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An Association of IL-6 and TNF Alpha Levels with Hashimoto Thyroiditis in Najaf Province/ Iraq

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Abstract

Background: Cytokines are important in autoimmune thyroid disease. Interleukins regulate immunity. Lack impairs immunity or causes autoimmune disorders. This study is aiming to investigate whether inflammatory cytokines (IL-6, TNF-α) levels in the blood correlate with Hashimoto thyroiditis.

Methods: In this study, we used an ELISA device to determine the levels of interleukins in the serum of 60 patients with Hashimoto's disease and 60 people as a control group. We diagnosed the patients based on their clinical condition and also examined their thyroid function and antibodies.

Results: According to the research findings, individuals with Hashimoto's thyroiditis had considerably higher levels of IL6 and TNF-α ($P < 0.001$) and could be used to tell the difference between HT patients and healthy people in the AUC analysis. A positive correlation between (antiTPO, antiTG, TSH) levels and (IL6, TNF-α) levels has also been demonstrated, which may indicate that these changes play a role in the development of HT.

Conclusions: This study clearly established that the levels of IL6, TNF alpha is strongly related with the risk of HT in individuals in Najaf Province, Iraq.

Key words: autoimmune thyroid disease; AITD; Hashimoto's thyroiditis; HT; interleukins; thyroid antibodies

Introduction: Hashimoto thyroiditis (HT), now considered the most prevalent autoimmune condition [1] In regions of the globe where iodine levels are sufficient, it is the primary cause of

hypothyroidism[2]. The precise processes responsible for the pathophysiology of HT remain incompletely elucidated, which is believed to result from a mix of genetic predisposition and environmental variables. This leads to a breakdown of tolerance in the immune system, leading to the autoimmune destruction of thyroid tissue and the onset of the illness[3]. There is an upward trend in the incidence of HT [4]. Clinical symptoms and biochemical markers (the presence of thyroid autoantibodies in the blood) are used to diagnose HT. Anti-thyroglobulin antibodies (TG Ab) and anti-thyroid peroxidase antibodies (TPOAb) are hallmarks of HT [5]. Females of any age are more likely to be affected by Hashimoto thyroiditis, but the condition is most common in middle-aged women [6]. From euthyroid to subclinical to obvious hypothyroidism, HT is linked to a spectrum of thyroid functioning states [7]. Thyrotropin (TSH) elevation and thyroid hormone deficiency characterise the overt hypothyroidism [8]. Hypothyroidism's complications include infertility, miscarriage, impaired fertility, mental retardation, cardiac ailments, and psychological issues, among others, if the condition is not addressed [9].

Cytokines, such TNF-alpha and IL-6, are indicators of hypothyroidism because of their important role in regulating the immune response in autoimmune disorders [10]. Interleukin-6 (IL-6) is a pro-inflammatory cytokine that assumes pivotal functions in the process of inflammation. It is a prominent contributor to the pathogenesis of chronic inflammatory diseases, autoimmune disorders, cancer, and cytokine storms [11]. Interleukin-6 (IL-6) is an important factor in the onset and progression of certain autoimmune diseases, as shown by elevated levels of this protein in these conditions [12]. IL-6 is a pleiotropic cytokine that a variety of cell types produce. Hypothyroidism has been linked to inflammatory mediators such as interleukin 6 [13]. An essential member of the TNF family, TNF-α serves as a mediator with several functions. Monocytes, macrophages, and T-cells are the primary producers of it [14].

Methods and Materials: The research was planned by recruited 60 patients with Hashimoto disorders and 60 healthy controls to evaluate association of IL-6 ,TNF-α levels with HT. They visited the endocrinologist consultant clinic at the Najaf Diabetes and Endocrinology Centre at Sadr City Medical Hospital from December 12, 2023 to March 6, 2024. The identification of HT in patients was based on their clinical examination and confirmation by biochemical tests. The name, age, sex and BMI, were gathered via a direct questionnaire and the patient's medical records. . The University of Al-Qadisiyah's College of Medicine gave this project ethical permission. A control group has been chosen; they exhibit neither hyperthyroidism nor hypothyroidism-related symptoms. Thyroid function tests revealed that they also had normal thyroid function.

Study Participants :Eligible participants were adult patients of the selected study. The sample size was determined to ensure sufficient statistical power. Inclusion criteria -age> 18 years, every one of these individuals had every clinical indication and symptom of Hashimoto's thyroiditis, in addition they had autoantibodies to thyroid antigen in the blood such as TPO and TG antigens. As well as high TSH value and low T3 and T4 levels. Exclusion criteria – age> 18-yeasr, Smoking and alcohol.

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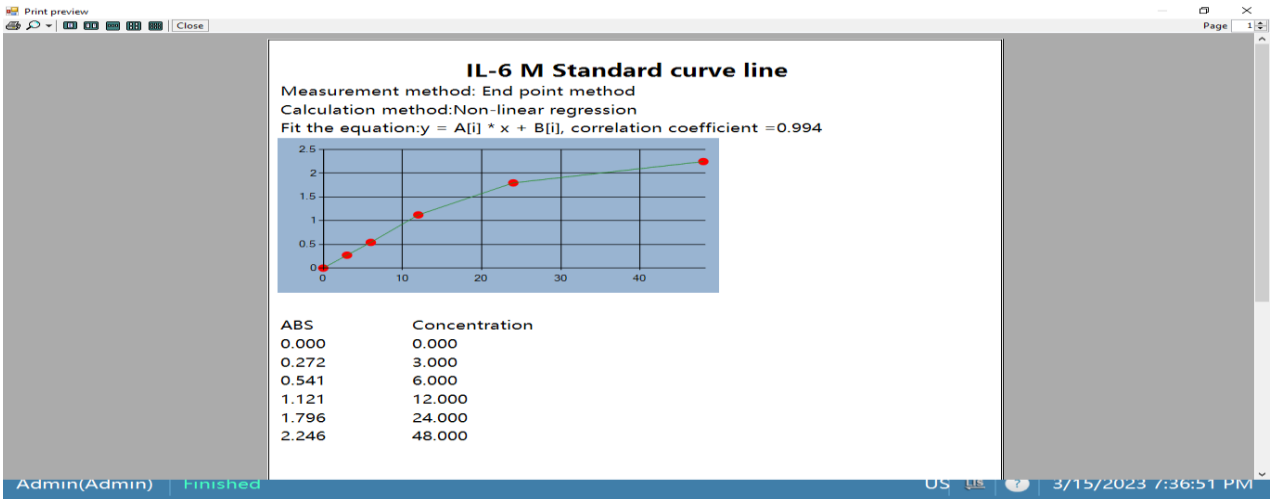
Blood sample collection : Using a disposable syringe, 4 mL of venous blood was drawn into a gel tube under aseptic conditions. After allowing the blood to clot, the serum was extracted using centrifugation for five minutes at 3000 rpm. The mixture was separated into into tiny Eppendorf tubes and kept at ¯20°C in order to evaluate thyroid function using the mini VIDAs device, conduct immunological tests to measure the concentrations of TG and TPO Ab, and then use the ELISA method to measure the levels of IL-6 and TNF-α levels in both HT patients and control group samples.

In the current study The Sun long Biotech Co. kit has been used that uses a single-step, double-antibody sandwich enzyme-linked immunosorbent assay method to measure Interleukin-6, TNF-α in human serum. The interleukins concentration in the samples is calculated by comparing their O.D. to a standard curve after a wavelength of 450 nm is used to spectrophotometrically measure the colour change to determine the Interleukin 6, TNF-α concentration in the samples. As shown in figure-1



Figure(1):IL-6 standard curve line

Ethical Certification

Every relevant guideline and rule pertaining to ethical conduct in clinical research was followed, and the study was carried out strictly in compliance with the Declaration of Helsinki's tenets. Preliminary authorization was granted to the study and all individuals gave informed consent before to participation. Additionally, the Scientific Research Methodology Ethics Committee of Al-Qadisiyah University's Medicine College, Microbiology Branch approved the study's design. by the document numbered 30/5121 in the date of December 20, 2023.

The statistical analysis: was carried out using SPSS statistics version 25.0. The biomarker findings and patient characteristics are provided as mean ±SD. The p value and OD ration at 95% confidence interval were found using the two-sample t-test and the Chi-square test. Each and every result was given as a percentage or as mean±SD. Significant results were defined as P values <0.05.

Results : The result of this study was based on the average age and gender of Hashimoto's thyroiditis patients and healthy people. It was not significant. As for the body mass index (BMI), the current results showed that there were highly statistically significant differences between patients with HT and control people according to BMI. Results of the analysis of thyroid function blood levels of T3 and T4 in patients are found to be considerably lower ($p < 0.001$) than those in the serum of healthy controls. However, the patient's serum TSH level is considerably greater ($p<0.01$) than the control group's serum TSH level. The following are the results of the anti-thyroid antibody analysis for patients with thyroiditis caused by Hashimoto's and healthy controls: The mean levels of anti-thyroid peroxidase (Anti-TPO) in the sick group were significantly higher ($P < 0.001$) than in the healthy control group, which were 802.36 ± 73.51 and 133.43 ± 6.56, respectively. Additionally, the sick group's mean levels of anti-thyroglobulin (Anti-TG) were greater at 657.85 ± 81.10 than those of the healthy control group at 116.9 ± 11.425. This difference was very significant ($P < 0.001$). Table 1. These results are consistent with the earlier publication, which said that increased serum TSH and low levels of T3 and T4 as well as raised levels of anti-TPO and anti-TG are biochemical and immunological markers of HT, respectively. [15].

Table (1): Antibody means and standard errors for Hashimoto's thyroiditis patients and healthy people

Characters	Patients with HT	Healthy Subjects	P .value
TPOAb	802.36 ± 73.51	133.43 ± 6.56	≤ 0.001
TGAb	657.85 ± 81.10	116.9 ± 11.425	≤ 0.001

Proinflamatory cytokines (IL6 and TNF alpha) Analysis Results

Table 2 displays a comparison of the blood levels of TNF-α and IL-6 between the patient group and the control group. The patients' group had considerably greater mean serum IL6 than the control group ($p < 0.001$). The patients' group had a considerably greater mean serum TNF-α than the control group ($p = < 0.001$).

Table(2): Comparison of the patients' group and the control group's serum concentrations of IL-6 and TNF-α

Characteristic	Patients Group *N* = 60	Control Group *N* = 60	*P*
Serum IL-6			

Mean ±SD	**9.85 ± 3.25**	**5.91 ± 2.81**	**< 0.001 † HS**
Range	**1.20 – 23.77**	**0.12-13.60**	
Serum TNF-A			
Mean ±SD	**28.28± 3.13**	**19.08 ± 2.04**	**< 0.001 † HS**
Range	**1.02 – 58.34**	**1.30-29.89**	

HS stands for highly significant at P < 0.001, n for number of instances, SD for standard error, and † for independent samples t-test.

Evaluation of IL6 levels : To assess the effectiveness of IL-6 levels in diagnosing Hashimoto's thyroiditis (HT), a receiver operating characteristic (ROC) analysis was performed. The results, detailed in Table 3 and Figure 1, suggest that IL-6 may be a promising diagnostic marker for HT.

Table (3): Receiver operating characteristic curve of IL-6 (> 6.91-fold) in HT disease

IL-6 Levels	**HT Patients** ***N*** **= 60**	**Healthy Control** ***N*** **= 60**
> 6.91	**42**	**18**
< 6.91	**18**	**42**
Sensitivity %	**70.0 %**	
Specificity %	**70.0 %**	
PPV %	**70.0 %**	
NPV %	**70.0%**	
AUC (95% CI)	**0.701 (0.597- 0.800)**	

AUC is for area under the curve, while CI stands for confidence interval.

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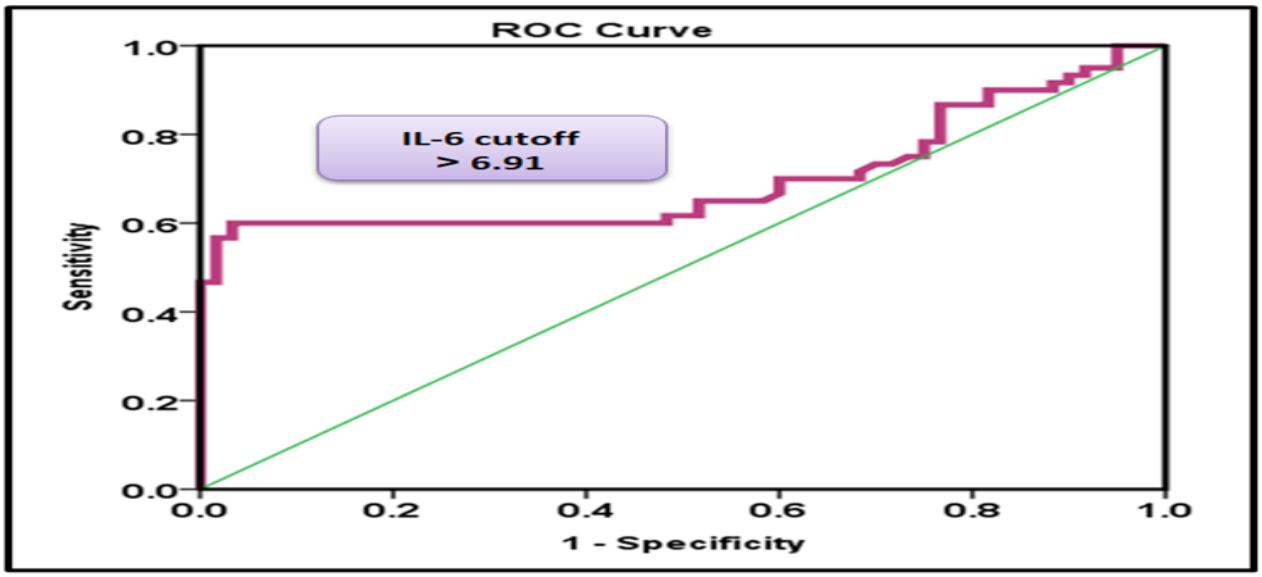

Figure (2): Examining the ROC curve for IL-6

Evaluation of TNF-α levels.

The diagnostic accuracy of employing TNF-α concentrations to differentiate patients with HT from healthy control participants was investigated using receiver operating characteristic (ROC) analysis; the findings are shown in table (4) and figure (2). Based on the current findings, TNF-α is regarded as a useful diagnostic marker.

Table (4): Receiver operating characteristic curve of TNF-α (> 22.35-fold) in HT disease

TNF-A Levels	HT Patients *N* = 60	Healthy Control *N* = 60
> 22.35	43	17
< 22.35	17	43
Sensitivity %	71.7 %	
Specificity %	71.7 %	
PPV %	71.7 %	
NPV %	71.7%	
AUC (95% CI)	0.718 (0.617- 0.820)	

AUC is for area under the curve, while CI stands for confidence interval.

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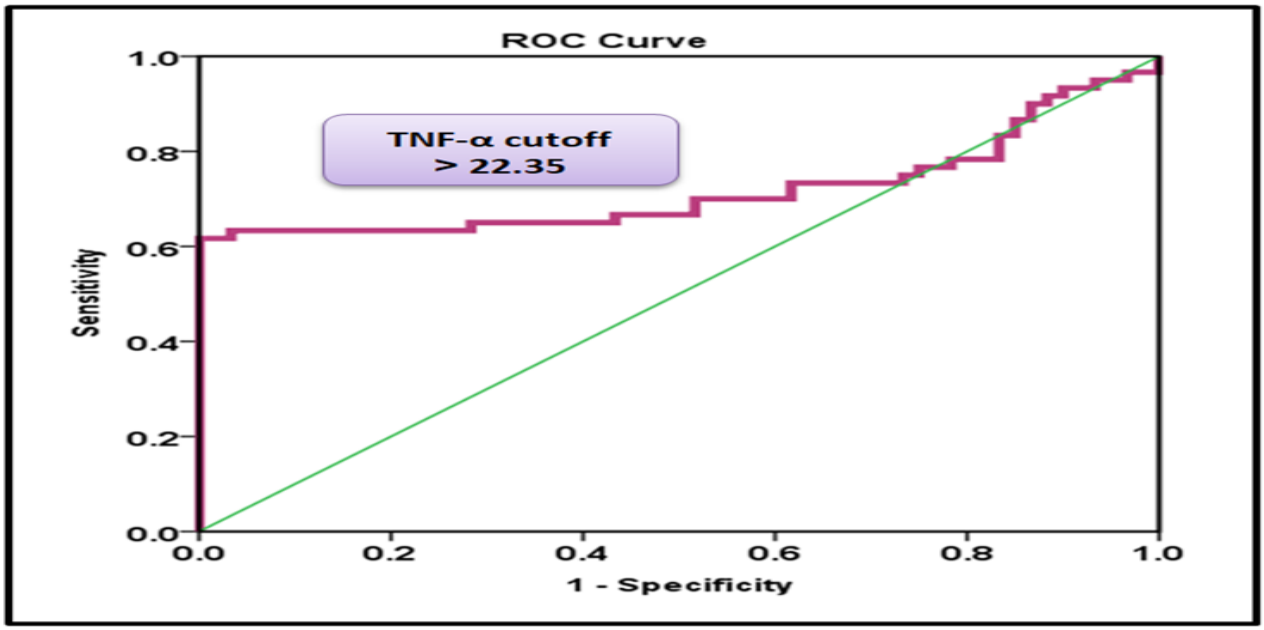

Figure (3): Analysis of the TNF-α ROC curve

Logistic regression correlations between IL6 and TNF-α. : The Logistic regression model show that the correlation between serum IL-6 in which have directly correlate with TNF-α among HT patients, as shown in figure (3), this finding may indicate that the HT condition increases IL-6 production in connection to TNF-α expression.

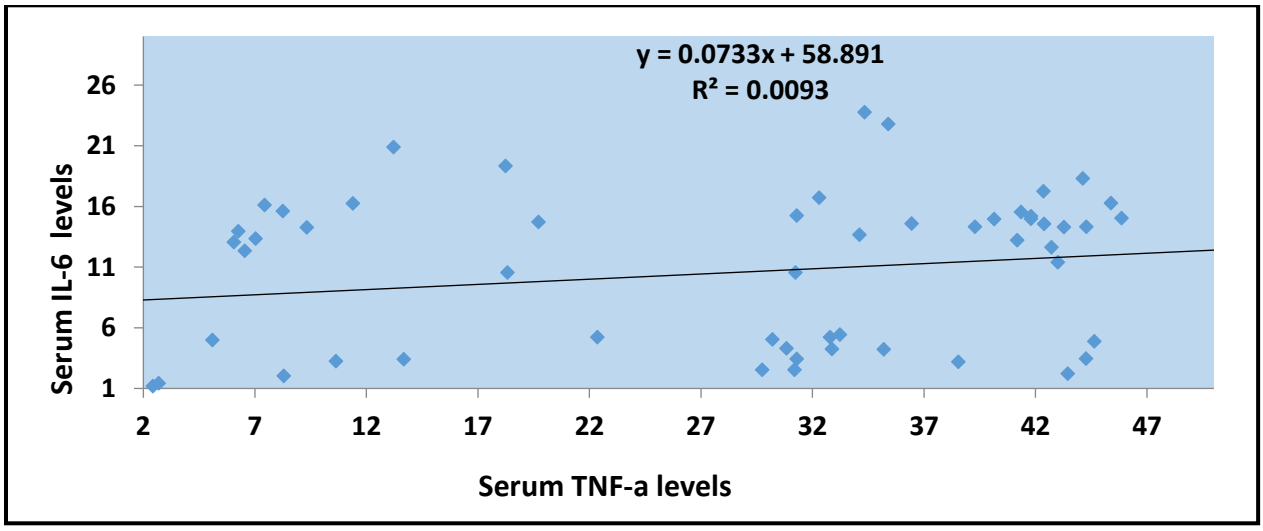

Figure (4): The Logistic scatter IL-6 and TNF among patients with HT.

Correlation between ILL6, TNF-α and other different characteristics.

The correlations between ILL6, TNF-α and other characteristics in patients with HT were shown in tables 5. The present results show non-significant correlation between immunological parameters and all characteristics.

Table (5): Correlation between immunological parameters and other different characteristics

Parameters	*IL-6*		*TNF-A*	
	R	***P***	***R***	***P***
TSH	**0.171**	**0.292**	**0.216**	**0.098**
T3	**-0.178**	**0.172**	**-0.112**	**0.394**
T4	**-0.183**	**0.162**	**-0.103**	**0.491**
Anti-TPO	**0.149**	**0.257**	**0.174**	**0.183**
Anti-TG	**0.119**	**0.363**	**0.192**	**0.142**

r: Correlation Coefficient.

Discussion : In the present investigation, the mean levels of IL-6 were 5.91 ± 2.81 and 9.85 ± 3.25 in the healthy control group and patients with HT, respectively; the mean level was significantly greater in the HT group than in the healthy control group (P<0.001).

According to this research, HT patients' IL-6 levels were obviously greater than the healthy control group. This aligns with previous findings indicating significantly elevated IL-6 concentrations in HT patients [16].

It has been shown that the early phases of T-cell activation and the development of certain autoantibodies, including TPO, are significantly influenced by intrathyroidal IL-6 production [17]. The IL-6 promotes the production of inflammatory cytokines such as TNF-α and the differentiation of Th17 cells [18].

A research found that interleukin-6, or IL-6, has a significant role in human Th17 differentiation. It is possible that HT patients' basal IL-6 production is greater than that of healthy controls. Reprogramming Tregs into Th17s is also possible via IL-6-dependent signaling. This improves Treg-to-Th17 cell conversion and decreases FOXP3 expression regulation [19]. In order to facilitate the onset of autoimmune illness, Th17 cells release a specific mix of cytokines, including as IL-17A, IL-17F, IL-21, and IL-22, which in turn activate and attract macrophages and neutrophils [20]. The present research found that the mean levels of TNF-α were 28.28± 9.13 in patients with HT and 19.08± 6.04 in healthy control subjects. Statistically, the mean level was significantly higher in the HT group compared to the healthy control group (P< 0.001).

The outcome of this study is comparable to previous research that indicated a significantly higher level of TNF-α in HT patients when contrasted with the control group [21]. According to research, TNF-α is expected to rise during active inflammation because it controls the production of other inflammatory cytokines [22].

In contrast to the present findings, patients with hypothyroidism had decreased levels of IL-6 and TNF-α [23]. The patients' use of L-thyroxine therapy may have contributed to the suppression of T helper type 1 cells, which inhibits the inflammatory process, and that could be an interpretation of the reverse-mentioned results [24]. The current results in this study demonstrated a positive relationship between IL-6 with the immune parameters TSH, antiTPO, and antiTg, but it is not significant, and this is consistent with the results of the previous studies [25]. One mechanism by which adipocytes secrete IL-6 is via the action of thyroid stimulating hormone [26]. This research's findings are consistent with another investigation that established a negative correlation between serum total T3 and IL-6 as well as total T4 and IL-6 [27]. One explanation for this condition is that IL-6 has an inhibitory effect on T4 deiodination. Inhibition of this enzyme may result in decreased conversion of T4 to T3[28]. In a second interpretation, T3 prevents the activation of the cytokine's primary downstream targets, which reduces IL-6 signaling[29].

Also, the test results were a positive correlation between TNF-α and TSH, antiTPO and antiTg but not significant, and a negative correlation with T3 and T4.

The findings of this investigation align with the findings of other researchers, demonstrating a favourable correlation between TNF-α and ATPO in cases of chronic autoimmune thyroid illness (cAIT) [10]. According to Polish researchers, increased cytokine concentrations can be a sign that Hashimoto's illness is mostly influenced by the hereditary elements that produce them [31].

Conclusion: This study suggests that both cytokines (IL6 and TNF-α) contribute to the pathogenesis of HT, and there was a statistically significant correlation between them and HT. These cytokines may be used as diagnostic markers, depending on the ROC curve.

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