Clinical and Experimental Health Sciences

The Relationship of Trace Element Levels with Obesity and Cardiovascular Health

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ABSTRACT

Objective: One of the most important factors affecting cardiovascular health is obesity. Trace elements, which play a role in every stage of metabolism, are also related to our cardiovascular health. The aim of this study was to determine serum trace element levels in individuals and to examine the relationship between trace elements and cardiovascular risk.

Methods: This cross-sectional study was conducted with individuals who applied to the outpatient clinic between 01.03.2022-31.04.2022. Sociodemographic characteristics, BMI, and Framingham risk score values were recorded. Serum iron, zinc, copper and selenium levels were analyzed in the laboratory.

Results: A total of 180 individuals were included in the study. Of the individuals, 33.3% were overweight and 32.8% were obese. The mean Framingham Risk Score (FRS) was 9.31±7.99 (1-37). FRS values of normal weight individuals (7.84±3.05) were lower than the mean FRS values of overweight (8.80±3.39) and obese (13.39 ± 6.24) groups (p<.001). There was a weak positive correlation between serum copper levels and BMI (r=.176 p=.018). No significant correlation was found between serum iron, zinc and selenium levels and BMI and FRS.

Conclusion: There was a weak positive correlation between copper levels and BMI values, however Se, Zn and Fe levels were not associated with BMI and FRS values. Randomized controlled trials are needed to introduce serum trace element determination in to practice in the diagnosis and follow-up of obesity and cardiovascular disease.

Keywords: Serum trace element, body mass index, Framingham risk score.

1. INTRODUCTION

Obesity and cardiovascular diseases (CVD), which are increasing in frequency in the general population, are two diseases that are closely related to each other in terms of both etiology and prevalence in the society (1). According to studies conducted in recent years, reactive oxygen derivatives formed as a result of oxidative stress and immune response triggered by cell damage come to the fore in the etiology of both diseases (2). Elements whose amount in the human body is less than 100 mg/kg are called trace elements. This group includes elements such as iron, selenium, chromium, copper, zinc, and iodine (3). A link has been established between deficiency or excess of these trace elements and many diseases (e.g. iron deficiency – anaemia or zinc deficiency – dermatitis) (4). Some trace elements such as zinc, copper, and selenium are closely associated with inflammation and peroxidation and may be responsible for the pathogenesis of cardiovascular disease and obesity (5,6).

Zinc (Zn) is essential for the maintenance of normal cellular structure and functions. The extracellular and intracellular levels of Zn are also related to cardiovascular health (7). According to Little et al., plasma Zn levels decrease with age and have a strong association with increasing CVD (8). Moreover, recent advances in cardiac biology and pathophysiology have highlighted the critical contribution of perturbations in Zn homeostasis to myocardial ischemia/reperfusion injury and

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the role of Zn signaling in cardioprotection against ischemia/reperfusion injury (9). Zn has a regulatory role in oxidative stress, inflammation, apoptosis and insulin secretion. In addition, Zn has roles in carbohydrate-lipid metabolism and cell division-regeneration (10). Many of these metabolic pathways are found to be impaired in obese patients (11). Considering these conditions, it may be thought that Zn deficiency or excess plays a role in the etiology of obesity. Obesity, oxidative stress and inflammation are factors known to predispose to cardiovascular diseases (12).

Iron (Fe) is an important mineral needed by almost all living organisms (13). The maintenance of iron homeostasis is essential for proper cardiac function. A growing body of evidence suggests that Fe imbalance is the common denominator in many subtypes of cardiovascular disease (14). Fe is a trace element that can affect the clinical course of many chronic diseases such as obesity, type 2 diabetes and atherosclerosis (15). In many studies, it has been associated with weight gain, cardiovascular disease and metabolic syndrome development, insulin receptor resistance and Type-2 diabetes due to the lack or excess of Fe and the inflammation caused by these conditions (16-18).

Copper (Cu) deficiency plays an important role in the unspecific manifestations of hematologic, neurologic, immunologic, dermatologic, cardiovascular, and skeletal defects. Cu in the body is one of the cofactors of enzymes involved in mitochondrial function, inflammatory response and anti-oxidative functions (19). Additionally, copper is involved in vascular changes in the heart. Kunutsor et al. showed that a higher serum Cu level increases the risk of atherosclerotic heart disease by regulating lipid metabolism, low-density lipoprotein oxidation, and inflammatory response (20).

Selenium (Se) plays an important role in the proper functioning of the entire human body. It is involved in the processes of reproduction, carcinogenesis, mechanisms of the immune response and in regulating the work of cardiovascular system (21). Recent studies have demonstrated the role of Se in the modulation of important molecular in adipose tissue (22,23). Therefore, both selenium deficiency and excess selenium may contribute to adipose tissue dysfunction and metabolic alterations that are particularly important in the context of obesity and cardiovascular disease.

It is hypothesized that excessive adiposity alters the absorption, distribution, metabolism, and excretion of micronutrients, thereby compromising their bioavailability and limiting their function in the body (24-26).

Few studies have examined the relationship between cardiovascular risk, obesity and trace elements together. In this context, the aim of the study is to determine the Framingham Risk Score and serum trace elements (copper, zinc, iron and selenium) and examine the relationship with obesity.

2. METHODS

2.1. Study Design

The cross-sectional study consisted of individuals who applied to the Family Medicine Polyclinic for periodic health examination between 01.03.2022 and 31.04.2022. Volunteers who applied to the family medicine outpatient clinic after the ethics committee approval and met the inclusion criteria were divided into 3 groups according to BMI. Individuals who applied from each group were included in the study by selecting consecutive odd numbers (1-3-5-7...) in order, randomisation was ensured. During the selection, an attempt was made to keep the age distribution, gender and smoking similar between group. Since the number of individuals in the population was unknown, the sample size was calculated using the appropriate formula. According to this calculation, taking into account a 10% margin of error, the study was completed with 180 people.

2.2. Exclusion Criteria

Those under 18 years of age, those with a psychiatric diagnosis that would impair cooperation, those who could not communicate, those with a diagnosis of syndromic obesity, those with known cardiovascular disease, those with a diagnosis of cancer, use of mineral supplements, and those with a diagnosis of gastrointestinal malabsorption were excluded.

2.3. Ethical Authorisation of the Study

Prior to the study, Necmettin Erbakan University Faculty of Medicine ethics committee approval was obtained (Number: 2021/3431 Date: 01.10.2021). After ethical approval, Scientific Research Project (BAP) support was obtained from Necmettin Erbakan University (Project number 221518001). Individuals were briefly informed about the purpose of the study and their verbal and written informed consent was obtained according to the principles of the Declaration of Helsinki.

2.4. Collection of Data

The sociodemographic introductory questionnaire form for the individuals included in the study was prepared by examining the literature on the subject. The form consisted of questions about sociodemographic characteristics such as marital status, age, employment status, presence of chronic diseases, medication use, education level and smoking status. Those who had a hemogram, total cholesterol, HDL and LDL cholesterol level, insulin level, fasting blood level and thyroid stimulating hormone (TSH) level planned in the last month or in the current examination, and those who also met the criteria were included in the study after their consent was obtained. The results of these individuals were obtained from the application files and recorded in the form. Blood pressures were measured with a suitable cuff in a

rested and sitting position. Shoes were removed and height was measured with a standard meter on a hard surface and weight was measured with a standard weighing device after removing excess clothing. Body mass index (BMI) of the participants was calculated in kg/m2.Those with BMI<25 kg/m2 were considered normal weight, those with BMI=25-30 kg/m2 were considered overweight and those with BMI≥30 kg/m2 were considered obese. Participants' waist circumference (WC) was measured above the umbilicus.

2.4.1. Framingham Risk Score

It is one of a number of scoring systems used to determine a person's ten-year risk of developing cardiovascular disease. There are two separate scoring for women and men. In the study, after calculating the parameters of age, smoking, systolic blood pressure, being on antihypertensive treatment, total cholesterol, HDL-cholesterol level, the ten-year cardiovascular disease risk of the participants was calculated via the website https://www.mdcalc.com/framingham-risk-score-hard-coronary-heart-disease. FRS classification was made according to the following ranges "Low risk (10-year risk of coronary heart disease < 10%)"; "Moderate risk (10-year risk of coronary heart disease 10-20%)"; "High risk (10-year risk of coronary heart disease > 20%)" (27).

2.4.2. Laboratory Analysis

Collection of Blood Samples

Human venous blood samples were collected in gel tubes containing clot activator. The blood samples were centrifuged in a Hettich Rotina 46R (Hettich Zentrifugen, Tuttlingen, Germany) refrigerated centrifuge at 40°C, 1000 g for 10 minutes and serum samples were separated.

Measurement of Serum Copper Levels

Cu levels in serum samples were measured by spectrophotometry using a Beckman Coulter AU 480 autoanalyzer (Beckman Coulter, Brea, California, USA) and kits, calibrators and controls from Archem (Archem Diagnostic Industry, Istanbul, Türkiye). Serum copper levels were calculated as µg/dL.

Measurement of Serum Zinc Levels

Zn levels in serum samples were measured by spectrophotometry on a Beckman Coulter AU 480 autoanalyzer (Beckman Coulter, Brea, USA) using a kit, calibrator and controls from Archem (Archem DiagnosticIndustry, Istanbul, Turkey). Serum zinc levels were calculated as µg/dL.

Measurement of Serum Iron Levels

Fe levels in serum samples were measured by spectrophotometry on a Roche Cobas c702 autoanalyzer (Roche Diagnostics GmbH, Mannheim, Germany) using kits, calibrators and controls from Roche (Roche Diagnostics GmbH, Mannheim, Germany). Serum Fe levels were calculated as µg/dL.

Measurement of Serum Selenium Levels

Se levels in serum samples were measured by inductively coupled plasma mass spectrometry (ICP-MS) on a NexION 350X ICP-MS analyzer (Perkin Elmer Inc., Shelton, Connecticut, USA) using kits, calibrators and controls from Perkin Elmer (Perkin Elmer Inc., Shelton, Connecticut, USA). Serum selenium levels were calculated as µg/L.

2.5. Statistical Analysis

Statistical analyses were performed using Microsoft Excel and Statistical Package for Social Sciences (SPSS) for Windows 22.0. Mean and standard deviation values of numerical data were calculated. Compliance with normal distribution was evaluated with the Kolmogorov-Smirnov test, and categorical and numerical data were compared with appropriate statistical analyzes such as chi-square, student-t test, and one-way ANOVA. Correlation analysis was used to determine the relationship between variables. In cases where there was a difference between groups, significance was evaluated with the Post-Hoc Tukey test. Significance value was accepted as $p< .05$.

3. RESULTS

The study was completed with 180 individuals. 50.0% of the individuals included in the study were male (n = 90). Of the participants, 76.12% (n = 137) were married and 47.22% (n = 85) had a university degree. Sociodemographic data of the participants are given in Table-1.

The mean age of the participants was 43.36±8.58 (30-65) years, mean systolic blood pressure was 117.96±12.46 mmHg and mean diastolic blood pressure was 76.17±9.35 mmHg. Mean FRS was 9.31±7.99 (1-37), and mean BMI was 27.58±5.70 (18-60.55) kg/m2. Individuals were 33.9% (n=61) normal weight, 33.3% (n=60) overweight and 32.8% (n=59) obese. Men were 34.4% normal weight, 33.33% overweight and 32.2% obese. For females, there was an equal distribution of 33.3% in each BMI group ($p > .05$). The mean FRS of the individuals was 7.84±3.05 in the normal weight group, 8.80±3.39 in the overweight group and 13.39±6.24 in the obese group. The mean FRS of the normal weight group were significantly lower than those of the obese and overweight groups ($p < .001$ and $p < .001$, respectively).

Mean trace element levels were measured as serum Fe 81.09±39.22 µg/dL, serum Zn 112.48±38.14 µg/dL, serum Cu 101.29±35.44 µg/dL and serum Se 83.03 ± 9.11 µg/L (Table 2). The mean trace element levels of the individuals who participated in the study were compared in groups formed according to BMI values. No statistically significant difference was found between the groups in terms of mean Fe, Zn, Cu and Se levels ($p > 0.5$). Comparison of mean trace element levels of individuals according to BMI and statistical analysis values are given in Table 3.

Table 1. *Distribution of the Sociodemographic Characteristics of the Participants*

	n	%
Sex		
Male	90	50.00
Female	90	50.00
Marital Status		
Married	137	76.12
Single	43	23.88
Educational status		
Primary school	44	24.44
Middle school	17	9.44
High school	34	18.89
University	85	47.22
Working status		
Working	127	70.56
Not-working	53	29.44
Chronic disease condition		
Yes	72	40.00
No	108	60.00
Use of medication		
Yes	63	35.00
No	117	65.00
Smoking		
Yes	89	49.44
No	91	50.56
Total	**180**	**100**

Table 2. *Demographic and clinical characteristics of the participants (n=180)*

Parameters	Mean ± SD	Min	Max
Age (Year)	43.36 ± 8.58	30	65
Systolic Blood Pressure (mmHg)	117.96 ± 12.46	90	167
Diastolic Blood Pressure (mmHg)	76.17 ± 9.35	50	101
Framingham Risk Score (FRS)	9.31 ± 7.99	1	37
Waist Circumference (cm)	95.63 ± 15.08	61	132
Body Mass Index (BMI)	27.58 ± 5.70	18.0	60.55
Serum Iron (µg/dL)	81.09 ± 39.22	12.20	237.50
Serum Zinc (µg/dL)	112.48 ± 38.14	36.0	336.0
Serum Copper (µg/dL)	101.29 ± 35.44	8.0	225.0
Serum Selenium (µg/L)	83.03 ± 9.11	52.30	99.60

Mean Cu levels were 103.70±31.66 µg/dl in the low FRS group, 85.21±33.84 µg/dl in the intermediate risk group and 111.80±44.23 µg/dl in the high risk group. Mean Cu values were statistically significantly lower in the intermediate risk group compared to the low and high-risk groups ($p < .01$; $p < .005$, respectively). There were no significant differences between the risk groups in terms of other trace element levels. Comparison of mean trace element levels of individuals according to FRS is given in Table 4.

Table 3. *Comparison of mean trace element levels of individuals according to BMI*

BMI*	Normal weight (n = 61)	Overweight (n = 60)	Obese (n = 59)		
Parameters	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	***F***	***p*****
Serum Iron (µg/dL)	88.04 ± 48.47	73.18 ± 32.74	81.94 ± 33.34	2.222	.112
Serum Zinc (µg/dL)	107.59 ± 40.47	110.86 ± 29.75	119.18 ± 42.66	1.475	.232
Serum Copper (µg/dL)	106.24 ± 40.77	97.41 ± 29.28	100.12 ± 35.24	.986	.375
Serum Selenium (µg/L)	83.45 ± 8.62	83.11 ± 9.26	82.51 ± 9.58	.161	.851

**BMI: Body Mass Index **One Way ANOVA*

Table 4. *Comparison of mean trace element levels of individuals according to Framingham Risk Score*

FRS	Low risk (n = 112)	Moderate risk (n = 37)	High risk (n = 31)		
Parameters	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	***F****	***p****
Serum Iron (µg/dL)	85.30 ± 38.09	77.90 ± 46.08	69.67 ± 32.41	2.100	.125
Serum Zinc (µg/dL)	114.30 ± 36.44	106.29 ± 30.60	113.29 ± 50.80	.618	.540
Serum Copper (µg/dL)	103.70 ± 31.66	85.21 ± 33.84	111.80 ± 44.23	5.714	**.005**
Serum Selenium (µg/L)	83.22 ± 9.43	83.54 ± 7.88	81.74 ± 9.49	.390	.677

**:One Way ANOVA*

4. DISCUSSION

Non-communicable diseases such as cardiovascular diseases (CVD), obesity, cancer, chronic respiratory diseases and diabetes are leading causes of morbidity and mortality in both developed and developing countries. Lifestyle changes such as healthy nutrition, regular physical activity and smoking cessation are necessary to prevent CVD (1). The oxidant or antioxidant functions of metals such as Fe, Zn, Cu and Se may also have effects on cardiovascular health (28). However, there is no consistent evidence that these supplements may affect CVD in healthy individuals without known nutritional deficiencies (29). Despite the known role of trace elements in maintaining general health, there is controversy regarding their specific effects on CVD risk. There are few studies in the literature examining the relationship between obesity, cardiovascular mortality risk and trace elements in Türkiye. This study is one of the few studies that simultaneously investigate Zn, Fe, Se and Cu elements along with obesity and CVD in individuals. the presented study, There was no evidence that trace element levels affect cardiovascular risk, although a correlation was found between serum trace element levels and lipid levels.

Obesity directly contributes to the development of cardiovascular risk factors such as dyslipidemia, type 2 diabetes, hypertension and sleep disorders (1). Recent data emphasize that abdominal obesity, as measured by waist circumference, is a marker of cardiovascular disease risk independent of body mass index (30). Thus, even in normal weight individuals, higher waist circumference (WC) may indicate higher CVD risk because WC is an indicator of abdominal body fat, which is associated with cardiometabolic disease and CVD and predicts mortality (31). The present study has demonstrated that those with a higher 10-year risk of coronary heart disease exhibit a higher waist circumference. In a large-scale study by Dhaliwal et al., it was demonstrated that central obesity is associated with a high FRS score (32). Given the close relationship between obesity and cardiovascular disease, it can be posited that this is also valid for central obesity (33).

Trace element levels in the human body have a great importance in the tissues of the cardiovascular system as well as in all tissues of the human body (15,21,34). Cu, a trace element, is essential for enzyme function and has an important role as both a pro-oxidant and an antioxidant. It acts as a catalytic cofactor of enzymes such as Cu/Zn superoxide dismutase, ceruloplasmin, and lysyl oxidase, which has a central role in the strength and integrity of the heart and blood vessels (35). Cu is also essential to mitochondrial respiration and Fe absorption. Elevated Cu levels may increase the production of reactive oxygen species (ROS) and consequently oxidative stress (36), resulting in the oxidation of lipids, proteins, DNA, homocysteine and other particles (37). Cu deficiency, on the other hand, can cause peroxidative damage (38). Both Cu deficiency and overload play key roles in atherogenesis. As an essential trace element, Cu has been considered to play an important role in lipid metabolism. High serum Cu was associated with elevated serum concentrations of TC and HDL cholesterol (39). The zinc-copper-blood pressure relationship is important because of the biochemical relationship between Zn and Cu and because both elements play important roles in blood pressure regulation (40). In this study, no correlation was found between Cu levels and BMI. However, Cu levels were higher in those with a higher 10-year atherosclerotic heart disease (ASCVD) risk.

Cheng et al (2022) observed negative associations of chromium (Cr) and Se with 10-year ASCVD risks in their study, in which they aimed to evaluate the factors that they thought could predict the relationship of trace elements with the 10-year risk of ASCVD in 607 elderly adults living in China. In addition, a positive relationship between Cr and HDL cholesterol and a negative relationship between Se and systolic blood pressure were found in both linear regression (41). In this study, a positive correlation was found between total cholesterol levels and Se levels. As the key component of glutathione peroxidase with unique antioxidant properties, Se has been considered to play an important part on lipid metabolism (22). Ju revealed that selenium concentrations were positively correlated with TC, HDL-c, TG and LDL-c (42). In the present study, no significant correlation was found between serum trace element levels and age, systolic and diastolic blood pressure, and TG levels.

Analysis of factors relevant to CHD identified associations between Fe levels and risk factors including inflammation, obesity, proatherogenic as well as antiatherogenic and antioxidant components. Such associations reveal the pathophysiologic mechanisms of the relationship between Fe and CHD. Fe trapped in the macrophages within the arterial wall serves as an oxidative stress mediator and has been identified as a novel risk factor for vascular disease progression (28). Cebi et al. investigated the relationship between iron and coronary heart disease and found that serum iron levels were lower in individuals with coronary heart disease (38). Iron deficiency (ID) is also an important predictor of cardiovascular events and all-cause mortality (43). Fe can also stimulate the formation of reactive oxygen species (ROC) and thus cause lipid peroxidation and atherosclerosis (44). However, several observational studies and meta-analyses have not supported the adverse effect of Fe status on CHD risk (27). This evidence challenged the hypothetical cardiotoxic effect of Fe and its role in the development of cardiovascular events. In the present study, no association was found between serum iron levels and 10-year ASCVD risk. In the NHANES-3 study, individuals were followed closely for 6 years in terms of cardiovascular diseases and low serum Se levels were found to be associated with high cardiovascular disease (45).

In a study conducted in postmenopausal women, it was reported that the daily intake of all minerals evaluated was not dependent on BMI (46). Another study found that high Se levels were associated with an increased risk of obesity, while high Cr levels were associated with a decreased risk of obesity (47). In a study evaluating the association of trace elements with obesity and hypertension in adult women, Fe and Cu were elevated in obese patients, Cu and Se content was higher in patients with hypertension. Zn levels were significantly lower in obese women with and without hypertension compared to healthy controls and normal weight women with hypertension (48). In the present study, no correlation was found between BMI and serum trace element levels.

A review of the literature revealed a paucity of studies investigating the relationship between 10-year ASCVD risk and serum trace element levels. The study's strength lies in its evaluation of trace elements in conjunction with BMI and 10-year ASCVD risk.

Limitations

This study has some limitations. First of all, we did not include the effect of daily consumed food and supplementary foods/pills in our study parameters. Second, the study was conducted on a limited number of participants. It cannot be generalized. It can be considered as a preliminary study for a large-scale study to be conducted in the future with more

samples from different regions of Türkiye. We think that more comprehensive studies are needed in which individuals' chronic diseases, nutritional status and geography are questioned, and factors that will affect trace element levels in the blood are minimized.

In conclusion, the results of study provide some evidence for the association of serum trace element levels with obesity and the risk of developing cardiovascular disease. There was no evidence that trace element levels affect cardiovascular risk, although a correlation was found between serum trace element levels and lipid levels. Considering the prevalence of cardiovascular diseases in the population, weight control may prevent death or disability due to cardiac causes. In this context, dietary interventions and appropriate physical activity for weight control in obese people need to pay more attention to both the quantity and quality of food. As family physicians, we are able to predict the risks that may occur as we constantly follow the individual from birth to death. The breadth of the facilities of the clinician in charge of diagnosis and follow-up in people with obesity and cardiovascular disease is an important issue. More well-designed, large-scale studies are needed to clarify the relationship between trace elements and cardiovascular health or evaluate the possibility of using these elements as biomarkers in clinical practice.

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