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Leptin as a Potential Marker for Autoimmune Hypothyroidism Predisposition in Euthyroid Males: A Study of Anti-TPO Antibodies

Dr. Hadeel Fakhri Hameed
FICMS. Pathology. Al-Emamain Al-Kadhymain Medical City/ Ministry of Health/ Baghdad-Iraq
Email addresss: hajoralwan@gmail.com

Abstract—Background*: Leptin is a peptide hormone that is secreted by adipose tissue and bears structural similarities with proinflammatory cytokines such as interleukin 6 and granulocyte colony-stimulating factor. On the other hand. Hashimoto thyroiditis is an autoimmune illness characterized by the destruction of thyroid cells by immunological processes involving both cells and antibodies.* ***Aim of study****: The current study aims to investigate whether the proinflammatory action of serum leptin has a role in the early pathogenesis of autoimmune thyroiditis by elevating anti-TPO antibodies.* ***Methodology****: This is a cross sectional study that included 120 participants comprised equal proportions of males and females (n = 60 per group) further stratified by BMI status (30 with BMI ≥ 30 and 30 with BMI<30 within each gender category).* ***Results****: Multivariate analysis revealed that serum leptin was significantly correlated with anti-TPO antibodies in both obese and non-obese males, whereas no such correlation was detected among females.* ***Conclusion****: This study has found that serum leptin is associated with increased levels of anti-TPO antibodies among obese and non-obese euthyroid males, which may reflect an underlying potential to develop subsequent autoimmune hypothyroidism.*

Keywords— *Leptin, Autoimmune Hypothyroidism, Anti-TPO Antibodies.*

I. INTRODUCTION

Leptin, a peptide hormone, is secreted by adipose tissue. Traditional explanations of leptin's role position it within the framework of regulating appetite, neuroendocrine function, and energy equilibrium, although it also seems to influence several other physiological processes. Several functions have previously been discovered, including metabolism, endocrine management, and immune function. There may yet be more that have not been found yet. Abnormal levels of leptin are linked to several metabolic diseases, such as obesity. The investigation of leptin physiology has enhanced our understanding of energy equilibrium and is anticipated to be crucial in discovering a remedy for the escalating obesity epidemic. The primary factors that have the greatest impact on the levels of leptin in the bloodstream are the body's total BMI, metabolic hormones, and gender. Leptin levels in the bloodstream are higher in females compared to males (1).

Leptin structure bears similarities with the widespread proinflammatory cytokines such as interleukin 6 and granulocyte colony-stimulating factor. Upon binding to its surface-bound receptors (LR), leptin initiates its functional activity. Leptin receptors are present in several kinds of cells, such as neurons, liver, pancreas, heart, and perivascular intestinal tissue (2). Moreover, the leptin receptor is a cytokine receptor (3).

Hashimoto thyroiditis is an autoimmune illness characterized by the destruction of thyroid cells by immunological processes involving both cells and antibodies. In iodine-sufficient nations, it is the primary cause of hypothyroidism. The gender disparity is significant, with a minimum ratio of 10 females to every male. The majority of women receive a diagnosis between the ages of 30 and 50 (4, 5). The cause of Hashimoto's disease is currently not well known. The majority of patients produce antibodies against various thyroid antigens, with the most prevalent being anti-thyroid peroxidase (anti-TPO). Positive TPO antibodies predict the onset of the clinical condition (6).

The current study aims to investigate whether the proinflammatory action of serum leptin has a role in the early pathogenesis of autoimmune thyroiditis by elevating anti-TPO antibodies.

II. METHODOLOGY

Study setting and design: This is a cross sectional study that included 120 participants and was conducted during the period from the 12th of February to the 4th of May 2024. Given that serum leptin levels are dependent upon BMI and gender, the sample comprised equal proportions of males and females (n = 60 per group) further stratified by BMI status (30 with BMI ≥ 30 and 30 with BMI<30 within each gender category). Exclusion criteria included previous thyroid disorders, autoimmune diseases, neck radiation, and thyrotoxic medications (e.g. amiodarone, lithium, etc.)

During the morning, 5 cc of fasting venous blood samples were withdrawn from each patient. These samples were then submitted for analysis to measure the levels of serum thyroxine, TSH, anti-TPO, and leptin. Radioimmunoassay was used to analyze serum leptin levels, using polyclonal rabbit anti-human antibodies.

Statistical analysis: Data was recorded into different quantitative and qualitative variables for the purpose of analysis. SPSS version 26 was used for data analysis. Data was summarized using measures of frequency (mean), dispersion (standard deviation), and tables. Independent

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sample t-test was used to compare between continuous variables. Fischer's exact test was employed to compare between categorical variables. Multivariate analysis was used to examine the correlation between anti-TPO antibodies and each of serum leptin, BMI, and age. A p value of less than or equal to 0.05 was assigned as a criterion for declaring statistical significance.

III. RESULTS

Statistical analysis reveals that serum leptin, thyroxine, and anti-TPO antibodies were significantly higher among females than males; as shown in table (1).

TABLE (1): Comparison of basic and laboratory parameters among males and females.

Variable	Gender		P-value
	Males (N=60)	Females (N=60)	
Age			
Mean ± SD	42.1 ± 12.0	39.6 ± 12.7	0.546
BMI			
	28.8 ± 5.5	29.1 ± 4.6	0.892
S. leptin			
Mean ± SD	7.9 ± 3.2	20.7 ± 8.8	<0.001
Leptin level			
Low	27	23	0.751
	45.0%	38.3%	
Normal	21	24	
	35.0%	40.0%	
High	12	13	
	20.0%	21.7%	
Serum thyroxine			
Mean ± SD	8.97 ± 2.27	9.2 ± 2.4	<0.001
Serum TSH			
Mean ± SD	3.9 ± 2.3	3.3 ± 2.2	0.861
Serum TPO antibody			
Mean ± SD	5.5 ± 10.3	10.3± 15.5	<0.001

When stratified according to BMI, Statistical analysis revealed that in both sexes, the obese group had significantly higher serum leptin than non-obese group; as shown in tables (2) and (3).

TABLE (2): Comparison of basic and laboratory parameters among non-obese and obese males.

Variable	Males (N=60)		P-value
	Non- obese (N=30)	Obese (N=30)	
Age			
Mean ± SD	43.1 ± 12.0	41.2 ± 12.2	0.544
BMI			
	24.1 ± 3.1	33.6 ± 2.3	<0.001
S. leptin			
Mean ± SD	4.9 ± 0.8	10.8 ± 1.8	<0.001
Leptin level			
Low	12	0	<0.001
	20.0%	0.0%	
Normal	37	17	
	61.7%	28.3%	
High	11	43	
	18.3%	71.7%	
Serum thyroxine			
Mean ± SD	9.0 ± 2.57	8.9 ± 1.9	0.902
Serum TSH			
Mean ± SD	4.0 ± 2.5	3.7 ± 2.1	0.594
Serum TPO antibody			
Mean ± SD	5.9 ± 9.1	5.1 ± 11.5	0.779

TABLE (3): Comparison of basic and laboratory parameters among non-obese and obese females.

Variable	Females (N=60)		P-value
	Non- obese (N=30)	Obese (N=30)	
Age			
Mean ± SD	38.9 ± 13.0	41.0 ± 12.5	0.511
BMI			
	25.3 ± 3.3	33.0 ± 1.8	<0.001
S. leptin			
Mean ± SD	12.8 ± 3.0	28.7 ± 4.4	<0.001
Leptin level			
Low	10	0	<0.001
	16.7%	0.0%	
Normal	41	14	
	68.3%	23.3%	
High	9	46	
	15.0%	76.7%	
Serum thyroxine			
Mean ± SD	9.4 ± 2.8	8.9 ± 2.0	0.401
Serum TSH			
Mean ± SD	3.4 ± 2.0	3.1 ± 2.3	0.624
Serum TPO antibody			
Mean ± SD	10.6 ± 17.3	10.1 ± 13.7	0.911

Multivariate analysis revealed that serum leptin was significantly correlated with anti-TPO antibodies in both obese and non-obese males, whereas no such correlation was detected among females; as shown in table (4).

TABLE (4): Multivariable regression model for serum levels of anti-TPO antibodies stratified according to gender and weight status. Results illustrated as regression coefficient (P-value).

Parameter	Male		Female	
	Nonobese (BMI ≤30)	Obese (BMI >30)	Nonobese (BMI ≤30)	Obese (BMI >30)
Age (per 10 years)	0.83 (0.328)	1.2 (0.236)	**2.14 (0.012)**	**1.89 (0.031)**
Serum Leptin	2.45 **(0.005)**	**1.42 (0.008)**	0.82 (0.153)	0.03 (0.899)
BMI	0.9 **(0.023)**	0.04 (0.603)	0.3 (0.649)	-0.2 (0.372)

IV. DISCUSSION

Autoimmune thyroid diseases (AITD) are the most prevalent organ-specific autoimmune diseases (ADs) and affect 2 - 5% of the population (7). The etiology of these diseases is not fully understood, but numerous causes have been proposed, including genetic predisposition, drugs, stress, pregnancy, infections, radiation exposure, and smoking (8). Recently, leptin has been implicated as a possible etiologic factor behind autoimmune thyroid disease.

Leptin, a hormone that is released in response to the quantity of fat tissue in the body, functions by inhibiting hunger signals in the hypothalamus. Furthermore, leptin has been linked to stimulation of the hypothalamic-pituitary axis, which in turn elevates TSH and thyroid hormones, to increase energy expenditure by the body (9).

Leptin is believed to have a role in the growth of natural T cells and encourages the development of T-helper 1 (Th1) cells, which produce pro-inflammatory cytokines including interferon gamma (IFNγ) and IL-2. Leptin also inhibits the synthesis of Th2 cytokines IL-4 and IL-10. Moreover, it hinders the growth and spread of T-regulatory cells (Treg),

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which are recognized as crucial agents in maintaining immunological tolerance (10-13). Several studies have shown that elevated levels of leptin may be linked to autoimmunity by influencing the T helper balance towards a Th1 phenotype and inhibiting the activity of T-regulatory (Treg) cells, leading to increased production of TPO-Ab (14).

In the present study, serum leptin was significantly linked with anti-TPO antibodies in both obese and non-obese males. Further research is needed to determine why this correlation was exclusively detected in males; however, possible explanations include higher estrogen levels in females, which is known to exert inhibitory effect on leptin (15).

MacIver et al. conducted a study investigating the relationship between serum leptin and anti-TPO antibodies. Their analysis included 2902 male and 3280 female participants. Interestingly, the study reported a positive correlation between leptin and anti-TPO antibodies specifically in non-obese males. This association was not detected among females and non-obese males (16). In 2010, Marzullo et al. conducted a study to investigate the concentrations of anti-TPO antibodies and leptin in 165 obese persons with a BMI of 35 or higher, as well as in 118 lean individuals with a BMI of 25 or lower. This study discovered a correlation between leptin and anti-TPO, irrespective of body mass index (BMI). Unfortunately, this study did not distinguish between male and female individuals for the purpose of analysis (17). A 2021 study conducted by Tomov et al. evaluated 95 patients with autoimmune hypothyroidism and 21 healthy controls and reported that the group of patients with hypothyroidism had significantly elevated levels of leptin compared to the healthy control group (18). According to the results of the research by Shebini et al., there was a significant risk of thyroid dysfunction in obese people, which show that obesity likely affects autoimmune thyroiditis via the activity of adipocyte proinflammatory leptin (19).

V. CONCLUSION

This study has found that serum leptin is associated with increased levels of anti-TPO antibodies among obese and non-obese euthyroid males, which may reflect an underlying potential to develop subsequent autoimmune hypothyroidism.

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