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Original Research Article

Metal toxicity and its correlation with endoplasmic reticulum stress, mitochondria functioning and gene expression analysis in occupationally exposed workers

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ABSTRACT

Background: Owing to the widespread presence of lead in the environment the possibility of endogenous exposure remains a serious health hazard. Lead enters in the body through inhalation and ingestion and adversely affects cells and targets the cell organelles.
Methods: Aim of this study was to examine the correlation of lead toxicity with the gene expression of endoplasmic reticulum (ER) (GRP78 and PERK), mitochondrial functioning (PINK1 and PARK7), apoptosis (Pro apoptosis (BAX and p53) and anti-apoptosis (Bcl-2 and c-Myc)) in occupationally exposed painters and battery workers compared with age matched control subjects. Lead levels were measured in the whole blood by using inductively coupled plasma mass spectrometry (ICP-MS) that allow very low-level detection limit of the elements. Gene expression analysis was performed by quantitative real time PCR (qPCR).
Results: Results of the study showed that the lead levels were significantly high in the painters and battery workers when compared with controls (41.37±20.71 µg/dl, 56.25±17.66 µg/dl and 6.55±2.02 µg/dl, respectively, $p<0.001$). Results of the gene expression analysis of ER stress, mitochondrial functioning and pro-apoptotic genes like GRP78, PERK, PINK1, PARK7, Bax and p53 were found significantly up-regulated in painters and battery workers, respectively. The Anti-apoptotic genes like Bcl-2 and c-Myc were found significantly down regulated in painters and battery workers.
Conclusions: Results of the study showed that increased level of Lead alter the gene expression of ER, mitochondrial functioning and apoptosis in occupationally exposed painters and battery workers.

Keyword: Lead toxicity, Endoplasmic reticulum, Mitochondria, Apoptosis, Occupational workers

INTRODUCTION

Lead is a frequent occupational and environmental pollutant that produces an extensive range of physiological, behavioral, and metabolic dysfunctions in humans. It can be found in leaded gasoline, water pipes, plastic, ceramics, paints, battery recycling etc. Ingestion of lead contaminated food or drink, as well as inhalation of lead contaminated dust particles or aerosols are the two main ways that people become exposed to lead worldwide.[1]

Lead toxicity is associated with cellular mechanisms such as calcium dysregulation, and oxidative stress that may alter ER homeostasis.[2] ER stress has been recognized as the crucial processes underlying xenobiotic toxicity. Despite having redox chemistry, the ER compartment is intrinsically related and dependent on a group of

organelles that work together to retain cellular homeostasis.[3] Besides being crucial for the ER to transmit proteins to mitochondria, it is also a crucial site for the synthesis, processing, and modification of proteins and also for breaking down of xenobiotics.[4]

Mitochondria are incredibly multi-purpose organelles that play a role in the body's vital functions. They are the primary locations in aerobic cells where adenosine tri phosphate (ATP) is generated.[5] In addition to serving as the center for energy metabolism, mitochondria also house a variety of anabolic and catabolic activities, calcium fluxes, and signaling pathways, including apoptosis.[6] Apoptosis is a dynamic cell death mechanism that is distinguished by morphological characteristics such as fragmentation of DNA, chromatin condensation and cell shrinkage. Apoptosis is required for tissue maintenance, embryogenesis, and serving as an anti-oncogenic mechanism.[7] Heavy metal exposure damages DNA through intrinsic mechanisms that include the pro-apoptosis protein like Bax and p53 that are responsible for apoptosis.[8] Tumor suppressor protein p53 causes apoptosis by up regulating the transcription of numerous pro-apoptotic genes and down regulating those that are anti-apoptotic.[9] Protein p53 is essential in inhibiting the development of tumors owing to its critical function in protecting the genome from mutations caused by DNA damage, this protein is also known as the "guardian of the genome".[10] Members of the B cell lymphoma-2 (Bcl-2) family encode anti-apoptotic genes such as Bcl-2, Bcl-xL, and c-Myc. These genes prevent apoptosis by either preventing release of mitochondrial apoptogenic factors into the cytoplasm, such as cytochrome c and apoptosis inducing factor (AIF), or by containing preforms of death-inducing cysteine proteases referred to as caspases.[11]

The present study was designed to assess the blood lead levels and evaluate gene expression of ER stress, mitochondrial functioning, and apoptosis in samples of occupationally exposed workers (painters and battery workers) and establish their association between gene expression analysis and lead exposure at their work place.

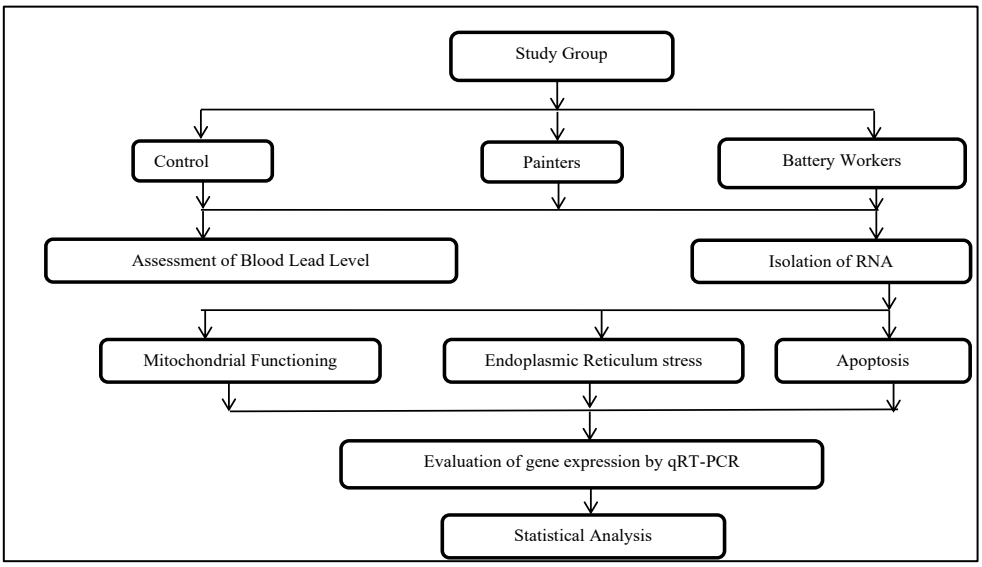

Figure 1: Study design.

METHODS

Study population

In this case-control study, 260 individuals were enrolled and divided into two groups: 1) occupationally exposed workers, (painters n=60, and battery workers n=70) (n=130) and age between 20-60 years with at least for more than 2 years of lead exposure. 2) Control group, composed of 130 subjects of comparable age matched between 20-60 years. The Institutional Ethics Committee of King George medical university Lucknow has approved the study (Ref. code: 113th ECM llB-PhD/P6) from December 2021 to December 2024. Study participants provided written informed consent to take a part in this study**.** A detailed study questionnaire, consisting of demographic and clinical information which included age, occupation, duration of occupation, eating habits like vegetarian, non-vegetarian, smokers, non-smokers, alcoholics, non-alcoholics, and previous health history was filled as for the inclusion and exclusion criteria. To ensure a fair and balanced trial and avoid biases, this study excludes those participants who had a history of chronic illness like immunological disorders, cardiovascular disease, diabetes, cancer, or recent infection.

Sample collection, preparation and storage

Five ml venous blood was collected from each subject in EDTA **(**Ethylenediamine tetra acetic acid) vials. Whole blood was used for estimation of lead level and whole blood stored in trizol for isolation of RNA. Samples were stored at -20^{0}C till imminent use.

Estimation blood lead level

Inductively coupled plasma-mass spectrometry (ICPMS, NexIon 2000) was used to measure the levels of lead in the blood after microwave digestion. The working calibration standards were prepared from stock lead solution of concentration 1000 ppm and diluted in 0.2% nitric acid. The calibration curve was prepared by different working standards as necessary. Following the digestion procedure, the reaction was carried out using one blank sample in each set simultaneously and the findings were reported as µg/dl for lead levels.

Microwave digestion

Microwave digestion system (Titan MPS, Perkin Elmer) was used to digest the blood samples included direct temperature control (DTC^{TM}), a temperature measurement system that allows the temperature of the sample in all vessel to be quickly determined and regulated and also equipped with direct pressure control (DPC^{TM}) , a contact free pressure monitoring system for a single reference vessels (standard 75 ml vessel 0….40 bar and high pressure 100 ml vessel 0…100 bar, vessels made of a TFM^{TM} pressure vessel body with TFM^{TM} cap). Before being pipetted, samples were liquefied and then mixed by vortexing for two minutes. After that, the samples were transferred into a closed vessel for the process of acid digestion. The reaction mixture was used blood sample 0.5 ml and Nitric acid 5 ml (Trace metal grade, thermo fisher scientific) in the vessel for microwave digestion. Once the vessels had sufficiently cooled, the clear solution that had been obtained during the acid digestion was stored in new tubes, total volume prepared up to 25 ml using Milli- Q (Triple distilled water) for the analysis of blood lead level.

RNA extraction and synthesis of cDNA

Total ribonucleic acid (RNA) was isolated from whole blood by using the organic extraction method. The quantity and purity of extracted RNA was determined by using nanodrop (Thermo scientific nanodrop 2000 spectrophotometer) and extracted RNA was converted to Complementary DNA (cDNA). cDNA was synthesized using protocol provided by manufacturer of High-capacity cDNA first strand reverse transcription kit from applied biosystems following reaction mixture preparation: 2× RT master mix was prepared by the components provided by the commercially available kit mentioned above before preparing the reaction tube. 10X RT buffer 2.0 µL, 25X dNTP mix (100 mM) 0.8 µL, 10x RT random primers 2.0 µL, multi scribe™ reverse transcriptase 1.0 µL, nuclease-free H_2O 4.2 µL. 10 µL of 2X RT master mix was pipetted into each individual tube. Then RNA sample 10 µl was pipetted into each tube to make up final volume 20 µL. The samples were run on thermo cycler at the following condition: 1 step at 25°C for 10 min, 2 step 37°C for 120 min, step 3 at 85°C 5 min and step 4 was holding time for infinite (∞) that was prescribed in the protocol.

Expression analysis by quantitative real-time PCR (qPCR)

In an applied biosystems 7500 fast real-time PCR System (Applied BiosystemsTM, USA), quantitative polymerase chain reaction was carried out using cDNA as a template, forward and reverse primers (given in Table 1), and SYBR Green in the TB Green Advantage® qPCR Premix (Takara Bio, Inc.). The 25 µl was the reaction volume, and the conditions were denaturation at 95^{0}C for 10 seconds x 40 cycles, 95^{0}C 05 seconds, 60^{0}C 20 seconds, and dissociation curve 95^{0}C 60 seconds, 55^{0}C 30 seconds and 95^{0}C 30 seconds, with GAPDH acting as an internal reference, the mRNA expression was normalized. In order to understand the data, fold change (2-ΔΔCT) expression values were computed using the CT values of each sample for each gene, including housekeeping. The Ct values of each housekeeping gene and mRNA were used to evaluate the data and determine fold change (2-ΔΔCT) expression values. In this work, the comparative Ct method (2-ΔΔCT) was employed, where ΔΔCT is the difference between ΔCT and the ΔCT calibrator value used to calculate it.

Table 1: Represent forward and reverse primer of selected genes.

Gene	Forward primer	Reverse primer
GRP-78 (HSPA-5)	GTCATCATCGCAGCATCTTTC	GTGTGACCTTGTTGCTCATATTC
PERK (EIF2AK3)	TATGGGAGTGAGGGTAGGTAAG	TCTGTGCCTCTTGCTGTTT
PINK1	AGAGCTGAAACCGCAGTAAA	CCCTAAGAACCCTTGTGTATCC
PARK7	ATCTTGGCTCATTTCGGTCTC	CGCATCTGTAGTCTCAGCTATTT
BAX	CCCACCTTCCTAAATGTCTGTC	TCCACCGCACACTAAAGATAAG
P53 (TP53)	ATAGCAGGGTTGCAGGTTAC	GGACTTAGACATCTGTGGGTTT
Bcl-2	TTAGTGACCTTGCAGCTTCTTT	GTCGTCACAGTTCCCAGTTTAG
c-Myc (MYC)	GGCTGGATACCTTTCCCATTT	GTGATGAGCTCCCAAATCTCTC
GAPDH	AGCTCACTGGCATGGCCTTC	CGCCTGCTTCACCACCTTCT

Statistical analysis

The obtained data was analyzed by using IBM SPSS software version 23. The chi-square test (χ^2 test) used to assess the relationship between two categorical variables. Graph Pad prism software 5.0 version also used. The Mann Whitney U test was applied for the analysis of non-parametric data and the Kolmogorov test of normality was

used to ensure that the data was normal. The Tukey post hoc HSD (Honestly significant difference) used to perform pairwise comparisons between groups. The unpaired t test compares the means of two different and independent groups in a dataset to determine significant difference between them. The $p<0.05$ was considered statistically significant for all tests.

RESULTS

Demographic characteristics

The demographic characteristics of occupationally exposed workers (painters and battery workers) and controls subjects were summarized by the age, gender, use of protective measures, smoking habits, dietary habits, alcohol consumption and previous health history. Age distributions similar among groups with no significant differences. Gender distribution showed notably significant differences across the group and females only present in the control and battery workers groups. The use of protective measures showed a highly significant difference. Regarding smoking habits, there were significant differences in groups. Dietary habits did not significantly differ among groups. Alcohol consumption showed notable changes amongst the group. On basis of previous health history, it is found that painters and battery workers were not suffering from any chronic illnesses.

Table 2: Demographic characteristic of the study subjects.

Demographic variables		Control		Painters		Battery workers		Significance	
		N	%	N	%	N	%	χ^2 test	P value
Age (in years)	20-30	27	20.8	15	25.0	15	21.4	0.98	0.987
	30-40	43	33.1	17	28.3	22	31.4		
	40-50	36	27.7	17	28.3	18	25.7		
	50-60	24	18.5	11	18.3	15	21.4		
Gender	Male	98	75.4	60	100.0	44	62.9	26.52	<0.001
	Female	32	24.6	0	0.0	26	37.1		
Use of protective measures	No	25	19.2	55	91.7	62	88.6	131.50	<0.001
	Yes	105	80.8	5	8.3	8	11.4		
Smoking habit	Non-smoker	110	84.6	20	33.3	9	12.9	106.90	<0.001
	Smoker	20	15.4	40	66.7	61	87.1		
Dietary habit	Vegetarian	87	66.9	33	55.0	41	58.6	2.93	0.231
	Non-vegetarian	43	33.1	27	45.0	29	41.4		
Alcohol	Non-alcoholic	116	89.2	31	51.7	23	32.9	70.37	<0.001
	Alcoholic	14	10.8	29	48.3	47	67.1		
Previous health history	No	130	100.0	60	100.0	70	100.0	NA	NA
	Yes	0	0.0	0	0.0	0	0.0		

*χ^2: Chi-square test, $p<0.001$, statistically significant

Blood lead level in painters and battery workers

Results of the study showed that blood lead level in painters and battery workers were significantly high ($p<0.001$) as compared to controls. The lead level found in painters, battery workers and control-41.37±20.71 µg/dl, 56.25±17.66 and 6.55±2.02 µg/dl respectively (Figure 2).

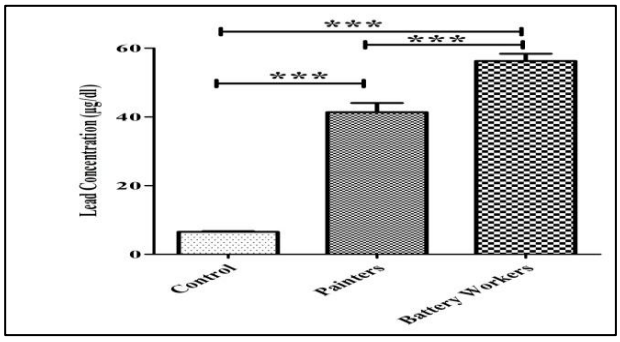

Figure 2: Blood lead level in painters, battery workers and control group.

***p<0.001 considered as statistically significant.

Quantitative expression analysis of ER stress, mitochondrial functioning and apoptosis genes

The expression levels of selected genes of ER stress such as GRP-78 were significantly up regulated with 0.354-fold and 6.621-fold increases in painters and battery workers respectively. Likewise, the gene expression of PERK was significantly up regulated with 2.750 -fold and 6.139 -fold in the painters and battery workers respectively (Figure 3). Mitochondrial genes PINK1 showed significantly up-regulated with 1.418-fold and 8.355-fold increases in painters and battery workers respectively and PARK7 genes of mitochondria also found up-regulated in painters and battery workers with 1.426-fold and 7.760-fold change respectively (Figure 4).

The expression level of pro-apoptotic genes Bax was found significantly up-regulated with 2.859 -fold and 10.130-fold in painters and battery workers respectively and p53 expression was also found significantly up-regulated in painters and battery workers with 0.896 -fold and 6.686 -fold respectively. On the contrary expression

analysis of anti-apoptotic genes, Bcl-2 was found significantly down-regulated with 2.259-fold and 9.233-fold in painters and battery workers respectively. Similarly, the expression of c-Myc was also found down-regulated with 2.956 -fold and 10.274 -fold in painters and battery workers respectively (Figure 5).

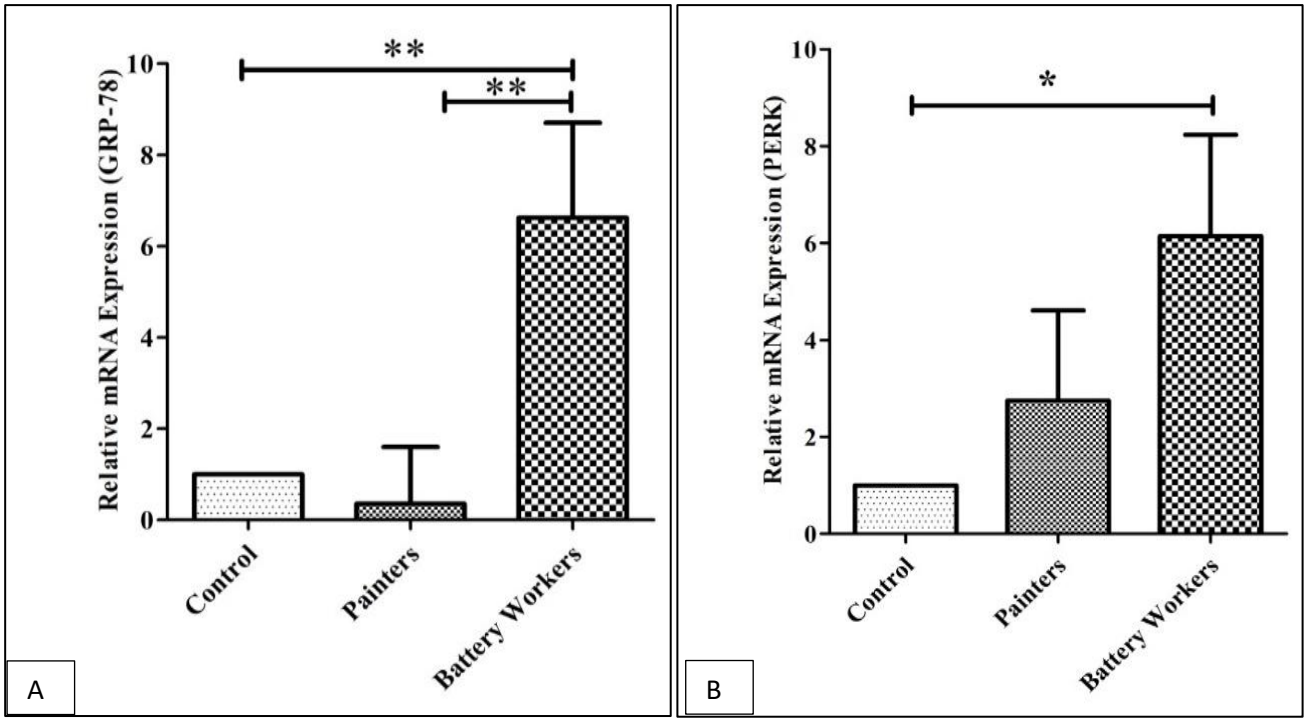

Figure 3 (A and B): Expression analysis of ER gene (A)-GRP-78 (HSPA5) and (B)-PERK (EIF2AK3) in painters and battery workers.

*p<0.05 significant, ** p<0.001 statistically significant.

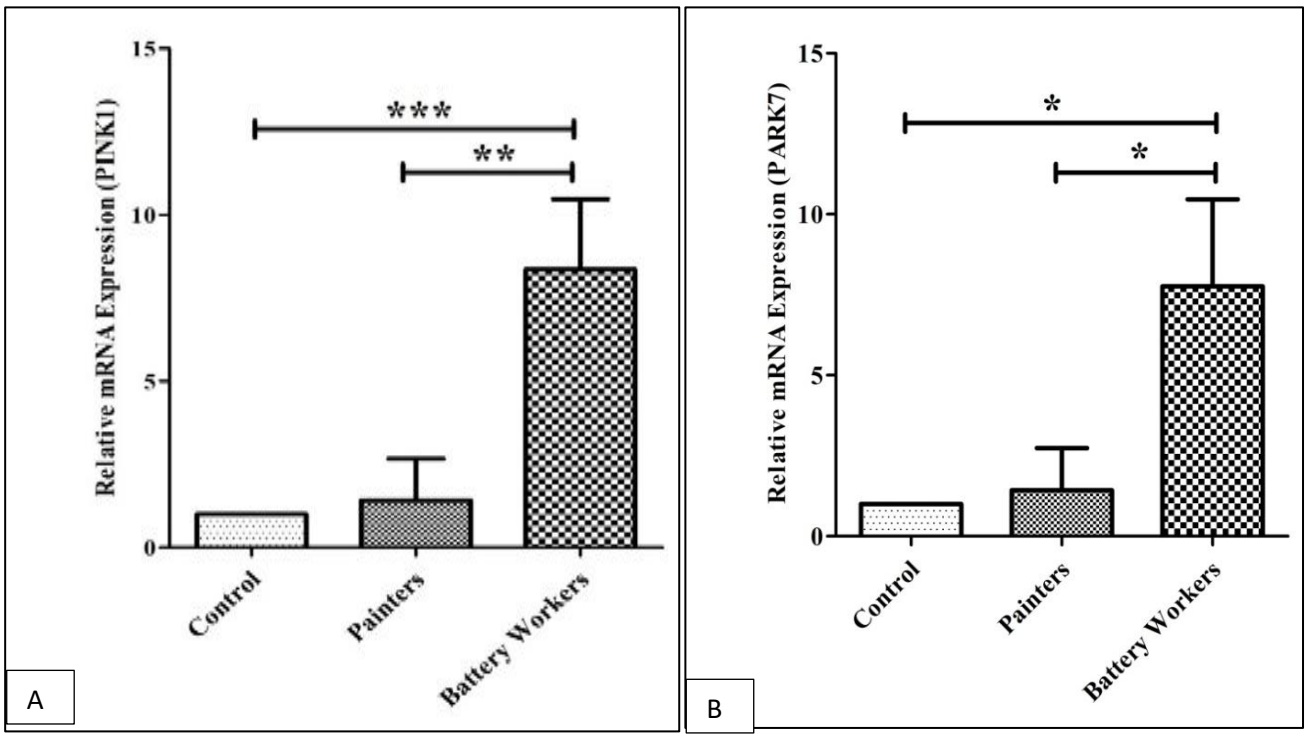

Figure 4 (A and B): Quantitative expression of mitochondrial genes (A)-PINK1 and (B)-PARK7 in painters and battery workers.

*p<0.05 significant, **p<0.001 statistically significant, ***p<0.0001 highly statistically significant.

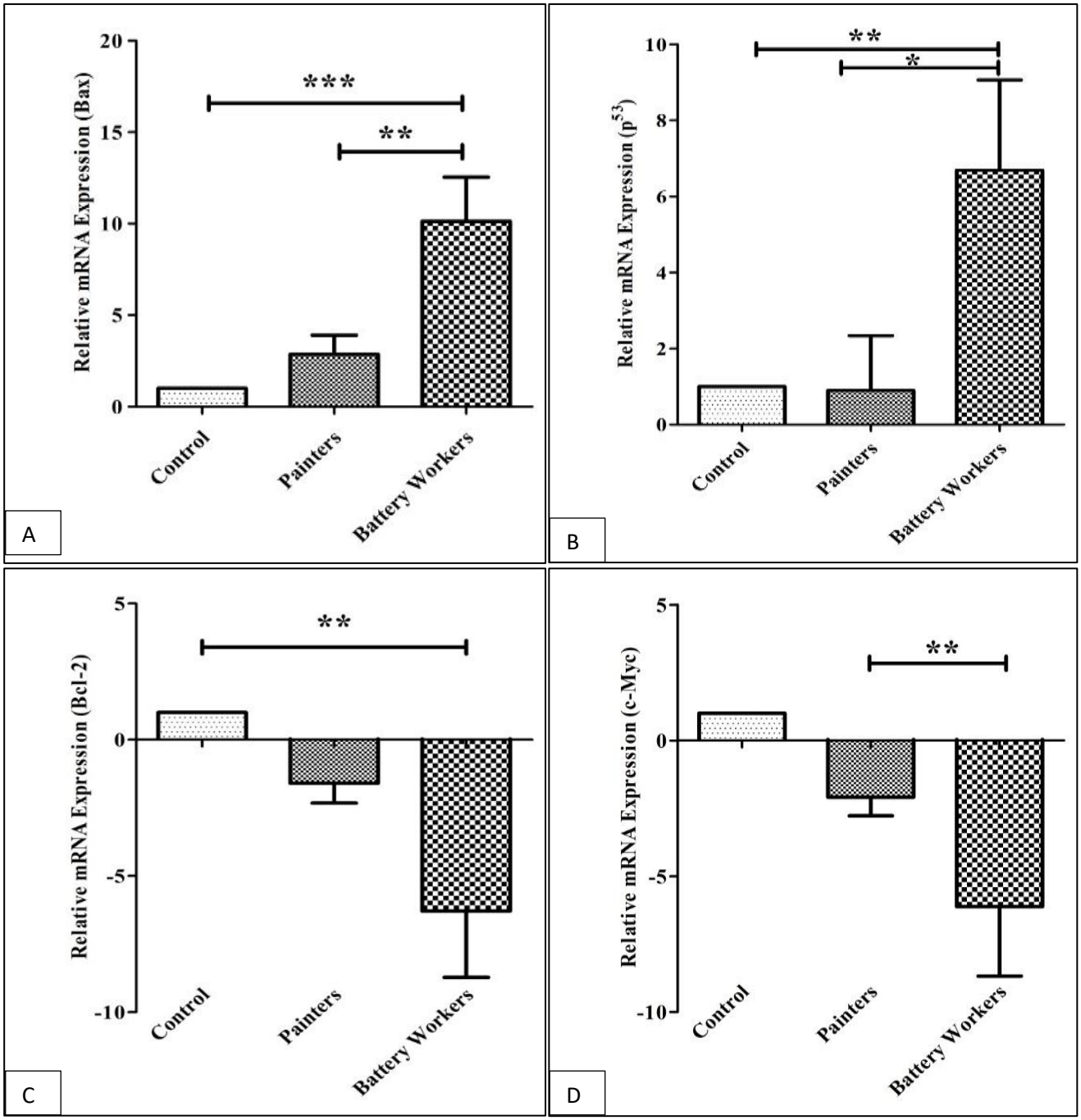

Figure 5 (A-D): Relative mRNA expression of apoptosis (both pro and anti-apoptotic genes) (A)-Bax, (B)-p53 (TP53), (C)- Bcl-2 and (D)-c-Myc (MYC) in painters and battery workers.

*p<0.05 significant, **p<0.001 statistically significant, ***p<0.0001 highly statistically significant

DISCUSSION

Lead is a widely used hazardous heavy metal. It has the potential to interfere with cellular and molecular functions of the cell. It inhibits the Na-K ATPase pump on the cell membrane, as well as vitamin D metabolism, heme synthesis, oxidative phosphorylation, and calcium uptake and metabolism. Lead binds to sulfhydryl (SH) groups, altering the structure and function of specific proteins and enzymes.[3]

Present study demonstrated that lead exposure was significantly different in painters, battery workers and controls group. Lead levels were substantially higher in painters 41.37±20.71µg/dl and 56.25±17.66 µg/dl in battery workers when compared with the controls 6.55±2.02 µg/dl. The findings of the current study are consistent with our previous report, Khan et al in which we reported that painters had higher blood lead levels than controls 21.56±6.43 µg/dl 2.84±0.96 µg/dl respectively.[12] A study by Goyal et al revealed the mean blood Lead level

of those employed in the welding and metal crafts sectors as 7.97±1.92 µg/dl which is still significantly high when compared to those who were not exposed.[13] Another study by Himani et al reported blood lead levels as 39.5±31.9 µg/dl in battery workers of Delhi-NCR region.[14] Similarly, in Andhra Pradesh, higher blood lead levels 25.26±2.121 µg/dl were reported by Singamsetty et al in battery workers.[15] The majority of lead is transported by erythrocytes after being absorbed into the bloodstream. The lead is freely diffusible in plasma component which is widely dispersed across several tissues, with notable quantities found in bone, teeth, liver, lungs, kidneys, brain, and spleen due to slow elimination rate it can accumulate in these organs and eventually cause multisystem toxicity, even at extremely low exposure levels.[16]

Furthermore, we had performed gene expression analysis of ER stress genes like GRP78 and PERK. Gene GRP78 was found to be significantly up regulated in painters and battery workers when compared with control. Similarly, PERK gene was also found up regulated in painters and battery workers when compared to the controls. Earlier Han et al reported alterations in ER stress related genes. Lead exposure significantly elevated the expression of GRP78 and PERK pathway genes related to ER stress.[17] A study by Su et al in lead exposed pheochromocytoma (PC12) cell line reported higher GRP-78 protein expression than that of the control group.[18] Another study by Sui et al showed that the expression of GRP-78 increased dramatically in does dependent manner 1, 10, and 100 nM in response to lead concentrations in mice. To validate lead toxicity in mice cardio fibroblasts, the levels of unfolded protein response (UPR) such as GRP94, GRP78 and peIF2α were also evaluated in lead exposure. It has been reported that GRP78 protein expression rise dramatically for up to 12 hours, with maximal increases of 3.44-fold when compared to controls.[19] Another study found that Lead can cause ER stress in chicken kidneys as measured by the level of the GRP78 protein, which is an ER stress marker. It has been reported that after lead exposure, GRP78 expression in mouse kidneys significantly increases.[20] ER is the place where membrane and secretory proteins fold in the cell. Physiological events that disrupt protein folding in the ER may induce ER stress and activate a complex of signaling pathways known as the UPR.[21] Through up regulating chaperones and inhibiting global protein synthesis, the UPR can improve cellular repair and long-term survival by lowering the load of unfolded proteins. Lead, a hazardous metal, can significantly increase the ER stress, impairing ER structure and function, and affecting the other cellular processes.[21]

Moreover, we observed PARK-7 and PINK-1gene expression analysis for mitochondrial functioning. Mitochondrial gene like PARK-7 was found to be up regulated in painters and battery workers as compared to controls. Likewise, PINK-1 gene was also found to be significantly up regulated in painters and battery workers when compared with the control.

Furthermore, we have performed gene expression analysis of apoptotic and anti-apoptotic genes. Our study reports, up regulated expression of pro apoptotic gene like Bax and p53 in painters and battery workers as compared to control. Results of our study are consistent with other research in animal model and cell line with lead induced toxicity. The expression levels of Bax, caspase-3, caspase-8, Bcl-2, Fas, and p53 were reported in a study by Zheng et al on-tiger fibroblasts treated with lead. The expression of pro apoptotic genes Bax, and p53 was found increased with increasing lead concentrations.[22] Another study by Xu et al showed the effect of lead on the p53, Bax, and Bcl-2 gene expressions in mouse liver. Following four weeks treated with 10, 50, and 100 mg/kg BW of lead acetate, p53 expression increased at the level of 10 mg/kg dosage.[23] Park et al reported that, BAX levels were significantly up regulated in high concentration of lead, whereas, p53 was up regulated in a dose-dependent manner when exposed to lead as compared with controls.[24] Another study by Yin et al reported increased mRNA expression in BAX and p53 genes in lead treated group when compared to the control group in chickens.[25]

On the contrary, in our study anti-apoptotic genes like Bcl-2 and c-Myc expression were significantly down regulated in battery workers and painters when compared with control. Previous research by Yin et al in animal model reported decreased expression of Bcl-2 gene in the lead exposed group when compared to controls.[25] Similarly, Zheng et al reported decreased expression of Bcl-2 gene when the Lead concentration increased in tiger fibroblast cell.[22] Another study by Restanty et al showed that the lead decreases the Bcl2 gene expression analysis in granulose cells antral follicle of female Wistar rats.[8] Moreover, it has been reported that lead contamination may be a serious health concern on various organ systems in the body, including the neurological system, gastrointestinal system, kidneys, hematological system, reproductive system, cardiovascular system, endocrine system, immune system, and the central nervous system.[26]

CONCLUSION

The present study demonstrated increased blood lead level and the up regulated expression of ER genes and the mitochondrial functioning genes. The apoptotic genes were also found up regulated, which is contrary to the expression of anti-apoptotic genes which were found down regulated in painters and battery worker when compared with control. Finding of the study and previous study showed that it may alter the homeostasis of the cell and further lead to effect on body organ and cause system toxicity. Thus, the conclusions from our study can be used as a starting point to develop more specific recommendations for enhancing workplace safety and reducing lead exposure of workers in the workplace. Workers exposed to lead should be screened periodically and informed about the harmful effects of lead exposure and the significance to taking preventive measures promptly. As far as we are aware, this was an innovative

study demonstrating lead exposure along with gene expression analysis in occupationally exposed painters and battery workers.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee King George's Medical University ((Ref. Code: 113th ECM llB-PhD/P6).

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