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Effects of Obesity on the Thyroid Hormone Levels: Retrospective Cross-Sectional Study

Obezitenin Tiroid Hormon Düzeyleri Üzerine Etkileri: Retrospektif Kesitsel Çalışma

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ABSTRACT Objective: The incidence of obesity is increasing. Thyroid dysfunction has been extensively studied in obesity. The aim of this study is to determine thyroid hormone levels in patients with obesity (Class I and II obesity) and morbid obesity, and to determine the correlation between body mass index (BMI) and thyroid hormones. **Material and Methods:** Data from one hundred fifty-seven patients with obesity, including 71 patients with a BMI of 30-39.9 kg/m^2 (Group 1) and 86 patients with morbid obesity with a BMI≥40 kg/m^2 (Group 2), and 60 control subjects with a BMI of 18.5-24.9 kg/m^2 were retrospectively reviewed. Thyroid hormone levels were compared. Consent was obtained from the patients and, if necessary, their legal representatives. The study was a retrospective cross-sectional study. Ethics committee approval was obtained for our study. **Results:** The mean age of obese and normal-weight individuals was similar (p=0.94). Thyroid-stimulating hormone (TSH) levels were higher in patients than in controls (3.7±1.8 µIU/mL and 2.5±1.7, respectively; p=0.01). The prevalence of subclinical hypothyroidism (SCH) was higher in patients than in controls (p=0.003). There was a positive correlation between TSH and BMI (r=0.44, p=0.001). In subgroup analysis, TSH level was similar in Group 1 and Group 2 (p=0.07). TSH was higher in Group 1 (p=0.03) and Group 2 (p=0.01) than in the control group. The frequency of SCH was similar in Group 1 and Group 2 (p=0.06). The frequency of SCH was higher in Group 1 (p=0.006) and Group 2 (p=0.002) than in the control group. **Conclusion:** TSH level was higher in patients with obesity than in healthy controls. There was a positive correlation between BMI and TSH. Thyroid hormone levels were similar in patients with a BMI of 30-39.9 kg/m^2 and morbid obesity. We recommend thyroid hormone screening in obesity.

Keywords: Obesity; thyroid hormones; thyroid-stimulating hormone

ÖZET Amaç: Obezite insidansı giderek artmaktadır. Obezitede tiroid disfonksiyonu kapsamlı bir şekilde çalışılmıştır. Bu çalışmanın amacı obez (Sınıf I ve II obezite) ve morbid obez hastalarda tiroid hormon düzeylerini belirlemek ve beden kitle indeksi (BKİ) ile tiroid hormonları arasındaki korelasyonu tanımlamaktır. **Gereç ve Yöntemler:** Obez 157 hastanın verisi, BKİ 30-39,9 kg/m^2 olan 71 birey (Grup 1), BKİ≥40 kg/m^2 olan 86 morbid obez birey (Grup 2) ve BKİ of 18,5-24,9 kg/m^2 olan 60 kontrol birey retrospektif olarak tarandı. Tiroid hormon seviyeleri karşılaştırıldı. Hastalardan ve gereğinde yasal temsilcilerinden onam alındı. Çalışmamız retrospektif kesitsel çalışmadır. Çalışmamız için etik kurul onayı alınmıştır. **Bulgular:** Obez ve normal kilolu bireylerin yaş ortalamaları benzer bulundu (p=0,94). Obez hastalarda tiroid uyarıcı hormon (TSH) düzeyleri normal kilolu kontrol grubuna göre daha yüksekti (3,7±1,8 µIU/mL ve 2,5±1,7, sırasıyla; p=0,01). Obezite grubunda subklinik hipotiroidizm prevalansı normal kilolu kontrol grubuna göre daha yüksekti (p=0,003). Obez hastalarda TSH konsantrasyonları ve BKİ arasında pozitif korelasyon saptandı (r=0,44, p=0,001). Subgrup analizde Grup 1 ve Grup 2'nin TSH seviyesi benzerdi (p:0,07). TSH Grup 1 (p=0,03) ve Grup 2'de (p=0,01) kontrol grubuna göre daha yüksek saptandı. Subklinik hipotiroidi sıklığı Grup 1 ve Grup 2'de benzerdi (p=0,06). Subklinik hipotiroidi sıklığı Grup 1 (p=0,006) ve Grup 2'de (p=0,002) kontrol grubuna göre daha yüksekti. **Sonuç:** Obez hastalarda TSH düzeyi sağlıklı kontrol grubuna göre daha yüksek idi. BKİ ile TSH arasında pozitif bir korelasyon bulunmaktadır. BKİ 30-39,9 kg/m^2 olan ve morbid obezitesi olan hastalarda tiroid hormon düzeyleri benzerdi. Biz obezitede TSH düzeylerinin taranmasını öneriyoruz.

Anahtar Kelimeler: Obezite; tiroid hormonları; tiroid uyarıcı hormon

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It is well known that the prevalence of obesity is increasing in both children and adults and both in our country and in other countries.[1,2] Obesity is a metabolic disorder usually caused by excessive and unhealthy food consumption and lack of physical activity.[1] Currently, body mass index (BMI) is used to determine obesity instead of body fat and muscle analysis. A BMI≥30 kg/m^2 indicates obesity; obesity Class I is BMI 30 to 34.9 kg/m^2; obesity Class II is BMI 35 to 39.9 kg/m^2; obesity Class III is BMI≥40 kg/m^2 and is also referred to as severe obesity.[1-3] Obesity has now been shown to contribute to the development of numerous chronic diseases, and studies have confirmed that hypertension, some cancers, hyperlipidemia, diabetes, cardiovascular disease, cholelithiasis, and nonalcoholic fatty liver disease, in particular, can develop secondary to obesity.[1,3-5] Overt hypothyroidism is characterized by a high blood level of thyroid-stimulating hormone (TSH) and a low level of free thyroxine (FT4), whereas subclinical hypothyroidism (SCH) is characterized by a high serum TSH level and a normal FT4 level.[6,7] Most cases of subclinical and overt hypothyroidism are due to chronic autoimmune thyroiditis, and a positive thyroid autoantibody level is helpful in making the diagnosis.[8-10] Overt hypothyroidism is associated with moderate weight gain, but the relationship between body weight and thyroid hormones in SCH is not yet clear.[11] While treatment with levothyroxine may result in moderate weight loss in overt hypothyroidism, its benefit in SCH is unclear.[11] Most studies consistently show that patients with obesity do indeed have elevated TSH levels compared with healthy controls.[12-15] In some studies where changes in thyroid function were observed with an increase in body weight, the authors pointed out that elevated TSH levels may also be secondary to obesity.[11,13,16-18] Although the mechanism of TSH elevation in obese individuals cannot be fully elucidated, it has been suggested that TSH resistance, which is similar to insulin resistance, may also exist in patients with obesity.[13] Another issue is the leptin molecule and the view that leptin resistance in obesity and increased leptin levels may be related to autoimmunity, thyroid hormone levels, and the effects of thyroid hormones.[13,16-18] The aim of this study is to determine the levels of circulating FT4, free triiodothyronine (FT3), and TSH in patients with a BMI of 30-39.9 kg/m^2 (Class I and II obesity) and morbid obesity and in normal-weight control subjects to determine whether there is a relationship between BMI and thyroid hormones and, in this context, to determine the frequency of newly diagnosed overt hypothyroidism and SCH in patients with obesity compared with the normal-weight population.

MATERIAL AND METHODS

This retrospective study was conducted at the University of Health Sciences Antalya Training and Research Hospital, Department of Endocrinology, and General Surgery. The Ethics Committee of the University of Health Science, Antalya Training and Research Hospital approved the study protocol dated August 19, 2021, and No. 12/2. All procedures were performed in accordance with the ethical rules and principles of the Declaration of Helsinki. Data from patients treated between January 2016 and January 2021 were studied. The inclusion criteria were as follows:

- 18-70 years old,
- Patients whose medical history, physical examination and laboratory tests including TSH, FT4, FT3 were accessible,
- Patients whose weight and height were measured in the endocrinology clinic and on the same scale,
- Patients who did not have a history of diseases associated with secondary obesity (Cushing's disease, hypotalamic diseases, genetic syndromes, etc.),
- Patients who did not have a history of thyroid disease or thyroid surgery,
- Patients who are not taking levothyroxine or thyroid medications,
- Patients who are not taking medications that affect thyroid tests, such as steroids, beta blockers, etc.
- Patients who have not had bariatric surgery in the past.

The exclusion criteria were as follows:

- Patients aged under 18 and over 70,
- Pregnant and lactating women,

- Patients with known thyroid disease, taking thyroid replacement therapy or anti-thyroid medications,
- Patients taking medications that affect thyroid tests, such as steroids, beta blockers, etc.
- Patients with a history of bariatric surgery,
- Patients with history of conditions associated with secondary obesity (Cushing's disease, hypotalamic disease, genetic syndromes, etc.)
- Patients whose weight and height were not measured in the endocrinology clinic and on the same scale.

One hundred fifty-seven patients with a BMI≥30 kg/m^2, including 71 patients with a BMI of 30-39.9 kg/m^2 (Group 1, Class I and Class II obesity) and 86 patients with a BMI≥40 kg/m^2 (Group 2, morbid obesity) who met the inclusion and exclusion criteria were included in the study. Sixty control subjects with a BMI between 18.5 and 24.9 kg/m^2 aged 18-70 years with no history of thyroid disease, no thyroid surgery, and no medication use with normal TSH, FT3, FT4, and anti-thyroid peroxidase antibodies (anti-TPO) levels were included in the study.

Participants' demographic characteristics, including sex, age, chronic diseases, medications, height, weight, and BMI results, as well as laboratory tests performed in the fasting state, including TSH, anti-TPO, FT3, and FT4, were scanned from the patients' computer data system, and retrospectively analysed. Height, weight, and BMI of the subjects were determined using the Densi automatic personal scale GL-150 (Densi, Türkiye). TSH, FT3, FT4, and anti-TPO were measured on a Beckman Coulter DxI800 using the chemiluminescence method (Beckman Coulter Inc. CA, USA). Anti-TPO antibodies had a cut-off value of 10 IU/mL in our laboratory. During these years, the TSH reference range at our institution was 0.3-5.8 uIU/mL, FT4 was 0.7-1.4 ng/L, and FT3 was 2.5-3.9 ng/L. SCH was defined as a TSH level between 4.5 and 10 mU/l with normal FT4 concentration.

STATISTICAL ANALYSIS

Continuous variables were characterised by descriptive statistics [number (n), percentage (%), mean±standard deviation]. To compare the 2 separate groups, either Student's t test or Mann-Whitney U test was used, depending on whether the data were parametric or not. For multiple comparisons, the one-way test ANOVA, followed by the Tukey test, was used. When performing correlation analyses, the Spearman test was used. The significance level was set at $p<0.05$. All analyses were performed using IBM SPSS 20.0 package program (IBM Corp Armonk, NY).

RESULTS

The mean age of the patients (patients with Class I, II and morbid obesity) was 39.6±10.2 years and that of the control group was 39.2±13.3 years (p=0.94). In both patients and controls, the majority were female: 127 (80.9%) in the patient group and 48 (80.0%) in the normal-weight controls (p=0.31). Mean TSH level was 3.7±1.8 μIU/mL in patients and 2.5±1.7 μIU/mL in controls; p-value was 0.01. FT3 (p=0.22) and FT4 (p=0.09) levels did not differ between patients and controls. In our retrospective 5-year review of the data, there were no patients with newly diagnosed overt hypothyroidism who were not taking medication. The frequency of SCH (n=18) was higher in patients than normal-weight controls (n=3) (p=0.003). Table 1 summarizes the clinical and hormonal parameters of the patients and the normal-weight control subjects. Patients were divided into 2 groups: Group 1 included 71 patients with BMI from 30 to 39.9 kg/m^2 (Class I and II obesity) and Group 2 included 86 patients with BMI≥40 kg/m^2 (morbid obesity).

Thyroid levels were reexamined in these 2 subgroups and in the control group and analyzed with the one-way test ANOVA (Table 2). There was no statistical difference between the groups in terms of gender (p=0.11), age (p=0.72), FT3 (p=0.38) and FT4 (p=0.94). There was a statistically significant difference between groups in TSH (p=0.01), body weight (p=0.001), BMI (p=0.001), and the frequency of SCH (p=0.002). According to post hoc analyzes performed to determine the source of significance between groups, TSH level did not differ between Group 1 and Group 2 (p=0.07). TSH levels were higher in both Group 1 and Group 2 than in controls (p=0.03 and p=0.01, respectively).

TABLE 1: Clinical and hormonal features of the patients and controls.

Parameters	Patients (BMI≥30 kg/m²)	Controls (BMI: 18.5-24.9 kg/m²)	p value
n	157	60	
F/M	127/30	48/12	0.31
Age (yrs.)	39.6±10.2	39.2±13.3	0.94
TSH (μIU/mL)	3.7±1.8	2.5±1.7	0.01*
FT3 (ng/dL)	2.9±0.4	3.0±0.5	0.22
FT4 (ng/dL)	1.2±0.2	1.1±0.4	0.09
Body weight (kg)	105.1±13.1	58.4±3.2	0.001*
BMI (kg/m²)	43.8±6.6	23.5±1.3	0.001*
SCH, n (%)	18/157 (11.4%)	3/60 (5%)	0.003*

*p<0.05 is statistically significant; BMI: Body mass index; TSH: Thyroid-stimulating hormone; FT3: Free triiodothyronine; FT4: Free thyroxine; SCH: Subclinical hypothyroidism.

TABLE 2: Study parameters between Group 1 and Group 2 subjects and control group.

Parameters	Group 1 (BMI: 30-39.9 kg/m²)	Group 2 (BMI≥40 kg/m²)	Control group (BMI: 18.5-24.9 kg/m²)	p value
n	71	86	60	
F/M	59/12	68/18	48/12	0.11
Age (yrs.)	38.6±15.2	40.9±11.6	39.2±13.3	0.72
TSH (μIU/mL)	2.9±2.0	3.1±2.8	2.5±1.7	0.01*#
FT3 (ng/dL)	3.0±0.2	2.9±0.4	3.0±0.5	0.38
FT4 (ng/dL)	1.1±0.6	1.2±0.3	1.1±0.4	0.94
Body weight (kg)	89.4±5.1	111.8±6.4	58.4±3.2	0.001*
BMI (kg/m²)	35.2±3.6	45.3±5.1	23.5±1.3	0.001*
SCH, n (%)	8/71 (11.2%)	10/86 (11.6%)	3/60 (5%)	0.002*&

*p<0.05 is statistically significant; *One-way ANOVA results of 3 groups, p<0.05 is statistically significant; #Statistical analysis was performed by ANOVA followed by Tukey's multiple comparison test, p=0.03 control Vs Group 1; p=0.01 control Vs Group 2; p=0.07 Group 1 Vs Group 2 & statistical analysis was performed by ANOVA followed by Tukey's multiple comparison test, p=0.006 control Vs Group 1; p=0.002 control Vs Group 2; p=0.06 Group 1 Vs Group 2; BMI: Body mass index; TSH: Thyroid-stimulating hormone; FT3: Free triiodothyronine; FT4: Free thyroxine; SCH: Subclinical hypothyroidism.

In Group 1, there were 8 patients with SCH (11.2%) and 6 of them had high anti-TPO levels. In Group 2, there were 10 patients with SCH (11.6%) and 8 of them had high anti-TPO levels. In the control group, all 3 patients with SCH had high anti-TPO levels. The frequency of SCH showed a significant difference between the three groups (p=0.002) (Table 2). According to post-hoc analyzes, the frequency of SCH did not differ between Group 1 and Group 2 (p=0.06).The frequency of SCH was higher in Group 1 and Group 2 patients than in the control group (p=0.006 and p=0.002, respectively). In the correlation analysis of the whole study population, BMI and TSH had a positive correlation (r=0.44 p=0.001). There was no significant correlation between FT3 (r=-0.01 p=0.62) and FT4 (r=-0.009 p=0.72) and BMI according to statistical analysis.

DISCUSSION

In our study, we found a correlation between BMI and TSH, but there was no significant correlation between FT3 and FT4 and BMI. SCH was more common in patients with obesity than in healthy people with a normal BMI. However, we found no significant difference in the frequency of SCH or the level of thyroid hormones in patients with morbid obesity and Class I and II obesity. Several studies suggest that circulating thyroid hormone levels vary in patients

with obesity.[12-15,19-21] In the study by Michalaki et al., which examined thyroid hormones in 144 patients with morbid obesity, TSH was elevated in patients compared with normal-weight individuals.[13] In this study, there was no comparison between severely obese patients and those with a BMI of 30-39.9 kg/m^2 because all patients were morbidly obese. The majority of patients were women, as in our study. The rate of newly diagnosed SCH in morbid obesity was 7.7% in this study, which was lower than in our study.[13] Bastemir et al. studied 224 obese or overweight women.[14] In this study, similar to ours, no correlation was found between FT4 and body weight and BMI, but a significant positive correlation was observed between TSH and BMI.[14] In their study, Mehta et al. found hypothyroidism in 14% of the subjects. This study included mainly subjects with a BMI of 30-40 kg/m^2, but also a small number of morbidly obese subjects.[19] Knudsen et al. demonstrated a positive correlation between BMI and TSH and a negative correlation between BMI and FT4 in a study with a large sample of 4,649 cases.[15]

Because our study was retrospective, we could not observe the change in thyroid hormones after patients lost weight, but literature studies indicate that thyroid levels improve after weight loss.[12,22] In a study by Sari et al in female patients, thyroid volume and TSH levels were higher in obese women than in nonobese women, although they were within the normal reference range.[12] They also found that thyroid volume and TSH levels regressed in women who achieved a 10% weight loss after 6 months of obesity therapy.[12] Juiz-Valiña et al. showed that TSH levels also decreased significantly in patients with morbid obesity and euthyroidism when weight loss was achieved through bariatric surgery.[22]

Some studies show that obesity is also associated with thyroid autoimmunity and that thyroid antibody titers are higher in obese individuals.[23,24] In the study by Alkaç et al., it was found that the rate of total overt hypothyroidism and SCH was 21.5% in patients with obesity. This study also showed that the presence of thyroiditis on ultrasound and the presence of thyroid autoantibodies were common in patients with obesity and euthyroidism.[23] In a study involving 165 patients with obesity and 118 normal-weight controls, it was found that FT3 and FT4 levels were lower, the incidence of hypothyroidism was higher, and the number of anti-thyroid antibodies was higher in patients with obesity compared with the control group. This study also examined leptin levels and found an association between leptin and autoimmune thyroiditis.[24]

It appears that in the studies conducted with children, results were similar to those obtained with adults. In a study of 308 children aged 6 to 17 years conducted by Bhowmick et al., it was found that 11.7% of obese children had TSH levels greater than 4 U/mL, compared with less than 0.7% in the control group.[20]

In our study, we found no significant difference in the frequency of SCH or the level of thyroid hormones in patients with morbid obesity and Class I and II obesity. This could be due to the small number of patients in our study and its design. However, there are studies in the literature that support this finding. In the study by Topaloğlu et al., TSH levels did not differ in obese patients with BMI<40 kg/m^2, BMI between 40 and 49.99 kg/m^2, BMI between 50 and 59.99 kg/m^2, and BMI>60 kg/m^2.[25] Sosa-López et al. reported no differences in TSH levels between patients with obesity Grade I, Grade II, and Grade III. However, they found an association with FT4 and obesity grade.[26]

With the improvement of molecular techniques, one of the studies on obesity genes, thyroid hormones, and receptors showed that thyroid hormones regulate the Tub obesity gene in rats.[27] The researchers explained that this Tub obesity gene is upregulated by T3 and that a lack of stimulation of the Tub obesity gene may lead to obesity due to an imbalance of thyroid hormones. Considering the studies suggesting that elevated TSH levels may occur secondary to obesity, Michalaki et al. emphasized that TSH resistance may occur as well as insulin resistance in obesity.[13] Duntas and Biondi pointed out that obesity-related low-grade inflammation and leptin resistance affect the immune system response and trigger autoimmunity.[16] García-Solís et al. studied adipokines, including leptin, and found that these substances can affect circulating thyroid hormone

levels and the mechanism of action of thyroid hormones.[17] In another study, leptin concentration is hypothesized to influence TSH secretion, and leptin is considered an important molecule in the relationship between obesity and thyroid hormone changes.[18] The increasing prevalence of obesity and the high TSH levels observed in this group give rise to the view that the normal TSH range may need to be redefined in epidemiological studies.[11]

The general similarities between the literature studies and our study are that the patients are predominantly women and that TSH is associated with obesity. While some studies found an association between FT3 and FT4 and weight, some, similar to our study, found no significant association. This could be due to differences in study design, such as the number of patients and inclusion and exclusion criteria.

We did not encounter newly diagnosed overt hypothyroidism and did not include patients diagnosed with hypothyroidism who were taking levothyroxine in this study, so we cannot provide information on the prevalence of overt hypothyroidism in our study. However, the increased frequency of SCH in the patients with obesity in our study supports the association between obesity and SCH. Also, because thyroid autoantibodies could not be measured in all participants, we cannot definitively say whether there is an association between thyroid autoimmunity and obesity. The high positivity of autoantibodies in both healthy controls and patients with SCH may suggest that the presence of autoimmune thyroid disease is common in SCH.

The retrospective nature of our study, the small number of patients, the small number of males, and the fact that thyroid autoantibodies could not be studied in the whole population are the main limitations.

In this retrospective study, we cannot say whether obesity causes increased TSH or whether SCH contributes to obesity. Although many studies have shown the association between body weight and thyroid hormone changes, the exact pathophysiology of this association is not yet clear. However, it appears that more detailed studies are needed to determine the etiopathogenesis.

CONCLUSION

Obesity is associated with high TSH levels. The incidence of SCH is increased in obesity. Further studies with larger populations are needed to understand the pathophysiology of thyroid hormone changes in obesity.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Işılay Kalan Sarı;* ***Design:*** *Işılay Kalan Sarı, Şeyma Yavuz;* ***Control/Supervision:*** *Şeyma Yavuz, Işılay Kalan Sarı, Serkan Ceylan;* ***Data Collection and/or Processing:*** *Serkan Ceylan, Işılay Kalan Sarı;* ***Analysis and/or Interpretation:*** *Işılay Kalan Sarı, Serkan Ceylan;* ***Literature Review:*** *Şeyma Yavuz, Işılay Kalan Sarı;* ***Writing the Article:*** *Şeyma Yavuz, Işılay Kalan Sarı;* ***Critical Review:*** *Işılay Kalan Sarı, Şeyma Yavuz;* ***Materials:*** *Serkan Ceylan.*

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