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Evaluation of Proinflammation Interleukin18 (IL-18) in Thyroid Disorders Patients in Najaf Province

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ABSTRACT

Background: *Iodine shortage or autoimmune illnesses can lead to thyroid problems. Graves' disease and Hashimoto's disease are examples of autoimmune thyroid diseases (AITDs) that develop when the immune system becomes unbalanced and attacks the thyroid gland. A subset of autoimmune disorders, AITDs target only one thyroid gland.* ***Aim the study:*** *Finding out how interleukins IL-18 affect thyroid disease patients is the primary goal of the study.* ***Methods:*** *Participants ranged in age from 18 to 70 and visited Sadr Medical City's Diabetes and Endocrinology department, the specialty of Al-Zahraa Laboratory, and other laboratories in Najaf Governorate between July and October 2023. Out of a total of 400 samples, 140 underwent immunodiagnostics, and the remaining 70 served as control groups.* ***Results*** *Test subjects were compared to a control group based on their T3, T4, and TSH concentrations, which were used to diagnose hypothyroidism and hyperthyroidism, respectively. Compared to both the control group and the other patients, those with hypothyroidism had substantially lower T3, T4, and TSH intensities, but a significantly higher TSH majority of the subjects tested had hypothyroidism. Following this, in addition to the doctor's clinical diagnosis, patients underwent specialized testing to identify the existence of antibodies linked to this illness (AITD), namely ATPO and ATG. Secondly, compared to normal controls, people with Graves' disease and Hashimoto's disease had much higher ATG levels, and patients with both Graves' disease and HD had much higher ATPO concentrations. 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%). the hypothyroid group consisted of 29 patients (78.6% of the total) and the non-smoking group of 27 patients (81.8%), with 8 hypothyroid patients (21.6%) and 6 non-smoking patients (19.4% of the total) serving as controls. Among the research groups, smoking status significantly altered the frequency distribution ($p = 0.0.03$). There was a significant mental state (p-value < 0.05 was 0.00001). When it comes to Hashimoto's and Graves', TSH, T3, T4, antTPO, and antTG bind. Researchers have shown that thyroid illnesses (namely Hashimoto's disease and Graves' disease) are associated with elevated serum IL-18 levels (9.665 and 9.636, respectively). Compared to the healthy group (mean = 9.192), there is no significant difference in the p-value ⊈ 0.05. Similarly, there is no significant difference between C1 and C2 (p-value $<$ 0.05).* ***Conclusion*** *of this study to the crucial role of interleukin-18 in individuals suffering from thyroid diseases. Thyroid disorders and mental status are distinct from pro-inflammatory cytokines, which have a positive correlation with psychopathology through multiple mechanisms affecting neurodevelopment, transmission, and synaptic plasticity; anti-TOP and anti-TG medications have a strong impact on IL18 and other pro-inflammatory cytokines. The "double effect" that women have makes thyroid diseases more common in women than in men. In terms of smoking, there was a notable difference in the frequency distributions across the study groups.*

Keyword: IL-18, Thyroid Disorders, Graves' disease.

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INTRODUCTION

About 5% of the global population suffers from an autoimmune disease. It is still very challenging to treat autoimmune disorders, which causes a lot of suffering for patients and costs a lot of money. When the immune system mistakes self-antigens for foreign invaders, it causes chronic inflammation and tissue damage, which can have serious consequences (1). These encompass a broad range of disorders affecting either individual organs or systems of organs. The prevalence and mortality rate of autoimmune disorders are disproportionately high in middle-aged women. As patients get older, it becomes clearer that autoimmune illnesses are more common in females than in males (2). This idea is supported by the fact that autoimmune illnesses may run in families and that a person can have many autoimmune problems. A case of "poly-autoimmunity" occurs when a single patient has two or more autoimmune disorders (ADs), in contrast to "familial autoimmunity" which describes ADs occurring in different members of the same nuclear family (3).

Thyroid autoimmune disease (AITD) An estimated 2-5% of the population suffers from autoimmune thyroid disorders (AITD), making it the most frequent kind of organ-specific autoimmune disease (AD) (**4).** At a rate of 5–15% for women and 5% for males, the prevalence of AITD is significantly different between the sexes. **(5).** Disorders such as Graves' disease (GD) and Hashimoto thyroiditis (HT) are included in AITD, along with others that are similar. Hypothyroidism, an underactive thyroid, is the typical outcome of Hashimoto's thyroiditis (HT), whereas hyperthyroidism, an overactive thyroid, is the hallmark of Graves' disease (GD). **(5).** The antigens found in the thyroid gland trigger responses from the immune system's cellular and humoral components. The process culminates in the production of autoantibodies, the infiltration of B and T cells, and the subsequent development of clinical symptoms. A decrease in the body's ability to endure immunological responses is the subject of the statement **(2).** One example of a systemic autoimmune disorder is Graves' disease (GD). This situation involves autoantibodies that target the thyroid follicular cells and their thyrotropin (TSH) receptor. **(6).** This leads to an increase in the size of these cells, which in turn causes hyperthyroidism due to an increase in thyroid hormone production. Hyperthyroidism is mostly caused by Graves' disease, which affects around 0.5% of the population and accounts for 50-80% of all cases. Visual problems, swelling of the lower extremities' skin, weakening of the proximal muscles, and a generalized expansion of the thyroid gland are all symptoms of GD. Inflammatory eye disease known as Grave's ophthalmopathy (GO) happens in around half of the people with GD because their antibodies react with receptors for thyroid-stimulating hormone (TSH). Another cell type that contains these receptors are adipocytes and retroocular fibroblasts. In around 5% of cases, the eye condition known as Graves' ophthalmopathy becomes severely manifested. **(8).**

The most common kind of autoimmune thyroid disease (AITD) is Hashimoto's thyroiditis (HT). Twenty to thirty percent of those who have it develop hypothyroidism as a result of the chronic inflammation it generates in the thyroid gland. **(9)** report on an autoimmune disorder characterized by the infiltration of lymphocytes into the thyroid gland. Scientists think this happens because antibodies are produced in response to both the thyroid protein and viral structures, due to the similarities between the two. The development of anti-thyroid peroxidase (anti-TPO) antibodies is a hallmark of Hashimoto

thyroiditis, which affects 90% of the population. The thyrocyte-killing processes of complement activation and antibody-dependent cell-mediated cytotoxicity can get underway when they land on these cells **(10).**

At first, it was thought that the body's only cells capable of producing the cytokine interleukins (IL) were white blood cells. Some cells in the body can produce interleukins, but other cells can do it as well, according to new research. They are essential for development, attachment, growth, motility, and the activation and differentiation of immune cells. Also, they have anti-inflammatory and pro-inflammatory effects. **(11).** During immune and inflammatory reactions, interleukins play an essential role in regulating cell proliferation, differentiation, and activation. Through their strong attachment to cell surface receptors, interleukins—a diverse set of proteins—are able to trigger a variety of cellular and tissue responses. Their secretion mechanisms might be either paracrine or autocrine. Many fields of clinical medicine have made use of interleukins in animal studies **(12).**

Commonly known as interleukin-18 (IL-18), The majority of interleukin-18 (IL-18) production occurs in macrophages, although hepatocytes and keratinocytes can also produce it. Identifying a co-factor involved in Th1 cell activation is the main objective. It improves the efficiency of natural killer (NK) cells and increases interferon gamma production **(13).** The study aims **to** perform blood serum concentration measurements of T3, T4, TSH, antithyroid peroxidase (TPO), and antithyroglobulin (TG), assess patient fluctuations, and compare results with control group. later on, compare the findings from the test subjects with the control group to determine the hyperthyroidism and hypothyroidism blood levels in people with immunological diseases. Evaluate the link between thyroid sickness and the blood levels of IL-6, IL-18, and TNF-α in people suffering from hyperthyroidism or hypothyroidism. Check your results against the control groups.

METHODOLOGY

Participants ranged in age from 18 to 70 and visited Sadr Medical City's Diabetes and Endocrinology department, the specialty of Al-Zahraa Laboratory, and other laboratories in Najaf Governorate between July and October 2023. Out of a total of 400 samples, 140 underwent immunodiagnostics, and the remaining 70 served as control groups.

Selection of Patient Groups.

After familiarizing ourselves with HT and GT by reading and consulting with three specialists, we used a standard questionnaire (Appendix 3) to collect sociodemographic information. The researcher and participants met in person for the filling process. Before sending a patient to the lab for testing, expert doctors took a thorough history and diagnosis that included the patient's occupational status, mental health, genetic information, weight and height measurements, and the severity of the disease.

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 Specialized 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.

People in this group (n = 70) seemed to be in good condition; they showed no symptoms of chronic illness, their thyroid function tests came back normal, and samples were taken without thyroid antibodies.

Evaluation using statistical methods

In order to compare the means of detection in the vaccinated cohort research, SPSS version 26 did a Nova test and a Chi-Square test after checking for data normality.

RESULTS AND DISCUSSION

Distribution of serum concentration by ELSA Immunoassay

Seventy cases and seventy controls undergoing treatment for thyroid disorders at public and private medical facilities were included in the 140 samples collected. The Elisa immunoassay measures IL18 blood concentrations and specific thyroid issue tests from both patients and controls.

Differences in Sociodemographic distribution among thyroid disorder patients and control

Table (1) shows that there is a significant increase in the proportion of patients and controls in the age groups 30–50 years old, with proportions of 7/33 (51.5%) and no statistical significance (probability value = 0.714) for hyperthyroidism.

The average age did not differ significantly among the groups of control individuals, patients with Graves' disease, and those with Hashimoto's thyroiditis (p = 0.071). Hypothyroidism was detected in 24 out of 37 subjects (64.9%) throughout three age groups: 30–50, 30–5, and 50 and above.

The age group in this study and earlier published articles dealing with hypothyroid disorder in adults was 30–50 years old, which is in agreement with **(13)** and **(14).** The median age of patients with hypothyroid disorder was 30–50 years old. Study participants with hyperthyroidism ranged in age from 30 to 50, which is consistent with there were 106 male and female patients seen for thyroid diseases, accounting for 75.7% of the total. Of them, 29/37 (78.4%) were hypothyroid, and 28/33 (84.8%) were hyperthyroid. In table (4.1-A), the percentage of males diagnosed with a thyroid issue was 34/140 (24.7%), although there was no statistical significance (p = 0.232).

According to a number of research, women are more infected to thyroid disorders in general, that agreement with **(15)** and **(16)** *That agreement with **Ngo *et al.*, (2014),** it may be caused by genetic, and hereditary variables, as well as agreement with (8). Also, the X chromosome aids and induces immune responses in the body in a far more diverse and diverse way than the Y chromosome does **(9).** Healthcare spending, quality of life, and direct and indirect economic costs are all negatively impacted by the chronic nature of these diseases. One of the leading causes of death for middle-aged women is autoimmune diseases, which disproportionately affect this population. Among autoimmune diseases, the preponderance of female patients becomes more apparent with age (**10).**

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%) **(15).**

More mutations are likely to develop due to the higher number of genes on the X chromosome. Because women include two X chromosomes and men only have one, the probability of getting autoimmune illnesses is greater in women than in men **(17).** Because they have two X chromosomes, women are more likely to develop autoimmunity. X chromosome genes have a "double effect" because of this, which is corroborated by**. (8).** Some people may have a genetic predisposition from paternal while others have a predisposition maternal depending on **(9).** This study was disagreement with **(17),** According to the World Health Organization (2023), body mass index (BMI) can be categorized into three groups: 18-24.9, 25-29.9, and 30 ≦. As shown in table (4.1A), there is no statistically significant relationship (p-value = 0.107) between BMI and thyroid disorders, whether hyper or hypoactive.

Levels of serum biomarkers are compared in this study. Results showed no statistically significant variations (p > 0.05) in blood biomarker levels between cases and controls with thyroid disorders according to employment and residence of patients with thyroid disorders **Table (2)**. This result agreement with the results reported by **(18) .** Body mass index (BMI), a major risk factor for many diseases. In a current study, that agreement with **19)** and **(20).** This study disagreement with **(21)**, that Who had a body mass index (BMI) of at least 30.0 kg/m2, there was a significant association between hypothyroidism and greater BMI. Agreement interpretation is examined in this study. Rapid economic development and changes in lifestyle have contributed to the epidemic of obesity that is afflicting both industrialised and developing countries**.** Worldwide, the prevalence of obesity has increased dramatically (**21).**

Obese children, adolescents, and adults have TSH levels that are either slightly higher than normal or above the upper limit of the normal range, according to research by **(22)**. These levels are also positively correlated with BMI, as reported (2**3).** It appears that in certain people, TSH and BMI are positively correlated.

There was a significant difference in the frequency distribution according to smoking among study groups (p = 0.0.03), as shown in table (4-1B). Among hypothyroid patients, 29 (78.6%) smoked, while among hyperthyroid patients, 27 (81.8%) smoked. In the control group, there were 6 (19.4%) smokers and 8 (21.6%) hypothyroid patients. Statistical analysis of patients and cases undergoing surgery for hypothyroidism or hyperthyroidism is lacking.

significance (p = 0.478).

Regarding Relative Risk 2.0, this agreement is relevant. (24). Wiersinga announced in 2019 that... It is yet unclear how thyroid hormone production is improved. One possible explanation is the

sympathetic stimulation that nicotine causes. Research by **(7) and (18)** has demonstrated that TSH levels are reduced among smokers. Smoking can cause a small increase in thyroid hormones, even in those who don't have any symptoms of hypothyroidism or hyperthyroidism **(25).**

The results of this investigation support the idea that smoking is a risk factor for thyroid disease. There is still much mystery around the exact way in which secondhand smoking affects the thyroid, although theories suggest that factors including hypoxia, the production of oxygen-free radicals, and secondhand smoke all play a part (**18**). Smoking tobacco negatively impacts Graves' disease (GD) (**2).** Antibodies would be produced against the presumed foreign material as a result of the immunological reaction **(9).**

Many effectors immune cells produce pro-inflammatory cytokines like IL6, IL18, etc., and these cytokines play an important role in inflammation and immunity; this study confirms what **(11)** found: cytokines cause an inflammatory immune response, which contributes to psychopathology via various mechanisms impacting neurodevelopment, neurotransmission, and synaptic plasticity. They serve as a barrier because they control neuronal cell transmission and neurotransmitter metabolism.

Comparison Serum level of Concentration IL18 in Patients and Control Groups with thyroid disorder

The mean difference of thyroid disorders (Hashimoto's disease was 9.665 and Graves' disease was 9.636) with IL18 is shown in Figure (1), which is a comparison analysis. When comparing the healthy group (mean = 9.192) to the C1 and C2 groups (p-value ¸ 0.05), no significant difference is seen (p-value < 0.05).

The correlation of concentration serum level of IL-18 with T3 IN patients and control.

In this study shown, correlation between concentration level for IL-18 cause with T3 effect in patient with thyroid disorder, and control

there was negative correlation, R^2 Linear = 8.444, (y=9.68, x= 0.18, p-value significant ≤ 0.05 **in Scatter plot (1).**

The correlation of concentration serum level of IL-18 with TSH in patients and control.

In this study shown, correlation between concentration level for IL-18 cause with effect of TSH in patient with thyroid disorder ,and control, there was negative correlation, R2 Linear was 0.007 there are weakness correlation ,(y=9.68, x= 0.03 ,p-value significant ≤ 0.05. **Scatter plot (2).**

The importance of IL-18 in the Th1-type immune response, IL-18 may have a key role in the autoimmune pathology of HT. Additionally, it has been shown in thyroid patient with HT, suggesting that IL-18 might be a secreted immunomodulation in HT according to **(26).** Anti-thyroid peroxidase (Anti-TPO) antibodies, found in 90% of individuals with Hashimoto thyroiditis, have the ability to activate complement and trigger antibody-dependent cell-mediated cytotoxicity, resulting in the destruction of thyrocytes **(23).**

The correlation of concentration serum level of IL-18 with TSH in patients and control.

In this study shown, correlation between concentration level for ant TOP cause with effect of TSH in patient with thyroid disorder, and control, there was positive correlation, ant TOP and TSH, R2 Linear was 0.02 there are positive weakness correlation, (y=3.59, x=

5.02, p-value significant ≤ 0.05, in **Scatter plot** (**3**).

The serum concentrations of anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies are directly correlate in the induction and diagnosis of autoimmune thyroid disorders (AITDs, according by **(27).**

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

Sociodemographic variables			Thyroid disorders				P value
			Hypothyroid n=35	Hyperthyroid n=35	control n=70	Total N=140	
Age group (Years)	<30	Count	4	9	13	26	
		%	11.4%	25.7%	18.6%	18.6%	
	30-50	Count	24	17	40	81	
		%	64.9%	51.5%	57.1%	57.9%	0.714
	>50	Count	7	9	17	33	
		%	18.9%	27.3%	24.3%	23.6%	
Sex	Female	Count	29	28	49	106	
		%	78.4%	84.8%	70.0%	75.7%	0.232
	Male	Count	6	7	21	34	
		%	16.4%	20.0%	30.0%	24.3%	
BMI Categories	18-24.9	Count	6	15	27	48	
		%	17.1%	42.8%	38.6%	34.3%	
	25-29.9	Count	15	11	33	59	
		%	40.5%	35.5%	47.1%	42.1%	0.107
	30 ≤	Count	14	9	10	33	
		%	37.8%	27.3%	14.3%	23.6%	
smoking	yes	Count	27	29	67	123	
		%	81.8%	78.4%	95.7%	87.9%	
	no	Count	8	6	3	17	0.03
		%	21.6%	19.4%	4.3%	12.1%	

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 (µUI/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**
IL18 (pg/ml)	**Hashimoto's**	**35**	9.66	7.85	**.002**	**6.97**	**12.36**
	Grave's	**35**	9.84	2.61	**.000**	**8.94**	**10.73**
	Normal	70	9.19	4.42	**.002**	**8.14**	**10.25**

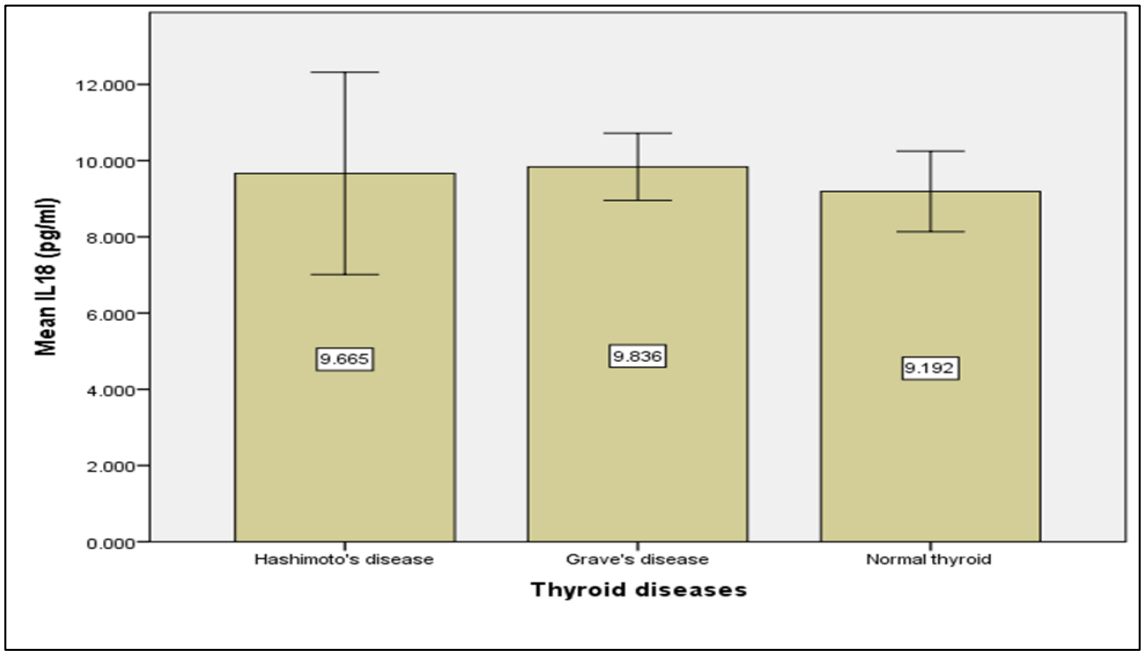
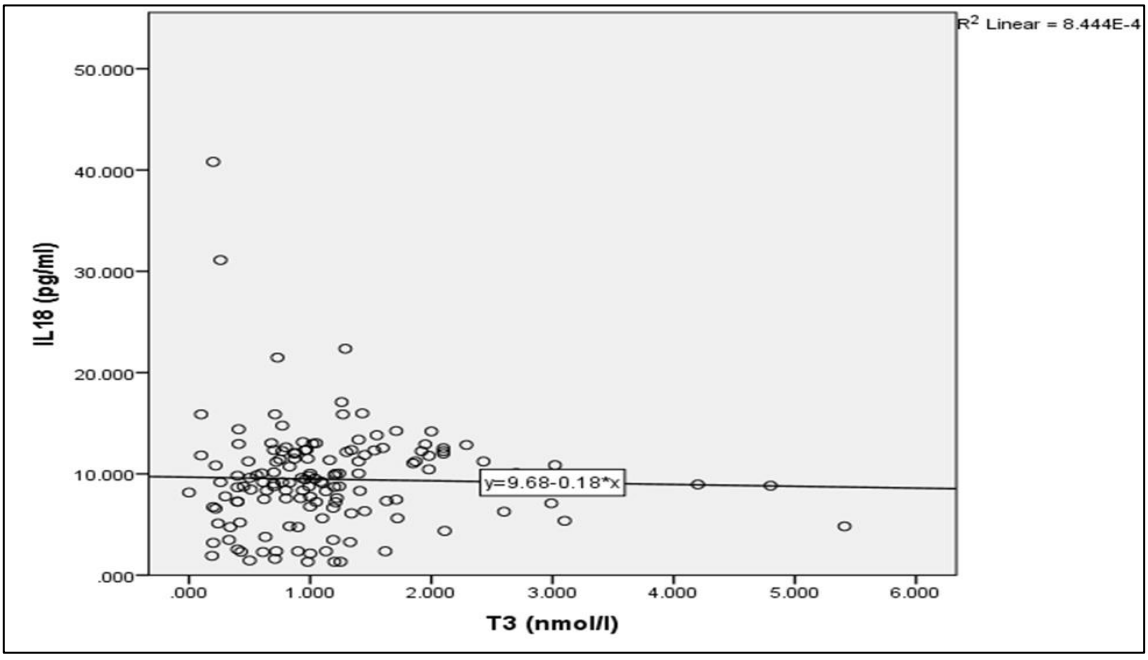
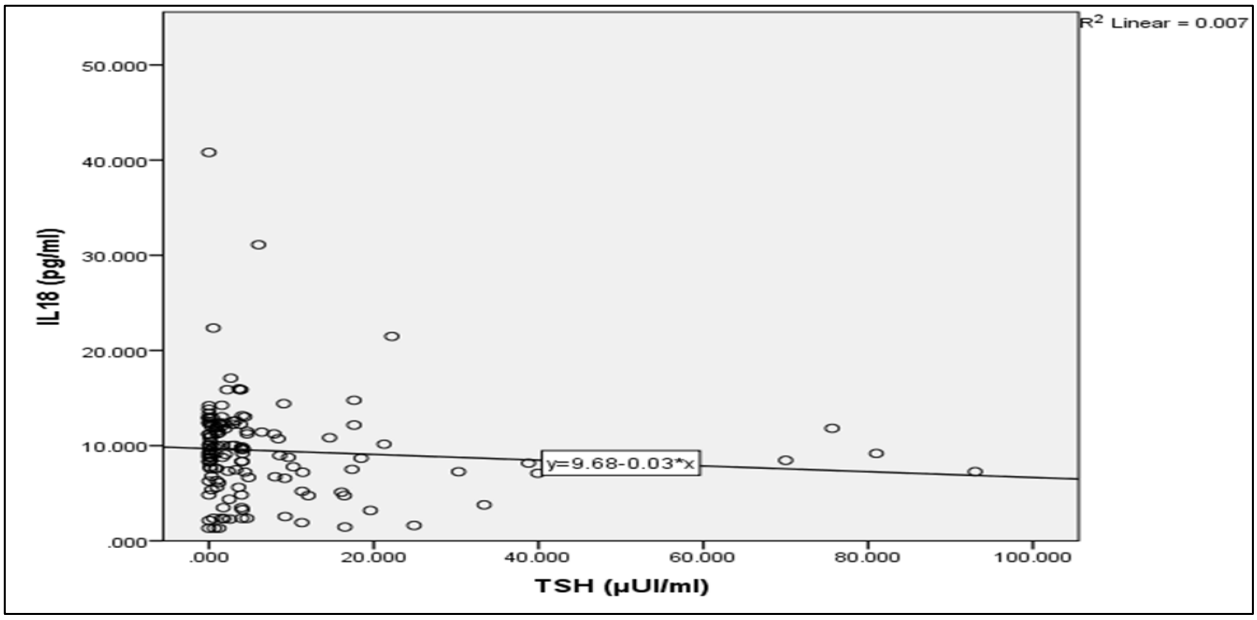


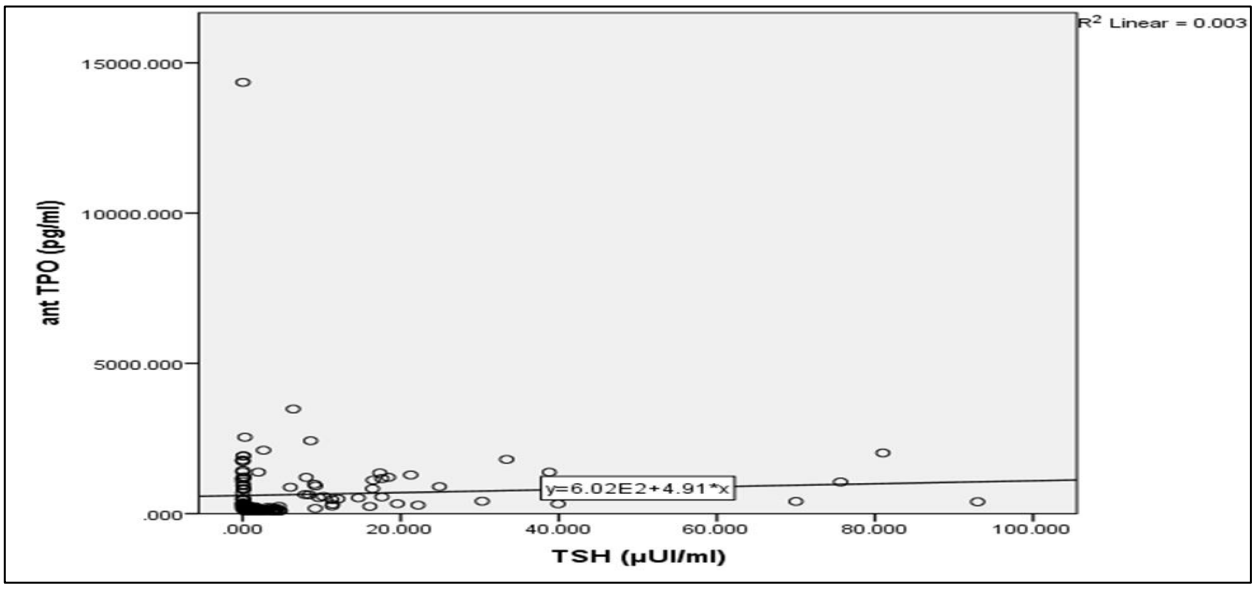
Figure (1): Comparative analysis mean difference of IL18 with thyroid disorder (hyperthyroid and hypothyroid) and control group (normal).



Scatter plot (1): correlation between IL18 and T3, R^2Linear = 8.444, (y=9.68, x= 0.18, negative predictive, p-value significant ≤ 0.05.



Scatter plot (2): correlation between IL_6 and TSH, R2 Linear was 0.007 there are weakness correlation, (y=9.68, x= 0.03, p-value significant ≤ 0.05.



Scatter plot (3): correlation between ant TOP and TSH, R^2 Linear was 0.003 there are positive weakness correlation, (y=6.02, x= 4.91, p-value significant ≤ 0.05.

CONCLUSION

Conclusion of this study to the crucial role of interleukin-18 in individuals suffering from thyroid diseases. Thyroid disorders and mental status are distinct from pro-inflammatory cytokines, which have a positive correlation with psychopathology through multiple mechanisms affecting neuro development, transmission, and synaptic plasticity; anti-TOP and anti-TG medications have a strong impact on IL18 and other pro-inflammatory cytokines. The "double effect" that women have makes thyroid diseases more common in women than

in men. In terms of smoking, there was a notable difference in the frequency distributions across the study groups.

RECOMMENDATION

1. To understand how IL18, a biomarker for autoimmune thyroiditis, can be used to diagnose the effect, and conduct additional research into phenotyping and genetics.

2. Use of Anti-TG, Anti-TOP, T3, T4 and TSH to screen or diagnose the condition and susceptibility of autoimmune thyroiditis.

3. When comparing concentrations of pro- and anti-inflammatory cytokines, RT-PCR testing is the optimal solution.

4. Use flow cytometry to check the percentages of T-reg and Th-cells for the patient group.

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