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" Modulation of the serum leptin by thyroid hormones: Observations in newly diagnosed thyrotoxic patients"

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ABSTRACT

Background: Leptin and thyroid hormones both are involved in regulation of energy metabolism. Many studies were conducted for studying the relationship and the interaction between the thyrostat and the lipostat which till present is incompletely understood. The aim of this work was to study the serum leptin levels in patients suffering from thyrotoxicosis, who are newly diagnosed treatment naïve patients, thus the association between leptin and thyroid hormones can be purified as much as possible.

Methods: a case control study conducted at Port-Said General hospital endocrine out-patient clinic. The study included 15 patients with thyrotoxicosis and 30 control euthyroid subjects (15 lean, 15 obese). All of the included patients are analyzed for thyroid profile and serum leptin.

Results: The results revealed a statistically significant difference regarding serum leptin between the thyrotoxic group and control obese. No correlation was found between serum

leptin and either BMI, TSH, Free T3 or Free T4 in each of the studied group, but a significant negative correlation was found between leptin and either free T3 and free T4 in the combined groups.

Conclusion: Serum leptin level is lower in treatment naive thyrotoxic patients when compared to euthyroid control. The serum leptin showed no correlation with either BMI or TSH, also no correlation was found between serum leptin and free T3 or free T4 in each of the studied group suggesting presence of other factors that indirectly affect and interconnect these two major endocrinal systems involving energy metabolism.

Key words: Leptin; thyroid disorder; thyrotoxicosis; thyroid hormone.

Introduction

Leptin is considered as a pleiotropic stress-responsive hormone, which has many actions in variable body systems. Leptin, with a molecular weight of 16-kDa protein, was first detected as a product of mature adipocytes before discovering other sites as a source of leptin in the body. Leptin is structurally related to cytokines, so it is sometimes referred to as an adipocytokine, which has a direct correlation with adiposity and nutritional status and has many circuits of feedback affected by body nutritional status. (Koeppen and Stanton, 2018)

Leptin action on metabolism has been governed by what is called adipostat, which is the physiological set point region in the hypothalamus that regulates body fat within narrow range based on energy intake and expenditure, thus higher leptin level results in decreased energy intake, energy stores, and adiposity with augmentation of energy use and vice versa. (Mechanick et al., 2018).

Thyrotoxicosis is a broad term which refers to higher levels of circulating thyroid hormones; these hormones is either produced by active thyroid hormone secretion or any other means (e.g., exogenous thyroid hormone ingestion). By comparison, hyperthyroidism is a form of thyrotoxicosis that is caused by excessive production of thyroid hormones from the thyroid

gland itself, either due to autonomous hormone secretion or thyrotropic stimulation. (Jonklaas and Cooper, 2020).

Grave's disease (GD) is considered the leading cause of hyperthyroidism accounting for 60-80% of hyperthyroid cases. The annual incidence of GD is 20-50 cases per 100,000 persons, and the lifetime risk is 3% & 0.5% in women and men respectively. **(**Zimmermann and Boelaert, 2015).

Thyroid hormones markedly influence the body weight, food intake and energy consumption. Many previous studies were conducted to investigate the possible relationship between leptin and thyroid hormones; the two molecules involved in the regulation of appetite and energy homeostasis, with variable conflicting results. (Chen et al., 2016).

Patients with disturbance of thyroid function often experience changes in body weight, food intake and thermogenesis and adipocyte function. Patients with thyrotoxicosis often exhibit decreasing weight despite good appetite, loss of fat, lipid storage depletion and diminished muscle mass. Glucose intolerance also is a common finding in 57% of patients and is induced mostly by insulin resistance in the liver and peripheral tissues. (Novodvorsky and Allahabadia, 2017).

Thyroid hormones and adipocytokines can influence each other, and can be influenced by body weight, body fat content, appetite and food intake, thermogenesis, insulin resistance, and glucose and lipid metabolism. The increase in the TSH and leptin levels associated with obesity could be an adaptive response to supply the high thermogenesis associated with increased the fat amount. Although thyroid function is usually normal in obese population, it is supposed that TSH and BMI are positively correlated. **(**Kyriacou, 2018).

The aim of this work was to study serum leptin levels in patients suffering from thyrotoxicosis who are newly diagnosed, before starting antithyroid medical therapy.

Methods

Study design: a case control analytic study that was carried out at Endocrine out-patient clinic, Port-Said General Hospital from January 2018 to August 2019.

Subjects: the study included 45 patients who are attending endocrine out-patient clinic. The patients were divided in to 2 groups: newly diagnosed thyrotoxic group (case group: included 15 patients); and control euthyroid group (30 patients), who were subdivided into 2 subgroups: obese control group with BMI ≥ 30 (15 patients), lean control group with BMI <30. (15 patients).

Inclusion criteria: Untreated newly diagnosed hyperthyroid with no recent history of body weight changes.

Exclusion criteria: Patients exhibited significant recent body weight changes, thyrotoxic patients with antithyroid therapy, patients with chronic diseases, Patients on medications (e.g.: insulin, oral hypoglycemic drugs, anti-hypertensive drugs, statins or other treatment for dyslipidemia, steroids, B-agonists), history of acute infectious disease or acute medical insult, pregnancy and lactation.

All subjects of the study were subjected to full history taking and detailed clinical examination, which include general examination, and local examination of different systems with thorough thyroid examination.

Routine investigations were done including: Complete blood picture, Liver function tests, Renal function tests, fasting blood glucose sample, 2h post prandial blood glucose, fasting lipid profile, fasting serum TSH, fasting free T3, free T4. Specific investigation for assessment of the serum leptin level by fasting venous sample in the morning, where the sample is allowed to clot for 10-20 minutes at room temperature, then centrifugation was done for 20 minutes at 2000-3000 RPM. The used Kits was an Enzyme-Linked Immunosorbent Assay (ELISA). (1008 Junjiang Inter.Bldg.228 Ningguo Rd. Yangpu Dist. Shanghai: China.**)**

Ethical Considerations:

The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Written informed consents were obtained from all patients.

Statistical analysis:

Data were analyzed using Statistical Program for Social Science (SPSS) (Version 25.0. Armonk, NY: IBM Corp.). Continuous variables were checked for normal Gaussian distribution by using Kolmogorov-Smirnov test. Continuous variables were expressed as the mean ± standard deviation (SD), for parametric data; or median and range (minimum - maximum) for non-parametric data. Categorical data were expressed as a number (percentage). For quantitative variables, independent sample t test was used for comparison in case of normally distributed data. For comparisons of quantitative variables among the three groups, one-way ANOVA was used if data was parametric, while Kruskal-Wallis (KW) test was used if data was non parametric. For categorical variables, they were compared using the Chi-square ($\chi 2$). Spearman's rank correlation was calculated to assess the correlations between leptin, and BMI, TSH, Free T4, Free T3, as data is non-parametric. Linear regression analysis served to assess the impact of thyroid hormones on serum leptin. A p value < 0.05 was considered statistically significant (S).

Results

The demographic data of the studied groups were matched regarding age, family history of thyroid disorders; However, they showed a significant difference regarding the gender (p value =0.002), whereas there was a female predominance in thyrotoxic group and control obese group (93.3% of participant was females). Also, BMI was significantly different between the studied groups (mean ± SD): thyrotoxic group (28.6 ± 5.47), control lean group (24.5 ± 3.9), control obese group (33.55 ± 3.41) with p value <0.001. (Table 1, 2)

As expected, statistically highly significant difference regarding free T3, T4, and TSH between the thyrotoxic group (case group), control groups with p value < 0.001. (Table 3,4)

Comparison between the studied groups regarding serum leptin using one-way ANOVA test, revealed statistically significant difference (with p value < 0.001), which was discriminated by post hoc test as a significance difference between Thyrotoxic group (2.34 ± 0.35) and either of control obese group (3.34 ± 0.65) (p value < 0.001), & control lean group (3.06 ± 0.41) (P value = 0.001). No significant difference was found on LSD comparison between each of the control groups. (Table 3,4)

No significant difference was found regarding serum leptin between males and females (p=0.648). Also, serum leptin showed no significant difference between subjects with either positive or negative family history of thyroid disorders. (p= 0.974). (Table 5)

The correlation of serum leptin with BMI and TSH showed a non-significant correlation, which was the same when the correlation was applied to each of the studied group (Table 6,8)

Correlation of the serum leptin with free T3, and free T4, using Spearman's rank correlation revealed a statistically significant negative correlation between serum leptin and either of free T3 (n=45, r = - 0.346, p= 0.007), or free T4 (n=45, r = - 0.322, p= 0.016) in the studied groups combined (Table 6, figure 1, figure 2); while on performing regression analysis only T3 was found to be associated with the serum leptin (Table 7). When the correlation was applied to each individual group the previously mentioned association was lost. (Table 8).

Table (1) shows comparison between the clinico-demographic parameters of the studied groups.

Clinico-demographic characteristics	**Groups**			**Test**	
	Thyrotoxic group	**Control lean group**	**Control obese group**	**χ^2/F**	**p**
	N=15 (%)	**N=15 (%)**	**N=15 (%)**		
Gender: Male Female	 1 (6.7) 14 (93.3)	 8 (53.3) 7 (46.7)	 1 (6.7) 14 (93.3)	12.600	**0.002***
Age (years): Mean ± SD Range	 37.73 ± 12.4 21 - 60	 29.4 ± 9.33 18 - 54	 39.47±13.23 17 - 55	3.134	0.054
BMI (kg/m^2)	**Groups**			**Test**	
	Thyrotoxic group	**Control lean group**	**Control obese group**	**F**	**P**
	N=15 (%)	**N=15 (%)**	**N=15 (%)**		
Mean ± SD **Range**	28.6 ± 5.47 22.1 – 41.4	24.5 ± 3.9 18 – 29.4	33.55 ± 3.41 30 – 42.1	16.307	**<0.001****
family history of thyroid disorder	**` Groups**			**Test**	
	Thyrotoxic group	**Control lean group**	**Control obese group**	**χ^2**	**p**
	N=15 (%)	**N=15 (%)**	**N=15 (%)**		
Negative **Positive**	15 (100) 0 (0)	11 (73.3) 4 (26.7)	13 (86.7) 2 (13.3)	4.615	0.099

χ^2= Chi-squared test, F One Way ANOVA, SD =standard deviation, BMI=body mass index, *p< 0.05 is statistically significant, **p≤0.001 is statistically highly significant

Table (2) LSD Comparison between the studied groups regarding body mass index (BMI):

(I) group (mean ± SD)	(J) group (mean ± SD)	Sig.
Thyrotoxic group (28.6 ± 5.47)	**control lean group (24.5 ± 3.9)**	**0.045***
	control obese group (33.55 ± 3.41)	**0.013***
Control lean group (24.5 ± 3.9)	**control obese group (33.55 ± 3.41)**	**<0.001****

****p< 0.05 is statistically significant, **p≤0.001 is statistically highly significant***

Table (3): thyroid profile and serum leptin in the study group.

Parameter	**Groups**			**Test**	
	Thyrotoxic group	**Control lean group**	**Control obese group**	**F/KW**	**p**
	N=15 (%)	**N=15 (%)**	**N=15 (%)**		
Free T3 (pmol/L)					
Mean ± SD	17.78 ± 10.97	6.29 ± 2.2	6.39 ± 2.02	15.170	**<0.001***
Range	17(6.7 – 52.9)	2.9 – 10.3	3.5 – 10		
Free T4 (pmol/L)					
Mean ± SD	35.75 ± 17.55	16.76 ± 4.39	15.84 ± 4.78	16.238	**<0.001***
Range	29.4(18 – 80)	9.8–23.3	9.2 – 24.5		
TSH (IU/L)					
Mean ± SD	0.06 ± 0.1	3.05 ± 0.87	3.33 ± 1.22	65.744	**<0.001***
Median (Range)	0.01(0 – 0.3)	2.9(1.6 – 4.4)	3.4(1.5 – 5)		
Serum leptin					
Mean ± SD	2.34 ± 0.35	3.06 ± 0.41	3.34 ± 0.65 [a,c]	16.624	**<0.001***
Range	1.75 – 3.14	2.34 – 4.16	2.19 – 4.63		

KW =Kruskal Wallis test, F =one-way ANOVA,
TSH= thyroid stimulating hormone, T3=triiodothyronine, T4=tetraiodothyronine ,
**p≤0.001 is statistically highly significant.

Table (4) LSD Comparison between the studied groups regarding leptin & thyroid hormones:

Variable	(I) group (mean ± SD)	(J) group (mean ± SD)	Sig.
Free T3 (pmol/L)	**Thyrotoxic group (17.78 ± 10.97)**	**control lean group (6.29 ± 2.2)**	**<0.001****
		control obese group (6.39 ± 2.02)	**<0.001****
	Control lean group (6.29 ± 2.2)	control obese group (6.39 ± 2.02)	0.999
Free T4 (pmol/L)	**Thyrotoxic group (35.75 ± 17.55)**	**control lean group (16.76 ± 4.39)**	**<0.001****
		control obese group (15.84 ± 4.7)	**<0.001****
	Control lean group (16.76 ± 4.39)	control obese group (15.84 ± 4.78)	0.973
TSH (IU/L)	**Thyrotoxic group (0.06 ± 0.1)**	**control lean group (3.05 ± 0.87)**	**<0.001****
		control obese group (3.33 ± 1.22)	**<0.001****
	Control lean group (3.05 ± 0.87)	control obese group (3.33 ± 1.22)	0.690
Leptin (IU/L)	**Thyrotoxic group (2.34 ± 0.35)**	**control lean group (3.06 ± 0.41)**	**0.001****
		control obese group (3.34 ± 0.65)	**<0.001****
	Control lean group (3.06 ± 0.41)	control obese group (3.34 ± 0.65)	0.312

**p≤0.001 is statistically highly significant

Table (5): Relation between serum leptin and both gender and family history of thyroid disorders:

Factors	Serum leptin		Test	
	Mean ± SD	**Range**	**t**	**p**
Gender:				
Male	3.1 ± 0.54	2.34– 4.157	0.459	0.648
Female	3 ± 0.64	2.1– 4.63		
Family history:				
Negative	3.2 ± 0.592	2.1 – 4.63	-0.031	0.974
Positive	3.01 ± 0.70	2.1 – 4.34		

t = Independent sample (t) test

Table (6): Correlation between serum leptin and the studied parameters in the overall population:

Parameters	**Serum leptin**	
	r	P
Age (years)	-0.037	0.779
BMI	0.044	0.737
Free T3	**-0.346**	**0.007***
Free T4	**-0.322**	**0.016***
TSH	0.145	0.267

r = Spearman rank correlation, *p<0.05 is statistically significant

Table (7): Linear stepwise regression analysis of the serum leptin with free T3 in the overall population:

	Unstandardized Coefficients		**Standardized Coefficients**	**t**	**p**	**95.0% Confidence Interval**	
	β	**SEM**	**β**			**Lower**	**Upper**
Free T3 (pmol/L)	**-0.027**	**0.01**	**-0.326**	**-2.626**	**0.011***	**-0.048**	**3.355**

*p<0.05 is statistically significant

Table (8): Correlation between serum leptin and age, BMI, thyroid hormones in each separate group:

Parameters	**Serum leptin**					
	Thyrotoxic group		**Control lean group**		**Control obese group**	
	r	P	r	P	r	P
Age (years)	-0.108	0.701	0.158	0.575	0.146	0.603
BMI	0.267	0.336	-0.046	0.869	-0.273	0.325
Free T3	0.132	0.638	-0.243	0.383	0.021	0.94
Free T4	0.089	0.751	-0.279	0.315	0.02	0.945
TSH	-0.010	0.971	-0.054	0.85	-0.111	0.694

r = Spearman rank correlation, *p<0.05 is statistically significant

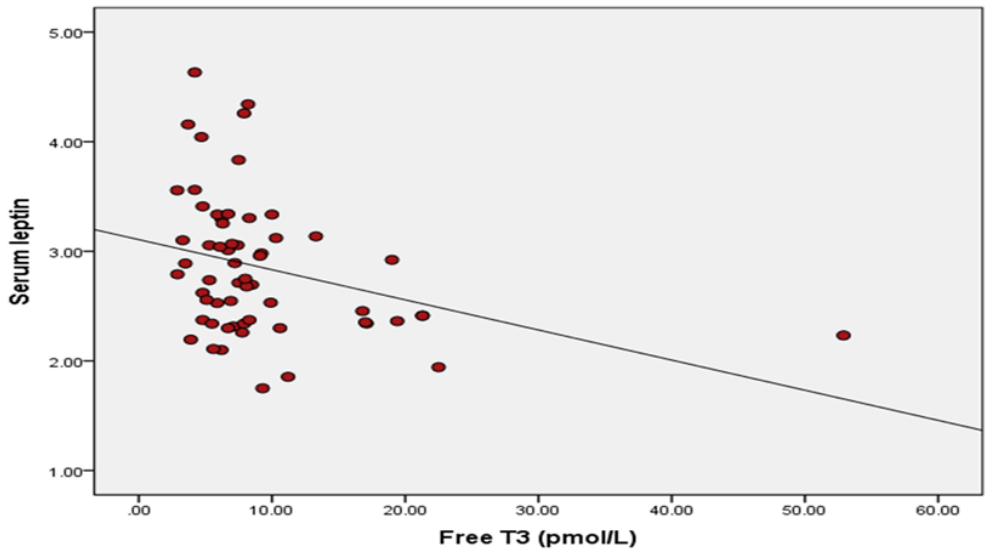

Figure (1) Scatter dot graph showing significant negative correlation between serum leptin and free T3 in the overall participants (r value = - 0.346, p=0.007)

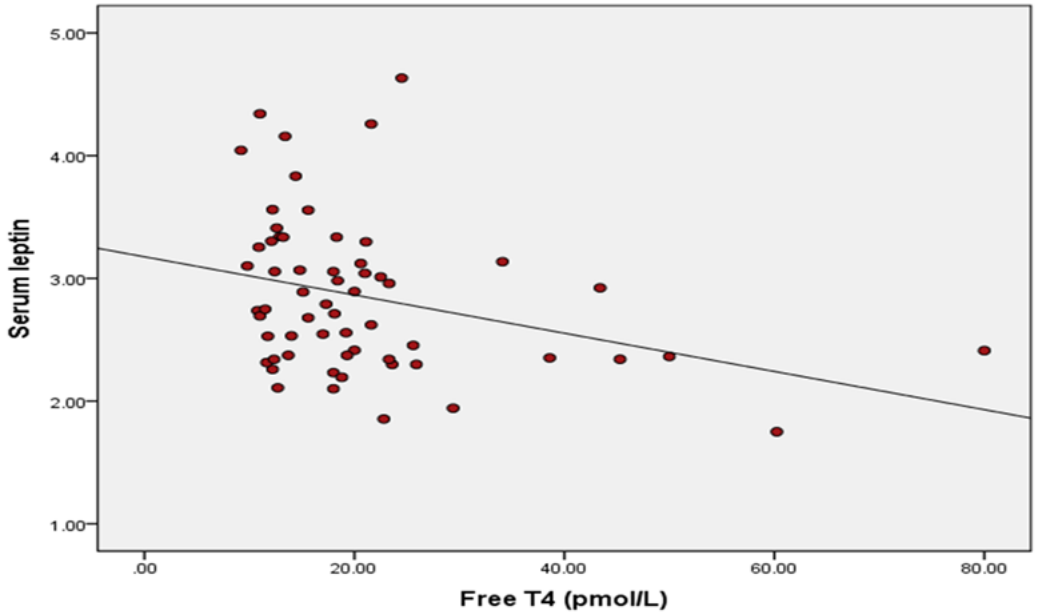

Figure (2) Scatter dot graph showing significant negative correlation between serum leptin and free T4 in the overall participants (r value = -0.322, p=0.016*)

Discussion

Leptin modulation of the thyroid axis is well demonstrated; however, the effect of thyroid axis components on serum leptin has not fully explained, whereas many studies that investigating the changes of serum leptin in patients with thyroid disorders showed variable conflicting results. (Chen, et al., 2016).

The main point of this research is to find the influence of excess thyroid hormones, in treatment-naïve thyrotoxic patients, on the serum leptin level to exclude the impact of antithyroid therapy. Also, the selected patients had no other chronic or metabolic disorders that may have an impact on the serum leptin. Thus, we can purify the association between leptin and thyroid hormones as much as possible.

The current study revealed a difference regarding the serum leptin between the studied groups, whereas the difference was significant between Thyrotoxic group (2.34 ± 0.35) and either of control obese group (3.34 ± 0.65) & control lean group (3.06 ± 0.41), with lower level of leptin in the thyrotoxic group, while the difference was insignificant between control lean group and control obese group.

It was noticed that the difference of the serum leptin between thyrotoxic and either of the control groups was matched with the significant difference regarding BMI, where P value = 0.045 when comparing thyrotoxic & lean group; and P value = 0.013 when comparing thyrotoxic & obese group. However, absence of significant difference regarding serum leptin between control lean and control obese group (P = 0.312) in spite of presence of significantly different BMI (P <0.001) can provide a suggestion that the BMI is not the only factor that impact the serum leptin; and that the variations in the serum leptin between groups are related to factors other than BMI such as the effect of thyroid hormones.

Hyperthyroidism is a condition of increasing thyroid hormones in the circulation, which is associated with thyroid hormone mediated activation of sympathetic nervous system. The fat cells are known to have expression of adrenergic receptors, which are stimulated by

norepinephrine to produce fatty acid hydrolysis and uncoupling of energy production, which may predispose to lower leptin level in such patients**.** (Maitra, 2018).

In the current study the serum leptin was lower in thyrotoxic than control group. Many researches had studied the changes in the serum leptin levels in patient with hyperthyroidism with a great heterogeneity in the results.

A study by Al-Shalah and Habib was conducted to focus on the changes of leptin in hyperthyroid disorder. The study included 47 newly diagnosed hyperthyroid patients and 30 matched control euthyroid subjects, whereas the serum leptin was assessed in both groups. It was found that the serum leptin was significantly lower in hyperthyroid (5.48± 2.72) than control group (35.59 ± 10.74); therefore, the authors suggested a negative effect of thyroid hormones on leptin secretion, evidenced by the results of some in vitro studies of the effect of thyroid hormones on the serum leptin**. (**Zabrocka,et al., 2006) (Luvizotto et al., 2012).

Also, the authors in the previous mentioned study suggested that lower leptin in hyperthyroidism may be responsible for increasing the appetite in such patients. **(**Al-Shalah & Habib, 2014).

Another study, by Baig et al., assessed the serum leptin on newly diagnosed hyperthyroid patients compared to control, found that the serum leptin was also lower in the patients than the control subjects, that was attributed, by the authors, to suppression of leptin gene expression by over activation of TSH receptors by auto antibodies**. (**Baig et al., 2003).

In this context, many other studies gave the same result with lower leptin level in hyperthyroidism. Iglesias et.al., found lower leptin level in both hypothyroid and hyperthyroid groups, which agrees with the finding in this current study, whereas the treatment of hypothyroidism was associated with increasing serum leptin, while no changes were observed after treatment of hyperthyroidism. (Iglesias et al., 2003).

Gesu, et al., found that leptin was positively correlated with TSH, thus it was elevated in patients with hypothyroidism and decreased in those with hyperthyroidism. **(**Gesu et al., 2016).

In contrast, Ozata et.al, showed an opposing result, with a significant higher leptin level in hyperthyroid patients as compared with both hypothyroid and control, which was owed, in that study, to the proposal previously mentioned of Yoshida et al., about the role of thyroid hormones on leptin secretion by 3T3-L1 adipocytes. **(**Yoshida et al.,1997) (Ozata, et al., 1998)

Otherwise, most of other studies conducted regarding this point, had shown no significant difference of the serum leptin in hyperthyroid subjects than control**. (**Santini et al., 2004).

When TSH, free T3, free T4 levels were compared between the studied population (Table 3), there was a highly significant difference ($p<0.001$), which is demonstrated by LSD comparison as a significant difference between thyrotoxic group and each of the control groups. (Table 4)

In this study a non-significant positive correlation was found between serum leptin and TSH with the same finding when the correlation was applied to each group separately (Table 6,8), which may suggest presence of other factors that affect energy expenditure and feedback mechanisms, such as free T3 level, free T4, peripheral deiodination status, heterogeneity in adipose masses of the studied population, feeding states, and autonomic activity.

A study by Ibrahim et al. found no significant correlation between serum leptin and TSH which made the authors suggest a complex regulatory interaction exists between leptin and thyroid function that possibly taking place either on the central (hypothalamus–pituitary) or peripheral (deiodinase activity) levels**.** (Ibrahim et al., 2016).

On the other hand, many studies (e.g. Delitalaa et al) have found a positive correlation between leptin and TSH**,** owing to the fact that leptin can act as a selective regulating factor of pro- TRH gene in the Para ventricular nucleus of the hypothalamus; it stimulates the

hypothalamic–pituitary–thyroid axis and modulates 5′-deiodinases in different tissues, depending on energetic status of animals**. (**Delitalaa et al. ,2018).

It has been demonstrated that the administration of recombinant TSH can induce a significant leptin release which is proportional to the adipose tissue mass. **(**Santini et al., 2010).

So, lack of correlation between serum leptin and TSH in some in vivo studies may further raise the question whether the in vitro effects of thyroid hormone on leptin synthesis are relevant when applied in vivo. **(**Considine, 2007).

In this study, the serum leptin revealed a significant negative correlation with free T3 and free T4 (n=45, r = - 0.346, p = 0.007, and n=45, r = - 0.322, p= 0.016, respectively) when correlation was applied to the overall population (Table 6). When the correlation was applied to each group in a separate manner, the significant negative correlation observed in the overall population was lost. (Table 8).

This finding is an example of statistical Simpson's paradox, which occurs when the association between two variables in combined groups is qualitatively different from the association between the same two variables in each group separately. This paradox mostly indicates presence of other uncontrollable factors that impact the relation between the 2 studied parameters (leptin, thyroid hormones) that when eliminated by partial association can give different result.

Many unpredictable factors can influence the serum leptin and the thyroid hormones that act as major confounders affecting the relationship between the 2 variables. For example, Leptin can be affected by the feeding status, central regulatory mechanisms as well as variation with ultradian rhythm. Also, the thyroid hormones can be influenced by peripheral deiodination status, trace element composition in diet and some environmental factors such as temperature. All of the above factors can make the pure association between the 2 variables difficult to be achieved and thus the casual relationship can't be assessed especially with retrospective nature of the current study.

Also, presence of smaller number of individuals in each group (15 subjects) compared to the total number (45 subjects) may predispose to variation in the correlation results.

A study by Ibrahim et al. found no significant correlation between serum leptin and either of free T3 or free T4 when the correlation was applied to each of the studied group (euthyroid, hypothyroid, and hyperthyroid group). The authors suggested that circulating thyroid hormones do not play a major role in the regulation of leptin synthesis and secretion, and other major determinants were present in their study, which were the gender and BMI. **(**Ibrahim et al., 2016).

On the other side, a study by Ruscica et al. found a negative correlation between leptin and free T3 during evaluating the relation between thyroid hormones and serum leptin in euthyroid elderly women, and the authors suggested that leptin may modulate hypothalamic, pituitary and peripheral 5′deiodinase activity, thereby reducing the conversion of T4 to T3, as suggested by experiments in animal models of Cabanelas et al. (Ruscica et al., 2008) (Cabanelas et al., 2008).

It is a well-known that there is a complex leptin-T3 crosstalk. Although leptin can stimulate T3 production via activation of T4 de-iodination into T3, higher T3 production resulting in increasing of heat production, and uncoupling protein 3 expression in the skeletal muscles and beta 3 adrenergic receptors. All of the mentioned factors can inhibit leptin expression in fat tissue, and lead to an inverse relation-ship between leptin and T3 level, which is peripherally and centrally regulated**. (**Zimmermann-Belsing et al., 2003)

In this current study, no significant correlation was found between serum leptin and BMI in the overall population which was the same finding when correlation was applied to each group separately. These findings were not matched with most of reviews discussing this point, which demonstrated a positive correlation between the degree of adiposity and serum leptin which is considered one of the important products of adipose system. (Ibrahim et al., 2016) (Abdu-Allah et al., 2011).

In the current study, the BMI was used as the only indicator for assessment of the degree of adiposity, which is less reliable indicator of body adiposity especially when used solely. This can explain absence of significant correlation between serum leptin and BMI in the current results.

In this context some authors recommended to assess the degree of body adiposity using BMI accompanied by other more reliable indicator of body adiposity such as using percent body fat calculation equations, waist and hip circumference and ratio, or through measuring total body fat content by bioelectrical impedance analysis (BIA), underwater weighing (UWW), dual-energy X-ray absorptiometry (DXA), computed tomography, and magnetic resonance imaging. (Peltz, et al., 2007).

Many of studies found a positive correlation between the serum leptin and BMI, which proposed the essential role of adipose tissues in influencing serum leptin. Abdu-Allah et al. found a positive correlation between leptin and both BMI ($p< 0.01$) and TSH ($p< 0.01$); and suggested that leptin can indirectly influence thyroid function through its central action on TSH independent of the BMI. **(**Abdu-Allah et al., 2011).

In the current study, there was a non-significant relation between the gender and serum leptin ($p =0.483$) (Table 5) which is most probably due to presence of unequal numbers of both sexes, with about 77.8 % of the studied population was females and about 22.2 % was males. This unmatched distribution will make the relation between the serum leptin and the gender less consistent. The samples of the studied population were chosen by systematic random sampling which highlights 2 known facts: the higher female predominance of thyroid disorders and higher prevalence obesity in females when compared to men. (Moini et al., 2020) (Hamdy et al., 2020)

Some of literature had found that leptin levels in the body show considerable variations between males and females with higher levels observed in women than in men. **(**Anusha et al., 2019) (Hunma et al. 2018).

The actual cause of this difference is not well established, which makes some authors owing that difference to variable fat distribution between males and females and to the difference in hypothalamic regulation of leptin production**. (**Kasacka et al., 2019).

Women have higher contents of subcutaneous fat in comparison to men with thicker layers of subcutaneous adipose tissue when compared with obese men. Also, the rate of free fatty acid storage in subcutaneous tissue is higher in women. **(**Kasacka, et al.,2019) (Morgan- Bathke et al., 2015).

Conclusion:

Serum leptin level is lower in treatment naive thyrotoxic patients when compared to euthyroid control. The serum leptin showed no correlation with either BMI or TSH, also no correlation was found between serum leptin and free T3 or free T4 in each of the studied group suggesting presence of other factors that indirectly affect and interconnect these two major endocrinal systems involving energy metabolism.

Disclosure of interest: the authors report no conflicts of interest; and all authors have participated in this research and have approved the final article

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