Selenium, Zinc, and Copper Status in Euthyroid Nodular Goiter: A Cross-Sectional Study

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Abstract

Background: It is known that some elements are needed for normal thyroid gland functions. Iodine and selenium are the most well-known trace elements necessary for thyroid metabolism. Selenium is involved in the formation of thyroid hormones and the structure of the deiodinases associated with the development of the thyroid gland. While the role of zinc in thyroid metabolism is at the T3 receptor level, the role of copper is yet not clear. **Objective:** To compare the levels of serum trace elements such as selenium, zinc, and copper between the patients with euthyroid nodular goiter and healthy participants. **Methods:** This cross-sectional study included 98 patients with euthyroid multinodular goiter and 83 healthy subjects without thyroid disease. The demographics, thyroid hormone levels, and thyroid ultrasonography of the participants were recorded. Venous blood samples were centrifuged and sera samples were stored at -80°C until analysis of selenium, zinc, and copper levels. The levels of trace elements were determined by inductively coupled plasma-mass spectrometry (ICP-MS). **Results:** While serum, zinc, and selenium levels were significantly higher in the control group than the nodular goiter group, the copper levels were similar in the two groups. Trace elements were not correlated with thyroid hormone levels and thyroid volumes. Patients in the nodular goiter group were analyzed according to their solitary and multiple nodule status. The solitary and multiple nodular goiter groups were similar in terms of copper, zinc, and selenium levels. **Conclusions:** Deficiency of selenium and zinc may be associated with nodular goiter. Replacement of these trace elements may be useful for the prevention of nodular goiter, especially in deficient regions.

Keywords: *Copper, selenium, thyroid nodule, trace elements, zinc*

Introduction

Some trace elements such as iodine, selenium, copper, and zinc can affect normal thyroid hormone synthesis and metabolism. The lack of these substances affects thyroid hormone homeostasis.[1,2] The relation of iodine and selenium with thyroid disease has been evaluated in many previous studies.[3-6] High concentrations of selenium may be present in thyroid tissue.[7] Selenium-containing proteins (selenoproteins) have important functions in the thyroid tissue. In addition, they play a role in antioxidant defense of thyroid against excessive hydrogen peroxidase exposure. They are also a part of the enzyme iodothyronine deiodinase which is involved in the activation and inactivation of thyroid hormone.[8] Therefore, selenium deficiency may result in a decrease in the production of the active T3 hormone. In particular, the sodium selenate (Se +4) form directly activates natural killer cells has an antileukemic effect and anticancer properties.[9,10] These anticancer properties have been proven by clinical and experimental studies.[11-13]

Zinc is a trace element that plays a role in cell proliferation and biochemical reactions in the body. Moreover, the thyroid is considered to have an important role in zinc hemostasis. The association between zinc and thyroid metabolism is based on the hypothesis that the nuclear T3 receptor contains zinc-binding protein.[14] Thus, thyroid hormones have an effect on zinc absorption and excretion.[15]

The role of copper in thyroid tissue is yet unclear. Moreover, as per data, it has been shown that inadequate or excessive uptake may affect thyroid hormone metabolism. Copper and zinc are well-known components of antioxidant defense. They serve as cofactors of some proteins in the modification of transcription factors and receptors in the regulation of critical

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cellular processes hence, these trace elements may lead to various pathophysiological consequences depending on the amount.[14]

The objective of the present study was to compare the levels of serum trace elements such as selenium, zinc, and copper between the patients with euthyroid nodular goiter and healthy participants.

Methods

Study design and inclusion criteria

The study design was cross-sectional. Around 98 patients with euthyroid multinodular goiter and 83 healthy subjects with no thyroid disease, who applied to Yozgat Bozok University, Endocrine Outpatient Clinic, between February 2018 and September 2018, were consecutively included in this study. The study protocol was in accordance with the Helsinki Declaration of 1975, as revised in 2000. Yozgat Bozok University Clinical Research Ethics Committee approved the study design (2017-KAEK-189_2018.02.27_13) and informed consent form was obtained from all participants.

The participants aged between 18–65 years with euthyroid multinodular goiter were included in the nodular goiter group. Participants without any thyroid disease, with normal thyroid ultrasonography, negative thyroid antibody, and normal thyroid function tests were included in the control group. Exclusion criteria were thyrotoxicosis, hypothyroidism, euthyroid with antithyroid drugs, euthyroid with thyroid drug replacement, positive thyroid antibody, chronic heart disease, renal failure, pregnancy, inflammatory diseases, malignancy, and taking trace elements supplements. Medical histories, age, gender weights, and heights were recorded. Body mass index (BMI) was calculated.

Laboratory analysis

Blood sampling: After fasting for 10–12 h, the venous blood samples were taken and centrifuged at room temperature for 5 min at 5000 rpm. The serum samples were analyzed on DxI 800 Access Immunoassay (Beckman Coulter Inc., Brea, CA, USA) using a direct chemiluminescence detection system to evaluate the levels of free T3, free T4, thyroid-stimulating hormone (TSH), antithyroglobulin (anti-Tg), thyroid peroxidase antibody (anti-TPO), selenium, zinc, and copper. For trace elements, the extracted serum was kept in ice bags at -80°C. All samples were transferred to the laboratory of Yozgat Bozok University Science and Technology Application and Research Center in cold chain conditions for the trace elements analysis. Sera samples (for selenium, zinc, and copper analysis) were taken and placed into tubes belonging to microwave oven digestion system (Milestone Start D) with supra pure nitric acid (HNO_3, 65%) and ultrapure water was added to the blood samples. The selenium, zinc, and copper levels of the digested samples in the microwave oven were determined by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) system (Thermo Scientific ICAP Qc, USA). The operating parameters were set as follows: RF power 1550 W, nebulizer gas 0.90 L/min, plasma gas 0.80 L/min, nebulizer pressure 3.00 bar, dwell time 0.01 and spray chamber temperature 3.0°C. The sampler probe was washed between injections by rinsing with ultrapure water for 30 s, followed by washing with 2% HNO_3 for 45 s then rinsing with ultrapure water for 45 s. After the wash steps, the instrument automatically ran the next sample. The r^2 value of the calibration curve was calculated as 0.9999 and the interval of the calibration was set at 0.5–1000 μg/L for selenium, zinc, and copper. Sample and standard of measurements were repeated three times. Method validations were performed with CRM-Seronorm™ Trace Elements Whole Blood L-2. CRM was measured five times on the same day and on different days. Moreover, the average of the repeated measurements was used for the validation of the method whereby the relative standard deviation (RSD) of the values did not exceed 5%.[16]

Thyroid ultrasonography

Ultrasonography was performed using Logic 700 (GE medical sys, Milwaukee, USA) at 7 MHz superficial probe. Thyroid volume was calculated using the formula maximal length × width × depth × π/6 of each lobe. Thyroid enlargement was defined as a thyroid volume of above 18 mL for women and above 25 mL for men.[17] The structure of the gland was classified as normal, solitary nodule, or multinodular. The same endocrinologist performed the ultrasonography in both groups.

Statistical analysis

Statistical analyses were calculated with the Statistical Package for the Social Sciences, version 20.0 (Chicago, IL, USA). A $P < 0.05$ was considered statistically significant. The Kolmogorov-Smirnov test was used for normality. The correlations between variables were evaluated by Pearson or Spearman's correlation analysis, as appropriate. Comparison of normally distributed variables was done by independent samples *t*-test while the comparison of non-normal variables was done by Mann-Whitney U-test.

Results

Descriptive features were shown in Table 1. The number of the participants in nodular goiter group was 98 (89 female and 9 male) and in the control group was 83 (71 female and 12 male). Mean age of the participants in nodular goiter group and the control group were 44.48 ± 11.67 years and 37.46 ± 12.61 years, respectively ($P < 0.01$). Free T3 and TSH were significantly higher in the control group than the nodular goiter group (2.85 ± 0.34 pg/mL vs. 2.71 ± 0.52 pg/mL, $P = 0.005$; 1.90 ± 0.99 mIU/mL vs. 1.60 ± 1.10 mIU/mL, $P = 0.006$,

Table 1: Descriptive features

	Nodular goiter *n*=98	Control *n*=83	*P*
Age (years)	44.48±11.67	37.46±12.61	**0.000**
Body mass index (kg/m^2)	30.15±5.74	29.5±7.59	0.236
Free T3 (pg/mL)	2.71±0.52	2.85±0.34	**0.005**
Free T4 (ng/mL)	1.02±0.11	0.99±0.14	**0.017**
TSH (mIU/mL)	1.60±1.10	1.90±0.99	**0.006**
Thyroid gland volume (mm^3)	11.48±5.57	8.78±3.49	**0.001**
Zinc (Zn) (µg/L)	1034.54±557.12	1421.14±759.2	**0.000**
Copper (Cu) (µg/L)	1293.75±249.33	1306.56±258.53	0.833
Selenium (Se) (µg/L)	64.92±13.74	70.00±17.20	**0.008**

Free T3=Free triiodothyronine, free T4=Thyroxine, TSH=Thyroid stimulating hormone, *P*=Pearson. Significant values (*P*<0.05) were bold

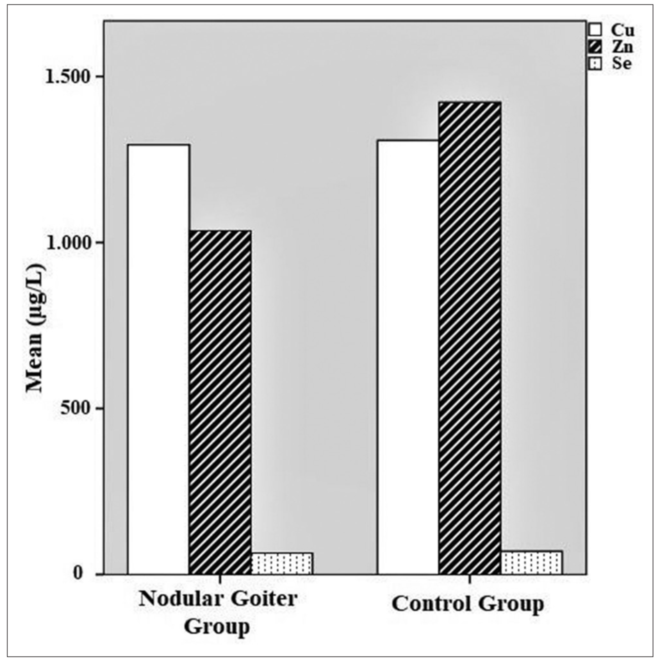

Figure 1: Serum selenium, copper and zinc levels of the nodular goiter and control groups. Column bars represent the mean of selenium, copper, and zinc levels

respectively). Free T4 was significantly lower in the control group than the nodular goiter group (0.99 ± 0.14 ng/dL vs. 1.02 ± 0.11 ng/dL, *P* = 0.017). However, thyroid gland volume was significantly lower in the control than the nodular goiter group (8.78 ± 3.49 mm^3 vs. 11.48 ± 5.57 mm^3, *P* = 0.001). Serum, zinc, and selenium levels were significantly higher in the control group than the nodular goiter group (1421.14 ± 759.2 µg/L vs. 1034.54 ± 557.12 µg/L, *P* < 0.01 and 70.00 ± 17.20 µg/L vs. 64.92 ± 13.74 µg/L, *P* = 0.008, respectively) [Figure 1]. There were no differences between the two groups in terms of BMI and copper levels.

The nodular goiter group was dichotomized according to the thyroid volumes as patients with high volume (>18 mm for female and >25 mm for male) and patients with normal volume. These two groups were statistically similar in terms of copper, zinc, and selenium levels (*P* = 0.746, *P* = 0.187, and *P* = 0.932, respectively).

Patients with nodules were analyzed according to their solitary and multiple nodule status. There was no significant difference between these two groups in terms of copper, zinc, and selenium (*P* = 0.828, *P* = 0.719, and *P* = 0.057, respectively). The positive correlations were found between copper and weight (r = 0.190, *P* = 0.011), BMI (r = 0.29, *P* < 0.01), selenium (r = 0.396, *P* < 0.01) and zinc (r = 0.155, *P* = 0.037). There were positive correlations between zinc and BMI (r = 0.165, *P* = 0.026), selenium (r = 0.23, *P* = 0.002), TSH (r = 0.151, *P* = 0.043), and copper (r = 0.155, *P* = 0.001). Selenium had positive correlations with zinc (r = 0.23, *P* = 0.002) and copper (r = 0.396, *P* = 0.001). The levels of trace elements were not correlated with thyroid hormone levels and thyroid volumes.

Discussion

The main finding of this study was the low serum selenium and zinc in the nodular goiter group. Selenium, in addition to iodine, is an important trace element of the thyroid gland. Abnormalities in iodine and selenium intake may cause thyroid dysfunction and structural changes in the thyroid gland. Due to moderate iodine deficiency, salt iodization has been mandatory since 1998 as a public health strategy[18] in Turkey. Despite the salt iodization, iodine deficiency continues in some regions in Turkey. However, according to a study conducted in 2007, iodine deficiency is not common in Yozgat.[19,20] After salt iodization, iodine screening between 2002 and 2007 showed that the median urinary iodine concentration increased from 56 µg/L to 116 µg/L.[19] According to these data, there is no significant iodine deficiency in Yozgat. Since the effect of selenium and iodine on the thyroid is interrelated, this provides a relatively safe basis for the study.

It has been reported that iodine deficiency and severe selenium may cause an increase in TSH levels and/or thyroid volume.[21,22] In Denmark, Rasmussen *et al*. reported that low serum selenium concentration was associated with a higher risk for an enlarged thyroid gland and for the development of thyroid nodules.[5] In a study by Derumeaux *et al*., there was no increased risk of thyroid nodules in patients with low serum selenium.[23] In the study with 6152 participants in China; 3038 individuals were included in the area containing sufficient selenium and 3114 persons were included in the area containing low selenium and the prevalence of thyroid diseases among the regions was evaluated. The prevalence of thyroid diseases including hypothyroidism, subclinical hypothyroidism, autoimmune thyroiditis, and diffuse goiter was higher in the group involved in the lower selenium-containing region.[24] This study is a multi-participatory study but the effect of thyroid hormones and autoimmunity diseases on selenium cannot be distinguished. We selected the patient and the control group from euthyroid status and negative thyroid antibodies so that selenium was not affected by other factors. In our study, selenium levels were significantly lower in patients with nodular goiter. As reported in previous studies, selenium deficiency is associated with a higher prevalence of thyroid disease. Hence, further data are required to prove that selenium has a protective effect against nodular goiter.[5,23,24]

The relationship between low serum selenium level and cancer is an important research topic. In a meta-analysis of 1291 patients, Shen *et al*. investigated the relation of serum selenium and copper levels with thyroid cancers.[25] They concluded that patients with thyroid cancer had lower serum selenium and higher copper levels than healthy controls. Jonklaas *et al*. evaluated 65 euthyroid patients undergoing thyroidectomy for thyroid cancer, suspected thyroid cancer, or nodular goiter and demonstrated a potential relationship between low selenium concentrations and high thyroid cancer grade.[26] This data suggests that the antioxidant properties of selenoenzymes in which selenium is involved are related to carcinogenesis and tumor progression.

Zinc is one of the trace elements in the human body. The relationship of this element with thyroid is that the thyroid hormone binding transcription factors involved in gene expression contain zinc.[27] A study reported that free T4 and T3 levels were significantly lower in patients with goiter and zinc deficiency.[8] Besides, serum zinc levels were reported to be low in hypothyroidism and high in hyperthyroidism[28] whereas Nishi *et al*. reported that serum zinc levels were similar between the patients with hypothyroidism and the control group.[29] Giray *et al*. did not find a significant difference in the zinc levels between nodular goiter and controls.[30] Our data showed that low zinc levels were associated with euthyroid nodular goiter but they were not associated with solitary or multiple nodular goiter. Zinc deficiency can play a significant role in the development of goiter nevertheless, different factors may play a role in the nodule increase.

Copper plays a role in both antioxidant and prooxidant events in the body. The data about the relationship between serum copper level and thyroid disease is conflicting. A study with rats showed a relation between copper deficiency and low plasma T3 level.[31] Giray *et al*.,[32] Kazi *et al*.,[33] and Blezewick *et al*.[34] reported that the serum copper level was lower in patients with nodular goiter compared to the control group whereas, in another study, the postoperative copper level of the patients with benign nodular gland was reported to be lower than the preoperative copper level.[35] In our study, no significant difference was found between the groups with respect to copper levels.

The present study has several limitations. Firstly, it is a cross-sectional study. Therefore, we could only make assumptions about possible etiological relationships. Longitudinal studies may be designed to determine the long-term influence of these parameters. Secondly, the sample size of this study population was relatively small. Thirdly, it reflects a single-center experience.

Conclusions

Low serum selenium and zinc levels may be related to the thyroid nodule formation. In regions with or without iodine deficiency, along with adequate iodine intake, adequate intake of selenium, and zinc may prevent the formation of thyroid nodules. Due to its anticancer properties, keeping the selenium level within the normal range may have a role in preventing the development of thyroid cancer. The cause-and-effect relationship can be more clearly demonstrated with large-scale, prospective studies.

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Conflicts of interest

There are no conflicts of interest.

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