Can we consider a lower cutoff value for diagnosis of subclinical hypothyroidism in patients with obesity based on leptin levels?

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Background
Thyroid hormones play a major role in thermogenesis, lipid, and glucose metabolism. Previous studies suggested that minor laboratory differences in thyroid function tests, within reference range, can contribute to increased incidence of weight gain. So, we aimed to investigate the possibility of a lower cutoff value of subclinical hypothyroidism in patients with obesity based on leptin levels to start treatment earlier and prevent further weight gain.
Results
Upon analysis of data from two groups obese (55 patients) and nonobese (35 patients) for whom serum leptin and thyroid-stimulating hormone (TSH) were measured to assess the relation between serum leptin and TSH levels in obese patients, the mean TSH level (mIU/l) of the obese group was 4.13±2.44, whereas in the control nonobese group was 2.32±1.19, and the mean leptin level (ng/ml) of the obese group was 47.25±28.03, whereas in the nonobese group was 4.90±3.13. The receiver operating characteristic curve showed that the diagnostic cutoff point for TSH was 4.09, with sensitivity of 41.8% and specificity of 88.6%, whereas the diagnostic cutoff point for leptin was 12.75, with sensitivity of 98.2% and specificity of 97.1%.
Conclusions
The results of the study showed that TSH levels more than 4.09 mIU/l can be considered diagnostic of subclinical hypothyroidism in obese people, similar to other population, apart from pregnant women. So, based on leptin levels, a lower cutoff value of TSH cannot be considered diagnostic of subclinical hypothyroidism in obese population.

Keywords:
leptin, obesity, subclinical hypothyroidism, thyroid-stimulating hormone

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Background

Obesity is a worldwide condition that has grown dramatically over the past 50 years. The prevalence of obesity has almost doubled between 1980 and 2008 worldwide, and increases have occurred in every region of the world [1]. Obesity can be considered a pandemic which is associated with other chronic relapsing comorbidities like diabetes and cardiovascular diseases [2].

Thyroid hormones regulate basal metabolism, thermogenesis, lipid and glucose metabolism, food intake, and fat oxidation [3]. Thyroid malfunction is correlated with alterations in body weight and configuration, body temperature, and total and resting energy expenditure liberated from physical activity. Minor thyroid malfunction, in the form of subclinical hypothyroidism, is evidenced to be related to important variations in body weight and being a risk factor for overweight and obesity [4].

Furthermore, it has been reported that the small changes in serum thyroid-stimulating hormone (TSH), which resulted from slight variations in L-thyroxine dose during replacement therapy, were correlated with significantly changed resting energy expenditure in hypothyroid cases [5]. Moreover, some studies have shown that slight variations in thyroid function even within laboratory reference range can contribute to the tendency to gain weight. A reverse relation between free T4 and BMI has been described, even when free T4 remains within normal range [6].

There are some suggestions to explain the changes in thyroid functions in obese patients. One hypothesis recommends that an elevated de-iodinase activity

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causes a high conversion rate of T4 to T3. This is translated as a defense way in overweight individuals able to avoid the accumulation of fat by increasing the energy expenditure [7]. Another possible way is the compensatory rise in secretion of TSH and free T3 in a trial to incapacitate reduced response of the tissue to thyroid hormones in the blood owing to the diminished appearance of both TSH and thyroid hormones in adipocytes of overweight patients [8].

Leptin is a peptide hormone generated principally by adipocytes, but it can be released in minimal amounts by other organs such as mammary gland, ovary, skeletal muscle, stomach, pituitary gland, and lymphoid tissue, probably for local action [9]. Leptin is proved to be a main manager of energy balance and body obesity. Moreover, leptin controls the glucose homeostasis, thermogenesis, autonomic nervous system, and neuroendocrine pathways. The suppression of leptin signaling in metabolic disorders, such as obesity and diabetes mellitus, indicates the significant role of this hormone in the development and physiological symptoms of these diseases [10].

It has thus been shown that congenital or acquired leptin deficiency is associated with decreased and less pulsatile gonadotropin levels and with thyroid axis abnormalities marked by aberrant levels of thyrotropin (TSH)-releasing hormone (TRH), conditions which may at least partially be attenuated by leptin administration. The mechanism is assumed to involve energy-deprivation signaled to the brain by hyperleptinemia [11]. Furthermore, leptin has direct effects on TRH neurons, regulating its synthesis not only by upregulating the expression of pro-TRH genes in the prevertebral nucleus of the hypothalamus and influencing the feedback regulation of TRH-secreting neurons by thyroid hormones but also by increasing promoter activities of prohormone convertase 1/3 and prohormone convertase 2, which are essential for activation of TRH from pro-TRH [12].

Aim

This is a case–control study to detect and analyze the relationship between serum leptin levels and serum TSH levels in obese patients and the possibility to discover lower cutoff values for diagnosis of subclinical hypothyroidism in patients with obesity based on leptin levels.

Patients and methods

A total of 55 obese patients fulfilling inclusion and exclusion criteria were recruited from the obesity clinic of Specialized Medical Hospital, Mansoura University, starting from December in 2017 to January 2019 (case group), in addition to 35 lean people from nurses, workers, and visitors of the same hospital whose BMI was less than 25 (control group). Ethics approval and consent to participate: This work was approved by our faculty Institutional Research Board (IRB) IRB code number: MS/17.03.84. Written and informed Consents were taken from all participants. Consents for publication were taken from all participants. This research was approved by Institutional Review Board (IRB) Mansoura Faculty of Medicine, Mansoura University.

(1) Inclusion criteria were as follows:
    (a) Male and female obese patients.
    (b) BMI more than 30.
(2) Exclusion criteria were as follows:
    (a) Diabetes mellitus.
    (b) Renal disease.
    (c) Liver disease.
    (d) Heart failure.
    (e) Pregnancy or lactation.
    (f) Oral contraceptive use, antidepressant, corticosteroids, or amiodarone.
    (g) Overt thyroid disease (palpable goiter or use of antithyroid drugs).

All participants of the study were subjected to the following:

(1) History taking, with stress on age, medical history (diabetes, hypertension, thyroid disease, and asthma), special habits such as smoking and alcohol intake, psychosocial history, drug history, family history, past history of thyroidectomy, cold intolerance, fatigue, and poor memory.
(2) Clinical examination:
    (a) Determination of weight and height for calculation of BMI:
    It is calculated by dividing weight (in kg) by square of height (m^2) [13].
    (b) Measurement of waist, hip circumferences (HC), and waist–hip ratio (WHR).
    The waist and hip measurements are performed in a standing position with arms at the side, legs placed one foot apart, with the weight equally divided over both legs [13].
    Waist circumference (WC): the margin of the last rib and the iliac crest was assessed by palpation and well demarcated on both sides. The tape is positioned horizontally in the middle between the well-demarcated areas on both sides and underwent firm wrapping throughout the abdomen. The patient is asked

to take inspiration, and the measurements are recorded during the expiration (the cases are not notified the actual time of measurement). The measurements are needed and reported to 0.1 cm. The average of which are reported with an accuracy of 1 cm [14].

HC: measurement of the maximal circumference over the buttocks was done. The tape is positioned at a horizontal plane, without indentation of the soft tissues. Three measurements are assessed and reported to 0.1 cm. The average of which are reported with an accuracy of 1 cm [14].

WHR was measured through this equation (WC/HC). A WHR of 0.7 for females and 0.9 for males revealed a strong correlation with the general health. Abdominal obesity is a WHR more than 0.9 in male sex and more than 0.85 in female sex [14].

(c) Triceps skin-fold thickness.
For obtaining a higher accuracy of measurement, the used calipers must be precisely calibrated and reach a stable pressure [13].

(3) Laboratory investigation:
   (a) Serum leptin level was done by enzyme-linked immunosorbent assay (ELISA) technique, sandwich type assay. It was done by Immunospec Corporation Kit catalog number: E18-073, GENTAUR USA. The assay sensitivity was 0.50 ng/ml and linearity was up to 100 ng/ml [15].
   (b) Serum TSH level was done by ELISA technique by use of Bio Check Inc. test kit with catalog number: Bc-1001, Genprice Inc, Logistics 547 Yurok Circle, San Jose, CA, USA. The assay procedure is sandwich ELISA in which TSH concentration is directly proportional to color intensity of the test sample. This assay sensitivity was 0.2 uIu/ml, and linearity was up to 25 uIu/ml [16].
   (c) Fasting blood glucose was done by glucose oxidase method using colorimetric human kit, Germany [17].

Statistical analysis

Analysis was done using SPSS, 20.0 (statistical package for social sciences, version 22.0), and the results were considered significant when the *P* value was less than 0.05.

Results

The obese group included 55 patients. The control lean group included 35 patients.

The mean age of the obese group was 39.62±10.77 years, whereas in the control group was 30.06±11.89 years (Table 1). The obese group included 33 (60%) males and 22 (40%) females, whereas the control group included 24 (69%) males and 11 (31%) females (Table 1).

The mean height of the obese group was 170.05 ±9.35 cm, whereas in the control group was 169.49 ±10.13 cm. The mean weight of the obese group was 102.01±12.92 kg, whereas in the control group was 65.25±9.91 kg. The mean BMI of the obese group was 35.34±4.66 kg/m^2, whereas in the normal group was 22.56±2.12 kg/m^2 (Table 2).

The mean TSH level of the obese group was 4.13±2.44 mIU/l, whereas in the control group was 2.32±1.19 mIU/l. The mean leptin level of the obese group was 47.25±28.03 ng/ml, whereas in the control group was 4.90±3.13 ng/ml. There was a strong correlation between female sex and higher leptin levels in both groups, whereas higher TSH level was strongly correlated to the female sex in the control group (Table 3).

There was a strong positive correlation between female sex and HC in obese groups, whereas higher NS, WC, HC, and triceps skin fold were strongly negatively correlated with the female sex in the normal group. Higher BMI was strongly correlated with female sex in the obese group (Table 4).

A linear regression analysis was conducted for predicting the leptin levels using the studied variables. Leptin level was plotted against each

Table 1 Clinical characteristics of the study groups

	Obese group	Nonobese group
Number	55	35
Age (years)	Mean=39.62±10.77	Mean=30.06±11.89
Sex	Male=33 (60%)	Male=24 (68.6%)
	Female=22 (40%)	Female=11 (31.4%)
Smoking	Smoker=41 (74.5%)	Smoker=22 (62.9%)
	Nonsmoker=12 (21.8%)	Nonsmoker=13 (37.1%)
	Ex-smoker=2 (3.6%)	Ex-smoker=0

Table 2 Height, weight, and BMI

	Obese group (*N*=55)	Nonobese group (*N*=35)	95% CI	*P*
Height (cm)	170.05±9.35	169.49±10.13	–3.58, 4.72	0.79
Weight (kg)	102.01±12.92	65.25±9.91	31.67, 41.85	? 0.001
BMI (kg/m^2)	35.34±4.66	22.56±2.12	11.11, 14.44	? 0.001

CI, confidence interval.

Table 3 Thyroid-stimulating hormone and leptin levels in obese versus control group

	Obese group (*N*=55)	Nonobese group (*N*=35)	95% CI	*P*
TSH (mIU/l)	4.13±2.44	2.32±1.19	0.93, 2.69	Ë 0.001
Leptin (ng/ml)	47.25±28.03	4.90±3.13	32.87, 51.82	Ë 0.001

TSH, thyroid-stimulating hormone. 95% CI, 95% of mean difference between both groups. *P* is significant when less than 0.05.

Table 4 Correlation between thyroid-stimulating hormone and different parameters in studied groups

TSH	Obese group (*N*=55)		Nonobese group (*N*=35)	
	É½	*P*	É½	*P*
BMI (kg/m^2)	0.120	0.382	0.030	0.866
Neck circumference (cm)	0.175	0.201	0.092	0.599
Waist circumference (cm)	0.061	0.659	0.349	0.040
Hip circumference (cm)	0.061	0.659	0.388	0.021
Waist–Hip ratio	0.019	0.892	0.201	0.247
Triceps skin fold (cm)	0.154	0.260	0.234	0.176
Leptin	0.242	0.048	0.066	0.706

95% CI, 95% confidence interval; HBA1c, hemoglobin A1c; TSH, thyroid-stimulating hormone. *P* is significant when Ë 0.05.

variable. Visual inspection of these plots indicated a linear relationship between the variables. There was homoscedasticity and normality of the residuals. The significant predictors for leptin are sex and BMI, as reported in Table 5.

A receiver operating characteristic (ROC) curve was done to determine a cutoff point for both TSH and leptin between obese and control groups. The ROC curve showed that the diagnostic cutoff point for TSH was 4.09 mIU/l, with sensitivity of 41.8% and specificity of 88.6%, whereas the diagnostic cutoff point for leptin was 12.75, with sensitivity of 98.2% and specificity of 97.1% (Table 6 and Fig. 1).

Table 5 A linear regression analysis for predicting the leptin levels using the studied variables

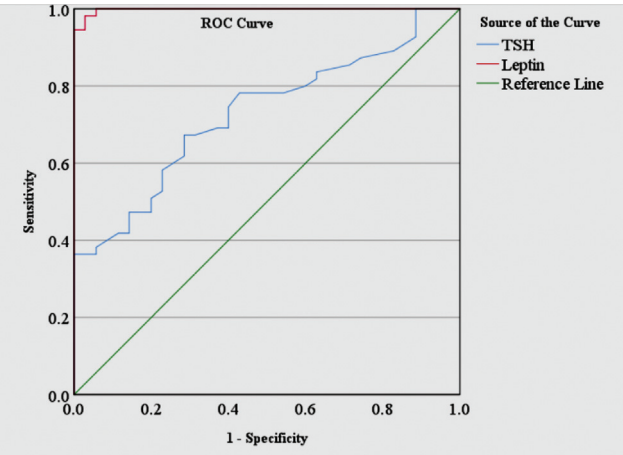
Leptin	*B*	95% CI for *B*	Constant	*R2*	*F*	*P*
Female Sex	16.903	8.462, 25.343	–76.436	62.1%	71.3	Ë 0.001
BMI	2.77	2.214, 3.326				

Table 6 Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of thyroid-stimulating hormone and leptin

	TSH	Leptin
Area under the curve	0.728	0.998
Diagnostic point	4.09	12.75
Sensitivity	41.8%	98.2%
Specificity	88.6%	97.1%
Positive predictive value	85.2%	96.4%
Negative predictive value	49.2%	97.1%
Accuracy	60%	96.7%

TSH, thyroid-stimulating hormone.

Figure 1



ROC curve Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of TSH and Leptin.

Discussion

Obesity is a serious public health problem, increasing morbidity and mortality and resulting in reduction of the quality of life. Leptin plays a clear role in obesity etiology, pathophysiology, and health outcomes. Some cases of severe obesity could be attributed to specific, rare, mutations of genes involved in the leptin pathway, resulting either in congenital leptin deficiency or in ineffective high levels of leptin and in leptin resistance [18]. Thyroid hormones play an important role in obesity [19]. The low thyroid hormone concentrations that characterize hypothyroidism are associated with lower energy expenditure and fluid retention, whereas hyperthyroidism is often associated with an increase in energy expenditure and weight loss [20].

This study was conducted to investigate the possibility of a lower cutoff value of serum TSH level in obese patients based on serum leptin levels. So, the serum TSH and leptin levels were measured with a group of obese patients (55 patients) as well as another control group of lean patients (35 patients).

As expected, anthropometric measurements in this study, that is, the weight, BMI, neck circumference, WC, HC, WHR, and triceps skin fold thickness, all

showed significantly higher values in obese patients. These findings are in agreement with previous findings [21].

In this study, leptin was significantly higher in obese patients versus nonobese controls. Many studies found that serum leptin concentrations are more than three times greater in individuals with obesity, compared with normal-weight individuals [22]. In addition to greater production of leptin, individuals with obesity may also be insensitive to endogenous leptin, thus creating a leptin-resistant state [23,24].

Regarding TSH level, in this study, it showed significantly higher values in obese patients compared with nonobese controls. This result is supported by a study done on obese adolescent, which found that TSH level increased in those patients, which could contribute to their increased risk for cardiovascular problems [25]. Moreover, another study showed that rise of TSH level in obese patients led to disturbance of their lipid profile [26].

In this study, there is a significant negative correlation between smoking and TSH level in nonobese group (P=0.037). A previous study on effect of smoking on thyroid found that current smoking in population surveys was associated with a slight dose-dependent fall of serum TSH, likely secondary to a rise of serum FT4 and FT3 induced by activation of the sympathetic nervous system independent of iodine intake [27].

Regarding leptin levels, also in this study, it showed a significant negative correlation with smoking (P=0.04). This result was supported by a previous study, which also found that leptin concentration was inversely correlated with nicotine dependence [28].

In this study, there was a significant positive correlation between leptin and BMI (P=0.04). This result is supported by a previous study which suggested that increased BMI with increased adipocytes could lead to increase leptin level in blood [23]. Moreover, leptin showed significantly a positive correlation with HC (P=0.03), which was in agreement with previous studies [29].

In this study, leptin was significantly higher in women than men subgroup. This result agreed with previous studies, which identified the brain as a producer of leptin by measuring of transcerebral leptin flux. Remarkably, they found that the female brain synthetizes more leptin than the male brain [30]. Moreover, another study found that women had higher circulating leptin levels by two to three times more than in men [29].

Leptin also showed positive correlation with TSH in obese group, with P value equal to 0.048. This result was supported by a previous study [31], which reflect the positive correlation between TSH and BMI recorded in certain cases [4]. Moreover, leptin, adjusted for BMI, was correlated with TSH [31], which suggests that the elevation in TSH and leptin levels in morbid obesity may be owing to the increase in fat quantities.

In this study, the ROC curve showed that the diagnostic cutoff value for TSH was 4.09, with sensitivity of 41.8% and specificity of 88.6%, whereas the diagnostic cutoff value for leptin was 12.75, with sensitivity of 98.2% and specificity of 97.1%. This shows that serum leptin levels are elevated in subclinical hypothyroidism. This finding was supported by the results of Teixeira *et al*. [32] who reported that serum leptin concentrations are elevated in subclinical hypothyroidism or overt hypothyroidism. A relationship between thyroid status and serum leptin is supported by the fact that levothyroxine treatment, to restore the euthyroid status, reduced serum leptin levels without significant effects on BMI [32].

Conclusion

This study showed that the cutoff value of TSH in obese patients was 4.09 mIU/l like nonobese, denoting that there is no need to adjust the reference range of TSH in obese patients in a way similar to pregnant women. So, based on these findings, TSH levels higher than 4.09 mIU/l can be considered subclinical hypothyroidism similar to the nonobese lean patients apart from pregnant women. However, further studies with larger number of participants are warranted to further confirm such findings.

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Authors' contributions: Mohammed A.E. Ahmed: data collection from case group and control group, and shared in writing. Omayma M. Saleh: shared in writing, shared in clinical part of the research, statistical analysis, and data reviewing and interpretation. She was our main supervisor of the work. Abeer Mesbah: responsible for the laboratory part of the research (TSH, leptin, and TPO) and shared in writing and data interpretation. Ahmed Albehairy: gave the idea of the work, shared in writing (main role), shared in clinical part and follow-up of patients, was responsible

for statistical analysis, and participated in data reviewing and interpretation.

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Conflicts of interest
There are no conflicts of interest.

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