

Study of the relationship between thyroid autoimmunity, obesity and serum leptin level in a sample of Egyptian individuals

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Abstract

Obesity is a worldwide health problem, and its prevalence is increasing steadily all over the globe. Leptin, mainly produced by adipocytes, was identified to modulate the immune system, as well as contributing to increased production of thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibody (TG-Ab). Autoimmune thyroiditis, mainly Hashimoto's thyroiditis, is believed to be the main cause of hypothyroidism in iodine sufficient regions, (TPO-Ab) and (TG-Ab) are the hallmarks of this disease. This study aimed to assess the relationship between thyroid autoimmunity, obesity and serum leptin level in a sample of Egyptian individuals. This study was a case control study which included 60 participants, recruited from the outpatient of the Internal Medicine Clinic at Ain Shams University Hospitals, during the period from February 2022 to October 2022. They were divided into two groups: Group 1 included 30 participants, have body mass index (BMI) >30 kg/m², and Group 2 included 30 participants, have BMI (18.5-25 kg/m²). We detected serum leptin, thyroid profile and thyroid antibodies using the enzyme linked immunosorbent assay and other immunoassays. Serum levels of leptin, thyroid-stimulating hormone (TSH) and glycated hemoglobin (HbA1c) were statistically significantly higher in group 1 than in group 2 ($p=0.0001$ for all). Also, there was a statistically significant positive correlation between serum leptin level and Anti-TPO in group 1 ($p=0.002$). In addition, in group 1, there was a statistically significant positive correlation between serum leptin level and TSH ($p=0.0001$). In conclusion, there is a relationship between thyroid autoimmunity and serum leptin level in obese subjects.

Keywords: Leptin, autoimmunity, obesity.

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Introduction

Obesity or increase in fat mass also alters the level of adipokines like leptin and adiponectin, which are released by the adipose tissue. Thus,

it is suggested that such altered levels of adipokines are involved in the pathogenesis of obesity associated diabetes.¹

The leptin gene, located on chromosome 7q32.1, codes for the protein hormone leptin,

and has 167 amino acids, is derived from adipose tissue.¹ Adipokines can work in autocrine, paracrine, or endocrine manners and produce crosstalk between adipose tissue and other organs.² Leptin appears to play a variety of roles in various cell types as a growth factor, including mediating energy expenditure, promoting puberty, signaling metabolic status, and regulating the metabolism of both the mother and the fetus.³

A study has shown a connection between thyroid autoimmune disease and obesity. The study concluded that thyroid autoimmunity is the cause of abdominal obesity and hyperlipidemia rather than being its consequence.⁴ However, other studies suggested that thyroid autoimmunity is a side effect of obesity.

The main causes of thyroid dysfunction include Hashimoto's thyroiditis and Graves' disease, which are prevalent autoimmune thyroid diseases. Immune cell dysregulation and abnormal cytokine expression are two features shared by Hashimoto's thyroiditis and Graves' disease. Due to its significant frequency in the general population and detrimental effects on human health, thyroid autoimmunity, which is defined as the presence of thyroid antibodies, has drawn more attention. Thyroid dysfunction and thyroid autoimmunity both negatively affect human health and raise the risk of cardiovascular disease and mortality, respectively.⁵

Obesity can either directly or indirectly impair immunological tolerance by influencing the release of adipokines (primarily leptin, adiponectin, and mucin) and/or cytokines (interleukin-6 and tumor necrosis factor- α).⁶

The thyrotropic axis (the hypothalamic pituitary thyroid axis), is responsible for thyroid feedback control. This axis is disrupted by obesity-related changes in the body's composition, hormonal activity, and cytokine profile, which also result in changes in the thyroid gland's structure. However, the information available thus far prevents us from stating with certainty whether these modifications are permanent or temporary and vanish following weight loss.⁷

Meanwhile, a meta-analysis study of thyroid antibodies showed the correlation between thyroid peroxidase antibodies (TPO-Ab) positivity and obesity, and that obesity is associated with 93% increased risk of developing positive TPO-Ab.⁸ Leptin is identified to mediate the immune system and contribute to increased production of TPO-Ab by shifting T helper balance towards to T helper 1 (Th1) cells phenotype and inhibiting the function of regulatory T (Treg) cells.⁸ Therefore, this study aimed to evaluate the relationship between thyroid autoimmunity, obesity and serum leptin level in a sample of Egyptian individuals.

Subjects and Methods

The current study included 60 participants with ages ranging between 35 and 50 years. Participants were recruited from the outpatient of the Internal Medicine clinic and the inpatient of the Internal Medicine Department at Ain Shams University Hospitals. They were divided into two groups: Group 1: included 30 obese participants whose body mass index (BMI) >30 kg/m² and Group 2: included 30 participants with BMI ranged 18.5-25 kg/m². BMI was calculated according to the World Health Organization (WHO) equation: (BMI calculated by weight (kg)/height² (m)). The recommended levels are 18.5–24.9 kg/m² as a normal BMI, and Obesity if BMI above 30 kg/m².

Patients were subjected to full history taking, clinical examination which included systolic and diastolic blood pressure, anthropometric measures (BMI, waist to hip ratio), neck examination, and evaluation of thyroid function and antibodies. These included thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroid hormone thyroxine (FT4), anti-thyroid peroxidase (anti-TPO), antithyroglobulin antibodies (anti-TG antibodies). Also, serum leptin level and glycated hemoglobin (HbA1c) were measured.

Exclusion criteria included subjects with previous history of thyroid, autoimmune disorder or family history of thyroid disease, previous history of lithium or amiodarone medication, chronic steroid treatment, and neck irradiation. Patients less than 35 years old,

menopause, and age above 50 years old, patients who had been prescribed hypo-caloric diets or therapies for weight control for at least 3 months before the study, and body weight was stable for the same period, they were also excluded from the study.

Methodology

A venous blood sample (5-7 ml) was withdrawn from each participant via sterile venipuncture then divided into two parts. The first portion was collected into a plain vacutainer for serum separation and used for the assessment of serum leptin level. Sera was also used for assessment of the thyroid profile (FreeT3, FreeT4, TSH) by the chemiluminescence immunoassay. Anti-TG antibodies by immunoassay, anti-TPO antibodies by immunofluorescence assay using a fully automated electro luminescence analyzer (CObas.e411, Roche diagnostic, Switzerland). The second blood portion was collected into EDTA containing tubes and used for assessment of glycated hemoglobin (HbA1c) by the Latex enhanced Immunoturbidimetry.

HbA1c % was calculated using a calibration curve using calibrator Kits (HbA1c Direct calibrator Kits, Beacon Company, India), according to the manufacturer's instructions. Reference Range, according to the American Diabetes Association, the recommended reference range: HbA1c (4.6% -5.6%) normal value, HbA1c (5.7 – 6.4 %) high risk group, HbA1c above 6.5% (Diabetic).

Serum Leptin Level was assessed using the sandwich enzyme linked immunoassay ELISA commercial kits (Human Iodine ELISA Kits, Kono Biotech Company, China), according to the manufacturer's instructions.

Expected values:

Group	Mean (ng/ml)	Range (ng/ml)
Lean Women	7.4	3.7 – 11.1
Lean men	3.8	2.0 – 5.6

Serum TSH, Free T4, Free T3 were assessed using chemiluminescence immunoassay (CLIA) commercial Kits (Ig Biotechnology Company, USA), according to the manufacturer's instructions. The normal reference range for

TSH, FreeT4, FreeT3 are as follows: FT3 (2.30 - 4.20 pg/ml), FT4 (0.89 – 1.76 ng/dl), and TSH (0.35 – 5.5 uIU/ml).

Anti-thyroglobulin antibodies and Anti thyroid-peroxidase antibodies were assessed using ELISA commercial Kits (Calbiotech A life science company, USA), according to the manufacturer's instructions. For anti-TPO antibodies, the obtained international units may then be interpreted as follows: <50 IU/ml, negative; 50-75 IU/mL, borderline positive; > 75 IU/ml, Positive. As regard the anti-TG antibodies, the obtained international units may be interpreted as follows: <100 IU/ml, negative; 100-150 IU/ml, borderline positive; and > 150 IU/ml, positive.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) IBM© version 23 and MedCalc© version 15. Quantitative data were expressed as Mean $\pm$ SD; and qualitative data expressed as number and percent of total. Comparative analysis was done using Student t test and Chi square tests for quantitative and qualitative data, respectively. Correlations were done with Pearson's product-moment correlation coefficient. The following tests were used: Mean (average): sum off all variables divided by total numbers of variables. Standard deviation (SD): the positive square root of variance. Pearson correlation co-efficient (r): this is a parametric correlation coefficient to measure the association between continuous variables that are both normally distributed. Inferential analyses were done for quantitative variables using independent t-test in cases of two independent groups with parametric data. In qualitative data, inferential analyses for independent variables were done using Chi square test for differences between proportions. While correlations were done using Pearson correlation for numerical parametric data. The linear regression model was used to find out independent factors affecting certain conditions. The Chi-square test was used for comparison of qualitative variables. The significance was defined at $p > 0.05$.

Results

HbA1c was significantly higher in Group 1 (obese participants) than in Group 2, with normal BMI (Table 1).

FT3 and TSH were significantly higher in Group 1 (Obese participants) than in Group 2, normal BMI (Table 2).

Leptin was significantly higher in Group 1 (Obese participants) than in group 2, (normal body mass index, BMI), (Table 3).

In Group 1 (Obese participants), there were several significant correlations between Anti-TPO, Anti-TG and Leptin with other studied parameters, as shown in Table 4.

Because TSH was the most sensitive test to detect early thyroid function affection, Table 5 shows the correlations between TSH and other studied parameters in the two studied groups.

Table 1. Comparison of glycated hemoglobin (HbA1c) level between Group 1 (Obese participants) and Group 2 (normal body mass index, BMI).

HbA1c (%)	Group 1 BMI > 30 kg/m ² No. = 30	Group 2 BMI (18.5 – 25 kg/m ²) No. = 30	*p-value
Mean ± SD	5.33 ± 0.40	4.81 ± 0.32	0.0001
Range	4.6 – 6	4.4 – 5.4	

*p ≤ 0.05 is significant.

Table 2. Comparison of the thyroid profile between Group 1 (Obese participants) and Group 2 (normal body mass index, BMI).

Thyroid profile		Group 1 BMI > 30 kg/m ² No. = 30	Group 2 BMI (18 – 25 kg/m ²) No. = 30	p-value
FT3 (pg/ml)	Mean ± SD	2.86 ± 0.38	2.56 ± 0.37	0.003
	Range	2.07 – 3.66	2.04 – 3.68	
FT4 (ng/dl)	Mean ± SD	1.35 ± 0.14	1.31 ± 0.15	NS
	Range	1.02 – 1.65	0.97 – 1.66	
TSH (uIU/ml)	Mean ± SD	4.62 ± 1.13	2.93 ± 0.49	0.0001
	Range	2.5 – 6.3	2.2 – 4	

p > 0.05 is not significant (NS).

Table 3. Comparison of Anti-TPO, Anti-TG antibodies and leptin between Group 1 (Obese participants) and Group 2 (normal BMI).

		Group 1 BMI > 30 kg/m ² No. = 30	Group 2 BMI (18 – 25 kg/m ²) No. = 30	p-value
Anti-TPO (IU/ml)	Median (IQR)	10.7(7.1 – 12.25)	8.73(6.8 – 11.65)	NS
	Range	5.9 – 64.7	3.95 – 28.55	
Anti-TG (IU/ml)	Median (IQR)	17.35(10.6 – 33.8)	13.15(10.4 – 19.4)	NS
	Range	9.4 – 93.5	8.8 – 46.3	
Leptin (ng/ml)	Mean ± SD	30.06 ± 4.78	8.43 ± 2.25	0.0001
	Range	17.23 – 37.2	5.4 – 11.28	

p > 0.05 is not significant (NS).

Table 4. Correlation of Anti-TPO, Anti-TG and Leptin with other studied parameters among Group 1 (obese group).

Studied parameters	Group 1 (BMI > 30 kg/m ²)					
	Anti-TPO		Anti-TG		Leptin	
	r	p-value	r	p-value	r	p-value
Anti-TPO	–	–	0.035	NS	0.533	0.002
Anti-TG	0.035	NS	–	–	0.161	NS
Leptin	0.533	0.002	0.161	NS	–	–
Age (years)	0.107	NS	0.238	NS	0.186	NS
Weight	0.511	0.004	0.031	NS	0.493	0.006
Height	0.110	NS	-0.062	NN	-0.356	NS
BMI	0.416	0.022	0.148	NS	0.863	0.0001
Waist Circumference	0.188	NS	0.110	NS	0.534	0.002
Hip circumference	0.217	NS	0.104	NS	0.548	0.002
Waist to Hip ratio	-0.306	NS	-0.064	NS	-0.366	0.047
Pulse	0.010	NS	0.110	NS	0.001	NNS
Systolic BP	0.168	NS	0.238	NS	0.576	0.001
Diastolic BP	0.192	NS	0.220	NS	0.437	0.016
HbA1c	0.216	NS	0.132	NS	0.638	0.0001
FT3	-0.079	NS	0.027	NS	0.104	NS
FT4	0.039	NS	0.011	NS	0.108	NS
TSH	0.451	0.012	0.304	NS	0.849	0.0001

$p > 0.05$ is not significant (NS).

Table 5. Correlation of TSH with other studied parameters among group 1 (Obese participants) and group 2 (normal BMI), as TSH is the most sensitive test to detect early thyroid function affection.

Studied parameters	TSH			
	Group 1		Group 2	
	r	p-value	r	p-value
Age (years)	0.247	NS	0.062	NS
Weight	0.480	0.007	0.471	0.009
Height	-0.469	0.009	0.223	NS
BMI	0.927	0.0001	0.459	0.011
Waist Circumference	0.710	0.0001	0.536	0.002
Hip circumference	0.708	0.0001	0.517	0.003
Waist to Hip ratio	-0.342	NS	-0.025	NS
Pulse	-0.143	NS	0.241	NS
Systolic BP	0.638	0.0001	-0.171	NS
Diastolic BP	0.552	0.002	0.047	NS
HbA1c	0.822	0.0001	0.082	NS
FT3	0.047	NS	-0.029	NS
FT4	0.024	NS	-0.140	NS
Final Anti-TPO	0.451	0.012	-0.161	NS
Final Anti-TG	0.304	NS	0.145	NS
Leptin	0.849	0.0001	0.180	NS

$p > 0.05$ is not significant (NS).

Discussion

The present study was carried out to investigate the relationship between thyroid autoimmunity, obesity and serum leptin level in a sample of Egyptian individuals. In addition, we studied the association between obesity and subclinical hypothyroidism. So that management of obesity can be used as a tool to lessen the incidence of hypothyroidism in population. Obesity is a worldwide health problem, and its prevalence is increasing steadily all over the globe. Obese subjects are at increased risk of acquiring dyslipidemia, elevated blood pressure, impaired glucose metabolism, and eventually cardiovascular and metabolic diseases.⁹

The adipocyte hormone leptin regulates appetite by inhibiting food intake and increasing energy expenditure via an interaction with specific leptin receptors located in the arcuate nucleus, the paraventricular nucleus and dorsomedial nuclei and the lateral hypothalamus.⁶

In the present study, with regard to the systolic diastolic blood pressure of the participants, there was a statistically significant difference between the two studied groups ($p=0.001$ and $p=0.036$, respectively). This was consistent with findings of a study in Korea by Kang, 2023, which included 2,550 males, and 2,938 females, aged from 10 to 80 years, to investigate the association between abdominal obesity and blood pressure. The study reported a statistically significant difference in systolic and diastolic blood pressure between the studied groups.¹¹

In the present study, there was no statistically significant difference in the pulse between the two studied groups ($p=0.637$). Also, in a study conducted in Greece by Stabouli et al., 2020, included 82 participants, classified into 2 groups: the first group has normal weight, and the second group included obese subjects. The study demonstrated no difference between the two studied groups ($p=0.137$).

In our study, there was a statistically significant difference in HbA1c between the two studied groups ($p=0.0001$). This goes in line with findings of a study in Indonesia by Sarnings et al., 2022, included 99 subjects classified into 4

groups according to BMI. The BMI in the groups were 18.5-24.9 kg/m², 25-29.9 kg/m², 30-34.9 kg/m² and >40 kg/m², respectively. There was a statistically significant difference in HbA1c level between the four studied groups, ($p<0.001$).

Also, a study in China by Guo et al., 2020, included 12,531 Chinese individuals (18–80 years). They were categorized into three groups according to BMI (normal, overweight and obese). The study showed a statistically significant difference in HbA1c level between the three studied groups ($p<0.001$).

Such results in this study and others can be explained as that obesity causes impaired adipose tissue function, inducing impaired secretion of adipokines into the circulation.¹³ Excess fat cells in the long term will cause fat cells to become resistant to the anti-lipolytic effects of insulin and result in an increase in the process of lipolysis and free fatty acids in the plasma.¹³ Free fatty acids will increase gluconeogenesis resistance and then trigger insulin in the liver and muscles as well as interfere with insulin secretion and obesity, increase the secretion of interleukin 6 and Tumor necrosis factor produced by adipocytes and monocyte derivatives. These lead to more insulin resistance, resulting in high circulating blood glucose and eventually the development of the macrophage condition that we call diabetes mellitus.¹³

However, a study carried out in Saudi Arabia by Mohareb et al., 2020, included 107 participants, classified into two groups (55 obese subjects, and 52 non-obese controls), showed no difference in HbA1c between the studied groups ($p=0.2$). The study included different population (Saudi people), classified into 2 groups: the first one (obese group) included participants whose BMI ≥ 30 kg/m² and the second group included non-obese group, participants whose BMI < 30 (including BMI (25-30 kg/m²) overweight participants).

In the present study, there was a statistically significant difference in FT3 level between the two studied groups ($p=0.003$). This agreed with findings of the study in Saudi Arabia by Mohareb et al., 2020, which showed a statistically significant difference in FT3 level between the studied groups ($p=0.001$).

In the present study, there was no difference in FT4 between the two studied groups ($p=0.286$). Similarly, a study in Zagazig, Egypt by Fadel et al., 2020, showed no difference in FT4 between the studied groups ($p=0.418$).

In the present study, there was a statistically significant difference in TSH between the two studied groups ($p=0.001$). These results agreed with the findings of a study in Italy by Mele et al., 2022, included 5,009 adults with obesity, their age ranged from 18 to 37 years, BMI ranged from 30 to 82.7 kg/m². The study population was classified into 5 groups according to BMI: (BMI < 34.9 kg/m²), (BMI 35–39.9 kg/m²), (BMI 40–49.9 kg/m²), (BMI 50–59.9 kg/m²), and (BMI > 59.9 kg/m²). The study showed a statistically significant difference in TSH between the 5 studied groups ($p=0.0001$).

Another study was conducted by Abozeid et al, 2018, in Tanta, Egypt, included 90 females aged (40– 50 years). They were classified into three groups (30 normal females), (30 obese females with normal thyroid function) and (30 obese females early diagnosed with subclinical hypothyroidism). The study reported a positive statistically significant difference in TSH between the three groups (p value <0.05), as the females with the higher BMI, have the higher TSH level. This positive statistically significant difference in TSH level between normal weight group and the obese group could be due to direct stimulating effect of TSH on pre-adipocyte differentiation which resulting in adipogenesis and fat mass accumulation with positive energy-balance.¹⁵

On the contrary, a study done in Mexico by Sosa-Lopez et al., 2021, included 186 participants, aged between 18 and 65 years old, classified into three groups according to BMI, (BMI 30 – 34.9 kg/m²), (BMI 35 – 39.9 kg/m²), and (BMI equal to or more than 40 kg/m²), measuring thyroid profile, anthropometric measures, anti-TPO antibodies, showed no difference in the thyroid profile between the three studied groups ($p=0.15$). However, that study compared 3 obese groups without including normal weight subjects.

It is evident from results of the present work that there is significant increase in TSH in the obese group more than the normal weight

group. Obesity was associated with changes in the secretion pattern of several hormones and causes slight increments in TSH levels even above the TSH normal threshold devoid of underlying thyroid dysfunction.¹⁷

In the present study, there was no difference in anti-TPO and anti-TG antibodies between the two studied groups ($p=0.600$ and $p=0.165$, respectively). Similarly, a study done at Poland by Walczak et al., 2022, included 181 euthyroid patients (147 women and 34 men, aged 18–65 years) with obesity BMI 30–39.9 kg/m² and severe (morbid) obesity (BMI $\geq$ 40 kg/m²), showed no difference in anti-TPO and anti-TG antibodies between the two studied groups.

However, a study done in Italy by Marzullo et al., 2010, included 283 participants, classified according to BMI into two groups: obese subjects and lean subjects, showed a statistically significant difference in anti-TPO and anti-TG antibodies between the studied groups ($p=0.01$ and $p=0.0001$, respectively).

In the present study, there was a statistically significant difference in leptin level between the two studied groups ($p=0.001$). Similarly, the study by Mohareb et al., 2020, in Saudi Arabia, showed a statistically significant difference in leptin level between the studied groups ($p<0.001$). Also, the study by Fadel et al., 2020, done in Zagazig, Egypt, showed a statistically significant difference in leptin level between the two studied groups ($p=0.007$).

Our study showed that in the obese group, there was a positive statistically significant correlation between leptin level and anti-TPO antibodies as the higher leptin level group has the higher anti-TPO antibodies level ($p=0.002$). Similarly, the study by Marzullo et al., 2010, done in Italy included 283 participants showed a positive statistically significant correlation between leptin level and autoimmune thyroid diseases ($p=0.001$).

Our study showed that in the obese group, there was a positive statistically significant correlation between leptin level and TSH as the higher leptin level group has the higher TSH level ($p=0.0001$). These results agreed with those of a study done in Italy by Mele et al., 2022, which showed a positive statistically significant correlation between leptin level and

TSH, as the higher leptin level group has the higher TSH level ($p=0.002$).

From the results of our study, we can conclude that TSH levels should probably not be the only parameter to be considered when diagnosing hypothyroidism in obese patients. The absence or evidence of autoimmunity, together with the measurement and analysis of the whole thyroid profile, are also parameters to consider.

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Author Contributions

All authors participated in the design of this study. SSH, KMM, AMB and SSH proposed the idea. Data collection and sampling was done by SSH. Data analysis and interpretation was done by AMB, HMA, NNA and SSH. Writing and revision of the manuscript were done by SSH, KMM, AMB, HMA, NNA and SSH. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The protocol of the study was reviewed and approved by the Research Ethical Committee of the Faculty of Medicine, Ain Shams University (MD 88/2021).

Informed consent

An informed written consent was obtained from each participant before being included in our study.

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