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Serum levels of iron, zinc, selenium, copper and oxidative stress in hypertensive patients: A comparative study of age-related changes in the governorate of Basrah, Iraq

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Abstract: Hypertension is the force of blood through blood vessels, where the heart works harder and blood vessels are under more pressure. The relationship between trace element levels and oxidative stress in hypertension is under investigation, with conflicting results. This study aimed to determine the relationship between concentrations of certain antioxidant trace elements (iron, zinc, selenium, and copper) and protein carbonyl concentration as an indicator of oxidative stress in the serum of hypertensive patients compared to the control group in Basra, Iraq, according to age. The study included 100 hypertensive patients (44 males and 56 females) compared to 50 healthy individuals (25 males and 25 females). Patients were divided into three age groups: 35–45, 46–56, and over 57 years. The study showed a significant decrease ($p<0.001$) in the mean concentration of all selected elements in the patients' serum compared to the control group. Conversely, the mean protein carbonyl level showed a significant increase ($p<0.001$) in patients compared to the control group. Trace element concentrations decreased in patients with increasing age, while carbonyl protein levels increased, especially in the third age group. The study also showed a significant negative correlation between protein carbonyl level and all trace elements at $p<0.001$. These results suggest that hypertension is associated with an imbalance in oxidative stress and trace elements. Monitoring trace element intake may help reduce oxidative stress and improve overall health in individuals with hypertension, especially with advancing age, by restoring the balance of essential elements and antioxidants in the body.

Keywords: *Copper, Hypertension, Iron, Protein carbonyl, Selenium, Trace elements, Zinc.*

1. Introduction

Blood pressure is defined, according to the American College of Cardiology/American Heart Association (ACC/AHA), as the force exerted by blood on the walls of arteries as it circulates through the body. Blood pressure is considered high if the systolic pressure is 130 mmHg or higher and the diastolic pressure is 80 mmHg or higher (1). According to the latest estimates, nearly one billion people suffer from high blood pressure globally, and this number is expected to rise to 1.5 billion by 2025 (2). This projected 50% increase within a decade highlights the epidemic nature of this condition. Recognizing the seriousness of this health problem, the world annually celebrates World Hypertension Day on May 17th, aiming to raise awareness and promote global efforts to combat this disease (3). At the physiological level, hypertension is closely linked to oxidative stress, a condition resulting from an imbalance between the production of reactive oxygen and nitrogen species (ROS and RNS) and antioxidant defenses in the body (4). This imbalance leads to a series of harmful physiological changes, including endothelial dysfunction, affecting the ability of blood vessels to dilate and constrict properly;

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increased inflammation, which plays a pivotal role in the development and exacerbation of cardiovascular diseases; and finally, a decrease in the availability of nitric oxide, an important vasodilator that helps regulate blood pressure. These factors collectively contribute significantly to the onset and development of hypertension (5-7). Research has largely focused on the role of major electrolytes, such as sodium and potassium, in regulating blood pressure. However, there is another group of nutrients that has not received the same attention, namely trace elements. These elements include iron, selenium, copper, and zinc, which are essential for many physiological processes in the body (8). Trace elements play a dual and complex role in the context of oxidative stress and hypertension. On one hand, some of these elements can act as powerful antioxidants, helping to combat oxidative stress and thus reduce the risk of hypertension. For example, the enzyme glutathione peroxidase contains selenium, while the copper-zinc superoxide dismutase enzyme contains copper and zinc in its structure. On the other hand, the catalase enzyme requires iron as a cofactor, and ceruloplasmin works to transport copper. Low levels of these trace elements lead to weakened antioxidant function, resulting in hyperactivity of oxidative stress, which causes many diseases (9,10). Conversely, abnormal distribution or excessive accumulation of these elements in the body can increase oxidative stress, which may contribute to hypertension (11). Studies have shown a positive relationship between blood ferritin levels, a marker of iron stores, and oxidative stress in individuals with hypertension (12). Moreover, research indicates that during pregnancy, superoxide concentrations, a measure of systemic oxidative stress, are associated with ferritin levels, suggesting a link between iron status and oxidative stress in preeclampsia, a hypertensive disorder (13). Additionally, studies have shown an association between elevated zinc levels and oxidative stress in hypoxia-induced pulmonary vasoconstriction, increasing our understanding of the molecular mechanisms involved in hypertension (14). Similar to zinc, although selenium is an essential trace element with an important role in the body's antioxidant system, at normal levels, selenium acts as an antioxidant and helps protect cells from oxidative damage. However, it can cause oxidative stress at very high concentrations, causing what is known as "selenium toxicity". In this case, selenium can cause an increase in the production of reactive oxygen species (ROS) that react with biological thiols, leading to the disruption of vital protein functions (15). High concentrations of copper play a pivotal role in causing oxidative stress in the body. Excess copper stimulates the Fenton reaction, leading to the production of highly reactive hydroxyl radicals. It also depletes the body's antioxidant stores, especially glutathione, and stimulates lipid peroxidation (16,17). Because trace elements play two different roles, it is both very important and very hard to figure out how they relate to high blood pressure. In light of this complicated background, the current study's goal is to compare the levels of iron, zinc, selenium, and copper in people with high blood pressure to those in a healthy comparison group. Also, the amounts of protein carbonyl will be checked to see if they show signs of oxidative stress in both groups. The study also wants to look into how age affects these levels in people with high blood pressure and how protein carbonyl levels are related to these levels.

2. Materials and Methods

2.1. Collection of Blood Samples

The point of this study was to compare two cases. Blood samples were taken from 100 people with high blood pressure, 44 men and 56 women. A medical history showed that their blood pressure was consistently high, with readings above 140/90 mmHg. This was confirmed by the hypertension unit at the health center in Al-Hartha District, North Basra. People who had diabetes, liver problems, heart problems, or kidney problems were not allowed to participate. The control group was made up of 50 people with average blood pressure, 25 men and 25 women. It looked like they weren't sick and had no family history of high blood pressure, heart disease, diabetes, or kidney disease. For both groups, the patients' ages ranged from 35 to 70 years old. All of the people who took part in the study gave their verbal approval.

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2.2. Preparation of Clinical Samples

Study samples were collected by drawing 5 ml of blood from both patients and control group using a butterfly needle from the vein. The blood was then transferred to tubes containing non-anticoagulant gel and left for 12 minutes. The tubes were placed in a centrifuge at a speed of 3000 rpm for 10 minutes to separate the serum from other blood components. Finally, the serum was divided into micro tubes. They were stored at -20 degrees Celsius for the evaluation of biochemical markers.

2.3. Biochemical Measurements

The normal colorimetric method with Abbott's ARCHITECT c 4000 systems was used to measure the amounts of iron, zinc, and copper in the serum of patients and the control group. These systems are made with cutting-edge technology to give accurate clinical data and be easy to use. All of the chemical factors that are measured by the device use a sample size of 6¼L. Based on the measured color intensity, the gadget figures out the concentration of elements in the sample on its own. The way each colored molecule absorbs light is different; it does so at a certain wavelength (18). To find out about selenium, a quick and accurate chemical method was used. This method is based on the reaction of tetravalent selenium with indole in pure, concentrated phosphoric acid, which creates a yellow substance that can dissolve in water. A range of 378 nanometers is used to measure absorption (19). The enzyme-linked immunosorbent assay ELISA method was also used to measure the amount of PC in the blood serum of all the subjects. PC is a sign of oxidative stress.

2.4 .Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 28 was used to do the statistical analysis of the data. T-tests were used to see how different groups compared on continuous factors. The one-way ANOVA and Tukey's post hoc test were used to compare more than two study groups. The numbers are shown as mean + standard error (SE). Additionally, Pearson's correlation coefficient was used for correlation coefficient research. A p-value of less than 0.05 meant that the results were statistically significant.

3. Results

The statistical analysis in **Table** 1 shows the element traces and protein carbonyl in hypertension patients as compared with the control groups. Hypertension patients have a mean SBP of 15.32 ± 0.19 HHmg, significantly higher than the control group's mean of 11.99 ± 0.07 HHmg ($p < 0.001$), while there was no significant difference in DBP between patients (8.07 ± 0.07 HHmg) and the control group (7.93 ± 0.04 HHmg) ($p = 0.195$). The results of the trace element in hypertension patients showed significantly ($p < 0.001$) lower than as compared with control groups in mean levels Fe of (12.24 ± 0.51 vs. 16.63 ± 0.43) (µmol/L), Zn of (5.14 ± 0.18 vs. 57.38 ± 1.72) µg/dL, Se of (18.95 ± 0.48 vs. 47.44 ± 0.69) µg/dL, and Cu of (61.31 ± 1.76 vs.77.44 ± 2.06) µg/dL. In contrast, a significantly higher mean PC level of 62.1 ± 1.46 ng/ml was observed in hypertension patients when compared with the control group of 29.02 ± 1.95 ng/ml ($p < 0.001$). Trace elements showed in **Table** 2 a significant ($p<0.001$) decrease in Fe levels as age increases. The mean Fe levels decreased from 16.86±0.72 (µmol/L) in the 35-45 age group to 11.1±0.8 and 10.43±0.69 (µmol/L) in the groups aged 46–56 and above 57 years, respectively. Similar to Fe, Zn levels also decrease with age. The mean zinc levels were lowest at 4.39±0.24 µg/dL in the >57 age group, less than 5.36±0.27 in the 45-56 age group, compared with 6.22±0.37 in the 35-45 age group. Se levels also show a decreasing trend with age; the mean Se levels decrease from 20.92 µg/dL in the 35-45 age group to 17.3 µg/dL in the group aged over 57, with a difference that is statistically significant ($p = 0.005$). Cu levels exhibit a statistically significant decrease ($p = 0.002$) with age. The mean copper levels decreased from 69.12±1.83 µg/dL in the 35-45 age group to 54.89±2.83 µg/dL in the group aged > 57. In contrast, PC levels significantly increase with age (49.39±2.03 ng/ml in the 35–45 group, 61.94±1.98 ng/ml in the 46–56 group, and 69.27±2.12 ng/ml in

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the >57 group). The results indicated **Table** 3, PC a highly significant negative correlation Fe (r = -0.468), Zn (r = -0.387), Se (r = -0.422), and Cu (r = -0.525).

4. Discussion

Free radicals have a high potential to react with other molecules, including fatty acids and proteins. When free radicals react with unsaturated fatty acids, they produce lipid peroxides. Lipid peroxides can then break down to form aldehydes, which are compounds containing a carbonyl group (C=O). Aldehydes react with proteins, leading to the formation of protein carbonyl compounds, which is an indicator of chronic oxidative stress. Protein carbonyls can accumulate over time. Therefore, it can be useful in diagnosing conditions that cause chronic oxidative stress, such as heart disease, vascular disease, cancer, and hypertension (20). The study indicates a significant increase in PC levels in hypertensive patients (Table 1). PC is produced due to oxidative stress that generates reactive oxygen and nitrogen species (RONS), which can disrupt the availability of nitric oxide and stimulate the accelerated conversion of nitric oxide to peroxynitrite, further contributing to oxidative damage. Nitric oxide (NO) is an important molecule that plays a vital role in vasodilation, improving blood flow, and lowering blood pressure. It also prevents the formation of blood clots and protects tissues from damage (21). Trace elements contribute to supporting natural antioxidants in the body, helping to protect cells from damage caused by oxidative stress. Keeping the right amounts of these elements in your body is important for your health and to avoid getting many illnesses. This study found that element amounts were significantly lower in patients than in healthy people, which is in line with what other studies (22) have found. Iron is an important part of many biological processes, including making oxygen radicals, moving electrons around, and speeding up reactions. Iron is an important metal because it can easily change into Fe2+ and Fe3+ ions. This is because iron can both donate and accept electrons (23). The human body needs iron to build oxygen transport proteins, especially hemoglobin and myoglobin, to form heme protein enzymes such as oxidase, catalase, peroxidase, and cytochromes containing iron that participate in electron transfer and redox reactions (24). Zinc ranks second after iron in terms of need. Its deficiency is closely linked to oxidative stress and vascular weakness. Some studies suggest a complex relationship between zinc levels and high blood pressure (HBP) (25). A study found that people with zinc deficiency were more prone to developing hypertension than those with normal zinc levels (26). Zinc deficiency may lead to the activation of the RAAS system, resulting in increased secretion of aldosterone, a hormone that causes sodium and water retention in the body, which may increase blood pressure (27). Selenium is a rare element present in antioxidant enzymes such as glutathione peroxidase. There is a direct relationship between selenium and GPx activity when selenium concentrations are low (28). GPx indirectly prevents platelet aggregation, thus preventing blood clotting, where its activity is protective against hypertension. It efficiently reduces hydroperoxides (29). Copper is an essential metal for the body. Copper is found throughout the body, with the highest concentration in the liver, brain, bones, and heart. Copper aids in immune function, is necessary for iron absorption from food, and plays an important role in red blood cell formation. Copper helps maintain bone and blood vessel health. It may help prevent osteoporosis and heart disease (30). The reason for copper deficiency in hypertensive patients is due to its important role in the antioxidant system by supporting the functions of many antioxidant enzymes, including the superoxide dismutase enzyme (Cu-SOD), responsible for converting excess oxygen ions (O2) to hydrogen peroxide (H2O2). It also plays an important role in the activity of glutathione peroxidase, which is responsible for converting hydrogen peroxide (H2O2) to water molecules (H2O) using glutathione (GSH) as an electron receptor (31). Since trace elements work as antioxidants and support the activity of other antioxidants, their concentration decreases with age due to consumption in the oxidative stress process. The main goal of this study was to look at how age affects the amounts of (Fe), (Zn), (Se), (Cu), and (PC) as a sign of oxidative stress in people with high blood pressure. The patients were split into three groups based on their ages: the first group was 35 to 45 years old, the second was 46 to 56 years old, and the third was over 57 years old. The study data in Table 2 showed that the average Fe levels for people with high blood pressure in three age groups went

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down, and the differences were very big (P<0.001). The study's results matched those of two other studies (32,33). Because oxidative stress rises when there isn't enough iron in the body, nitric oxide levels drop. This can cause high cholesterol and high blood pressure (34). Like Fe, the average amounts of Zn dropped with age, and the differences were very big (P<0.001). The study results were consistent with one study (35). Zn deficiency reduces the function of Cu-Zn/SOD enzymes that act as antioxidants, as Zn stimulates the SOD enzyme. A decrease in this enzyme, which is considered the body's first line of defense, increases the formation of free radicals (36). The average Se levels showed a downward trend with the three age groups, with a statistically significant difference (p = 0.005). The reason for its decreased levels in patients is attributed to the high oxidative stress state that patients are exposed to due to increased free radicals such as hydrogen peroxide, superoxide, and reactive oxygen species, which cause the inefficiency of antioxidants in their work and their deficiency, of which Se is an important element. The results of the current study are in line with the results of a previous study (37). There is a statistically significant drop in the average Cu levels with age (p = 0.002). A copper shortage can get worse when you have high blood pressure because it can cause you to lose copper through urine (38). The study found that protein carbonyl levels went up significantly with age, but not trace element levels. This difference was highly statistically significant (P<0.001). This backs up the idea that older patients are more likely to have higher oxidative stress (39). We looked at the relationship between protein carbonyl (PC) and all the trace elements that were studied in people with high blood pressure (Table 3). At the 0.001 level of significance, the results showed a strong negative association. A drop in trace element amounts is linked to free radicals being too active, proteins and lipids being more easily oxidized, and damage to blood vessels, all of which lead to high blood pressure (40,41).

5. Conclusion

Hypertension is associated with an imbalance between oxidative stress and trace element levels in the body. There is growing interest in trace element and antioxidant levels with increasing age in patients with hypertension. The results suggest that trace element and protein carbonyl levels can be used as indicators to assess oxidative stress status in patients with hypertension.

Ethical approval

This study was performed according to the ethical rules for medical research involving human participants of the Declaration of Helsinki (1964). Ethical approval was received from the ethical and research committee of the University of Basrah, College of Education for Pure Sciences, Department of Chemistry, with the number (3335/18/3) on 3/11/2021. Informed consent was obtained from all caregivers of participated.

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Table 1.
The concentrations trace element (Fe, Zn, Se, Cu) and protein carbonyl (PC) in the blood serum hypertension patients and control groups.

Parameters	Mean ±SE		
	Patients n=100	Control n=50	p-value
SBP (HHmg)	15.32±0.19	11.99±0.07	<0.001*
DBP (HHmg)	8.07±0.07	7.93±0.04	0.195
Fe (µmol/L)	12.24±0.51	16.63±0.43	<0.001*
Zn (µg/dL)	5.14±0.18	57.38±1.72	<0.001*
Se (µg/dL)	18.95±0.48	47.44±0.69	<0.001*
Cu (µg/dL)	61.31±1.76	77.44±2.06	<0.001*
PC (ng/ml)	62.1±1.46	29.02±1.95	<0.001*

Note: *Significant differences at p-value <0.05. Independent T-test.

Table 2.
The concentrations trace element (Fe, Zn, Se, Cu) and protein carbonyl (PC) in the blood serum hypertension patients to age.

Parameters	Age groups (year)			p-value
	35_45 n=25	46_56 n=30	> 57 n=45	
Age (year)	42.88±0.53	50.93±0.4	61.87±0.54	<0.001*
Trace Elements				
Fe (µmol/L)	16.86±0.72	11.1±0.8	10.43±0.69	<0.001*
Zn (µg/dL)	6.22±0.37	5.36±0.27	4.39±0.24	<0.001*
Se (µg/dL)	20.92±0.83	19.79±0.75	17.3±0.77	0.005*
Cu (µg/dL)	69.12±1.83	64.43±3.22	54.89±2.83	0.002*
protein carbonyl				
PC (ng/ml)	49.39±2.03	61.94±1.98	69.27±2.12	<0.001*

Table 3.
Correlations of protein carbonyl (PC) with trace elements (Fe, Zn, Se, Cu) in hypertension patients.

Variables		Fe (µmol/L)	Zn (µg/dL)	Se (µg/dL)	Cu(µg/dL)
PC (ng/ml)	r	-0.468**	-0.387**	-0.422**	-0.525**
	p	0.0001	0.0001	0.0001	0.0001

Note: **Correlation is significant at the 0.01 level.

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