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Role of TGFβ1 in Modulating Lipid Profile in Patients with Hashimoto's Thyroiditis

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ABSTRACT

Background:*Hashimoto's thyroiditis, an autoimmune condition primarily affecting the thyroid gland, leads to persistent inflammation and impaired thyroid function. Conversely, transforming growth factor beta-1 (TGF-β1) is a crucial protein that regulates various cellular processes, including immune responses and tissue remodeling. Present research aimed to explore the correlation between TGFβ-1 levels in Hashimoto's Thyroiditis (HT) patients and their lipid profile levels, to achieve this.* ***Method:*** *A case-control study involved 90 female participants aged 20-53 years, comprising diagnosed Hashimoto's thyroiditis patients, and an equal number of age and gender-matched healthy volunteers. The levels of TGF–β1, T3, T4, TSH, fT3, fT4, Anti TPO, Anti-TG, were investigated using the ELISA method. Moreover, the study groups' analysis included measuring, cholesterol, TG, LDL, HDL, and vLDL using specific commercial kits.* ***Result:*** *The findings revealed a highly significant variation in TGFβ1 levels between the HT patients group and healthy group, highlighting the potential role of TGF-β1 in Hashimoto's thyroiditis.emia as compared with healthy group.*

Keywords: TGFβ1, Hashimoto's Thyroiditis, Lipid profile .

Article Information

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INTRODUCTION

Hashimoto's thyroiditis (HT), also referred to as autoimmune thyroiditis, stands as the most prevalent organ-specific autoimmune disease affecting the thyroid (Hiromatsu, Satoh *et al.* 2013). While some patients maintain a euthyroid state for prolonged periods, others experience hypothyroidism at the disease's onset. The primary immune mechanism in HT involves the infiltration of cytotoxic lymphocytes into the thyroid gland, resulting in the death of thyroid cells and clinically presenting as various forms of thyroid dysfunction. Additionally, HT prevails as the leading cause of goitrous hypothyroidism in regions with sufficient iodine supplies.

The development of Hashimoto's thyroiditis (HT) is influenced by a combination of genetic predisposition and dysregulation of immune mechanisms. Autoimmune destruction of the thyroid gland is facilitated by immune cell reactivity, guided by regulatory and effector cytokines (Ouyang, Filvaroff *et al.* 2009, Syed 2016). Although the precise role of cytokines in HT development remains uncertain and inconclusive (Morikawa, Derynck *et al.* 2016), there is substantial scientific evidence supporting the significant role of TGFβ1 in the pathophysiology of autoimmune thyroid diseases (Kardalas, Maraka *et al.* 2021). TGFβ1's impact on the severity and progression of autoimmune thyroid disease is condition-specific, influenced by factors like the rate of TGFβ1 synthesis, the specific genotypic and phenotypic features of the autoimmune thyroid disease, and the activation of distinct signaling pathways (Sacristán-Gómez, Serrano-Somavilla *et al.* 2023). Moreover, the development of Hashimoto's thyroiditis (HT) has been associated with

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various autoimmune disorders, such as primary adrenal hypo function, Gravis disease, rheumatoid arthritis, pernicious anemia, gluten enteropathy, lupus disease, and type 1 diabetes (Delamater, de Wit *et al.* 2018). Many pathogeneses are attributed to the interaction of hereditary and environmental factors (Ye, Leung *et al.* 2017).

One of the factors potentially influencing HT development is obesity. Obesity impacts thyroid function by disrupting the pituitary-hypothalamic portion and adipose tissue, and it activates thyroid autoimmunity through leptin (Mavromati and Jornayvaz 2021). Leptin, a hormone released by adipose tissue, plays a crucial role in chronic inflammation, leading to alterations in thyroid gland shape and hormone output. Research has indicated that obesity increases susceptibility to thyroid autoimmune disease progression, with leptin being a key player in this mechanism (Versini, Jeandel *et al.* 2014). As a low-grade chronic inflammatory disease, obesity triggers the release of cytokines from adipose tissue and other inflammatory cells, including Interleukin-1 (IL-1), Interleukin-6 (IL-6), and Tumor Necrosis Factor Alpha (TNF-α), which suppress the expression of mRNA and sodium-iodide (Na/I) symporter. Additionally, these cytokines can induce vasodilation, affecting the permeability of blood vessels in the thyroid gland and causing functional and morphological changes in the thyroid (Fontenelle, Feitosa *et al.* 2016).

In conclusion, Hashimoto's thyroiditis (HT) remains a complex disease with a multifaceted etiology involving genetic, immunological, and environmental factors. Although the role of cytokines, including TGFβ1, in HT development is not fully understood, their significance in the pathogenesis and severity of autoimmune thyroid diseases is widely acknowledged (Kardalas, Maraka *et al.* 2021, Sacristán-Gómez, Serrano-Somavilla *et al.* 2023). Furthermore, obesity's impact on thyroid function and autoimmune processes presents an interesting avenue for future research (Mavromati and Jornayvaz 2021).

MATERIALS AND METHODS

Study Design A comprehensive case-control research was undertaken, involving 90 female participants between the ages of 20 and 53. This diverse group was comprised of diagnosed Hashimoto's thyroiditis patients and an equal number of healthy volunteers, carefully matched for age and gender. Rigorous inclusion and exclusion criteria were applied during subject selection, aiming to create a homogeneous group of patients with Hashimoto's thyroiditis.

Methods In this study, a venous whole blood sample of five milliliters was obtained from each participant and allowed to clot at room temperature. Subsequently, the samples were centrifuged at 5000xg for 5 minutes. The resulting sera were collected and stored at -18ºC until they were ready to be used for measuring, the levels of TGF–β1, T3, T4, TSH, fT3, fT4, Anti TPO, Anti-TG, were investigated using a Sandwich ELISA method from Sunlong company, Chain. Moreover, the study groups' analysis included measuring, cholesterol, TG, LDL, HDL, and vLDL using specific commercial kits.

Statically analysis

The statistical analysis of the data obtained in this study was performed using the 26th edition of the Statistical Package for the Social Sciences (SPSS). The results were expressed in terms of Mean ± Standard Deviation (Mean ± S.D.). For comparing the results of the two groups included in the study, the Student's t-test was utilized. To assess the relationships among the measurable factors in the study, Pearson's correlation analysis was applied. A p-value less than 0.05 ($p < 0.05$) was considered statistically significant, indicating the presence of significant associations between the variables.

RESULT AND DISCUSSION

The primary aim of this study was to investigate the TGF–β1 levels and lipid profile and their potential role as a susceptibility factor in Hashimoto's thyroiditis (HT). Additionally, the research sought to explore the relationships between metabolic characteristics and various biochemical parameters associated with HT in Iraqi individuals. The parameters under

investigation were categorized into three groups: demographic factors (including age, body mass index [BMI], systolic and diastolic blood pressure), thyroid function tests (such as T3, T4, TSH, free T3 [fT3], free T4 [fT4], anti-thyroid peroxidase [anti-TPO] antibodies, and anti-thyroglobulin [anti-TG] antibodies), and metabolic characteristics (comprising glucose, insulin, Homa IR, triglycerides [TG], cholesterol, LDL, VLDL, and HDL). Regarding the statistical analysis, no significant differences in age were observed between the HT patients and the corresponding control group (p=0.435). However, there was a highly significant increase in BMI among the HT patients compared to the healthy control subjects (p=0.0001). Moreover, both systolic and diastolic blood pressure measurements showed a significant increase in HT patients when compared to the healthy control subjects (p=0.0001). These findings suggest that individuals with HT tend to have higher BMI and blood pressure levels, potentially indicating associations between HT and these parameters (Yang, Xia *et al*. 2022). The detailed results can be found in Table 1.

Table 1: Demographic Characteristics of Study Group

Parameters	Healthy women Mean ± SD	Patient women Mean ± SD	P Value
Age (year)	37.571 ± 11.496	42.340 ± 10.231	0.435
BMI (Kg/m^2)	23.602 ± 2.859	32.303 ± 5.604	0.000
WHR	0.776 ± 0.059	0.960 ± 0.105	0.005
Systolic blood pressure (mmHg)	115.500 ± 8.149	146.000 ± 18.516	0.000
Diastolic blood pressure (mmHg)	73.625 ± 7.925	87.700 ± 11.438	0.000

*P value < 0.05 was significant, P value >0.05 was insignificant

Table 2: Levels of (Mean ± SD) of Biochemical Tests and TGFβ1 in Sera of Study Group.

Markers	Control No. Mean ± SD	Patients No. Mean ±SD	P Value
T3 nmol/L	2.243 ± 0.955	0.893 ± 0.193	0.004
T4 nmol/L	121.679 ± 16.910	51.593 ± 9.941	0.000
TSH µmol/ml	1.714 ± 0.860	10.151 ± 11.213	0.009
fT3 pmol/L	3.132 ± 0.444	1.684 ± 0.259	0.030
fT4 pmol/L	1.006 ± 0.230	0.445 ± 0.139	0.0001
Anti-TG IU/ml	138.603 ± 58.246	422.444 ± 115.061	0.0001
Anti-TPO IU/ml	225.647 ± 67.019	593.234 ± 192.442	0.001
TGFβ1	13.027 ± 3.812	21.459 ± 5.975	0.02

P value < 0.05 was significant, P value >0.05 was insignificant

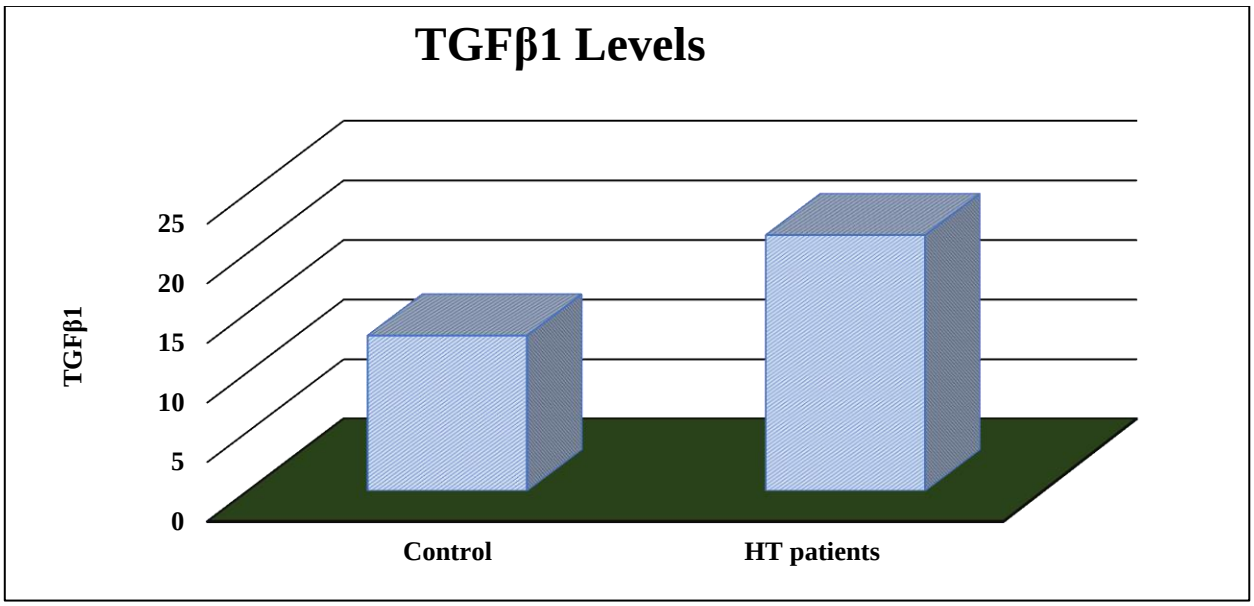

Table 3: Correlation of TGF-β1 with metabolic Characteristics.

Variables	Pearson Correlation ®	Significant
Blood Glucose (mmol/L)	0.795**	0.0001
Insulin (pmol/L)	0.321*	0.023
Homa IR	0.327*	0.020
Cholesterol (mg/dL)	0.318*	0.028
Triglyceride (mg/dL)	0.397*	0.011
HDL-C (mg/dL)	-0.177	0.218
LDL-C (mg/dL)	0.916**	0.0001

P value < 0.02 was significant, P value >0.02 was no significant.

DISCUSSION

The study created a set of observations, including a significant increase in TSH, anti-TPO, and anti-TG levels in HT patients when compared with healthy Control and reported a significant decrease in the levels of T3, T4, fT3 and fT4 in the sera of HT patients group when compared with healthy Control. Also, a significantly higher mean serum level of TGF-β1 was observed in HT patients compared to the controls in this study. One-way analysis of variance 22 was used to compare tow means of TGFβ1 levels. A p-value of ≤ 0.02 was considered statistically significant. Hardy–Weinberg equilibrium (HWE) was tested for patients, controls, and combined groups using the Chi-square test. P-values <0.02 were determined as significant. A significantly higher mean serum level of TGF-β1 was observed in HT patients compared to the controls in this study. Various studies have identified a cascade of related pathways that are activated by TGFβ1. For instance, one study demonstrated a substantial increase in Glucose transporter 1 (GLUT1) expression in fibrotic liver tissues of both humans and mice, which aligns with the research results of Wan et al. (Wan, Xia *et al.* 2019). GLUT1, a significant glucose transporter, is widely

expressed in mammals and its expression is regulated by changes in metabolic status and oxidative stress. It is also considered an essential marker for liver carcinogenesis and metabolic liver diseases (Cho, Moon *et al.* 2020). Elevated TGF-β1 levels lead to increased gene expression of key enzymes, including GLUT1, in the glycolytic pathway. This, in turn, enhances glucose consumption, intracellular lactate production, and glycolytic flux by hepatic stellate cells (HSCs). The study's results are consistent with previous researches exploring the mechanism of metabolic reprogramming in pulmonary fibrotic fibroblasts, indicating that TGF-β1 induces aerobic glycolysis and drives metabolic reprogramming during stromal cell transdifferentiating (Xie, Tan *et al.* 2015). The upregulation of GLUT1 expression contributes to an elevated glycolytic rate, increased lactic acid production, and enhanced glucose-dependent metabolic pathways within the cells. Conversely, the addition of a TGF-β1 receptor inhibitor leads to a significant decrease in GLUT1 expression, highlighting the association between GLUT1 expression and TGF-β1 signaling (Roh, Yoon *et al.* 2017, Zhou, Cheng *et al.* 2021). TGFβ1 levels have been assessed in diabetes through animal models and human studies, revealing that acute and chronic hyperglycemia induces TGFβ1 expression. Research on rats induced with diabetes showed higher TGFβ1 expression during the initial stages of hyperglycemia (Bilen, Calik *et al.* 2021). Another study demonstrated elevated TGFβ1 levels in type 2 diabetic individuals compared with controls, and these levels correlated with metabolic control. TGF-β1 has been identified as a key cytokine in obesity and insulin resistance, playing a pivotal role in the development of diabetic nephropathy due to its fibro genic properties (Demir, Nawroth *et al.* 2021, Tang, Liu et al. 2022). Increased circulating TGF-β levels have been documented in type 2 diabetes mellitus and hypertension, though not in insulin resistance, suggesting relevant pathophysiological implications (Gómez-Bernal, Quevedo-Abeledo *et al.* 2023).

Transforming growth factor-beta (TGF-β), a multifunctional cytokine, plays a role in the regulation of cellular growth and is produced by various tissues, including adipose tissue (Li, Fan *et al.* 2022, Ren, Li *et al.* 2022). The correlations between TGF-β and obesity, however, are contradictory. Some studies propose that the reduction of TGF-β1, an ant lipogenesis factor, plays a crucial role in obesity pathogenesis (Mărginean, Mărginean *et al.* 2016, Lebda, El Agaty *et al.* 2022). Conversely, other studies suggest that the level of TGF-β1 in adipose tissue increases in the presence of insulin (Pan 2020). Similarly, Barretto et al. found lower levels of TGF-β in obese children without any correlation with lipid or insulin resistance (Barretto, Boa-Sorte *et al.* 2020), while another study indicated an indirect proportional relationship between serum TGF-β levels, BMI, and waist circumference (Añón-Hidalgo, Catalán *et al.* 2019).

Correlation of TGF-β1 with metabolic Characteristics

Some studies have suggested that TGFβ1 is involved in the pathogenesis of autoimmune thyroid diseases, including Hashimoto's thyroiditis. TGFβ1 is known to modulate the immune response by promoting regulatory T-cell development and inhibiting pro-inflammatory T-cell responses. Dysregulation of TGFβ1 signaling may contribute to the breakdown of self-tolerance and the development of autoimmune condition (Lopes, Lens *et al.* 2022, Wan and Flavell 2008, Ke, Greenawalt *et al.* 2023). Regarding lipid profiles, hypothyroidism, which can result from Hashimoto's thyroiditis, is known to be associated with alterations in lipid metabolism. Hypothyroid patients often experience increased levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides, while high-density lipoprotein cholesterol (HDL-C) levels may decrease. These lipid profile changes are typically related to the lack of thyroid hormones rather than direct actions of TGFβ1 (Ejaz, Kumar *et al.* 2021, Nicholls, Lincoff *et al.* 2018, Leemans, Couderq *et al.* 2019).

It's important to note that the relationship between TGFβ1 and lipid profiles in patients with Hashimoto's thyroiditis might not have been extensively studied or well-established up

until last update. Research in the field of autoimmune thyroid diseases and lipid metabolism is ongoing, and new findings may have emerged beyond knowledge cutoff.

CONCLUSIONS

In conclusion, TGFβ1 is known to play a crucial role in immune regulation and has been implicated in the pathogenesis of autoimmune diseases, its direct influence on lipid metabolism is not thoroughly understood. The alterations in lipid profiles commonly observed in hypothyroidism, which can be a consequence of Hashimoto's thyroiditis, are primarily due to the lack of thyroid hormones and the resulting impact on lipid metabolism. Hypothyroidism often leads to increased levels of total cholesterol, LDL cholesterol, and triglycerides, along with decreased levels of HDL cholesterol. While TGFβ1 may be involved in the immune dysregulation seen in autoimmune thyroid diseases, its specific role in modulating lipid profiles remains uncertain. It is possible that TGFβ1, through its immune-regulatory effects, could indirectly influence lipid metabolism in some manner, but the mechanisms are not fully elucidated.

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