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Association Between Leptin Hormone and Thyroid Hormone Levels in Hypothyroid, Hyprethyroid and Euthyroid Subjects

Maher K. Ibrahim[1, *], Abdul-Monaim H. Al-Samarrai[2], Khudhair A. Khudhair[1]

[1]Department of Biochemistry, College of Medicine, University of Tikrit, Tikrit, Iraq
[2]Department of Chemistry, College of Education, University of Samarra, Samarra, Iraq

Abstract

Leptin is a hormone secreted by adipose tissues and is considered as a satiety hormone, it is known to be an important regulator of food intake and energy storage. Disturbance of thyroid function is associated with marked changes in both body weight and energy expenditure, and it has therefore been the subject of much research to study the mutual roles of leptin and thyroid hormones in this respect. Very few researches are done to investigate the possible association of serum leptin and thyroid hormones in Iraq. Despite intensive research in this field, results are still not very clear. Objective of this study was to find any possible association of serum leptin levels and thyroid hormones. This prospective, randomized study was conducted in Baghdad; Iraq. The subjects were selected from Medical City Hospital. Serum samples were collected from 180 individuals; 56 (31%) of them were males and 124 (69%) females. The patients classified into three groups, two groups for thyroid dysfunctions patients (hypothyroid and hyperthyroid patients) and the third group as control group (euthyroid). The body weight of each individual was measured using a carefully calibrated weighing balance. The height of each individual was measured to calculate BMI ratio. Blood samples were taken early in the morning, 12 hours postprandial. The serum samples were stored at (−20°C) until required for thyroid hormones (Total and Free T3, T4 & TSH) and plasma leptin measurements (by using ELISA). To determine if serum leptin levels are affected by thyroid dysfunction, we measured its concentration in serum samples from 55 euthyroid controls, mean age 36.9±9.9 yr and 125 subjects: 74 patients with hypothyroidism, mean age 44.3±7.0 yr, and 51 patients with hyperthyroidism, mean age 43.5±6.9 yr. Mean leptin levels in the euthyroid (3.69±1.94 ng/ml), hypothyroid (4.97±2.61 ng/ml) and hyperthyroid (2.36±1.26 ng/ml) groups were significantly different. The results showed no significant correlation in serum leptin and T3, T4, FT3, FT4, TSH either in the hypothyroid or in the hyperthyroid and euthyroid control group of patients. These data suggest that leptin levels are not affected by thyroid dysfunction. There was a significant positive correlation between BMI and leptin level ($r = 0.29$, $p = .03$) in euthyroid controls, ($r = 0.35$, $p = .01$) in hypothyroid and ($r = 0.33$, $p = .01$) in hyperthyroid. Serum leptin levels in males were lower than those recorded in females [hypothyroid patients; 4.4±2.1 and 5.1±2.7 ng/ml; $P>0.05$: hyperthyroid patients; 2.0±0.63 and 2.5±1.45 ng/ml; $P>0.05$: euthyroid; 3.2±1.8 and 3.9±2.0 ng/ml; $P>0.05$]. In conclusion, leptin hormone was no significantly correlated with thyroid hormone function in eu-, hypo-, and hyperthyroid patients. Leptin level is highly correlation with the BMI might be confirmed that BMI and gender are the major determinant of leptin levels.

Keywords

Leptin, Hyperthyroidism, Hypothyroidism, Euthyroidism

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* Corresponding author
E-mail address: Maher_r22@yahoo.com (M. K. Ibrahim)

1. Introduction

Leptin is a 146-amino acid protein hormone encoded by the ob gene, it is an important circulating signal for the regulation of body weight [1] and secreted by adipocytes in response to an increase in fat mass [2]. Since its discovery, leptin has been the subject of an enormous amount of work especially within the fields of nutrition, metabolism and endocrinology. It is believed to be involved in interacts with putative receptors in the hypothalamus decreasing appetite, increasing energy expenditure and regulating body weight [3, 4]. In thyroid disorders there are changes in basal metabolic rate, oxygen consumption, appetite and body weight. Thyroid hormones (TH) are important regulators of both basal and total energy consumption, and modulate the activity of several enzymes involved in lipid metabolism [5].

Although TH and leptin are both involved in the regulation of energy metabolism, the precise interrelationship between the two endocrine systems (leptin and TH) is presently incompletely understood and still controversial [6-19]. This might have to do with interference of major factor controlling the serum concentration of leptin; fat mass and gender. BMI and the fat mass of the body shows as a strong relationship exist with serum leptin concentration and is presumably the most important physiological determinant [20]. A clear sexual dimorphism of serum leptin concentration is noted, with leptin levels in females being twice as high as in males [21] as well as other studies differed in terms of patient characteristics, length of treatment (if performed), and method for measuring serum leptin. It is therefore not surprising that extreme variation in the results was seen. A large number of studies investigated the relationship between thyroid dysfunctions and circulating levels of leptin, but the reported results were highly conflicting both in basal conditions and after correction of the thyroid dysfunction. In hypothyroid subjects serum leptin was found to be increased [3, 6, 15, 17, 18, 22], decreased [7, 9, 12, 23] and unchanged [8, 10, 11, 13, 24, 25] compared with a control group and/or euthyroid subjects. In hyperthyroid subjects serum leptin was increased [7, 8, 14], decreased [3, 6, 22, 23] and unchanged [9, 10-13, 16, 18, 24, 25].

The aim of this study has been to provide new data on the relationship between plasma leptin levels in relation to thyroid dysfunction.

2. Materials and Methods

2.1. Subjects

We studied 180 adult patients (124 females and 56 males) aged 20-63 years with thyroid disorders: 74 were affected with autoimmune primary hypothyroidism (55 females, 19 males), 51 with hyperthyroidism (35 females, 16 males) and 55 with euthyroid control (34 females, 21 males). Body weight, height and body mass index (BMI; kg/m^2) were determined for each patient. Thyroid function was assessed by measuring serum fasting total and free triiodothyronine (TT3, FT3), total and free thyroxine (TT4, FT4), and thyrotropin (TSH). Serum leptin levels were measured at (900 h) after an overnight fast.

2.2. Assays

Serum leptin levels were determined by Enzyme-linked immunosorbant assay (ELISA). Also circulating levels of TT3, FT3, TT4, FT4 and TSH were measured by ELISA technique.

2.3. Statistical Methods

All data were analyzed using SPSS software for Windows, 13 (SPSS, Inc. Chicago, USA). Age, BMI, serum TSH, TT4, FT4, TT3, FT3 and leptin levels were compared among the various groups of patients using Student's t-test and within each group by linear regression analysis. Data are expressed as means±S.D.

3. Results

Serum TSH was 15.12±8.9 mU/l in hypothyroid a highly significant increase compared to 1.96±1.00 mU/l (mean±SD) in euthyroid patients and 0.15±0.08 mU/l in hyperthyroid patients. TT3 and TT4 levels were 0.45±0.32 ng/l and 3.67±1.59 µg/dl a significant decrease in the hypothyroid compared to 1.28±0.28 ng/l and 8.18±1.87 µg/dl in the euthyroid, 2.89±1.17 ng/l and 14.83±3.71 µg/dl in the hyperthyroid group respectively.

FT3 and FT4 were 1.15±0.66 and 0.53±0.31 ng/l in the hypothyroid also show a highly significant decrease compared to 2.65±0.82 and 1.31±0.29 ng/l in euthyroid controls, 4.8±1.27 and 3.73±1.47 ng/l in the hyperthyroid group respectively (Table 1).

Table 1. Serum TT3, TT4, FT3, FT4 level and TSH level for eu-, hypo-, and hyperthyroid patients.

Parameter / Groups	TSH mlU/L mean±SD	TT3 ng/ml mean±SD	TT4 µg/dl mean±SD	FT3 pg/ml mean±SD	FT4 ng/ml mean±SD
Euthyroid	1.96±1.00	1.28±0.28	8.18±1.87	2.65±0.82	1.31±0.29
Hypothyroid	15.12±8.9*	0.45±0.32*	3.67±1.59*	1.15±0.66*	0.53±0.31*
Hyperthyroid	0.15±0.08*,π	2.89±1.17*,π	14.83±3.71*,π	4.8±1.27*,π	3.73±1.47*,π

*P < 0.05 when compared to euthyroid. πP < 0.05 when compared hyperthyroid versus hypothyroid group.
SD; standard deviation.

Serum leptin in hypothyroid patients was significantly higher than in euthyroid controls (4.97±2.61 ng/ml vs 3.69±1.94 ng/ml, P < 0.05). While serum leptin in hyperthyroid patients was significantly lower than in euthyroid controls (2.36±1.26 ng/ml vs 3.69±1.94 ng/ml, P < 0.05) (Table 2 and Fig. 1)

Table 2. Serum leptin level for eu-, hypo-, and hyperthyroid patients.

Groups / Parameter	Euthyroid (n=55)	Hypothyroid (n=74)	Hyperthyroid (n=51)
Leptin (ng/ml) mean±SD	3.69±1.94	4.97±2.61*	2.36±1.26*,π

*P < 0.05 when compared to euthyroid. πP < 0.05 when compared hyperthyroid versus hypothyroid group.
SD; standard deviation. n= Number of subjects.

The difference found between hypothyroidism and hyperthyroidism patients was mainly due to the significantly different BMI in the two groups (30.73 vs 25.11 kg/m^2; P <0.05), (Table 3) and possibly to the concomitant sex hormone.

The mean serum leptin levels in males with thyroid disorders and euthyroid group were in general lower than those recorded in females, [hypothyroid patients; 4.4±2.1 and 5.1±2.7 ng/ml; P>0.05: hyperthyroid patients; 2.0±0.63 and 2.5±1.45 ng/ml; P>0.05: euthyroid; 3.2±1.8 and 3.9±2.0 ng/ml; P>0.05 respectively] (Table 4).

The statistical analysis of the results showed the serum leptin levels in non-obese was lower than those recorded in obese [hypothyroid patients; 3.83±1.5 and 5.8±2.1 ng/ml; p<0.05: hyperthyroid patients; 2.31±1.2 and 2.54±1.2 ng/ml; P>0.05: euthyroid; 3.34±1.6 and 3.96±1.3 ng/ml; P>0.05] (Table 5).

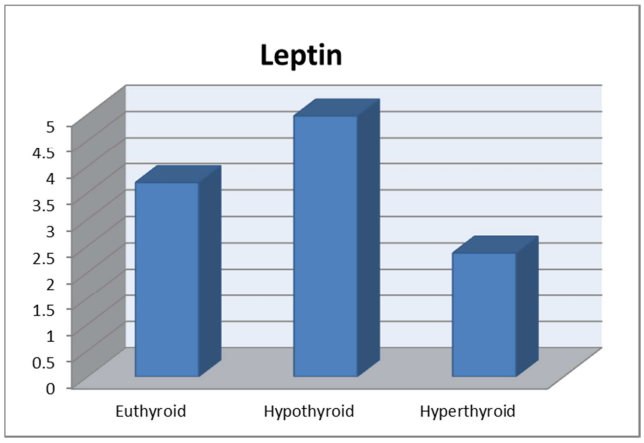


Figure 1. Serum leptin hormone levels in eu-, hypo-, and hyperthyroid patients.

Table 3. The mean±SD of BMI for eu-, hypo-, and hyperthyroid patients.

Groups / Parameter	Euthyroid	Hypothyroid	Hyperthyroid
BMI (kg/m^2) mean±SD	28.29±4.3	30.73±4.3*	25.11±3.5*,π

*P < 0.05 when compared to control. πP < 0.05 when compared hyperthyroid versus hypothyroid group.
SD; standard deviation.

Table 4. Serum levels of leptin in male and female for eu-, hypo-, and hyperthyroid patients.

Diagnosis	Euthyroid		Hypothyroid		Hyperthyroid	
Groups	Male	Female	Male	Female	Male	Female
Leptin (ng/ml) (mean ± SD)	3.2±1.8	3.9±2.0	4.4±2.1	5.1±2.7	2.0±0.63	2.5±1.45

SD; standard deviation.

Table 5. Serum levels of leptin in obese and non-obese for eu-, hypo-, and hyperthyroid patients.

Diagnosis	Euthyroid		Hypothyroid		Hyperthyroid	
Groups	Obese	Non- obese	Obese	Non-obese	Obese	Non-obese
Leptin (ng/ml) (mean ± SD)	3.96±1.3	3.34±1.6	5.8±2.1	3.83±1.5*	2.54±1.2	2.31±1.2

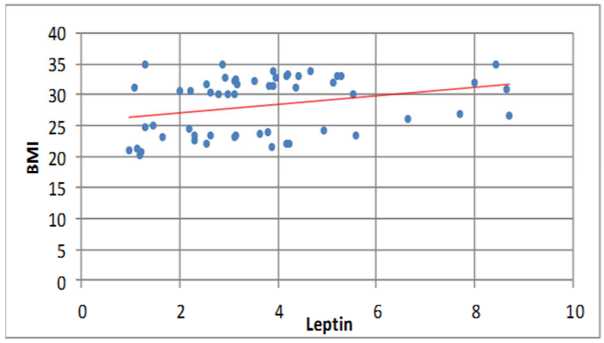
*P < 0.05 when compared to obese group. SD; standard deviation.

The correlation coefficient for leptin and the BMI in eu-, hypo-, and hyperthyroid patients was (r=0·29, P=0·03), (r=0·34, P=0·01), (r=0.33, P=0.01) respectively, (Fig. 2), with no evident relationship with the thyroid hormone status (Table 6).

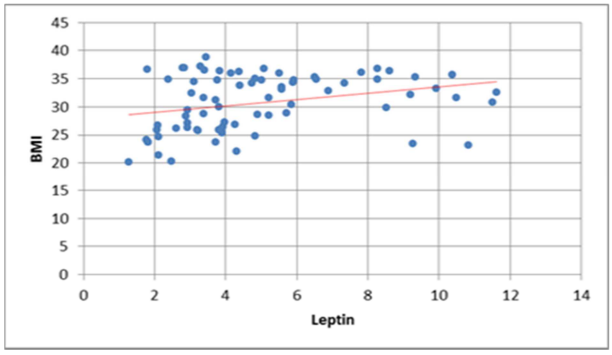
Table 6. Correlation of serum leptin to biochemical parameters for eu-, hypo-, and hyperthyroid patients.

variables	Serum Leptin (ng/ml)					
	Euthyroid		Hypothyroids		Hyperthyroids	
	R	P	R	P	R	P
Age (years)	-0.03	0.82	-0.08	0.45	0.169	0.23
BMI (kg/m^2)	0.29	0.03	0.35	0.01	0.33	0.01
T3 (ng/ml)	0.15	0.24	-0.06	0.56	0.054	0.70
T4 (µg/dl)	-0.06	0.66	-0.012	0.91	-0.04	0.74
FT3 (pg/ml)	-0.14	0.28	-0.09	0.41	-0.22	0.08
FT4 (ng/dl)	-0.11	0.38	-0.058	0.62	-0.18	0.19
TSH (µIU/ml)	0.12	0.34	0.19	0.10	0.24	0.08

R= correlation coefficients. P= P-values



(a)



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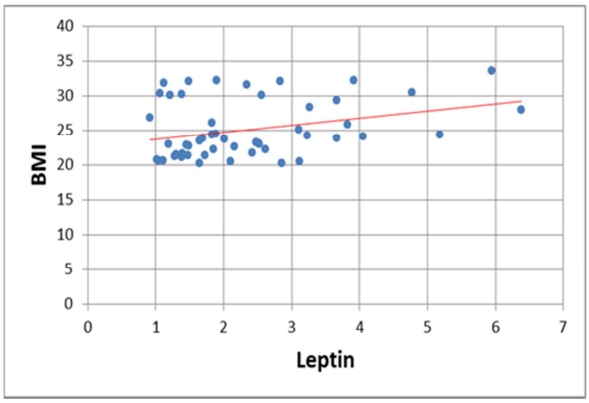

(c)

Figure 2. Positive correlation between leptin levels and BMI, a) in euthyroid b) hypothyroid and c) hyperthyroid group.

4. Discussion

There are conflicting results as to the effects of TH on the production of leptin, with suggestions that TH has inhibitory, stimulatory or no effect on levels of leptin.

In this study, there was no significant correlation between serum leptin and TH levels in eu-, hypo-, and hyperthyroid patients (Table 6). Other workers in the field [8, 11, 13, 17, 24, 25] suggested that leptin levels are not affected by thyroid dysfunction and observed circulating TH do not appear to play any relevant role in leptin synthesis and secretion. These findings supported our observations. Similar results by Sesmilo et al [10] who studied 16 patients with hypo- and 17 patients with hyperthyroidism, all of autoimmune origin, before therapy and every 6–8 weeks until euthyroidism was reached, BMI which correlated with serum leptin concentrations. No correlation was found between serum leptin and TH levels at any time during the study. Similarly, Corbetta et al [13], also found that circulating TH do not appear to play any relevant role in leptin synthesis and secretion and also founded females with either overt hypo- or hyperthyroidism after L-thyroxine therapy show differences in their standard deviation score, a subtle interaction between sex steroids and thyroid status in modulating leptin secretion, at least in women, may occur.

The present results clearly suggest that circulating TH do not play a major role in the regulation of leptin synthesis and secretion. Thus the ability of TH to regulate energy expenditure does not operate through variations in serum leptin levels. In contrast, they do not support previous studies in humans showing decreased leptin concentrations in hypothyroid patients [12] and in Zucker rats, demonstrating a decrease in leptin mRNA in response to T4 administration [(26)]. In the latter case, the significant loss of animal weight and the consequent decrease in adipose stores probably account for the reduced leptin gene expression.

In agreement with other reports [21, 27, 28, 29], we found

that serum leptin concentrations recorded in both normal controls and patients with thyroid disorders were characterized by high variability, the major determinants of which are BMI and gender. This figure is documented by the significant correlation between leptin levels and BMI in any group of patients with thyroid disorders, and by the finding that leptin levels in males are consistently lower than those found in females. Serum leptin levels are known to increase with the percentage of body fat and, to a lesser degree with the BMI. This was confirmed in our study (Table 5). Leptin showed significant positive correlation with BMI at (r=0.29; p=0.03) in euthyroid and (r=0.35; p=0.01) in hypothyroid and (r=0.33; p=0.01) in hyperthyroid groups (Table 6 and Figure 2). This result was expected; since the major source of leptin in the human body is the adipose tissue and the greater adipose tissue mass the greater is the leptin level.

This result supported by other studies that demonstrated serum leptin levels showed significant positive correlation with BMI. Yoshida et al [9] who revealed that, serum leptin levels were correlated significantly with BMI in the hypothyroid, hyperthyroid, and normal groups. Kennedy et al. [30] who reported in both men and women, fasting leptin levels were highly correlated with BMI. Similarly, Perry et al [31] also found the major factor controlling serum leptin is BMI as a strong relationship exists with serum leptin concentration. Van Gaal et al [32] who reported that circulating leptin levels appears to be one of the best biological markers of obesity and hyperleptinemia is directly reflect the amount of body fat. Other study by Kautzky-Willer et al [17] which agrees with our study it was reported higher leptin levels in obese hypothyroid subjects than in obese euthyroid subjects. Also our result supported by other study such as Baig et al [33] and Considine et al [20] that demonstrated serum leptin concentrations in lean and obese subject reflects the amount of adipose tissues and is directly proportional with fat contents.

Higher leptin levels in females are in agreement with a recently published study demonstrating the involvement of sex hormones in the regulation of leptin synthesis [21]. In addition, *ob* gene messenger RNA expression is increased in obese females compared with obese males [2].

The higher leptin levels in females than in males have previously been reported in population studies (Lonnqvist et al [2]; Saad et al [21]; Wabitsch et al [34], Baumgartner et al [35]) has been proposed that leptin levels in females being twice as high as in males and the higher leptin levels in females due to the different pattern of fat deposition and/or the role of sex hormones. Many studies support that sex hormones, in particular estradiol in women and testosterone in men, may be important contributors to the variations in serum leptin concentrations [36-38]. Second possibility for these sex differences in leptin concentrations may be explained by differences in the body composition. It is known that, females are likely to have a greater percentage of body fat than males [38, 39].

5. Conclusion

Lack of effects of circulating thyroid hormone levels on serum leptin concentrations. Leptin level for females was higher than leptin level for males. BMI in eu-, hypo- and hyper-thyroidism has been proved to be the major influencing variable of circulating leptin levels.

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