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Original Article

Hyperthyroidism may be associated with hypoleptinemia in spite of insulin resistance

Hipertiroidizm insulin rezistansına rağmen hipoleptinemi ile ilişkili olabilir

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ABSTRACT

Aim: Influences of thyroid hormones on leptin levels are controversial. We aimed to evaluate serum leptin levels in women with hyperthyroidism before and after treatment.

Material and Methods: Newly diagnosed 27 hyperthyroid women (age 35±10 years, body mass index (BMI) 26.21±5.44 kg/m^2) and 30 healthy women were included the study. BMI, body fat mass (FM) and fat percent (F%) were determined. Standard oral glucose tolerance test (OGTT) was performed and area under the curve (AUCglu120) of glucose for determined insulin resistance was measured in all subjects. Serum leptin levels were determined with radioimmunoassay before and after treatment.

Results: Serum leptin levels in hyperthyroid patients were lower than control subjects (19.95±19.81 and 35.90±22.73 ng/dl, $p<0.01$). Leptin levels in hyperthyroid state were also lower than in euthyroid state (19.95±19.81 and 24.54±19.99 ng/dl, $p=0.028$) in the hyperthyroid group. With the treatment of hyperthyroidism serum leptin levels showed significant increase and it became indifferent from control subjects. However antropometric parameters did not show any significant difference with the treatment. AUCglu120 values in hyperthyroid women were higher than control subjects (165704±3276 and 12567±2102 mg.min/dl, respectively and $p<0.001$). After the treatment, AUCglu120 values decreased and it became indifferent from control subjects in hyperthyroid women.

Conclusions: Serum leptin levels were low in women with hyperthyroidism and hypoleptinemia can be corrected with tretament of hyperthyroidism. Low serum leptin levels in hyperthyroidism can not be explained with differences in body fat and BMI. More importantly, glucose disposal may impair in hyperthyroidism and it may recover with euthyroidism independent from serum leptin levels.

Key Words: Hyperthyroidism, leptin, insulin resistance, BMI

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ÖZET

Amaç: Tiroid hormonlarının leptin üzerine etkisi tartışmalıdır. Biz hipertiroidili kadınlarda tedavi öncesi ve tedavi sonrası serum leptin düzeylerini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Yeni tanı konulan 27 hipertiroidili kadın (yaş 35±10 yıl, vücut kitle indeksi (BMI) 26,21±5,44 kg/m²) ve yaş ve BMI'I benzer 30 sağlıklı kadın (yaş 36±10 yıl, BMI 25,48±6,97 kg/m²) çalışmaya alındı. BMI, vücut yağ kitlesi (FM) ve yağ yüzdesi (%F) belirlendi. Standart oral glukoz tolerans testi yapıldı ve insulin direncini belirlemek için glukozun eğri altında kalan alanı (AUCglu120) her kişi için hesaplandı. Serum leptin düzeyleri tedavi öncesi ve tedavi sonrası radioimmunoassay ile belirlendi.

Bulgular: Hipertiroidili hastalarda serum leptin düzeyleri kontrol grubundan düşüktü (19,95±19,81 ve 35,90±22,73 ng/dl, p<0,01). Hipertiroidi grubunda hipertiroid koşullarda leptin düzeyleri de ötiroid durumdan daha düşüktü (19,95±19,81 ve 24,54±19,99 ng/dl, p=0,028). Hipertiroidi tedavisi ile serum leptin düzeyleri belirgin olarak artış gösterdi ve kontrol grubundan farksız hale geldi. Fakat antropometrik parametreler tedavi ile belirgin farklılık göstermedi. Hipertiroidili kadınlarda AUCglu120 değerleri kontrol grubundan yüksekti (165704±3276 ve 12567±2102 mg.dk/dl, p<0,001). Tedavi sonrasında hipertiroidili kadınlarda AUCglu120 değerleri azaldı ve kontrolden farksız hale geldi.

Sonuçlar: Serum leptin düzeyleri hipertiroidili kadınlarda düşüktür ve hipertiroidinin tedavisi ile hipoleptinemi düzeltilebilir. Hipertiroidide düşük serum leptin düzeyleri vücut yağı ve BMI ile açıklanamaz. Daha da önemlisi hipertiroidide glukoz dağılımı bozulabilir ve serum leptin düzeylerinden bağımsız olarak ötiroidizm ile iyileşebilir.

Anahtar Kelimeler: Hipertroidizm, leptin, insulin rezistansı, vücut kitle indeksi

Introduction

Alterations in the thyroid hormones are frequently associated with changes in body weight and anthropometric measurements [1]. The hyperthyroid patients lose weight in spite of the increase in appetite and food intake because of the increase in basal metabolism [2]. However, hyperthyroidism is also associated with insulin resistance. But, the exact mechanism responsible for insulin resistance induced by hyperthyroidism has not yet been fully elucidates. Thyroid dysfunction may have a relationship with insulin resistance as well as impaired insulin secretion [2-4]. Insulin secretion from the pancreatic beta cells relatively increases in hyperthyroid conditions. Although hepatic insulin resistance is well established in hyperthyroid subjects, there is less information on the effect of insulin in peripheral tissues and in particularly the adipose tissue [5,6]. Adipocytokines which are regulated by thyroid hormones may play a role in the development of insulin resistance in hyperthyroidism [7].

Leptin mainly secreted from adipocytes and it play a major role in body weight regulation. Energy homeostasis, body weight, and food intake are also regulated by leptin [2]. Leptin is thought to be a negative feedback "lipostatic signal" to the hypothalamic centers controlling energy homeostasis and food intake [8]. Although both thyroid hormones and the leptin have the similar roles in energy homeostasis, the changes in leptin levels in thyroid dysfunctions have not been cleared up yet. Leptin mRNA and serum leptin concentrations correlate with body mass index and body fat mass [1,9,10]. During weight loss, serum leptin concentrations reduced to a level below that predicted by change in fat mass. Previously studies showed controversial results with in serum leptin concentrations in hyperthyroid state [9,11-13]. The changes in leptin and thyroid hormone levels could also be related to insulin secretions or insulin actions [6]. In addition, insulin may stimulate releasing of leptin from adipose tissue [14]. Santini et al [15] also reported that acute rhTSH administration in hypothyroid subjects under l-thyroxine therapy produces a rise in serum leptin. This increase was proportional to the adipose mass suggesting that a functioning TSH receptor was expressed on the surface of adipocytes. Siemińska et al [16] previously indicated that serum leptin levels correlated positively with BMI, waist to hip ratio, TSH, and IL-6. In that study, Hashimoto's thyroiditis was characterized by an increased production of IL-6 but did not have a direct influence on leptin or adiponectin serum levels. However, the relationships among with insulin resistance, thyroid hormones and leptin have not been definitively identified in patients with hyperthyroidism.

The aim of this study is to determine the alterations of leptin levels and insulin resistance in female patients with hyperthyroidism before and after anti-thyroid treatment.

Material and Methods

Newly diagnosed 27 hyperthyroid women due to toxic multi nodular goiter (aged 35±10 years, BMI: 26.21±5.44 kg/m²) and age- and BMI-matched 30 healthy euthyroid women (age 36±10 years, BMI 25.48±6.97 kg/m²) included the study. Diagnosis of hyperthyroidism was based on decrease of TSH levels, increase of free T4 (fT4) and free T3 (fT3). Euthyroidism was defined as normal thyroid function tests. (The limits of normal ranges were FT3: 1.9-3.4 pg/ml, FT4: 0.7-1.7 ng/dl, TSH: 0.28-4.00 mIU/l). Hyperthyroid patients were evaluated with ultrasonography and scintigraphy. None of patients were taking any medication, including antithyroid drugs before the study. Patients with history of diabetes mellitus or other endocrine disease such as Cushing syndrome, polycystic ovary syndrome excluded from the study.

a- Anthropometric evaluations: Body weights and body heights were measured without shoes and in light clothing. BMI was expressed as

weight (kilograms) per height (meters) squared. Body fat mass (FM) and fat percent (F%) were determined by the bioelectrical impedance (BODY-FAT Monitor OMRON BF300).

b. Laboratory evaluations: After 12 hours overnight fasting, standard oral glucose tolerance test (OGTT) was performed with 75 g glucose at between 8.00 and 9.00 am [17]. Glucose, leptin, hemogram and routine biochemical parameters including lipid profile were measured in blood samples obtained in the beginning of OGTT (0 minute). Other blood samples for glucose level were collected at 30th, 60th, 90th, and 120th minutes, respectively. All blood samples were centrifuged and separated immediately and serum samples were stored at-80 ºC until assayed. Glocose disposal was determined with area under the curve of glucose (AUCglu120) during OGTT [18]. All patients treated with propylthiouracil (300-800 mg/day) until euthyroid state was provided (mean 12±2 weeks). All final blood samples were drawn approximately 3 weeks after achieving euthyroid period. After obtained euthyroidism; anthropometric measurements, body fat analysis, leptin levels, OGTT, and AUCglu120 during OGTT were repeated, and the results were compared with healthy control group.

Plasma leptin levels were measured by radioimmunoassay (Human Leptin IRMA DSL-2300 kit, Bio-dsl, St. Charles, MO, USA), with intraassay and interassay coefficient of variation were 1.44-2.44% and 4-5.1%, respectively. Free T3 and free T4 were determined by competitive chemiluminescence emission tecnic and TSH levels by Sandwich Chemiluminescence Immuno Assay (Roche Diagnostics, Meinhaim, Germany). Glucose levels were determined using the glucose oxidase method with an automated glucose analyzer (Beckman, Fullerton, CA, USA).

Statistical Analysis: Results were expressed as mean±standard deviation. ANOVA test were used in comparison of groups. Bonferroni multiple comparisons test was used in post-hoc analysis. The differences between before and after treatment were calculated with paired-t test. Independent-t test was used in comparison of control and patiens group. The relationships between variables were evaluated with Pearson's correlation test. Value $p < 0.05$ was accepted as statistically significant.

Results

Serum thyroid hormone profiles in hyperthyroid patients were fT3: 13.52±8.72 pg/ml, fT4: 4.75±2.60 ng/dl, and TSH: 0.02±0.05 mIU/L, respectively before the treatment. TSH, free T3, and free T4 levels were normalized after 3 months of anti-thyroid therapy. In euthyroid state, serum thyroid hormone profiles were found fT3: 2.45±4.86 pg/ml, fT4: 0.96±0.37 ng/dl, and TSH: 1.99±1.51 mIU/L (p=0.0001, p=0.0001, p=0.0001, respectively) after the treatment (Table-1).

Serum leptin levels in hyperthyroidic patients were lower than control subjects (19.95±19.81 ng/dl and 35.90±22.73 ng/dl respectively, p<0.01). After the treatment, serum leptin leves showed significant increments (24.54±19.99 ng/dl, p<0.02) and it became different from control subjects, also. All leptin results were shown in Table-1.

Mean body weight was 67.66±13.01 kg and mean BMI was 26.21±5.44 kg/m² in hyperthyroid patients. Mean body weight and mean BMI values increased with treatment insignificantly [70.0±12.5 kg (p>0.05) and 27.31±4.84 kg/m² (p=0.05)]. There were significant correlations between serum leptin levels and BMI both of hyperthyroid and euthyroid state in same patients (before the treatment r = 0.392, p=0.043; after the treatment r=0.590, p=0.002). Serum leptin levels were also related to body fat mass in hyperthyroid patients (before treatment r=0.395, p=0.042; after treatment r=0.731, p=0.0001). But, body fat mass did not change after the treatment.

We found negative correlations between serum leptin levels and thyroid hormones in hyperthyroid patients (fT3 and leptin levels r=-0.406, p=0.009; fT4 and leptin levels r=-0.403, p=0.01, respectively) (Figure 2), but there was no relationship between serum leptin and TSH levels.

In OGTT, glucose intolerance in 18 patients and overt diabetes mellitus in 5 patients with hyperthyroidism were determined according to ADA criteria (n=27) (19). In hyperthyroid patients, mean glucose levels at baseline, 30th and 60th minutes were higher than those of the control subjects (p=0.01, p=0.0001 and p=0.01, respectively). The results of all plasma glucose levels during OGTT were presented in Figure-1.

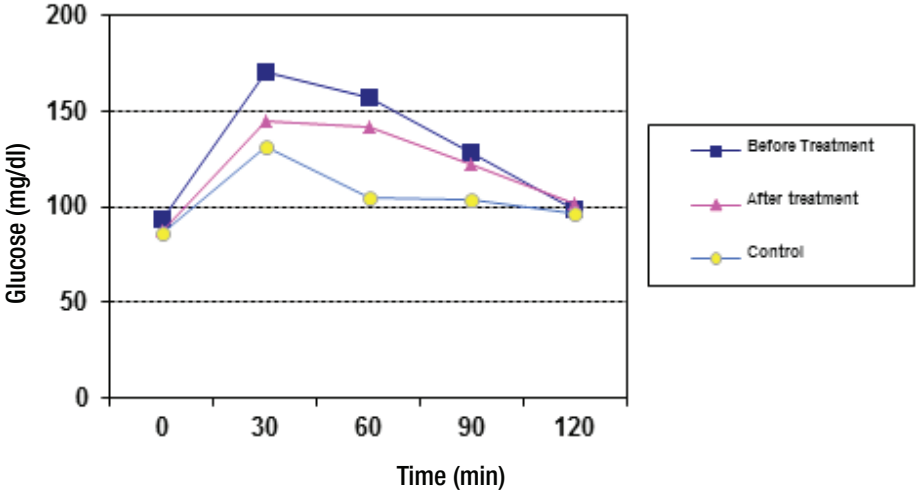

Figure-1. Plasma glucose concentrations in hyperthyroid patients and in control subjects during oral glucose test before and after treatment.

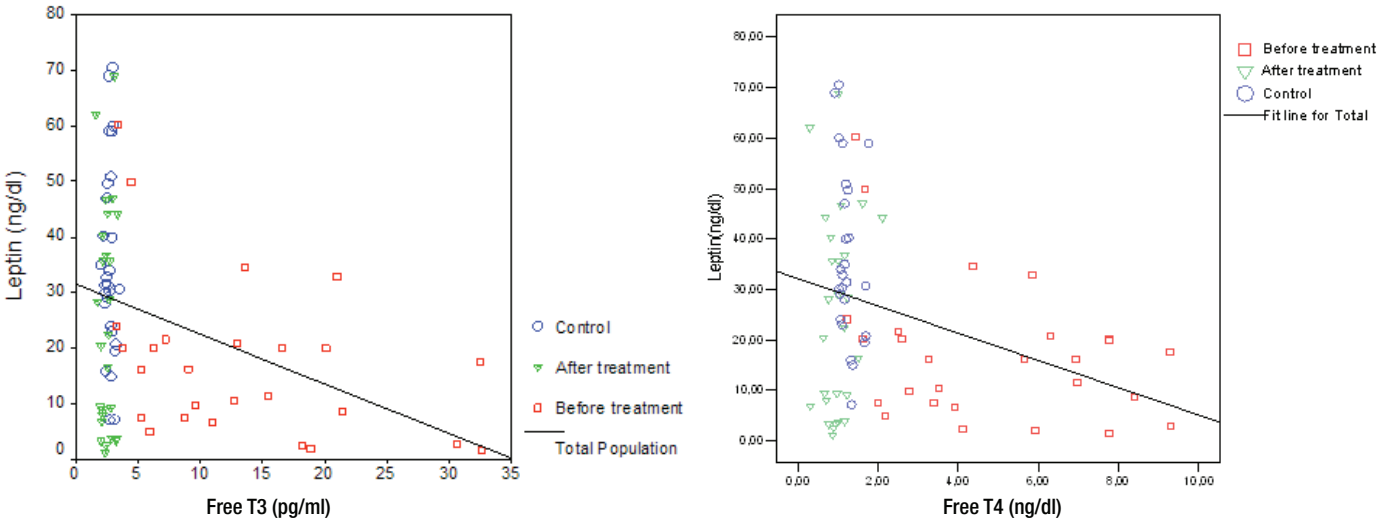

Figure 2: Corelations with serum leptin and serum thyroid hormone levels in hyperthyroid and control subjects

In control group AUCglu120 was found as 12567±2102 mg.min/dl whereas it was 16570±3276 mg.min/dl before the treatment and 15123±3735 mg.min/dl after the treatment in hyperthyroid women. In accoring to our results, mean AUCglu120 in hyperthyroid group was significantly higher than control subjects (p=0.001). When the same patients established to euthyroid state, AUCglu120 values were not different from control group. There was no correlation between AUCglu120 and serum leptin levels, BMI values, and thyroid functions. All the results of study population were presented in Table 1.

Table 1: Characteristics of control subject and hyperthyroid patients before and after treatment.

	Control (C) Subjects (n:30)	Patients (n:27)		P value		
		BT (n=27)	AT (n=27)	(BT-AT)	(BT-C)	(AT-C)
Age (yr)	36.2±10,7	35±10	35±10	NS	NS	NS
Weight (kg)	62.78±15,28	67.66±13.01	70.07±12.53	NS	NS	NS
BMI (kg/m^2)	25,48±6.97	26.21±5.44	27.31±4.84	NS	NS	NS
Fat mass (kg)	19.25±12.39	19.05±9.64	19.60±9.31	NS	NS	NS
Fat percent	27.84±11.47	26.84±10.23	27.44±10.14	NS	NS	NS
fT3 (pg/ml)	2,90±0,32	13.52±8.72	2.45±4.86	0.0001	0,0001	NS
fT4 (ng/dl)	1,21±0,21	4.75±2.60	0.96±0.37	0.0001	0,0001	NS
TSH (mIU/l)	1,83±0,68	0.020±0.05	1.99±1.51	0.0001	0,0001	NS
Leptin (ng/dl)	35.90±22.73	19.95±19.81	24.54±19.99	0,028	0,015	NS

BT: Before treatment **AT:**After treatment **C:**Control subjects **NS:**Non-significant

Discussion

A landmark finding of our study was serum leptin levels were significantly lower in hyperthyroid patients than control subjects. Influence of thyroid hormones on leptin secretion is complex and partially recognized. The relationship between thyroid hormones and leptin production in hyperthyroid subject was studied previously, but results of investigations of serum leptin levels in patients with hyperthyroidism are controversial [20-24]. Although most of them found no effect of hyperthyroidism on leptin levels, some authors claimed relative hypoleptinemia in hyperthyroid patients [20-25]. But, these studies did not clarify whether a relationship between insulin resistance and hyperthyroidism was occured despite of change of leptin levels.

Two possible mechanisms may play a role on low leptin levels in hyperthyroidsm. First, low serum leptin levels may be related to alterations of anthropometrical parameters such as BMI, body fat mass and fat distribution. But, our findings demonstrated that mean BMI, fat mass, fat percent in hyperthyroid patients were not different from control subjects; therefore, we think that reduced body fat mass and BMI in hyperthyroid female patients may not responsible from hypoleptinemia. Thyroid hormones, which increase the basal metabolic rate and thermogenesis, have been reported to be one of leptin's regulating factors because alterations in thyroid status might lead to compensatory changes in circulating leptin [21,26]. Our results also indicated that an inverse relationship existed between thyroid hormones and serum leptin

concentrations, and this relationship was not the results of changes in body fat stores. Also, we determined that serum leptin levels increased after obtained euthyroidism. Although BMI and body fat mass increased after the treatment, changes in these parameters were not statistically meaningful. Whether thyroid hormones are directly involved in regional differences in adipose tissue remains to be elucidated. In fact, serum leptin levels may be related to either moderately increases in BMI and fat mass [27]. A previously study demonstrated that during the first 3 months of recovery from hyperthyroidism, priority was given to the replenishment of skeletal muscles and intra peritoneal adipose tissue, but not to subcutaneous adipose tissue [28]. The mechanism behind the early preferential recovery of visceral adipose tissue compared to subcutaneous adipose tissue after treatment of the thyrotoxic condition can only be speculated upon [29]. There was no apparent explanation for this phenomenon in previous studies. It was reported that increment in serum leptin levels after obtained euthyroidism accompanied by a parallel increase in fat mass during weight gain [10,30-32]. On the contrary, Zimmermann-Belsing et al [12] found a relative increase in leptin concentration in patient during treatment for hyperthyroidism than the body fat mass increase.

Second, thyroid hormones may affect on serum leptin levels independent of body fat composition. Some studies performed in rats have also demonstrated a negative influence of thyroid hormones on serum leptin levels [13]. Fain et al [33] showed that leptin mRNA concentrations were decrease within 8 h after T3 administrations. On the other hand, Teixeira PF et al [34] reported that serum leptin concentrations are elevated in postmenopausal women with subclinical hypothyroidism or overt hypothyroidism (OH). More importantly, LT-4 treatment was associated with a reduction of serum leptin concentrations in the OH group in the absence of significant effects on BMI ($p=0.008$). These authors suggest that in women, hypothyroidism influences either leptin secretion or degradation. Interestingly, our study showed that low serum leptin levels in hyperthyroid conditions were increased when thyroid status was controlled with antithyroid treatment. This significant increasing of leptin levels, after achieved normalization of thyroid hormones, might be related to influence of thyroid hormones on leptin levels. Furthermore, other investigators infused T4 or T3 to rats and observed reductions in plasma leptin levels [13]. It was postulated that T3-induced alterations in adipocyte sensitivity to catecholamines could explain how thyroid dysfunction gives rise to altered plasma leptin concentrations [35]. But, further investigations should be performed for resolving on this subject.

The relationship between leptin and carbohydrate metabolism in hyperthyroid patients was not completely understood. According to our results, hyperthyroid women tend to be more insulin resistant than control group. This observation considered that insulin resistance may be induced by hyperthyroid condition [36]. In agreement with previous results, glucose tolerance was impaired in the hyperthyroid subjects [37,38]. Recently, a study also reported that both of hyperthyroid and subclinical hyperthyroid patients displayed higher postprandial AUC glucose levels in OGTT [39]. Also, in a clamp study, it was demonstrated presence of insulin resistance in untreated hyperthyroid patients [3]. Our findings are in agreement with previous studies associated with resistant to insulin in hyperthyroidism. High thyroid hormone levels may regulate leptin secretion or may effect of insulin in adipose tissues. It seems that insulin resistance in hyperthyroidism is not only primarily at the liver which may be explained by increased endogenous glucose production through more rapid glycogenolysis and gluconeogenesis but also, glucose uptake in adipose tissue may decreased [40]. Experimental studies demonstrated that prolonged intravenous leptin infusion causes an increase of glucose use by an increase of tissues' insulin sensitivity [41]. On the contrary, leptin induces gluconeogenesis in the liver, inhibits insulin release from pancreatic beta cells, and probably also causes break-down of insulin receptors in type 2 diabetic patients [42]. But, low leptin concentrations find in obese patients with poorly controlled type 2 diabetes who show insulin deficiency [42]. Therefore, the leptin level may depend on many conflicting factors for effect on glucose metabolism [42]. However, acute intravenous and intracerebroventricular administrations of leptin, induce an increase in whole-body glucose uptake but a decrease in hepatic glycogen content independently of plasma insulin concentrations [43]. Our results suggested that insulin resistance might be associated with hyperthyroidism, and was not mediated by a reduction in serum leptin levels. It seems to be no causal relationship between insulin resistance and serum leptin levels in hyperthyroid subjects. In addition, adipose tissue is an active endocrine organ releases a number of bioactive mediators associate with insulin resistance excluding leptin such as resistin, adiponectin, interleukin 6 and tumour necrosis factor α. Recently, a study pointed out that insulin-stimulated glucose transport in isolated monocytes of patients with hyperthyroidism was decreased compared with euthyroid subjects [44]. Decreased fractional postprandial glucose uptake in adipose tissue, increased fasting lipolysis, increased interleukin 6, and tumour necrosis factor alpha may be associated to its development [45] .

We concluded that serum leptin levels decreased in hyperthyroidism. Low serum leptin levels in hyperthyroidism can not be explained with differences in body fat and BMI. Serum leptin levels increased with obtaining of euthyroidism. Hyperthyroid patients tend to be glucose intolerance, and this glucose disposal may be recovered with euthyroidism independent of serum leptin levels.

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