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Evaluation of Pro- and Anti-inflammatory Cytokines IL-17 and IL-33 in Autoimmune Hyperthyroidism

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Abstract: Hyperthyroidism is a medical condition characterized by the excessive production and release of thyroid hormones by the thyroid gland. It has diverse etiologies, clinical manifestations, and treatment options. Among the contributing factors to the development of thyroid disease are cytokines, which influence both the immune system and thyroid follicular cells. Notably, cytokines such as IL-17 and IL-33 play critical roles in autoimmune thyroid diseases by promoting inflammation and modulating immune responses. This study aimed to evaluate the serum levels of IL-17 and IL-33 in Iraqi individuals diagnosed with hyperthyroidism. A total of 60 hyperthyroid patients (21 males and 39 females, aged 17–40 years) and 30 healthy controls (8 males and 22 females) were enrolled. Blood samples were collected, and serum levels of IL-17 and IL-33 were measured using standard ELISA techniques. The results demonstrated a statistically significant increase in IL-17 concentrations in patients with hyperthyroidism (39.480 ± 9.665 ng/L) compared to controls (25.695 ± 4.448 ng/L) ($p \leq 0.01$). Similarly, IL-33 levels were significantly elevated in the patient group (1247.745 ± 966.963 ng/L) compared to the control group (32.788 ± 47.741 ng/L) ($p \leq 0.01$). These findings suggest a potential role for IL-17 and IL-33 in the immunopathogenesis of hyperthyroidism, highlighting their value as possible biomarkers for disease progression.

Keywords: Autoimmune Disorder; Inflammation; Graves' Disease; Cytokines; Thyroid-Stimulating Hormone

1. Introduction

The clinical presentation of hyperthyroidism includes a wide range of systemic symptoms such as increased appetite, sleep disturbances, emotional instability, fatigue, muscle weakness, and reduced fertility. Other common features include menstrual irregularities, frequent bowel movements, hand tremors, cardiac arrhythmias, heat intolerance, and excessive sweating. Additional symptoms may involve elevated blood glucose levels, skin changes, psychological disturbances, nausea, vomiting, shortness of breath, and weight fluctuations [1].

The most common form of hyperthyroidism is Graves' disease (GD), an autoimmune disorder with a complex pathophysiology. GD is primarily caused by autoantibodies directed against the TSH receptor (TSHR), which bind to thyroid follicular cells and stimulate unregulated production of thyroid hormones. This results in systemic hypermetabolism and increased physiological activity across multiple organ systems [2,3].

Cytokines are key immunomodulators involved in both pro-inflammatory and anti-inflammatory responses. They are produced by a variety of immune and non-immune cells and play a central role in mediating inflammatory processes within both the innate and adaptive immune systems [4]. In the context of thyroid disease, cytokines influence thyroid follicular cells and are implicated in the development and progression of autoimmune thyroid

disorders by promoting inflammation and sustaining immune activation [5].

Interleukin-17 (IL-17) is a pro-inflammatory cytokine primarily secreted by T helper 17 (Th17) cells, a subset of $CD4^+$ T lymphocytes. First identified by Yao in 1995, IL-17 plays a critical role in both innate and adaptive immunity. It contributes to epithelial barrier function, initiates inflammatory responses, and supports B cell activation in response to specific stimuli. Extensive research has demonstrated the involvement of IL-17 in various pathological conditions, including autoimmune diseases, viral infections, cardiovascular disorders, nonalcoholic fatty liver disease, hematological and solid tumors, and neurological diseases [6]. Elevated IL-17 levels have been observed in malignancies such as colorectal, gastric, non-small cell lung cancer, and hematological cancers. It is considered a potential biomarker for tumors like breast, lung, gastric, and oral squamous cell carcinomas. Several studies have also reported increased IL-17 expression in autoimmune thyroid diseases, particularly Hashimoto's thyroiditis (HT) [7].

In hyperthyroidism, particularly in autoimmune forms like Graves' disease (GD), IL-17 contributes to immune dysregulation. It directly stimulates the production of IL-23 and induces inflammatory pathways by activating neutrophils. These, in turn, release other cytokines and mediators, including TNF-α, NOS-2, IL-1, IL-6, and chemokines. Endothelial cells respond to IL-17 by amplifying these pro-inflammatory signals. IL-17 also enhances T cell responses, sustaining chronic inflammation [8,9]. Notably, several studies have demonstrated a strong association between Th17 cells that secrete IL-17 and the pathogenesis of GD [10].

Interleukin-33 (IL-33) is a member of the IL-1 cytokine family and is unique in that it functions both as a nuclear transcription factor and an extracellular signaling molecule. It is mainly produced by non-hematopoietic cells, such as fibroblasts, epithelial cells, and endothelial cells, under both homeostatic and inflammatory conditions [11,12]. IL-33 can be released constitutively or in response to tissue injury or immune stimulation. While the precise molecular mechanisms of its production remain unclear, free IL-33 acts as a cytokine by binding to its receptor (ST2) on target cells. It plays a dual role in immune responses, either promoting inflammation or modulating immune activity, depending on the context [12]. IL-33 is produced by various cell types, including epithelial and endothelial cells, as well as immune cells like dendritic cells and macrophages. It is particularly implicated in the pathogenesis of autoimmune diseases (ADs), where it contributes to the dysregulation of immune tolerance. These diseases include psoriasis, type 1 diabetes (T1D), rheumatoid arthritis (RA), inflammatory bowel diseases (IBDs), uveitis, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), multiple sclerosis (MS), and autoimmune thyroid diseases (AITDs) [13].

Therefore, the present study aimed to evaluate the serum levels of IL-17 and IL-33 in Iraqi individuals diagnosed with hyperthyroidism, to explore their potential roles in disease pathogenesis and immune dysregulation.

1.1. Etiology of Hyperthyroidism

Hyperthyroidism is a medical disorder characterized by excessive levels of thyroid hormones in the body's tissues. This condition may result from increased synthesis of thyroid hormones, excessive release of preformed hormones, or exposure to external sources of thyroid hormone. The primary causes of increased hormone production include Graves' disease, toxic multinodular goiter (TMNG), and toxic adenoma [14].

Graves' disease, the most common cause of hyperthyroidism, is an autoimmune disorder in which thyroid follicular cells are stimulated by thyrotropin receptor antibodies (TRAb). This stimulation leads to thyrotoxicosis and thyroid gland hypertrophy [15]. The disease tends to occur more frequently in females, especially those with a personal or family history of autoimmune conditions. It often presents with a vascular diffuse goiter and may be associated with Graves' orbitopathy (GO), a manifestation of autoimmune inflammation affecting the orbital tissues [16].

Graves' disease is most prevalent between the ages of 40 and 60. Dysregulation of T-cell function plays a critical role in the pathogenesis by promoting the production of TRAb, which not only activate TSH receptors on thyroid cells. However, it may also interact with orbital fibroblasts and antigens [17]. While the term "Graves' disease" is often used to describe patients with both clinical and biochemical evidence of hyperthyroidism, some cases may require a more precise definition. In certain patients, the disease may progress to spontaneous euthyroidism or hypothyroidism due to autoimmune-mediated thyroid destruction [18]. Graves' ophthalmopathy, a common complication, causes proptosis (eyeball protrusion) due to inflammation and swelling of orbital muscles and connective tissue [19].

Toxic multinodular goiter (TMNG) is another common cause of hyperthyroidism, characterized by auto-

nomously functioning thyroid nodules that produce excess thyroid hormones independent of TSH regulation. TMNG typically does not regress spontaneously, and many patients require definitive treatment such as radioiodine therapy or surgery [18].

Another rare but important cause is pituitary thyrotropin-secreting adenomas (TSHomas), which lead to secondary hyperthyroidism. These tumors cause inappropriate TSH secretion despite normal thyroid function. Although rare, comprising less than 2% of all pituitary adenomas, the widespread use of ultrasensitive TSH assays and the measurement of free T4 and T3 have facilitated earlier and more accurate diagnosis [20].

Silent thyroiditis is an autoimmune condition marked by the destruction of thyroid follicles, leading to the passive release of stored thyroid hormones into the bloodstream. This process may be triggered by certain medications, such as interferon-α, lithium, interleukin-2, or amiodarone, as well as physiological changes, including postpartum thyroiditis [21].

Micronutrients also play a critical role in thyroid health. Iodine, in particular, is essential for the synthesis of thyroid hormones. While iodine deficiency remains a major global cause of thyroid dysfunction, excessive and prolonged iodine intake—such as overuse of iodized salt—can paradoxically increase the risk of autoimmune thyroid disorders and either hypothyroidism or hyperthyroidism [22].

Other nutritional and hormonal factors may influence thyroid function. For example, vitamin B12 deficiency can contribute to pernicious anemia, and disruptions in insulin or adrenal hormone production may also affect thyroid balance [23]. Additionally, smoking is known to impair thyroid hormone activity and iodine uptake. At the same time, certain psychiatric medications, such as lithium, are associated with hypothyroidism and may influence the appearance of thyroid nodules [23].

1.2. Pathogenesis of Hyperthyroidism

Hyperthyroidism is primarily defined as a condition of thyroid gland dysfunction, specifically primary hyperthyroidism, characterized by excessive production of thyroid hormones. The clinical diagnosis is typically supported by elevated levels of circulating free thyroxine (fT4) and/or triiodothyronine (T3), accompanied by suppressed levels of serum thyroid-stimulating hormone (TSH) [24].

Endogenous causes of primary hyperthyroidism include Graves' disease, toxic multinodular goiter, toxic adenoma, and painless thyroiditis. Among these, Graves' disease is the most common cause in developed countries. This autoimmune disorder typically affects individuals between the ages of 20 and 50, and it is significantly more prevalent in women, by a factor of five to ten, compared to men. The condition was first described in 1834 by the Irish physician Robert Graves [25]. Graves' disease is mediated by thyrotropin receptor antibodies (TRAb), which continuously stimulate the TSH receptor, bypassing the normal negative feedback mechanism of the hypothalamic-pituitary-thyroid axis. This leads to glandular hypertrophy, increased iodine uptake, and elevated synthesis and secretion of T3 and T4 hormones.

Since TSH receptors are expressed in various tissues throughout the body, extrathyroidal manifestations are frequently observed. These include pretibial myxedema, thyroid acropachy, and Graves' orbitopathy, all of which are attributed to the action of TRAb on non-thyroidal tissues.

Although the precise pathogenesis of Graves' disease remains unclear, both genetic and environmental factors are implicated. Studies suggest that genetic predisposition accounts for approximately 79% of the risk, while environmental factors account for the remaining 21%. Key environmental triggers include smoking, excessive iodine intake, selenium deficiency, and vitamin D deficiency. Furthermore, individuals with a family history of hyperthyroidism or other autoimmune diseases, such as myasthenia gravis or type 1 diabetes mellitus, are at higher risk of developing Graves' disease [26].

1.3. Epidemiology of Hyperthyroidism

The prevalence of hyperthyroidism varies globally, largely influenced by dietary iodine intake. Women are disproportionately affected compared to men. Additional risk factors include smoking, insufficient or excessive iodine consumption, selenium deficiency, genetic susceptibility, and the use of certain medications. Graves' disease (GD) is the leading cause of hyperthyroidism in younger adults, with its peak incidence observed between the ages of 30 and 50. In contrast, toxic multinodular goiter (TMNG) is more common in the elderly and represents a major cause of hyperthyroidism in that population [27].

In iodine-sufficient regions, hyperthyroidism remains prevalent, although at varying rates. For instance, in South Korea, the median urinary iodine concentration (UIC) was 293.9 μg/L—above the WHO's recommended levels—according to the National Health and Nutrition Examination Survey IV. In 2018, the prevalence of hyperthyroidism in South Korea was 0.25%, with age-adjusted incidence rates of 40.3 and 105.5 per 100,000 for males and females, respectively [28]. Comparatively, in other iodine-sufficient countries, prevalence rates range from 0.1% to 2.5%, with annual incidence between 25.8 and 81.6 per 100,000 individuals [27]. In US, Grave's disease is the most common etiology of hyperthyroidism, accounting for 60–80% cases of hyperthyroidism followed by subacute thyroiditis (15–20%), toxic multinodular goiter (10–15%) and toxic adenoma (3–5%). Females are more commonly affected by thyroid disorders as compared to male. Peak age of occurrence is second to fifth decade of life [29].

A systematic review and meta-analysis of 17 studies from 1975 to 2012 estimated the prevalence of hyperthyroidism in Europe at 0.75%, while hypothyroidism affected 3.05% of the population [30]. In Iran, subclinical thyroid dysfunction was more common than overt disease, with subclinical hyperthyroidism affecting 0.9–3.7% of the population [31]. A 2016 French study involving 1,572 hyperthyroid patients reported that 73.3% had Graves' disease, and 85% of them were women [32].

Globally, hyperthyroidism affects populations in both iodine-deficient and iodine-sufficient areas. In Europe, dietary iodine imbalances contribute significantly to hyperthyroidism, alongside autoimmune conditions. In the United States, Graves' disease is the predominant cause among younger individuals, while toxic nodular goiter is more common in older adults. The prevalence is estimated at 0.8% in Europe and 1.3% in the U.S. Women have an incidence rate of 82 per 100,000 person-years, compared to 16 per 100,000 for men [14–33]. Mild to moderate iodine deficiency can also lead to the development of toxic goiter. Programs promoting universal salt iodization have effectively reduced the prevalence of iodine deficiency in many regions.

In Iraq, a 2021 survey in Duhok, Kurdistan, identified 540 cases of subclinical hyperthyroidism, comprising 177 males and 363 females. The majority of cases occurred in individuals aged 40–69 and 20–39, with 164 and 128 cases in females, respectively [34].

Another study conducted in Baghdad (2020), in collaboration with the National Diabetes Center and Al-Mustansiriyah University, assessed 1,800 patients over six months. The findings revealed that overt hyperthyroidism accounted for 3% of cases (27.8% males and 72.2% females), while subclinical hyperthyroidism accounted for 4% (18.3% males and 81.7% females). The proportion of euthyroid, subclinical, and overt hyperthyroidism statuses was significantly higher in females: 75.7%, 6.2%, and 18.1%, respectively [35].

A more recent study from Libya (2021) reported a 1.68% prevalence of overt hyperthyroidism. In contrast, overt hypothyroidism was reported in 0.78%, while subclinical hypothyroidism was found in 0.9% of participants [36].

1.4. Signs and Symptoms of Hyperthyroidism

Hyperthyroidism presents with abroad spectrum of clinical symptoms, which vary based on age, gender, disease severity, and comorbid conditions. The most common manifestations include weight loss despite increased appetite, tachycardia, restlessness, tremors, muscle weakness, heat intolerance, excessive sweating, and sleep disturbances [37,38]. Gastrointestinal symptoms such as frequent bowel movements or diarrhea are also frequently observed, along with fatigue, irritability, and emotional lability [39].

Endocrinological and metabolic disturbances are also characteristic of this condition. Patients often exhibit hyperglycemia due to increased insulin degradation, altered secretion, and disrupted glucose metabolism [40]. Dysregulation of adipocytokines—including adiponectin, leptin, resistin, vaspin, and visfatin—has been documented in individuals with hyperthyroidism, although findings remain inconsistent [41]. Although appetite is commonly increased, weight loss remains a hallmark symptom, likely due to increased thermogenesis, impaired oxidative phosphorylation, and direct central effects of thyroid hormones on the hypothalamus [42].

On a cellular level, hyperthyroidism leads to elevated oxygen consumption, mitochondrial respiratory chain dysfunction, ATP depletion, and increased production of reactive oxygen species (ROS) [43]. These biochemical alterations contribute to many systemic manifestations, including neuropsychiatric symptoms such as anxiety, agitation, and insomnia. In children and adolescents, such symptoms are often initially misdiagnosed as ADHD or anxiety disorders, delaying appropriate endocrine evaluation [44]. Adrenergic hyperactivity can also manifest as hypertension, palpitations, atrial fibrillation, and widened pulse pressure [39–44].

In females, menstrual irregularities such as hypermenorrhea and fertility issues are common. Dermatological signs include moist, warm skin and sometimes hair thinning or onycholysis. In elderly patients, classic signs such as goiter, tremor, and hyperactivity may be subtle or absent, making diagnosis more challenging. However, they may present with cardiovascular complications such as atrial fibrillation, osteoporosis, and even embolic events [44]. Additionally, Graves' ophthalmopathy tends to be more severe in older patients and smokers, while goiter is less commonly observed in the elderly population [44].

If left untreated, thyrotoxicosis may result in serious complications including neuropsychiatric disturbances, osteoporosis, circulatory collapse, and, in rare cases, sudden death.

1.5. Diagnosis of Hyperthyroidism

Hyperthyroidism can be diagnosed through a combination of clinical evaluation, laboratory testing, and imaging studies. These complementary methods aim to assess the functional status of the thyroid gland, identify the underlying etiology, and evaluate the extent of glandular involvement [45].

1.5.1. Clinical Examination

A physical examination is often the first step in evaluating suspected hyperthyroidism. Clinicians may palpate the neck to detect thyroid enlargement, nodularity, or tenderness. Ocular signs such as proptosis, lid lag, periorbital edema, and conjunctival injection may indicate Graves' disease [46]. Additional findings may include tachycardia or arrhythmias (detectable via stethoscope), fine tremors (revealed by outstretched hands), warm, moist skin, and nail changes such as onycholysis.

1.5.2. Laboratory Investigations

Thyroid function tests (TFTs) remain the cornerstone of diagnosis for hyperthyroidism. These typically include measurement of:

- Thyroid-stimulating hormone (TSH) – usually suppressed in primary hyperthyroidism.
- Free thyroxine (fT4) and triiodothyronine (T3) – typically elevated in hyperthyroid states [47,48].

Because TSH is highly sensitive to even minor fluctuations in circulating thyroid hormones, it is considered the initial screening test for suspected hyperthyroidism, also known as thyrotoxicosis. Suppose free T4 levels are normal while TSH is suppressed, total T3 measurement is recommended to detect T3 toxicosis, which may occur in early Graves' disease, toxic multinodular goiter (TMNG), or a toxic adenoma [49].

1.5.3. Imaging Techniques

Several imaging modalities are used to evaluate the structure and function of the thyroid:

- **Thyroid Ultrasound**: A non-invasive imaging technique utilizing high-frequency sound waves to assess thyroid size, morphology, vascularity, and nodularity. Hypoechoic and reticular patterns may indicate lymphocytic infiltration or fibrosis, while irregular hypoechoic areas suggest glandular destruction [50,51].
- **Radioactive Iodine Uptake (RAIU) Scan**: This functional study involves oral administration of a small, safe dose of radioactive iodine. The uptake is measured after 6–24 hours using a gamma probe, revealing the gland's iodine absorption capacity. Elevated uptake suggests Graves' disease or toxic nodules, whereas low uptake may be consistent with thyroiditis [52].
- **Thyroid Scintigraphy**: Often used in conjunction with RAIU, this test visualizes the functional activity of thyroid tissue and helps differentiate between diffuse uptake (Graves' disease) and focal uptake (toxic adenoma or TMNG) [53].

2. Materials and Methods

This cross-sectional study enrolled a total of 60 patients diagnosed with hyperthyroidism, including 21 males and 39 females, aged between 17 and 40 years. Participants were recruited from Baquba Teaching Hospital in

Diyala Province and Balad Hospital in Salah al-Din Province, Iraq. The study was conducted over five months, from October 2024 to February 2025.

The diagnosis of hyperthyroidism was established by consultant endocrinologists based on clinical signs and symptoms, as well as laboratory findings, specifically elevated serum levels of free triiodothyronine (T3), free thyroxine (T4), and suppressed thyroid-stimulating hormone (TSH) concentrations.

A structured questionnaire was used to obtain demographic and lifestyle data, including name, age, sex, and smoking status. Patients with a history of cardiovascular disease, renal failure, or those currently receiving lipid-lowering agents or antioxidant supplements were excluded, as these conditions or medications could influence oxidative stress biomarkers and cytokine expression levels.

A control group of 30 age- and sex-matched healthy individuals (8 males and 22 females) with no personal history of thyroid disorders or other chronic illnesses was included for comparison.

For each participant, 5 mL of venous blood was drawn under aseptic conditions. Blood samples were left to clot at room temperature and subsequently centrifuged at 3000 rpm for 10 minutes. The resulting serum was separated and stored at –20°C until further analysis.

Serum concentrations of interleukin-17 (IL-17) and interleukin-33 (IL-33) were measured using commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kits, according to the manufacturer's protocols.

Statistical analysis was performed using SAS software (version 9.1; SAS Institute Inc., 2012). Data were presented as mean ± standard deviation (SD). Differences in cytokine levels between hyperthyroid patients and controls were assessed using independent sample t-tests, with statistical significance defined as $p \leq 0.01$.

3. Results and Discussion

3.1. Concentration of IL-17 in Hyperthyroidism Patients and Control Group

The current study investigated the serum concentration of interleukin-17 (IL-17) in patients with hyperthyroidism compared to a healthy control group. The results showed that IL-17 levels were significantly elevated in the hyperthyroidism group (39.480 ± 9.665 ng/ml) compared to the control group (25.695 ± 4.448 ng/ml). The difference was statistically significant ($p = 0.001$, $p \leq 0.01$).

This significant increase in IL-17 concentration among hyperthyroid patients may reflect the involvement of inflammatory and autoimmune mechanisms, especially in disorders such as Graves' disease, where Th17-mediated immune responses are known to be active. These findings suggest that IL-17 may serve as a potential biomarker for immune activity in hyperthyroidism, as shown in **Table 1**.

Table 1. Concentration IL-17 in hyperthyroidism patients and control groups.

Statistical Analysis		Study Group		*p*-Value
		Patients N = 60	Control N = 30	
IL17 (ng/l)	Mean	39.480	25.695	0.001
	SD	9.665	4.448	
** ($p \leq 0.01$)				

Note: IL-17: Interleukin-17; SD: Standard Deviation; ng/ml: Nanograms per milliliter; $p \leq 0.01$ indicates a statistically significant difference between groups. Values are expressed as mean ± SD.

The findings of the present study demonstrated a significant elevation in serum IL-17 levels in patients with hyperthyroidism compared to the healthy control group. This increase may be attributed to the autoimmune nature of hyperthyroidism, in which the immune system erroneously targets the thyroid gland, leading to an inflammatory response mediated by various cytokines, including interleukin-17 (IL-17) [54].

IL-17 is a pro-inflammatory cytokine predominantly produced by T helper 17 (Th17) cells, which play a central role in mediating autoimmune responses. The increased IL-17 levels observed in hyperthyroid patients suggest the involvement of Th17-driven inflammation in the pathogenesis of the disease [55]. Certain individuals may exhibit a genetic predisposition to enhanced Th17 cell differentiation and IL-17 production, contributing to disease susceptibility and severity.

The current findings align with previous studies reporting elevated IL-17 concentrations in patients with hyperthyroidism, supporting the hypothesis that IL-17 plays a contributory role in disease development [55]. IL-17 facilitates the recruitment of neutrophils and promotes the secretion of additional pro-inflammatory mediators and chemokines, thereby amplifying the immune response. It also acts as a crucial mediator, bridging innate and adaptive immunity by influencing epithelial barrier function and B-cell activation [56].

Autoimmune thyroid diseases such as Graves' disease are characterized by the breakdown of immunological self-tolerance, leading to autoantibody production and T-cell-mediated tissue destruction. Several studies, including ours, have reported increased IL-17 levels in patients with Graves' disease, highlighting its pathogenic relevance in thyroid autoimmunity [57].

However, contrasting evidence exists. A study reported lower IL-17 levels in untreated Graves' disease patients compared to healthy individuals, and no significant changes were detected before and after treatment [58]. These discrepancies may be due to differences in study design, disease stage, or treatment status, underscoring the complexity of IL-17 regulation in thyroid pathology.

IL-17 plays a vital role in host defense by inducing cytokines and antimicrobial peptides, as well as altering T-cell responses. Nevertheless, dysregulated IL-17 production can contribute to the development of various autoimmune and inflammatory conditions [59]. Increased Th17 cell populations and IL-17 secretion have been documented in patients with Graves' disease, supporting the notion that IL-17 exacerbates thyroid inflammation and may contribute to disease progression [60].

In line with our findings, Duan et al. (2018) demonstrated that Th17 cells and IL-17 are actively involved in the autoimmune mechanisms underlying hyperthyroidism. This highlights the potential for targeting IL-17 or Th17-related pathways as novel therapeutic strategies to modulate immune responses in patients with hyperthyroidism [61].

3.2. Concentration of IL-33 in Hyperthyroidism Patients and Control Groups

The results of the present study demonstrated a significant difference in serum interleukin-33 (IL-33) levels between hyperthyroid patients and healthy controls. Patients diagnosed with hyperthyroidism exhibited markedly elevated IL-33 concentrations (1247.745 ± 966.963 ng/ml) compared to the control group (47.741 ± 32.788 ng/ml). This difference was statistically significant ($p \leq 0.01$).

The substantial increase in IL-33 levels among hyperthyroid patients suggests a possible role for this cytokine in the pathogenesis of hyperthyroidism. IL-33 is a pro-inflammatory mediator that amplifies immune responses and has been implicated in various autoimmune and inflammatory diseases. Its elevated levels in hyperthyroid patients may reflect underlying immune dysregulation, particularly in autoimmune thyroid conditions such as Graves' disease, as shown in **Table 2**.

Table 2. Concentration of IL-33 in hyperthyroidism patient and control groups.

Statistical Analysis		Study Group		*p*-Value
		Patients N = 60	Control N = 30	
IL33(ng/l)	Mean	1247.745	47.741	0.001
	SD	966.963	32.788	
		** ($p \leq 0.01$)		

Note: IL-33: Interleukin-33; SD: Standard Deviation; ng/ml: Nanograms per milliliter; ** $p \leq 0.01$ indicates a statistically significant difference between groups. Values are expressed as mean ± SD.

The results of the present study revealed elevated levels of interleukin-33 (IL-33) in individuals diagnosed with hyperthyroidism compared to the control group. Hyperthyroidism often results from an autoimmune condition in which the immune system specifically targets and damages the thyroid gland, leading to chronic inflammation. These findings suggest a potential role for IL-33 in the pathogenesis and possibly the treatment of hyperthyroidism [62].

Our results align with those of previous studies, such as Shakerian et al. (2022), which also reported significantly elevated IL-33 levels in individuals with hyperthyroidism. The expression of IL-33 in the epithelial cells of the thyroid gland suggests its involvement in both local and systemic inflammatory and autoimmune processes [63]. IL-33 amplifies immune and inflammatory responses, and its release from damaged thyroid cells may serve as a prognostic marker for the disease. It promotes the activation of T and B cells, leading to increased produc-

tion of pro-inflammatory cytokines, which further exacerbate inflammation and contribute to the development of a hyperthyroid state.

Moreover, IL-33 may play a critical role in modulating inflammatory responses not only in hyperthyroidism but also in hypothyroidism (26). As a cytokine that binds to the ST2 receptor, IL-33 is rapidly released from both immune and non-immune cells in response to cellular stress, thereby triggering a cascade of immune and inflammatory reactions. Interestingly, IL-33 has shown both tumor-promoting and tumor-inhibiting effects, depending on the targeted cell types, the IL-33/ST2 expression levels, the surrounding tissue microenvironment, and the overall cytokine milieu [64].

Initially thought to activate mast cells primarily and T helper 2 (Th2) cells to elicit type 2 immune responses, IL-33 is now known to exert broad immunological effects. Current evidence indicates that IL-33 has a significant stimulatory effect on group 2 innate lymphoid cells (ILC2s), regulatory T cells (Tregs), Th1 cells, CD8+ T cells, and natural killer (NK) cells. These diverse functions highlight the multifaceted nature of IL-33 in maintaining tissue and metabolic homeostasis, regulating inflammation, combating infections, modulating tumor progression, and contributing to central nervous system disorders [65].

4. Conclusion

This study demonstrated significantly elevated serum levels of IL-17 and IL-33 in Iraqi patients with hyperthyroidism compared to healthy controls, suggesting a strong association between these pro-inflammatory cytokines and the pathogenesis of the disease. The marked increase in IL-17 and IL-33 supports their potential role in driving immune-mediated inflammation and thyroid dysfunction. These findings highlight the relevance of IL-17 and IL-33 as possible biomarkers for hyperthyroidism and may provide insight into future therapeutic targets aimed at modulating immune responses in affected individuals.

Author Contributions

Conceptualization, M.M. and R.J.; methodology, M.M.; software, M.M.; validation, M.M. and R.J.; formal analysis, M.M.; investigation, M.M.; resources, M.M.; data curation, M.M.; writing—original draft preparation, M.M.; writing—review and editing, M.M.; visualization, M.M.; supervision, R.J.; project administration, M.M. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

This research received ethical approval from the Ethics Committee of the National Center of Hematology, Mustansiriyah University, under approval number nch-erc-p-25-1 dated 1 February 2025. All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee, as well as the 1964 Declaration of Helsinki and its later amendments.

Informed Consent Statement

All patient data were handled in accordance with ethical standards and institutional guidelines to ensure confidentiality. Personal identifiers were removed or anonymized prior to analysis, and all participants' information was kept strictly confidential.

Data Availability Statement

The data generated and analyzed during the current study are not publicly available due to patient confidentiality and ethical restrictions. However, they are available from the corresponding author on reasonable request and with appropriate ethical approval.

Conflict of Interest

The authors declare no conflict of interest.

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