Relationship of IL-33 and IL-17 with Thyroid Stimulate Hormone (TSH, Triiodothyronine (T3), Tetraiodothyronine (T4) in Patient with Hashimoto Disease

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Abstract

Background: The primary goal of this research was to examine the potential effects of IL-17, IL-33, TSH, T3, and T4 on thyroid gland function and hypothyroidism, specifically in patients with Hashimoto's disease. **Methods:** This case-control multicenter trial was conducted from December 11, 2023, to September 9, 2024, including 102 female and 28 male patients diagnosed with hypothyroidism, along with 34 female and 14 male healthy controls. The study assessed TSH, T3, T4, IL-33, and IL-17 levels in both groups to determine their association with Hashimoto's disease. **Results:** Patients with hypothyroidism exhibited significantly higher levels of TSH (39.52 vs. 2.18, p=0.0001) and T3 (16.99 vs. 100.64, p=0.0001), while T4 levels were significantly lower (2.759 vs. 1.904, p=0.0077) compared to healthy controls. However, no significant differences were observed in IL-33 (576.82 vs. 600.87, p=0.847) and IL-17 (141.81 vs. 143.81, p=0.854) levels between patients and controls. Additionally, age and gender had no significant impact on these parameters, except for a significant gender-related difference in patient distribution (p=0.0006) and a significant difference in the control group (p=0.0487). **Conclusion:** The study confirms significant alterations in TSH, T3, and T4 levels in hypothyroidism patients, reinforcing their role in Hashimoto's disease diagnosis and management. However, IL-33 and IL-17 do not show a significant association with the disease, indicating that other immune factors may contribute to its pathophysiology. Further research is needed to explore additional inflammatory markers and their potential role in thyroid dysfunction.

Keyword: Hashimoto's Disease, Hypothyroidism, Thyroid Hormones, IL-17, IL-33.

Introduction

When the thyroid gland cannot produce enough triiodothyronine (T3) and thyroxine (T4), a person has developed hypothyroidism. The causes for this include many factors, such as iodine deficiency, low levels of TSH hormones in general, and other influences on the processes involved in how much TSH gets released. This deficiency can present a variety of symptoms, including weight gain,

Access This Article Online

Quick Response Code:

Website: www.jnsbm.org

DOI: https://doi.org/10.5281/zenodo.15231934

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Submitted: 12th February, 2025 **Received:** 28th March, 2025
Accepted: 03rd April, 2025 **Published:** 06th April, 2025

How to Cite This Article: Ali N A A, Abbas M I, Khorsheed O A, Ahmed A M, Mahmood S A, Mohammed S F. Relationship of IL-33 and IL-17 with Thyroid Stimulate Hormone (TSH, Triiodothyronine (T3), Tetraiodothyronine (T4) in Patient with Hashimoto Disease. J Nat Sc Biol Med 2025;16:157-164

depression, constipation, muscle aches, and increased sensitivity to cold. In some instances, individuals may develop a goitre, resulting in visible swelling in the neck.[1] If left untreated during pregnancy, hypothyroidism can lead to congenital iodine deficiency syndrome, which may adversely affect a child's neurological and physical growth.[2] Iodine deficiency is well-established as the leading global cause of hypothyroidism.[3] However, in areas where iodine is adequately consumed, Hashimoto's thyroiditis emerges as the primary factor. Other contributing factors include past radioactive iodine treatments, dysfunctions of the pituitary or hypothalamus, congenital defects of the thyroid, certain medications, and previous thyroid surgeries. Diagnosis of hypothyroidism generally relies on blood tests that assess levels of thyroid-stimulating hormone (TSH), as well as T3 and T4 hormones. Women, particularly those aged 60 and above, display a higher prevalence of hypothyroidism compared to men. In middle-aged women, symptoms of this condition may frequently be mistaken for those of menopause.[4] Initially, Hashimoto's thyroiditis can cause thyroid enlargement, leading to the formation of a goitre that may later decrease in size due to ongoing damage to thyroid tissue.[5] Mild or subclinical hypothyroidism has also been associated with increased rates of infertility and miscarriage.[6] In newborns, hypothyroidism can manifest as lethargy, difficulties with feeding, constipation, macroglossia (enlargement of the tongue), umbilical hernia, dry skin, jaundice, low body temperature, inadequate weight gain, hoarse crying, and reduced muscle tone.[7] Hormonal imbalances, particularly an excess of oestrogen [8], have been linked to thyroid dysfunction, as they can disrupt the regulation of thyroid hormones. A decrease in T3 and T4 levels results in a lowered metabolic rate, impacting numerous physiological processes.[9] The thyroid primarily secretes thyroxine (T4), which is subsequently converted into its active form, triiodothyronine (T3), through the action of iodothyronine deiodinase enzymes in various tissues in a selenium-dependent manner.[10] The synthesis of thyroid hormones necessitates both iodine and tyrosine, with the thyroid actively extracting iodine from the bloodstream and incorporating it into thyroglobulin. This process is regulated by TSH, which is secreted by the pituitary gland and influenced by iodine availability and overall TSH secretion levels.[11] An autoimmune condition known as Hashimoto's thyroiditis gradually diminishes thyroid function. However, in the early stages, there may be few individual symptoms, although thyroid enlargement may cause a painless goitre. As the disease progresses, patients can suffer from fatigue, constipation, depression, hair loss, weight gain, and general malaise.[12] Without early treatment, Hashimoto's thyroiditis may lead to complications such as hypertension, cardiovascular disease, heart failure, hypercholesterolaemia, and pregnancy-related problems (2). Family history of autoimmune disorders – and a family history of autoimmune disorder – is a major risk factor for Hashimoto's thyroiditis.[13] It is diagnosed with laboratory tests of TSH, T4, and autoantibodies against thyroid antigens. Differential diagnosis is critical, as other thyroid-related diseases, including nontoxic nodular goitre and Graves' disease, can have overlapping symptomatology.[14] The standard treatment for Hashimoto's disease is levothyroxine replacement therapy.[15] So, if hypothyroidism is excluded, treatment may not be required, but goitre management strategies may be applied. Though consuming an excessive amount of iodine is risky, it remains an important nutrient, particularly for pregnant women. This condition is most common in women, usually between 30 and 50.[16] In cases with established hypoplasia goitre, the chronic phase of autoimmune thyroiditis can gradually decrease the goitre to its normal size due to recurrent damage to thyroid follicles.[17]

Severe complications of autoimmunity-induced hypothyroidism, whilst rare, can include myxedema coma, which is potentially life-threatening and requires urgent medical attention, pleural effusions and pericardial effusion.[18] Thyroid hormone release is governed by TSH, which stimulates the secretion of T4. Most T4 undergoes conversion to T3 in peripheral organs like the liver, with about 20% directly produced by the thyroid gland.[19] TSH secretion occurs throughout life, experiencing elevations during periods of growth and physiological stress. The hypothalamus secretes thyrotropin-releasing hormone (TRH), stimulating the anterior pituitary to produce TSH. In contrast, somatostatin—a hormone synthesised by the hypothalamus—functions as an inhibitor of TSH production. This regulatory mechanism functions through negative feedback: low T3 and T4 levels prompt TSH release, while high levels suppress it.[20] In cases where both TSH and T4 levels are abnormally low, the presence of central hypothyroidism or dysfunction of the TSH-TRH axis may be considered, requiring further clinical evaluation. Chronic subacute thyroiditis (SAT) can show specific laboratory findings, which may include low-normal TSH and T3, elevated reverse T3 (RT3), and normal T4 levels. Among patients with a history of autoimmune thyroid disease, the absence of autoantibodies may indicate the presence of SAT, even if TSH levels appear normal. Considering the pulsatile nature of TSH secretion, caution is warranted in interpreting laboratory results, as TSH levels can fluctuate based on circadian and ultradian rhythms.[21] Pro-inflammatory cytokines, including interleukin-17 (IL-17), are synthesised by T-helper 17 (Th17) cells in response to interleukin-23 (IL-23) activation. IL-17, in conjunction with interleukin-1 and tumour necrosis factor (TNF), is essential to inflammatory processes. Increased IL-17 signalling has been associated with many autoimmune disorders, such as psoriasis.[22] Interleukin-33 (IL-33), a significant cytokine, is part of the IL-1 family and modulates cytokine production associated with Th2 cells, mast cells, and group 2 innate lymphoid cells. IL-33 mainly interacts with its receptor ST2 (IL1RL1), expressed mainly in Th2-

type immune cells. Various cell types, including fibroblasts Mast cells, dendritic cells Macrophages, osteoblasts, and endothelial cells Epithelial cells all synthesise IL-33. The gene that encodes IL-33 is called "IL-33".[23, 24]

Literature Review

The intricate subtle interaction between the body's proinflammatory and anti-inflammatory reactions is perhaps the most significant and compelling area of research into autoimmune diseases within the domain of contemporary medical science.[25] It is of paramount value to the body's capacity to maintain the state of homeostasis, as well as to the body's response to a multitude of pathogens and injuries that the body will inevitably bear within a lifetime. Over the last couple of years, a staggering explosion of the number of inflammatory factors that have been defined and characterised occurred. These inflammatory factors have the potential to have a considerable impact on the pathogenesis of a multitude of diseases that encompass a broad range of autoimmune diseases within their category of diseases.[26] These diseases afflict a variety of individuals within a wide range of backgrounds to the loss of their quality of life in a multitude of ways. An extensive understanding of this interaction, together with the key participants involved, is of value regarding novel therapy approaches that can potentially assuage the afflictions of the diseases that are involved. Scientists and researchers are increasingly fascinated by the subtle intricacies of this interaction, with the interaction of inflammatory factors with each other within the intricate web of the body's response of the body's immune response being a key area of research.[27] Of the multitude of factors that have a considerable impact on the body's response, various cytokines are central players regarding the transmission of cellular signals within the intricate response of the body's immune response. A particularly notable inflammatory player that is unveiled is interleukin-33 (IL-33), a molecule that is produced by injury-damaged or traumatised cells that are repeatedly exposed to pollution, irritants, and a very broad range of environmental stressors.[28] These can significantly shape and redefine the landscape of the immune response in several significant ways to generate potential change not simply of the immune response at the injury site but with significant implications that can have a body-wide effect on the immune response and overall outcome of affected individuals. Importantly, IL-33 is present within a biologically stable state within a range of bodily fluids such as blood and complex tissue matrices, a potentially useful marker that is significant to properly detect and monitor inflammatory response within a range of clinical applications. Another key player that significantly feeds into this complex multifaceted web of immune responses is Interleukin-17A (IL-17A), a key ulcerative inflammatory agent that works to enhance and promote both immune responses and body-wide reactions to worsen existing conditions and the overall outcome of affected individuals. The presence of the two could significantly support diagnostic and treatment approaches to combat the conditions. IL-17 is a tissue that is rich in the presence of IL-17 that is significantly infiltrated by neutrophil granulocytes, a group of white blood cells that are well known to have a significant role to play in the coordination of the immune response.[29] Infiltration is then followed by the presence of monosteocarcinoma cells that are central to the coordination of this intricate inflammatory response landscape. Not only do their interactions strengthen the immune response, but they also generate a dynamic environment that significantly influences the behaviour of other immunocompetent cells responding to a range of stimuli. Infiltration results in a strong discharge of various degradative enzymes that are central to the induction of extensive tissue destruction since they degrade cellular structures and break down elements of the extracellular matrix to ultimately compromise the integrity of the involved tissues. These enzymes also have a central role to play in efforts to neutralise microorganisms that may inhabit the affected tissues to add to the overall complications and challenges to the body of the affected patient. The interaction between the neutrophils and the tumour cells also serves to highlight the intricacies of the inflammatory response and the implications of the response to the state of the disease.[30] The dynamic and intricate interactions between the various inflammatory agents have a significant impact that determines the overall response of the body to the various immunocompetent agents involved. The intricate interaction results in a cascading sequence of events that ultimately determines the overall well-being of the affected patient, their state of well-being, and their quality of life. Further detailed research has indicated that both IL-33 and IL-17A exhibit a remarkable ability to influence the synthesis of Thyroid Stimulating Hormone (TSH). This influence subsequently leads to elevated levels of essential thyroxine hormones in the bloodstream, specifically triiodothyronine (T3) and tetraiodothyronine (T4). These developments thus establish a critical link between immune responses and hormonal regulation, highlighting the interconnected nature of the endocrine and immune systems in maintaining physiological balance and health. However, despite all of this strong evidence, the surprising and alarming thing to note is that a glaring conspicuous lack of comprehensive research fully studying the complex interaction and potential effect of these interleukins with the various aforementioned hormones exists.[31, 32] This glaring lacuna within the existing research critically presents a major opportunity and significant area of research to study much deeper the complex interaction of the inflammatory mediators with each other and perhaps the complex pathophysiology of a range of autoimmune diseases. These thorough investigations present promising directions to devise novel treatment approaches and extensive interventions that could substantially enhance the lives of the affected individuals with disabling and problematic conditions, ultimately giving a much-enhanced quality of life to the affected. The relationship of IL-33 with TSH, T3, and T4 was meticulously explored in a comprehensive study involving 74 individuals. In this study, researchers aimed to gather data on the interactions between these hormones and the inflammatory factors present.[33] Among these participants, 39 were identified as patients suffering from Hashimoto's disease, a condition diagnosed, monitored, and treated within an oncology setting, which included both treated and non-treated individuals. The remaining portion consisted of healthy volunteers who served as crucial controls for the study. Importantly, the interrelationship between IL-17 and the levels of TSH, T3, and T4 was also examined within the same group of patients. This examination sought to uncover and elucidate how interleukins might collectively influence serum levels of TSH, T3, and T4, specifically in those diagnosed with Hashimoto's disease.[34] Up until this point in time, there has been relatively little data presented that potentially connects the influence of IL-33 and IL-17A with the autoimmune processes occurring within the thyroid gland itself. Previous studies have delved into the complex and multifaceted relationship of IL-33 and IL-17 with the various critical functions of a healthy human thyroid. The exploration of these critical questions holds the potential to significantly enhance our understanding of the intricate relationship that exists between autoimmunity and the overall function of the thyroid gland.[35] As has been previously detailed by various scientific teams and research groups, the presence of aggressive responses within the immune landscape of the thyroid gland in patients with Hashimoto's disease has been extensively noted and documented in multiple studies. Such aggressive immune responses are also suggested by the presence of temple-like structures surrounding the thyroid gland, where Th17 cells and IL-17A are absorbed and engaged by the surrounding tissue.[30] Furthermore, the observed enlargement of thyroid volume among these patients may be a direct consequence of inflammation induced by the pathological accumulation of lymphocytes. This underscores the significance of considering the interactions of these interleukins when studying thyroid-related autoimmune conditions, as understanding these connections could lead to better management and treatment approaches for affected individuals.[36]

Patients and Procedures

Study Design and Participant Recruitment

This research was conducted on 102 women and 28 male patients from Iraq with hypothyroidism and 34 female and 14 male Iraqi control diagnosed according to Hospital Endocrinology from December 12, 2023, to September 9, 2024, in classification criteria for hypothyroidism.

Collection of Data

All patients and the control group underwent thorough clinical examinations and history collection. Length of the illness, demographic information, and the existence of concurrent chronic conditions, including (DM) and (HTN), as well as the history of medicines. Measurements of immune variables were part of laboratory studies of IL-17 and IL-33 levels by ELISA instrument, as well as measurement of TSH, T3, and T4 hormone levels.

Table 1: Comparison of the Control and Patient Groups in Hormones Level.

Group	Mean ±SE		
	TSH (Nmol/L)	T4 (ng/dl)	T3 (ng/dl)
Patients	39.52 ±4.85	16.99 ±2.83	2.759 ±0.18
Control	2.18 ±0.36	100.64 ±4.24	1.904 ±0.08
T-test	15.932	10.593	0.623
P-value	0.0001**	0.0001**	0.0077**

** (P≤0.01).

Table 2: Comparison between Patients and Control Groups in IL-33 and IL-17.

Group	Mean ±SE	
	IL-33 (ng/ml)	IL-17 (ng/ml)
Patients	576.82 ±67.39	141.81 ±4.79
Control	600.87 ±92.84	143.81 ±12.41
T-test	147.54 NS	21.626 NS
P-value	0.847	0.854

NS: Non-Significant.

Table 3: Effect of Gender in Parameters Study of Patients Group.

Parameters	Gender		P-value
	Male	Female	
TSH (Nmol/L)	43.61 ±11.19	38.40 ±5.41	0.665 NS
T4 (ng/dl)	10.21 ±1.68	18.85 ±3.54	0.173 NS
T3 (ng/dl)	3.38 ±0.76	2.59 ±0.11	0.0497 *
IL-33 (ng/ml)	591.84 ±106.89	572.69 ±74.41	0.906 NS
IL-17 (ng/ml)	149.93 ±11.83	139.58 ±5.19	0.452 NS

* (P≤0.05), NS: Non-Significant.

Table 4: Effect of Age In Parameters Study of Patients Group.

Parameters	Age groups (year)			P-value
	<30 yr.	30-40 yr.	>40 yr.	
TSH (Nmol/L)	38.20 ±8.35	47.01 ±11.03	36.01 ±6.98	0.631 NS
T4 (ng/dl)	12.38 ±2.69	18.19 ±5.20	19.30 ±5.31	0.491 NS
T3 (ng/dl)	3.06 ±0.54	2.53 ±0.20	2.69 ±0.20	0.471 NS
IL-33 (ng/ml)	679.91 ±111.80	330.06 ±91.25	653.93 ±113.29	0.0491 *
IL-17 (ng/ml)	130.91 ±8.62	145.96 ±9.70	146.52 ±7.12	0.389 NS

* (P≤0.05), NS: Non-Significant.

Table 5: Distribution of Sample Study According to Gender and Age in Patients Group.

Factors		Patients No. (%)	Control No. (%)	P-value
Gender	Male	28 (21.54%)	34 (70.83%)	0.0006 **
	Female	102 (78.46%)	14 (29.17%)	
Age groups (year)	<30 yr.	38 (29.23%)	18 (37.50%)	0.0487 *
	30-40	34 (26.15%)	12 (25.00%)	
	>40 yr.	58 (44.62%)	18 (37.50%)	

* (P≤0.05), ** (P≤0.01).

These p-values indicate the following:
In hypothyroidism patients, TSH, T4, and T3 were made of (39.52, 16.99, and 2.759), respectively; it was compared to healthy control subjects (2.18, 100.64, and 1.904), where p=0.0077, where there is a high significant difference, as shown in table 1, while evaluation of hypothyroidism patients for IL-33 and IL-17 was made of (576.82 and 141.81),

respectively; it was compared to healthy control subjects (600.87 and 143.81), where p=0.854, where there is a high significant difference, as shown in table 2. Effect of gender in parameters study of patients group where P= was equal (0.665, 0.173, 0.0497, 0.906 and 0.452, respectively) for TSH, T4, T3, IL-33, and IL-17, respectively, where there is a non-significant difference, as shown in table 3. Effect of age in parameters study of patients group where P= was equal (0.631, 0.491, 0.471, 0.0491 and 0.389, respectively) for TSH, T4, T3, IL-33, and IL-17, respectively, where non-significant difference, as shown in Table (4). The distribution of the sample studied by gender and age in the patient and control groups yielded p-values of 0.0006 and 0.0487, respectively, indicating a very significant difference in patients and a substantial difference in controls, as seen in Table 5.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) software (2019) was used to identify the impact of distinct groups (patients and control) on research parameters. The T-test was used to significantly compare the means. The Chi-square test was used to significantly compare percentages at the 0.05 and 0.01 probability levels in this investigation.

Results and Discussion

The prevalence of clinical hypothyroidism is higher in older adults,[37] hypothyroidism is high in patients over 40 years compared with control, with a significant difference p= 0.04, as shown in Table 5.

Females are seven times more likely than males to have it,[38] hypothyroidism is in females more than males, with a very significant difference p= 0.006, as shown in Table 5. TSH levels may vary from normal to low due to secondary (pituitary) or tertiary (hypothalamic) factors, but a reduction in T4 correlates with an increased thyrotropin (TSH) level in primary (thyroid) causes.[39] Normal T4 levels in the presence of increased TSH levels are referred to as subclinical hypothyroidism. Thyrotropin-releasing hormone, synthesised by the hypothalamus, modulates the anterior pituitary gland's secretion of TSH and the thyroid gland's production of thyroid hormones [T3] and [T4].[40] Hyperthyroidism may develop if the amount of TSH is low. If the TSH level is high, a serum T4 level should be assessed. In your study, TSH and T3 hormones are elevated, as shown in Figures 1 and 3, respectively, where the difference is highly significant (p= 0.0001 and 0.0077), respectively. While the T4 level is decreased, as shown in Figure 2, where the difference is highly significant (p= 0.0001). Patients with hypothyroidism have higher levels of IL-33, particularly in the overt group, which may be linked to a variety of inflammatory and autoimmune conditions, indicating that IL-33 plays a critical role in causing abnormal local and systemic damage.[38] In our study, the effect of IL-33 in Hashimoto disease patients was non-significant, where P=0.847, which is a non-significant difference, as shown in figure 4. The primary effector cytokine that encourages end-stage inflammation is L-17, which is mostly generated and secreted by Th17 cells.[41] There are notable variations in IL-17 blood levels between all Hashimoto disease patients and healthy controls. Elevated blood levels in the newly identified euthyroid stage relative to controls. Patients with hypothyroid Hashimoto disease had lower serum levels, which rose with T4 therapy, indicating that hypothyroidism may have an impact on serum IL-17 levels. Similar results regarding IL-17 serum levels in the hypothyroid stage.[37] The diminished humoral and cell-mediated immunity in this functional state may be associated with reduced IL-17 levels in hypothyroidism.[42] In our study, the effect of IL-17 in Hashimoto disease patients was non-significant, where P=0.854, with a significant difference, as shown in Figure 5. To provide deeper insight into the lack of significant correlation between IL-33, IL-17, and Hashimoto's disease, we have expanded the discussion by comparing our findings with previous studies on IL-33 and IL-17 in other autoimmune diseases. This comparative analysis highlights potential variations in immune responses across different conditions and explores possible reasons for the observed non-significance in our study. These additions strengthen the interpretation of our results and suggest directions for further investigation into the immunological mechanisms underlying Hashimoto's disease. However, it is important to acknowledge that the relatively small sample size in our study may have influenced the statistical power of these findings. Future studies with larger and more diverse populations are necessary to further validate the observed trends and assess the potential role of IL-33 and IL-17 in Hashimoto's disease with greater accuracy.

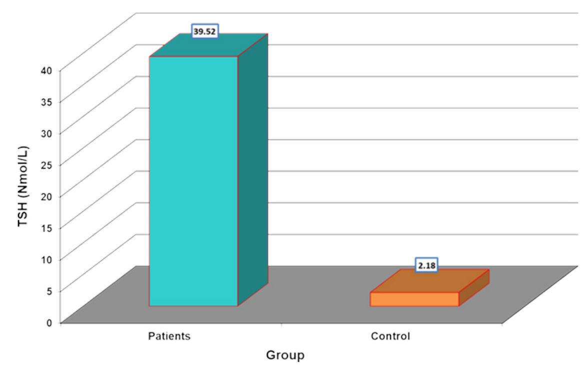

Figure 1: Comparison between Patients and Control Groups in TSH.

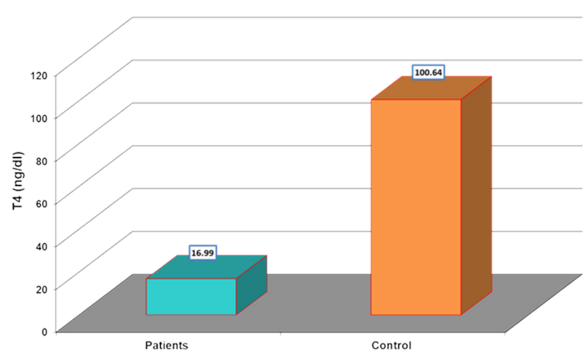

Figure 2: Comparison between Patients and Control Groups in T4.

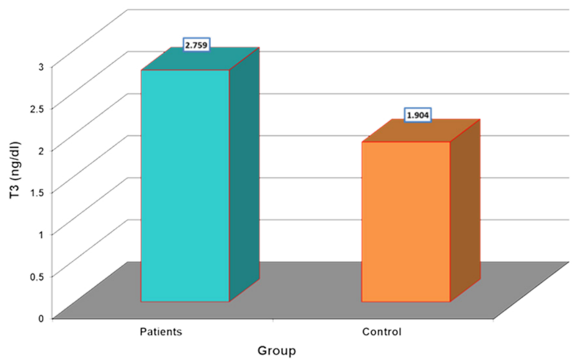

Figure 3: Comparison between Patients and Control Groups in T3.

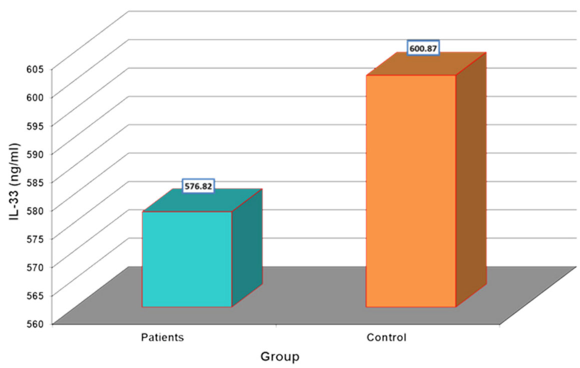

Figure 4: Comparison between Patients and Control Groups in IL-33.

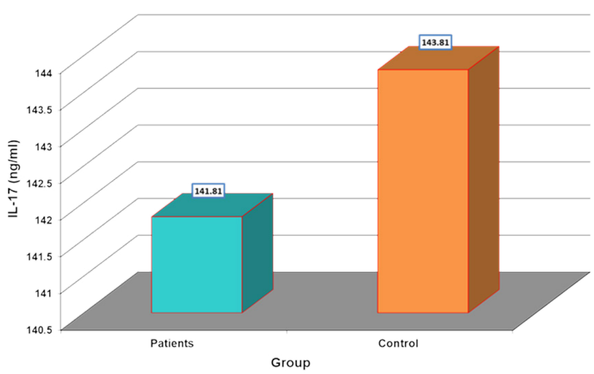

Figure 5: Comparison between Patients and Control Groups in IL-17.

Conclusion

This study demonstrates a significant difference in TSH, T3, and T4 levels between patients with Hashimoto's disease and the control group, confirming thyroid dysfunction in affected individuals. However, IL-33 and IL-17 levels did not show a significant difference, suggesting that these interleukins may not play a direct role in Hashimoto's disease pathophysiology or that their effects are influenced by other immune factors. The findings reinforce the well-established association between Hashimoto's disease and hormonal imbalance, particularly the elevated TSH and altered T3 and T4 levels observed in patients. While inflammatory markers like IL-33 and IL-17 have been implicated in autoimmune diseases, their role in Hashimoto's thyroiditis remains unclear, requiring further investigation. Overall, this study highlights the need for continuous monitoring of thyroid hormones in managing Hashimoto's disease.

However, it is important to acknowledge that the relatively small sample size in our study may have influenced the statistical power of these findings. Future research should incorporate larger and more diverse populations to validate these results and explore additional inflammatory markers to better understand the immune mechanisms contributing to this condition.

Clinical Implications and Future Directions

The findings of this study confirm significant alterations in TSH, T3, and T4 levels in patients with Hashimoto's disease, reinforcing their role in disease diagnosis and management. However, while these results highlight the importance of monitoring thyroid hormones in clinical practice, they also raise the need for specific intervention strategies.

One potential clinical application of these findings is the early identification of subclinical hypothyroidism in patients at risk of Hashimoto's disease. Given the observed hormonal imbalances, clinicians should consider routine thyroid function screening, particularly for individuals with a family history of autoimmune thyroid disorders or those exhibiting early symptoms. Additionally, personalised treatment approaches, such as optimising levothyroxine therapy based on individual hormonal profiles, may improve disease management.

Although IL-33 and IL-17 did not show significant associations with Hashimoto's disease in this study, their potential role in inflammatory pathways warrants further investigation. Future research should explore whether targeting these cytokines could have therapeutic implications for managing autoimmune thyroid conditions.

Overall, integrating these findings into clinical practice can aid in refining diagnostic protocols and tailoring hormone replacement therapies, ultimately improving patient outcomes. Further studies with larger sample sizes and longitudinal designs will help establish more precise clinical recommendations.

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