



The Influence of Thyroid Hormones on Leptin and Resistin Levels in Hyperthyroid Female Patients

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ABSTRACT

Background: Hyperthyroidism or thyrotoxicosis occurs due to excess release of thyroid hormone. These hormones regulate the body's energy balance and have effects on adipokine level. There are several reports suggesting interrelation between adipokines (resistin and leptin) with thyroid dysfunction. **Objectives:** This study was established to investigate the effect of thyroid hormones in hyperthyroidism state on the level of some adipokines, leptin and resistin; in comparison with control. **Patients and Methods:** The present study included 50 Iraqi female patients with hyperthyroidism with age ranged between 30-58 years and 30 healthy controls with age ranged between 30-53 years. Serum samples were collected from study groups. The levels of thyroid hormones (TSH, T4 and T3) were determined by using automated Chemiluminescence Immunoassay (CLIA) analysis system. Detection of leptin hormone and resistin hormone levels in the serum were determined by an enzyme linked immunosorbent assay (ELISA) kits. **Results:** The results revealed that serum leptin levels were significantly low ($P < 0.004$) in hyperthyroid patient groups as compared to control, and there were significant negative correlations between T4 and leptin ($P < 0.0001$); also, T3 and leptin ($P < 0.05$). Resistin hormone level increased non-significantly ($P > 0.05$) than control level; and there was significant negative correlation between TSH and resistin ($P < 0.035$). **Conclusion:** The study shows that there is complex interrelation between adipocytokines (leptin and resistin) with thyroid gland and pituitary gland. Leptin levels were decreased in hyperthyroid patients than control and associated negatively with T4 and T3 levels, while resistin levels were increased non-significantly than control and associated negatively with TSH level. They affect each other in their physiological function in the human body.

Keywords: Hyperthyroidism, Leptin, Resistin

INTRODUCTION

Hyperthyroidism or thyrotoxicosis occurs due to excess release of thyroid hormone due to an overactive thyroid gland or passive release of the stored hormone. Hyperthyroidism should be considered the potential illness whenever TSH level is subnormal [1,2]. Thyroid hormones serve as regulators of various processes in the body; stimulate resting metabolic rate and heat production, influence cell proliferation and development, modulate response to other hormones, change metabolism of carbohydrate, protein, and lipids, increase in energy expenditure, and thermogenesis in adipose tissue. Disturbances in thyroid function lead to changes in body weight, muscle mass and fat tissue [3].

Adipokines, including diponectin, resistin and leptin are of adipocyte-derived hormones; there are several reports suggesting interrelation between adipocytokines and thyroid dysfunction [4]. Thyroid hormones regulate the body's energy balance and have effects on adipokine level [5]. Thyroid-stimulating hormone (TSH) receptors have been found in the adipose tissues, indicating that they play a role in the regulation of the adipocytokines which are involved in the regulation of energy balance [3].

Adipocytokines have autocrine, paracrine, and endocrine functions on several organs. They seem to regulate thermogenesis, immunity, feeding, and neuroendocrine functions [6,7]. Adipokines are also involved in the pathophysiology of numerous diseases, thus, adipokines exert potent modulatory actions on target tissues and cells involved in various immune cells [8-10].

The cytokine-like structure of leptin is indicative of its function in regulating immune responses, mainly produced

by mature adipocytes; also by intestine, placenta, mammary glands, gastric fundic epithelium, skeletal muscle, brain, joints and bone [11]. Leptin expression is also regulated by a wide range of inflammatory mediators such as lipopolysaccharide (LPS) and cytokines (TNF- α , IL-6, and IL-1 β) during acute inflammatory responses [8,12].

Additionally, leptin increases thyroid hormone levels [13]. It affects thyroid metabolism by indirect effects, it may also affect thyroid axis in acute manner. Leptin administration reverses the fasting induced suppression of hypothalamus-pituitary-thyroid axis at the central level by upregulating TRH expression in the hypothalamus [4].

Besides TSH stimulates leptin secretion by a direct effect on adipocytes, probably via TSH-receptors on the surface of adipocytes; positive association between leptin and TSH can be caused by this direct effect of TSH on leptin secretion by adipocytes [4,14].

Resistin is a relatively new and poorly studied adipokine. It is secreted primarily by preadipocytes and less by mature preadipocytes of abdominal localization, but mainly produced by monocytes and macrophages [15,16]. The relevance and physiological role of resistin in humans remain unclear [17].

The studies reported different results of resistin concentration in patients with hyperthyroidism and hypothyroidism [18]. Some studies have shown that resistin levels are increased in patients with hyperthyroidism and thyrotoxicosis, its concentration decreased with normalizing thyroid hormone status following treatment [19,20]. In other study, serum resistin levels in patients with Graves' disease decreased and on the other hand it increased in Hashimoto's and simple goiter patients [21]. In recent years the role of resistin in thyroid function has been noticed and considered by researchers. So far disagreements relation studies have been reported about resistin and thyroid disorders [22]. This study was established to investigate the effect of thyroid hormones in hyperthyroidism state on the level of some adipokines (leptin and resistin); in comparison with control.

PATIENTS AND METHODS

This study was carried out on 50 females of Iraqi hyperthyroid patients their age ranged between 30-58 years, were rounded up from Nuclear Medicine and Radiation Therapy Department, Educational Oncology Hospital. Beside 30 female volunteer subjects as control, their ages and gender were matched with patients, their ages ranged between 30-53 years. Serum samples were collected from study groups.

Approximately (4 ml) of human blood was collected intravenous from patient and control groups under aseptic technique, centrifuged at 3000 rpm for 10 minutes. Serum of blood was immediately separated, divided into aliquots and kept at -20°C until used.

All patients and control had no complained of other chronic or systemic diseases, and pregnant women were excluded from the study. The diagnosis of hyperthyroidism was based on the clinical features and biochemical tests, depending on decline level of TSH hormone and elevated levels of T4 and T3 in the serum by using automated Chemiluminescence Immunoassay (CLIA) analysis system produced by Shenzhen New Industries Biomedical Engineering Co., Ltd (SNIBE). Detection of leptin hormone and resistin hormone levels in the serum was determined by using ELISA kits produced by Komabiotech, Korea.

The Statistical Analysis System- SAS (2012) program was used to effect of difference factors in study parameters. t-test was used for comparison between means. Estimation of correlation coefficient between variables was done in this study [23].

RESULTS

The results presented in this study are based on the analysis of 50 hypothyroid female patients compared with 30 volunteer as apparently healthy control. The age of hyperthyroid patients ranged between 30-58 years, with mean age of 36.6 ± 1.3 years, while in control group ranged between 30-53 years, with mean age of 33.2 ± 1.5 years.

The results of this study revealed that mean levels \pm SE of serum TSH are decreased significantly ($p < 0.001$) in hyperthyroid patients group (0.67 ± 0.11 μ IU/ml) as compared to mean level \pm SE of control group (2.11 ± 0.09 μ IU/ml). On the other hand, mean level \pm SE of serum T4 and T3 (122.45 ± 4.72 and 1.82 ± 0.12 ng/ml) are increased significantly ($P < 0.001$) in patients group as compared to controls level of T4 and T3 (77.19 ± 3.96 and 1.30 ± 0.06 ng/ml) respectively; these results illustrated in Table 1. These results confirmed the diagnosis of hyperthyroidism which is characterized by decline TSH and elevated T4 and T3 hormone levels as compared with control.

Table 1 Levels of thyroid hormones in hyperthyroid patients and control

Group	Statistical variables	TSH	T4	T3
Control (N= 30)	Mean	2.11	77.19	1.3
	Median	2.29	80.6	1.26
	SD	0.56	22.4	0.33
	SE	0.09	3.96	0.06
Hyperthyroidism (N=50)	Mean	0.67	122.45	1.82
	Median	0.52	129.9	1.7
	SD	0.61	33.38	0.75
	SE	0.11	4.72	0.12
P-value	-	0.0001 **	0.0001 **	0.0001 **

SD: Standard deviation; SE: Standard Error; **: Highly Significant (P<0.001).

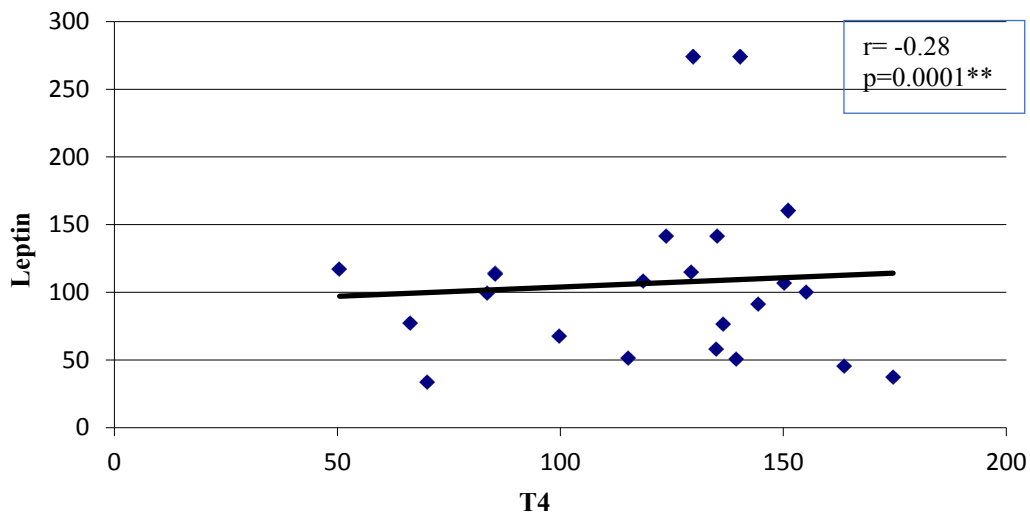


Figure 1 Correlation between T4 and leptin

The result in Table 2 showed that the mean level ± SE of leptin are decreased significantly (p<0.005) in hyperthyroid patients (105.24 ± 8.50 pg/ml) as compared with mean level of control (151.87 ± 15.19 pg/ml). While the mean levels of resistin are increased non-significantly (P>0.05) in patients group (120.31 ± 9.67 pg/ml), as compared with controls level (93.90 ± 12.80 pg/ml).

Table 2 Levels of leptin and resistin hormones in hyperthyroid patients and control

Group	Statistical variables	Leptin	Resistin
Control (N= 30)	Mean	151.87	93.9
	Median	119.3	66.64
	SD	85.94	72.41
	SE	15.19	12.8
Hyperthyroidism (N=50)	Mean	105.24	120.31
	Median	99.26	83.61
	SD	60.15	68.38
	SE	8.5	9.67
P-value	---	0.0049 **	0.0993 ^{NS}

Pearson correlation applying on serum parameters, demonstrated in Table 3, found significant negative correlation between T4 level and leptin level (r= -0.28, P=0.001), demonstrated in Figure 1; also, there is significant negative correlation between T3 level and leptin level (r=-0.21, P=0.050), demonstrated in Figure 2. While resistin hormone level showed significant negative correlation with TSH level (r= -0.23, P=0.035), demonstrated in Figure 3. There is non- significant correlation between leptin hormone and resistin hormone levels (r=0.15, P=170), as shown in Figure 4.

Table 3 Correlation coefficient between parameters study

Serum clinical parameters	Statistical variables	TSH	T4	T3	Leptin	Resistin
TSH	r	-	-0.52	-0.5	0.18	-0.23
	P	1	0.0001**	0.0001**	0.101 ^{NS}	0.035 *
T4	r	-0.52	-	0.46	-0.28	0.14
	P	0.0001**	1	0.0001**	0.0001**	0.187 ^{NS}
T3	r	-0.5	0.46	-	-0.21	0.046
	P	0.0001**	0.0001**	1	0.050 *	0.675 ^{NS}
Leptin	r	0.18	-0.28	-0.21	-	0.15
	P	0.101 ^{NS}	0.0001**	0.050 *	1	0.170 ^{NS}
Resistin	r	-0.23	0.14	0.046	0.15	-
	P	0.035 *	0.187 ^{NS}	0.675 ^{NS}	0.170 ^{NS}	1

R: Correlation coefficient; * P<0.015; ** P<0.01; ^{NS}: Not significant

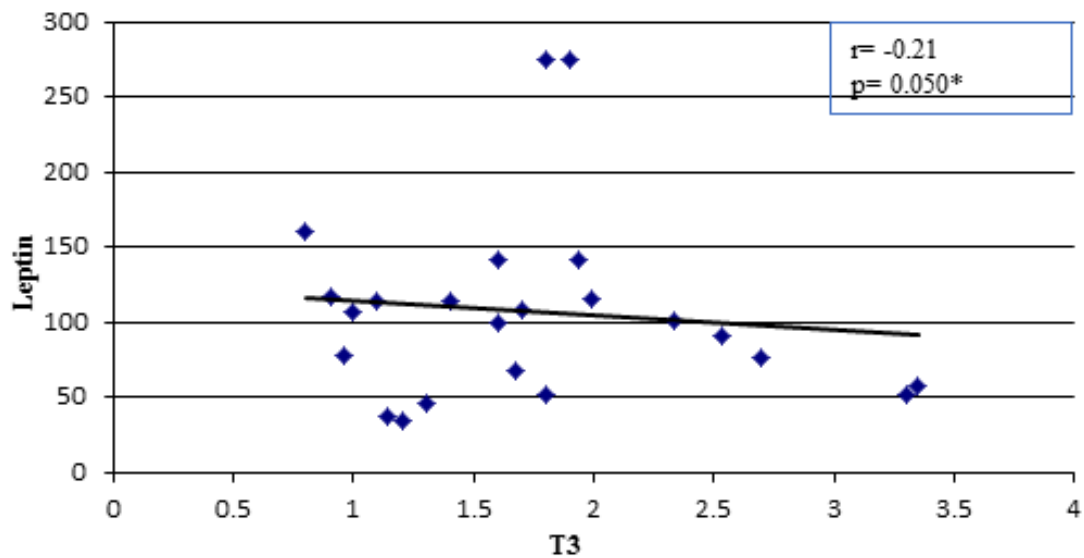


Figure 2 Correlation between T3 and leptin

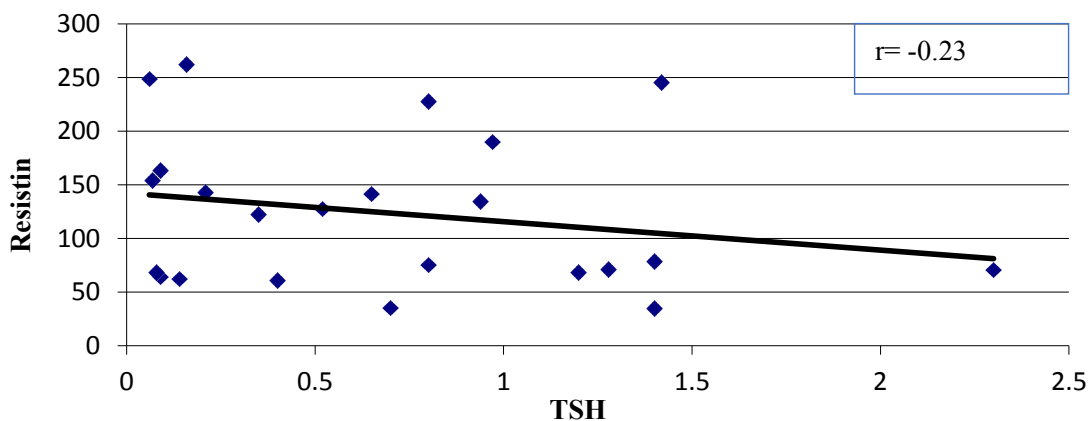


Figure 3 Correlation between TSH and resistin

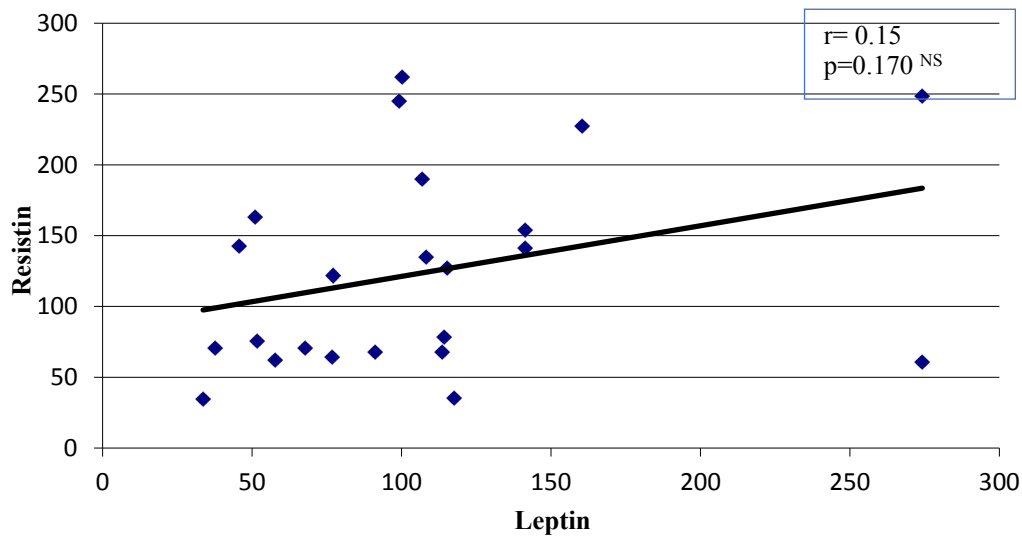


Figure 4 Correlation between leptin and resistin

DISCUSSION

Hyperthyroidism or thyrotoxicosis is one of the most common thyroid diseases, characterized by abnormal circulating levels of thyroid hormones and thyroid-stimulating hormone (TSH); that cause abnormal regulator of various processes in the body [24]. The adipocytokines serve as causative or protective factors in the development of disorders in the states of thyroid dysfunction. Abnormal levels of adipocytokines (leptin and resistin) in hypo- and hyperthyroidism have been reported with controversial results [3].

Previous studies investigating the associations between thyroid functions and adipocytokines are conflicting due to different patient characteristics, coexisting autoimmunity, and probably nutritional status.

The results of this study about decreased leptin hormone level significantly in hyperthyroid patients are compatible with study of Ibrahim, et al., founded that serum leptin in hyperthyroid patients was significantly lower than in euthyroid controls; while serum leptin in hypothyroid patients was significantly higher than in euthyroid controls [25]. Another study by Chen, et al., reported elevated serum levels of leptin in hypothyroid group but decreased in hyperthyroid group [24].

However, the current results are incompatible with results of Nakamura, et al. [26] and Diekman, et al. [27] indicate that serum leptin is slightly increased in subjects with moderate hyperthyroidism, possibly due to the direct action of thyroid hormone, and the levels decline in accordance with the attainment of euthyroidism. On the other hand, Yaturu and his colleagues indicated that serum levels of leptin did not change with change in the thyroid functional status [19].

The results of Pearson correlation demonstrated in Table 3 and Figures 1 and 2 observed that there is significant negative correlation between leptin level with T4 and T3 hormone level respectively; which confirmed current result of decline leptin level in hyperthyroidism patients.

There are conflicting results regarding the effects of thyroid hormones on the serum level of leptin, with suggestions that thyroid hormones have inhibitory, stimulatory or no effect on levels of leptin.

Serum thyroid hormones also seem to affect leptin levels. *In vivo* and *in vitro* rat studies established that increased serum T3 leads to a deprivation in leptin mRNA expression at white adipose tissue and serum leptin levels [28]. On the other hand, leptin has a stimulatory effect on the release of TSH [29]. Also, there is suggestion involve the existence of direct stimulatory effect of leptin on T4 released from the thyroid gland [30]. Leptin regulates central and peripheral iodothyronine deiodinase activity and conversion of T4 to T3; also increases D2 activity centrally and leads to an increase of T3. Both thyroid hormones and leptin affect each other and may regulate body composition and metabolism by complex mechanisms [4,31].

Regarding increased resistin level non-significantly in hyperthyroid patients, which confirmed by Pearson correlation

demonstrated in Table 3 and Figure 3 observed that there is significant negative correlation between resistin level with TSH; There was agreement with results of study conducted by Koyuncu, et al. observed serum resistin level of hyperthyroid group was higher in comparison to control group, but that elevation was not statistically significant [32]. Furthermore, Yaturu with his assistants reported increased resistin level significantly in Graves' patients as hyperthyroid group than control subjects, and it was positively correlated to FT4 and FT3 and negatively correlated to TSH concluded that thyroid function has effect on adipocyte hormones resistin [19]. However, Krassas, et al., [20] found that serum resistin levels of hyperthyroid patient group were higher than those of control group, where these levels decreased after normalization of thyroid hormones in hyperthyroid patients.

In 2006, another study by Krassas, et al., [33] did not observe any difference between control and patient groups in resistin level. After a 4-5-month treatment, normalization of thyroid hormone levels did not result in a significant change in resistin levels. Additionally, Iglesias, et al., [18] reported that serum resistin levels were similar in hypothyroid and euthyroid subjects.

Hedayati, et al., [22] and Chen, et al., [24] explained that both hypothyroid and hyperthyroid groups exhibited higher serum levels of resistin compared to control; and serum levels of resistin were positively associated with FT3. Results of the non-linear analyses in a combined group and multivariable linear regression analyses in separate groups are consistent, indicating that there are significant associations between adipokines and thyroid function. Moreover, the relationship between resistin and FT4 exhibited a U-shape in nonlinear regression, indicating varied mechanisms are involved in the relationship between thyroid hormones and resistin in different thyroid states [24].

Adipocytes express high levels of TSH receptors which function similar to those in thyroid [34], indicating that TSH participates in the regulation of adipocyte functions including secreting adipokines like resistin. Studies investigating thyroid disorders and their consequences on adipokine profiles are limited and results are highly variable and conflicting [24,34]. Finally, alterations in resistin levels by other adipocytokines can be the reason for this conflicting data on resistin levels and thyroid status. It is suggested that changes in resistin levels can act as an adaptive mechanism in thyroid dysfunction [4].

CONCLUSION

The current study shows that there is complex interrelation between adipocytokines (leptin and resistin) with thyroid gland and pituitary gland; decreased leptin level in hyperthyroid patients than control associated negatively with T4 and T3 levels, while increased resistin level non-significantly than control that associated negatively with TSH level. They affect each other in their physiological function in the human body.

DECLARATIONS

Conflict of Interest

The author has disclosed no potential conflicts of interest, financial or otherwise.

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