14,15,16 AND 17 WILD TYPE FOR GSTT1 ,LANE-2, 3,4,6,7,11,13,14 AND 17 WILD TYPE GSTM1,LANE-10 LADDER 100bp,LANE-6, 11 NULL TYPES FOR GSTT1 ,LANE-1, 5,8,9,12,15 AND 16 NULL TYPES FOR GSTM1,ALBUMIN (350 bp) was used as an internal control.

Genotype distributions of GSTM1 & GSTT1 genes

In our study, we genotyped GSTM1 and GSTT1 polymorphisms in 150 steel industry workers and in 146 control subjects. GSTM1 wild gene was found to be present in 65.1% of the control subjects and in 62.7 % of steel industry workers and GSTM1 null gene was found to be present in 34.9% of the control subjects and in 37.3 % of the steel industry workers. Similarly GSTT1 wild gene was present in 62.3% of the control subjects and in 61.3% of steel industry workers and GSTT1 null gene was present in 37.7% of the control subjects and in 38.7% of steel industry workers.

Table 1 Chromosomal aberrations in peripheral blood of steel industry workers exposed to steel dust.

GROUP	No. of blood Samples collected	No. of blood Samples successfully screened	No. of metaphases screened	Chromosomal Aberrations				
				Gap	Break	Dicentric	polyploids	Total no of chromosomal abberations
Study group	150	111	11100	200(1.80)	191(1.72)	206(1.85)	232(2.09)	397(3.57%)
Control group	146	140	14000	89(0.63)	78(0.55)	82(0.58)	71 (0.50)	160(1.14%)

100 metaphases were analyzed for each sample. Values in the parentheses indicate percentages. Gaps and polyploids were not included in total number of aberrations.

Table-2 shows an increase in percentage of frequency of sister chromatid exchanges (SCEs) in the peripheral blood lymphocytes of steel industry workers compared to controls. The frequency of SCE per cell in the steel industry workers was 4.13 as against 1.21 in controls.

Table 2 Sister Chromatid Exchanges in peripheral blood of workers exposed to steel dust

Group	Number of blood samples Collected	Number of blood samples Screened	Number of metaphases screened	Total number of SCEs	SCE / Cell
Study Group:	150	129	2150	8900	4.13
Control Group	146	130	3100	3780	1.21

50 metaphases were analyzed for each sample

Molecular analysis of GSTM1 and GSTT1 genes

Multiplex PCR based approach was employed to determine the genetic polymorphisms of GSTM1 and GSTT1 genes. Amplicons of 215bp and 480bp indicated the presence of GSTM1 and GSTT1 (Fig 1).

Table 3 Genotype distributions of GSTM1 & GSTT1 polymorphisms in steel industry workers and controls

Genotype	Steel industry workers (n=150)	Controls (n=146)	X^2	OR (95% CI)	*p* value
GSTM1 (wild/wild)	94(62.7)	95(65.1)	1	Reference	
GSTM1 (null /null)	56(37.3)	51(34.9)	0.18	1.11(0.67-1.83)	0.66
GSTT1 (wild/wild)	92(61.3)	91(62.3)	1	Reference	
GSTT1 (null/null)	58(38.7)	55(37.7)	0.03	1.04(0.63-1.71)	0.86

P- Value was calculated by $\chi 2$ test with 2 x 2 contingency table and considered <0.05 as significant.*

The statistical analysis showed the differences in the frequency of genotypes between controls and steel industry workers were statistically non significant as shown in Table-3.

Table-4 shows the distribution of GSTM1 and GSTT1 polymorphisms in controls and steel industry workers with chromosomal aberrations. The results showed that the frequency of chromosomal aberrations in different genotypes of GSTM1 and GSTT1 was almost same in controls. However significant increase in chromosomal aberrations was noted in the GSTM1 null genotype in steel industry workers indicating induction of chromosomal aberrations is associated with the GSTM1 polymorphisms. Further the results indicated that GSTT1polymorphisms are not associated with chromosomal aberrations in steel industry workers.

Table 4 Distribution of *GSTM1* and *GSTT1* genotypes in subjects and controls and mean CA frequency

Genotype	Steel industry workers with CA			Controls with CA		
	(*n* = 150)	CA (Mean ± SD)	*P* Value	(*n* = 146)	CA (Mean ± SD)	*P* Value
GSTM1 (wild/wild)	94	28.7 ± 1.05	0.02*	95	24.0 ± 2.5	0.12
GSTM1 (null /null)	56	29.5 ± 3.02		51	24.75 ± 2.22	
GSTT1 (wild/wild)	92	26.25 ± 5.93	0.11	91	24.15 ± 1.91	0.15
GSTT1 (null/null)	58	27.5 ± 1.04		55	25.75 ± 1.01	

*$p<0.05$ significant. Values are Mean ± SD data

Table- 5 shows the distribution of GSTM1 and GSTT1 polymorphisms in controls and steel industry workers with sister chromatid exchanges. The results showed that the frequency of sister chromatid exchanges in different genotypes of GSTM1 and GSTT1 was almost same in controls. However significant increase in sister chromatid exchanges was noted in the GSTM1 null genotype in steel industry workers indicating induction of sister chromatid exchanges is associated with the GSTM1 polymorphisms. Further the results indicated that GSTT1polymorphisms are not associated with sister chromatid exchanges in steel industry workers.

Table 5 Distribution of *GSTM1* and *GSTT1* genotypes in subjects and controls and mean SCE frequency

Genotype	Steel industry workers with SCE			Controls with SCE		
	(*n* = 150)	SCE (Mean ± SD)	*P* Value	(*n* = 146)	SCE (Mean ± SD)	*P* Value
GSTM1 (wild/wild)	94	29.01 ± 1.38	0.0003*	95	27.25 ± 2.76	0.56
GSTM1 (null /null)	56	28.25 ± 0.88		51	27.5 ± 1.93	
GSTT1 (wild/wild)	92	27.95± 0.17	0.36	91	32.5 ± 4.27	0.16
GSTT1 (null/null)	58	28.05 ± 1.04		55	33.50 ± 3.87	

*$p<0.05$ significant. Values are Mean ± SD data

DISCUSSION

Epidemiological studies in steel industry workers have shown that exposure to steel dust increases the risk of developing health problems such as lung tumors, diabetes, rheumatoid arthritis, hypertension and cardiovascular diseases in male steel industry workers (Roberto Cappelletti *et al*., 2016). Chromosomal anomalies and genetic damage are the major causes for cancer and hence identifying reliable cytogenetic markers to understand cancer risk is very important for public health. Analysis of chromosomal changes and sister chromatid exchange are very reliable and sensitive biomarkers for predicting cancer risk and the same have been employed in our study. The results showed that occupational exposure to steel dust significantly elevated both chromosomal aberrations and sister chromatid exchanges in the peripheral blood lymphocytes of the workers.

Our results are in agreement with that of Topaktas *et al* (2002) who reported significantly elevated chromosomal aberrations in iron and steel plant workers in Turkey. Myslak and Kosmider (1997) also demonstrated CAs and SCEs in stainless steel workers. Elias (1989) also showed increased frequency of CAs and SCEs in peripheral blood of stainless steel welders.

The steel dust contains nickel, chromium iron, manganese, cobalt, vanadium etc and hence the cytogenetic damage might be attributed to the combined effects of these metals. Cornelia (2002) demonstrated carcinogenicity and mutagenicity of heavy metals like chromium, nickel cadmium, cobalt in steel industry workers. Recently Mulyana., *et al* (2015) demonstrated genotoxic risks in the form of cytogenetic damage in workers occupationally exposed to high levels of metals like nickel, chromium, iron manganese, calcium, etc. Exposure to these metals occurs via inhalation, ingestion or skin contact, from which the most common occupational route is inhalation (Lide 1998, Wise *et al*., 2004).

Cr and Cr compounds have been tested for genotoxicity in a variety of short-term tests using different end-points (De Flora *et al*., 1990, Manning *et al*., 1994, Stearns *et al*., 2002, Quievryn *et al*., 2003). Workers occupationally exposed to Cr are considered to be at an elevated risk for developing cancer (Langard 1990, Rosenman and Stanbury 1996, De Flora 2000, Gibb *et al*., 2000). Induction of chromosomal aberrations in human peripheral blood lymphocytes by chromate compounds were reported earlier by Quievryn *et al*., (2003). However the present results were attributed to the observations made by Sarto *et al*., (1982) in peripheral blood lymphocytes of chromate workers, exposed to chromium containing fumes. Similar findings were reported by several workers among the smoker groups, occupationally exposed to rubber, heavy metals and also in plastic workers which will support the present investigation (Van-Hummelen *et al*., 1994, Wei Gu *et al*., 1996, Werfel *et al*., 1998). Occupational exposure to Cr and Ni in welders showed a significant increase in micro nucleated cells compared with controls (Danadevi *et al*., 2004). Ladon *et al*., (2004) showed an increased chromosomal translocations and aneuploidy in peripheral blood lymphocytes of workers who are occupationally exposed to chromium, nickel and cobalt.

In addition studies carried out in animal models also showed evidence for an increase in sister chromatid exchanges and chromosome aberrations in cultured Chinese Hamster cells exposed to fume particles from stainless steel welding. (Koshi 1979, Baker *et al*., 1986). Hedenstedt *et al*., (1977), Maxild *et al*., (1978) have shown that welding fumes coming from stainless steel welding are mutagenic to the exposed workers. However, evidence for the carcinogenicity of welding fumes and gases in humans evaluated by the International Agency for Research on Cancer (IARC) as limited and in animals as inadequate.

GSTM1 is one of the most key subclasses of GSTs, which has potent protective role against cancer compared to other GST

subtypes (Lavender *et al*., 2009). Among the GST's GSTM1 preferentially detoxifies carcinogens derived from tobacco, whereas GSTT1 causes the biotransformation of many toxins. Any alterations due to genetic polymorphisms affect the activities of these genes, thereby increasing the genotoxic risk in humans (Peddireddy *et al*., 2016). Null GSTM1 genotypes have been demonstrated to be most commonly associated with risk of cancers.

Our study provides an opportunity to assess the impact of genetic polymorphisms of GSTM1 and GSTT1 on the relationship between cytogenetic damage and cancer risk. GSTM1 is a marker of susceptibility to the induction of cytogenetic damage by a certain class of mutagens (Nielsen *et al*., 1996, Wiencke *et al*., 1990) and the lack of this GSTM1 isoform being associated with reduced efficiency in binding genotoxic substrates, including epoxides. The polymorphic genes which involved in the metabolism of xenobiotics may modulate the levels of biomarkers arising from environmental and occupational exposure to genotoxic agents (Pavanello and Clonfero 2000). Knowledge of the real impact of genetic polymorphisms as biomarkers is a key of significance in understanding the processes of genetic damage involved in mutagenesis and carcinogenesis (Ginsberg *et al*., 2009, Norppa, 2004, Sram and Binkova, 2000).

In the present investigation, the polymorphisms of GSTT1 and GSTM1 genes was studied in steel industry workers and an attempt was made to find out whether any association exists between polymorphisms of these genes and cytogenetic damage. The study provides evidence for the association of GSTMI gene polymorphism and cytogenetic damage in steel industry workers. No studies have been carried out on the association of gene polymorphisms with genotoxic effects and this is the first study on this aspect.

The results of our experimental studies indicated that GSTM1 is a marker of susceptibility to the induction of cytogenetic damage. The study revealed that null genotype of GSTM1 gene was associated with induction of cytogenetic damage in steel industry workers. Our findings indicate that occupational exposure to steel dust might induce cytogenetic damage. Hence preventive and therapeutic measures may be considered for steel industry workers to nullify the adverse effects of steel dust.

CONCLUSIONS

The study reveals that there is a significant increase in the frequency of chromosomal aberrations and sister chromatid exchanges in the peripheral blood lymphocytes of steel industry workers. Also our study has confirmed positive association between increased cytogenetic damage and occupationally exposure to steel dust and GSTM1 null genotype. Hence appropriate precautionary measures have to be taken to prevent or minimize the exposure of the workers to steel dust.

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Conflict of Interest: None of the authors of this paper had any personal or financial conflicts of interest.

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