

Evaluation of Proinflammation Interleukin IL-6 in Thyroid Disorders Patients in Najaf Province

Naser Adris Naser¹ and Thikra Abdullah Mahmood²

^{1,2} Faculty of Medicine, University of Kufa, Najaf, Iraq.

ABSTRACT

Background: Problems with thyroid disorders can be caused by iodine deficiency or autoimmune diseases. Autoimmune thyroid disorders (AITD) are caused by an instability of the immune system that leads to an immune attack on the thyroid gland such as Graves' disease or Hashimoto's disease. Specific autoimmune diseases that affect a specific thyroid gland are known as AITDs. The study aims to identify the effect of interleukins (IL-6) on patients with thyroid disease. The current study includes more than 400 total samples, of which 140 samples underwent immunodiagnostics' and were divided into 70 control groups: 35 Graves' illness and 35 Hashimoto's illness patients who visited Sadr Medical City (Diabetes and Endocrinology) and the specialty of Al-Zahraa Laboratory and some laboratories in Najaf Governorate from July 2023 to October 2023, ages 18–70. Concentrations of thyroid hormones T3, T4, and TSH were measured to identify patients with hypothyroidism or hyperthyroidism and compared to a control group. It has been found that patients with hypothyroidism enjoyed significantly lower intensities of T3, T4, as well as TSH, while their TSH degree increased significantly compared to the rest of the patients and the control group. Most of the patient samples were from hypothyroid patients. After that, special tests were performed to detect the presence of specific antibodies associated with this disease (AITD), namely ATPO and ATG, in addition to the clinical diagnosis of patients by the doctor. Secondly, ATG was significantly increased in patients with Hashimoto's compared with patients with Graves' and fit controls, and ATPO concentration was significantly elevated in both patients with GD and HD compared with healthy controls. This study showed a higher incidence of AITD in females, as it was in Graves (84.8%) and Hashimoto's (77.1%), and the age group 30–50 years was more frequent in Graves (51.5%) and Hashimoto's (62.9%). smoking in the hypothyroid 29 (78.6%) and 27 (81.8%) patients, while in the non-smoking patients, the control was 8 (21.6%) hypothyroid and 6 (19.4%). There was a significant difference in the frequency distribution according to smoking among study groups ($p = 0.003$). Mental status was significant ($p\text{-value} \leq 0.05$ was 0.00001). TSH, T3, T4, antTPO, and antTG are binding with Hashimoto's and Graves'. In immunological studies, the degree of IL-6 in serum is significantly higher in thyroid disorders (Hashimoto's disease was 9.665 and Graves' disease was 9.636) in the $p\text{-value} \leq 0.05$ compared with the healthy group (mean = 9.192), Comparative analysis shows the mean difference in concentration level of IL6 among patients with thyroid disorders. There's an important variation in the mean concentration of IL6 among patients with thyroid groups (Hashimoto's disease was 5.513 and Graves' disease was 5.541), though the concentration mean of the control group was 8.111. **Conclusion:** Anti TOP and AntiTG have a strong effect on interleukin-IL-6. Compared to the control group, individuals with hyperthyroidism and hypothyroidism had significantly lower IL6 levels. Pro-inflammatory cytokines, such as IL6 and others, have a positive correlation with psychopathology through various mechanisms impacting neurodevelopment, transmission, and synaptic plasticity; these differences are significantly different from those between thyroid disorders and mental status. Females are more likely to suffer from thyroid disorders than males because of the "double effect" that women produce. The frequency distributions of the research groups differed significantly with respect to smoking.

Keyword: IL-6, Autoimmune Disease, And Thyroid Disorders.

Article Information

Received: June 09, 2024; Revised: August 17, 2024; Online: September, 2024

INTRODUCTION

Autoimmune diseases are defined as conditions in which the immune system mistakenly attacks and damages the body's own tissues and organs. Experts believe that a disturbance in the body's ability to tolerate its own tissues and/or a malfunction in immune response regulation cause autoimmune diseases(1). Local triggers in non-immune target tissue, caused by genetic and/or environmental factors, may cause the immune system to attack the target tissue excessively. Currently, we know that an inherited genetic defect accounts for around 5–10% of all cancer cases, with environmental factors and lifestyle decisions responsible for the remaining 90–95%. They have shown that environmental factors, such as infection, stress, obesity, aging, and smoking, are more likely to induce chronic inflammation, contrary to the notion that pre-neoplastic cells primarily trigger oncogenesis (2)

The presence of many autoimmune conditions in an individual and the occurrence of autoimmune disorders within a family provide support for this concept. While "familial autoimmunity" refers to the occurrence of several autoimmune diseases (ADs) in various members of a nuclear family, "poly-autoimmunity" specifically describes the presence of two or more ADs in a single patient. A study conducted by Anaya and colleagues in 2007. According to (3). Autoimmune thyroid disease (AITD) According to Dayan and Daniels (1996), autoimmune thyroid disorders (AITD) are the most common organ-specific autoimmune diseases (ADs), affecting 2–5% of the population. There is a significant difference in the prevalence of AITD across genders, with women being affected at a rate of 5–15% and men at a rate of 5% (4).

The thyroid is a small gland with a butterfly-like shape, located in the neck immediately below the Adam's apple. Rona, Z. P., "Optimising Thyroid Health." The breadth is around two inches. Triiodothyronine (T3) and thyroxine (T4) are endocrine hormones synthesised by the thyroid gland that regulate the metabolic processes of the body. (5). When necessary, T4 transforms into T3, with T3 being the more physiologically active form. Binding to blood proteins renders most T3 and T4 hormones inactive. They only become active when they detach from the protein and

engage with iodine and proteins obtained from the food (Agate et al., 2008). Thyroid gland disorders are the most common endocrine diseases globally, consisting of three main clinical categories: iodine deficiency, thyroid enlargement, and thyroid cancer. (6). Hyperthyroidism and hypothyroidism are prevalent conditions that arise from either an overabundance or a deficiency of thyroid hormone production. Common thyroid-related illnesses comprise Hashimoto's thyroiditis, Graves' disease, goitre, thyroid nodules, and thyroid cancer (7)

Hyperthyroidism Hyperthyroidism is a medical disorder characterised by the overproduction and release of an excessive quantity of thyroid hormones by the thyroid gland. Conversely, thyrotoxicosis is the medical term for having an excessive amount of thyroid hormones in the blood, regardless of where they come from. Overt hyperthyroidism is when the thyroid stimulating hormone (TSH) levels are too low or not present at all, and the levels of triiodothyronine (T3) and/or thyroxine (T4) are too high (8).

Graves' disease (GD) is a systemic autoimmune condition. In this case, there are thyroid-stimulating autoantibodies that attack the thyrotropin (TSH) receptor on thyroid follicular cells. As a result, these cells become larger, there is a rise in the synthesis of thyroid hormones, and hyperthyroidism develops.

Graves' disease impacts around 0.5% of the population and is the main contributor to hyperthyroidism, accounting for 50–80% of all cases. Bobanga (9). The clinical manifestations of GD encompass a diffuse enlargement of the thyroid gland (as seen in Figure 1), ocular complications, oedema of the skin on the lower extremities, and muscular debility in the proximal muscles. Grave's ophthalmopathy (GO), an inflammatory eye illness, occurs in around 50% of individuals with GD due to the reaction of their antibodies with thyroid-stimulating hormone (TSH) receptors. Retroocular fibroblasts and adipocytes also contain these receptors. Approximately 5% of those diagnosed with Graves' disease experience severe Graves' ophthalmopathy (10).

A thyroid gland that is not functioning at its normal level is the hallmark of hypothyroidism. Untreated hypothyroidism can result in hypertension, dyslipidemia, infertility, cognitive deterioration, and neuromuscular dysfunction. Hypothyroidism is a condition that occurs when there is an inadequate quantity of thyroid hormone. This condition can be caused by several factors and is characterised by a range of symptoms. Untreated hypothyroidism increases the likelihood of sickness and mortality (11). Hashimoto thyroiditis is the main contributor to hypothyroidism in the United States, but globally, the leading factor is inadequate consumption of dietary iodine. The patient's state might vary from being asymptomatic to developing myxedema or coma. At present, simple blood tests may easily detect hypothyroidism and treat it by injecting an exogenous thyroid hormone (12). Common symptoms of hypothyroidism include dry skin, sensitivity to cold, difficulty with bowel movements, slowed thinking, weight gain, rough skin, swelling, a slow heart rate, and delayed relaxation of the Achilles tendon reflex. The symptoms often develop slowly

and show significant similarities between individuals with thyroid disorders and those without. The signs and symptoms of thyroid dysfunction exhibit limited sensitivity and specificity (13).

Hashimoto's thyroiditis (HT) is the predominant form of autoimmune thyroid disease (AITD). It causes long-lasting inflammation of the thyroid tissue, leading to hypothyroidism in around 20–30% of people report on an autoimmune disorder characterised by the infiltration of lymphocytes into the thyroid gland. Researchers believe this phenomenon occurs because the thyroid protein bears resemblances to viral structures, triggering the creation of antibodies that react to both (14). Hashimoto thyroiditis is characterised by the presence of anti-thyroid peroxidase (anti-TPO) antibodies in 90% of individuals. It is possible for them to start complement activation and antibody-dependent cell-mediated cytotoxicity, which kills thyrocytes (15).

Initially, it was believed that leukocytes were the sole producers of interleukins (IL), a kind of cytokine, in the body. However, further investigations have revealed that various other cells in the body also have the ability to create interleukins. They have vital roles in the activation and differentiation of immune cells, as well as in the processes of growth, development, mobility, and attachment. Furthermore, they exhibit both pro-inflammatory and anti-inflammatory properties (16). Interleukins have a crucial role in controlling the development, differentiation, and activation of cells during inflammatory and immunological responses. Interleukins are a heterogeneous group of proteins that may elicit a range of cellular and tissue reactions by binding strongly to receptors located on cell surfaces. They have both paracrine and autocrine capabilities. Animal research uses interleukins to study several areas of clinical

medicine (17). Interleukin-6 (IL-6) T and B lymphocytes, fibroblasts, and macrophages synthesize interleukin-6 (IL-6). The virus primarily targets B cells and hepatocytes. IL-6 mostly works by helping B-cells differentiate and speeding up the activation of acute-phase proteins (18).

The research aims to Measure the concentrations of T3, T4, TSH, antithyroid peroxidase (TPO), and antithyroglobulin (TG) in the blood serum, analyze the variations in patients, and compare the findings with those of the control group. thereafter, conduct tests to ascertain the blood levels of hyperthyroidism and hypothyroidism in individuals with immunological disorders, and thereafter compare the obtained results with those of the control group. Assess the blood concentrations of IL-6 and analyze their impact on thyroid illness in individuals with hyperthyroidism or hypothyroidism. Compare the findings with those of the control group.

METHODOLOGY

The current study includes more than 400 total samples, of which 140 samples underwent immunodiagnostics' and were divided into 70 control groups: 35 Graves' illness and 35 Hashimoto's illness patients who visited Sadr Medical City (Diabetes and Endocrinology) and the specialty of Al-Zahraa Laboratory and some laboratories in Najaf Governorate from July 2023 to October 2023, ages 18–70.

Selection of Patient Groups

We gathered sociodemographic information using a standard questionnaire after reading extensively about HT and GT and having three experts check its validity. The filling technique was a face-to-face meeting between the researcher and the subjects. For more information, including the genetic history of the disease, the patient's psychological state, the workplace, measuring height and weight,

and writing down the severity of the disease, expert doctors took a comprehensive history and diagnosis before sending the patient to the laboratory for testing.

The inclusion criteria:

The study included all patients, Physicians diagnosed patients in the present study as having either HT or GT. The diagnostic criteria of the Najaf Diabetes and Endocrinology Centre at Sadr City Medical Hospital, Al-Zahraa Specialised Laboratory and some laboratories close to a doctor were used to diagnose HT and GT patients.

These standards are:

1. Presence of clinical features of HT or GT in addition to confirmatory thyroid function tests.
2. The presence of autoantibodies in the blood against thyroid antigens (mainly anti-thyroid, anti-TPO, and anti-Tg). Laboratory diagnostic examination (T3, T4, TSH).
2. The age of puberty for both sexes.
3. Taking questionnaire information from healthy patients (control).

• Exclusion criteria include any patient with:

1. Age under 18 years old.
2. Recent blood transfusions (within the last six months).
3. History of thyroidectomy or radioactive iodine.
4. Patients with other diseases such as rheumatoid arthritis, T1DM, SLE, or celiac disease.
5. Non-thyroid systemic disorders such as acute or chronic hepatic, renal, cardiovascular, cerebrovascular, benign, and malignant diseases.
6. Women who are pregnant or taking birth control pills.

7. All participants (patients and controls) had their hemolytic, jaundice, and lipemic index (HIL) samples excluded.
8. Alcoholic.
9. People who did not agree to participate in the study.

Control group.

Total numbers in this group ($n = 70$) consisted of people who appeared to be healthy, had no signs of chronic disease, had a normal thyroid based on thyroid function testing, and did not have thyroid antibodies at the time of sample collection.

Evaluation using statistical methods

Following a check for normalcy in the data, SPSS version 26 ran a Nova test and a Chi-Square test to compare the means of detection in the vaccinated cohort study.

RESULTS AND DISCUSSION

Distribution of serum concentration by ELSA Immunoassay

140 samples were taken from patients with thyroid abnormalities, consisting of 70 cases and 70 controls, who were receiving treatment at hospitals and private centers for thyroid illnesses. Samples are collected from both patients and controls to measure blood concentrations of IL18, IL6, TNF-alpha, and specific thyroid problem tests using the Elisa immunoassay.

Differences in Sociodemographic distribution among thyroid disorder patients and control

Distribution of age groups, shows an increase in the age groups (30-50 years old) from thyroid disorders patients and control, in order to <30, 30-5, and >50 years old, which their proportions and Hyperthyroid 17/35 (48.6%), while the, there is statistical not

significance (probability value = 0.490), as shown in **Table (1)**.

There was no statistically significant variation in the average age between patients with Hashimoto's thyroiditis, patients with Graves' illness, and control participants ($p = 0.490$). In this study found Hypothyroid 24/35 (68.5%) at age groups (30-50 years old), to <30, 30-5, and >50 years old, In current study hypothyroid disorder was (30-50 years old), that agreement with **(19:20)** the average age of patients with Hypothyroid disorder was (30-50 years old), the age group in the presented study and previous published articles studies in same line that dealing with Hypothyroid disorder in adults.

The total proportion of individuals present for thyroid disorders of male and female was 106 (75.7%) included 29/35 (82.8%) hypothyroid and 28/35 (80.0%) was hyperthyroid. The proportion of males present for thyroid disorders was 34/140 (24.7%), there no statistical significance ($p = 0.277$), in **table (1)**. According to a number of research, women are more infected to thyroid disorders in general, that agreement with **(21)**, That agreement, it may be caused by genetic, and hereditary variables, as well as agreement with **(22)**. In addition, there is a great deal of variety and diversity regarding immunity located on the X chromosome than on the Y chromosome, aiding and inducing immunological responses in the body.

The persistent nature of these disorders imposes a substantial load on the consumption of healthcare services, both in terms of direct and indirect economic expenses, as well as the overall quality of life. The majority of autoimmune disorders have a higher incidence in middle-aged women and are among the primary causes of mortality for this patient demographic. The female-to-male ratio for autoimmune illnesses gets increasingly

pronounced as patients age (23). Impacting 2-5% of the population with notable gender disparities (specifically, affecting women at a rate of 5-15% and males at a rate of 5%).

The increased number of genes on the X chromosome significantly raises the probability of further mutations occurring. Women have a higher likelihood of developing autoimmune disorders compared to males because to the presence of two X chromosomes in women and only one in men (24). Females have a higher likelihood of developing autoimmunity due to the presence of two X chromosomes. This results in a "double effect" of X chromosome genes, as supported by (25). Some people may have a genetic predisposition from paternal while others have a predisposition maternal depending on. This study was in disagreement with (26)

Table (1) shows, BMI can be classified according to the WHO; 2023 into three categories (18-24.9, 25-29.9, and $30 \leq$), in this study there is no significant difference (p-value = 0.0163) between BMI and thyroid disorder (hyper and hypothyroid).

The present study compares serum biomarker levels. According to occupation and residency of patients with thyroid disorders, This study discovered there were statistically significant changes ($p > 0.05$) in the levels of blood biomarkers between cases and control with thyroid disorders. This result disagreement with the results reported by (27). Obesity (BMI), is one of the most no significant health hazards. In a current study, that agreement with (28)

This study agreement with (29), that Who had a body mass index (BMI) of at least 30.0 kg/m², there was a no significant association between hypothyroidism and greater BMI. In this study disagreement interpretation With

due to swift economic growth and shifts in lifestyle, obesity has emerged as a prevalent health issue in both developed and developing nations Obesity rates have surged globally.

According to a study by (30), it was found that TSH levels in obese children, adolescents, and adults are either at the upper limit of the normal range or slightly increased. These levels are also positively correlated with BMI, as reported by (31). This suggests that there is a positive association between TSH and BMI in certain individuals, This current result, smoking there are found significant different between smoking among hypothyroid 29(82.8%) and 27(77.1%) from hyperthyroid while in not smoking patients and control was 8(22.8%) hypothyroid and 6(17.1%), There was significant difference in the frequency distribution according to smoking among study groups ($p = 0.0133$), in table (1), This agreement pertains to Relative Risk 2.0. (32). The process by which thyroid hormone synthesis is enhanced remains unidentified. Nicotine-induced sympathetic activation has been suggested as a potential cause. Research by (33) has demonstrated that TSH levels are reduced among smokers. Smokers without any indications of hypothyroidism or hyperthyroidism may have a slight elevation in thyroid hormones as a result of smoking.

This study conducted that smoking can also contribute to the development of thyroid illness. The precise mechanism by which tobacco smoke impacts the thyroid is not fully understood; however, it has been proposed that variables such as tobacco smoke, hypoxia, and the generation of oxygen-free radicals may have a role (Zhang et al., 2019). Smoking tobacco negatively impacts Graves' disease (GD) (34). Antibodies would be produced against the presumed foreign material as a result of the immunological reaction.

Table (1): Relationship between Sociodemographic characteristics and thyroid disorders (number of cases and control=140) .

Sociodemographic variables			Thyroid disorders				P value
			Hypothyroid	Hyperthyroid	control	Total	
			n=35	n=35	n=70	N=140	
Age group (Years)	<30	Count	4	9	13	26	0.490
		%	11.4%	25.7%	18.6%	18.6%	
	30-50	Count	24	17	40	81	
		%	68.5%	48.6%	57.1%	57.9%	
	>50	Count	7	9	17	33	
		%	20.0%	25.7%	24.3%	23.6%	
Sex	Female	Count	29	28	49	106	0.232
		%	82.8%	80.0%	70.0%	75.7%	
	Male	Count	6	7	21	34	
		%	17.1%	20.0%	30.0%	24.3%	
BMI Categories	18-24.9	Count	6	15	27	48	0.0166
		%	17.1%	42.8%	38.6%	34.3%	
	25-29.9	Count	15	11	33	59	
		%	42.8%	31.4%	47.1%	42.1%	
	30 ≤	Count	14	9	10	33	
		%	40.0%	25.7%	14.3%	23.6%	
Smoking	yes	Count	27	29	67	123	0.0133
		%	77.1%	82.8%	95.7%	87.9%	
	No.	Count	8	6	3	17	
		%	22.8%	17.1%	4.3%	12.1%	

Mean concentration level of IL6 (ng/ml) with thyroid disorder in cases and control :

In figure (1) of this study showed Comparative analysis of mean difference of concentration level IL6 among patients with thyroid disorder. There is a significant difference in mean of concentration of IL6 among patients with thyroid groups (Hashimoto's disease was 5.513 and Graves' disease was 5.541), while compared with the concentration mean of control group was (8.111). Thyroglobulin antibody levels can be

high in both Hashimoto's and Graves' illness Furthermore these antibodies can affect thyroglobulin levels. This study provides evidence of a causal relationship between IL-6 and macrophage inflammatory response on the risk of hypothyroidism and healthy individuals with (35). cytokines such as IL6 that are produced by many effector immune cells, these cytokines have an important role in immunity and inflammation. There was a considerable rise in interleukin-6 (IL-6) levels in the hyperthyroid group.

Figure (1): Comparative analysis of mean difference of concentration level IL6 among patients with a thyroid disorder (hyperthyroid and hypothyroid) group and control group (normal)

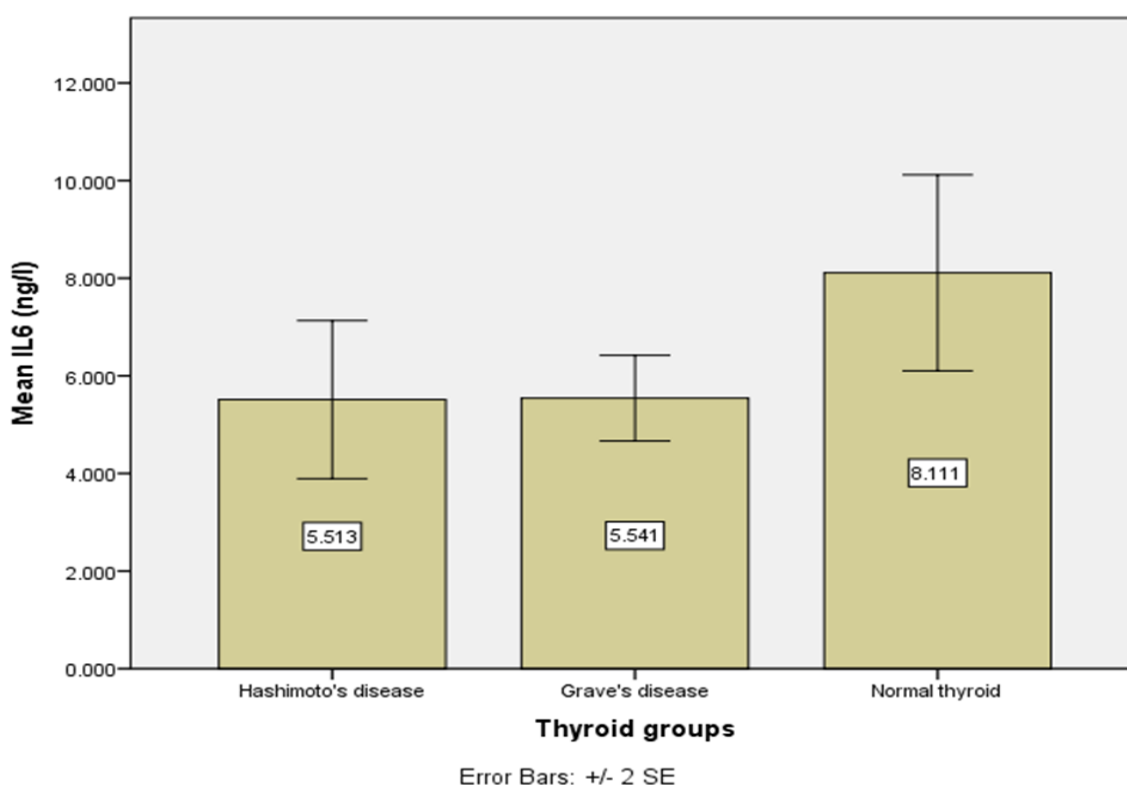


Figure 1: Relationship between Serum Biomarkers concentration of patients with thyroid disorder and controls.

The analysis of Table (2) revealed a statistically significant difference. In this result shows ,that is significant different between TSH and Hashimoto's disease to 35/70(50.0%), was mean (23.27) , SD± 2.68 and (95% CI = 15.48-31.05 , p-value ≤ 0.05

was) ,while T3 mean=0.67, SD± 0.08 and 95%CI=0.04-0.95 /justificat signification). tT3 mean=0.67, SD± 0.08 and 95%CI=0.04-0.95 justification signification). while T4 mean=5.01, SD± 2.27 and 95%CI=4.23-5.79) signification). This study agreement with (36).

Demonstrates that in cases of hypothyroidism, there is a drop in levels of T3 and T4, while levels of TSH increase. Conversely, in cases of hyperthyroidism, there is an increase in levels of T3 and T4, while levels of TSH fall. This aligns with the present research. The thyroid disease is one of the most common medical conditions and cannot be distinguished between hypo- and hyperthyroidism depending on clinical features because the signs and symptoms are non-specific, especially in females; therefore, most researchers recommend depending on the level of TH in the blood to distinguish between them (18).

The study done by (37) was in agreement with the previous study that confirmed that thyroid function can depend on the level of thyroid stimulating hormone (TSH) as the initial screening test for suspected patients with thyroid disease, as it is the key hormone for diagnosing hyperthyroidism and hypothyroidism because the level of TSH is controlled by a negative feedback mechanism, and more than this, any tiny changes in the level of TSH can lead to changes in thyroid functions.

The relative of Anti TOP and Hashimoto's disease were 35/70(50.0%), mean was (722.89), $SD\pm$ was 2.68 and 95% CI (15.48-31.05 /significant different) ,while T3 mean was 0.67, $SD\pm$ was 0.08 and 95%CI was (448.52-927.26 / signification). The relative of Anti TG and Hashimoto's disease was 35/70(50.0%), mean was(722.89) , $SD\pm$ was 2.68 and 95% CI was (15.48-31.05 /significant different) ,while T3 mean was 0.67, $SD\pm$ was 0.08 and 95%CI was (448.52-927.26 / signification). There is significant different between IL18 and (Hashimoto's disease CI was 6.97 - 12.36, Graves' disease CI was 8.84 - 10.25/ signification) ,

There is no significant different between IL18 and (Hashimoto's disease CI=- 6.97 - 12.36, Graves' disease CI was 8.84 -10.25/ signification) , there is positive relationship between TSH and Graves's disease to 35/70(50.0%), was mean (0.34) , $SD\pm$ 0.13 and (95% CI 0.01-0.24 /justification significant different) ,while T3 mean=1.53, $SD\pm$ 1.13 and 95%CI=1.14-1.92 /justificat signification). while T4 mean=12.72, $SD\pm$ 9.53 and 95%CI=9.45-15.99) signification).

In the current study agreement with (38). These results showed that patients with Graves' disease had extremely substantial increases in T3 and T4 levels as well as a highly significant decrease in TSH levels when compared to control subjects. Because T3 and T4 are on the pituitary and hypothalamic axes, the source of these antibodies is immune-competent plasma cells, and the antibodies bind with TSHR and block it, leading to the start and increase of T3 and T4 synthesis and production regardless of a decrease in TSH.

According to (39). Graves' illness is the most frequent cause of hyperthyroidism (GD), which increases the effectiveness of thyroid gland tissue and causes hyperactivity in the production of one or both thyroid hormones (T3 and T4). In order to quickly identify Graves' disease, a total T3/T4 ratio and TSH value may be utilised .Variations in T3 and T4 levels, as well as TSH, are goitre markers, according to (40),

The relative of Anti TOP and Graves's disease were 35/70(50.0%), mean was (722.89) , $SD\pm$ was 2.68 and 95% CI (15.48-31.05 /significant different) ,while T3 mean was 0.67, $SD\pm$ was 0.08 and 95%CI was (448.52-927.26 / signification). According to Anti TOP and graves's disease were 35/70(50.0%), was mean (722.89) , $SD\pm$ was 2.68 and 95% CI was(15.48-31.05 /significant different) ,while T3 mean=0.67, $SD\pm$ 0.08 and

95%CI=448.52-927.26 / signification).

The relative of Anti TG and Graves's disease was 35/70(50.0%), mean was(722.89), $SD \pm$ was 2.68, and 95% CI was (15.48-31.05 /significant different), while T3 mean was 0.67, $SD \pm$ was 0.08 and 95%CI was (448.52-927.26 / signification). That was a significant different between IL18 and (Hashimoto's disease 95% CI was 6.97 - 12.36, Graves' disease 95% CI was 8.84 -10.25/ signification).

There was a significant different between IL6 and (Hashimoto's disease CI was 3.87-7.16/ signification difference), while in Graves's disease 95% CI was 6.97 - 12.36 / signification). This table had shown, that relationship between TNF - α and Hashimoto's disease CI was 18.35 – 36.09 / signification difference), while in Graves's disease 95% CI was 21.96-28.60 / signification), all over was decretive in **table (2)**.

The T3, T4, and TSH readings fell within the usual range. Primary hypothyroidism is characterised by a TSH level higher than 5.5 mIU/ml and lower than normal levels of T3 and T4. Primary hyperthyroidism is characterised by a TSH level below 0.3 mIU/ml and elevated levels of T3 and T4 hormones.

Subclinical hypothyroidism is a condition characterised by a TSH level higher than 5.5 mIU/ml, although T3 and T4 levels remain within the normal range. Subclinical hyperthyroidism is characterised by a TSH level lower than 0.3 mIU/ml, but T3 and T4 levels remain within the normal range. Normal values depend on guidelines for the detection of thyroid disorders **(41)**

Table 2 compares blood thyroid-stimulating hormone (TSH) levels in individuals with Hashimoto's Thyroiditis(HD), Graves' disease(GD), and a control group. Those with Hashimoto's Thyroiditis had the highest mean serum TSH then patients with Graves' disease and the control group, followed by 23.27 ± 2.68 (μ UI/ml), 0.34 ± 0.13 (μ UI/ml), and (μ UI/ml), and 2.43 ± 1.67 (μ UI/ml) respectively, in **table (1)**

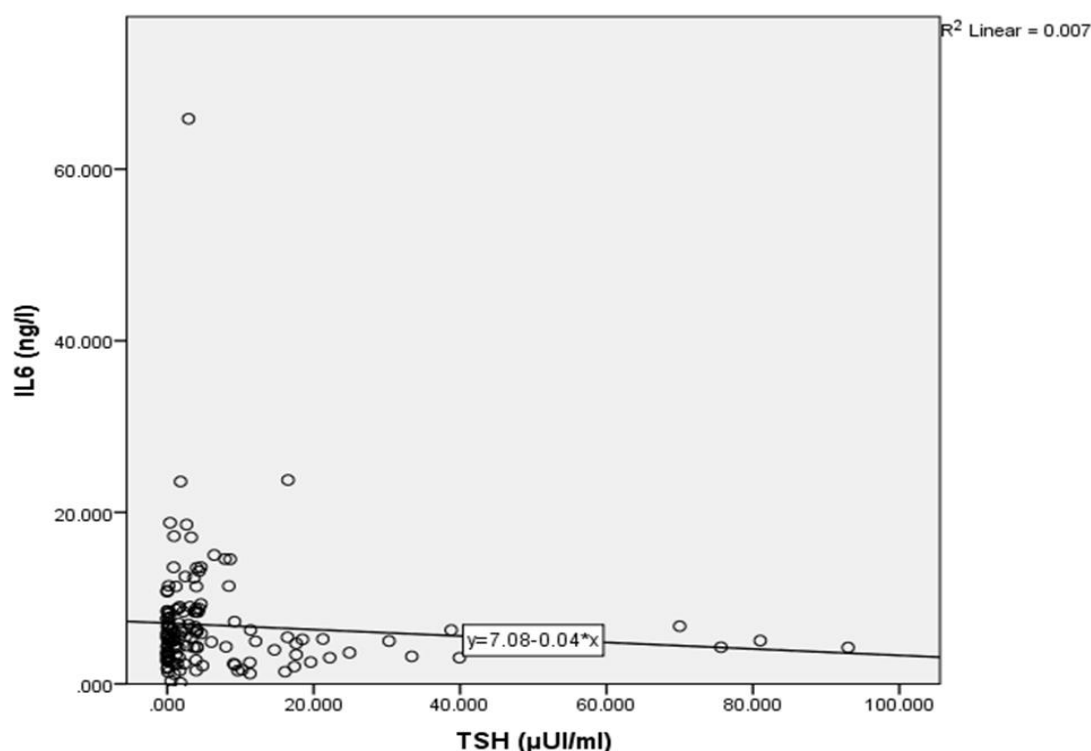
The disparity in average serum TSH levels across the research groups was extremely significant ($p < 0.05$). The mean blood TSH levels showed a significantly significant difference between the control group and individuals with Hashimoto's thyroiditis ($p < 0.05$). The mean blood TSH levels showed a significantly significant difference between the control group and individuals with Graves' illness ($p < 0.05$). The mean blood TSH levels exhibited a highly significant difference ($p < 0.05$) between individuals with Graves' illness.

The correlation of concentration serum level of IL-6 with TSH in patients and control.

In this study shown, the correlation between concentration level of IL-6 cause with effect of TSH levels in patients with a thyroid disorder, and control, there was a negative correlation, R^2 Linear was 0.007 there is weakness correlation, ($y=7.08$, $x= 0.04$, p -value significant ≤ 0.05). This study agreement with**(13)**, Some interleukins, such as IL-6, may inhibit the pituitary thyroid, that IL-6 levels have the potential to indicator of the extent of hypothyroidism. This is due to the observed negative correlation between serum IL-6 levels and TSH levels in individuals diagnosed with autoimmune hypothyroidism, **Scatter plot (1)**.

Table 2: The relationship between Serum Biomarkers concentration of patients with thyroid disorder and controls (No.=140)

Biomarkers		No. of cases=70 Normal =70	Mean	Std. Deviation	P-value	95% Confidence Interval for Mean	
						Lower Bound	Upper Bound
TSH (μ UI/ml)	Hashimoto's	35	23.27	2.68	.000	15.48	31.05
	Grave's	35	0.34	0.13	.000	0.01	0.24
	Normal	70	2.43	1.67	.000	2.03	2.82
T3 (nmol/l)	Hashimoto's	35	0.67	0.80	.330	0.40	0.95
	Grave's	35	1.53	1.13	.000	1.14	1.92
	Normal	70	1.18	0.50	.330	1.06	1.30
T4 (nmol/l)	Hashimoto's	35	5.01	2.27	.000	4.23	5.79
	Grave's	35	12.72	9.53	.002	9.45	15.99
	Normal	70	31.62	40.99	.000	21.85	41.39
ant TPO (pg/ml)	Hashimoto's	35	928.76	685.75	.031	693.20	1164.32
	Grave's	35	1297.85	2350.91	.002	490.28	2105.42
	Normal	70	159.37	240.77	.031	101.96	216.78
antTG (pg/ml)	Hashimoto's	35	722.89	798.73	.276	448.52	997.26
	Grave's	35	608.76	361.69	.000	484.52	733.01
	Normal	70	123.92	87.72	.276	103.01	144.84
IL6 (ng/l)	Hashimoto's	35	5.51	4.79	.000	3.87	7.16
	Grave's	35	5.54	2.60	.000	4.65	6.43
	Normal	70	8.11	8.40	.000	6.11	10.11



Scatter plot (1): correlation between IL₆ and TSH, R^2 Linear was 0.007 there are weakness correlation, ($y=7.08$, $x= 0.04$, P-value significant ≤ 0.05).

CONCLUSION

Anti TOP and AntiTG have a strong effect on interleukin-IL-6. Compared to the control group, individuals with hyperthyroidism and hypothyroidism had significantly lower IL6 levels. Pro-inflammatory cytokines, such as IL6 and others, have a positive correlation with psychopathology through various mechanisms impacting neurodevelopment, transmission, and synaptic plasticity; these differences are significantly different from those between thyroid disorders and mental status. Females are more likely to suffer from thyroid disorders than males are because of the "double effect" that women produce. The frequency distributions of the research groups differed significantly with respect to smoking.

REFERENCES

- 1-Jacob Berman and Brenda Conaway,(2023).An *autoimmune disorder* occurs when the body's immune system attacks and destroys healthy body tissue by mistake.
- 2-Grivennikov, S. I., Greten, F. R. and Karin, M. (2010). Immunity, inflammation, and cancer. Cell 140:883]
- 3- Anaya, J.-M., Castiblanco, J., Rojas-Villarraga, A., Pineda-Tamayo, R., Levy, R. A., Gómez-Puerta, J., . . . Cervera, R. (2012). The multiple autoimmune syndromes. A clue for the autoimmune tautology. Clinical reviews in allergy & immunology, 43, 256-264.
- 4-Antonelli, A., Ferrari, S. M., Corrado, A., Di Domenicantonio, A., & Fallahi, P. (2015). Autoimmune thyroid disorders. Autoimmunity

reviews, 14(2), 174-180.

5- Al-sofy, R. A., Hussein, T. A., & Brakhas, S. A. (2022). Estimation of Free T3, free T4 and TSH Levels in a Sample of Iraqi Autoimmune Urticarial Patients. *Iraqi journal of biotechnology*, 21(2), 688-692.

6- Al-Suhaimi, E. A., & Khan, F. A. (2022). Thyroid Glands: Physiology and Structure. In *Emerging Concepts in Endocrine Structure and Functions* (pp. 133-160): Springer.

7- Kshash, E. A., & Gijir, E. Y. Study About Women with Thyroid Disorders.

8- RossDouglas, S., BurchHenry, B., CooperDavid, S., Carol, G., Luiza, M., RivkeesScott, A., . . . WalterMartin, A. (2016). 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid*.

9-Bobanga, I. D., & McHenry, C. R. (2019). Treatment of patients with Graves' disease and the appropriate extent of thyroidectomy. *Best Practice & Research Clinical Endocrinology & Metabolism*, 33(4), 101319.

10-Menconi, F., Marcocci, C., & Marinò, M. (2014). Diagnosis and classification of Graves' disease. *Autoimmunity reviews*, 13(4-5), 398-402.

11-Dunn, D., & Turner, C. (2016). Hypothyroidism in women. *Nursing for women's health*, 20(1), 93-98.

12-Patil N, Rehman A, Jialal I. Hypothyroidism. In: *StatPearls [Internet]*. StatPearls Publishing; 2020. Updated August 10, 2020. Accessed January 5, 2021. www.ncbi.nlm.nih.gov/books/NBK519536 NIH external link

13- Canaris, G. J., Steiner, J. F., & Ridgway, E. C. (1997). Do traditional symptoms of hypothyroidism correlate with biochemical

disease? *Journal of general internal medicine*, 12(9), 544-550.

14- Ragusa, F., Fallahi, P., Elia, G., Gonnella, D., Paparo, S. R., Giusti, C., . . . Antonelli, A. (2019). Hashimoto's thyroiditis: Epidemiology, pathogenesis, clinic and therapy. *Best Practice & Research Clinical Endocrinology & Metabolism*, 33(6), 101367.

15- Peng, C. C.-H., Huai-En Chang, R., Pennant, M., Huang, H.-K., & Munir, K. M. (2020). A literature review of painful Hashimoto thyroiditis: 70 published cases in the past 70 years. *Journal of the Endocrine Society*, 4(2), bvz008.

16- Vaillant, A. A. J., & Qurie, A. (2022). Interleukin. In *StatPearls [Internet]*: StatPearls Publishing.

17- Akdis M, Burgler S, Cramer R, Eiwegger T, Fujita H, Gomez E, Klunker S, Meyer N, O'Mahony L, Palomares O, Rhyner C, Ouaked N, Schaffartzik A, Van De Veen W, Zeller S, Zimmermann M, Akdis CA. Interleukins, from 1 to 37, and interferon- γ : receptors, functions, and roles in diseases. *J Allergy Clin Immunol*. 2011 Mar;127(3):701-21.e1-70.

18- Petes, C., Mariani, M. K., Yang, Y., Grandvaux, N., & Gee, K. (2018). Interleukin (IL)-6 inhibits IL-27-and IL-30-mediated inflammatory responses in human monocytes. *Frontiers in Immunology*, 9, 256.

19- Omidan, N., Zahir, S. T., & Fateh, A. (2019). Cytological and Pathological Evaluation of Hashimoto's Thyroiditis. *Maedica*, 14(2), 98.

20- Staii, A., Mirocha, S., Todorova-Koteva, K., Glinberg, S., & Jaume, J. C. (2010). Hashimoto thyroiditis is more frequent than expected when diagnosed by cytology which uncovers a pre-clinical state. *Thyroid Research*, 3(1), 1-7.

- 21- Shrestha, S. K., Karmacharya, K., Giri, M., Bajracharya, M. R., & Jha, S. ,(2017). Relationship of thyroid peroxidase antibody test with abnormal thyroid function tests. *Journal of Pathology of Nepal*, 7(2), 1172–1175.
- 22- Shah, K. J., & Mandal, R. K. ,(2021). Prevalence of Anti Thyroid Peroxidase Antibody in Hypothyroid Patient.
- 23- Anaya, J.-M. (2010). The autoimmune tautology. *Arthritis research & therapy*, 12(6), 1-3
- 24- Fariha Angum,Tahir Khan, Jasndee Kaler,Lena Siddiqui, and Azhar Hussain,(2019). The Prevalence of Autoimmune Disorders in Women: A Narrative Review. *Cureus Journal*.12(5): e8094.
- 25-Nesterova TB, Popova BC, Cobb BS.,(2008). Dicer regulates Xist promoter methylation in ES cells indirectly through transcriptional control of Dnmt3a. *Epigenetics Chromatin Journal*.1:2.
- 26- (Hassanein Fadel Mohammed Al-Sabak and Mohammed Emad Mansur,(2018). Estimation of Orexin-a and Pcsk9 as a Biomarker for the Diagnosis of Thyroid Disorder In Patients Women; thesis.)
- 27- Ma, J., & Xiao, L. (2010). Obesity and depression in US women: results from the 2005–2006 National Health and Nutritional Examination Survey. *Obesity*, 18(2), 347-353.
- 28- Asvold BO, Bjoro T, Vatten LJ.,(2013). Associations of TSH levels within the reference range with future blood pressure and lipid concentrations: 11- year follow-up of the HUNT study. *Eur J Endocrinol*.169(1):73–82.
- 29-Schurz, H., Salie, M., Tromp, G., Hoal, E. G., Kinnear, C. J., & Möller, M. (2019). The X chromosome and sex-specific effects in infectious disease susceptibility. *Human genomics*, 13, 1-12.
- 30- Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* (2017) 377(1):13–27. doi: 10.1056/NEJMoa1614362
- 31- Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the global burden of disease study 2013. *Lancet* (2014) 384(9945):766–81. doi: 10.1016/S0140-6736(14)60460-8
- 32- Iacobellis G , Ribaudo MC , Zappaterreno A , Iannucci CV , Leonetti F 2005 Relationship of thyroid function with body mass index, leptin, insulin sensitivity and adiponectin in euthyroid obese women. *Clin Endocrinol (Oxf)* 62:487–491
- 33- Vettor R , Mingrone G , Manco M , Granzotto M , Milan G , Scarda A , Lombardi A , Greco AV , Federspil G 2003 Reduced expression of uncoupling proteins-2 and -3 in adipose tissue in post-obese patients submitted to biliopancreatic diversion. *Eur J Endocrinol* 148:543–550
- 34- Xue, H., Yu, X., Ma, L., Song, S., Li, Y., Zhang, L., Yang, T., & Liu, H. (2015). The possible role of CD4+ CD25 high Foxp3+/CD4+ IL-17A+ cell imbalance in the autoimmunity of patients with Hashimoto thyroiditis. *Endocrine*, 50(3), 665–673.
- 35 Cara Murphy, BA and Ankur Gupta, MD,(2020). MON-458 Elevated Thyroglobulin Level in Benign Thyroid Nodule. *J Endocr Soc*. May 8; 4(Suppl 1): MON-458.
- 36- **Eman Habib Kadhom and Nada Jafer MH. Radh (2023), IL-6 Concentration in**

Patients with Hyperthyroidism in Connection to their Periodontal Health. The current issue of the Al-Kindy College Medical Journal is Volume 19, Number 1, published in 2023.

37- **Vinu V, Chitnis P, and Gupta VK (2012)** Evaluation of thyroid dysfunction among type 2 diabetic patients. International Journal of Pharmacy and Biological Sciences.

38- Wartofsky, L. and Dickey, R.A. (2005). Controversy in clinical endocrinology: the Evidence for a narrower thyrotropin reference range is compelling. J. Clin. Endocrin. Metab., (90):5483-8.

39- Sarah AL-Huchaimi and Mahdi Hussain

Al-Ammar (2023) Immunological and Molecular study of Interleukin 4 , 5 and CXCL-9 in patients with Auto-Immune Thyroiditis; thesis).

40- Hüser, S., Guth, S., Joost, H. G., Soukup, S. T., Köhrle, J., Kreienbrock, L., ... & Kulling, S. E. ,(2018). Effects of isoflavones on breast tissue and the thyroid hormone system in humans: A comprehensive safety evaluation. Archives of toxicology, 92(9), 2703-2748).

41- Diana T, Olivo PD, Kahaly GJ.,(2018). Thyrotropin Receptor Blocking Antibodies. Horm Metab Res. Dec;50(12):853-862.