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ORIGINAL PAPERS

Evaluation of TNF-α, IL-8, and IL-6 in Thyroid Disorder Patients Leading to Thyroidectomy

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Abstract

Introduction: This study was carried out to investigate the immunological role of some cytokines in patients suffering from thyroid disorders (nodular hyperplasia, thyroid cancer, hypothyroidism, and thyrotoxicosis). Therefore, this study aimed to assess several immunological factors associated with clinically diagnosed thyroid disorders in patients who decided to undergo thyroidectomy.

Methods: It was conducted at specialized outpatient and governorate laboratories in the period from September 2024 to November 2025. Eighty female individuals participated in this study, and serum samples were collected from these individuals before the operation. Alongside them, another set of serum samples was collected from twenty healthy female individuals to compare different cytokine levels between these two groups. ELISA kits were used to evaluate the serum levels of tumor necrosis factor α (TNF-α), interleukin 8 (IL-8), and interleukin 6 (IL-6).

Results: In non-toxic goiter patients, there was a significant increase (P≤0.01) in the IL-8 and IL-6 levels; there were no significant differences between non-toxic goiter patients and the control group in the levels of TNF-α. In toxic goiter patients, there was a significant increase (P≤0.01) in the TNF-α, IL-8, and IL-6 levels. In hypothyroidism patients, there was a significant increase (P≤0.01) in the TNF-α, IL-8, and IL-6 levels. Also, in thyroid cancer patients, there was a significant increase (P≤0.01) in the TNF-α, IL-8, and IL-6 levels.

Conclusion: The present study results support the fact that cytokines play essential roles in the development and prognosis of thyroid disorders. It indicates that measurements (TNF-α, IL-8, and IL-6) can be considered diagnostic tests to predict thyroid disorders.

Keywords: Goiter, thyroid gland, tumor necrosis factor α, interleukin 8, interleukin 6.

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INTRODUCTION

The thyroid gland was first described by Vesalius, who called it "Glandular laryngitis" since he incorrectly expected that this gland lubricated the larynx. The word thyroid, coined by Thomas Wharton, derived from the Greek word "Thyreos" meaning "an oblong shield" and "Eidos" meaning form[1].

The thyroid gland is a butterfly-shaped gland located just inferior to the larynx (voice box), with the right and left lateral lobes located on either side of the trachea. Connecting the lobes is a mass of tissue called an isthmus that lies anterior to the trachea. The thyroid glands have a small third lobe called the pyramidal lobe[2]. The gland has an abundant blood supply, receiving 80–120 ml of blood per minute[3].

Thyroid disorder is a public health problem among a large number of endocrinopathies. About 5% of the world's population is affected by different thyroid diseases. Most of the diseases affecting the thyroid gland, like goiter, are usually associated with enlargement of the gland and require medical and surgical intervention[4].

The thyroid hormones, thyroxine (T4), and triiodothyronine (T3) are essential for normal growth and development[5]. Thyroid-stimulating hormones (TSH) act upon the thyroid gland to initiate thyroid hormone production[6]. Thyroid hormone is necessary for normal brain development; extremely low levels of thyroid hormone during gestation and the neonatal period result in mental retardation[7]. The risk of women compared to men is more elevated (approximately 6/1)[8]. Autoimmune thyroid diseases (AITD) are the most frequent autoimmune disorders and result from an immune assault on the thyroid, and they are classified as "T cell-mediated organ-specific autoimmune disorders"[9]. AITD includes two main clinical presentations: Autoimmune thyroiditis (AT) and Graves' disease (GD). The clinical hallmarks of GD and AT are thyrotoxicosis and hypothyroidism, respectively. The prevalence of AITD is about 5%[10]; however, the prevalence of antithyroid antibodies (ATA) may be even higher. The risk of women compared to men is more elevated (approximately 6/1)[11]. Hypothyroidism is more frequent in older people[12]. There is a great geographic variability, and the prevalence of AITD and thyroid antibodies differs with race[13].

The incidence of AITD is more elevated in subjects living in iodine-sufficient areas in comparison to those in iodine-deficient areas[14]. The incidence rate of AITD is increasing, even if it is not possible to know whether this is due to a higher accuracy of diagnostic procedures[15]. The main objective of this study is to evaluate the immunomodulatory role of several factors in patients with thyroid disorders, and then compare them with a control group or healthy subjects. Identify the reasons and know the important future readings of these standards. The objectives of this study were achieved through the following protocol steps: patients with thyroid disorders are diagnosed by a specialist physician, and cytokine concentrations (interleukin 6 (IL-6), interleukin 8 (IL-8), and tumor necrosis factor-α (TNF-α)), are measured using ELISA technology[16].

PATIENTS AND METHODS

The study was carried out at Diyala Teaching Hospital in Baquba, Iraq; from September 2024 to November 2025. The study included 80 female patients, after their condition was confirmed through medical and clinical examinations by doctors who were specialized in this field. Also, a random group that included 20 healthy women was chosen as a control group. The ethical approval was done as a normal process for all human individuals involved in it. *The Medical Ethics Committee of Tikrit University College of Medicine had approved the present study with a code number (IQ. TUCOM.REC.2024.248).* An ethical standard agreement statement for each individual who participated in the current study, considering the Helsinki Declaration through the World Medical Association, was revised in 2000 at Edinburgh. The management reviewed the study protocol to ensure that it respected participants' rights, maintained confidentiality, minimized potential risks, and upheld principles of beneficence and justice.

The Study design

The study design included grouping patients according to cases of thyroid disorders. The first group included patients with nodular hyperplasia, the second group those who suffered from thyrotoxicosis, the third group those who suffered from hypothyroidism, and the last group those who suffered from papillary thyroid carcinoma.

Collection of Samples

The current study included 80 blood samples collected from females with thyroid disorders and from healthy females. Venous samples were taken before the thyroidectomy was performed for the patients and the control group. Blood samples were drawn from the median

cubital vein or from another vein if it was not accessible. Then 5 ml of blood was taken and placed in the gel tube, and the gel tube was placed in a cooler box (containing an ice pack) until it was transported to the laboratory unit and centrifuged for 10 minutes at 6000 rpm. After whole blood apheresis, the serum was extracted using a micropipette, and then 2 ml of serum was placed in three Eppendorf tubes for immunoassays. They are then stored in a deep freezer (-20°C).

Immunological tests

The levels of Immunological tests [interleukin 6 (IL-6), interleukin 8 (IL-8), and tumor necrosis factor-α (TNF-α)] were estimated by following the steps provided with their ready-made analysis kit according to the manufacturer's special instructions (SunLong Biotech / China) regarding ELISA technology.

Statistical analysis

The statistical analysis was carried out by using a statistical program (Minitab) and comparison between groups, which was made by using one-way analysis of variance ANOVA and testing the arithmetic means for parameters by using Duncan's multiple range test to determine significant difference, especially between groups. The level of statistical significance was taken at ($P \leq 0.01$)[17].

RESULTS AND DISCUSSION

Demographic distribution of the study population

The present study showed that in 80 patients suffering from various thyroid diseases, the final clinical diagnosis was determined as follows: There were 47 cases (59%) suffering from the non-toxic nodular goiter, whereas 11 individuals (14%) suffered from the thyrotoxicosis, and there were 17 individuals (21%) suffering from the hypothyroidism. The findings also revealed that there were 5 individuals suffering from the malignant tumor (6%), as shown in Table 1.

Concentrations of IL-6 in patients and control groups

The (mean ± SD) of IL-6 concentrations for non-toxic nodular goiter, toxic goiter patients, hypothyroidism, thyroid cancer papillary and control groups respectively were (17.62 ± 1.39) pg/mL, (29.18 ± 3.58) pg/mL, (35.26 ± 2.29) pg/mL, (56.24 ± 5.84) pg/mL, and (8.94 ± 0.97) pg/mL, as shown in Figure 1.

Table 1. Percentage of pathological diagnoses for patients with thyroid gland distributed by number.

Pathological diagnosis	Number	Percentage
G1- Non-Toxic Goiter	47	59 %
G2- Toxic Goiter	11	14 %
G3- Hypothyroidism		
a. Hashimoto	10	21 %
b. Lymphocyte	7	
G4- Thyroid Cancer		
a. Papillary	5	6 %
Total	80	100

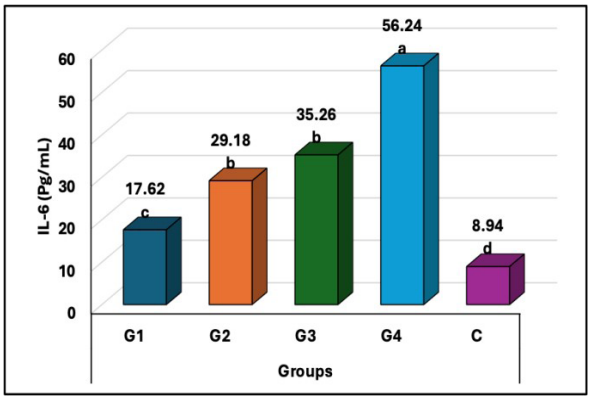

Fig.1. Concentrations of IL-6 (pg/mL) in patients and control groups (*) The similar letters mean that there are no significant differences between groups and the different letters mean that there are significant differences between them at a potential level $P \leq 0.01$(**). G1:Non-Toxic Goiter, G2:Toxic Goiter, G3:Hypothyroidism, G4:Thyroid Cancer, and C: Healthy Individuals (Control).

A growing body of evidence suggests that inflammation plays a major role in various thyroid diseases. In this study, a significant difference was observed between the five groups (for IL-6); it increased more in the thyroid groups than in the control group.

The significant elevation of IL-6 levels in patients with hyperthyroidism compared to the control group is consistent with studies by Jha et al and Rija et al[18,19] who focused on this cytokine and reported its important role in the development of hyperthyroidism. They observed that IL-6 plays a role in vascular inflammation because it has different biological activities in different target cells.

The thyroid gland produces IL-6, which is stimulated by antibodies to TSH receptors, IL-1, and possibly TSH receptors. It has been suggested that in patients with GD, the degree of increase may represent the severity of the condition due to higher IL-6 levels

in some studies[20]. According to a study conducted by Jha et al[18], hyperthyroid patients with active GD ophthalmopathy were found to have higher IL-6 serum concentrations than those without eye disease. Previous studies have shown that hyperthyroidism, especially caused by GD and toxic adenoma, is associated with high levels of IL-6 in the blood. These elevations were not consistent, and it remained difficult to distinguish between the role of thyroid hormones in this elevation and the role of the predominant autoimmune inflammatory process in GD[20].

The present results supported the hypothesis that hypothyroidism is associated with increased levels of inflammatory markers compared to controls, which may underlie the risk of cardiovascular disease in patients with hypothyroidism. Found that serum levels of IL-6 were significantly higher in hypothyroid patients compared to euthyroid controls. This is in agreement with Hussein et al., who reported that patients with hypothyroidism had low-grade chronic inflammation, which was confirmed by significant elevation of C-reactive protein (CRP) and IL-6 sensitivity[21].

The significantly higher concentrations of IL-6 and TNF-α in subclinical hypothyroidism patients were supported by a previous study[22]. In contrast to the present findings, the hyperthyroid patients had elevated serum levels of the cytokine IL-6, and hypothyroid patients had low levels of IL-6[20]. According to a study conducted by Shihan et al[23], it was found that increased levels of IL-6 were found in women with hyperthyroidism. However, hypothyroidism did not significantly reduce serum IL-6. Serum IL-6 that was normalized after disease remission suggests that it is related to follicular cell damage.

It found a significant positive relationship between blood TSH levels and inflammatory markers in hypothyroid patients. Gupta[24] also reported a significant increase in IL-6 levels in patients with subclinical hypothyroidism compared to healthy thyroid controls, which was also positively associated with serum TSH levels. Abdalla[22] found a significant negative correlation between serum total T3 and IL-6, and total T4 and IL-6.

TSH stimulates the release of IL-6 in adipocytes[25]. IL-6 plays a major role in the early stages of inflammation and also plays a modulatory role during the atherosclerotic process. It helps in accelerating atherosclerosis by producing CRP in the liver[23]. TNF-α is involved in systemic inflammation and also induces the acute phase reaction. It is also an important stimulator of IL-6 production[26]. It acts at every level of the hypothalamic-pituitary-thyroid axis to produce different changes in the axis[27].

These findings were supported by Tayde[28] IL-6 was significantly elevated in hypothyroid cases compared to healthy controls, and after treatment with levothyroxine, all markers decreased significantly. Also reported a significantly higher level of TNF-α in patients with hypothyroidism, but did not return to normal after normalization of thyroid function. In contrast, the current study population was newly diagnosed hypothyroid patients, who regained elevated inflammatory markers after treatment with levothyroxine, demonstrating the role of early treatment in resuming normal levels of markers[29].

It reported significantly higher levels of serum IL-6 in patients with benign thyroid diseases and thyroid cancer, compared to healthy controls[30]. Multiple studies have consistently reported that, compared to healthy controls, circulatory IL-6 levels were significantly higher in patients with various conditions such as malignant tumors, colorectal cancer[31], breast cancer[32], pancreatic cancer[33], gastric cancer[34], stomach and intestinal cancers[35], and others. This study also observed that IL-6 was able to promote the spread of oropharyngeal cancer[36].

Concentrations of IL-8 in patients and control groups

The (mean ± SD) of IL-8 concentrations for non-toxic nodular goiter, toxic goiter patients, hypothyroidism, thyroid cancer papillary and control groups respectively were (16.53 ± 1.18) pg/mL, (20.52 ± 2.45) pg/mL, (42.01 ± 3.62) pg/mL, (61.72 ± 6.89) pg/mL, and (9.36 ± 1.27) pg/mL, as shown in Figure 2.

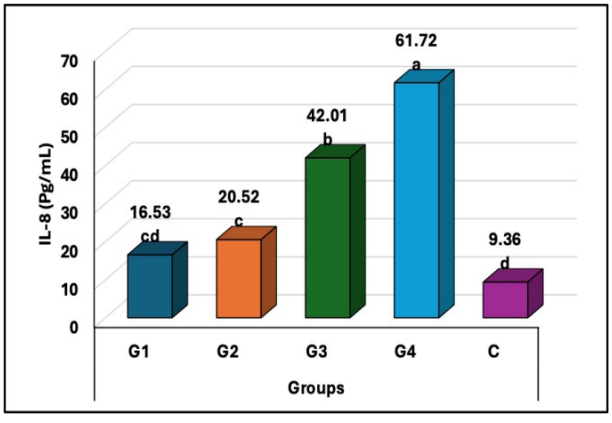

Fig. 2. Concentrations of IL-8 (pg/mL) in patients and control groups. The similar letters mean that there are no significant differences between groups and the different letters mean that there are significant differences between them at a potential level $P \leq 0.01$(**). G1:Non-Toxic Goiter, G2:Toxic Goiter, G3:Hypothyroidism, G4:Thyroid Cancer, and C: Healthy Individuals (Control).

Serum IL-8 levels were significantly elevated in all patients with thyroid disorders (goiter, autoimmune thyroid disorders, and thyroid cancer) compared to healthy individuals. Statistically significantly higher levels of each of these cytokines were found in patients with PTC. Similar to the present study, it demonstrated significant differences in IL-8 levels in euthyroid patients and normal controls[37].

Also, significantly elevated levels of IL-8 in patients with GD and nodular goiter compared to respective healthy control groups[38]. In contrast to these studies, Krassas and colleagues found that IL-8 levels were not elevated in GD, toxic nodular goiter, and HT[39]. Another study showed increased levels of cytokines, including IL-8, in patients who repeatedly develop thyroid disease syndromes followed by allogeneic bone marrow transplantation[40].

Increased levels of IL-8 have also been observed in patients with other malignant tumors. It was also found that the serum level of IL-8 was significantly elevated in most patients with Hepatocellular Carcinoma (HCC) compared with healthy subjects[41]. In fact, an elevated serum level of IL-8 has been found to be a diagnostic marker in soft tissue sarcoma[42], B-cell chronic lymphocytic leukemia[43], primary gastrointestinal non-Hodgkin lymphoma[44], and malignant melanoma[45]. Therefore, the elevated levels of both cytokines in the serum of thyroid cancer patients may be due to their overproduction in cancer cells and their subsequent release into the circulation. The incidence of thyroid cancer in thyroid cancer patients with higher levels of IL-8 compared to healthy subjects increased with increasing disease stage.

High serum IL-8 level correlates with large tumor size and advanced tumor stage in patients with HCC[46]. Increased IL-8 expression has been found in many tumors, and in some studies, IL-8 serum and/or tissue levels correlate with tumor progression and metastasis[47]. Therefore, this finding also supports a role for IL-8 in thyroid cancer development. Finally, monitoring serum IL-8 levels can help differentiate patients with thyroid disease from healthy individuals, and IL-8 appears to play a role in the pathogenesis of thyroid disease and may represent a target for innovative diagnosis and treatment.

The difficulties encountered likely arise during the differential detection of benign and malignant thyroid conditions because they both have commonalities in basic mechanisms. It is well documented that hypothyroidism cancer often occurs in the context of autoimmune thyroid diseases (AITDs), especially Hashimoto's thyroiditis (HT) and Graves' disease (GD)[48]. It has already been suggested that AITDs predispose to malignant transformation by establishing the tumorigenic microenvironment, where RET/PTC rearrangements are well tolerated to maintain inflammation operations[49]. In fact, many studies have documented that it alters the production of cytokines and chemokines in GD and HT, resulting in the initiation and maintenance of inflammatory and immune reactions[50].

In this study, a large percentage of patients suffer from thyroid disease, and they were also diagnosed with thyroiditis, primarily HT. And so on, activation of inflammation-related mechanisms, in particular induction of the inflammatory transcription program, was observed in both benign and malignant thyroid glands. The conditions make their differentiation by cytokine concentrations somewhat difficult, and provide a reasonable solution and explanation for the lack of statistically significant differences between patient groups in our observations.

Concentrations of TNF-α in patients and control groups

The (mean ± SD) of TNF-α concentrations for non-toxic nodular goiter, toxic goiter patients, hypothyroidism, thyroid cancer papillary and control groups respectively were (15.66 ± 0.92) pg/mL, (27.35 ± 2.85) pg/mL, (27.10 ± 2.46) pg/mL, (56.89 ± 5.03) pg/mL, and (12.37 ± 0.99) pg/mL, as shown in Figure 3.

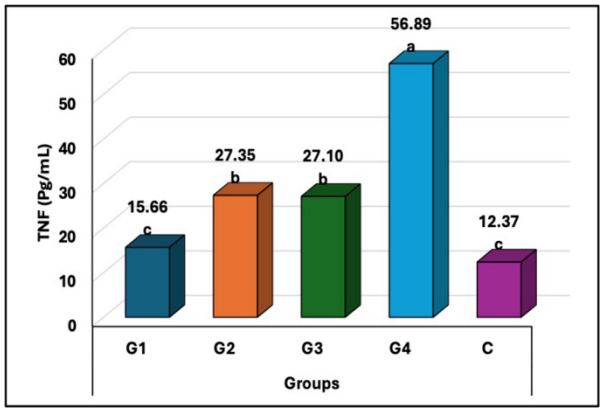

Fig. 3. Concentrations of TNF-α (Pg/mL) in patients and control groups. The similar letters mean that there are no significant differences between groups and the different letters mean that there are significant differences between them at a potential level P ≤ 0.01(**). G1: Non-Toxic Goiter, G2: Toxic Goiter, G3: Hypothyroidism, G4: Thyroid Cancer, and C: Healthy Individuals (Control).

Serum TNF-α levels were significantly elevated in patients with thyroid disorders (PTC, GD, and HT) compared to healthy individuals, whereas there were no significant differences in patients with goiter. TNF-α: It is an important cytokine involved in systemic inflammation[51]. TNF-α is an inflammatory cytokine produced mainly by monocytes and macrophages with pleiotropic effects. It binds to cell surface receptors and prevents the usual rise in intracellular calcium concentrations, resulting in the activation of multiple signal transduction pathways, enzymes, and transcription factors[52].

The present study revealed that serum TNF-α was significantly higher in PTC patients, compared to healthy individuals. However, it noted that patients with thyroid disease tend to have lower TNF-α level compared to normal controls[53], and TNF-α act as a growth inhibitor of PTC cell lines[54]. Another study showed that the average TNF-α levels measured in tumor patients were not significantly different from those observed in the control group[55].

Cytoplasmic TNF-α was found to be significantly higher in primary tumors of PTC patients compared to patients with benign thyroid diseases. TNF-α expression was only significantly positively associated with the presence of calcification in tumors, suggesting that TNF-α is likely involved in the development of calcification in tumors[56]. The present results may use TNF-α as a risk indicator for PTC and may have a role in tumor progression and prognosis in patients with thyroid cancer. Investigation into the role of cytokines in the onset and course of autoimmune thyroid diseases has been ongoing for decades. The pro-inflammatory cytokine, TNF-α, is involved in the induction and maintenance of immune responses. It is thought to play a crucial role in autoimmune thyroid diseases, including GD and HT[57].

Since it has been reported that TNF-α is usually short-lived in peripheral blood, various changes in TNF-α serum levels have been reported in patients with hyperthyroidism and hypothyroidism. In contrast, High serum levels of TNF-α have been reported in patients with GD, who were unable to return to normal after 6 weeks of taking antithyroid medications. Elevated levels of TNF-α in the serum of GD patients may affect the systemic response to the disease or the reciprocity between antigen and antibody within the thyroid gland. Increased cytokines in the thyroid may lead to the production of other cytokines by autoreactive cells, thus perpetuating the autoimmune reaction[58].

CONCLUSION

The results of this study indicate that all types of thyroid disorders are more common in females than in males. It was noted that thyroid cancer was less common among thyroid diseases, as pathological changes were observed, in addition to noticeable alterations in the levels of cytokines. The incidence of thyroid diseases is not limited to a specific demographic area, and the study results support the fact that cytokines play essential roles in the development and prognosis of thyroid disorders. The current study indicates that measurements (TNF-α, IL-8, and IL-6) can be considered diagnostic tests to predict thyroid disorders.

Ethics Statement and Conflict of Interest Disclosures

Financial support and sponsorship: All authors have declared that no financial support was received from any organization for the submitted work.

Ethics Consideration: The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by the patient participant in this study.

This study was approved by the Institutional Research Board and Ethics Committee.

Conflict of interest: No known conflict of interest correlated with this publication.

Availability of data and materials: The data used and/ or analyzed throughout this study are available from the corresponding authors upon reasonable request.

Competing interests: The authors declared that they have no competing interests.

The use of generative AI and AI-assisted technologies: The authors did not use in this article generative AI and AI-assisted technologies.

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