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Assessment of the relationship between vascular diseases and exposure to toxic metals

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ABSTRACT

Aims: Understanding the factors in the etiology of vascular diseases is crucial for prevention. This study assesses the relationship between toxic metal exposure and vascular disease development.

Methods: Blood samples from 41 healthy volunteers and 48 cardiovascular disease patients were analyzed using inductively coupled plasma mass spectrometry (ICP-MS). The participants' health data were obtained from hospital records.

Results: ICP-MS results showed higher levels of As (5.97 µg/L), Cd (0.44 µg/L), Hg (0.48 µg/L), Pb (37.10 µg/L), Se (75.76 µg/L), Cu (1611.99 µg/L), Mn (14.55 µg/L), Co (0.14 µg/L), Mo (1.93 µg/L), and Ni (0.25 µg/L) in the experimental group. Conversely, Zn (557.0 µg/L), Cr (4.12 µg/L), and Sb (2.35 µg/L) levels were lower. Triglyceride (135.99 mg/dl), folate (8.77 ng/dl), and T3 (1.30 ng/dl) were higher, while HDL (44.13 mg/dl) was lower in the experimental group.

Conclusion: These findings suggest a potential relationship between higher exposure to certain toxic metals and the development of vascular diseases. The higher concentrations of toxic metals in the blood of patients with vascular diseases underline the need for further research to confirm these associations and explore potential mechanisms.

Keywords: Toxic metals, vascular diseases, ICP-MS, cardiovascular health, environmental exposure

INTRODUCTION

Vascular system pathologies, besides affecting their own tissue, also impact the organs it supplies blood to and overall health. Cardiovascular disease is a leading cause of death worldwide.[1,2]

Deaths due to non-communicable diseases were 38 million in 2012, and this number is estimated to rise to 52 million by 2030. Among these, cardiovascular diseases rank first, accounting for 37%.[3] The Lancet Commission on Investing in Health states that every country could reduce premature deaths from major health issues, including cardiovascular diseases, by approximately 50% by 2050 through strategic investments in prevention and treatment.[4] According to the 2019 data from the Turkish Statistical Institute, cardiovascular diseases rank first among causes of death, accounting for 36.8%. They are followed by tumors at 18.4% and respiratory system diseases at 12.9%. Of the deaths caused by cardiovascular diseases, 39.1% are due to ischemic heart disease, 22.2% are due to cerebrovascular diseases, and 25.7% are due to other heart diseases.[3] In the United States, between 8 and 12 million people are affected by peripheral arterial disease (PAD), with an overall prevalence ranging from 3% to 10%. This prevalence rises to nearly 50% in individuals over the age of 85. In Europe, some studies, particularly from the northern regions, have reported a prevalence of up to 17.8%.[5] The presence of PAD is itself an indicator of a poor prognosis, and the survival rates of these patients are worse than many cancer types. In men with advanced PAD, the five-year mortality rate is worse than prostate cancer and similar to colon cancer. Therefore, patients diagnosed with PAD should be effectively treated to address risk factors.[6] Even more importantly, primary prevention by identifying risk factors and preventing the development of the disease is crucial. Risk factors include unhealthy diet, environmental factors, tobacco use, inadequate physical activity, hypertension, obesity, diabetes mellitus, dyslipidemia, as well as gender, age, and family history, among others. The connection between nutrition and lifestyle as preventable risk factors has been established through studies conducted to date.[7]

In recent times, soil pollution, which has increased due to industrialization and urbanization, has reached levels that can pose a threat to living organisms. With the rising environmental and soil pollution, people's exposure to toxic

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metals through air, water, and food has increased. In addition to these factors, the likelihood of exposure to toxic metals is also increasing for individuals working in various industrial sectors. Among these toxic metals, lead (Pb), cadmium (Cd), and arsenic (As) exposure play a significant role. Following exposure to these toxic metals, cell damage and various health problems can occur due to oxidative stress-induced inflammation.[8]

Increasing studies suggest that the harmful effects of metals may largely arise from their specific effects on the vascular system. The functioning of the vascular system involves complex interactions between vascular endothelium, vascular smooth muscle, the immune system, the nervous system, and even the local chemical/metabolic environment of individual organs. Toxic metals contribute to the development of various pathological diseases such as edema, atherosclerosis, and hypertension by targeting the vascular system. Additionally, the vascular effects of toxic metals also contribute to the formation of specific organ damages.[9,10]

Exposure to many metals can lead to bleeding and edema in tissues such as the lungs, and the reason for this is the disruption of endothelial barrier integrity due to exposure to toxic metals. Furthermore, studies have demonstrated that exposure to high concentrations of cadmium and arsenic inhibits angiogenesis.[10-13] Epidemiological studies have shown that lead and cadmium may play a role in the development of hypertension.[14]

This study aimed to determine the relationship between toxic metals, whose adverse effects on the cardiovascular system have been demonstrated in various studies, and vascular diseases.[8-12,15]

METHODS

Research Population

The study population was comprised of individuals attending the Cardiovascular Surgery Clinic (for the patient group) and Family Medicine Clinic (for the control group) at the Yozgat Bozok University Research Hospital. Permission for the study was obtained from the Clinical Researches Ethics Committee of Bozok University (Date: 25.08.2021, Decision No: 2017-KAEK-189-2021.08.25_01). All procedures were carried out in accordance with the ethical rules and the principles.

Research Methodology

The study was completed with the participation of 89 individuals aged 18 and over who applied to the cardiovascular surgery (for the patient group) and family medicine (for the control group) clinics, met the acceptance criteria for the study and agreed to participate in the research. Individuals who refused to fill out the consent form, those who were not in the specified age group, and those in the control group who had chronic and vascular diseases were not included in the study. In addition, hospital records were utilized to obtain information about the health data of the individuals included in the study. The collected blood samples were stored at -20°C until the planned sample size was reached.

Preliminary Preparation of Samples

The pre-preparation process of the samples was conducted with the optimization of the method developed by Türksoy et al.[16] for blood. All pre-preparation processes of the study were carried out in the Bozok University Faculty of Medicine Research Laboratory. One milliliter of blood samples was taken, and then, 5 ml of suprapure nitric acid (HNO_3), 2 ml of hydrogen peroxide (H_2O_2), and 3 ml of distilled water were added for the dissolution process. The dissolved samples were filtered and transferred in 15 ml polypropylene tubes for analysis by inductively coupled plasma mass spectrometry (ICP-MS). The samples were stored at 4°C in 15 ml polypropylene tubes until they were delivered to the device.[16]

Determination of Toxic Metal Levels by ICP-MS

The ICP-MS system was utilized to determine the levels of arsenic (As), copper (Cu), zinc (Zn), manganese (Mn), selenium (Se), chromium (Cr), mercury (Hg), lead (Pb), cadmium (Cd), tin (Sn), cobalt (Co), aluminum (Al), molybdenum (Mo), antimony (Sb), and nickel (Ni) in dissolved blood samples. The method developed by Türksoy et al.[16] was employed for this purpose. Calibration curves with a total of 11 points were constructed for each heavy metal, and the results were evaluated based on these calibration curves.

Statistical Analysis

The statistical analysis of the study was conducted using the SPSS 25.0 (Statistical Package for the Social Sciences) software package. Descriptive statistics, including mean, standard deviation, and minimum-maximum values, were employed to present an overview of the data. The Kolmogorov-Smirnov test was utilized to assess the normal distribution of the data. The Mann-Whitney U test was employed to evaluate data that did not follow a normal distribution.

RESULTS

Our study included the participation of 41 individuals in the control group and 48 individuals in the experimental group. In the control group, 15 participants were male, and 26 were female. In the experimental group, there were 25 male participants and 23 female participants. The potential toxic metal levels in the participants' blood were determined through ICP-MS analysis, and the results revealed statistically significant differences in the levels of most of these metals between the control and experimental groups. The average levels of As (3.86 µg/L), Cu (932.4 µg/L), Mn (5.98 µg/L), Se (60.07 µg/L), Hg (0.04 µg/L), Pb (16 µg/L), Cd (0.20 µg/L), Co (0.05 µg/L), Mo (0.36 µg/L), and Ni (0.02 µg/L) in the blood of the control group were significantly lower than those in the experimental group ($p<0.05$). Additionally, the levels of Zn (1589.1 µg/L), Cr (15.42 µg/L), and Sb (2.45 µg/L) in the control group were significantly higher than those in the experimental group ($p<0.05$). There was no significant difference between the control and experimental groups in terms of Sn (1.68 µg/L) and Al (3.06 µg/L) levels ($p>0.05$). **Table 1** presents the toxic metal levels detected in the control and experimental groups.

In our study, the blood biochemical data of the control and experimental groups were also evaluated. The experimental

Table 1. Toxic metal levels

	Control group				Experimental group				† Normal limits in blood (µg/L)	p
	Mean	Std. deviation	Min.	Max.	Mean	Std. deviation	Min.	Max.		
As (µg/L)	3.86	1.39	1.30	9.71	5.97	1.36	2.90	9.84	<12	**0.001***
Cu (µg/L)	932.40	263.39	600.99	1611.99	1485.44	466.53	924.25	3120.77	850-1900	**0.001***
Zn (µg/L)	1589.10	456.07	1070.32	2802.13	557.00	317.21	218.87	1880.19	660-1100	**0.001***
Mn (µg/L)	5.98	2.94	2.18	14.55	17.77	4.02	11.10	35.35	4.7-18.3	**0.001***
Se (µg/L)	60.07	12.46	34.16	85.67	75.76	16.90	51.19	128.98	70-150	**0.001***
Cr (µg/L)	15.42	3.37	5.25	19.00	4.12	1.53	2.89	10.00	0.7-28	**0.001***
Hg (µg/L)	0.04	0.06	0.01	0.30	0.48	0.32	0.19	1.76	<10	**0.001***
Pb (µg/L)	16.00	6.25	2.15	28.07	37.10	27.63	8.03	92.20	<100	**0.001***
Cd (µg/L)	0.20	0.06	0.10	0.42	0.44	0.27	0.29	1.59	<5	**0.001***
Sn (µg/L)	1.68	0.79	0.65	3.83	1.86	0.78	0.58	3.38	<5	0.228
Co (µg/L)	0.05	0.50	0.01	0.26	0.14	0.06	0.08	0.42	<1	**0.001***
Al (µg/L)	3.06	1.86	0.12	13.33	3.75	4.84	0.10	25.09	<6	0.38
Mo (µg/L)	0.36	0.33	0.02	1.53	1.93	3.43	0.02	24.00	0.3-2	0.001*
Sb (µg/L)	2.45	1.54	0.67	9.32	2.35	0.23	1.72	2.71	<10	**0.001***
Ni (µg/L)	0.02	0.01	0.01	0.08	0.25	0.12	0.02	0.71	<10	0.001*

* p<0,05, † The American Conference of Governmental Industrial Hygienists (ACGIH)
Note: The table displays the mean, standard deviation, minimum, and maximum values for each toxic metal in the control and experimental groups. The p-values indicate the statistical significance of the differences between the groups.
Abbreviations: As: Arsenic, Cu: Copper, Zn: Zinc, Mn: Manganese, Se: Selenium, Cr: Chromium, Hg: Mercury, Pb: Lead, Cd: Cadmium, SN: Tin, Co: Cobalt, Al: Aluminum, Mo: Molybdenum, Sb: Antimony, Ni: Nickel

group showed higher mean values for triglyceride (135.99 mg/dl), folic acid (8.77 ng/dl), BUN (13.32 mg/dl), serum creatinine (0.87 mg/dl), and T3 (1.30 ng/dl) compared to the control group (p<0.05). The mean value of HDL (44.13 mg/dl) in the experimental group was lower than in the control group (p<0.05). There was no significant difference between the groups in LDL, Vit B12, AST, ALT, TSH, albumin, and ferritin values (p>0.05). The blood biochemical values are provided in **Table 2**.

DISCUSSION

Metals, in addition to being present in various environmental settings, are also found in trace amounts in living organisms, playing significant roles in various biological processes. Today, due to industrialization and the impact of environmental pollution, toxic metals have become widespread in ecosystems, posing a threat to human health. It is known that these toxic metals interact with numerous identified and unidentified cellular components and processes in the biological system and cardiovascular system, leading to toxicity.[17] Toxic metal exposure prominently involves the impairment of antioxidant protective mechanisms, leading to oxidative stress. Additionally, toxic metals can induce cardiovascular toxicity through various mechanisms such as DNA damage and lipid peroxidation.[18] Non-communicable diseases, including cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes, account for a significant portion of global disease and mortality rates.[19] Studies have provided evidence that exposure to certain toxic metals is associated with an increased risk of not only strokes but also cardiovascular risks.[10,15] Toxic metals exert negative effects on vascular health by increasing oxidative stress and inflammation, causing endothelial dysfunction, and disrupting calcium balance. Individuals exposed to heavy metals such as As, Pb, Cd, and Hg have been shown to have a higher risk of atherosclerosis, heart disease, and stroke.[20] Determining the etiology of vascular diseases will facilitate the implementation of preventive measures. In this context, our study aims to determine the potential levels of toxic metals in individuals with vascular diseases and

Table 2. Biochemical values

	Control group				Experimental group				p
	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	
Triglycerides (mg/dl)	107.80	56.69	35.60	254.10	135.99	77.64	52.40	448.00	**0.037***
HDL (mg/dl)	55.59	13.55	30.40	85.60	44.13	9.16	29.40	67.30	**0.001***
LDL (mg/dl)	91.06	30.38	45.52	180.60	95.25	26.39	57.18	149.00	0.403
Vitamin B12 (pg/dl)	372.12	230.33	162.60	1629.00	366.63	142.45	191.60	799.10	0.693
Folic acid (ng/dl)	5.87	2.74	1.63	12.99	8.77	7.79	3.26	44.94	**0.018***
AST (U/L)	17.31	6.02	10.40	40.20	17.34	6.13	9.60	40.10	0.985
ALT (U/L)	18.29	0.21	7.20	65.40	19.67	11.32	9.10	65.40	0.233
BUN (mg/dl)	10.44	3.50	5.30	24.60	13.32	3.86	7.40	22.30	**0.001***
Serum creatinine (mg/dl)	0.78	0.21	0.48	1.48	0.87	0.26	0.49	1.80	**0.047***
TSH (µIU/ml)	2.08	1.11	0.27	5.19	2.49	2.55	0.33	13.00	0.797
T3 (ng/dl)	0.34	0.49	0.23	0.47	1.30	0.11	1.08	1.68	**0.001***
Albumin (g/L)	47.50	3.53	37.50	54.00	45.50	4.08	35.70	52.00	0.052
Ferritin (ng/ml)	52.61	49.55	4.67	239.80	74.18	68.48	4.67	202.80	0.397

* p<0,05
Note: The table displays the mean, standard deviation, minimum, and maximum values for each toxic metal in the control and experimental groups. The p-values indicate the statistical significance of the differences between the groups. SD: Standard deviation, Min: Minimum, Max: Maximum, HDL: High density lipoprotein, LDL: Low density lipoprotein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen, TSH: Thyroid stimulating hormone, T3: Triiodothyronine

compare them with the levels of potential toxic metals in a control group consisting of healthy individuals.

Actually, excessive intake of trace elements essential for the human body, such as Se, Zn, and Mn, can also lead to the development of poisoning symptoms. The high-dose toxicity of Zn can lead to ulcers, pulmonary edema, irritation in mucous membranes, and respiratory tract irritation.[21] Mn can cause Parkinson's disease.[22] The long-term high intake of selenium is associated with hair loss, changes in nail morphology, skin lesions (redness and swelling), and central nervous system disorders (paralysis, paresthesia, and hemiplegia).[23] In our study, the level of Zn identified in the experimental group was found to be lower compared to the control group, while Se and Mn levels were higher. The lower level of Zn in the experimental group consisting of individuals with vascular disease compared to the control group is in line with the literature. This finding is supportive of previous studies conducted on the subject. Zn is crucial for the functioning of over 3000 proteins in the body, involved in various physiological processes, including growth, immune function, tissue maintenance, wound healing, lipid and glucose metabolism, and the synthesis of testicular hormones. It has been suggested that Zn deficiency contributes to the increased vascular calcification.[24] Shin et al.[25] demonstrated that Zn increased smooth muscle viability in rat aortic cell lines. Voelkl et al.[26] found that high phosphate conditions increased the level of NF-KB, a key regulator of vascular calcification, in aortic smooth muscle cells. They also observed that this increase was prevented by supplementation with zinc sulfate ($ZnSO_4$). Chen et al.[27] identified a relationship between a high dietary intake of Zn and a lower likelihood of severe abdominal aortic calcification in adults in the United States during the years 2013-2014.

Although the exact role of Hg in the development of cardiovascular diseases is not fully understood, it is known to play a role in the development of oxidative stress and inflammation, which contribute to endothelial and renal dysfunction.[28] Hu et al.[29] identified an association between chronic exposure to Hg and an increased risk of all-cause mortality, as well as fatal/non-fatal ischemic heart diseases in a study examining the relationship between exposure to mercury and the incidence of cardiovascular disease and death. Lin et al.[30] conducted a study to assess the relationship between heavy metal levels and acute ischemic stroke. They found that individuals who experienced acute ischemic stroke had lower Hg levels according to their research. The results we obtained in our study are supportive of the findings in Hu et al.[29] regarding Hg.

In a study conducted by Ikediobi et al.[31] they investigated the response of antioxidant enzymes and redox metabolites to Cd-induced oxidative stress in rat liver cells. According to the findings, after the application of Cd to the rats, there was a decrease in the levels of superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), and glutathione peroxidase (GPx), while there was an increase in malondialdehyde (MDA) levels. The study suggested that this oxidative stress may play a role in the harmful effects induced by Cd, such as the development of lung, prostate, and testicular cancers.[31] In Prozialeck et al.[32] review study titled "vascular endothelium as a target of Cd toxicity," it is suggested that vascular endothelium may be one of the primary targets of in-vivo Cd toxicity. The study indicates that non-lethal concentrations of Cd exposure can target vascular endothelial cells at various molecular levels, including cell adhesion molecules, metal ion carriers, and protein kinase signaling pathways.[32] In the studies conducted by Kishimoto et al.[33] to evaluate the effects of Cd on human vascular endothelial cells, they reported that Cd inhibited tube formation in human umbilical vein endothelial cells (HUVEC) in a dose-dependent manner. They suggested that this inhibition could negatively impact capillary network formation.[33] Our study's findings, indicating elevated levels of Cd in the experimental group, are consistent with the views of Kishimoto et al.[33] This alignment supports the idea that high Cd levels may contribute to an increased risk of cardiovascular disease.

Harlan's[34] study, conducted on the U.S. population to assess the relationship between blood Pb levels and blood pressure, indicated that, in line with numerous previous studies, there was a demonstrated association between Pb exposure and hypertension. In his study, Harlan analyzed data obtained from the national health and nutrition examination survey II for individuals aged 12-74, highlighting a significant correlation between hypertension and Pb exposure.[34] The high detection of Pb in the experimental group in our study is in line with Harlan's[34] findings. Although the blood levels of As, Cd, Hg, Pb, Co, Ni, and Mo in our findings were below the accepted toxic values, they were significantly higher compared to the population in the control group without vascular diseases. This result suggests that there may be an association between cardiovascular disease and elevated blood levels of toxic metals, even at low levels. Indeed, previous studies have demonstrated that the mentioned toxic metals can accelerate atherosclerosis and have serious toxic effects on the cardiovascular system.[39-43] In the majority of conducted studies, toxic effect doses of toxic metals have been individually investigated for each substance. In a multifactorial pathology such as atherosclerosis, we consider it possible that heavy metals may play an accelerating role in the process through the cumulative effect of low doses.

Toxic metals can induce oxidative stress by generating reactive oxygen species (ROS), including superoxide radicals, hydrogen peroxide, and nitric oxide. This process triggers lipid peroxidation, leading to impaired immune function and the accumulation of immune complexes. Consequently, it may cause changes in weight, hyperglycemia, an increase in triglycerides, low-density lipoprotein cholesterol (LDL-c), and elevated blood pressure levels.[35] There is a strong relationship between high triglyceride levels and low HDL levels with cardiovascular diseases.[36] In our study, the high triglyceride levels and low HDL levels identified in the experimental group are supportive of the literature. In a study by Liu et al.[37] where they evaluated the relationship between serum folate and vitamin B12 levels in patients with type 2 diabetes and cardiovascular disease mortality, both low and high serum B12 levels, as well as low serum folate levels, were found to be significantly associated with the risk of cardiovascular

disease mortality. In a study conducted by Li et al.[38] to assess the relationship between folic acid supplementation and cardiovascular diseases, they demonstrated that folic acid supplementation was associated with a 4% reduction in the risk of cardiovascular disease. Our study's finding of high levels of folic acid in the experimental group is not in line with the literature. The discrepancy between our study and the literature regarding folic acid suggests that volunteers in the experimental group with cardiovascular disease may have been taking folic acid supplements.

CONCLUSION

We believe that the study contributes to understanding the effects of toxic metal exposure and biochemical changes on human health. However, investigating the effects of exposure with a larger number of participants and through prospective studies that consider multiple factors will provide more enlightening information to better understand these impacts. The findings from this study, demonstrating the association between toxic metal exposure and cardiovascular diseases, will serve as a crucial data source for epidemiological and clinical studies exploring this relationship.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study received ethical approval from Bozok University Clinical Researches Ethics Committee (Date: 25.08.2021, Decision No: 2017-KAEK-189-2021.08.25_01).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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