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The Relationship between Iodine and Selenium Levels with Anxiety and Depression in Patients with Euthyroid Nodular Goiter

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ABSTRACT

Objectives: Selenium and iodine are essential microelements for normal body functions. These two elements play important roles in thyroid metabolism. The potential relationship between thyroid diseases and mental disorders have been demonstrated. We aimed to investigate the relationship between selenium and iodine levels with anxiety and depression in patients with euthyroid nodular goiter (ENG). ***Methods***: In this cross-sectional study, we enrolled 102 consecutive patients with ENG who attended the endocrine outpatient clinic between January 2018 and June 2018. We noted the patient's demographics, thyroid ultrasound imaging, thyroid hormones, and urinary iodine concentration (UIC) results. We also obtained venous blood samples for serum selenium measurement. The same psychiatrist completed the Beck Anxiety Inventory (BAI) and Hamilton Depression Rating Scale (HDRS) for all participants. The study population was dichotomized according to the median values of selenium levels and UIC. ***Results:*** BAI and HDRS scores were significantly higher in the low selenium group than the high selenium group (p = 0.032 and p = 0.042, respectively). BAI scores were significantly higher in the low UIC group than the high UIC group (p = 0.007). ***Conclusions:*** Low selenium and UIC levels may contribute to the development of anxiety and depression, independent of thyroid functions, in patients with ENG. In these patients, selenium and iodine replacement may be useful for the prevention of anxiety and depression, especially in deficient regions.

Selenium and iodine are important trace elements in human metabolism and are also essential for thyroid function. Iodine is the main component of thyroid hormones, namely, thyroxine (T4) and triiodothyronine (T3). Selenium is present in the thyroid gland in high concentrations, and this suggests that selenoproteins may contribute significantly to the integrity and functioning of the gland.[1–3]

Selenium-dependent glutathione reductase and selenoproteins are important for their antioxidant activity, which is vital for the protection of the organism. Selenium affects the metabolic pathways by changing the activity of selenoproteins and plays a role in cellular defense against oxidative stress. Selenium concentration regulates the expression of selenoproteins. Different selenium concentrations may affect immunity and energy metabolism diversely.[4]

There are different chemical forms of selenium. In particular, sodium selenate (Se^{+4}) directly activates natural killer cells, and has anti-leukemic effects and anti-cancer properties.[5,6] These anti-cancer properties have been proven by clinical and experimental studies.[7–9] Selenium deficiency deteriorates the immune system by affecting the thymus, which is responsible for the production of macrophages and lymphocytes.[9] In contrast, excess selenium is also toxic. Hair loss, skin and nail lesions, bone weakening, nausea, and diarrhea have been reported with intake above 400 μg/day.[10,11] Selenium may be derived from plant and animal sources. The main sources of selenium in the diet are cereals, meat, fish, shellfish, milk, and nuts.[4]

Thyroid diseases are manifested when the thyroid gland is unable to provide the body with sufficient hormones. A goiter is an enlargement of the thyroid, and the most common cause of the condition has been accepted as an inadequate intake of iodine in the daily diet. Multinodular goiter disease is a common condition that is characterized by the slow growth of soft nodules in the thyroid.[12]

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Anxiety and depression are psychiatric disorders that are commonly observed in society and have been associated with chronic diseases such as thyroid function disorders. The negative effects of chronic diseases are known to affect mental health.[13,14] Hypothyroidism and hyperthyroidism are associated with an increased risk of depression.[15,16] Previous studies have evaluated the relationship of trace element levels with anxiety and depression in nodular goiter. However, the association of trace elements with anxiety and depression, specifically in patients with euthyroid nodular goiter (ENG), has yet to be evaluated.

We aimed to evaluate the relationship between selenium and iodine levels with anxiety and depression in patients with ENG.

METHODS

A total of 102 participants (92 female and 10 male) between the ages of 18 and 80, who applied to the endocrine outpatient clinic between January 2018 and June 2018, were included in this cross-sectional study. Bozok University Clinical Research Ethics Committee approved the study (2017-KAEK-189_2017.12.21_16), and informed consent was obtained from all individual participants included in the study. The study was conducted following the principles of the Declaration of Helsinki (Edinburgh 2000 revision). After a physical examination, height, weight, body mass index (BMI), medications, smoking habits, and family history of thyroid disease and psychiatric disease were noted. Analyses of free T3 (FT3), free T4 (FT4), thyroid-stimulating hormone (TSH), anti-thyroglobulin, and anti-thyroid peroxidase were performed on DxI 800 Access Immunoassay (Beckman Coulter Inc., Brea, CA, USA) using a direct chemiluminescence detection system. Euthyroidism was defined as TSH, FT3, and FT4 levels are in normal range. Urinary iodine concentration (UIC) was measured by Sandell Coldhoff method with spectrophotometry. Thyroid ultrasonography was performed using Logic 700 (GE medical sys, Milwaukee, USA) with a 7 MHz superficial probe.

Venous blood samples for selenium were obtained after 10–12 hours fasting, and samples were centrifuged at room temperature for five minutes at 5000 RPM. The extracted serum was kept in ice bags and stored in deep freezers at -80 °C. Serum (1 mL) samples were taken and placed into Teflon tubes belonging to microwave digestion system (Milestone Start D-Microwave Digestion System). Then, 5 mL suprapur nitric acid (HNO_3, 65%) and 5 mL of ultrapure water were added to the blood samples and digested in the microwave system. The samples were transferred to 50 mL polypropylene tubes, and the total volume was completed to 20 mL with ultrapure water.[17] The selenium levels of the digested samples in the microwave system were determined by the 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 2.7 °C. The sampler probe was washed between injections by rinsing with ultrapure water for 30 seconds, followed by washing with 2% HNO_3 for 45 seconds, then rinsing with ultrapure water for 45 seconds. 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 0.5–1000 μg/L for selenium. The limit of detection of selenium was determined based on the standard deviation (SD) of the response and the slope of the calibration curves and was 0.204 mg/L. The sample and standard of measurements were repeated three times. Method validations were performed with certified reference material (CRM)-Seronorm™ Trace Elements Whole Blood L-2 (for selenium range 128–193 mg/L). CRM was measured five times on the same day and different days. Moreover, the average of the repeated measurements was used for the validation of the method, whereby the relative SD of the values did not exceed 5%.[18]

After thyroid assessment was finished in the endocrine outpatient clinic, patients were referred to the psychiatry outpatient clinic. The Beck Anxiety Inventory (BAI)[19] and Hamilton Depression Rating Scale (HDRS)[20] were completed by the same psychiatrist. A 21-item BAI was scored from 0 to 3 points, depending on the severity of each symptom. The final score (range; 0–63 points) was calculated by summing the results for all items. A psychiatrist completed the HDRS score by observing the patients and asking the questions on the scale. Then, the points of the items were collected. The highest possible score was 53.

Patients were excluded from the study in cases of thyrotoxicosis, hypothyroid, euthyroid with antithyroid drugs, euthyroid with thyroid replacement therapy, selenium and iodine supplement use, positive thyroid antibody, chronic heart disease, renal failure, pregnancy, inflammatory diseases, malignancy, and diagnosis of psychiatric disease.

The study population was dichotomized according to the median values of selenium and urinary iodine.

Statistical analyses were calculated using SPSS Statistics (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). The Kolmogorov-Smirnov test was used for normality. Comparisons among the groups were performed using an independent samples *t*-test for variables distributed normally and Mann-Whitney U test for non-normally distributed variables. Correlation of the study parameters was assessed by Pearson or Spearman's correlation analysis, as appropriate. A *p*-value < 0.050 was considered statistically significant.

Table 1: Descriptive features of participants (n = 102, 92 female and 10 male).

Parameters	Mean ± SD/ Median (range)
Age, years	44.6 ± 11.6
Weight, kg	76.7 ± 15.4
Height, m	159.1 ± 7.3
BMI, kg/m^2	30.2 ± 5.9
Free T3, ng/dL	2.7 ± 0.3
Free T4, ng/dL	1.0 ± 0.1
TSH, mIU/L	1.35 (0.35–4.90)
Urinary iodine, mg/day	93.45 (21.80–600.00)
Serum selenium, ng/mL	63.17 (38.36–118.42)
Thyroid volume, cm^3	9.62 (4.80–33.00)
BAI	17.7 ± 5.4
HDRS	8.50 (0.00–53.00)

Normally distributed data were expressed as the mean±standard deviation (SD), while nonparametric were expressed as the median and range. BMI: body mass index; T3: triiodothyronine; T4: thyroxine; TSH; thyroid-stimulating hormone; BAI: Beck Anxiety Inventory; HDRS: Hamilton Depression Rating Scale.

RESULTS

The general demographics and clinical characteristics of the participants are summarized in Table 1. Selenium and UIC values were non-normally distributed. The median values of serum selenium and UIC were 63.17 ng/mL (38.36–118.42) and 93.45 mg/day (21.80–600.00), respectively.

The participants were divided into two groups according to their median selenium levels: low (selenium level ≤ 63.17 ng/mL) and high (selenium level > 63.17 ng/mL). The groups were similar in terms of age, weight, height, BMI, FT3, FT4, TSH, UIC, and thyroid volume. BAI and HDRS scores were significantly higher in the low selenium group than the high selenium group ($p = 0.032$, $p = 0.042$, respectively) [Table 2].

The participants were divided into two groups according to their median UIC: low (UIC ≤ 93.45 mg/day) and high (UIC > 93.45 mg/day). The groups were similar in terms of age, weight, height, BMI,

Table 2: Demographics and clinical characteristics in the low and high selenium groups.

Parameters	Low serum selenium n = 51	High serum selenium n = 51	*p*-value
Age, year	45.7 ± 12.5	43.4 ± 10.6	0.319
Weight, kg	73.8 ± 15.4	79.6 ± 14.9	0.056
Height, m	158.7 ± 7.5	159.5 ± 7.1	0.06
BMI, kg/m^2	29.2 ± 5.8	31.3 ± 5.8	0.086
Free T3, ng/dL	2.7 ± 0.3	2.7 ± 0.3	0.921
Free T4, ng/dL	1.0 ± 0.1	1.0 ± 0.1	0.643
TSH, mIU/L	1.50 (0.35–4.90)	1.22 (0.38–4.60)	0.482
Urinary iodine, mg/day	88.90 (21.8–600)	100.20 (26.30–600.00)	0.385
Thyroid volume, cm^3	9.30 (4.87–33.00)	9.74 (5.7.00–32.15)	0.385
BAI	19.6 ± 8.2	15.9 ± 9.2	0.032
HDRS	10.00 (2.00–53.00)	8.00 (0.00–25.00)	0.042

BMI: body mass index; T3: triiodothyronine; T4: thyroxine; TSH; thyroid-stimulating hormone; BAI: Beck Anxiety Inventory; HDRS: Hamilton Depression Rating Scale.
Low serum selenium ≤ 63.17 ng/mL. High serum selenium > 63.17 ng/mL.
Values are presented as the mean±standard deviation (SD) and median (minimum-maximum), p-values < 0.050 are statistically significant.

Table 3: Demographics and clinical characteristics in the low and high UIC groups.

Parameters	Low UIC (n = 50)	High UIC (n = 50)	*p*-value
Age, years	46.0 ± 10.9	44.0 ± 11.7	0.382
Weight, kg	78.0 ± 15.2	75.6 ± 15.8	0.450
Height, m	158.8 ± 8.1	159.1 ± 6.2	0.836
BMI, kg/m^2	30.8 ± 5.5	29.9 ± 6.3	0.452
Free T3, ng/dL	2.6 ± 0.3	2.7 ± 0.3	0.368
Free T4, ng/dL	1.0 ± 0.1	1.0 ± 0.12	0.256
TSH, mIU/L	1.46 (0.44–4.49)	1.32 (0.35–4.90)	0.425
Serum selenium, ng/mL	62.80 (38.36–111.07)	63.63 (44.27–118.42)	0.326
Thyroid volume, cm^3	9.40 (4.80–32.15)	9.70 (4.90–33.00)	0.326
BAI	20.0 ± 8.1	15.2 ± 9.1	0.007
HDRS	9.00 (0.00–53.00)	7.50 (0.00–42.00)	0.425

UIC: urinary iodine concentration, low ≤ 93.45 mg/day and high > 93.45 mg/day; BMI: body mass index; T3: triiodothyronine; T4: thyroxine; TSH; thyroid-stimulating hormone; BAI: Beck Anxiety Inventory; HDRS: Hamilton Depression Rating Scale.
Values are presented as the mean± standard deviation (SD) and median (minimum-maximum), p-values < 0.050 are statistically significant.

FT3, FT4, TSH, serum selenium, thyroid volume, and HDRS score. BAI score was significantly higher in the low UIC group than the high UIC group ($p = 0.007$) [Table 3].

Serum selenium levels were negatively correlated with the BAI (r = -0.262, $p = 0.008$) and HDRS (r = -0.149, $p = 0.010$). The UIC was negatively correlated with the BAI score (r = -0.248, $p = 0.013$).

DISCUSSION

Anxiety and depression scores were significantly higher in the low selenium group, and anxiety scores were significantly higher in the low iodine group in patients with ENG. Furthermore, serum selenium was negatively correlated with anxiety and depression scores, and iodine level was negatively correlated with the anxiety score.

Selenocysteine, as a form of selenium, is included in the structure of selenoproteins. Glutathione peroxidase, thioredoxin reductase, and selenoprotein P protect tissues from lipoperoxidation and oxidative damage.[11,21] Increased levels of stress biomarkers have been reported in depression in recent studies, and this suggests that oxidative stress may be an important factor in the pathogenesis of depression.[22,23] High underground water selenium levels were associated with lesser depression symptoms.[24] High selenium levels have been associated with low geriatric depression scale scores in another study.[25] Furthermore, selenium supplementation has been reported to prevent postpartum depression, which affects about 6.5–12.9% of women in the first postpartum year.[26]

Selenium is required for the synthesis and metabolism of thyroid hormones since it is included in the structure of iodothyronine deiodinase. Thyroid hormones have long been associated with neuropsychiatric findings such as mood disorders, cognitive function disorders, and other psychiatric symptoms.[27] Patients with ENG were enrolled in this study to avoid the thyroid hormone effect. As a result, thyroid hormone levels were similar in both groups, whereas BAI and HDRS scores were significantly higher in the low selenium group. Our results suggest that, in patients with ENG, selenium may be associated with anxiety and depression independent of thyroid hormone levels. Selenium may have a protective role against anxiety and depression, possibly due to its protective effect on oxidative stress.

A new thyroid follicle cell formation has to be stimulated to develop a goiter. The thyroid gland increases its uptake of iodine in the event of insufficient iodine in the diet. In particular, T4 hormone production decreases in favor of T3, and this change causes increased TSH. Minor increases in TSH can cause thyroid enlarging effects, especially in regions of iodine deficiency.[28,29] Iodine deficiency is the most frequent cause of hypothyroidism. T4 is converted to T3 by type 2 deiodinase, a selenoprotein produced by the glial cells in the brain.

In population-based studies, increased prevalence of depression and anxiety was observed in patients with hypothyroidism and hyperthyroidism.[30] Another study detected no association between thyroid hormones and anxiety and depression in the general population,[31] and in patients with hyperthyroidism secondary to Graves' disease,[32] respectively. Although the TSH, FT4, and FT3 levels were similar between the groups, anxiety scores were significantly higher in the lower urinary iodine group in our study. While our results indicated an inverse relationship between urinary iodine and anxiety scores, no significant relationship was observed between depression scores and iodine.

Our results suggest that in patients with ENG, selenium may be inversely related to anxiety and depression, and iodine may be inversely related to anxiety regardless of the effect of selenium and iodine on thyroid functions. The inverse relationship of selenium with anxiety and depression can be explained by the protective effect of selenium on oxidative stress. The mechanism of the inverse relationship between iodine and anxiety is not clear. Prospective, large scale, randomized clinical trials are needed to elucidate the relation of these elements with anxiety and depression.

Our study has several limitations. Firstly, it is a cross-sectional study. Therefore, we could make assumptions about only 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.

CONCLUSION

Low selenium and iodine levels may contribute to the development of anxiety and depression, independent of thyroid functions, in patients with ENG. In these patients, selenium and iodine replacement may be useful for the prevention of anxiety and depression, especially in deficient regions. Longitudinal studies may be designed to determine the long-term influence of these parameters on anxiety and depression.

Disclosure

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