Senses Sci (Educ Sci Tech) 2022: 9 (2) 1588- 1596
doi: 10.14616/sands-2022-2-15881596

Article

Clinical evidence to support the role of leptin in the mediation of hyperthytropinemia of obesity

Aliaa Aly El-Aghoury[1], Ola Atef Sharaki[2], Amira Mostafa Roshdy Mansour[1,] Tamer Mohamed El-Sherbiny[1]

[1]Endocrinology unit, Internal medicine Department, Faculty of Medicine, Alexandria University, Alexandria, Egypt.
[2]Clinical and chemical pathology Department, Faculty of Medicine, Alexandria University, Alexandria, Egypt.

*Correspondence**:** Amira Mostafa Roshdy Mansour. Tel. +20-1286507062**.** Address**:** 7 Gaafar Ibn Abi Talib, Sidi Beshr Qebli, Montaza 2, Alexandria, Egypt. Email: dr.amira.mostafa2011@gmail.com

Abstract

Background: Obesity is a common health problem. In obesity, thyrotropin (TSH) levels are at the upper limit of the normal range or slightly elevated and positively correlated with body mass index. Leptin resistance and hyperleptinemia is also common in obesity. *Material & Method*: This was a cross-section study of 80 subjects grouped into 2 groups; obese euthyroid subjects with BMI more than 35 (n = 40) and normal subjects with normal BMI (n = 40). TSH, Free T4, and Leptin were measured and anthropometric measures were taken. *Results*: TSH was significantly higher in obese subjects versus the control (mean ± SD 2.04 ± 1.51 μIU/mL vs1.46 ± 0.96 μIU/mL, p = 0.024). *Conclusion*: These results lead us to confirm that leptin level has an important role in the link between hyperthyrotropinemia and obesity.

Keywords: Obesity, leptin, TSH

Introduction

Obesity is a public health crisis because of its increasing prevalence and association with a high risk for life-threatening conditions. (1) By 2030, 57.8% of the world's population, will be overweight or obese. (2) Egypt has the highest rate of obesity in the world as more than one in three Egyptians is obese. (3)

Thyroid hormones are the key elements that affect resting energy expenditure. (4) They promote thermogenesis in brown and white adipose tissue. (5) In obese persons, thyrotropin (TSH) levels may be slightly elevated or at the upper limit of normal range and are positively correlated with body mass index. (6) The alterations of thyroid functions in obesity are explained by different mechanisms.

In obesity, there is a change in the activity of deiodinases leading to a high rate of T4 to T3 conversion as a defensive mechanism that can prevent future weight gain by raising basal metabolic rate and total energy expenditure. (7, 8) Also, the high level of leptin in obese persons may act directly on TRH-secreting neurons on Paraventricular Hypothalamic Nucleus through leptin receptors (9, 10) leading to stimulation of transcription of prothyrotropin-releasing hormone, which leads to increases in TRH and TSH concentrations. In addition, Leptin modulates thyroid gland's responsiveness to TSH, inhibits iodide uptake and expression of the sodium/iodide symporter and thyroglobulin. Also, Leptin increases the production of free T3 and decreases serum free T4 due to its stimulatory effect on the activity of deiodinases (D1). (11,12) On the other hand, TSH may directly enhance preadipocytes differentiation into adipocytes and the synthesis of leptin by adipocytes via its receptors in adipose tissue. (13, 14) Moreover, Inflammatory cytokines in obesity such as tumor necrosis factor α lead to inhibition of mRNA expression of the sodium/iodide symporter resulting in reduced iodide uptake in thyroid cells. (15)

In clinical practice, diagnosis of subclinical hypothyroidism in obese individuals is challenging. Therefore, hypothyroidism should only be suspected in obese individuals with modestly elevated TSH levels after assessing plasma levels of thyroid hormones, and thyroid autoantibodies. (16, 17) Since obesity and hyperthyrotropinemia are common health problems, and very commonly coexist in the same patients, we conducted this study to confirm in a clinical settings the relation of circulating leptin to hyperthyrotropinemia that is commonly observed in obese persons.

Methods

Study design, setting and participants

This was a prospective cross-sectional study. The study was conducted on 80 euthyroid subjects divided into two groups according to their BMI; 40 obese subjects (BMI ≥ 35 kg/m2), and 40 normal BMI (BMI ≥ 18.5 and <25 kg/m2) group. Obese subjects were enrolled from the obesity clinic at the Alexandria Main University Hospital between January, 2018 and October, 2021. The inclusion criteria were as follows: healthy subjects, between the age of 18-60 years, euthyroid and

tested negative for ATA (thyroid peroxidase antibody test). The exclusion criteria were as follows: patients with a history of liver or renal disorders (eGFR<60 ml/min), medication history that included taking drugs that alter the thyroid status. Persons with thyroid diseases, goiter, nodular and heterogenous thyroid gland by ultrasound, antithyroid peroxidase antibodies, acute non-thyroidal illness were also excluded. The Research Ethics Committee at College of Medicine, Alexandria University approved the research protocol and consent forms were obtained from participants before the beginning of the study.

Methods

Detailed history taking and thorough clinical examination were done for each participant. Anthropometric measures were taken including weight, height, waist circumference and body mass index (BMI), all according to the WHO protocols. Serum calcium, Albumin and creatinine were measured, and Estimated Glomerular Filtration Rate (eGFR) was calculated by CKD-EPI equation. Serum levels of thyroid-stimulating hormone, thyroid peroxidase antibody test, and free thyroxine were measured by Electrochemiluminescence immunoassay (ECLIA). Leptin was measured using Enzyme linked immunosorbent assay (ELISA).

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

The used tests were:

1- Chi-square test
For categorical variables, to compare between different groups.

2- Student t-test
For normally distributed quantitative variables, to compare between two studied groups.

3- Mann Whitney test
For abnormally distributed quantitative variables, to compare between two studied groups.

4- Spearman coefficient
To correlate between two distributed abnormally quantitative variables.

Results

Serum concentrations of TSH were demonstrated to be higher in the obese euthyroid group than the normal weight euthyroid group (p=0.024) (**Table 1**)

It was found that there was significant difference (p <0.001) between the two groups regarding Leptin, with the obese euthyroid group having higher median than the normal weight euthyroid group (Table 1).

Table (1): Comparison between the two studied groups according to different lab parameters

			Euthyroid Obese subjects (n = 40)	Healthy subjects with normal BMI (n = 40)	Test of significance	P
Demographic data	Sex	Males Females	22.5% 77.5%	42.5% 57.5%	◎²=3.647	0.056
	Age (years)	Mean ± SD.	43.88 ± 9.04	31.78 ± 10.19	t=5.618*	<0.001*
Anthropometric measurements	Weight (kg)	Mean ± SD.	110.75 ± 15.54	59.50 ± 7.06	t=18.987*	<0.001*
	Height (cm)	Mean ± SD.	162.65 ± 9.29	165.0 ± 8.10	t=1.206	0.231
	BMI (kg/m2)	Mean ± SD.	41.86 ± 4.82	21.83 ± 1.83	t=24.553*	<0.001*
	Waist Circumference (cm)	Mean ± SD.	124.60 ± 12.39	77.44 ± 7.97	t=20.249*	<0.001*
Renal functions	Urea (mg/dl)	Mean ± SD.	26.95 ± 7.04	25.35 ± 6.69	t=1.042	0.301
	Creatinine (mg/dl)	Mean ± SD.	0.77 ± 0.10	0.74 ± 0.18	t=0.941	0.35
	Creatinine clearance by CKD EPI (mls/min/1.73m2)	Mean ± SD.	100.40 ± 7.01	110.71 ± 9.16	t=5.653*	<0.001*
Albumin	Albumin (g/dl)	Mean ± SD.	4.47 ± 0.31	4.72 ± 0.21	t=4.263*	<0.001
Hormonal profile	TSH (μIU/mL)	Median (IQR)	1.60 (1.16 – 2.36)	1.16 (0.82 – 2.18)	U= 566.0*	0.024*
	Free T4 (ng/dL)	Mean ± SD.	1.14 ± 0.15	1.24 ± 0.17	t=2.580*	0.012*
	Anti TPO (IU/ml)	Median (IQR)	10.35 (9.21 – 12.7)	9.87 (9.22 – 11.4)	U= 686.0	0.273
	leptin (ng/ml)	Median (IQR)	40.0 (20.7 – 64.5)	4.85 (2.2 – 11.75)	U= 117.50*	<0.001*

SD: Standard deviation, *IQR: Inter Quartile Range*

◎²: Chi Square test *t: Student t-test*

U: Mann Whitney test

p: p value for comparing between euthyroid obese subjects and healthy subjects with normal BMI

**: Statistically significant at p ≤ 0.05*

Regarding the correlations between TSH and various parameters, TSH was found to have a significant positive correlation with BMI (rs = 0.222, p=0.048) and Leptin (rs =0.263, p =0.018) (**Table 2, Figure 1, 2**).

Table (2): Correlation between the Leptin, TSH, and BMI in each group and total sample

	Total (n = 80)		Obese (n = 40)		Normal (n = 40)	
	r_s	p	r_s	p	r_s	p
TSH vs Leptin	0.263*	0.018*	-0.096	0.558	0.355*	0.025*
TSH vs BMI	0.222*	0.048*	0.083	0.612	-0.041	0.803

rs: Spearman coefficient **: Statistically significant at p ≤ 0.05*

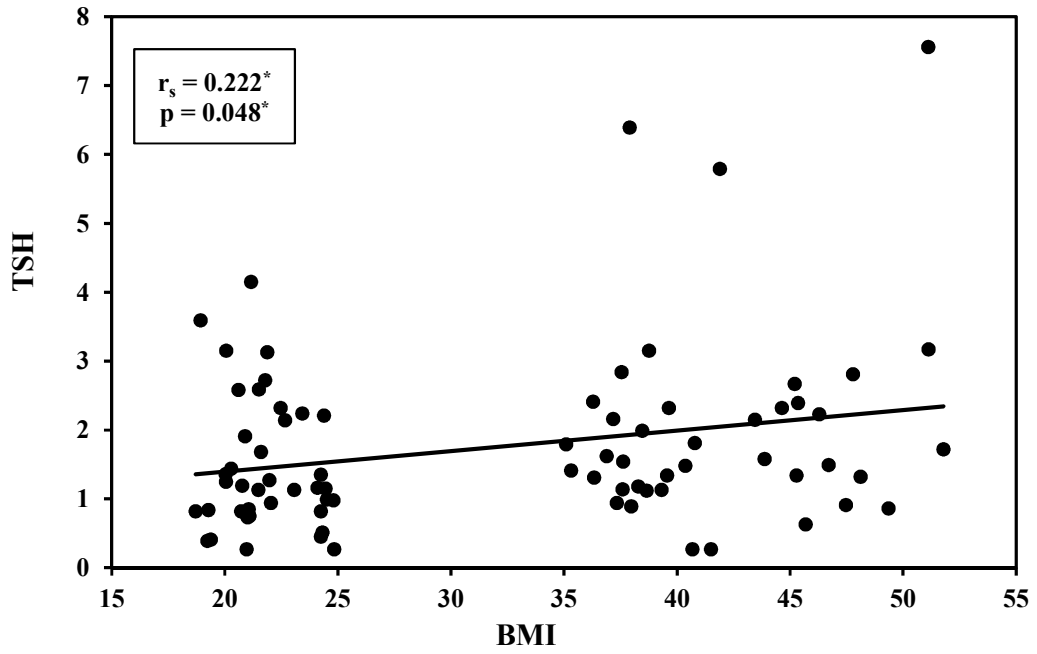

Figure (1): Correlation between TSH with BMI in total sample

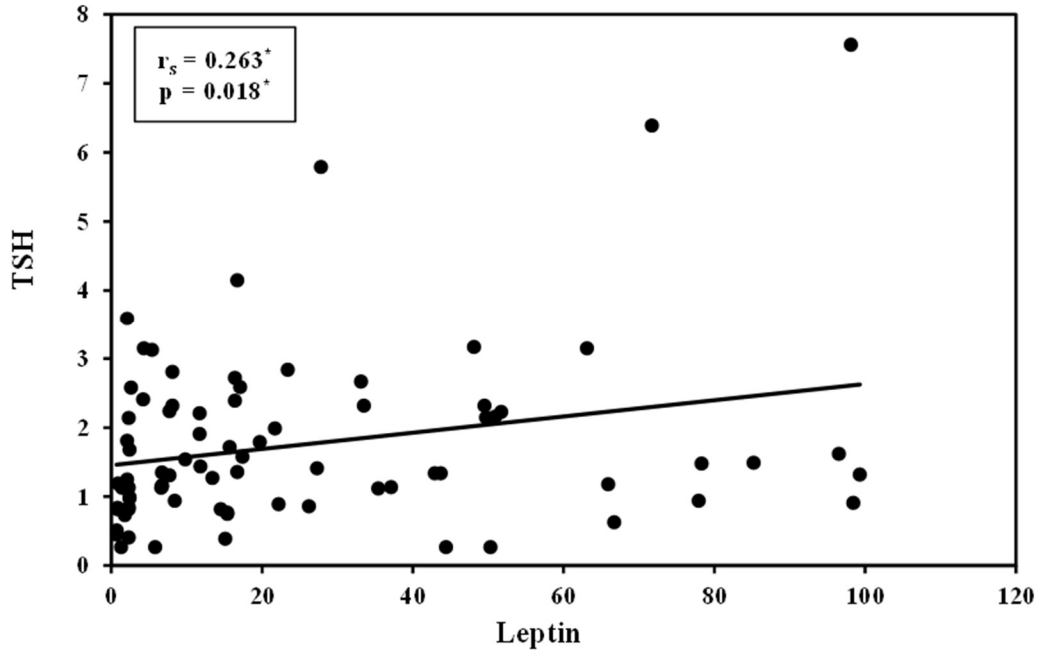

Figure (2): Correlation between TSH with Leptin in total sample

Discussion

The current study is a cross sectional study which attempted to investigate the relationship between thyrotropin and leptin in euthyroid obese subjects. We aimed to confirm that leptin may be responsible for hyperthyrotropinemia that observed in obese persons.

The current study has showed that TSH was significantly higher in the obese euthyroid group than the normal weight group and it was positively correlated with BMI and Leptin.

In accordance with the current study findings, Ali et al. conducted a cross-sectional study of 140 euthyroid people divided into two groups: a low-TSH group (TSH between 0.3 and 2.0 mIU/L, n=73) and a high-TSH group (TSH between 2.0 and 5.5 mIU/L, n=67), and discovered that the high-TSH group had higher BMI than the low-TSH group after adjusting age, sex, calorie intake, total carbohydrate, fat intakes, and physical activity. (18)

Additionally, Cari M et al. found that there was an increase in serum TSH levels for every 1-quartile increase in BMI in euthyroid men (3.8% [95% CI 0.8%, 6.8%]) and euthyroid women (4.0% [95% CI 1.6%, 6.5%]) who were 20 years of age and older and had TSH, fT(3), and fT(4) levels between 0.5-4.49 mIU/L, 2.5-3.9 pg/mL, and 0.6-1.6 ng/dL, respectively. Also, they discovered a positive correlation between serum TSH levels and waist circumference. (19)

Also, Paolo M et al. reported that Weight loss significantly affected TSH (-6.3%), FT3 (-3.3%) and FT4 levels (3.9%) ($p<0.001$ for all) in euthyroid subjects with severe obesity after completion of a 4-wk inpatient multidisciplinary dieting program. (20)

The impairment of thyroid function may be primary and the BMI change may be secondary or vice versa.

From the above studies, we conclude that obesity may be associated with hyperthyrotropinemia or even the increased serum TSH level within the normal range. Different mechanisms explain the change in TSH level that occurred in obesity; such as thyroid hormone resistance, thyroid autoimmunity, increased activity of thyroxine 5-deiodinase as a defense mechanism capable of burning fat. (21, 22) Leptin is another explanation for the association between BMI and TSH as observed by Betry C et al.. They found that both BMI and leptin were positively correlated with TSH. Also, they reported that independent of BMI, TSH and leptin remained to have a significant correlation. So, they concluded that leptin concentration in obese individuals is related to the relationship between TSH and BMI. (23)

The relation between TSH and leptin is complex. Leptin has been shown to regulate D2 (to promote the conversion of T4 to T3), regulate TRH neurons. Plasma TSH levels and leptin have similar circadian rhythms and are highly organized and pulsatile, according to research by Mantzoros et al. They also found near- superimposable peak values using a cosinor analysis. (24) On the other hand, several research suggested that TSH directly affects adipocytes to promote leptin release. (25)

Conclusion

From the results of the present study, it is obvious that leptin may be responsible for hyperthyrotropinemia or even slight increase in TSH level within the normal range in obesity.

Acknowledgments: The authors would like to express their gratitude for the support of the Department of internal medicine and Department of Clinical and Chemical Pathology, Alexandria University, Egypt.

Competing interests

No competing interests exist

Funding support

This research did not receive any specific grant from funding agencies

Authorship

All authors state that this manuscript has been read and approved by all the authors, the requirements for authorship as stated earlier in this document have been met and each author believes that the manuscript represents honest work.

References

1. Pugliese G, Liccardi A, Graziadio C, et al. Obesity and infectious diseases: Pathophysiology and epidemiology of a double pandemic condition. Int J Obes. 2022 Mar;46(3):449-65.
2. Linghu E. Obesity and chronic diarrhea: a new syndrome? Chin Med J. 2022 May 6:10-97.
3. World Health Organization (WHO). Global tuberculosis control: key findings from the December 2009 WHO report. Wkly Epidemiol Rec. 2010;85(09):69-79.
4. Walczak K, Sieminska L. Obesity and thyroid Axis. Int J Environ Health Res. 2021 Sep 7;18(18):9434
5. Volke L, Krause K. Effect of thyroid hormones on adipose tissue flexibility. Eur Thyroid J. 2021 Mar 1;10(1):1-9
6. Lu D, Yuan Z, Gao Y, Liu W, Zhang J. Central Obesity Is Associated with Variations in TSH and ACTH Levels among Euthyroid Obese Individuals. Int J Endocrinol. 2022 Mar 10;2022.
7. Stephanie T, Anthony U, Sheela N. Cardiometabolic risk in obese children. Ann N Y Acad Sci. 2018;1411(1):166-83.
8. Yadav J, Jain N, Dayal D. Alterations of thyroid function in overweight and obese children: An update. Indian J Child Health. 2018;5:145-50.
9. Warren W, Martin G. Leptin and the maintenance of elevated body weight. Nat Rev Neurosci. 2018;19: 95-105.
10. Witkowska-Sędek E, Kucharska A, Rumińska M, Pyrżak B. Thyroid dysfunction in obese and overweight children. Endokrynol Pol. 2017;68(1):54-60.
11. Adamczewska K, Adamczewski Z, Lewiński A, Stawerska R. Leptin Does Not Influence TSH Levels in Obese Short Children. Front. Endocrinol. 2022;13
12. Hecht F, Cazarin J, Rossetti CL, Rosenthal D, Araujo RL, Cavvalho DP. Leptin negatively regulates thyroid function of Wistar rats. An Acad Bras Cienc. 2021 Aug 20;93.
13. Duntas L. New insights into the hypothalamic-pituitary-thyroid axis. Acta Endocrinol. 2016;12(2):125-9.
14. Fontenelle LC, Feitosa MM, Severo JS, et al. Thyroid Function in Human Obesity:Underlying Mechanisms. Horm Metab Res. 2016;48(12):787-94.
15. Aurangabadkar G, Boddu SK. Hypothyroidism and obesity: Is there a bidirectional link? What is the impact on our clinical practice? Thyroid Res Pract. 2020 Sep1;17(3):118.
16. Sosa-López JG, Alarcón-González P, Sánchez-Hernández VH, et al. Impact of obesity on the thyroid profile, long-term experience at the General Hospital of Mexico," Dr. Eduardo Liceaga". Rev Med Hosp Gen. 2021 Mar;84(1):4-10.
17. Rotondi M, Leporati P, La Manna A, et al. Raised serum TSH levels in patients with morbid obesity: is it enough to diagnose subclinical hypothyroidism. Eur J Endocrinol. 2009 Mar;160(3):403-8.
18. Ali R , Mohamadreza K , Fatemeh I, et al. Relationship between Body Mass Index, Waist-to-Hip Ratio, and Serum Lipid Concentrations and Thyroid-Stimulating Hormone in the Euthyroid Adult Population. Iran J Med Sci. 2017 May;42(3):301-5.

19. Kitahara CM, Platz EA, Ladenson PW, et al. Body fatness and markers of thyroid function among U.S. men and women. PloS One. 2012;7(4):e34979.
20. Marzullo P, Minocci A, Mele C, et al. The relationship between resting energy expenditure and thyroid hormones in response to short-term weight loss in severe obesity. PLoS One. 2018 Oct 19;13(10):e0205293.
21. Santos MI, Limbert C, Marques FC, Rosário F, Lopes L. Childhood obesity, thyroid function, and insulin resistance–is there a link? A longitudinal study. J Pediatr Endocrinol Metab. 2015 May 1;28(5-6):557-62.
22. Al Mohareb O, Al Saqaaby M, Ekhzaimy A, et al. The Relationship Between Thyroid Function and Body Composition, Leptin, Adiponectin, and Insulin Sensitivity in Morbidly Obese Euthyroid Subjects Compared to Non-obese Subjects. Clin Med Insights Endocrinol. Diabetes Clinical Medicine Insights: Endocrinology and Diabetes. 2021 Feb;14:1179551420988523.
23. Betry C, Challan-Belval MA, Bernard A, et al. Increased TSH in obesity: Evidence for a BMI-independent association with leptin. Diabetes Metab J. 2015 Jun 1;41(3):248-51.
24. Mantzoros CS, Ozata M, Negrao AB, et al. Synchronicity of frequently sampled thyrotropin (TSH) and leptin concentrations in healthy adults and leptin-deficient subjects: evidence for possible partial TSH regulation by leptin in humans. J Clin Endocrinol Metab. 2001 Jul 1;86(7):3284-91.
25. Menendez C, Baldelli R, Camina JP, et al. TSH stimulates leptin secretion by a direct effect on adipocytes. J Endocrinol. 2003;176:7–12.