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Assessment of micronutrient intakes, anxiety states and risk factors affecting disease development in individuals with hypothyroidism

Avaliação da ingestão de micronutrientes, níveis de ansiedade e fatores de risco que afetam o desenvolvimento de doenças em indivíduos com hipotireoidismo

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ABSTRACT

Objective
This study aimed to assessment the risk factors affecting development of hypothyroidism and to examine the selected dietary micronutrient intakes of primary hypothyroidism, subclinical hypothyroidism and euthyroid individuals comparing the healthy control group, and to evaluate the relationship between dietary micronutrient intakes and serum thyroid hormones. Additionally, this study planned to observe anxiety severities in different hypothyroidism groups.

Methods
This case-control study was carried out with 120 individuals: 60 in the patient group and 60 in the control group. The patient group was further subdivided into primary hypothyroidism, subclinical hypothyroidism, and euthyroid groups. A questionnaire and the Beck Anxiety Inventory were administered to all participants. 24-hour food consumption records, anthropometric measurements, biochemical parameters were taken.

Results
When serum vitamin D level increased by one unit (ng/mL), risk of disease decreased by 1%; and when age (year) increased by one unit, risk of disease increased by 5.1%. Dietary micronutrient intakes were similar in all groups. There were negative correlations between serum T4 levels and selenium intake in primary hypothyroidism group, and serum TSH levels and copper intake in subclinical hypothyroidism group, and serum TSH levels and iodine intake in control group.

Beck Anxiety Inventory scores of patient groups were higher than control group. There was no statistically difference between primary, subclinical and euthyroid hypothyroidism groups in terms of anxiety scores.

Conclusion
Serum vitamin D level and age affected the risk of hypothyroidism. Micronutrient intake was associated with thyroid parameters. Anxiety was higher in hypothyroid patients, independent of thyroid hormone levels.

Keywords: Anxiety. Hypothyroidism. Micronutrients. Vitamin D.

RESUMO

Objetivo
Este estudo teve como objetivo avaliar os fatores de risco que afetam o desenvolvimento do hipotireoidismo e examinar os consumo de micronutrientes dietéticos selecionados em indivíduos com hipotireoidismo primário, hipotireoidismo subclínico e eutireoideo, comparando-os com o grupo controle saudável, e avaliar a relação entre os consumo de micronutrientes dietéticos e as hormonas tiroideias séricas. Além disso, este estudo objetivou observar a gravidade da ansiedade em diferentes grupos de hipotireoidismo.

Métodos
Este estudo de caso-controle foi realizado com 120 indivíduos: 60 no grupo pacientes e 60 no grupo controle. O grupo pacientes foi ainda subdividido em hipotireoidismo primário, hipotireoidismo subclínico, e grupos eutróide. Um questionário e o Inventário de Ansiedade de Beck foram administrados a todos os participantes. Foram recolhidos registos de consumo alimentar diário (i.e., 24 horas por dia), medições antropométricas, e parâmetros bioquímicos.

Resultados
Quando o nível de vitamina D no soro aumentou uma unidade (ng/mL), o risco de doença diminuiu 1%; e quando a idade (ano) aumentou uma unidade, o risco de doença aumentou 5.1%. A ingestão de micronutrientes na dieta foi semelhante em todos os grupos. Verificaram-se correlações negativas entre os níveis séricos de T4 e a ingestão de selênio no grupo com hipotireoidismo primário, e entre os níveis séricos de TSH e a ingestão de cobre no grupo com hipotireoidismo subclínico, e entre os níveis séricos de TSH e a ingestão de iodo no grupo controle. Pontuação do Inventário de Ansiedade de Beck dos grupos pacientes foram superiores ao grupo controle. Não houve diferença estatística entre os grupos de hipotireoidismo primário, subclínico e eutireoideo em termos de pontuação de ansiedade.

Conclusão
O nível sérico de vitamina D e a idade afetaram o risco de hipotireoidismo. A ingestão de micronutrientes foi associada aos parâmetros da tireoide. A ansiedade foram maior nos doentes com hipotireoidismo, independentemente dos níveis da hormona tiroideia.

Palavras-chave: *Ansiedade. Hipotireoidismo. Micronutrientes. Vitamina D.*

INTRODUCTION

Thyroid dysfunctions are common health problems. Hypothyroidism is one of the most common thyroid problems with 99% of cases being Primary Hypothyroidism (PH). The PH is characterized by decreased levels of the thyroxine hormone (T4) and increased levels of the Thyroid Stimulating Hormone (TSH, thyrotropin) which are produced and secreted from the thyroid gland [1]. There are various factors affecting the thyroid gland, pituitary, or hypothalamus in the etiology of hypothyroidism. Those that directly affect the thyroid gland are autoimmune thyroid disease, trophoblastic tumors, thyroid hormone resistance, radioactive iodine therapy, antithyroid drugs, iodine deficiency or excess, lithium, and radiation; while those that affect the pituitary and hypothalamus are trauma, tumor, surgical operations, infiltrative disorders, inflammatory diseases, infection and drugs [1]. In addition to these, stress, tobacco use, gender, age factor, vitamin D, and selenium deficiencies are other suspected etiological causes [1-5]. Micronutrients that are frequently deficient, especially

in autoimmune thyroid disease, are iodine, selenium, iron, zinc, copper, magnesium, potassium, as well as vitamins A, B, C, and D [5]. However, associations between micronutrient intakes and thyroid markers are remains unclear [6,7]. Besides, studies examining dietary micronutrient intakes in different types of hypothyroidism are quite limited [8].

Adequate iodine intake is necessary for the production of thyroid hormones [5]. The main dietary sources of iodine include seafood such as shrimp, sardines, cod, salmon, tuna; animal products such as milk, yogurt, eggs; and fruits such as cranberries, blueberries, and strawberries [9]. 71% of the world's population has access to iodized salt thanks to the iodized salt programs implemented in many countries such as the United States, China, India, Iran, and Switzerland, the problem of iodine deficiency has been prevented [10]. While iodine deficiency is a risk factor for endemic goiter, hypothyroidism and cretinism, excess iodine intake may also be a risk factor for hypothyroidism, hyperthyroidism, autoimmune thyroid diseases [11,12]. Selenium (Se) is an essential micronutrients with many functions ranging from antioxidant and anti-inflammatory effects to active thyroid hormone production. Se plays an important role in thyroid hormone homeostasis with selenoenzymes and selenoproteins in which it is included such as glutathione peroxidase, thioredoxin reductase, and iodothyronine deiodinase [13]. The main sources of Se are animal meats, seafood, Brazil nuts, and unprocessed grains [8]. Its deficiency has been associated with thyroid diseases including hypothyroidism, subclinical hypothyroidism, goiter [14]. Although the important roles of iodine and selenium on thyroid metabolism are known, the causal relationship between dietary intakes and thyroid parameters is not clear [15,16]. Fewer studies have examined the association between selenium and thyroid hormones, and current findings are inconsistent. A cross-sectional study from Latvia found higher plasma selenium level was associated with lower TSH, but not T3 and T4 [17]. In a randomized controlled trial among 491 Danes, Winther et al. found that selenium supplementation could affect thyroid function by reducing serum TSH and FT4 concentrations [18]. In contrast, two other studies, one in the UK, and the other in New Zealand, found no association between selenium intervention and thyroid hormone concentrations [19,20].

While it is better known that selenium and iodine play important roles in the synthesis and metabolism of thyroid hormones, the effects of other trace elements such as copper (Cu) and zinc (Zn) on thyroid hormones have yet to be determined [21]. It is known that copper (Cu) is associated with the metabolism of tyrosine, an amino acid required for the production of thyroid hormones, and imbalances in copper levels have been associated with some thyroid diseases in the literature [22]. According to data obtained from the US National Health and Nutrition Examination Survey in 2011-2012, serum Cu levels were found to be positively correlated with free and total T4 levels in women and total T4, T3 levels in men [23]. A meta-analysis conducted in 2020 reported that patients with hypothyroidism showed lower serum Zn levels compared to healthy controls but serum Cu levels did not differ significantly between groups [24]. In a different study with healthy Koreans, serum Cu levels were positively correlated with free T4 levels for both sexes [21]. Data on trace elements and their effects on the thyroid status remain inconsistent [25].

Vitamin D deficiency has attracted attention all over the world in recent years and has also become important in thyroid diseases. It has both endogenous and exogenous sources. As an endogenous source, the skin enables the body to synthesize vitamin D through sunlight. Foods that are exogenous sources are oily fish (sardines, salmon, cod), liver, egg yolks, and sun-dried mushrooms [26,27]. The ideal serum range was determined to be 30-80 ng/mL with <30 ng/mL considered insufficient [28]. In the National Health and Nutrition Examination Survey (VI), which examined the relationship between hypothyroidism and vitamin D, low vitamin D levels were found

to increase the risk of autoimmune hypothyroidism [29]. The relationship between vitamin D and thyroid functions is not clear; however if there is a possible relationship, it is thought to be through the immune system [30]. Pezeshki et al. conducted a pilot randomized clinical trial in 2020 to investigate the effectiveness of vitamin D therapy on subclinical hypothyroidism. They emphasized that the use of vitamin D supplements significantly reduces mean TSH levels as well as the need for vitamin D screening and treatment in subclinical hypothyroid individuals [31]. Increasing evidences suggest that vitamin D insufficiency may be a risk factor for hypothyroidism.

It is known that patients with primary hypothyroidism have higher anxiety levels than healthy individuals. Although the causal relationship has yet to be clarified, there are studies linking this comorbidity with serum TSH or T4 levels [32-34]. A study conducted in 2022 in China found that even T4 levels in the reference ranges were associated with anxiety severity [34]. Research by Lang et al. determined that as the TSH levels of individuals with subclinical hypothyroidism increased, anxiety symptoms increased [35]. However, it is not known whether there is a gradually increasing anxiety state in euthyroidism, subclinical hypothyroidism and primary hypothyroidism, respectively. This study aimed to assessment the risk factors affecting the development of the hypothyroidism and to examine the selected dietary micronutrient intakes of primary hypothyroidism, subclinical hypothyroidism and euthyroid individuals comparing the healthy control group, and to evaluate the relationship between dietary micronutrient intakes and serum thyroid hormones in all groups. Additionally, this research planned to observe whether there will be a gradually increasing state of anxiety in different hypothyroidism groups.

METHODS

This prospective, case-control study was approved by the Ethics Committee of Ankara Yıldırım Beyazıt University (Project No: 2019-485) and was carried out in accordance with the Declaration of Helsinki. All volunteers included in the study signed an informed consent form. The study, conducted between 2019 and 2021, involved 120 individuals, aged 18-64 years, who attended the internal medicine outpatient clinic of a university hospital in Turkey (Due to pandemic period restrictions, work was suspended from March 2020 to February 2021). Individuals were divided into two groups: 60 patients diagnosed with hypothyroidism and 60 control patients. The patient group was further divided into three equal subgroups: the Primary Hypothyroidism group (newly diagnosed and not receiving medication), Subclinical Hypothyroidism group (newly diagnosed and not previously diagnosed with hypothyroidism), and Euthyroid group (previously diagnosed as primary hypothyroidism and receiving L-T4 treatment).

Primary hypothyroidism was defined as TSH >5.33 μIU/mL (normal reference range, 0.38 to 5.33) with T4 <0.61 ng/dL (normal reference range, 0.61 to 1.20). Subclinical hypothyroidism was defined as TSH >5.33 μIU/mL while T3 and T4 were within normal reference ranges (for T3, 2.60 to 4.37 pg/mL; for T4, 0.61 to 1.20 ng/dL). Exclusion criteria of the study were diabetes, cancer, history of thyroid operation, psychological diseases, liver-kidney disease, pregnancy, and lactation. Blocked randomization method was used for age-gender distribution in the patient and control groups. Also, all groups were matched in terms of socioeconomic status, diet, and other diseases (not included in the exclusion criteria). As a result of the power analysis performed using the G*Power 3.0.10 program, the power of the study was determined as 90.2% with a 5% margin of error.

A descriptive questionnaire in which demographic characteristics, health information, anthropometric measurements, and nutritional habits were questioned, was administered to all individuals participating in the study via the face-to-face interview method by the researcher.

In order to evaluate the micronutrient intake of individuals, food consumption records were taken by the researcher with a 24-hour retrospective reminder method. The nutrient values of the foods and beverages consumed were calculated using the "Nutrition Information System" Turkish software version 9.0 (BEBIS Inc, Istanbul, TR). Assessment of individuals' daily micronutrient intake was made according to the "Dietary Reference Intake" [36].

The Beck Anxiety Scale, developed by Beck et al. [37], was used to evaluate the anxiety status of individuals. The Turkish version of the scale was made by Ulusoy et al. [38]. The scale consists of 21 questions which offer 4 response options: "none" – 0 points, "mild" – 1 point, "moderate" – 2 points, and "severe" – 3 points. When an individual's responses are added up, 0-7 points are considered minimal anxiety, 8-15 points are mild, 16-25 points are moderate, and 26-63 points are severe anxiety symptoms.

Body weight (kg), height (cm), waist circumference (cm), mid-upper arm circumference (MUAC) (cm), and hip circumference (cm) measurements were taken by the researcher. The body weight of the individuals was evaluated with a calibrated portable scale with an accuracy of 0.1 kg. Height was measured using a non-stretch tape measure and by providing the Frankfurt plane. Body Mass Index (BMI) values were calculated by dividing the body weight of individuals by their height in meters squared [39]. Waist circumference was measured midway between the lowest rib and the crista iliac, and hip circumference was measured at the widest line of the hip. The MUAC was measured midway between the acromion and the olecranon prominence, with the individual's arm bent 90°.

Blood samples were taken from each participant after a 10-12 hour night fast. Biochemical tests were analyzed in the laboratory of the university hospital and the test results were obtained from the hospital database.

The data obtained from the study were evaluated with the IBM®SPSS® version 24.0 (SPSS Inc, Chicago, IL, USA) statistical package program. Frequency tables and descriptive statistics were used to interpret the findings. Data normality was assessed by the Shapiro–Wilk test. The Shapiro–Wilk test is more appropriate method for small sample sizes (<50 samples) although it can also be handling on larger sample size while Kolmogorov–Smirnov test is used for n ≥50. Parametric methods were used for measurement values that comply with normal distribution. In accordance with parametric methods, the "ANOVA" test (F-table value) method was used to compare the measurement values of three or more independent groups. For pairwise comparisons of variables with significant differences for three or more groups, the Tukey test was applied according to the homogeneity of variances. Non-parametric methods were used for measurement values that did not comply with normal distribution. In accordance with non-parametric methods, the "Kruskal-Wallis H" test (χ^2-table value) method was used to compare the measurement values of three or more independent groups. Bonferroni correction was applied for pairwise comparisons of variables with significant differences in three or more groups. "Pearson" correlation coefficient was used to examine the relationships of two quantitative data with normal distribution, and "Spearman" correlation coefficient was used when at least one of them was not normally distributed. "Pearson-χ^2" cross-tabulations were used to examine the relationships between two qualitative variables. To examine the disease risk factor, all patients at various clinical levels were evaluated as a single patient group. The backward binary logistic regression method was applied by comparing this patient group with the control group. $p<0.05$ in all analyses was accepted as a statistically significant difference.

RESULTS

The mean age of the patient group (PG) was 36.33±11.50 years, and the control group (CG) was 30.63±10.06 years (p>0.05). The majority of individuals in both groups were women (83.3% of women for both groups) and most of the individuals in both groups were married (p<0.05) (unshown data). The distribution of the individuals participating in the study according to their anthropometric measurements is shown in Table 1. Body weight, BMI, waist circumference, hip circumference, waist/hip ratio, and MUAC means of women and men in PG were higher than those of CG (p>0.05).

The distribution of individuals according to their biochemical parameters is given in Table 2. Serum vitamin D levels were 14.45±9.68 ng/mL in PHG, 12.80±6.96 ng/mL in SHG, 15.05±7.88 ng/mL in EG, and 20.72±25.51 ng/mL in CG. There was no significant difference between the serum vitamin D and serum vitamin B12 levels of the groups (p>0.05). There was no significant difference between the mean daily intake of selenium, iodine, copper, and zinc (p>0.05) (Table 3).

Table 1 – Anthropometric measurement mean and standard deviation ($\overline{X}$±SD) values of individuals.

Anthropometric Measurements	Patient Group (n=60)			Control Group (n=60)
	Primary (n=20)	Subclinical (n=20)	Euthyroid (n=20)	
	$\overline{X}$±SD	$\overline{X}$±SD	$\overline{X}$±SD	$\overline{X}$±SD
Female				
Body weight (kg)	74.87±16.80	78.06±18.75	76.70±15.51	71.13±18.60
Height (cm)	160.84±5.25	160.82±4.33	159.15±6.54	161.88±5.88
BMI (kg/m^2)	28.93±6.29	30.23±7.30	30.49±6.79	27.14±7.02
Waist Circumference (cm)	93.36±15.79	97.60±16.39	99.55±15.85	89.90±17.04
Hip Circumference (cm)	106.54±11.84	111.73±13.94	120.95±12.45	106.53±14.12
Waist/hip ratio	0.88±0.09	0.87±0.07	0.88±0.07	0.84±0.08
MUAC (cm)	30.18±4.69	31.67±4.72	32.55±3.58	29.15±5.03
Male				
Body weight (kg)	88.11±11.66	90.83±8.40	–	78.60±8.17
Height (cm)	173.85±4.74	176.67±8.50	–	173.40±5.56
BMI (kg/m^2)	29.20±4.24	29.40±5.57	–	26.20±3.06
Waist Circumference (cm)	98.25±2.21	102.00±2.82	–	96.38±6.14
Hip Circumference (cm)	104.33±2.52	104.00±1.42	–	102.29±4.35
Waist/hip ratio	0.94±0.02	0.98±0.04	–	0.94±0.05
MUAC (cm)	31.67±2.52	30.50±0.71	–	30.29±2.63

Note: BMI: Body Mass Index; MUAC: Mid Upper Arm Circumference.

Table 2 – Mean, standard deviation ($\overline{X}$±SD), and median (IQR) values for biochemical parameters.

Biochemical Parameters	Patient Group (n=60)						Control Group (n=60) [4]		p-value	Reference Values
	Primary (n=20) [1]		Subclinical (n=20) [2]		Euthyroid (n=20) [3]					
	$\overline{X}$±SD	Median [IQR]	$\overline{X}$±SD	Median [IQR]	$\overline{X}$±SD	Median [IQR]	$\overline{X}$±SD	Median [IQR]		
TSH (µIU/mL)	34.54±23.68	29.7 [38.9]	6.78±1.50	6.4 [1.5]	2.28±0.99	2.4 [1.9]	2.18±1.14	2.1 [1.7]	0.000[a.c.d]	0.38-5.33
T3 (pg/mL)	2.97±0.42	3.0 [0.4]	3.57±0.42	3.6 [0.5]	3.71±0.43	3.7 [0.5]	3.58±0.40	3.6 [0.7]	0.000[b.e]	2.60-4.37
T4 (ng/dL)	0.51±0.09	0.5 [0.2]	0.80±0.12	0.8 [0.2]	1.00±0.011	1.0 [0.1]	0.88±0.15	0.9 [0.3]	0.000[a.f.g]	0.61-1.20
Vitamin B12 (pg/mL)	213.35±87.56	175.5 [139.0]	238.05±188.40	169.5 [164.3]	189.35±66.86	181.5 [71.0]	196.27±75.34	191.0 [89.0]	0.911[a]	126-505
Vitamin D (ng/mL)	14.45±9.68	10.8 [9.7]	12.80±6.96	11.1 [9.5]	15.05±7.88	13.1 [13.1]	20.72±25.51	16.6 [14.7]	0.076[a]	30-100

Note: [a] Kruskal-Wallis Test, [b] ANOVA, [c] [1-2,3,4], [d] [2-3,4], [e] [1-2,3,4], [f] [1-2,3,4], [g] [3-2,4], TSH:Thyroid Stimulating Hormone, T3:Triiodothyronine, T4:Thyroxine.

Table 3 – Mean, standard deviation ($\overline{X}$±SD), and median (IQR) Values of daily micronutrient intakes of individuals.

Dietary Minerals	Patient Group (n=60)						Control Group		*p*-value
	Primary (n=20)		Subclinical (n=20)		Euthyroid (n=20)		(n=60)		
	$\overline{X}$±SD	Median [IQR]	$\overline{X}$±SD	Median [IQR]	$\overline{X}$±SD	Median [IQR]	$\overline{X}$±SD	Median [IQR]	
Selenium (µg)	21.69±22.77	17.2 [29.2]	13.37±23.06	7.1 [16.1]	11.99±11.52	13.1 [19.5]	16.25±20.31	14.3 [18.3]	0.239
Iodine (µg)	128.40±68.60	120.9 [68.3]	122.23±56.10	115.8 [103.0]	112.98±49.61	102.3 [56.3]	130.15±75.82	117.1 [93.3]	0.869
Copper (mg)	1.81±0.82	1.8 [1.1]	2.06±3.10	1.4 [0.8]	1.45±0.84	1.3 [0.4]	1.45±0.80	1.3 [0.7]	0.129
Zinc (mg)	10.31±3.84	9.8 [5.6]	8.42±6.07	7.5 [4.4]	9.98±3.59	9.1 [4.9]	9.17±4.33	7.7 [5.6]	0.094

Note: Kruskal-Wallis Test.

When the relationship between serum TSH levels and micronutrients was examined, it was determined that individuals in SHG had a negative relationship with copper intake (r=-0.506; *p*=0.023) (Table 4). There was also a negative correlation between serum TSH levels and iodine intake in individuals included in CG (r=-0.315; *p*=0.014). There was no significant relationship between serum TSH levels and selenium or zinc intakes of individuals (*p*>0.05). Individuals in PHG had a negative relationship with selenium intake (r=0.482; *p*=0.032) (Table 4).

The risk factors affecting the development of thyroid disease in individuals are evaluated in Table 5. Gender, tobacco use, daily dietary selenium intake, and iodine intake did not show significant relationships with hypothyroid disease risk, while serum vitamin D levels and age were found to affect disease risk. The risk of disease decreased by 1% when the serum vitamin D (ng/mL) level increased by one unit (OR=0.990, *p*=0.023). When age (year) increased by one unit, the risk of disease increased by 5.1% (OR=1.051, *p*=0.012).

Table 4 – Correlation of serum TSH and T4 levels with micronutrients.

Dietary Micronutrients	TSH				T4			
	Patient Group (n = 60)			Control Group (n=60)	Patient Group (n=60)			Control Group (n=60)
	Primary (n=20)	Subclinical (n=20)	Euthyroid (n = 20)		Primary (n=20)	Subclinical (n=20)	Euthyroid (n=20)	
Selenium								
r	0.148	0.223	0.148	0.068	-0.482	-0.093	0.059	0.260
p	0.534	0.345	0.533	0.606	**0.032**	0.698	0.805	0.092
Iodine								
r	0.320	0.015	0.059	-0.315	-0.317	0.043	-0.101	0.125
p	0.169	0.950	0.806	**0.014**	0.174	0.856	0.673	0.423
Copper								
r	-0.094	-0.506	0.158	-0.071	-0.265	0.170	-0.388	0.032
p	0.694	**0.023**	0.560	0.590	0.258	0.473	0.091	0.839
Zinc								
r	0.238	-0.140	0.285	-0.109	-0.130	0.042	-0.173	0.053
p	0.313	0.556	0.223	0.405	0.586	0.860	0.466	0.735

Note: Pearson and Spearman Test. TSH: Thyroid Stimulating Hormone; T4: Thyroxine.

Table 5 – Determination of factors affecting the development of hypothyroid disease.

Variable	B	S.H.	Wald	SD	*p*	OR	95% Confidence Interval (OR)	
							Upper	Lower
Age (year)	0.049	0.020	6.291	1	**0.012**	1.051	1.011	1.092
Gender	0.243	0.553	0.192	1	0.661	1.275	0.431	3.770
Tobacco Use	0.171	0.556	0.094	1	0.759	1.186	0.399	3.525
Selenium	0.003	0.006	0.244	1	0.621	1.003	0.992	1.014
Serum Vitamin D	-0.010	0.004	5.161	1	**0.023**	0.990	0.981	0.999
Iodine	0.004	0.005	0.662	1	0.416	1.004	0.994	1.014
Constant	-1.854	1.125	2.713	1	0.100	0.157		

Note: CCR: 81.4%, $\chi^2_{(8)}$=10.742; *p*=0.217.

The mean anxiety score of PHG was 14.10±8.10, SHG was 13.35±9.66, EG was 14.75±9.54, and CG was 7.23±5.68 (p=0.000) (unshown data). While the Beck Anxiety Inventory scores of PHG, SHG, and EG were significantly higher than CG (p=0.000), there was no significant difference between the groups (p>0.05).

Since the number of tables specified for the article was exceeded, the tables expressed as "unshown" could not be presented. These tables were given in the supplementary materials.

DISCUSSION

The current study evaluated the risk factors affecting the development of the hypothyroidism and examined the selected dietary micronutrient intakes of primary hypothyroidism, subclinical hypothyroidism and euthyroid individuals comparing the healthy control group and assessed the relationship between dietary micronutrient intake and thyroid parameters. Additionally, this study observed the anxiety severities in different hypothyroidism groups. The statistical power of the sample was calculated and power of the study was determined as 90.2% with 95% confidence.

There are limited studies comparing dietary micronutrient intakes in primary hypothyroidism, subclinical hypothyroidism and euthyroidism. Also this study contributes to the literature by examining the risk factors of the hypothyroidism in order to provide reasonable and preventive measures against this common disease.

Iodine is essential for the functioning of the organism as a whole, including the proper functioning of the thyroid [5]. In this study, an inverse relationship was found between increased iodine intake and serum TSH level in the control group (Table 4). However, when the mean daily iodine intake of the groups is examined, it should be considered that the intake was less than the recommended value (150 µg/day) (Table 3) [36]. Although the majority of all groups used iodized salt (unshown data), the insufficiency may be due to low dietary iodine intake and preparation, cooking, storage losses. This finding supports studies showing that insufficient iodine intake increases the risk of hypothyroidism in healthy individuals [40,12]. In an in-vitro study conducted with thyroid cells obtained from Hashimoto patients, Xu et al. observed that apoptosis in the cells increased as the concentration of iodine applied externally to the cells increased. It has also been reported that autophagocytic processes are suppressed and free radicals increase. This situation is thought to be due to the possible oxidation effect of iodine [41].

There are some hypotheses regarding the protective effect of selenium against thyroid diseases. These effects include reducing the expression of HLA-DR antigens on the thyrocyte surface, causing a decrease in the concentrations of antithyroid antigen antibodies, controlling the lymphocyte B-dependent immunological response, inhibiting the production of proinflammatory cytokines, reducing the synthesis of leukotrienes and prostaglandins, protecting the thyroid gland against oxidative stress, optimizing TH production, and transport through induction of selenoprotein synthesis [42]. In research Liu et al. reported that the increased dietary selenium intake was negatively correlated with T4 in U.S. adults A significant decrease in serum T4 levels was shown compared to the control group [15].The negative correlation between the selenium intake of PHG and T4 in the present study (Table 4) is in line with the above findings. An ELSA-Brazilian study conducted with 14 283 people demonstrated that increased dietary selenium intake decreased the risk of subclinical hypothyroidism [8]. In this study, no relationship was observed between Se intake and thyroid hormones in SHG. This may be due to the fact that the average daily selenium intakes of all groups in this study are considerably lower than the amounts in the literature (50-100 µg/day). (Table 3) [43].

A case-control study of Rasic-Milutinovic et al. showed that serum trace element levels including Cu, Zn, and Mn were significantly higher in patients with hypothyroidism [44]. Differently, a recent retrospective study examining the effects of serum micronutrients on thyroid parameters showed that Zn and Cu levels exhibited a significant and strong positive correlation with T4 and free T4 levels [45]. In a study, with 219 healthy men, Meeker et al reported a monotonic decrease in TSH levels as serum Cu levels increased [46]. Giray et al. found the Cu levels of people diagnosed with multinodular goiter to be higher than healthy controls [47]. The present study observed that copper intake increased in SHG while serum TSH level decreased. This finding was similar to the results of Meeker et al. (Table 4) [46]. However, unlike Meeker et al. the present research investigated dietary Cu intake not serum Cu levels [46]. Considering the other groups in this study, in parallel with Jain's study, no relationship was found between Cu intake and thyroid hormones [23]. When Cu intake was evaluated, it was seen that all groups had a higher Cu intake than the daily recommended amount (900µg/day) (Table 3) [36]. Additionally, no relationship was found between dietary Zn intake and thyroid hormones in present study (Table 4). Dietary Zn intakes of the groups were slightly below the Dietary Reference Intake values (11mg/day) (Table 3) [36]. It should be noted that increased Cu intake may also affect the absorption of other trace elements such as Se, I, Zn, and Fe. Studies examining the relationship between dietary Cu intake and thyroid metabolism are limited and more are needed [23,45,46].

Errors inherent to the method of evaluating food consumption may explain why there was no differences in mikronutrient intake between the groups, which influence the standardization of portions and household measures during the evaluation, the memory of the respondents, the sample size and the heterogeneity of dietary patterns, making it impossible to evaluate food consumption without errors [48]. We also emphasize here that the researchers who preformed the evaluation were different than the ones involved in statistical analyses.

Because vitamin D plays an important role in the modulation of the immune system, it is closely related to autoimmune thyroid diseases [9]. Through a meta-analysis, Taheriniya et al. indicated that patients with HT or hypothyroidism had significantly lower serum vitamin D levels compared to healthy subjects [10]. Likewise, some studies have shown an inverse relationship between serum 25(OH)D levels and thyroid peroxidase antibody (TPO-Ab), anti-thyroglobulin (Tg-Ab) levels [49,50]. However, it is also thought that low 25(OH)D levels in HT patients may be a consequence of the disease. Increased body fat mass due to hypothyroidism in HT and other comorbid autoimmune diseases may predispose individuals to vitamin D deficiency [51]. In this study, although the mean serum vitamin D levels of the control group were higher than the patient group, the difference was not significant (p>0.05) (Table 2). The small sample size may have affected the significance of the result. The mean vitamin D levels of all groups were below the reference value, which may be due to the fact that the individuals are often unable to get sufficient vitamin D through dietary sources as well as low rates of nutritional supplement use. Additionally, this study was carried out in the winter season which may have exacerbated the insufficiency. Besides, present study determined that the risk of disease decreased by 1% when the serum vitamin D level increased by one unit (Table 5).

Hypothyroidism has the most frequent incidence in the 30-50 age group with prevalence increasing with age [52]. In this study, the mean age of PG was 36.33±11.50 years and that of CG was 30.63±10.06 years. When the age (year) factor increased by one unit, the risk of disease increased by 5.1% (Table 5). The findings of the present study are quite similar to the literature.

Junior et al. reported that anxiety was observed 3 times more in patients with primary hypothyroidism compared to the euthyroid control group (p<0.05). There was no significant

relationship between serum TSH levels and the prevalence of anxiety [53]. Yarpuz et al. showed that thyroxine treatment administered to patients with subclinical hypothyroidism significantly reduced Beck Anxiety Inventory scores in patients [54]. In the present study, Beck Anxiety Inventory scores in PHG, SHG, and EG were found to be higher than the CG (p=0.00) (unshown data), which is a result similar to what has been seen in the literature. However, there was no statistically significant difference between PHG, SHG, and EG in terms of anxiety scores (p>0.05). This may be due to the fact that the duration of the disease period of patients with PHG and SHG is not known. Increased serum TSH levels for PHG and SHG may be associated with increased anxiety scores. However, the significant difference in EG compared to CG differs from the result in the study by Yarpuz et al. [54]. This situation similar to the study of Gomez et al. suggests that even hypothyroid individuals with drug therapy and normal serum thyroid hormones may be at risk for anxiety [55]. Factors such as regular health checks and regular drug therapy may affect the anxiety state in EG. Further, there are some hypotheses about this anxiety situation [56-58]. In euthyroid individuals, despite normal TSH levels, low T3 levels can be found in the brain. This condition, called "hypothyroid brain", has been associated with polymorphisms in deiodinase enzymes and mutations in proteins that regulate the transport of thyroid hormones in the brain [56-58]. Panicker et al. observed that individuals with the deiodinase variant had worse 'psychological well-being' scores even under L-T4 treatment [58]. Some symptoms associated with the hypothyroid brain are increased thyrotropin-releasing hormone and decreased transthyretin levels in the cerebrospinal fluid [58]. Another hypothesis is that the higher anthropometric measurements such as body weight, BMI, MUAC, and waist circumference in euthyroid individuals compared to controls may affect the anxiety state [35]. In this study, body weight, BMI values, waist circumference, and MUAC measurements of euthyroid women were higher than the control group (Table 1). More studies are needed to clearly explain the mechanism of anxiety in euthyroid individuals [56-58].We also emphasize here that this study has some limitations. We used the 24-hour recall to assess micronutrient intake, because it has been widely used in food consumption studies [59,60]. The low correlation between measurement error in nutrient estimates explains the preference for 24-hour recall over other methods. However, the instrument depends on the patient's memory and may present evaluation errors if an atypical food pattern is used as reference. The lack of a significant difference in the dietary intake of the groups may be shortcomings of tools we used. Additionally, in the backward approach, the Logistic Regression method used to determine the factors affecting the disease may potentially cause biases because of the exclusion of variables due to multiple hypothesis tests. Another limitations of the study are the small number of samples and possible biases in patient or control selection. In this study conducted during and immediately after the pandemic, no male patients were found for the euthyroid patient group. Therefore, the gender distribution of the control group was adjusted accordingly. In future, studies with larger samples are needed to clarify the causal relationship between dietary micronutrient intake and thyroid parameters.

CONCLUSION

This study has shown that although primary hypothyroidism, subclinical hypothyroidism and euthyroid patients do not differ in terms of micronutrient intake, there may be a relationship between dietary intake of some micronutrients and thyroid parameters. For this reason, it is important for patients to have an adequate and balanced diet. Sufficient and balanced intake of micronutrients associated with thyroid health such as iodine, selenium, copper, and zinc should be provided with the diet. Individuals with a diagnosis of hypothyroidism should also be evaluated in

terms of psychological problems. In this study, we observed that low serum vitamin D level and increasing age increases the risk of hypothyroidism. Therefore, thyroid function screenings should be performed at regular intervals. Besides, routine monitoring of serum vitamin D is recommended in patients with hypothyroidism. To keep vitamin D levels within appropriate limits, patients with hypothyroidism should consume vitamin D sources regularly in their diet and sunbathe for 15-30 minutes 2-3 times a week with their hands, face, and arms exposed to the sun. Vitamin D supplements may be considered depending on deficiency severity. There is a need for multicenter and longer-term studies with a higher number of cases so that the results are meaningful.

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CONTRIBUTORS

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