

Study of Resistin and Leptin in patients with Thyroid Dysfunction

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Abstract: Background: Leptin and resistin are adipocytokines associated with body mass, insulin resistance and inflammation. Data linking adipokines with thyroid hormones are confusing. **Aim:** Evaluation of leptin and resistin in patients with thyroid dysfunction. **Subjects and methods:** 28 patients with hyperthyroidism, 26 patients with hypothyroidism and 24 age and gender matched control subjects were included in the study. BMI was calculated. Serum concentrations of TT3, FT4, TSH, resistin and leptin were measured by ELISA. **Results:** A higher BMI (29.4 ± 2.1) kg/m², TSH (21.7 ± 2.4) Mu/L and leptin (34.9 ± 2.8) ng/ml were found in the hypothyroid group compared with the hyperthyroid group BMI (23.7 ± 2.7) kg/m², TSH (0.07 ± 0.03) Mu/L and leptin (9.7 ± 1.8) ng/ml. The hyperthyroid group exhibited a significant increased TT3 (6.6 ± 1.6) nmol/L, FT4 (2.6 ± 0.1) Pmol/L and resistin (13.8 ± 3.7) ng/ml compared with the hypothyroid group TT3 (0.3 ± 0.1) nmol/L, FT4 (0.68 ± 0.04) Pmol/L and resistin (6.3 ± 3.4) ng/ml. Resistin correlated significantly and negatively with TSH ($P < 0.01$) and BMI ($P < 0.01$) and positively with TT3 ($P < 0.01$) and FT4 ($P < 0.05$). Leptin correlated positively with TSH ($P < 0.01$) and BMI ($P < 0.01$) and negatively with TT3 ($P < 0.01$) and FT4 ($P < 0.05$). Factors affecting resistin level in a multivariate logistic regression analysis were sex, TT3 and FT4. Leptin is affected only by sex and TSH. The cutoff level of leptin associated with hyperthyroidism is 15.3 ng/ml with sensitivity of 100%, and specificity of 60%. **Conclusion:** Thyroid hormones have direct effect on resistin but not leptin. Leptin may affect the thyroid function indirectly through its central action on TSH independent of the BMI. Leptin level of 15.3 ng/ml is associated with hyperthyroidism.

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1. Introduction

For decades, the adipose tissue was considered as a mere store for fat that plays a passive role in energy metabolism. Now, it is widely accepted that the adipose tissue is the largest ever endocrine organ [1,2]. It secretes a lot of hormones, named adipocytokines or adipokines that control feeding, thermogenesis, immunity, reproductive hormones, and neuroendocrine function [2]. This new look towards the adipose tissue has emerged after the discovery of the obese gene and leptin [3].

Resistin is a cysteine-rich 92 amino acid protein. It is an adipocytokine, discovered in 2001, and has been linked to insulin resistance and the development of type 2 diabetes mellitus [4]. In addition, it has been linked to the obesity associated inflammatory state [5].

Leptin is a messenger of satiety from the fat cells to the brain, a regulator of insulin and glucose metabolism and plays a role in energy balance and body weight by neuroendocrine mechanisms [6]. It is, another adipocytokine, produced exclusively in

proportion to fat mass specially the subcutaneous fat. It circulates in the plasma in a free form or bound to leptin-binding proteins. Leptin is produced in larger quantities in subcutaneous adipose tissue than in visceral adipose tissue [7]. A fall in leptin mediates weight gain through the hypothalamus to increase appetite, decrease energy expenditure, and modify neuroendocrine functions [8].

Thyroid function, even within the reference range, is associated with changes in body weight [9,10]. However, the pathogenesis of this link between thyroid function and body weight is not clear and it must consider not only changes of thyroid hormones, but also body fat distribution, obesity duration and the state of low grade inflammation [11].

Thyroid hormones act on several aspects of metabolic and energy homeostasis controlling body weight, thermogenesis, as well as lipolysis in adipose tissue. Similarly, adipocytokines have multiple effects on several tissues acting on the energy homeostasis. Hence the increased concern about the

possible relationship between adipocytokines, thyroid status, and thyroid dysfunction[12].

Aim of the work

The purpose of the present study is to evaluate the relationship between leptin and resistin and thyroid hormones in patients with thyroid dysfunction.

2. Subjects and Methods

Subjects:

The protocol for this study followed the ethical standards of this institution. Patients were selected from the outpatient clinic, Internal Medicine Department, Faculty of Medicine, Menofia University. Fifty four patients (23 men and 31 women) aged 34-53 years, and 24 apparently healthy controls (10 men and 14 women) aged 36-58 years which represent the control group. Patients were classified according to their thyroid status into two groups; the hyperthyroid group which included 28 patients (13 men and 15 women) and the hypothyroid group which included 26 patients (10 men and 16 women). Patients with clinical symptoms of thyroid eye disease (other than mild forms), other comorbidity or who were receiving medications were excluded from the study. In all patients and controls measurements of height and body weight were carried out. BMI was calculated as the ratio of body weight to body height squared (kg/m^2).

Sample collection and preparation:

Five milliliters of blood were obtained at 9 AM from all participants under aseptic condition by venipuncture on their routine clinical visits after overnight fasting for at least 8 hours. Samples were centrifuged and serum stored at $-20\text{ }^\circ\text{C}$ until assayed. All patients were subjected to the following:

Laboratory methods:

The serum concentrations of TT3, FT4, and TSH were measured by commercial ELISA Kit (ALPHA DIAGNOSTIC INTERNATIONAL, USA).

The serum concentration of resistin was measured using a commercial enzyme immunoassay kit (Phoenix Pharmaceuticals Inc., Belmont, CA, USA). The assay was performed on 96-well polystyrene plates pre-coated with secondary antibody that can bind to the Fc fragment of the primary antibody; the Fab fragment of the primary antibody binds specifically with resistin.

Serum concentration of leptin was measured using a commercial LINCO Human Leptin ELISA Kit (Cat.#EZHL-80SK) This assay is a direct Sandwich ELISA based, sequentially, on capture of human leptin by a polyclonal rabbit anti-human leptin

antibody immobilized on a 96-well microtiter plate. Interassay and intra-assay reproducibility was analyzed by the manufacturer by determining the coefficients of variation, which ranged between 3.6 and 7.8 and between 4.1 and 5.4%, respectively.

Statistical analysis

IBM SPSS Statistics 19 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses and P value 0.05 (two-tailed) was considered statistically significant for all analyses. Descriptive statistics are given as mean \pm S.D. for all variables. Group differences were analyzed by Student t test and Mann Whitney test, for normally distributed and non-normally distributed. Pearson's correlation (2-tailed) coefficient was used to evaluate the association between serum leptin with clinical measurement and thyroid hormones. All variables which associate with serum leptin were included in a univariate analysis. All significant variables at $p < 0.05$ were included in a multivariate analysis. ROC curve was used to detect cutoff levels associated TSH using medcalc software.

3. Results

This is a cross sectional study to detect factors that affect both serum leptin and serum resistin levels in patients with thyroid dysfunction. No significant difference was found between all groups as regarding the age and sex.

As expected, BMI shows statistically significant higher level in the hypothyroid group (29.4 ± 2.1) kg/m^2 than the control group (25.4 ± 2.6) kg/m^2 which was higher than the hyperthyroid group (23.7 ± 2.7) kg/m^2 . Similarly, TSH level was statistically higher in the hypothyroid group (21.7 ± 2.4) mU/L than the control group (2.8 ± 0.9) mU/L which was higher than the hyperthyroid group (0.07 ± 0.03) mU/L. As regarding FT₄, It was higher in the hyperthyroid group (2.6 ± 0.1) ng/L than the control group (1.75 ± 0.49) ng/L which was higher than the hypothyroid group (0.68 ± 0.04) ng/L. Similarly, TT3 was higher in the hyperthyroid group (6.6 ± 1.6) nmol/L than the control group (2.1 ± 0.8) nmol/L which was higher than the hypothyroid group (0.3 ± 0.1) nmol/L (Table 1).

A highly significant difference was found among all groups as regarding serum leptin with the highest value in the hypothyroid group (34.9 ± 2.8) ng/ml followed by the control group (11.2 ± 2.7) ng/ml and the lowest value in the hyperthyroid group (9.7 ± 1.8) ng/ml. Serum resistin was statistically higher in the hyperthyroid group (13.8 ± 3.66) ng/ml than both the hypothyroid (6.316 ± 3.413) ng/ml and the control group (6.900 ± 1.968) ng/ml. However, no significant difference was found between the

hypothyroid and the control group (Table 1). Figure 1 shows the mean leptin and resistin levels in all groups.

Correlative analysis between both serum leptin and resistin with both clinical measures and thyroid hormones:

To identify factors that may associate with both serum leptin and serum resistin levels, we performed correlative analysis between both serum leptin and serum resistin from one side and both clinical and thyroid hormones from the other side. A highly significant positive correlation was found between serum leptin and both BMI ($r=0.770$, $P<0.01$) and TSH ($r=0.980$, $P<0.01$). A highly significant negative correlation was found between serum leptin and both FT4 ($r=0.884$, $P<0.01$) and TT3 ($r=-0.773$, $P<0.01$) (Table 2). Figure 2 shows the correlation between serum leptin and TSH. On the other hand, serum resistin positively correlated with FT4 ($r=0.641$, $P<0.01$) & TT3 ($r=0.805$, $P<0.01$). Serum resistin also significantly but negatively correlated with both BMI ($r=-0.571$, $P<0.01$) and TSH ($r=-0.502$, $P<0.01$) (Table 2).

Multi-variate logistic regression analysis:

In a multivariate logistic regression analysis serum leptin with the correlated variables in addition to age and sex as confounding factors, only sex and TSH were highly significant with odd ratio of 0.105 and 0.920 respectively (Table 3).

Receiver Operating Characteristic (ROC) curve:

When plotted the serum leptin concentration against TSH level as a classifying variable, it gives a significant value with area under the curve (AUC) of 0.874. Positive cases were defined by TSH below normal control values. The best cutoff value was 15.3 ng / ml with a sensitivity of 100% and specificity of 60%. Figure 3 shows the ROC between serum leptin and TSH in the whole population.

4. Discussions

The present study is a cross sectional study designed to demonstrate the adipocyte hormones namely leptin and resistin in relation to thyroid functional status. The findings of this study showed that resistin concentrations are statistically increased in hyperthyroid patients and decreased in hypothyroid patients in comparison to the control group. These results agree with two studies who reported a significant high resistin level in hyperthyroid patients [13,14]. On the other hand, Iglesias et al., found a reduced resistin level in hyperthyroid patients [15]. These conflicting results may be due to the small number of patients (20

patients) in the latter study which lack any significant statistical power.

In the hypothyroid group resistin level was similar to the control group but significantly lower than the hyperthyroid group. Similar to the present results, Krassas et al., concluded that hypothyroidism is not associated with changes of resistin level [16]. Meanwhile, Owecki et al. in 2008 showed a significant reduction in resistin level after thyroxin withdrawal [17]. Botella et al., reached to an opposing result with an increase in resistin level after thyroxin withdrawal [18]. However, these studies were short term studies on a small number of patients.

In the present study, a significant positive correlation was found between resistin and thyroid hormones and a significant negative correlation with TSH. This correlation may be causal or association. Many studies tried to explain these results. In rats, changes in resistin level are secondary to thyroid function. This may partially explain the insulin resistance state in hyperthyroidism [19]. Pedro and Juan, thought in a different way and concluded that hyperthyroidism is associated with weight loss despite increased appetite and elevated metabolic rate. Weight loss is associated with increased endogenous resistin in human [20,21]. In a multivariate logistic regression analysis, factors which affect resistin level were sex, TT3 & FT4. Similar studies demonstrated clearly the significant higher resistin level in males [23].

Several groups have studied the relationship between serum leptin and thyroid function with conflicting data [22-26]. The present study showed that leptin concentrations were increased in hypothyroid patients and decreased in hyperthyroid patients. Serum leptin correlated positively with TSH and BMI. On the other hand, it correlated negatively with TT3 & FT4. This was in agreement with several studies [7].

In 2003, Iglesias et al., demonstrated a low leptin level in patients with both hyperthyroidism and hypothyroidism [15]. However, they concluded also the increased level of leptin in hypothyroid patients after treatment. Yatura et al., confirmed the association between thyroid function and resistin but they didn't find any relation between leptin and thyroid function [13]. This opposing data may be related to the sampling. The authors mentioned that they withdrew the samples in the morning not at a fixed time. They also didn't mention if the patients were fasting or not. These two points are critical as serum leptin level has a circadian rhythm reaching a peak in the early morning hours and a lowest level in late morning [26]. Serum leptin also is markedly changed with the fed state [27].

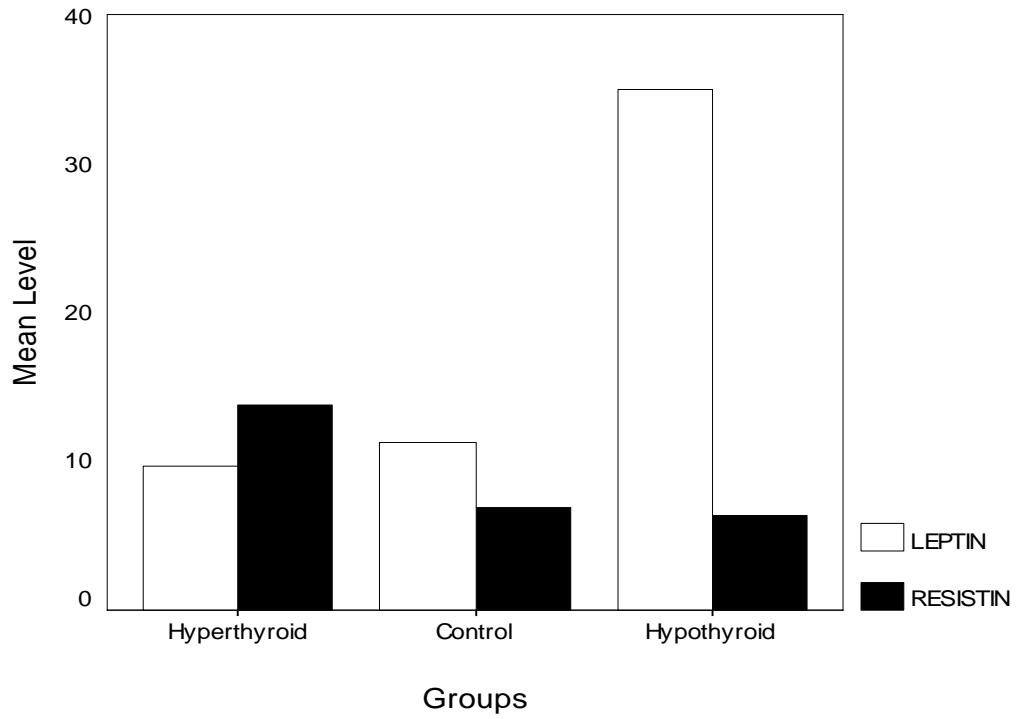


Figure 1: Mean leptin and resistin concentrations in different groups.

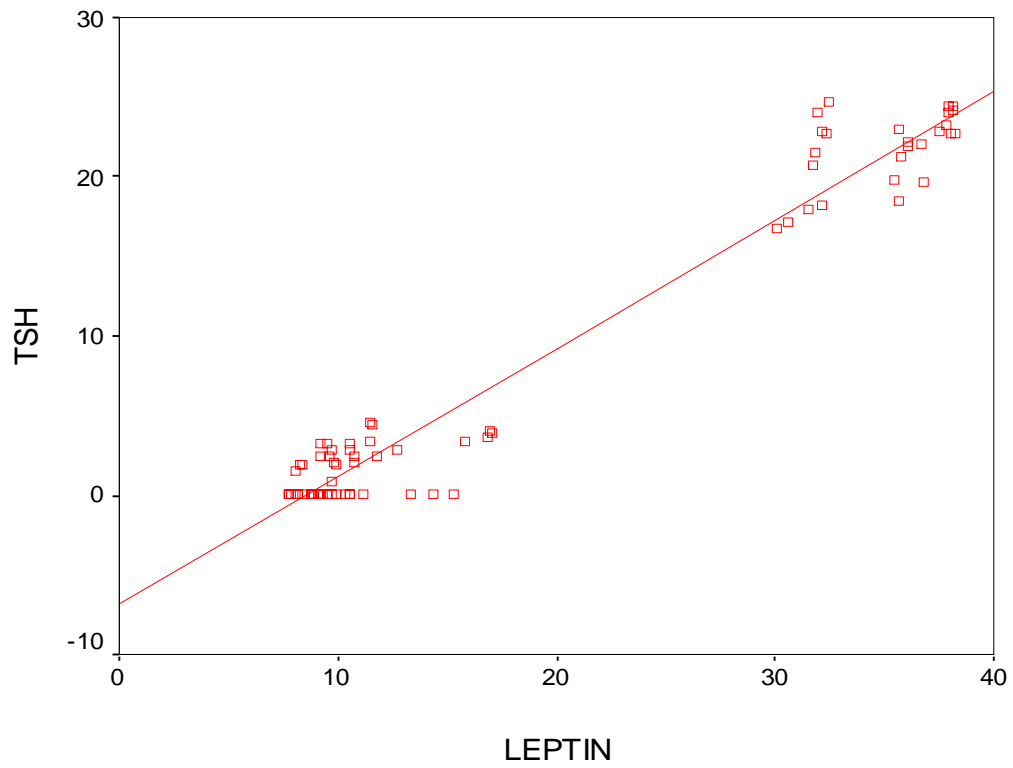


Figure 2: Correlation between serum leptin and TSH in all groups.

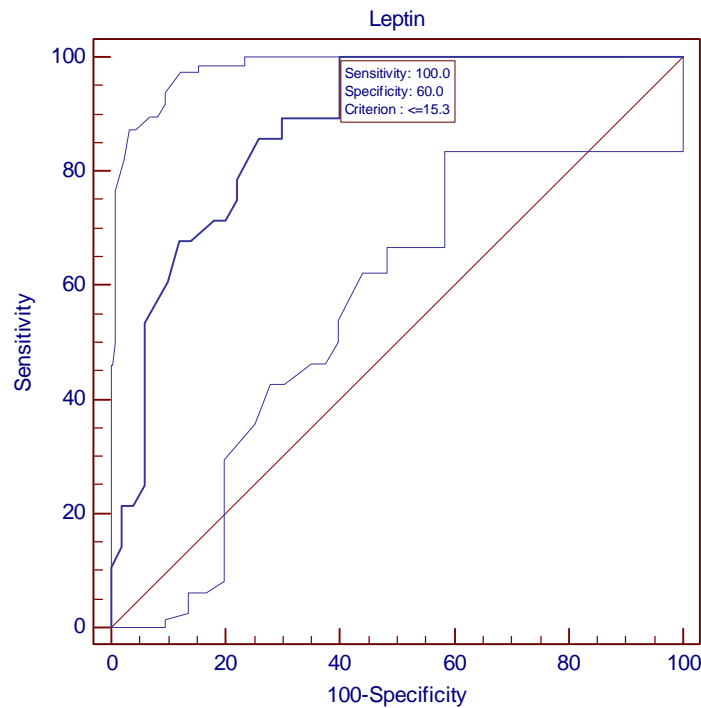


Figure 3: ROC curve between serum Leptin and TSH in the whole group.

Table (1): A comparison between the three groups regarding the anthropometric and Laboratory parameters (mean \pm SD).

Groups	Hyperthyroid Gp (No=28)	hypothyroid Gp (No=26)	control Gp (No=24)	P 1	p2	p3
Age (years)	43.9 \pm 8.5	45.2 \pm 4.7	45.6 \pm 7.6	0.455	0.808	0.508
Gender (Male /Female)	13 / 15	10 / 16	10/14	0.405	0.157	0.267
BMI (Kg/m ²)	23.7 \pm 2.7	29.4 \pm 2.1	25.4 \pm 2.6	0.025	0.000	0.000
TSH (mU/L)	0.07 \pm 0.03	21.7 \pm 2.4	2.8 \pm 0.9	0.000	0.000	0.000
FT4 (ng/L)	2.6 \pm 0.1	0.68 \pm 0.04	1.75 \pm 0.49	0.000	0.000	0.000
TT3 (nmol/L)	6.6 \pm 1.6	0.3 \pm 0.1	2.1 \pm 0.8	0.000	0.000	0.000
Resistin	13.8 \pm 3.66	6.316 \pm 3.413	6.900 \pm 1.968	0.000	0.000	0.467
Leptin (ng/ml)	9.7 \pm 1.8	34.9 \pm 2.8	11.2 \pm 2.7	0.019	0.000	0.000

P1: Significance between the hyperthyroid and hypothyroid groups.

P2: Significance between the hyperthyroid and control groups.

P3: Significance between the hypothyroid and control groups.

Table2. Pearson correlation analysis between both serum Leptin and Resistin with clinical and biochemical results

Parameter	S. Leptin		S. Resistin	
	Correlation	P value	Correlation	P value
AGE	0.003	0.981	0.083	0.469
BMI	0.770	0.000	-0.571	0.000
TSH	0.980	0.000	-0.502	0.000
TT3	-0.773	0.000	0.805	0.000
FT4	-0.884	0.000	0.641	0.000

Table 3: Multivariate logistic regression analysis of all markers with both serum leptin and Serum Resistin

Parameter	S. Leptin			S. Resistin		
	B	OR	P Value	B	OR	P Value
AGE	7.600	-0.045	0.320	1.938	0.465	0.643
SEX	2.518	0.105	0.000	2.726	-5.038	0.000
BMI	0.161	0.047	0.185	0.174	1.209	0.231
TSH	1.117	0.920	0.000	2.883	0.433	0.666
TT3	0.362	0.088	0.080	2.201	9.014	0.000
FT4	1.301	0.094	0.186	3.116	-2.667	0.009

In accordance with the present results, Baig et al., demonstrated a significant correlation between BMI and serum leptin but they didn't find a correlation between serum leptin and patients with hypothyroidism. A drawback of this study is the small number of patients investigated (only 21 males) [24].

The relationship between serum leptin and thyroid hormones may be bidirectional and it needs a lot of studies to explain it. Several studies suggested that thyroid hormones affect serum leptin through its effect on the body fat composition which is the main source of leptin[28]. Others suggested that thyroid hormones are regulators of leptin mRNA expression which may mediate the weight changes associated with thyroid dysfunction[29]. Others suggested that both changes in thyroid function and leptin levels are secondary to changes in body fat composition and no causal relationship is found between them[20,30,31].

To further evaluate factors which may affect serum leptin, multivariate logistic regression analysis

was done. Only sex and TSH were significant while age, BMI and thyroid hormones had insignificant effect on serum leptin level. This is in agreement with Mantzoros et al., who confirmed the close pulsatile association between TSH and serum leptin. They concluded that leptin may regulate TSH pulsatility and circadian rhythmicity [26]. Of interest, patients with congenital leptin deficiency demonstrate central hypothyroidism. Moreover, this hypothyroid state is corrected by intervention with leptin administration[32].

From another point of view, TSH also can influence leptin release. Menendez et al., demonstrated that TSH stimulates leptin secretion by a direct effect on adipocytes[33]. This opinion is further supported by the changes in leptin level with intervention with the administration of thyroid hormone[15].

For detection of the cutoff level of serum leptin with hyperthyroidism as TSH the classifying variable a ROC curve was done. The best cutoff level was 15.3 ng/l with a sensitivity of 100%, Specificity of 60% and

an area under the ROC curve (AUC) of 0.874. To the best of our knowledge this is the first study to detect this cutoff level.

5. Conclusion

The relationship between adipokines, namely, resistin and leptin with thyroid dysfunction is bidirectional and dynamic. In other words, changes in one arm are associated with changes in the other arm independent of body fat composition. Although both markers correlated with thyroid function, only sex and TSH has an effect on leptin while sex, TT3 and FT4 affect the resistin level. A cutoff level of 15.3 ng/l is associated with marked changes in TSH with a sensitivity of 100%, Specificity of 60% and an area under the ROC curve (AUC) of 0.874.

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