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# EXPLORING THE INTERPLAY BETWEEN TUMOR NECROSIS FACTOR-ALPHA AND INTERLEUKIN-17 IN THE AUTOIMMUNE THYROID DISEASE

**Mohammad Abdulazeez Ali[1], Shaymaa Z. ALrumaidh[2] , Zahraa Mohammed Abdulazeez[3]**

[1]Collage of Health and Medical Technique, Sawa Private University, Iraq.
[2]Biology department/ collage of Science, university of Thi-Qar
[3] Collage of Dentistry, University of AL Muthanna, Iraq
Corresponding Author Email Address:
mohammed.ali@sawauniversity.edu.iq
shymaa1980@utq.edu.iq
zahraa.abd2207p@covm.uobaghdad.edu.iq

**Abstract**

The purpose of this study was to investigate the association between autoimmune thyroid disorders and the interaction between the inflammatory factors interleukin-17 (IL-17) and tumor necrosis factor-alpha (TNF-α). Between May 2023 and October 2023, the study was carried out, with two primary groups involved :Group for thyroid diseases: 95 people with thyroid problems that have been clinically verified (Hashimotos 49 patients and gravies 46 patients) .46 participants who seemed healthy made up the control group .All participants had venous blood samples taken, and thyroid hormone levels (TSH, T4, and T3) as well as cytokine levels (TNF-α and IL-17) were measured .The findings demonstrated a statistically significant correlation between autoimmune thyroid disorders and TNF-α and IL-17 levels. Notably, the thyroid had much higher quantities of these cytokinesillness sick group in contrast to the control cohort .These results provide credence to the possibility that TNF-α and IL-17 contribute to inflammation aggravation and the development of autoimmune thyroid diseases. The findings highlight the need for more investigation to fully comprehend the underlying processes driving this association. The work adds to our understanding of the intricate etiology and pathophysiology of autoimmune thyroid diseases by shedding light on the interactions between pro-inflammatory cytokines and these illnesses.

**Introduction:**

The thyroid gland is a crucial component of the endocrine system, which is essential for growth, development, and metabolism. Thyroid autoimmune diseases such Graves' disease and Hashimoto's thyroiditis have increased in frequency in recent years (1). TNF-α and interleukin-17 (IL-17) are two immune proteins that are strongly linked to these illnesses and typically exhibit abnormalities in the immune system response (2,3).

Numerous cells, including immune cells, generate tumor necrosis factor-alpha (TNF-α), a significant inflammatory cytokine with significant effects on inflammation.( 4)

Conversely, T helper cells (Th17) are the primary producers of interleukin-17 (IL-17), a cytokine that is crucial for both acquired immunity and inflammation (5). An rising number of autoimmune illnesses, including thyroid issues, have been associated with these two cytokines

(6,7).Thyroid diseases are becoming more commonplace worldwide, and it's likely that this trend will continue in the ensuing decades (8,9). Another major health issue in Iraq is thyroid diseases (10,11,12). These studies have shown that women are more likely than males to experience thyroid problems. More recently, a cross-sectional research carried out in Basrah, Iraq, discovered that a significant portion of the sample population had hyperthyroidism (3.1%) and hypothyroidism (12.1%) (13). In Karbala, Iraq, another research revealed hypothyroidism prevalence of 9.6% and hyperthyroidism prevalence of 2.4%, respectively, with a much greater frequency in females than in males (14).

Moreover, autoimmune thyroid illnesses, such as Graves' disease and Hashimoto's thyroiditis, were revealed to be the most prevalent causes of thyroid dysfunction in a retrospective research conducted in Baghdad, Iraq, during a 5-year period of time (15). The increasing prevalence of thyroid problems among Iraqis and the necessity for a deeper comprehension of the underlying processes causing these autoimmune ailments are highlighted by these findings. Alubadi et al. (2018) proposed that cytokines are a key factor in the enhancement of inflammation in patients with hypothyroidism, and that a serologic test for this cytokine might aid in the selection of more successful treatment regimens for people who are still experiencing symptoms of the condition (16). This. This study aims to explore the interactions between IL-17 and TNF-alpha and their association with autoimmune thyroid conditions.

**Materials and Methods:**

**Study Design :**

The study was carried out between May and October of 2023. There were two primary groups in the study:

Thyroid condition Group: Endocrinologists at the Diabetes and Endocrines Medical Center in Nasiriyah City identified a total of 95 people as having thyroid diseases that were clinically verified (Hashimotos 49 patients and gravies 46 patients ). 46volunteers in the control group appeared to be in good health, had normal hormone test results, and showed no signs of thyroid malfunction in their clinical appearance.

**Sample Collection and Processing**

Five to ten milliliters of venous blood were drawn from each participant. Following the transfer of the samples to sterile plain tubes and a 10-minute centrifugation at 2500 rpm, the separated serum was split into two aliquots and stored at -20°C until additional analysis could be performed. This procedure aids in preventing frequent thawing and freezing, which may compromise the analytes' stability. (17).

**Hormone Assays**

Thyroxine (T4), triiodothyronine (T3), and thyroid-stimulating hormone (TSH) levels were measured using the Minividis Kit for thyroid hormone (T3, T4, and TSH) provided by Biomerieux SA/ France, which is an enzyme immunoassay for the detection of total T3, T4, and TSH.

**Cytokine measurements**

were performed using a commercially available Bio source micro plate to measure serum interleukin-17 (IL-17) and tumor necrosis factor α (TNF-α). ELISA Kits for the quantitative determination of cytokines in human serum/ Creative Diagnostics/USA.

**Statistical analysis:**

The data were presented as mean ± S.D and analysed using SPSS software version 20 by using the ANOVA test to compare the parameters between three groups including patient groups ( Hashimotos , Graves groups ) and control group and the significance when p≤ o.o5. the relationships between parameters determined by used Pearson correlation coefficient ..

**Results**:

**1-Biochemical Parameters ( TSH, T4 and T3 Levels )**

Individuals diagnosed with Hashimoto's Disease exhibited markedly elevated TSH levels (47.8784 ± 109.4937 mIU/L) in contrast to the control group (2.1383 ± 1.0934 mIU/L) and Graves' Disease group (1.3784 ± 1.1561 mIU/L). Similarly, patients with Graves' Disease demonstrated significantly elevated T4 levels (119.6757 ± 46.329 nmol/L) in comparison to the control group (92.0252 ± 13.7136 nmol/L) and Hashimoto's Disease group (80.64 ± 38.2413 nmol/L). Compared to the normal group (1.6226 ± 0.3998 nmol/L) and the Hashimoto's Disease group (1.6161 ± 0.9293 nmol/L), patients with Graves' disease had considerably higher T3 levels (100.77 ± 1.1604 nmol/L).

All the observed differences in thyroid hormone levels between the groups were statistically significant ($p < 0.05$) .

**Table 1. Comparison of thyroid hormone levels in control, Hashimoto's disease , and Graves' disease groups**

The significancy between the three groups were performed *p≤ 0.05 , **p≤ 0.01

| | Hormones Levels Mean ± SD | | | |
|---|---|---|---|---|
| | Control N=46 | Hashimoto s' Disease N=49 | Graves' Disease N+46 | P value |
| TSH mIU/L | 2.1383 ± 1.0934 | 47.8784 ± 109.4937 | 1.3784 ± 1.1561 | 0.003** |
| T4 nmol/L | 92.0252 ± 13.7136 | 80.64 ± 38.2413 | 119.6757 ± 46.329 | 0.00001** |
| T3 nmol/L | 1.6226 ± 0.3998 | 1.6161 ± 0.9293 | 100.77 ± 1.1604 | 0.008** |

**2 - Cytokines levels in studied groups**

In comparison to the control group, the Hashimoto and Graves groups have considerably greater levels of TNF-α. This suggests that increased production of the pro-inflammatory cytokine TNF-α may be linked to the Hashimoto and Graves illnesses.

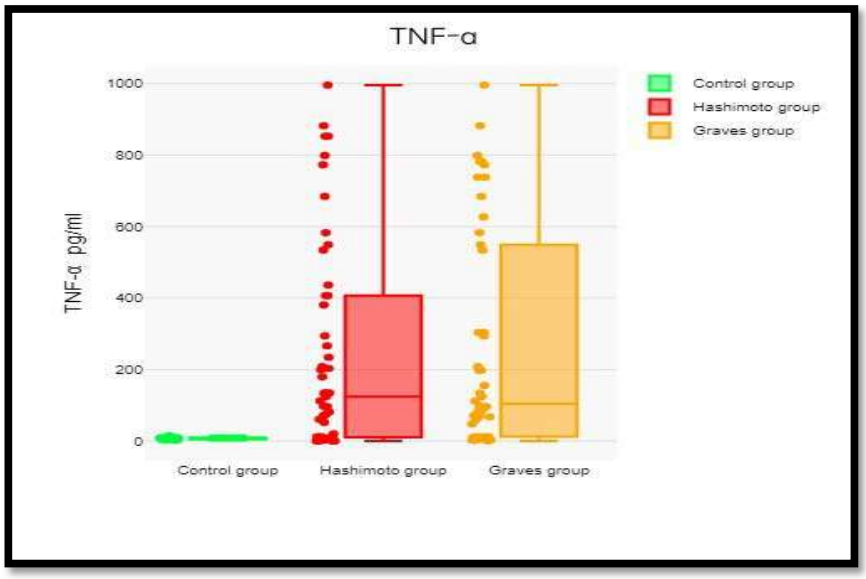



**Figure (1) Evaluation of serum TNF-α levels in control group and patients groups**

The various thyroid disease disorders are highly correlated with the levels of interleukin-17 (IL-17). The greatest levels of IL-17 are seen in patients with Graves' disease, followed by those with Hashimoto's disease; the lowest amounts are found in the control group.

Because of the statistically significant variations in IL-17 levels among the research groups, it is possible that this cytokine contributes to the development or progression of thyroid autoimmune diseases including Hashimoto's disease and Graves' disease. The increased variation seen in the Hashimoto and Graves groups might be attributed to individual variations in the immune response or the heterogeneity of the underlying disease processes.

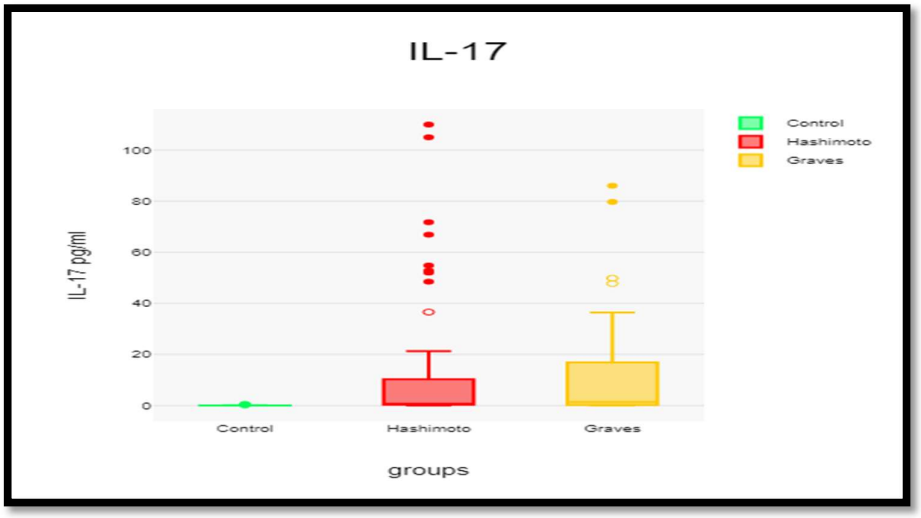



**Figure (2) Evaluation of serum IL-17 levels in control group and patients groups**

**Correlation analyses**

For the sick group and the control group, independent correlation analyses were carried out. Positive associations that were linked and statistically significant at the 0.05 level were found for the Hashimoto's group (Figure 3) and the Graves group (Figure 4) respectively.In other

words, for both the Hashimoto's patient group (Figure 3) and the Graves patient group (Figure 4), positive correlational connections that were statistically significant at the 0.05 level were found. These findings show that certain of the factors under study had significant correlations with one another for each of the two groups..

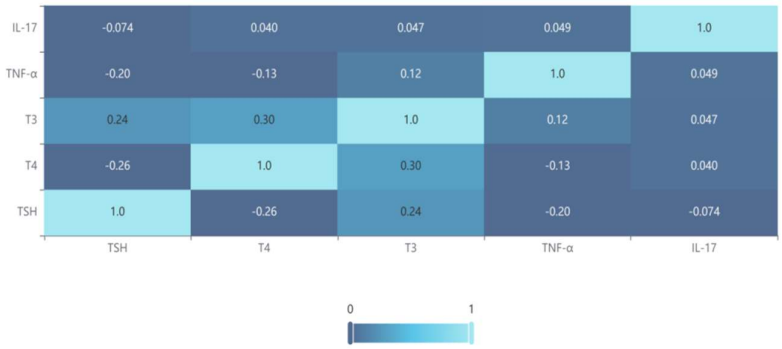
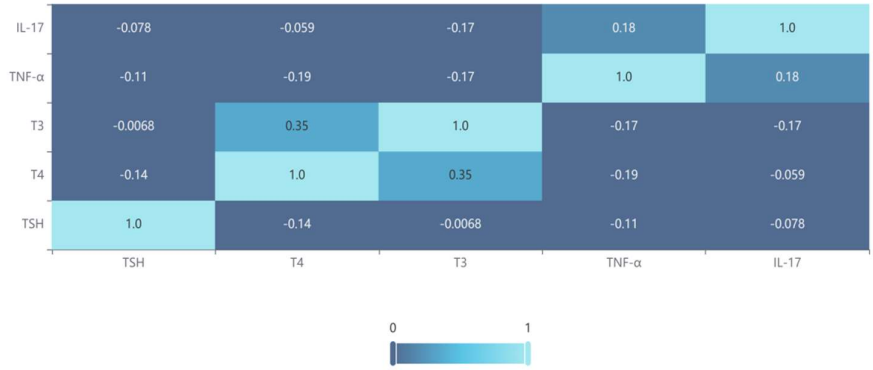



**Figure (3) Correlations between parameters in hashimotos group :T3, T4, TSH, TNF, IL-17 . ( p value at the 0.05 were significant ).**

The study showed significant Correlation at the 0.05 level between thyroid hormone T3 and T4 but no significant correlation was found between other parameters

**Figure (4) Correlations between parameters in Graves group :T3, T4, TSH, TNF, IL-17 . (p value less than 0.05 were significant)**




The thyroid hormones T3 and T4 and TSH revealed significant correlations at the 0.05 level in the research, but no significant correlations were detected between the other measures .

**Discussio**n

The current investigation compared the levels of thyroid hormones (TSH, T4, and T3) in three groups of patients: control, Hashimoto's thyroiditis, and Graves' disease. The three groups' levels of each hormone varied statistically significantly ($p<0.05$), according to the data. The Hashimoto's thyroiditis group's higher TSH values are in line with how primary hypothyroidism often manifests in this autoimmune disease. This result is consistent with other

recent research, including a meta-analysis published in 2021 by Effraimidis et al., which found that TSH levels were considerably greater in Hashimoto's patients than in healthy controls (18).In terms of T4 levels, the findings showed that, in comparison to the control group, the Hashimoto's group had lower concentrations and the Graves' illness group had greater concentrations. This pattern is widely recognized in the literature and it represents the pathophysiology that underlying these thyroid conditions. Similar patterns in T4 levels were also seen in various thyroid disease conditions by Chaker et al. in their 2020 research (19).

T3 levels were significantly higher in the Graves disease group and similar to the control group in the Hashimoto's group. This is in line with the normal thyroid hormone profile seen in Graves' illness, when thyrotoxicosis—a recognizable condition—is caused by increased peripheral conversion of T4 to T3. These results were supported by a recent longitudinal research conducted by Burch et al., which found that Graves' patients had much greater T3 concentrations than healthy persons (20) . Interestingly, Magda Ghazy's research on a cohort of Egyptian patients with Graves' disease and Hashimoto's thyroiditis also supports the current findings. Her study found similar trends in thyroid hormone levels, which adds more support to the distinct profiles of these autoimmune thyroid disorders (21). The underlying pathophysiological processes of Graves' disease and Hashimoto's thyroiditis can be responsible for the observed variations in thyroid hormone levels between the research groups. Whereas Graves' disease is an autoimmune ailment marked by stimulation of the thyroid gland, resulting in hyperthyroidism and suppressed TSH, Hashimoto's disease is defined by autoimmune-mediated destruction of the thyroid gland, resulting in hypothyroidism and raised TSH levels.

The results of this study indicate that, in comparison to the control group, the groups with Graves' disease and Hashimoto's thyroiditis had considerably higher TNF-α levels. This finding suggests that elevated levels of the pro-inflammatory cytokine TNF-α may be linked to certain autoimmune thyroid disorders.

In contemporary research, the function of TNF-α in the etiology of autoimmune thyroid diseases has been extensively described. Effraimidis and Wiersinga's review from 2021 said that TNF-α is essential for the dysregulation of the immune response seen in both Graves' disease and Hashimoto's thyroiditis (22). Particularly, it has been demonstrated that TNF-α stimulates the growth and survival of autoantibodies specific to the thyroid, which are indicative of various autoimmune diseases.

A 2019 research by Caturegli et al. about Hashimoto's thyroiditis showed that people with this illness had higher TNF-α levels in their thyroid glands, which contribute to the inflammatory destruction of thyroid tissue and the ensuing hypothyroidism (23). Additionally, circulating TNF-α levels were found to be considerably greater in Hashimoto's patients compared to healthy controls in a 2020 meta-analysis conducted by Chaker et al. (24).

Elevated TNF-α has been connected to the generation of thyroid-stimulating antibodies in Graves' disease, which causes the typical hyperthyroidism. TNF-α levels were considerably higher in Graves' patients and linked with the severity of the illness, according to a 2021 longitudinal investigation by Burch et al. (25).

The results of this study show a clear correlation between the various thyroid disease states investigated and the levels of the pro-inflammatory cytokine interleukin-17 (IL-17). According to the results, patients with Hashimoto's thyroiditis and Graves' disease had the greatest and lowest amounts of IL-17, respectively, while the control group has the lowest levels. The

observed variations in IL-17 concentrations among the research groups, which are statistically significant, indicate that IL-17 may have a substantial impact in the etiology and/or development of autoimmune thyroid diseases.

Recent studies have looked closely at the role of IL-17 in the onset of Hashimoto's thyroiditis and Graves' disease. T helper 17 (Th17) cells that produce IL-17 are essential for the start and upkeep of the autoimmune response in both situations, according to a review published in 2021 by Duntas and Perros (26). It has been demonstrated that IL-17 stimulates the synthesis of thyroid-stimulating antibodies in Graves' disease, which causes the condition's distinctive hyperthyroidism (27). Similar to this, IL-17 plays a role in the inflammatory destruction of thyroid tissue in Hashimoto's thyroiditis, leading to hypothyroidism (28).

The more variable IL-17 levels seen in the groups with Hashimoto's and Graves' diseases might be attributed to individual variations in the immune response or the diverse nature of the underlying illness processes. According to a 2020 research by Eshaghi et al., the degree of thyroid dysfunction in Hashimoto's patients was correlated with their IL-17 levels, indicating that the disease's stage and clinical presentation may be related to variations in IL-17 concentrations (29).According to a 2019 study by Wang et al., there is a correlation between the activity and severity of Graves' disease and IL-17 levels; greater IL-17 concentrations are associated with more prominent clinical signs (30). Given that the research sample most likely comprised people at various stages of the disease's development, this discovery may help to explain the higher variability seen in the Graves' disease group.

The thyroid hormones T3 and T4 have a strong positive association that has been documented in the literature. The thyroid gland is principally responsible for the synthesis and secretion of thyroid hormones. The main secretory product is T4 (thyroxine), which is subsequently transformed in peripheral tissues into the more potent T3 (triiodothyronine) (31). The homeostatic processes that closely control thyroid hormone synthesis and metabolism are reflected in the close coupling between T3 and T4 levels.

Serum T3 and T4 concentrations are strongly positively correlated in both healthy persons and thyroid disease patients, according to several studies (32, 33). This is due to the fact that the enzyme 5'-deiodinase uses T4 as its main substrate to catalyze the conversion of T4 to T3, the form of thyroid hormone that is more physiologically active (34). Thus, the well-established physiological link between these two thyroid hormones and the observed strong correlation between T3 and T4 levels in the current investigation are congruent.

It is possible that these immune indicators are controlled independently of the thyroid hormone axis given the absence of substantial correlations seen between the thyroid hormones and other measures, such as thyroid autoantibodies and other immunological variables. Thyroid autoimmune disorders, such as Graves' disease and Hashimoto's thyroiditis, are distinguished by the generation of autoantibodies against antigens unique to the thyroid, which may have an impact on thyroid function (35). Thyroid autoimmunity and thyroid hormone levels, however, have a complicated interaction that varies based on the stage and severity of the autoimmune process (36). Strong positive relationships between blood T3 and T4 concentrations in healthy persons and patients with thyroid problems have also been documented in recent investigations (37, 38). This well-established physiological association is consistent with the strong correlation that was seen in the Graves disease group .

The research also found a statistically significant positive correlation ($p<0.05$) between

the TSH and T4 levels in the Graves' disease group. This finding deviates somewhat from the expected inverse connection between T4 and TSH.

Stimulatory autoantibodies against the TSH receptor can lead to greater thyroid hormone production and release in autoimmune thyroid illnesses like Graves' disease, even in the presence of elevated circulating TSH levels (39). The observed positive correlation in the Graves' illness group might be explained by the possibility that the normally inverse relationship between T4 and TSH has uncoupled.

More subsequent studies have shown similar results of positive relationships between T4 and TSH in patients with Graves' disease, highlighting the way this autoimmune condition interferes with regular feedback mechanisms (40, 41.(

In the group with Graves' disease, the study found no statistically significant connections ($p \geq 0.05$) between the thyroid hormones (T3 and T4) and the inflammatory markers interleukin-17 (IL-17) and tumor necrosis factor (TNF).

This discovery implies that, in the setting of Graves' illness, the regulation of certain immunological markers could not depend on the direct thyroid hormone axis. The pathophysiology of Graves' disease is known to be mostly influenced by thyroid autoantibodies; however, research on the function of other inflammatory cytokines, such as TNF and IL-17, is still underway (42, 43).

Although the intricate interactions between thyroid function, autoimmunity, and other immunological mediators in Graves' disease have been studied recently, the linkages remain unclear (44, 45). This study's absence of substantial associations between the inflammatory indicators and thyroid hormones suggests that other paths and processes may control these parameters.

**Conclusion :**

The complex and multifactorial relationships between thyroid function and the immune system warrant further investigation, as reflected by the lack of significant correlations between thyroid hormones and other immune parameters.

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