JPMA (Journal Of Pakistan Medical Association) Vol 53 ,No.5,May 2003

Serum Leptin level in Hyperthyroid Female Patients

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Abstract

Objective: To evaluate potential role of serum leptin level in hyperthyroid female patients and find out its relationship with BMI.

Setting: Atomic Energy Medical Centre and Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi.

Methods: Serum leptin, FT3, FT4, TSH, serum triglyceride, total cholesterol, HDL-C, LDL-C were determined in 30 newly diagnosed untreated hyperthyroid female patients and 22, age, sex and BMI matched lean control group (BMI <25) and 22 obese control female group (BMI >30). The female patients identified from thyroid OPD of AEMC, JPMC, Karachi, through thyroid profile results and sign and symptoms of the disease. The clinical history was taken and physical examination performed.

Results: A significant difference $p<0.001$ was found in serum leptin level in hyperthyroid female patients when compared with control groups. Serum leptin level significantly correlated with BMI in both normal groups ($p < 0.001$).

Conclusion: Decreased levels of serum leptin in hyperthyroid patients suggest important interaction of FT3, FT4, and TSH with leptin (JPMA 53:176; 2003).

Introduction

Leptin, the ob gene product, is a peptide hormone, secreted by adipocytes.1 Leptin plays an important role in the regulation of food intake, energy expenditure and body weight.

When leptin binds to specific receptors in the hypothalamus it reduce\s appetite and increases caloric expenditure. When leptin was administered to deficient ob/ob mice, it resulted in decrease food intake, weight loss and energy expenditure.2,3 In addition, administration of leptin to rats deprived of food corrected many of the neuroendocrine changes (e.g. the decrease in the release of thyroid hormone) that occur as a result of food deprivation.4 Furthermore, serum immunoreactive leptin levels show a strong positive correlation with body fat and Body Mass Index (BMI).5-7

Thyroid hormones are essential for the regulation of important processes involved in thermogenesis, energy consumption and many other metabolic reactions. in a high percentage of hyperthyroid patients, decreased body weight, increased appetite and increased thermogenesis are characteristic features. As both thyroid hormones and leptin have effects on similar aspects of body homeostasis, many studies have been done for evaluating the potential interaction of leptin and thyroid hormones, but they had conflicting results, due to small number of patients and they included both sexes (male and female) in the same study. This study was designed with comparatively large number of patients of one sex (female), to investigate the potential interaction of circulating thyroid hormones with leptin and also to evaluate the relationship between serum leptin levels and BMI in hyperthyroid patients and lean and obese control subjects.

Subjects and Methods

Thirty female patients (20-40 years) were identified with newly diagnosed untreated thyrotoxicosis (Graves' disease). Graves' diseases was defind as clinical and bio-chemical hyperthyroidism in the presence of smooth goiter, with or without ophthalmopathy. New patients were identified through their thyroid profile results and examined prior to the initiation of treatment. All patients were systematically examined and symptoms and signs of thyroid disease were confirmed. Subjects with diabetes mellitus, pregnancy, hypothalamic or pituitary disease and sick euthyroidal syndrome were excluded.

Subjects were weighed in light clothing and height was recorded, along with waist circumference measured at the level of the umbilicus and hip circumference measured at the level of the greater trochanter. Body mass index (weight in Kg/height in square meter) and waist hip ratio (W/H ratio) was calculated by the formula.

Forty-four clinically and biochemically euthyroid healthy control subjects were identified from general population. The euthyroid subjects were divided into two control groups, lean (BMI <25) and obese (BMI >30). Subjects with diabetes mellitus, hypothalamic or pituitary disease and those lactating were excluded.

After obtaining consent of the patients and normal subjects, blood samples were taken in the morning after overnight fasting (12-14 hrs) and after centrifugation serum was frozen immediately at -20°C until assayed.

Samples were analyzed in one run at the end of the study, to omit in between analytical variations. Serum triglyceride, total cholesterol and HDL-C were analyzed enzymatically, using the kits supplied by spinreact, Spain. LDL-C was calculated by the Friedwald's formula. Glucose determination was done by enzyme oxidase method. Serum leptin was measured by ELISA using kit supplied byDiagnostic System Laboratories (DSL), U.S.A., which was sensitive to 0.05 ng/ml. FT4, FT3 and TSH were measured by radioimmunoassay using immunotec kit supplied by Beckman Coulter Company, France, at Gamma counter (Capintec Inc) in RIA laboratory of Atomic Energy Medical Centre, J.P.M.C., Karachi.

Statistical analysis

The results are expressed as mean ± SEM and differences in thyroid profiles and leptin were tested by student's t-test.

Results

Table 1 compares the anthropometric parameters of hyperthyroid female patients and both the control groups (lean and obese females). Age, height, weight, BMI, waist hip (W/H) ratio of hyperthyroid female patients were approximately similar to that of control lean group. Weight, BMI, waist and hip circumference and W/H ratio of control obese group were significantly high as compared with lean control group and hyperthyroid female patients.

Table 1. Anthropometric parameters in hyperthyroid patients and euthyroid lean and obese control.

Parameters	Hyperthyroid patients	Euthyroid lean	Euthyroid obese
Age (years)	31.77±1.97	30.41±1.66	31.95±1.95
Height (cms)	154.36±1.60	156.77±1.99	155.22±1.29
Weight (kg)	48.86±2.14	52.18±2.12	81.12±4.80*
BMI (kg/m2)	20.18±0.77	21.39±0.78	33.57±0.84*
Waist circumference (cms)	65.09±1.68	70.86±1.73	94.64±2.43*
Hip circumference (cms)	85.50±1.87	90.18±1.43	104.23±2.31*
W/H ratio	0.76±0.01	0.78±0.02	0.91±0.01*

* P<0.001 when euthyroid obese control subjects compared with hyperthyroid patients.

Table 2 Biochemical charecterstics

Parameters	Hyperthyroid patients n = 30	Euthyroid lean n = 22	Euthyroid obese n = 22
FT4 ng/dl)	4.25±0.73	1.06±0.03**	1.09±0.05**
FT3 (pg/dl)	23.45±2.21	2.39±0.09**	2.25±0.08**
TSH (IU/ml)	All <0.01	1.60±0.21**	2.01±0.23**
Leptin (ng/dl)	13.55±1.84	20.25±2.15**	48.27±3.81**
Triglyceride (mg/dl)	98.03±5.78	140.93±16.15*	153.36±19.57*
Total Cholesterol (mg/dl)	138.24±2.94	193.50±8.76**	201.93±11.94**
HDL-C (mg/dl)	34.12±1.42	36.64±0.97NS	40.93±2.81*
LDL-C (mg/dl)	83.54±3.43	129.64±8.20**	131.21±9.55**
FBS(mg/dl)	95.78±1.87	79.43±1.97**	91.57±1.74 NS

* $p<0.05$

** $p<0.001$ when euthyroid lean and obese control subjects compared with hyperthyroid patients.

Table 2 explains and compares the mean values (± SEM) of thyroid hormones (FT_4, FT_3), TSH, leptin , lipids (total Cholesterol, Triglycerides) and lipoproteins (HDL-Cholesterol, LDL-Cholesterol). The mean value for FT_4 and FT_3 are significantly high, where as TSH was significantly low in hyperthyroid female patients when compared with control groups. The mean (± SEM) value of leptin in female hyperthyroid patients was 13.55±1.84 ng/ml as compared to control lean and control obese groups, 20.70±2.15 ng/ml and 49.27±3.81 ng/ml respectively. The three groups differed significantly in their serum leptin levels ($P<0.001$). Serum leptin levels of lean and obese control groups were higher than hyperthyroid female patients.

Discussion

Leptin decreases appetite, increases thermogenesis and regulates body weight. Decreased body weight, increased appetite and increased thermogenesis are characteristic features in majority of hyperthyroid patients. Therefore the role of leptin in thyroid disorders has been the point of interest since the mid of 1996 by many research workers.

Yoshida et al[8] found that direct effect of T_3 on fully differentiated adipocytes showed stimulation of leptin expression and secretion. Ozata and colleagues[9] found plasma leptin levels to be increased in hyperthyroidism and decreased in hypothyroidism. In an in-vitro study Fain et al[10] observed increased leptin mRNA expression in hypothyroid rats, and a reduction in expression in response to T_3 treatment.

Our results show significantly decreased concentration of serum leptin in hyperthyroid patients. Our results agree better with, in-vitro study by Escobar Morreale et al[11], who observed that thyroidectomized rats infused either with placebo or with high doses of thyroid hormones causing hyperthyroidism showed elevated and suppressed leptin levels respectively, compared to intact animals infused with placebo. Zimmermann Belsing et al[12], observed that serum leptin level in thyrotoxic patients increased significantly after 12 months of treatment compared to both normal subjects and their own base line. Our results are similar to the findings of Pinkney et al[13] who observed relative hypoleptinemia in well-characterized population of patients with clinically and biochemically confirmed hyperthyroidism. Similarly Al-Shoumer et al.[14] also observed low leptin concentration in Arab women with hyperthyroidism. Obermayer-Pitsch et al[15]

found that the base line, leptin concentrations were significantly decreased in all hyperthyroid patients as compared with controls. However, some studies have found no correlation in serum leptin level in hyperthyroid patients when compared with control subjects.[16-18]

In 1997, Mantzoros et al[19] observed that short term hyperthyroidism induced by the administration of T_3 has no effect on circulating leptin levels in healthy male volunteers. In 2000 Miyakawa et al[20] and Matsubara et al[21] found no change in serum leptin level in hyperthyroid female patients before and after treatment. No differences in serum concentration or adipose tissue secretion of leptin or TNF-alpha were observed by Wahren et al[22] neither before nor during antithyroid treatment and were comparable with euthyroid controls.

TSH receptors have been identified in adipose tissues[23] and therefore we can not deny the possibility that TSH might directly regulate leptin gene expression. In our study hyperthyroid group consisted of the patients with Grave's disease, who had auto antibodies activating the TSH receptors. May be the over activity of TSH receptor causes suppression of secretion of leptin in adipocytes. There is another possibility that T_3 induced alteration in adipocytes sensitivity to catecholamines can give rise to altered serum leptin concentrations in hyperthyroid patients.

Thyroid hormones produce overactivity of sympathetic nervous system, resulting in the increase release of norepinephrine from sympathetic nerve endings in adipose tissue. The fat cells express adrenergic receptors that are stimulated by norepinephrine, causing fatty acid hydrolysis and also uncouple energy production from fat storage of hyperthyroid patients.[24] This explains how thyroid dysfunction gives rise to altered plasma leptin concentrations. In experimental studies, the administration of beta-adrenoceptors agonists led to the rapid disappearance of ob gene mRNA[25-27] and the administration of the beta-antagonist propranolol partially reverses this effect.[28] It has been shown that infusion of isoprenaline in humans acutely suppresses leptin concentration[29,30], confirming the potential role for catecholamines in the acute regulation of leptin. Therefore, the results of the present study may be interpreted in the context of adipocyte beta-adrenoceptor sensitivity.

Leptin has in rodents and human subjects been shown to correlate highly significantly with BMI or percentage body fat in both men and women.[31,33] Women in general have higher percentage of body fat and higher ratio of subcutaneous to visceral fat. Serum leptin is strongly related to fat mass and even stronger to subcutaneous fat, which has been shown to secrete more leptin.[34]

In conclusion, we have found that serum leptin level is related with BMI in normal control subjects (lean and obese) and significant decreased level is found in hyperthyroid patients. In lean and obese control subjects serum leptin level reflects the amount of adipose tissues and is directly proportional with fat contents. It is suggested that the low serum leptin level in hyperthyroid patients is due to hyperadrenergic state found in these patients and/or it may be the result of suppression of leptin gene expression due to overactivity of TSH receptors by auto antibodies.

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