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ORIGINAL ARTICLE

Serum Leptin Levels in Newly Diagnosed Patients With Hypothyroidism: Single Center Experience.

Naglaa H. Fadel[1], Eman A. Al-Shorbagy[2], Jehan Saeed[2], Saad S. Al-Osh[3], Mohamed H. Assy [2]

1)Internal Medicine Department, Faculty of Medicine, Port-Said University, Egypt
2)Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt
3)Clinical Pathology Department, Faculty of Medicine, Zagazig University, Egypt

Corresponding author
Naglaa H. Fadel, Department of Internal Medicine, Faculty of Medicine, Port-Said University, Egypt
E-mail:
Dr_naglaa_fadel@yahoo.com

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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 study is to find a significant change in the serum leptin of patients suffering from hypothyroidism, 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 Zagazig university endocrine out-patient clinic. The study included 15 patients with hypothyroidism 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 hypothyroid group and control obese. No correlation was found between serum leptin and either of BMI, TSH, Free T3 or Free T4 in each of the studied group, but a significant negative correlation was found between leptin and either of free T3 or free T4 in the combined groups.

Conclusion: Serum leptin level is lower in treatment naive hypothyroid 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; hypothyroidism; thyroid hormone.

INTRODUCTION

Leptin is considered as a pleiotropic stress-responsive hormone, which has many actions in variable body systems. Although leptin firstly was considered as an ancient anorexic agent that has a key role during starvation; its action now has been expanded as an immune-modulator, a growth factor, and as a central player in cardio-metabolic networking research. **[1]**

Leptin, which has 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; thus 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. **[2].**

Hypothyroidism is considered the second most prevalent endocrine disorders after diabetes mellitus in the United States. Hypothyroidism has an incidence rate of about 18 per 1000 population especially women with male to female ratio about 1:10 .The prevalence rate is about 2-3% of overall population with increasing prevalence with advancing age that reaches 5% in nursing home population. **[3].**

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. **[4]**
Patients with disturbances of thyroid function often experience changes in body weight, food intake, thermogenesis and adipocyte function, whereas in hypothyroidism the patients show a decreased appetite and a slight weight gain mainly due to retention of fluid by hydrophilic glycoprotein deposits in the different tissues. Oxygen consumption, heat production and basal metabolic rate as well as lipolysis are reduced in hypothyroid patients. These metabolic and body composition alterations might be accompanied by changes in serum adipocyte-derived proteins including leptin level. **[5]**
Thyroid hormones and adipocytokines can influence, or be influenced by many factors; such as body weight, body fat content, appetite, food intake, thermogenesis, insulin resistance, and glucose and lipid metabolism. Although thyroid function is usually normal in obese population, it is known that TSH and BMI are positively correlated. The increase in TSH and leptin associated with obesity could be an adaptive response to supply the high thermogenesis due to the increased fat amount. **[6]**
The aim of this study is to find a significant change of the serum leptin in patients suffering from hypothyroidism who are newly diagnosed, before starting replacement therapy for their disorder.

Methods

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.

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

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

Inclusion criteria: Subjects that visited endocrine outpatient clinic who are newly diagnosed hypothyroidism with no recent history of body weight changes.

Exclusion criteria: Patients exhibited significant recent body weight changes, hypothyroid patients receiving replacement 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 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 Kits used 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. Approval by IRB research committee of Zagazig Faculty of Medicine was included.

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 was matched regarding age, family history of thyroid

disorders; However, it showed a highly significant difference regarding the gender (p value <0.001), whereas there was a female predominance in hypothyroid group (100% of participant was females), and control obese group (93.3% of participant was females). Also, BMI differ significantly between studied groups (mean ± SD): hypothyroid group (32.68 ±10.12), control non-obese group (24.5 ± 3.9), control obese group (33.55 ± 3.41). (Table 1)

As expected, statistical significant difference regarding TSH between the hypothyroid group (case group), control groups with p value < 0.001. No statistical difference was detected between the studied populations, regarding free T3 and free T4. (Table 2)

Comparison between the studied groups regarding serum leptin revealed statistically significant difference (with p value = 0.007) using one way ANOVA test, which was discriminated as a significance difference between hypothyroid group (2.66 ± 0.59) and control obese group (3.34 ± 0.65), using LSD comparison (p=0.002).No significant difference was found on LSD comparison between each other pairs. (Table 2)

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 positive and negative family history of thyroid disorders. (p= 0.974). (Table 3)

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 4, 5)

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 4, figure 1, figure 2). However, when the correlation was applied to each group separately it was insignificant. (Table 5).

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

Clinico-demographic characteristics	**Groups**			**Test**	
	Hypothyroid group	**Control lean group**	**Control obese group**	**χ^2/F**	**p**
	N=15 (%)	**N=15 (%)**	**N=15 (%)**		
Gender: Male Female	 0 (0) 15 (100)	 8 (53.3) 7 (46.7)	 1 (6.7) 14 (93.3)	15.833	<0.001
Age (years): Mean ± SD Range	 36.47 ± 9.71 20 - 54	 29.4 ± 9.33 18 - 54	 39.47±13.23 17 - 55	3.37	0.044
BMI (kg/m^2)	**Groups**			**Test**	
	Hypothyroid group	**Control lean group**	**Control obese group**	**F**	**P**
	N=15 (%)	**N=15 (%)**	**N=15 (%)**		
Mean ± SD **Range**	32.68 ±10.12 20.2 – 53.2	24.5 ± 3.9 18 – 29.4	33.55 ± 3.41 30 – 42.1	8.671	0.001**
family history of thyroid disorder	**` Groups**			**Test**	
	Hypothyroid group	**Control lean group**	**Control obese group**	**χ^2**	**p**
	N=15 (%)	**N=15 (%)**	**N=15 (%)**		
Negative **Positive**	10 (66.7) 5 (33.3)	11 (73.3) 4 (26.7)	13 (86.7) 2 (13.3)	1.684	0.431

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

Table (2): shows comparison of the studied groups as regards thyroid profile, serum leptin

Parameter	Groups			Test	
	Hypothyroid group	Control lean group	Control obese group	F/KW	p
	N=15 (%)	N=15 (%)	N=15 (%)		
Free T3 (pmol/l)					
Mean ± SD	6.53 ± 1.72	6.29 ± 2.2	6.39 ± 2.02	0.054	0.948
Range	2.89 – 9.9	2.9 – 10.3	3.5 – 10		
Free T4 (pmol/l)					
Mean ± SD	14.69 ± 3.47	16.76 ± 4.39	15.84 ± 4.78	0.89	0.418
Range	10.77 –21.6	9.8–23.3	9.2 – 24.5		
TSH (IU/L)					
Mean ± SD	14.74 ± 13.54[a]	3.05 ± 0.87	3.33 ± 1.22	29.553	<0.001**
Median (Range)	8.9 (5.4 – 50)	2.9(1.6 – 4.4)	3.4(1.5 – 5)		
Serum leptin					
Mean ± SD	2.66 ± 0.59 [a,c]	3.06 ± 0.41	3.34 ± 0.65 [a,c]	5.547	0.007*
Range	2.1–4.34	2.34 – 4.16	2.19 – 4.63		

KW =Kruskal Wallis test, TSH thyroid stimulating hormone, T3=triiodothyronine, T4=tetraiodothyronine, **p≤0.001 is statistically highly significant. [a] hypothyroid group,
[c] control obese group
F =one way ANOVA, p≤0.001 is statistically highly significant
[a,c] The difference in serum leptin is significant between hypothyroid and control obese group

Table (3): 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 (4): Correlation of the serum leptin with BMI, TSH, Free T3 and Free T4 applied to the overall population:

Parameters	Serum leptin	
	r	P
BMI	0.044	0.737
TSH	0.145	0.267
Free T3	-0.346	0.007*
Free T4	-0.322	0.016*

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

Table (5): Correlation of the serum leptin with BMI, TSH, Free T3 and Free T4 applied to each group separately:

Parameters	Serum leptin					
	Hypothyroid group		Control lean group		Control obese group	
	r	P	r	P	r	P
BMI	-0.418	0.121	-0.046	0.869	-0.273	0.325
TSH	0.055	0.844	-0.054	0.85	-0.111	0.694
Free T3	-0.032	0.909	-0.243	0.383	0.021	0.94
Free T4	0.096	0.732	-0.279	0.315	0.02	0.945

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

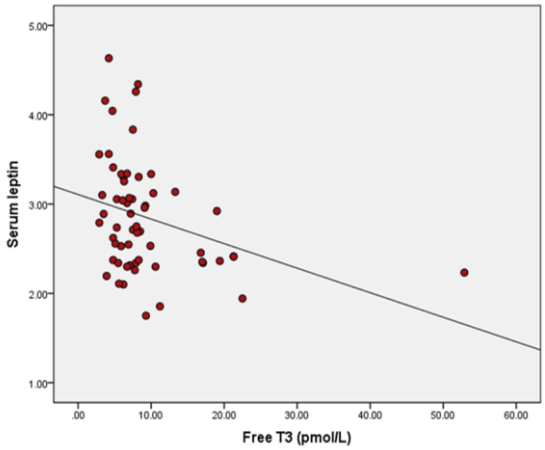

Figure (1) Scatter dot graph showing significant negative correlation between serum leptin and free T3 of the overall population

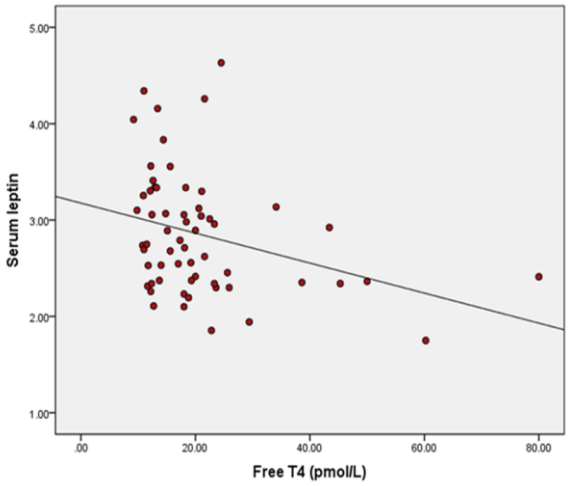

Figure (2) Scatter dot graph showing significant negative correlation between serum leptin and free T4 of the overall population

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. **[4].**

The main point of this research is to find the influence of hypothyroidism on the serum leptin level in treatment naïve patients, who had no other chronic or metabolic disorders, to exclude the impact of levothyroxine therapy and metabolic disorders 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 hypothyroid group (2.66 ± 0.59) and control obese group (3.34 ± 0.65) with lower level of leptin in the hypothyroid group, while the difference was insignificant between control lean group and either of hypothyroid or control obese group.

It was noticed that the difference of the serum leptin between hypothyroid and obese groups was present in spite of absence of significant difference in BMI both groups (32.68 ±10.12, 33.55 ± 3.41 for hypothyroid and obese respectively). Also, in spite of presence of significance difference between hypothyroid group and lean group regarding BMI (32.68 ±10.12, and 24.5 ± 3.9, respectively), LSD comparison between both groups, regarding serum leptin, failed to show significant difference (p=0.057).

The previous finding 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.

Many researches had studied the changes in the serum leptin levels in patient with hypothyroidism with a great heterogeneity in the results. In the current study the serum leptin was lower in hypothyroid than control group which can be explained by the state of reduction of energy expenditure and metabolic rate in hypothyroidism. The metabolic rate seems to be directly correlated with the serum leptin. **[7]**

A study by **Iglesia et al.**, leptin level was significantly lower in hypothyroid group with significant restoration of the leptin level to normal by treatment of hypothyroidism with fixed BMI, a finding which suggests the impact of thyroid hormones on the serum leptin regardless the degree of adiposity. **[8]**

A study by **Yoshida et al**. had found that the serum leptin level was lower in patient with hypothyroidism, with a positive correlation between serum leptin and BMI in the overall studied population. Their finding was suggested to be related to the effect of thyroid hormones, whereas **Yoshida et al.** have declared in another study that thyroid hormones can increase expression of leptin mRNA, and leptin secretion by 3T3-L1 adipocytes, a finding which clearly showed that a normal physiological levels of T3 is needed to stimulate leptin expression and secretion that when decreased as in hypothyroidism can subsequently decrease serum leptin levels. **[9]**

Another explanation was suggested by authors in the previously mentioned study, which was the role of higher TSH in suppression of leptin gene expression. The authors supposed that the known lipolytic effect of TSH, through beta-3 adrenergic receptors, may cause decrease in leptin gene expression based on a finding of decreased leptin level with beta-3 adrenergic receptors agonists. **[10]**

In contrary side, the study by **Chen et al.** found a significant higher serum leptin level in hypothyroid subject, which was significantly correlated with TSH level and BMI. This finding made the authors suggesting a direct stimulatory effect of TSH on adipocytes**. [4]**

A study by **Santini et al.** found that serum leptin level didn't change with change of the thyroid function. **[11]**

When TSH levels were compared between the studied population (Table 2), there was a highly significant difference ($p<0.001$) using Kruskal Wallis test. On pairwise comparison, the difference was significant between hypothyroid (14.74 ± 13.54) and either of control groups (3.05 ± 0.87 for lean, 3.33 ± 1.22 for obese), which is expected logic finding.

As regards free T3 and free T4, there was no statistical significance between hypothyroid group and either of control groups, which can be explained by presence of about 40% of hypothyroid group in the subclinical range, who have higher TSH level in the context of normal or near normal free T3 and free T4, while the remaining 60% having clinical hypothyroidism.

It is a well-known that the serum TSH response to changes in serum free T4 is logarithmic, so as a very minor change in the free T4 resulting in great changes in TSH levels, thus in subclinical cases the TSH changes precede the change in serum free T4 may by many years. **[12].**

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 product of adipose system. **[13][14]**

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. **[15]**

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. **[13]**

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 4, 5), 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**.[14]**

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**. [16]**

It has been demonstrated that the administration of recombinant TSH can induce a significant leptin release which is proportional to the adipose tissue mass. **[17]**

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. **[18]**

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 4). When the correlation was applied to each group in a separate manner, the significant negative correlation observed in the overall population was lost. (Table 5).

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.

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. [14]

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. [19] [20]**

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**. [21].**

In the current study, there was non-significant relation between the gender and serum leptin (p =0.483) (Table 3) which is most probably due to presence of unequal numbers of both sexes, with about 83.33% of the studied population was females and about 16.7% 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. **[22][23]**

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. **[24][25]**

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**. [26]**

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. **[26][27]**

Conclusion:

Serum leptin level is lower in treatment naive hypothyroid 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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