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The Genetic and Physiological Alteration in Welders Exposed to Welding Fumes

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Abstract

Background: Due to the variable effects of welding fumes, welders who are exposed to metal fumes during welding may acquire a number of dangers, some of which may result in genetic defects and illnesses.

Objective: Our research attempts to elucidate the consequences of metal vapours on the physiologic and genetic fronts.

Methods: Blood and hair sampling were conducted on 50 welder and 20 non-welders, from Anbar governorate, blood was collected from peripheral blood for physiological analysis, and hair was collected and preserved to measure heavy metals concentration.

Results: Genetic analysis showed a present SNP in the site rs1972619149, whereas all welders and non-welders appeared to have the mutant type allele (C) as dominant, while site rs201595223 didn't show any SNP, and all welders and non-welders appeared to have the wild type allele (C) as dominant.

The WBC mean value of the welders categorised by working duration (7.326±0.636 - 8.42±1.694 109/L) and age ranging (7.645±0.959 - 8.08±1.399 109/L) were both substantially higher than that of the non-welder group (6.45±0.378 109/L). The PLT mean value of welders categorised by working period (221.714±25.241 - 263.5±17.512 109/L) and age ranges (217.529±15.947 - 245.846±17.915 109/L) was much lower than the non-welder group (250.5±14.07 109/L). The Mn mean value varied between 0.225±0.139 and 0.722±0.378 mg/Kg for welders categorised by age and between 0.205±0.098 and 0.644±0.408 mg/Kg for welders grouped by working period. The Cd mean value of welders categorised by working duration (1.618±0.684 - 4.466±2.513 mg/Kg) and age (1.618±0.421 - 2.344±0.834 mg/Kg) was substantially greater than that of the non-welder group (0.452±0.052). In comparison to the non-welder group (2.3±0.075 mg/Kg), the Mg mean value of welders categorised by age ranged (2.043±0.127 - 2.276±0.049 mg/Kg) and ranged (2.042±0.125 - 2.226±0.058 mg/Kg) in welders grouped by working duration.

Conclusions: According to our research, the XRCC1 gene is susceptible to a wide range of substances, particularly heavy metals, which may result in low- to moderate-level alterations that are deemed harmful. Furthermore, we propose that elevated WBC, reduced PLT count, and elevated Mg levels are caused by elevated levels of Mn and Cd. Additional research is required to determine the precise mechanism by which welding fumes affect human health.

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Introduction

Welding is considered one of the oldest occupations, historians think it began amid the bronze ages by joining more than two metals together using heat and high pressure (Grill, 2023). Welding fumes are mainly consisted of metal oxides (CCOHS, 2023), and particulate matter is generated by reaching the melting point of all metals included in the process, thus the fumes are formed and then vaporized into suspended solids which are mainly consisted of molten welding electrode and metal alloy (Taube, 2013). XRCC1 is a repair gene that primarily employs the base excision repair (BER) mechanism (Hanssen-Bauer et al., 2012). Through its NH2- and COOH-terminal regions, the XRCC1 protein serves as a scaffold for other repair enzymes, including POLβ, APE1, hOGG1, and DNA ligase 3 (Sterpone & Cozzi, 2010). Every single nucleotide polymorphism (SNP) on the XRCC1 gene influences the expression of the gene, which lowers the efficiency of XRCC1 protein repair. For instance, the SNP in 399 codons in the BRCT region of the XRCC1 protein may cause an incomplete repair when it interacts with Poly-(ADP-ribose) polymerase (PARP). The BRCT1 area is crucial for the repair of single strand breaks (SSBs), although the 399 SNP had no discernible impact on XRCC1 function. Conversely, the SNP located on the tenth exon altered the secondary structure of the protein, indicating that more research is necessary to fully comprehend the impact of SNP on the functioning of the XRCC1 protein (Sterpone & Cozzi, 2010).

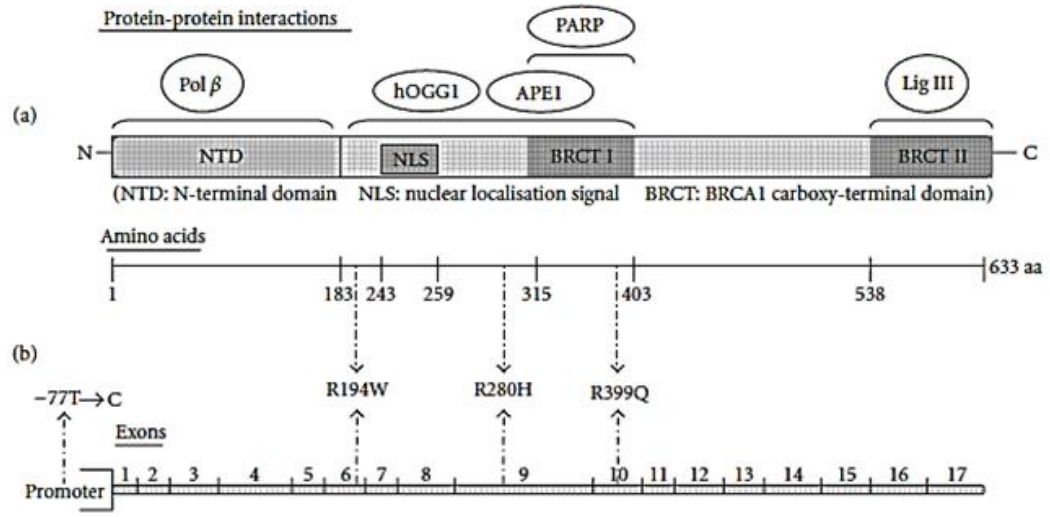

Figure 1: Human XRCC1 protein and gene structure. (a) The diagram shows XRCC1 domains and the regions of interaction with other components of BER. (b) The diagram shows the structure of the gene with the most common and studied single nucleotide polymorphisms (SNPs).(Sterpone & Cozzi, 2010)

Lung, kidney, blood, and lymph malignancies may result from welding fume exposure, suggesting that welding fumes can cause genotoxicity including chromosome aberration, dysregulated sister chromatid exchange, and a high frequency of micronuclei (IARC, 2018). Studies reveal that welders who are exposed to welding fumes have higher levels of iron, manganese, chromium, and lead than non-welders. These results are consistent with the composition of welding electrodes, which is thought to be a dangerous source of heavy metals. In contrast, welders have higher levels of iron than non-welders, which can cause serious tissue damage that can result in fibrosis (Mumby et al., 2011). Further research (Reismala et al., 2015; Gil et al., 2011) revealed that welders had greater levels of chromium than control groups. Chromium, a polyvalent heavy metal with the poisonous form Cr+6, is one of the heavy metals that leaked during the welding process.

In contrast, Cr+3 may enter the body regularly via food and drink. The fact that Cr+6 may cross the cell membrane even more readily than Cr+3 makes it more hazardous (Reismala et al., 2015). Regarding aluminum, research revealed a clear distinction between welders and non-welders due to its ability to be tested in blood, bones, urine, and stool; nevertheless, there is insufficient data to establish a correlation between levels of aluminum exposure and blood and urine aluminum levels (ATSDR, 2008). Nikel cannot be metabolized and would be eliminated with urine, but it may build up within lung tissue and be absorbed into the bloodstream (ATSDR, 2005). Research has shown that exposure to lead, whether short- or long-term, may have negative effects on the immune system and trigger a variety of immunological responses, including autoimmunity, inflammatory disorders, and anaphylaxis (Mitra et al., 2022). However, the inflammatory tests shown that the capacity of phagocytes and natural killer are lowered after exposure. Cadmium exposure has also been discovered to have an inhibitory impact on the immune system, and even minimal exposure may cause a severe immunological response (Cuneo et al., 2010).

Materials and Methods

Study Design

The investigation was carried out while the welders were at work. There were fifty welders and twenty controls. The workers mostly used carbon steel electrodes to weld mild steel, and the controls were medical facility secretaries. The enrolment was carried out in 2022, Welders went through a quick survey about (age, accumulated work period, marriage and children status , and smoking habits) On the same day of the questionnaire, blood sampling was performed during worktime, also hair was collected from welders to analyze heavy metals concentration.

Ethic Statement

The research was authorized by Anbar University's regional ethics council, and all subjects provided written, informed permission to participate.

Genetic Analysis

The Genetic analysis was conducted using the TETRA-ARMS PCR method on two SNPs (rs1972619149), (rs201595223), after extracting DNA from whole blood, for both welders and non-welders.

Hematological Measurements

The same day that the blood was drawn, measurements were made. Participants' blood was drawn using a standard 5-milliliter disposable syringe into two-milliliter plain tubes and three-milliliter EDTA tubes. The blood was then analyzed using an automated hematology analyzer (CBC) to determine the WBC count and WBC differentials.

Heavy Metals and Minerals Measurements

Measurements of Heavy metals were performed after a week of samples collection, hair was preserved in a glass screw tube until then, samples were digested first and measured using Atomic Absorption spectrophotometer (AAS), Cadmium (Cd) and Manganese (Mn) concentration tests was performed on the samples using AAS , while Calcium (Ca) and Magnesium (Mg) concentrations were measured using Fujifilm chemical analyzer, and Zinc (Zn) concentration was measured using semi auto spectrophotometer.

Statistical analysis

The statistical analyses were conducted using SPSS 21.0 (SPSS Inc, Chicago, IL, USA) with a one-tailed significance level of $P<0.05$ and a 95% confidence interval (CI).

Results

Welders were distributed into two groups, the first one was based on Age (18-32), (33-47), (48-60) years old, the second one was based on working period (1-7), (8-19), (20-40) Years.

The Genetic analysis results for the site (rs1972619149) table (1), photo (1) showed that there's a SNP at the sample level, the mutant type (C allele, 188 BP) showed a significant appearance in every welder and control sample, while the wild type (G allele, 144 BP) didn't appear at all. And so, it's clear for this matter that the mutant type is the dominant in the sample population.

Table 1. rs1972619149 Allele frequency

SNP:1 (rs1972619149) Genotype	Welders No.50(%)	Control No.20(%)	Welders Allele frequency	Control Allele frequency
GG	0(0%)	0(0%)	0	0
GC	0(0%)	0(0%)	-	-
CC	50(100%)	20(100%)	100	100

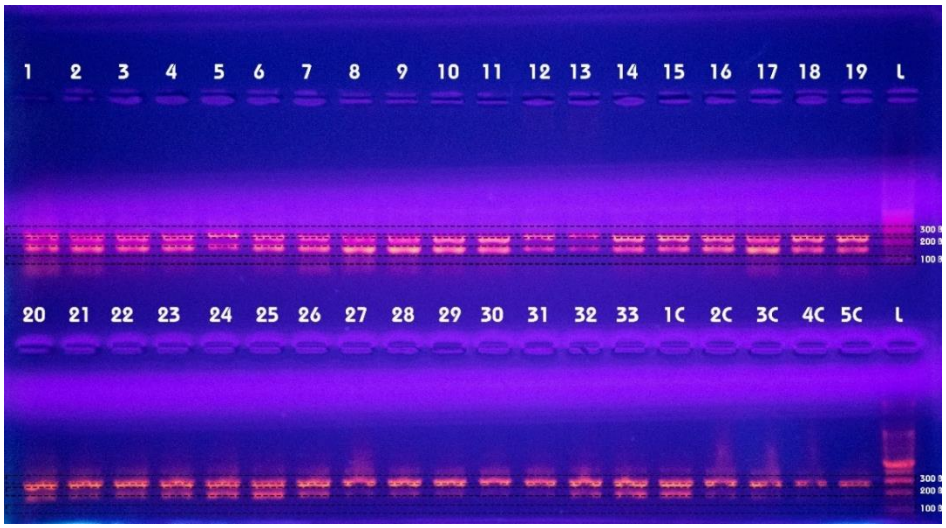

Photo 1. Electrophoresis results of the site rs1972619149 for some of the study samples

Table 2. rs201595223Allele frequency

SNP:1 (rs201595223) Genotype	Welders No.50(%)	Control No.20(%)	Welders Allele frequency	Control Allele frequency
CC	50(100%)	20(100%)	100	100
CG	0(0%)	0(0%)	-	-
GG	0(0%)	0(0%)	0	0

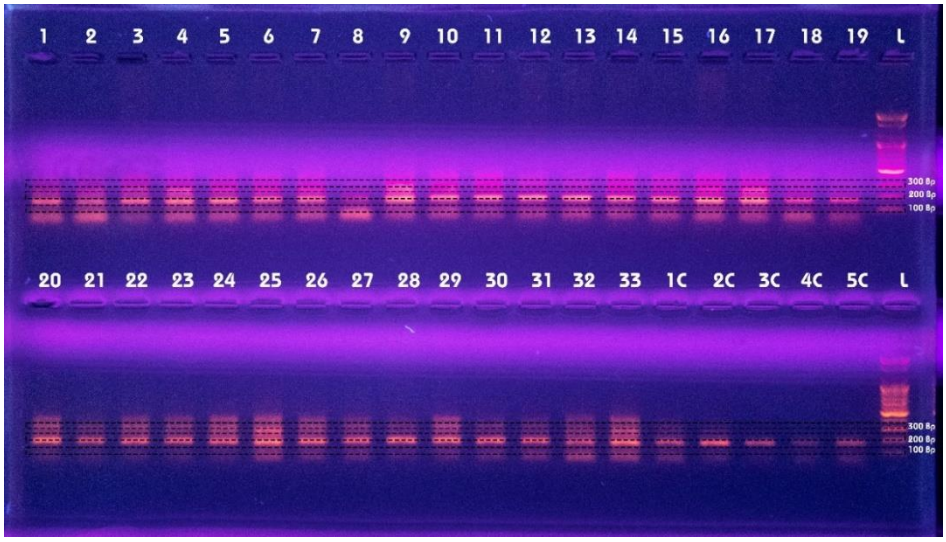

Photo 2. Electrophoresis results of the site rs201595223 for some of the study samples

While the results for the site (rs201595223) table (2), photo (2) showed that there's no SNP at all, the wild type (C allele, 189 BP) appeared in every single sample of both welders and controls, with no appearance of the mutant type (G allele, 164 BP).

Table 3. Mean and Confiecance interval of the physiological and chemical parameters to the study participants according to Age

Table 3. Mean and Confiecance interval of the physiological and chemical parameters

Parameters	18 - 32 Years No. 26		33 - 47 Years No. 17		48 - 60 Years No. 7		Control No. 20
	Mean (±CI)	p-value	Mean (±CI)	p-value	Mean (±CI)	p-value	Mean (±CI)
Ca (mg/dL)	9.319±0.136	0.463	9.371±0.19	0.308	9.329±0.357	0.463	9.31±0.137
Mg (mg/dL)	2.154±0.066	0.003	2.276±0.049	0.306	2.043±0.127	0.003	2.3±0.075
Zn (µg/dL)	137.86±14.928	0.247	158.6±28.812	0.293	136.743±35.177	0.308	148±24.471
Mn (mg/Kg)	0.242±0.135	0.007	0.225±0.139	0.016	0.722±0.378	0.007	0.058±0.016
Cd (mg/Kg)	1.618±0.421	0.001	2.136±1.119	0.005	2.344±0.834	0.003	0.452±0.052
WBC (10^9/L)	7.645±0.959	0.016	7.653±0.885	0.012	8.08±1.399	0.042	6.45±0.378
Lymph%	29.377±2.928	0.035	26.64±2.338	0.004	31.38±4.818	0.162	35.013±5.027
Mid%	6.95±0.796	0.288	7.613±0.897	0.329	7.42±1.249	0.448	7.313±0.971
Gran%	63.686±3.124	0.038	65.747±2.95	0.010	61.2±5.003	0.185	57.675±5.541
PLT (10^9/L)	256.913±14.955	0.272	217.529±15.947	0.002	219.714±23.697	0.026	250.5±14.07

As seen in Table (3), when all welders were categorised by age (18–32), (33–47), and (48–60) years old, in comparison to the non-welder group (6.45±0.378 10^9/L), the mean value of White blood cells (WBC) count in the welders' groups (7.645±0.959 10^9/L, p=0.016), (7.653±0.885 10^9/L, p=0.012), and (8.08±1.399 10^9/L, p=0.042) was substantially higher at p≤0.05. The non-welder group (57.675±5.541 10^9/L) p≤0.05 had a significantly lower mean value of granulocyte ratio% than the welder age groups (18–32 and 33–47, respectively) (63.686±3.124 %, p=0.038), (65.747±2.95 %, p=0.010), while the age group 48–60 (61.2±5.003 %, p=0.185) had a marginally significant p≤0.05. While the age group 48-60 years old (31.38±4.818 %, p=0.162) was marginally significant at p≤0.05, the mean value of the lymphocyte's ratio % in the welders' age groups 18-32 and 33-47 years old (29.377±2.928 %, p=0.035) and 26.64±2.338 %, p=0.004) was significantly lower than the non-welder group (35.013±5.027 %) at p≤0.05. The age group of 18-32 years old (245.846±17.915 %, p=0.345) was marginally significant at p≤0.05, while the mean value of Plateltes (PLT) count in the welders' age groups of 34-47 and 48-60 years old (217.529±15.947 10^9/L, p=0.002), and 219.667±28.039 10^9/L, p=0.046), was significantly lower than the non-welder group (250.5±14.07 10^9/L) p≤0.05. The average Manganese Mn Concentration in the welders' groups was notably greater than that of the non-welder group (0.058±0.016 mg/Kg) at p≤0.05, at 0.242±0.135 mg/Kg, p=0.007, 0.225±0.139 mg/Kg, p=0.016, and 0.722±0.378 mg/Kg, p=0.007). In comparison to the non-welder group (0.452±0.052 mg/Kg), the mean value of Cadmium (Cd) concentration in the welders' groups (1.618±0.421 mg/Kg, p=0.001), (2.136±1.119 mg/Kg, p=0.005), and (2.344±0.834 mg/Kg, p=0.003) was substantially greater.

Table 4. Mean and Confiecance interval of the physiological and chemical parameters to the study participants according to comulative work time

Parameters	1 - 7 Years No. 17		8 - 19 Years No. 31		Over 20 Years No. 7		Control No. 20
	Mean (±CI)	p-value	Mean (±CI)	p-value	Mean (±CI)	p-value	Mean (±CI)
Ca (mg/dL)	9.467±0.22	0.125	9.294±0.125	0.431	9.314±0.361	0.492	9.31±0.137
Mg (mg/dL)	2.142±0.074	0.003	2.226±0.058	0.067	2.043±0.127	0.003	2.3±0.075
Zn (µg/dL)	148.875±26.71	0.481	144.076±17.995	0.401	140.7±32.731	0.366	148±24.471
Mn (mg/Kg)	0.392±0.271	0.017	0.205±0.098	0.003	0.644±0.408	0.019	0.058±0.016
Cd (mg/Kg)	1.618±0.684	0.003	1.944±0.732	0.001	4.466±2.513	0.010	0.452±0.052
WBC (10^9/L)	8.344±1.797	0.037	7.326±0.636	0.013	8.42±1.694	0.042	6.45±0.378
Lymph%	26.722±5.198	0.018	29.404±2.136	0.029	27.44±4.942	0.028	35.013±5.027
Mid%	7.033±1.188	0.363	7.37±0.68	0.462	7.26±1.291	0.475	7.313±0.971
Gran%	66.278±5.225	0.019	63.226±2.39	0.043	65.3±5.382	0.037	57.675±5.541
PLT (10^9/L)	263.5±17.512	0.134	224.29±15.297	0.009	221.714±25.241	0.040	250.5±14.07

After classifying every welder according to the cumulative working time (1–7, (8–19), (20–40) Years table (4). The non-welder group's WBC count (6.45±0.378 10^9/L) was substantially lower than the welders' (8.344±1.797 10^9/L, p=0.037), 7.326±0.636, p=0.013, and 8.42±1.694 10^9/L, p=0.042) mean values. Granulocyte ratio percentages in the welder groups (66.278±5.225 %, p=0.019), (63.226±2.39 %, p=0.043), (65.3±5.382 %, p=0.037) were all considerably higher on average (57.675±5.541 %) at p≤0.05. Significantly lower than the non-welder group (35.013±5.027 %) at p≤0.05 was the mean value of the lymphocyte ratio% in the welders' groups (26.722±5.198 %, p=0.018), (29.404±2.136 %, p=0.029), and (27.44±4.942 %, p=0.028), respectively. The PLT count mean value for the welders' groups aged 8-19 and 20-40 years was found to be substantially lower at p≤0.05 than that of the non-welder group (250.5±14.07 10^9/L), while the group aged 1-7 years (263.5±17.512 10^9/L, p=0.134) was marginally significant at p≤0.05. The average Mn concentration in the welders' groups was notably greater than that of the non-welder group (0.058±0.016 mg/Kg) p≤0.05, at 0.392±0.271 mg/Kg, p=0.017, 0.205±0.098 mg/Kg, p=0.003), and 0.644±0.408 mg/Kg, p=0.019, respectively. In comparison to the non-welder group (0.452±0.052 mg/Kg) p≤0.05, the mean value of Cd concentration in the welders' groups (1.618±0.684 mg/Kg, p=0.003), (1.944±0.732 mg/Kg, p=0.001), and (4.466±2.513 mg/Kg, p=0.010) was considerably greater.

Comparing other WBC cells (mid%) to non-welders, no discernible differences seemed to exist. Additionally, there was no significant difference found in blood metals and minerals (Ca, Zn) (mg/dL) between welders and non-welders, with the exception of magnesium (Mg), which was statistically significant at p≤0.05 in the age groups of 18–32 (2.154±0.066 mg/dL, p= 0.003) and 47–60 (2.043±0.127 mg/dL, p= 0.003), as well as in the working period groups of 1–7 (2.142±0.074 mg/dL, p= 0.003) and 20–40 years (2.042±0.125 mg/dL, p= 0.003). In these groups, the levels of magnesium were significantly lower than those of the non-welder group (2.3±0.075 mg/dL). In contrast to the non-weaker group, the age group 33–47 (2.276±0.049 mg/dL, p=0.306) and working time group (2.226±0.058 mg/dL, p=0.067) showed marginal significance.

Discussion

It is well known that polymorphism, which is primarily responsible for phenotypic changes, and the presence of variable alleles in repair genes can affect the efficiency of the repair mechanism. This, in turn, affects how repair proteins react to different internal and external agents that affect DNA at the tissue and cellular levels. Moreover, raising the likelihood of getting different types of cancer. (Sterpone & Cozzi, 2010). Furthermore, via its interaction with repair enzymes, SSB repair is recognised to constitute the primary mechanism of XRCC1 (Cuneo & London, 2010). Additionally, when mutations cause XRCC1 to become inactive, PARP becomes overactive, which hinders the repair proteins' ability to reach the damage site and results in an incomplete repair process. This phenomenon primarily affects the cerebellum, despite research showing that XRCC1 is highly expressed throughout the brain, particularly in the cerebellum (Ahmed et al., 2009). According to a different research, infertility, sensory neuropathy, and cerebellar ataxia may all result from a homozygous mutation in XRCC1.

The findings of the blood parameters also revealed a normal monocyte ratio but an elevated WBC count, granulocyte ratio, and lymphocyte ratio. Research has indicated a correlation between iron overload and a decreased lymphocyte ratio. This is attributed to the deleterious effects of certain biochemical products that arise from iron overload on the immune system, such as the depletion of CD4+ T lymphocytes due to their shortened cell life, which also impairs the phagocytic activity of CD8+ and CD28- T lymphocytes, leading to the death of polymorphonuclear leukocytes and monocytes, and changes in the production and function of macrophage cytokines (Wang et al., 2009; Nairz et al., 2014). Additionally, research revealed that NTBI inhibits the proliferation of lymphocytes by

increasing their absorption of iron. According to Pahl et al. (2015), this phenomena might help to explain why iron-overloaded workers' humoral immune systems are impaired.

According to one research (Huang et al., 2022), there is clinical evidence of a relationship between raised eosinophil count and cadmium (Cd), suggesting that Cd may play a role in allergic reactions that are linked to elevated proinflammatory mediator levels (Paniagua et al., 2019).

According to Wu et al.'s research from 2021, manganese exposure has been linked to immune system function. Unlike iron, manganese has two roles in modulating redox oxidation state, and the part it plays varies on its quantity. The host used Mn-SOD to combat oxidative damage, but innate immunity, exemplified by monocytes and neutrophils, secretes calprotectin to chelate manganese and restrict its levels in the body. Nutritional immunity is the term for this two-pronged approach (Hood et al., 2012). Pharmaceutical strategy design has a new orientation because to this mechanism. Manganese metabolism may be targeted to treat inflammatory diseases, viral infections, and cancer by enhancing the effects of tumour immunotherapy. It appears that manganese effectively enhances the inflammatory response and improves the innate immunity, affecting the T lymphocytes' signalling factors (Wu et al., 2021). According to previous research (Andjelkovic et al., 2019), welders with high lead exposure had low PLT counts. Our analysis likewise reveals a lower PLT count, which may be the effect of welding fumes heavy metal exposure. Because calcium is a key second messenger in platelet activation, lead chemically competes with calcium on its active binding sites and replaces it (Sauk et al., 1991). This has a variety of negative effects on the body's mechanisms, including the mechanism responsible for producing platelets (Dean 2010). According to Zhao et al.'s 2022 research, cadmium negatively impacts rat megakaryocytes. According to the research, exposure to cadmium reduced platelet counts but had no impact on red blood cell counts. This suggests that cadmium only affects megakaryocytopoiesis and has no negative effects on erythropoiesis (Zhang et al., 2016; Zhao et al., 2018). However, it is difficult to draw direct parallels since all of these findings were based on brief exposure.

The study's findings indicate that welders' PLT counts were lower than those of controls. This could be because welding fumes contain heavy metals, such as cadmium (Cd) (Zhao et al., 2022). Cadmium affects mice's megakaryocyte cells, which lowers PLT counts but has no effect on RBC counts, suggesting that cadmium affects megakaryocytopoiesis but not erythropoiesis (Zhang et al., 2016). Lead is another heavy metal that is undoubtedly present in welding fumes. A study (Andjelkovic et al., 2019) found that exposed individuals had a decreased PLT count, which is consistent with the findings of our study. Lead replaces calcium on its active binding sites, competing with it and changing a variety of biological activities (Rădulescu & Lundgren, 2019), including PLT count because calcium is a key second messenger in the activation of platelets (Dean, 2010).

Because welders are continuously exposed to welding fumes, the findings of the heavy metals analysis indicated that welders had greater concentrations of Mn and Cd than non-welders. According to studies (Keen et al., 2013), there are a number of different reasons why Mn can be toxic, including oxidative damage, endocrine gland defects, negative effects on iron and calcium metabolism, and changes in mitochondrial activity brought on by Mn's inhibitory role on the mitochondrial respiratory chain (Zhang et al., 2003). Magnesium may cause neurotoxicity by affecting glial cell activity. Moreover, Mn toxicity may persist long after exposure is stopped, resulting in additional harm such protein aggregation and inflammation. Research has also shown that inhaling Mn may cause a variety of inflammatory reactions, such as WBC and phagocytes infiltrating the injured tissues. (2012) Williams et al.

However, research (Rafati Rahimzadeh et al., 2017) revealed that exposure to low concentrations of Cd may have negative effects on living things, impact cell division,

cause apoptosis by influencing DNA repair mechanisms both directly and indirectly, and produce reactive oxygen species (Rani et al., 2013). According to Patrick (2003), cadmium may also block the respiratory chain, change how the mitochondria operate, and result in chromosomal aberration and mutations (Joseph et al., 2009). The toxicity of Cd is shown by its capacity to deplete antioxidants like glutathione (GSH) and to accelerate the production of reactive oxygen species (ROS) such superoxide, hydrogen peroxide, and hydroxyl radicals. According to Filipič et al. (2012), copper also inhibits other enzymatic antioxidants such manganese superoxide, catalase, and copper/zinc dismutase.

According to Brama et al. (2012), cadmium may change the activity of caspases and nitrogen-activated protein kinases (MRPKs), which can indirectly cause apoptosis. It can also change the amounts of calcium ions. According to one research, cadmium affects endothelium and contributes to sclerosis (Fagerberg et al., 2012). Additionally, it affects endothelium relaxation, which raises blood pressure (Eum et al., 2008). Furthermore, according to Lampe et al. (2008), breathing in cadmium might irritate the respiratory system. However, the ATSDR regards cadmium as one of the heavy metals that is most important in causing cancer in humans.

However, having enough magnesium can lessen the damage caused by heavy metals because magnesium induces various detoxification pathways (Speich et al., 1989). Magnesium depletion occurs when heavy metals compete with magnesium on the active sites of absorption in the small intestine and brain. Magnesium plays a critical role in heavy metal detoxification.According to a research, cadmium and magnesium may interact, disrupting the metabolism of magnesium (Matović et al., 2010). However, because of the several roles that magnesium performs in the body, additional research suggests that the likelihood of Cd replacing Mg is not well established or studied. Additionally, it implies that cadmium interferes with the absorption of magnesium, affecting magnesium homeostasis. However, according to some findings, consuming extra magnesium may lessen the negative effects of cadmium poisoning (Bulat et al., 2008, 2012).

Conclusion

Since all welders and controls had the same mutation, our study concludes that exposure to heavy metals as particulate matter in welding fumes can cause mutations in the XRCC1 gene, which may be responsible for various uncertain effects. However, since both welders and controls are exposed to the same effector but at different levels and from different sources, we suggest further research to better understand the primary cause of the mutation. Additionally, exposure to heavy metals might result in an epically granulocyte-inflated WBC count. It also affects haematological homeostasis by lowering PLT count. These results demonstrate the need for greater research to fully comprehend the harmful effects of welding fumes on modern workers and the need of taking more safety measures to lessen the negative effects of occupational exposure to fumes and particle metals.

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