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SERUM ZINC AND COPPER VARIATIONS IN PATIENTS WITH HYPERTHYROIDISM

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Abstract

Zinc (Zn) and Copper (Cu) levels in hyperthyroidism have been investigated in previous studies but results were not the same. It is indicated that Cu and Zn deficiency adversely affect the endocrine system, thyroid hormone secretion and production. Also, numerous biochemical processes and cell proliferation are affected by Zinc and Copper concentration change. We investigated the level of these trace elements in Iranian patients with hyperthyroidism.

Thirty-five patients with diagnosed primary hyperthyroidism, according to suppressed Thyroid Simulating Hormone levels(TSH), were included in this case-control study. We used laboratory data from 35 healthy participants as a control group. Sex and age matching was done for selecting a proper control group. Data gathering was done from patients' medical documents. The serum concentrations of T_3 and T_4 were determined in all participants with chemiluminescence kits (Liaison, France). The calorimetric method was used to measure Zn and Cu levels with colorimetric assays kits (Bayerex Fars, Iran) at wavelength 560 nm with sensitivity of 5µg/dl. The mean age of hyperthyroid group and control group were 34.74±7.09 years and 34.91±6.55 years, respectively. Female to male ratio was 2:1. No significant difference was seen between two groups according to their sex (P = 0.8). The mean Zn concentration in a hyperthyroid and control groups was 62.99±8.52 µg/dl and 96.94±10.70 µg/dl, respectively (P<0.001). The mean serum Cu concentration was 102.7±8.15 µg/dl in hyperthyroid group and 88.88±10.53 µg/dl in corresponding controls (P<0.001). Association between age and serum Zn and Cu was not significant statistically. Hyperthyroid patients had significantly elevated Cu and decreased Zn concentrations according to their controls. We found no association between age, serum Zn and Cu concentrations and thyroid hormones.

Keywords: *copper, zinc, hyperthyroidism, element, TSH, thyroid hormone.*

Introduction

Hyperthyroidism is a common endocrine disease occurs when thyroid hormone increases in tissues. Excessive production or release of hormone or using drugs should be considered in these patients. In the United States, Graves disease is the most common cause of hyperthyroidism. Its clinical presentation is not the same in different patients and ranges from asymptomatic to severe metabolic imbalance, affecting entire human body's systems such as the growth of organs [*Cabello G, Wrutniak C, 1989*] and cardiovascular system. In hyperthyroidism, heart rate is increased and peripheral vascular resistance is decreased. Hence, patient encounters a high cardiac output state and high susceptibility to supraventricular tachycardia. Even subclinical hyperthyroidism increases risk of cardiovascular mortality [*Fazio S et al., 2004*]. Thyroid hormones regulate body's metabolic rate and affects blood components. Growth

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hormone activity is affected by thyroid hormones [*Cabello G, Wrutniak C, 1989]*. Cellular respiration is controlled by thyroid hormones via changing in gene expression. It has been shown that mRNA and mitochondria are two components affected in this phenomenon. Previous studies have indicated the relationship between thyroid hormones and trace elements and their interaction in maintaining the body metabolism in a steady state [*Pillar T, Seitz H, 1997]*. Studying these interactions can provide a better understanding of metabolism chain and its regulation.

Although trace elements have a low amount in the human body, they are very important for metabolic processes. Trace elements are divided into two groups; essential and non-essential elements. A deficiency syndrome is resulted from lacking of an essential trace element. [*Versieck J, 1985*]. Some of the important elements include selenium, iron, and manganese, copper (Cu), and zinc (Zn). Deficiency, lack and increase of trace elements can cause irreparable damages [*Siddiqui K, Bawazeer N, 2014*].

It is indicated that Cu and Zn deficiency adversely affect the endocrine system. Their deficiency can be a result of poor diet state or loosing too much of them from the body [*Porter K et al., 1977*]. Zn is an important element for numerous biochemical processes and cell proliferation [*MacDonald K, 2000*]. Many metalloproteins contain Zn. Liver alcohol dehydrogenase carbonic anhydrase and alkaline phosphatase are the enzymes containing Zn [*McCall K et al., 2000*]. It is indicated that thyroid function affects the metabolism of Zn [*Etebary S et al., 2010*].

On the other hand, Cu is important in thyroid hormone secretion and production. Cu deficiency causes glucose intolerance which shows insulin like activity of Cu. Hypercholesterolemia in chronic Cu deficiency makes a person susceptible to atherosclerosis and its serious adverse events. Also insulin resistance is associated with thyroid hormone change. Zn helps muscle and fat tissue to use blood glucose. Insulin receptor needs Zn to start its signaling. [*Siddiqui K, Bawazeer N, 2014*].

Thyroxine tyrosinase enzyme that converts tyrosine into melanin contains Cu. In one study, rats with Cu deficiency had increased T_3 level but their Thyroid stimulating hormone (TSH) and T_4 levels was similar to those with normal Cu level. Rats with Cu deficient diet had 5% decreased weight gain compared to control group [*Kralik A et al., 1996*]. Cu helps thyroid gland to produce thyroxine (T4) also Cu prevents blood cells from over absorption of T4. T3 receptor is a nuclear receptor which includes Zn-binding proteins. Hence, Zn and Cu can affect thyroid function potentially. (Miyamoto *et al.*, 1991)

Diagnosis of hyperthyroidism is based on history and physical examination and then measurement of thyroid hormones and TSH. Importance of thyroid hormones and essential nutrients such as Zn and Cu for our body has made them a favorite subject for research. Treatment of very ill patients especially in Intensive Care Units (ICU) is very difficult. Every disease influence body metabolism negatively. More effective treatments can be found especially for very ill subjects if we know how to regulate body metabolism by using different hormones and nutrients [*Economidou F et al., 2011*].

Conflicting results of previous studies such as [*Kralik A et al., 1996*] which showed a higher level of Cu in hyperthyroid rats and the study done by [*Aihara K et al., 1984*] which showed a lower level of Cu in hyperthyroid patients shows that we need more investigations to evaluate different aspects of correlation between trace elements and metabolism and thyroid function. In current study we evaluated Zn and Cu changes in patients with hyperthyroidism.

MATERIALS AND METHODS

Between June until September 2015, 35 patients with diagnosed primary hyperthyroidism, according to suppressed TSH levels, were included in this case-control study. Diagnosis of hyperthyroidism was based on signs and symptoms of the patients such as pulse rate above 100 per minute continuously, new onset of intolerance to heat along with overeating and suppressed TSH level [*Longo D et al., 2011*]. These patients were referred to do the analysis by internal specialists and super-specialists. In this study inclusion criteria were having suppressed TSH level (below 0.1 mU/ml in the *chemiluminescence* kit produced by Diasorin (Italy) that assessed with Liaison (Italy-French), and not taking medication for disease and exclusion criteria included having drug-induced hyperthyroidism, pregnancy, being younger than 25 or older than 50 years, being hospitalized because of a serious disease. We

used data from 35 healthy participants as a control group. The healthy control group was selected from healthy participants who accepted to join this study. Sex and age matching was done for selecting a proper control group. Data gathering was done from patients' medical documents.

All devices and solutions for measuring serum Cu and Zn and thyroid hormone kits already tested to measure their accuracy and approved after quality control. The calorimetric method with a spectrophotometer wavelength 560 nm was used to measure Zn and Cu levels with colorimetric kits (Bayerex Fars, Iran) by a chemistry auto-analyzer BT-3000 (Italy) with *sensitivity of 5µg/dl*. Finally, Zn and Cu levels were compared between groups. C*hemiluminescence* kits(DiaSorin, Italy) were used for thyroid function test with an Liaison aparatus (Italy-French). Samples maintained at -20ºC until the time of analysis.

Statistical analysis; Interpretation and statistical analysis were done by SPSS 16. Descriptive statistical methods (frequency, percentage) were used as a statistical survey. Independent t-test was used to compare the quantitative data. Pearson correlation test was used to find a probable correlation between variables. A P value below 0.05 was considered as significant.

Results

The mean age of hyperthyroid group and control group were 34.74±7.09 years and 34.91±6.55 years, respectively (P=0.92). Female to male ratio was 2:1. No significant differences were seen between two groups according to their sex. (P=0.8) The mean serum Zn concentration in hyperthyroid and control group was 62.99±8.52 µg/dl and 96.94±10.70 µg/dl, respectively (P<0.001). Figure 1 shows Zn level in the hyperthyroid patients and their corresponding controls. The mean serum Cu concentration was 102.7±8.15 µg/dl in hyperthyroid group and 88.88±10.53 µg/dl in corresponding controls (P<0.001). Figure 2 shows Cu level in hyperthyroid patients and their corresponding controls. Our study showed a negative correlation between Cu and serum T3, and a negative correlation between Zn level and T4 and T3, the correlation between Zn and T4 was positive, but in statistical analysis, none of these correlations were signifi-

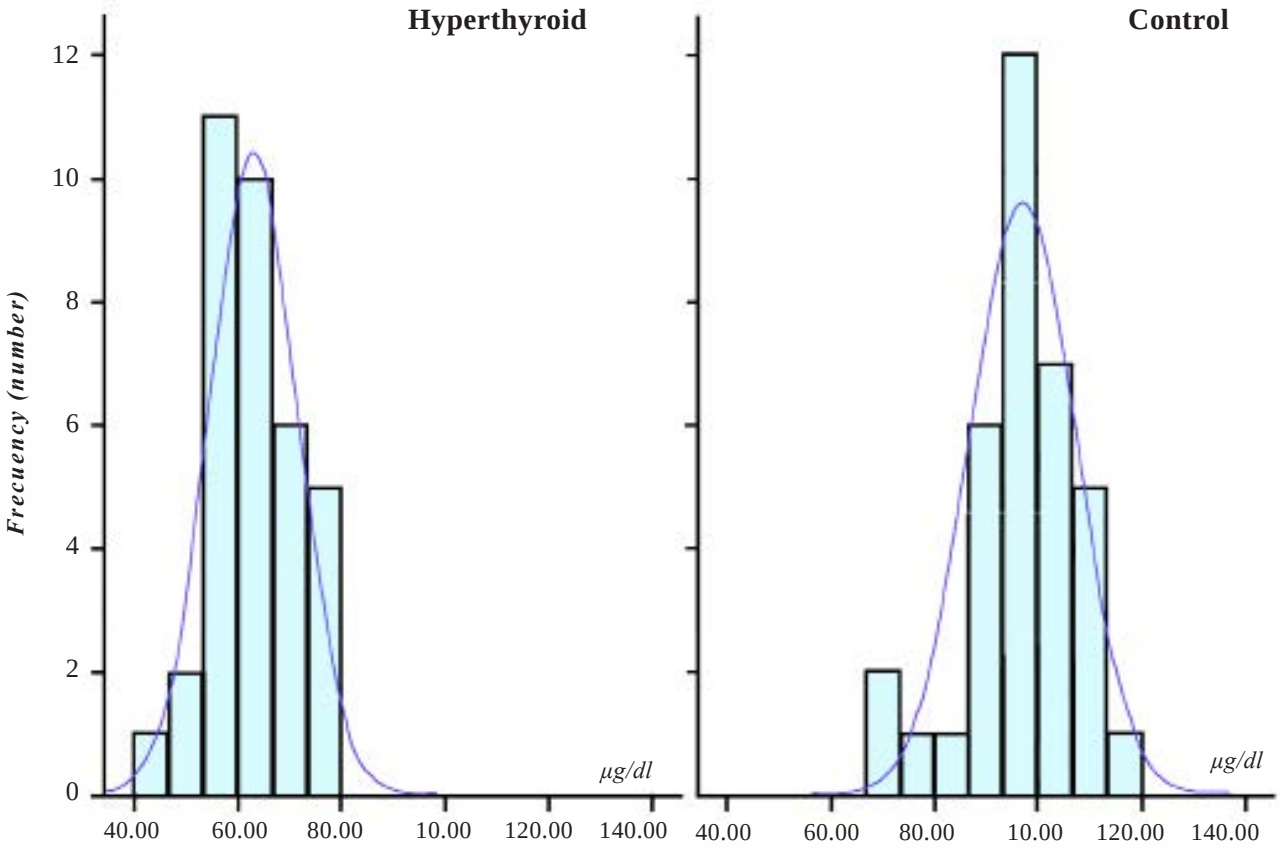

Figure 1: *Zinc level in hyperthyroid patients and controls due to frequency distribution.*

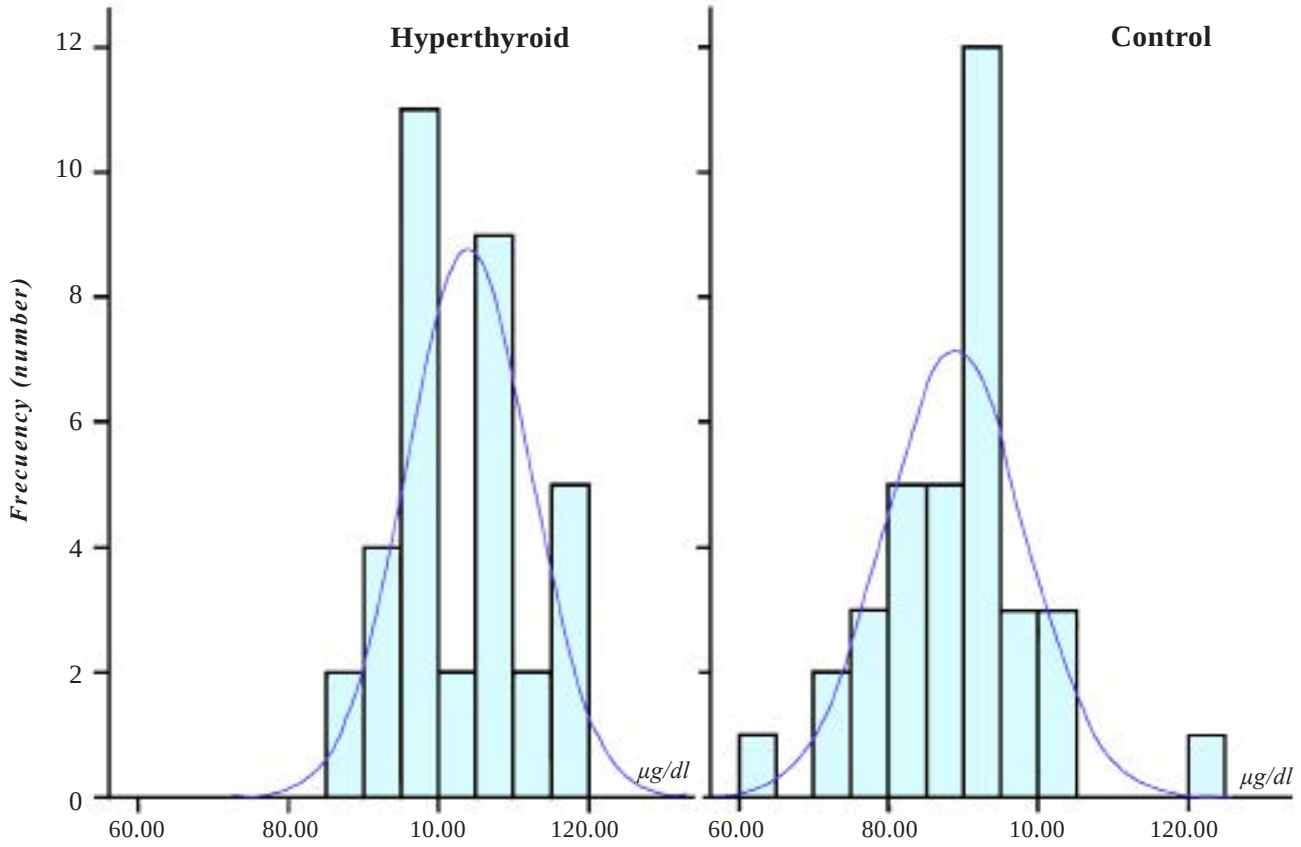

FIGURE 2: Copper level in hyperthyroid patients and control due to frequency distribution.

cant (Table 1). Also, association between age and serum Zn and Cu was not significant statistically.

DISCUSSION

Previous studies have demonstrated association between Zn and Cu with hyperthyroidism [*Aihara K et al., 1984; Nishi Y et al., 1980b*]. Zn is an essential trace element for TRH synthesis [*Pekary A et al., 1991*], converting T4 to T3 [*Chen M et al., 1998*] and proper function of thyroid hormone receptors [*Baltaci A et al., 2003; Baltaci A et al., 2004*]. Cu influences thyroid hormone biosynthesis. Prasad A et al showed that thyroid hormones regulate Zn transport in kidney and intestine of mice [*Prasad A, 1995*]. In the current study we investigated serum Zn and Cu concentrations in patients with newly presented hyperthyroidism and found significantly higher serum Cu and lower serum Zn concentrations according to healthy controls. Hence, taking antihyperthyroid agents is a possible reason for controversy in results of different studies. Serum Zn is mainly bounded to and transported by albumin. Serum albumin level decreases in the hyperthyroid state, decreased Zn-albumin complex can lead to increased ultrafiltrable serum Zn which accelerates Zn excretion in urine *[Dolev E et al., 1988; Nishi Y et al., 1980a*]. This can explain lower Zn level even at the beginning of hyperthyroidism. [*Cousins R, 1985; Foote J, Delves H, 1984*]. In addition, Zn plays an important role in protein metabolism in the human body, so decreasing serum Zn concentrations can impair albumin production and low serum albumin level can worsen serum Zn depletion [*Kahn A et al., 1965; Wolman S et al., 1979]*.

On the other hand, about 90% of Cu is transported in bloodstream via ceruloplasmin [*Harris E, 2001*], Cu excretes in bile [*Adelstein S, Vallee B, 1961*]. Ce-

TABLE 1:
Correlation between Zn and Cu with thyroid hormones in hyperthyroid group.

Variables	r (Pearson correlation)	P value
T_3 and Cu	-0.134	0.44
T_4 and Cu	-0.061	0.72
T_3 and Zn	-0.211	0.22
T_4 and Zn	0.156	0.37

ruloplasmin increases significantly in hyperthyroid patients [*Aliciguzel Y et al., 2001*]. Excretion of Cu is very slow [*Adelstein S, Vallee B, 1961*]. Hence, increased ceruloplasmin and slow excretion of Cu from the body can explain elevated Cu level in hyperthyroidism. Both Zn and Cu are absorbed by metallothioneins, increased Cu level of hyperthyroidism can inhibit metallothioneins from Zn absorption [*Fosmire G, 1990*].

Enhanced metallothionein sequestration in the liver and subsequent increase in interleukin-6 and increased serum level of ceruloplasmin as an acute phase reactant in hyperthyroidism can explain decreased serum Zn and elevated serum Cu in these patients *[Maes M et al., 1999b*]. Jain and Choi reported a positive association between free T_4 and plasma Cu concentration in both genders [*Jain R, Choi Y, 2015*]. Zhang F et al. (2004), reported a positive association between plasma Zn and Cu level and T3 and T4. Jain showed that in men Zn was associated with lower levels of FT_4 and TT_4. Conversely, Cu was associated with higher levels of FT4 and TT4 [*Jain R, 2014*]. Similarly, our results, Oneaghala et al. showed no association between trace elements and T_3 and T_4 thyroid hormones [*Onyeaghala A et al., 2012*]. Studies with a larger number of patients can help us to get more precise results. The underlying factors resulted in hyperthyroidism may play a significant role in trace element regulation. In Baltaci *et al.* study, hyperthyroidism was induced by extrinsic drugs and higher Zn level in this study may be due to different mechanism [*Baltaci A et al.,* 2013]. Hence, intrinsic factors such as genetic factors may have different effects on trace elements comparing to extrinsic factors such as drugs and nutrition. By studying these factors in future we can evaluate this theory.

Conclusin

Hyperthyroid patients had significantly elevated plasma Cu and decreased serum Zn concentrations according to their controls. We found no association between age, thyroid hormones (T_3, T_4) and serum Zn and Cu concentrations.

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