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Serum Zinc, Copper and Ceruloplasmin Levels in Type 2 Diabetic Patients

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Abstract

Our objective was to investigate the possible alterations in serum zinc, copper and ceruloplasmin levels in type 2 diabetes. Fifty patients with type 2 diabetes mellitus (23 male, 27 female) who were being treated and followed by Gazi University Internal Medicine Obesity and Diabetes Clinic and 30 healthy volunteers (12 male, 18 female) were included in the study. Serum zinc and copper levels were measured by atomic absorption spectroscopy and ceruloplasmin oxidase activity was determined spectrophotometrically. While zinc levels of female diabetics were found to be significantly lower than female control group, there were no significant differences neither between male patients and male controls, nor between patient group and control group. There was no statistically significant difference in serum copper levels between patient and control groups. However, in both groups, copper levels of female subjects were found significantly higher than males. Ceruloplasmin oxidase activities were higher in patient group compared with controls and both in male and female patient groups compared with their respective controls. There was a positive correlation between serum copper and ceruloplasmin oxidase activity. These results imply that serum ceruloplasmin oxidase activity in type 2 diabetic patients and zinc levels in female type 2 diabetics show important alterations.

1. Introduction

Diabetes Mellitus (DM) is the absolute or relative insufficiency or ineffectiveness of insulin secreted from pancreatic beta cells, as a result of a series of pathological events caused by genetic and immune structure. It is a chronic metabolic disease that causes disruptions of protein, carbohydrate and lipid metabolisms. (Brunton, 2016; Powers, 2008) Today, it is accepted as an epidemic in many developed and developing countries and ranks fourth among the top five causes of death in most developed countries. (Nielsen, Jensen, & Magid, 1994) Type 1 DM, which develops as a result of the loss of insulin production because of the destruction of beta cells in the islets of Langerhans in pancreas, is generally seen in childhood and early adulthood. (Newman et al., 1987; Uusitupa, Niskanen, Siitonen, Voutilainen, & Pyörälä, 1993; Zimmet, 1992) Type 2 DM is characterized by insulin resistance in peripheral tissues and insulin secretion insufficiency of pancreatic beta cells. It is a major health problem affecting millions of individuals. (Garber, 2000; Pham, Pham, Pham, Miller, & Pham, 2007)

Zinc (Zn) is the second most abundant trace element in the human body and is involved in many metabolic events such as gene expression, DNA synthesis, enzyme catalysis, storage and release of hormones, neurotransmission, memory, vision, growth, and development. (Sanjeevi, Freeland-Graves, Beretvas, & Sachdev, 2018; Vallee & Falchuk, 1993) Zinc is an element directly related to insulin physiology by playing a role in its synthesis, storage and secretion, ensuring its structural integrity, and preserving its three-dimensional structure. Therefore, insulin secretion from pancreatic islet cells is negatively affected in zinc deficiency. (Kinlaw, Levine, Morley, Silvis, & McClain, 1983; Nobels, Rillaerts, D'Hollander, Van Gaal, & De Leeuw, 1986)

Although the level of copper (Cu) in the body is relatively low (up to 100 mg), it is extremely important in the fulfilment of bodily functions as it is a structural element of some enzymes. (Grace & Lee, 1990) It has been reported that copper metabolism also changes in diabetes, but the role of copper in glucose homeostasis has not been adequately explained. (Walter et al., 1991)

Ceruloplasmin (Cp) is the main carrier of copper in human plasma and in healthy individuals, approximately 90-95% of total copper in the circulation is found in its structure. (Fox, Mukhopadhyay, & Ehrenwald, 1995; Mateescu et al., 1995) Although ceruloplasmin is a metalloenzyme with antioxidant properties, it promotes vasculopathic effect at increasing levels. (Shukla, Maher, Masters, Angelini, & Jeremy, 2006)

There are studies showing that changes in serum zinc and copper levels are associated with increased glycosylated haemoglobin (HbA1c). (Viktorínová, Toserová, Krizko, & Duracková, 2009) While it has been stated that the metabolisms of trace elements and inorganic compounds are affected in diabetes mellitus, the reason behind this has not been elucidated. (Gödény, Borbély-Kiss, Koltay, László, & Szabó, 1986; Walter et al., 1991) Zinc and copper, which are essential components of many enzyme systems, are frequently investigated in the studies on diabetes in recent years.

In this study, we aimed to investigate any possible alterations in serum zinc, copper and ceruloplasmin activity levels in DM and also assess if sex of the

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individual has an effect on the differences between these parameters.

2. Material and Method

2.1. Study groups and inclusion criteria

Fifty type 2 diabetic patients (23 male, 27 female), who were treated by the Obesity and Diabetes Clinic of Gazi University Faculty of Medicine (Department of Internal Diseases, Section of Endocrinology and Metabolism), and 30 healthy volunteers (12 male, 18 female) were included in the study. Patients were diagnosed with type 2 DM after the assessment of their fasting and postprandial blood glucose levels, and HbA1c values and were being followed by monthly and quarterly controls by the Diabetes-Obesity outpatient clinic. They had no complications associated with type 2 DM (nephropathy, retinopathy, diabetic foot etc.), malnutrition or diseases related to malabsorption. Patients who were taking multivitamin, zinc and/or copper supplements, and who have kidney disease were excluded.

Ethics approval was obtained from Gazi University Non-Invasive Clinical Research Ethics Committee (approval decision number: 376). All individuals were given detailed information about the study and asked to sign the informed consent form.

2.2. Measurement of serum zinc, copper levels and ceruloplasmin activity

Peripheral venous blood samples were taken from all participating individuals and serums were separated by centrifugation. Serum parameters were analysed in Gazi University Faculty of Medicine Medical Biochemistry Laboratory. Serum zinc and copper levels were measured using a Shimadzu AA-7000 series atomic absorption spectrometer. (Pollard, 1981) Serum ceruloplasmin oxidase activity was evaluated spectrophotometrically. (Sunderman & Nomoto, 1970)

2.3. Statistical evaluation

SPSS (Statistical Package for Social Sciences) version 15 was used to evaluate the data obtained from the study. Student's t-test was used to determine any differences between the groups and Pearson correlation test was performed for correlation analysis. $P < 0.05$ was considered statistically significant.

3. Results

Levels of zinc, copper and ceruloplasmin activities of groups, including male and female subgroups, are shown in Table 1.

While there was no statistically significant difference between the zinc levels of male and female patients ($p > 0.05$), zinc levels of males in the control group was found to be significantly lower than females ($p < 0.05$). When zinc levels of patient and control groups were compared, no statistical significance was found ($p > 0.05$). There was no significant difference in zinc levels of males between patient and control groups ($p > 0.05$), however, zinc levels of females in control group were significantly higher compared with females in patient group ($p < 0.01$).

In both patient and control groups, copper levels of females were found to be higher than males ($p < 0.05$). There was no statistically significant difference between copper levels of patient and control groups ($p > 0.05$).

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Table 1: Serum zinc, copper and ceruloplasmin activity levels (Mean ± SD) of control and diabetic groups with sex subgroups

		Zn (µg/dL)	Cu (µg/dL)	Cp (U)
Control Group (n=30)	**Male (n=12)**	94.75 ± 22.78	121.33 ± 16.72	292.17 ± 66.06
	Female (n=18)	111.06 ± 18.32†	135.78 ± 21.94†	327.22 ± 85.03
	Total	104.53 ± 21.44	130.00 ± 20.98	313.20 ± 78.73
Diabetes Group (n=50)	**Male (n=23)**	99.52 ± 17.11	109.35 ± 26.78*	372.48 ± 85.48*
	Female (n=27)	96.07 ± 10.18*	137.93 ± 32.54†	401.70 ± 117.59*
	Total	97.66 ± 13.76	124.78 ± 33.03	388.26 ± 105.09*

* Compared with their respective controls $p < 0.05$
† Compared with male subgroup of the same group $p < 0.05$

There was no significant difference between males and females in terms of ceruloplasmin activities in both the patient and control groups ($p > 0.05$). Mean ceruloplasmin activity of the patient group was found to be significantly higher than control group ($p < 0.01$). In addition, there was a significant difference between ceruloplasmin activities of patient group males and females compared with control group males and females, respectively ($p < 0.05$).

When correlation analysis were performed (Table 2), very weak negative correlations between zinc levels and copper levels ($r = -0.179$) and zinc levels and ceruloplasmin activities were found, which was not statistically significant ($p > 0.05$). There was a positive correlation between copper levels and ceruloplasmin activities ($r = 0.545$, $p < 0.01$) (Figure 1).

Table 2: Correlations (r values) between zinc, copper and ceruloplasmin

	Cu	Cp
Zn	-0.179	-0.081
Cu	1	0.545**

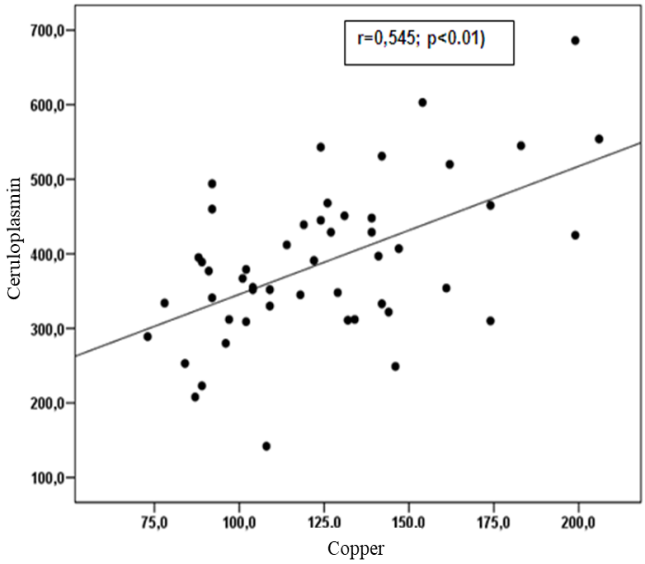

Figure 1: Correlations (r values) between zinc, copper and ceruloplasmin

4. Discussion

Diabetes Mellitus (DM) is an endocrine metabolic disease that occurs due to insulin deficiency or resistance to insulin's effect and causes complications in almost all systems. (Brunton, 2016; Powers, 2008) The incidence of diabetes, which has

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become one of the most common diseases in human history, is increasing day by day and is becoming a global epidemic. (Beletate, El Dib, & Atallah, 2007) Type 2 diabetes mellitus, an important health problem affecting 200 million individuals worldwide, is characterized by variable rates of insulin resistance, progressive β-cell dysfunction, and varying levels of insulin secretion deficiency in some individuals. (Arslan, 1996; Burant, 2004) It is thought that the incidence of diabetes will increase even faster. (Satman et al., 2002) As the prevalence of type 2 diabetes increases, morbidity and mortality due to diabetes mellitus and its complications also increase. It is known that diabetes causes many serious complications such as coronary heart disease, chronic renal failure, retinopathy and nephropathy. (Rehman & Akash, 2017)

Zinc, the second most abundant trace element after iron in the organism, is necessary for many immune and hormonal events, and for the activity of more than 300 enzymes. It plays an important role in many physiological events, such as cell proliferation, wound healing, bone formation, membrane stability, growth and development, pregnancy, fertility, brain functions, taste, and appetite. (Prasad, 2013; Skalnaya, Skalny, & Tinkov, 2017)

Copper is the third most abundant trace element in the human body. It is found in the body as a structural element of some metalloenzymes, such as ceruloplasmin and superoxide dismutase. These enzymes play a major role in redox reactions and antioxidant defense. It has been suggested that copper has an insulin-like structure and promotes lipogenesis. Some studies conducted in recent years have shown that diabetic patients may have abnormal serum copper levels. (Olaniyan et al., 2012)

Ceruloplasmin, which contains approximately 90-95% of the circulating total copper in healthy individuals, prevents the formation of free oxygen radicals and lipid peroxidation. (Sarkar et al., 2010) In the studies conducted, there were different results about serum zinc and copper in type 2 diabetes. Various researchers have found in their studies that serum zinc levels were lower in diabetic patients than in the healthy controls. (Al-Maroof & Al-Sharbatti, 2006; Huma, Yahya, & Saqib, 2011; Masood et al., 2009; Sinha & Sen, 2014) They also showed that there was a negative correlation between serum zinc levels and both serum glucose levels. (Sinha & Sen, 2014) and basal HbA1c values in the diabetic group and that zinc supplementation was beneficial for improving the glycaemic control and reducing HbA1c levels. (Al-Maroof & Al-Sharbatti, 2006)

In the studies of Zhang et al., (Zhang et al., 2017) which evaluated 19 trace elements in the serum of patients with type 2 diabetes, Rusu et al., (Rusu et al., 2001) which examined serum magnesium, zinc and copper levels in diabetic patients, and El-zebda, (El-Zebda, 2006) which evaluated serum copper and zinc levels in diabetic and hypertensive patients, serum copper and zinc levels were found to be higher in diabetic patients compared to control groups.

In the study conducted by Atari-Hajipirloo et al., (Atari-Hajipirloo, Valizadeh, Khadem-Ansari, Rasmi, & Kheradmand, 2016) type 2 diabetic patients and their first-degree non-diabetic relatives were included. They found that serum zinc levels were lower, and copper and iron levels were higher in diabetic patients and their first-degree relatives compared to control group. HbA1c levels were shown to be positively correlated with copper and iron levels, and negatively correlated with zinc levels.

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In the study of Olaniyan et al., (Olaniyan et al., 2012) on Nigerian patients with type 2 diabetes, serum copper levels were significantly higher and serum zinc levels were significantly lower in diabetic patients compared to the healthy controls.

Kurtul et al. (Kurtul, Pençe, Çil, Aksoy, & Erman, 2007) investigated the relationship between serum zinc and copper levels, gender and age in type 2 diabetes. Serum zinc levels were found to be lower and copper levels were found to be higher in diabetics compared to healthy individuals. In all age groups, lower zinc and higher copper levels were found in diabetics compared with controls. No statistically significant difference was found between zinc values of men and women in healthy and diabetic individuals. Copper levels were higher in women than men. It was observed that copper values increased with age in the healthy and diabetic groups, and the copper levels of women were higher than that of men in each age group. In our study, while there was no difference between the copper levels of the patient and control groups, copper levels of females in both groups was higher than in males and zinc levels were lower in the female patient group compared with their controls.

In studies in which serum copper, magnesium and HbA1c levels (Supriya, Pinnelli, Murgod, & Raghavendra, 2013) and heavy metal levels (Raudenska et al., 2017) were evaluated in patients with type 2 diabetes, copper levels were found to be increased in diabetes patients compared with healthy controls. Halaçoğlu et al. (Halaçoğlu & Suher, 2012) aimed to investigate the relationship between the regulation of diabetes mellitus and serum trace elements in their study including well-controlled diabetic patients (HbA1c 37 ≤ 6.5), poorly controlled diabetes patients (HbA1c > 6.5), and healthy women without diabetes. They found mean serum zinc levels of 130.33 ± 53.73 μg/dL in the well-controlled diabetes group, 101.83 ± 24.84 μg/dL in the poorly controlled diabetes group, and 110.47 ± 30.97 μg/dL in control group and showed that there was a statistically significant difference between the groups. Serum copper levels were significantly higher in the poorly controlled diabetes group compared with both the well-controlled diabetes group and the control group.

The fact that the results are different from each other in the studies performed varies according to the age, gender, duration of diabetes, medicines patients use, blood glucose control status and whether there are complications due to diabetes. The previous studies demonstrated that patients with type 2 DM are characterized by a significant elevation of serum ceruloplasmin concentrations. (Daimon et al., 1998; Memişoğullari & Bakan, 2004) Despite this, no correlation was found between ceruloplasmin and blood HbA1c levels. (Daimon et al., 1998) Moreover, certain studies have demonstrated a significant decrease in serum ceruloplasmin levels in type 2 DM. (Sarkar et al., 2010) Data obtained by Skalnaya et al. (Skalnaya et al., 2017) demonstrated a significant elevation of serum ceruloplasmin in postmenopausal women with prediabetes. At the same time, the levels of ceruloplasmin in type 2 DM patients were not different from the control levels. Elevation of serum copper levels without a simultaneous change in circulating ceruloplasmin concentrations may be indicative of increased ‘free copper’ levels. Also, taking into account the role of Cp in iron transport, diabetes-related perturbations in ceruloplasmin levels may at least partially contribute to alteration in iron metabolism. In particular, it has

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been demonstrated that ceruloplasmin deficiency results in altered iron export from nonintestinal cells.

In the study conducted by Azevedo et al., (Azevedo, Fernandes, Lisboa, Fontes, & Manso, 1980) serum copper and ceruloplasmin levels in diabetics were quite high compared with the healthy control group; however, copper levels in short-term diabetes patients were found to be higher than those with long-term diabetes. In addition, a positive correlation was found between copper and ceruloplasmin.

The results of our study and these studies show that ceruloplasmin oxidase activity is increased in diabetic patients. In addition, there is a positive correlation between copper and ceruloplasmin oxidase activity. A limited number of publications on ceruloplasmin oxidase activity in patients with type 2 diabetes mellitus could be found in the literature reviews.

5. Conclusion

Our results showed that serum ceruloplasmin oxidase activity in type 2 diabetic patients and zinc levels in female type 2 diabetics show important alterations. From this point of view, our study supports the relevant literature and is a guide on this matter.

Conflicts of interest

Authors declare that there is no conflict of interest..

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