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# Alterations of Serum Leptin Levels in Patients with Autoimmune Thyroid Disorders

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# Abstract

**Background:** Thyroid dysfunction is accompanied with significant metabolic alterations that affect body weight, appetite, and energy expenditure, as well as lipid and carbohydrate metabolism. Leptin, an adipokine produced by adipocytes, regulates food intake and energy storage. Thyroid hormones and leptin share some physiological effects. Changes in leptin have been shown in patients with dysfunction of the thyroid; however, the results are contradictory. The aim of this study was to evaluate the circulating levels of leptin in patients with Graves disease (GD) and Hashimoto thyroiditis (HT) before and after normalization of thyroid function compared with the control group.

Methods: Newly diagnosed adult patients with GD, HT, and healthy euthyroid controls were recruited. Various clinical and biochemical parameters, including thyroid function tests and serum leptin level, were assessed before and after treatment and compared between groups.

**Results:** Data from 56 patients with HT, 54 patients with GD, and 54 healthy controls were analyzed. Serum leptin levels of patients with HT ( $30.96 \pm 3.88 \text{ ng/mL}$ ) were found to be significantly higher than the controls ( $22.35 \pm 4.72 \text{ ng/mL}$ ) (p<0.001), whereas patients with Graves had lower serum leptin levels ( $14 \pm 4.54 \text{ ng/mL}$ ) (p<0.001). In patients with HT, serum leptin levels showed a significant decrease after treatment (31 vs 27 ng/mL; p<0.001), while in patients with GD, leptin increased significantly after treatment (14 vs 17 ng/mL; p<0.001).

**Conclusion:** The present study showed that serum leptin levels increased in patients with HT and decreased in those with GD than the control group. However, after treatment, leptin decreased in the Hashimoto group and increased in the Graves group, although it was still significantly different from the control group.

Keywords: Graves Disease, Hashimoto Disease, Leptin

## Conflicts of Interest: None declared

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# Introduction

Hyper and hypothyroidism are the most common thy-

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## roid disorders, characterized by abnormal levels of circu-

#### *†What is "already known" in this topic:*

Previous research suggests a direct relationship between thyroid hormones and leptin. Due to the contradictory results of existing studies, we design this study aims to determine serum leptin concentration in patients with newly diagnosed Hashimoto's thyroiditis and Graves' disease; both before therapy and after normalization of thyroid dysfunction compared to the control group.

#### $\rightarrow$ *What this article adds:*

This study showed that serum leptin levels were higher in patients with Hashimoto's thyroiditis than Graves' disease as well as the control group. However, after treatment, leptin decreased in the Hashimoto group and increased in the Graves group, although it was still significantly different from the control group. lating thyroid hormones and thyrotropin. Thyroid hormones play an important role in regulating various processes. These hormones stimulate the basal metabolic rate and heat production, affect cell proliferation and differentiation, modulate responses to other hormones, and affect carbohydrate, lipid, and protein metabolism. Thyroid dysfunction causes changes in body weight, appetite, adipose tissue, and muscle mass. Patients with hypothyroid gain weight despite decreased appetite, while patients with hyperthyroid lose weight despite increased appetite. Thyroid hormones and adipokines share some physiological effects, such as regulating the energy expenditure, besides the glucose and lipid metabolism (1-3).

Food intake and energy expenditure are processes that are significantly controlled by central and peripheral molecule signaling. Animal and human studies have confirmed that leptin is a major regulatory hormone, which acts as a satiety factor (4). Leptin is a 16 kDa cytokine that contains 167 amino acids. It is encoded by the ob gene. Adipose tissue is an active hormonal system that produces and secretes different bioactive substances. Leptin is one of the adipokines that is released by the adipose tissue and modulates energy homeostasis as well as lipid and glucose metabolism. Therefore, there seems to be an interaction between thyroid function and adipose tissue (5, 6).

Thyroid dysfunction can affect the function of adipose tissue, which contributes to the development of metabolic disorders. Also, changes in lipolysis are observed in patients with thyroid dysfunction (7, 8). Previous research suggests a direct relationship between thyroid hormones and leptin. Leptin can stimulate thyroid-stimulating hormone (TSH) secretion (9), while TSH can stimulate the leptin release from the adipose tissue (10, 11).

However, the effect of thyroid hormone disorders on leptin varies in different clinical studies. Because of the contradictory results of existing studies and problems of previous studies, such as insufficient sample size, the inclusion of heterogeneous study groups, autoimmune and nonautoimmune causes of hypothyroidism and hyperthyroidism, treated and untreated patients, and lack of matching of confounding factors (eg, the body mass index (BMI)), we designed this study to determine serum leptin concentration in large numbers of patients with newly diagnosed autoimmune hypothyroidism (Hashimoto thyroiditis (HT)) and autoimmune hyperthyroidism (GD), both before therapy and after normalization of thyroid dysfunction compared with the matched control group in terms of age, sex, and BMI.

## Methods

The current research was performed on newly diagnosed patients with HT and GD referred to endocrine health care centers in Zahedan (Iran) from April 2019 to September 2020. Those with a minimum age of 18 years were continuously enrolled using the consecutive sampling technique. Euthyroid healthy individuals who referred for check-up tests were chosen as the control group. They did not have a personal or family history of autoimmune thyroid disease. The control group was matched with case groups based on age, sex, and BMI. The inclusion criteria were newly diagnosed GD or HT. The patients with evidence of acute or chronic infectious disease, malignancies, consumption of antidyslipidemia drugs, antihypertensive drugs, thyroid drugs, and oral contraceptives in the past 6 months were excluded from the study.

After completing the questionnaire, including information regarding the age, sex, past medical history, drug history, and family history, patients were evaluated in terms of height and weight. Height in standing position using a stadiometer and body weight using a digital scale were measured. The BMI was calculated by dividing weight in kilograms by height squared in meters.

GD was defined as increased free tetraiodothyronin (FT4) and free triiodothyronine (FT3) in association with suppressed TSH (normal FT4: 0.8-1.8 ng/dL, normal FT3: 2.3-4.2 pg/mL, and normal TSH: 0.4-4.2 mIU/L) and positive TSH-Rec-Ab (normal TRAB: up to 1.75 IU/L) and HT was defined as decreased FT4 and FT3 in association with elevated TSH and positive Anti-TPO (normal: up to 16 Iu/mL) or Anti-Tg (normal: up to 100 Iu/mL). Patients with HT were treated with 75-125 microgram per day levothyroxine and patients with GD were treated with 20 to 30 mg methimazole per day. Blood samples were recruited 12 weeks after treatment. If euthyroidism was achieved, serum leptin level was measured.

Blood samples were taken from participants after 12 hours of fasting and between 8 and 9 AM.

After collection, serum samples were stored at -70 °C until assay. Thyroid function tests, serum levels of leptin, and serum lipid levels were evaluated in patients with GD and HT before and after treatment as well as in the control group. Leptin was measured before and after treatment in patients as well as in the control group with Human leptin ELISA Kit (ZellBio GmbH, Germany). The intra-assay coefficient of variation for leptin was 4.3% and the interassay coefficient of variation was 3.1%. Lipid profile was measured using enzymatic colorimetric tests. Inter-assay and intra-assay coefficients of variation were 2.4% and 0.8% for total cholesterol and 1.9% and 0.5% for triglycerides, respectively. FT4, FT3, and TSH using immunochemiluminescent assays by an automated analyzer (Diagnostic Products LIAISON) were measured. The intraassay coefficient of variation for T4 was 3.9%. The interassay coefficient of variation was 3.1 %. These values for T3 were 4.5% and 1.9%, respectively. TSH assay has intra-assay coefficients of variation of 4%. The inter-assay coefficient of variation was 3.3%. Anti-thyroid peroxidase (normal range < 16 IU/mL), anti-thyroglobulin (normal range < 100 IU/mL), and TSH-Rec-Ab (normal range: < 1.75 IU/L) were measured by immunochemiluminescent assays employing commercial kits.

We conducted study procedures after the ethical principles of the research committee (either organizational or national). In addition, we respected the principles of the 1964 Helsinki declaration and its amendments. The ethics committee of the Zahedan University confirmed the study protocol (ethical code: IR.ZAUMS.REC.1399.072). Informed consent was obtained from all participants.

## **Statistical Analysis**

The study variable was described with descriptive statistics, like frequency, percentage, and mean with standard deviation. The mean difference of a numerical variable in the 3 study groups of patients with GD, HT, and a healthy control group was analyzed with 1-way analysis of variance (ANOVA) test. Furthermore, a post-hoc comparison was conducted based on Bonferroni correction for pairwise comparison. We used Pearson chi-square or the Fisher exact test for testing the association between categorical variables with the study group. The paired t test and the Wilcoxon signed-rank test were used for pre- and posttest comparison as appropriate. The correlation between the numerical variable was assessed with Pearson's correlation coefficient. P<0.05 was considered statistically significant. All analyses were conducted with Stata statistical software (StataCorp).

# Results

In this study, data from 56 patients with HT, 54 patients

Table 1. Clinical Features and Biochemical Characteristics of Participants at Baseline

Tuble 1: Chinear Features and Biochennear Characteristics of Farticipants at Basenne									
Variable	Hashimoto Group	Graves Group	Control Group	Р					
Number	56	54	54						
Sex (% women)	78.6	77.8	77.8	0.993					
Age (years)	35.29 (10.65)	36.22 (8.77)	36.00 (8.64)	0.862					
BMI (Kg/m <sup>2</sup> )	23.90 (3.61)	22.75 (4.14)	22.79 (4.04)	0.222					
FT4 (ng/dL)	0.45 (0.16) <sup>a</sup>	3.12 (0.75) <sup>b</sup>	1.27 (0.19) °	< 0.001					
FT3 (pg/mL)	1.65 (0.52) <sup>a</sup>	6.69 (1.64) <sup>b</sup>	3.61 (0.45) °	< 0.001					
TSH (mIu/L)	79.65 (21.42) <sup>a</sup>	0.02 (0.01) <sup>b</sup>	1.58 (0.82) <sup>b</sup>	< 0.001					
Total cholesterol (mg/dL)	207.95 (51.72) <sup>a</sup>	134.02 (28.55) <sup>b</sup>	140.76 (40.77) <sup>b</sup>	< 0.001					
LDL-C (mg/dL)	140.03 (49.31) <sup>a</sup>	75.85 (19.99) <sup>b</sup>	80.00 (32.54) <sup>b</sup>	< 0.001					
HDL-C (mg/dL)	46.61 (8.75) <sup>a</sup>	37.87 (11.82) <sup>b</sup>	43.15 (13.16) <sup>b</sup>	< 0.001					
Triglyceride (mg/dL)	131.28 (68.75) <sup>a</sup>	101.20 (48.23) <sup>b</sup>	89.15 (61.57) <sup>b</sup>	0.001					
VLDL (mg/dL)	25.82 (13.55) <sup>a</sup>	20.18 (9.63) <sup>b</sup>	17.61 (12.30) <sup>b</sup>	0.001					
Leptin (ng/mL)	30.96 (3.88) <sup>a</sup>	$14.00(4.54)^{b}$	22.35 (4.72) °	< 0.001					

-BMI, body mass index; FT4, free thyroxin; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone; LDL-C, low density lipoprotein-cholesterol, HDL-C: high density lipoprotein-cholesterol; VLDL, very low-density lipoprotein.

-Data are shown as mean (SD) or number, percentage. Values are means (SD); differences were assessed by the ANOVA test. <sup>a,b,c</sup>. Post hoc comparison based-on Bonferroni method. Different subscript letters (<sup>a, b, c</sup>) in the same row of variables reflect significant (p < p.05) difference between the means while same subscript letters in one row reflect nonsignificant difference between the means of the 3 group (Hashimoto, Graves and control).



Fig. 1. Box and whiskers plot of serum levels of leptin in Hashimoto, Graves, and control groups

78% of the participants were women with a mean age of 36 years. There was no statistically significant difference between gender distribution, mean age, and BMI in the 3 groups. Serum leptin levels of patients with HT ( $30.96 \pm$ 3.88 ng/mL) were found to be significantly higher than the controls ( $22.35 \pm 4.72$  ng/mL) (p<0.001), whereas patients with GD had lower levels ( $14 \pm 4.54$  ng/mL) (p<0.001). Clinical features and biochemical characteristics of study participants at baseline are shown in Table 1. Figure 1 also shows the serum distribution of leptin at baseline in the 3 study groups.

In the HT group, a significant correlation was found between leptin and TSH (r=0.321, p=0.016). Other correlations between leptin and laboratory biomarkers in the 3 study groups were not significant.

with GD, and 54 healthy controls were analyzed. About

Biochemical characteristics of patients with GD and HT before and after treatment are compared in Table 2. In patients with HT, serum leptin levels showed a significant decrease after treatment, while in patients with GD, leptin

<i>Table 2.</i> Biochemical Characteristics of Patients with Hashimoto and Graves Before and After Treatment								
Variable	Hashimoto Group			Graves group				
	Before Treatment	After Treatment	Р	Before Treatment	After Treatment	Р		
BMI (Kg/m <sup>2</sup> )	23.90 (3.61)	23.38 (3.56)	< 0.001	22.75 (4.14)	23.29 (4.22)	.013		
FT4 (ng/dl)	0.45 (0.16)	1.29 (0.29)	< 0.001	3.12 (0.75)	1.30 (0.27)	<.001		
FT3 (pg/ml)	1.65 (0.52)	3.44 (0.53)	< 0.001	6.69 (1.64)	3.74 (0.80)	<.001		
TSH (mIu/L)	79.65 (21.42)	1.97 (1.04)	< 0.001	0.02 (0.01)	1.63 (0.98)	<.001		
Total cholesterol (mg/dl)	207.95(51.72)	170.73(35.49)	< 0.001	134.02(28.55)	183.83 (40.62)	<.001		
LDL-C (mg/dl)	140.03(49.31)	104.82(29.62)	< 0.001	75.85 (19.99)	117.30(30.64)	<.001		
HDL-C (mg/dl)	46.61 (8.75)	41.80 (8.54)	< 0.001	37.87 (11.82)	47.65 (12.65)	<.001		
Triglyceride (mg/dl)	131.28(68.75)	122.02(59.68)	0.265	101.20(48.23)	94.94 (29.45)	.286		
VLDL (mg/dl)	25.82 (13.55)	24.23 (12.02)	0.343	20.18 (9.63)	18.81 (5.95)	.240		
Leptin (ng/ml)	30.96 (3.88)	27.03 (3.17)	< 0.001	14.00 (4.54)	17.28 (4.29)	<.001		

-BMI, body mass index; FT4, free thyroxin; FT3, free triiodothyronine; TSH, thyroid stimulating hormone, LDL-C, low density lipoprotein-cholesterol; HDL-C, High density lipoprotein-cholesterol; VLDL, very low-density lipoprotein.

-Values are means (SD); differences were assessed by the paired t test or the Wilcoxon signed-rank test, depending on the normal distribution of variables.

increased significantly after treatment, although it was still significantly different from the control group (p<0.001).

## Discussion

The results of the present study showed that serum leptin levels were higher in patients with HT than GD as well as the control group. The serum leptin levels decreased after 12 weeks of receiving levothyroxine in the euthyroid state, and this reduction was statistically significant. We observed that serum leptin levels increased in patients with GD after 12 weeks of treatment in the euthyroid state, and this increase was statistically significant. However, these changes in serum leptin levels after treatment were still significantly different from the control group (p< 0.001). This may be due to the difference in BMI between the case groups and the control group after treatment. The relatively short follow-up period in this study could be another reason for this difference.

Human studies on the effect of thyroid function on serum leptin levels have not indicated any consistent results. Some studies (12-16) reported an increase in the serum leptin level in patients with hypothyroid, while some other studies reported a reduction in these patients (17, 18). Furthermore, some studies did not report any changes in patients with hypothyroid relative to patients with euthyroid in the control group (19-21). Moreover, some studies of patients with hyperthyroidism showed an increase in serum leptin levels (15, 18, 22), whereas other studies found a reduction in serum leptin (13, 23-25); additionally, in some studies, the serum leptin level remained unchanged (19, 26, 27).

It is not clear why the results of previous studies are different and sometimes contradictory. Various factors, such as autoimmunity, leptin pulsatility, leptin-binding proteins, sex, fertility status, differences in the characteristics of study populations, autoimmune or nonautoimmune causes of thyroid dysfunction, exposure or nonexposure to treatment, duration of treatment, and different measurement methods for leptin assay may be influential (28). Therefore, it is not unreasonable to expect distinct results in different studies.

The current study is similar to a cross-sectional study by Chen et al (29), which was performed on 197 newly diagnosed patients with hypothyroid, 230 patients newly diagnosed with hyperthyroid, and 355 control patients with euthyroid. It was found that patients with hypothyroid had higher serum leptin levels. Furthermore, the results of our study are consistent with a study by Guzel, which indicated an increase in leptin levels of 25 patients with subclinical hypothyroidism and 25 patients with overt hypothyroidism (30). In addition, El-Zawawy et al in a study on 240 hypothyroid and 120 normal age- and sex-matched individuals found that hypothyroidism was associated with the increased serum leptin concentrations (31).

Moreover, the results of the present study on the reduction of serum leptin levels in patients with hyperthyroid are consistent with the findings reported by Ibrahim et al, which showed that serum leptin levels were significantly lower in patients with hyperthyroidism than in the control euthyroid group. On the other hand, the serum leptin level was higher in patients with hypothyroidism than in the controls in this study (32).

Leptin was originally thought to be an antiobesity hormone. However, today, it is known to signal a switch from the fed to starved state, suggesting an important interplay between thyroid hormones and leptin (33). Patients with thyroid dysfunction usually return to a normal thyroid state within the first 2 to 3 months after treatment, although changes in the body composition continue for months (34, 35). Nevertheless, it is not clear whether leptin contributes to this complication.

Clearly, there is a link between leptin and the thyroid gland, owing to the effects of leptin on the negative feedback mechanism of thyroid hormone regulation and thermogenesis. Considering the effect of insulin, leptin is involved in regulating thyrotropin-releasing hormone secretion in the hypothalamus. In the fasting state, where insulin decreases, T3 inhibits the accumulation of leptin messenger ribonucleic acid in adipocytes, whereas the opposite occurs in the postprandial state and in the presence of increased insulin levels (36).

In addition, it has been shown that leptin itself can stimulate T3 production by activating the conversion of T4 to T3 (37, 38). Also, the increased level of T3, similar to thyrotoxicosis, can increase heat production, the expression of uncoupling protein-3 (UCP-3) in the muscle tissue (39), and  $\beta$ 3 adrenergic receptors (24, 40). An increase in these 3 factors inhibits leptin expression in the adipose tissue (33, 41), which represents an inverse relationship between leptin and T3, both in the central and peripheral

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tissues. In contrast, low levels of T3 in patients with hypothyroidism lead to decreased leptin expression, decreased T4 to T3 conversion, decreased  $\beta$ 3 adrenergic receptors, and reduced heat production and UCP-3 concentration in the muscles. Leptin is also involved in the central regulation of the thyroid hormone (42).

In patients with euthyroid, the serum leptin level, known as a satiety factor, increases with an increase in the fat mass and decreases with its reduction. According to previous studies, leptin levels are associated with BMI in both patients with hyperthyroidism and hypothyroidism (19). In the current study, because the groups were matched in terms of BMI, the difference in serum leptin levels could not be attributed to this factor at baseline. However, there was a significant difference in BMI before and after treatment. The role of difference in BMI during the 3-month follow-up should be considered in these results.

In this study, we tried to provide an acceptable sample size of a homogeneous population of patients with autoimmune hypo- and hyperthyroidism who have recently been diagnosed and have not yet been treated. Furthermore, all 3 groups were matched in terms of age, sex, and BMI. However, the present study had some limitations. The duration of patient follow-up was only 3 months. If the patients were followed up for longer periods after euthyroidism, perhaps more significant changes in serum leptin levels would have been observed after treatment.

### Conclusion

In conclusion, the results of the present study showed that serum leptin levels increased in patients with HT and decreased in those with GD. However, after treatment, leptin decreased in the HT group and increased in the GD group, although it was still significantly different from the control group. Further studies are required to determine the exact mechanism of thyroid hormones and leptin interactions.

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#### **Ethics Approval and Consent to Participate**

We conducted study procedures after obtaining the ethical principles of the research committee (either organizational or national). In addition, we respected the principles of the 1964 Helsinki declaration and its amendments. The ethics committee of the Zahedan University confirmed the study protocol (ethical code: IR.ZAUMS.REC.1399.072). Informed consent was obtained from all participants.

# **Conflict of Interests**

The authors declare that they have no competing interests.

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