Influence of Primary Hypothyroidism on Serum Leptin Level

Maryam S. Mohammad*, Abdul Hussein A. Farage*,Aras A. Abdullah**

ABSTRACT:

BACKGROUND:
Leptin is the protein product of the ob gene, secreted by adipocytes. It has been suggested that it may plays an important role in regulating appetite and energy expenditure, but beside that, little is known about the physiological actions of leptin in humans.

OBJECTIVE:
To evaluate a possible influence of primary hypothyroidism on serum leptin levels.

METHODS:
Fifty-six newly diagnosed patients with primary hypothyroidism (40 females and 16 males) and 32 normal controls matched for age, ethnic status and body mass index (BMI) were studied. Body mass index (BMI; kg/m2), thyroid function(using enzyme-linked immunoflourescent assay) and serum levels of leptin, thyroid autoantibodies (measured by enzyme-linked immunosorbant assay) and lipid profile(measured by enzymatic colourimeteric assays) were assessed in all studied subjects.

RESULTS:
No significant difference in serum leptin levels was recorded between hypothyroid patients and controls (16.3±14.9; 14.8 ± 12.9, P> 0.05), but women in each group had significant higher leptin concentrations than men (patients: 19.6 ±16.3 vs. 8.3 ±5.0; controls: 19.0 ±14.4 vs. 7.7 ±4.1; P< 0.05). Serum levels of cholesterol ($p<0.002$), LDL-cholesterol ($p<0.004$) and atherogenic ratio ($p<0.03$) were generally higher in patients than controls. The serum leptin concentration correlated positively with BMI within both patients ($r=0.32$; $p<0.016$) and controls ($r=0.28$; $p<0.024$). However, no association was demonstrated between values of serum T3, T4, TSH, triglyceride, HDL-cholesterol and thyroid auto antibodies.

CONCLUSION:
Circulating thyroid hormones do not appear to play any significant effect on leptin levels in patients with primary hypothyroidism.

***KEY WORDS*:** leptin, lipids and lipoproteins, primary hypothyroidism.

INTRODUCTION:

Leptin is a 167-amino acid protein hormone encoded by the ob gene and secreted by adipocytes in response to an increase in fat mass. It seems to be a key molecule in the feedback loop that regulates energy balance. Leptin has a dual action: it decreases the appetite and increases energy consumption, causing more fat to be burned [(1)].

In fact, both ob/ob and db/db mice are characterized by numerous abnormalities, such as severe insulin resistance, infertility, decrease in lean body mass, cold intolerance and hypothermia, while administration of leptin to ob/ob mice results in a reduction in food intake, an increase in locomotor activity (with an increase in oxygen consumption) and a reduction in body weight [(1)]. As substantial variability in serum leptin levels occurs among individuals with comparable degrees of obesity, other factors in addition to the amount of body fat appear to regulate leptin secretion. Previous reports suggested a role for insulin, glucocorticoids, catecholamines and sex hormones [(2)].

In thyroid disorders there are changes in basal metabolic rate, oxygen consumption, and appetite and body weight. Thyroid hormones are important regulators of both basal and total energy consumption, and modulate the activity of several enzymes involved in lipid metabolism [(3)]. They are therefore a major component in the regulation of energy balance and body composition in humans.

As both thyroid hormones and leptin have effects on similar aspects of body homeostasis, the present work studied circulating leptin concentration in patients with primary hypothyroidism before replacement therapy. In addition, a group of control subjects matched for age, sex and body mass index (BMI) were studied. Because there is no data in literature on the status of leptin in Kurdish population, the subjects in the present study were Kurdish residents of Sulaimania city.

*Department of Biochemistry.
**Department of Medicine, College of Medicine, University of Sulaimani.

MATERIALS AND METHODS:

The present study was conducted on 56 adult patients with primary hypothyroidism attended the Hormonal Laboratory of Al-Shahid Hadi Consultation Clinic in Sulaimani in the period between March 2007 and September 2007.They were 40 females (19- 65 years) and 16 males (20-58 years) with BMI of 26.6 ± 4.8kg/ m^2 .

The study was approved by medical college ethical committee and all cases were diagnosed clinically by a consultant physician and the diagnosis was confirmed in laboratory by the thyroid function tests. The aim of the study was explained to the patients who gave their informed consent. Failure of thyroid function was due to partial thyroidectomy for nodular goiter in 24 patients and to autoimmune thyroiditis, diagnosed by positive anti-thyroid peroxidase (TPO) and / or anti-thyroglobulin (Tg) antibodies in the remaining 32 patients. Those patients who had concomitant renal, hepatic or cardiac disease or who had been treated with drugs such as thyroxine, estrogens and anti-inflammatory agents, which could affect the variables of the study, were excluded.

In addition to hypothyroid patients, a thirty two apparently healthy volunteers matched for age; sex and BMI and they were not complaining of any acute or chronic illnesses with normal thyroid function assist by cartful clinical and laboratory estimations (i.e. no history of thyroid diseases and normal T3, T4 & TSH values) were used as control group.

After noting the name, age and sex, venous blood samples were drawn. Serum was separated and assays were performed within 24 hrs for thyroid and lipid profiles. Serum for assays of leptin and thyroid antibodies was separated and freezed until assayed within one week.. Freezing –thawing were avoided.

Serum total T3 (normal range 0.92 – 2.33 nmol/l), total T4 (normal range 60.0 – 120.0 nmol/l) & TSH (normal range 0.25 – 5.0 mIU/l) were measured by enzyme linked immunofluoresent assay (ELFA) on a minividas (Biomereiux, France). Serum levels of leptin (DRG Co, German), anti-thyroid peroxidase (TPO) and anti-thyroglobulin (Tg) (Monobind Inc, USA) were measured by enzyme linked immunosorbant assays (ELISA): samples providing a levels more than 40 IU/ml for anti TPO and 125 IU/ml for anti Tg were graded as positive. Serum total cholesterol (TC) and triglycerides (TG) were measured by enzymatic colourimetric assays (Teco Diagnostics, USA). High density lipoprotein -cholesterol (HDL-C) was determined enzymatically in the supernatant after dextran-magnesium-induced precipitation of other lipoproteins. Low density lipoprotein - cholesterol (LDL-C) was calculated using the Friedwald's formula [4].

Statistical analysis:

Results were expressed as mean ± SD. Differences between hypothyroid patients and control group were assessed using student's t – test. Correlations between variables were assessed by calculating Pearson's correlation coefficients. P values < 0.05 were considered significant

RESULTS:

Subjects Characteristics

Table 1 presents clinical and biochemical data for the study participants. There were significant differences between hypothyroid patients and controls in T3, T4, and TSH levels. Table 1 also shows a significant higher levels of total cholesterol, LDL-C, atherogenic ratio, TPO and Tg while no significant differences between hypothyroid patients and controls in age, BMI, height, weight, triglyceride and HDL- C were observed.

Serum leptin level comparative study:

Serum levels of leptin in hypothyroid patients in comparison to controls were represented in table 2. As seen in both hypothyroid and control groups, serum leptin levels in males were significantly lower than those recorded in females [hypothyroid patients; 8.3 ± 5.0 and 19.6 ± 16.3 ng/ml; P < 0.009: controls; 7.7 ± 4.1 and 19.0 ± 14.4 ng/ml; P < 0.001].While no significant differences in serum leptin levels were found between the overall hypothyroid patients and controls (16.3 ± 14.9 and 14.8 ± 12.9; P> 0.05) respectively.

Serum leptin correlation study:

Table 3 shows the correlation of serum leptin to the studied clinical and biochemical parameters in hypothyroids and controls. Serum leptin values significantly correlated with BMI in both hypothyroid patients and controls, with no evident relationship with the thyroid status, lipid profiles and thyroid autoantibodies.

DISCUSSION:

Although much has been learned regarding the leptin, its physiology and the precise role it plays in endocrine system remain to be defined. One of the difficulties inherent to these studies lies in the fact that leptin physiology seems to be rather different in humans and rodents. Not only is the circadian rhythm of its plasma levels different but also its regulation and the relationship with other hormones have been shown to differ [2, 5].

The current study results confirm and extend previous clinical studies showing that hypothyroidism does not alter circulating leptin concentrations and that the ability of thyroid

hormones to regulate energy expenditure does not operate through variation in serum leptin level [6-8]. In contrast, our results do not support the clinical studies in human showing high [9, 10] or low [11, 12] serum leptin concentrations in hypothyroid patients compared with a control group or euthyroid subjects as well as they are in sharp contrast with that of Escobar- Morreale et al study on rats which demonstrated a negative influence of thyroid hormones on leptin levels, independent of the changes in body weight, due to the thyroidal effect [13].

The reasons for these conflicting results are not clear but the studies different in terms of patients' characteristics and methods for measuring serum leptin as well as evaluation of the body composition. For example, the studies in human that showed a decreased serum leptin concentration in hypothyroid patients [11, 12] were in response to thyroxine administration which associated with a significant loss of weight and that the consequent decrease in adipose stores probably accounts for the reduced leptin levels. On the other hand, the studies that reported higher serum leptin levels were either not used matched BMI values or that the actual BMI data were not given nor was it stated whether the two patients and control groups had similar and comparable BMI values. For example, Chen et al [10] studied twenty premenopausal women in comparison to twenty controls that were not BMI matched. Their hypothyroid patients had a higher BMI and also higher serum leptin concentration compared with euthyroid controls. In the present study as well in previous studies that reported no overall differences in serum leptin levels, the BMI values for patients were matched those of controls.

In agreement with other reports [5, 14], the current study found that serum leptin levels in both normal controls and hypothyroid patients were characterized by high variability, the major determinant of which are BMI and gender. This is documented by the finding of significant correlation between serum leptin levels and BMI in both study groups, the hypothyroid patients and controls, and also by the finding that leptin levels in males are consistently lower than those found in females(Table 2).

In addition, the statistical analysis of data definitely indicates that no relationship between serum leptin and thyroid hormone levels exists and that the BMI of patients of the two sexes were not significantly different. This may suggest that leptin regulatory mechanisms in females are more delicately regulated than in males, which may attributed to the following possibilities: First, through circulating sex steroid hormone variations; this suggestion can be supported by previously reported data indicated that circulating androgens but not estrogens have a suppressive effect on leptin secretion [15] and the second possibility for these sex differences in leptin concentrations may be explained by differences in the body composition. It is known that, at any given BMI, women are likely to have a grater percentage of body fat than men. Leptin mRNA expression is higher in subcutaneous than in visceral fat depots[16,17].

Table 1: Clinical and biochemical characteristics of the study groups.

Variables Mean ± SD	Hypothyroids	Controls
Subjects (No.)	56	32
Sex (males/females)	16/40	12/20
Age (years)	35.9 ± 14.0	37.3 ± 13.0
Height (m)	161.7 ± 8.0	160.8 ± 8.2
Weight (kg)	66.3 ± 10.1	64.0 ± 7.7
BMI(kg/m^2)	26.6 ± 4.8	24.8 ± 3.0
Cholesterol(mg/dl)	198.3±37.1*	175.7 ± 21.0
Triglyceride(mg/dl)	167.5 ± 57.6	155.7 ± 44.9
HDL-C(mg/dl)	31.1±7.7	30.7 ± 4.9
LDL- C (mg/dl)	132.8±33.1*	113.9 ±19.4
Atherogenic Ratio	6.73 ± 2.0*	5.9 ± 1.15
TPO(IU/ml)	123.3±171.0*	21.4 ± 25.3
Tg (IU/ml)	449.9 ± 821.0*	86.0 ± 47.8
TSH(µU/ml)	26.8± 22.35*	2.17 ± 1.43
T3 (nmol/l)	0.74 ± 0.2*	1.78 ± 0.40
T4 (nmol/l)	42.5 ± 19.5*	85.0 ± 18.8

*Refer to the significant difference from the control group ($P < 0.05$); SD= standard deviation.

Table 2: Serum levels of leptin in hypothyroid patients in comparison to controls (mean ± SD).

Study Subjects (n)	Serum leptin (mean ± SD) (ng/ml)
Hypothyroids (56)	16.3 ± 14.9
6	
• Male(16)	8.3 ± 5.0
• Female(40)	19.6 ± 16.3*
• Autoimmune (32)	17.7 ± 15.5
• Thyroidectomy(24)	15.8 ± 13.4
Controls (32)	14.8 ± 12.9
• Male(12)	7.7 ± 4.1
• Female(20)	19.0 ± 14.4**

*, ** refer to the significant difference from the corresponding gender ($P < 0.05$), n; sample size, SD; standard deviation.

Table 3: Correlation of serum Leptin to studied clinical and biochemical parameters in hypothyroids and controls.

variables	Serum Leptin (ng/ml)			
	Hypothyroids (n=56)		Controls (n=32)	
	R	P	R	P
BMI (kg/m^2)	0.32	0.016	0.287	0.024
Cholesterol (mg/dl)	-0.166	0.22	-0.189	0.3
Triglyceride (mg/dl)	-0.17	0.209	-0.036	0.84
HDL-C (mg/dl)	0.133	0.328	0.191	0.34
VLDL-C (mg/dl)	-0.17	0.209	-0.036	0.84
LDL- C (mg/dl)	-0.16	0.23	-0.135	0.282
Atherogenic Ratio	-0.183	0.178	-0.194	0.126
TPO (IU/ml)	-0.133	0.328	-0.046	0.71
Tg (IU/ml)	0.042	0.76	-0.029	0.87
T3 (nmol/l)	-.071	0.60	0.033	0.79
T4 (nmol/l)	0.095	0.484	-0.079	0.53
TSH (µIU/ml)	-0.019	0.89	-0.132	0.47

CONCLUSION :

Circulating thyroid hormones do not appear to play any significant effect on leptin levels in patients with primary hypothyroidism.

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