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EFFECT OF SOME BIOCHEMICAL PARAMETERS AND HUMERAL IMMUNITY ON TSH RECEPTORS IN THYROID DISORDERS PATIENTS

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By Aqeel Abd Almurtadha Kadhım ALTAHER

February 2022

We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science

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ABSTRACT

EFFECT OF SOME BIOCHEMICAL PARAMETERS AND HUMERAL IMMUNITY ON TSH RECEPTORS IN THYROID DISORDERS PATIENTS

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Master of Science in Chemistry

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TSH-R Ab is the better hyperthyroidism marker especially with patient's immune thyroid Graves' hyperthyroidism (GH) and Hashimoto's hypothyroidism (HH) are the opposite ends of the clinical expression of autoimmune thyroid diseases (AITD). In this study 50 patients with thyroid dysfunction and control group consisting of 50 healthy. Elevated TSHR-Ab levels, it was associated with an increase in FT4, FT3 and T.G with decrease TSH level, so its had an immune response. The values of interleukin -6 and TNF are also increased. The results show that a significant increased between TSH-R Ab with FT4, FT3 and T.G in patients with control and also male with female when compared with controls. The results show that was a clearly significant decreased between TSH-R Ab with TSH in among patients, control and even male with female. Decrease significant with S.C, TG, and LDL-C among patients, control because hyperactivity for thyroid secretion and HDL no significant. The results show that a significant decrease with S.C, HDL, and LDL-C in male and female and T.G no significant. Our study showed a positive correlation between TSH-R Ab with FT4, FT3, T.G, TNF and IL-6 while be a negative correlation with TSH.

2022, 42 pages

Keywords: TRAB, Graves disease, Hyperthyrodism, Tumor necrosis factor-alpha

ÖZET

TİROİD HASTALARINDA BAZI BİYOKİMYASAL PARAMETRELER VE HUMERAL BAĞIŞIKLIĞIN TSH RECEPTORLARINA ETKİSİ

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TSH-R Ab, özellikle hastanın immün tiroidi Graves hipertiroidizmi (GH) ile daha iyi hipertiroidizm belirtecidir ve Hashimoto hipotiroidizmi (HH), otoimmün tiroid hastalıklarının (AITD) klinik ifadesinin zıt uçlarıdır. Bu çalışmada tiroid bozukluğu olan 50 hasta ve 50 sağlıklı kontrol grubu oluşturuldu. Yüksek TSHR-Ab seviyeleri, TSH düzeyinde azalma ile FT4, FT3 ve T.G'de artış ile ilişkilendirildi, bu nedenle bir bağışıklık yanıtı vardı. İnterlökin -6 ve TNF değerleri de yükselir. Sonuçlar, kontrol grubundaki hastalarda ve ayrıca erkek ve kadın hastalarda FT4, FT3 ve T.G ile TSH-R Ab arasında kontrollere göre anlamlı bir artış olduğunu göstermektedir. Sonuçlar, hastalarda, kontrollerde ve hatta erkeklerde, kadınlarda TSH-R Ab ile TSH arasında belirgin bir şekilde anlamlı bir azalma olduğunu göstermektedir. Hastalar arasında SC, TG ve LDL-C ile anlamlı azalma, kontrol çünkü tiroid sekresyonu ve HDL için hiperaktivite anlamlı değildir. Sonuçlar, erkek ve kadında S.C, HDL ve LDL-C ile anlamlı bir düşüşün ve T.G'nin anlamlı olmadığını göstermektedir. Çalışmamız TSH-R Ab ile FT4, FT3, T.G, TNF ve IL-6 arasında pozitif, TSH ile negatif korelasyon göstermiştir.

2022, 42 sayfa

Anahtar Kelimeler: TRAB, Graves hastalığı, Hipertiroidizm, Tümör nekroz faktörü-alfa

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Aqeel Abd Almurtadha Kadhim ALTAHER
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LIST OF SYMBOLS

%	Percent
±	Plus-minus
°C	Degrees celsius
g	Gram
IU	International units
L	Liter
mg	Milligram
mL	Milliliters
pg	Picogram
µg	Microgram
µL	Microliter

LIST OF ABBREVIATIONS

AITD	Autoimmune thyroid diseases
FT3	Free triiodothyronine
FT4	Free thyroxine
GD	Graves disease
GH	Graves' hyperthyroidism
HDL	High-density lipoprotein
HT	Hashimoto's thyroiditis
IL-6	Interleukin-6
LDL	Low-density lipoprotein
LPL	Lipoprotein lipase
STg	Serum thyroglobulin
TG	Triglyceride
T3	Triiodothyronine
T4	Thyroxine
TAO	Thyroid associated orbitopathy
TH	Thyroid hormone
TNF-α	Tumor necrosis factor-alpha
TPO	Thyroid peroxidase
TRH	Thyrotropin releasing hormone
TSH	Thyroid stimulating hormone
TSHR	Thyroid stimulating hormone receptors
VLDL	Very low-density lipoproteins

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1. INTRODUCTION

The thyroid is gland looks like butterfly in shape that located low in front of the neck. The thyroid consists of two lobes, linked through a bridge (isthmus) in the middle. It preforms a fundamental function in the basic metabolic rate (BMR) arrangement also activate somatic and phesychic out growth in addition to the important role in calcium metabolism (Bamanikar *et al*. 2014).

The major labor of the thyroid gland is hormones producing T4 and T3 which are essential for the organizing of metabolic proceeding throughout the body. Thyrotropin (thyroid-stimulating hormone) is created via the frontal pituitary gland the major task of which Graves disease are the most wide spread reasons of thyroid hormones an esxaggerated mamufacturing of thyroid hormones are Graves disease, toxic multinodular goiter and toxic adenoma thyroid (Mondul *et al*. 2012).

TSH-R Ab is a part from receptors of the glycoprotein hormone a subset of category A (GPCRs). This receptor is signficant as well togather with respect to pathophysiology like self immune (inclusive ophthalmopathy) or non-autoimmune thyroid defective as well expansion of cancer (Kleinau *et al*. 2017). This of the thyroid implicates increased of thyroid hormones is exaggerated condensation of TH in tissues which bring about through increasing thyroid hormones synthesis enormous releasing frome thyroid hormones preforming, an endogenous or exogenous extrathyroidal provenance.

Graves disease are the most wide spread reasons of overproduction thyroid hormones (Kravets 2016). Worldwide, the most common cause of all thyroid disorders is lack of iodin enviromental this include hypothyrodisim, however in iodin adcuacy spaces, Hashimotos disease (chronic autoimmune thyroiditis) is the most popular reason for thyroid failure (Chiovato *et al*. 2019).

The Aims of the study, for understanding thyroid disorders state by cytokines action. To clearly the role of biochemical markers as evidence for sickness development, and to simplify whether the thyroid disorder associated with an immune response is permanent or temporary. For conforming coefficient correlation between the deferent types of cytokines and other biomarkers with TSH receptor Ab.

2. LITERATURE REVIEW

2.1 Thyroid Gland

Thyroid gland looks like butterfly endocrine gland located infront of the neck. It situated profound to the platysma, stern thyroid and Stern hyoid muscles. The thyroid gland and its hormones preforme multiple phases functions in the development of organ and in the homeostatic monitoring of essential physiological mechanisms like body growth and energy disbursement in all vertebrate (Balasubramanian 2015).

on the cellular scale, the hormone of thyroid spend their impact after planned mechanisms ease bound to the thyroid hormone receptor. In the hypothalamus, signs from an extent of metabolic pathways containing appetite and temperature in Figure 2.1. Energy substrates Availability, hormones and another biologically energetic molecules assemble to preserve plasma thyroid hormone at the appropriate level to preserve energy homeostasis (Mc-Aninch and Bianco 2014).

At the tissue level thyroid hormone actions on metabolism are controlled by transmembrane transporters, deiodinases and thyroid hormone receptors (Tseng *et al*. 2010).

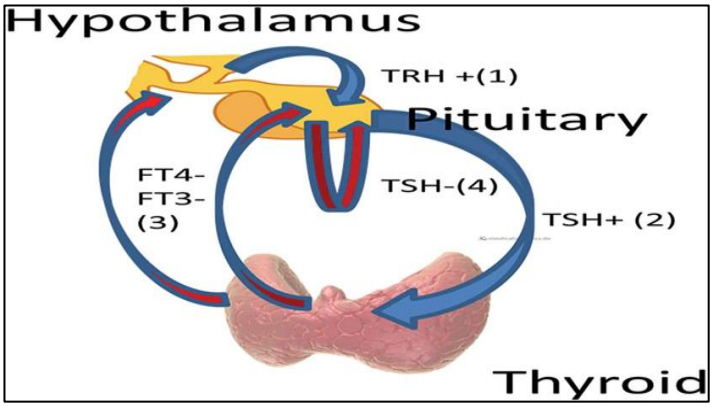

Figure 2.1 The HPT axis, a negative feedback loop of the hypothalamus pituitary thyroid axis (Fitzgerald and Bean 2018)

2.2 Thyroid Hormone Dysfunction

2.2.1 Hypothyroidism

Hypothyroidism influences to 5% from the generic inhabitance further more rating 5% being undetected (Chiovato *et al*. 2019). Common in the female more than the male (Chakrabarti *et al*. 2016).That distinguished via a depressed serum FT4 concentricity and a serum TSH concentration that is not elevated in approprite (Doshi *et al*. 2008).

The central hypothyroidism symptoms and signs, which comprise tiredness, depression, cold intolerance, dyspnoea, skin dryness, constipation, bradycardia and hyporeflexia, are commonly alike except it is milder than those of prime hypothyroidism so the goitre is rarely toexisting (Larson and Gostas 2020).

2.2.2 Hyperthyroidism

Hyperthyroidism can be as defined the excessive output and releasing thyroid hormone through the thyroid gland which is leading to unsuitable elevating in serum levels. The disproportionate quantity of thyroid hormone will lead to an instant metabolic condition (Devereaux and Tewelde 2014).

Approximately 20 times more female than male have hyperthyroidism. Differentiate through the hyper metabolic status because of the excessive free serum thyroxine FT4 and/or free triiodothyronine FT3 (Livolsi and Baloch 2018). Hyperthyroidism exist in both genders togather with a series of excess appetite, losing weight, intolerance to heat, trembling, irregular heart beat, emotional changes and discomfort. Sweating, diarrhea, troubles in menstrual, fertility damage, abnormal mental development, sleeping troubles, sight irritation, exhastion and muscle languideness and thyroid amplification (Gabrielson *et al*. 2019).

2.3 Autoimmune Thyroid Diseases

(AITDs) are most commonly autoimmune illness influencing about 5% of the generic inhabitance with prevalence in women (AITD) (Casto *et al*. 2021). AITD in generl low riskiness but seriously can influence on the life style that taking into consideration their raised expansion (Orgiazzi 2014).

(GH) and Hashimoto's hypothyroidism (HH) are on the contractive ends for the clinical expression of autoimmune thyroid diseases (Lin *et al*. 2016).

2.3.1 Graves disease

Graves' disease (GD) defines as the most prevalent reason for hyperthyroidism in the regions full of iodine. Cause of the disease is appearance of activating TSH receptor autoantibodies (TSH-R Ab) guiding to hyperthyroidism. Annually the incident of this disease was reported range about (20 to 50) cases per 100,000 persons (Ehlers *et al*. 2019).

Most of researchers come to agreement that GD is probably a multifactorial disease because of a complicated interaction of genetic and non-genetic elements that driving to lossing of immune toleration to thyroid antigens and to the starting with a sustained autoimmune response (Marinò *et al*. 2015).

GD the particular reason for the disease has been recognized, GD occur because of immediate stimulation for the thyroid epithelial cells through TSH receptor antibody (TSH-R Ab). GD detection is depending on the series of clinical symptoms and signs put together with the biochemical determining for serum thyroid stimulating hormone (TSH) and free thyroid hormone levels (FT4). Serum levels detection of autoantibodies orientated versus the TSH receptor, thyroid peroxidase (TPO) or thyroglobulin (Tg) could be usful in well-regulation for therapy strategy (Rapoport and McLachlan 2018).

2.3.2 Hashimoto disease

HT was identified in 1912 by Hakaru Hashimoto but not till the 1950 had its autoimmune aspect been shown. Latest years have demonstrated that HT evolution rely on an immune disorder in the person with genetic capability jointly with ecological elements (Pyzik *et al*. 2015).

Affecting up to 2% of generic inhabitance. It is more prevalent among in female than male with ratio of (5-10). The annually infection of HT around the world approxymately (0.3-1.5) cases per 1000 individual (Ahmed *et al*. 2012). HTdefine as a chronic inflammation in the thyroid gland intiatively described before a century but as yet inadequately (Caturegli *et al*. 2014).

The most prevalent laboratory autocomes that shown a risen and depressed rates of free thyroxine (FT4) and thyroid–stimulating hormone (TSH) (Caturegli *et al*. 2014).

HT is related with different degrees of thyroid with thyroid autoantibodies production as the most popular thyroid peroxidase antibodies (TPO-Ab), thyroglobulin antibodies (Tg-Ab) and with lymphocytic inltration (Liontiris and Mazokopakis 2017).

2.4 Biochemical Markers

2.4.1 TSH-R Ab

TSH-R Ab in general recognized as TRAb, This is a combination of various antibodies that can be further most calssified as thyroid stimulating antibodies (TSAb), thyroid inhibiting antibodies (TBAb), and indifferent antibodies relying on their respective labours on the TSHR (Kotwal and Stan 2018).

TRAbs calculation is more beneficial in the dispersively identification of hyperthyroidism (Syme *et al*. 2011). TSH-R Ab act as a major role in GD evaluation, Graves ophthalmopathy (GO) and pretibial myxedema (Kotwal and Stan 2018).

2.4.2 Thyroid stimulation hormone

TSH (thyrotropin) define as a glycoprotein secreted from the frontal pituitary gland that is organized by passive findings from the free thyroid hormones serum (T4 and T3) (T4 and T3) (Esfandiari and Papaleontiou 2017).

Caliculations of TSH is a critical examination test for thyroid disorder and it is count more primary beneficial test of thyroid function for the patients large majority (2–4) (Henze *et al*. 2017). As well it is seriously to npay attention that TSH levels may rise with age and that because the relative elevation in biologically passive isoforms of TSH (Soh and Aw 2019).

2.4.3 Free thyroxine and free triiodothyrodonine

FT4 and FT3 are providing more worthy and economical strategy to evaluate functions of thyroid. In consistent with the free hormone hypothesis, it is the thyroid hormones (0.02% of TT4 and 0.2% of TT3) free fragments that spends biologic efficacy at the cellular scale. While protein-bound hormone is counted as biologically inefficient (Soldin *et al*. 2013).

2.4.4 Thyroglobulin

T.g a vast glycoprotein, acts as 80% of the wet weight frome the thyroid and it is co-secreted along with thyroid hormone. Tg is the primal biochemical tumor marker that utilized in patients recurrence detection with differentiated thyroid cancers. Defect of the normal thyroid formation produce leak from Tg, and elevated serum levels are found in patients with goiter. In multinodular goiter, Tg levels can reach highly levels that

interfer together with those found in metastatic thyroid cancer patients (Spencer *et al*. 2014).

2.4.5 Lipid profile

Serum lipid profiles measuring become now nearly a routine test. The test contains four basal parameters: total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides. Usually it could be done in fasting blood sample. Fasting points to (12–14 h) overnight whole dietary limitation except water and medication. This may correct due to two major causes (Sabini *et al*. 2018).

For calculating serum lipid profile, as a tradition we utilize fasting blood specimen. Although it has been the most crdible procedure for lipid profile testing (Ghildiyal *et al*. 2020).

Hyperthyroidism showed an increased excretion of cholesterol via the bile together with unshifted or increased enterohepatic circulation of bile acids A reduction in HDL-C levels as well being noticed in hyperthyroidism (Erem 2006).

2.5 Immune Markers

2.5.1 Interleukin-6

IL-6 (which is a glycosylated protein of 21-28 kDa) is a multifunctional cytokine that plays a central role in host defence due to its wide range of immune (Reihmane and Dela 2014).

IL-6 is an inflammatory cytokine made by different cells like lymphocytes and monocytes. In GD patients, the levels of TSH-R Ab serum correspond with peripheral T cells numbers bound to IL-6 (Inoue *et al*. 2011).

2.5.2 Tumor necrosis factor

TNF (17 kDa protein) is composed of 157 amino acids as a homotrimer in solution that is in main produced via macrophages activation, T lymphocytes and natural killer (Chu 2013).

A proinflammatory cytokine, TNF-alpha (TNF-α) shows immunological and metabolic efficacious involved in the inducment and conservation of immune responses. In the thyroid gland the proinflammatory cytokine may exert its functions in collaboration with infiltrating immunocompetent cells. In the latest years, scholars have dedicated additional interest to the unusual expression of cytokines in Graves' disease (Zhu *et al*. 2020).

3. MATERIALS AND METHODS

3.1 Study Design

The cases-control design included 100 subjects (50 Thyroid disorder and 50 normal controls) with period of collection from 15/4/2021-20/9/2021 at Endocrinology Center in Dhi Qar governorate and Al-Hussein Teaching Hospital. The patients group was 50 persons (18 males and 32 female) with thyroid disorder. The control group which comprised 50 individuals (25 males and 25 females).

3.2 Chemicals and Reagent

In this study we used Chemicals Reagents TSHR, TSH, FT4, FT3, Tg Kits, and TNF, IL 6 kits and Lipid profile as shown in Table 3.1.

Table 3.1 Chemicals and reagent in the study

NO.	KİTS	COMPANY AND ORİGİN
1.	TRAB	Roche-Germany S.N 53573911
2.	TSH	Roche-Germany S.N 57429803
3.	FT4	Roche-Germany S.N 47808501
4.	FT3	Roche-Germany S.N 48943651
5.	Tg	Roche-Germany S.N 55070201
6.	TNF	BT LAB-China S.N 202104235
7.	IL 6	BT LAB-China S.N 202105003
8.	Cholesterol	Roche-Germany S.N 52764501
9.	T.G	Roche-Germany S.N 47998701
10.	HDL	Roche-Germany S.N 54215401
11.	LDL	Roche-Germany S.N 53583301

3.3 Instruments

In this study we used devices from well-known companies of global origin such as Germany, Japan and China, and these products are famous for their accuracy as shown in Table 3.2.

Table 3.2 Instruments used in the study

NO.	MATERİALS	COMPANY AND ORİGİN
1.	cobas c111	Roche- Germany
2.	Cobas e400	Roche-Germany
3.	ELISA washer and reader	Mindray-china
4.	Centrifuge	Kokusam-Japan
5.	Pipette /10-100 µL 100-1000 µL	Eppendorf -Germany
6.	Refrigerator	Turkey-beko

3.4 Experimental Procedures

3.4.1 Measurement of TRAB

Competition principle: Total duration of assay 27 minutes, incubate 30 µL from serum specimen, treated with pretreatment buffer solution (ATSHR PT1) and pretreatment reagent buffer (ATSHR PT2), both of which composed of a pre-formed immune complex of solubilized pTSHR and biotinylated anti porcine TSH receptor mouse monoclonal antibody. The TSHR complex is allowed to react with TRAb in the patient's serum. as well as incubation The addition of buffer solution allows TRAb to react with the TSHR complex further. as well as incubation The ability of bound TRAb to prevent the binding of marked M22 is measured after streptavidin adding that coate micro particles and a human thyroid stimulating monoclonal autoantibody (M22) tagged by a combination of ruthenium. The biotin interaction with streptavidin bounds the whole complex to the solid stage. and the interaction combination is inhaled for the measurement cell, whereas the fine particles pin down in the magnetic form on the face of electrode. ProCell II M is later utilize to remove any unrestrained chemicals. When a voltage is applied to the electrode, chemiluminescent emission is result which is indicated via a photomultiplier. Otocomes are obtained utilizing a calibration curve generated via 2 point calibration on the device and a major curve delivered via the cobas interface.

3.4.2 Estimation of TSH

Monoclonal TSH biotinylated certain antibody and a monoclonal TSH particular antibody tagged react with a ruthenium compound for creating a sandwich combination when 50 μL of material is incubated. as well as incubation late then the streptavidin-coated microparticles were added, the combination of biotin with streptavidin binds the complex to the solid stage, and The interaction combination which is inhaled for the measurement cell, whereas the fine particles are trapped in the magnetic form on the electrode's face. ProCell/ProCell M is thereafter utilized for removing any unchained compounds. When a voltage is applied to the electrode, chemiluminescent emission is result, that is discovered via a photomultiplier. and Results are obtained utilizing a calibration curve established via 2point calibration on the devise in addition to a major curve given via the reagent barcode or barcode.

3.4.3 Estimation of FT3 and FT4

Competition principle: Total duration of assay 18 minutes, Incubate 15 μL from specimen plus an anti-T3 antibody tagged together with a ruthenium compound, plus incubation: Biotinylated T3 and streptavidin-coated fine roparticles were added after that. With the creation of an antibody hapten complex, the tagged antibody's still free binding sites become occupied. Biotin and streptavidin interact to bind the whole complex to the solid stage. In the measurement cell, the reaction mixture is aspirated. The micro particles are magnetically caught on the electrode's surface. Pro Cell/Pro Cell M thereafter utilized for removing any unchained componants. While a voltage application to the electrode, chemiluminescent emission is result, which is then discovered via a photomultiplier. The outocomes determined by utilizing a calibration curve generated via 2 calibration points on the instrument and a major curve provided via the reagent barcode.

3.4.4 Estimation of thyroglobulin

Sandwich principle: Total duration of assay 18 minutes, Tg from 35 µL of specimen, biotinylated monoclonal Tg particular antibody, and monoclonal Tg particular antibodies tagged togatherwith ruthenium complexa) create a sandwich combination. as well as the compound incubation becomes linked to the robust phase together with addings treptavidin-coated micro particles because of the reaction of biotin and streptavidin. The interaction compound is inhaled for the measurement cell, whereas the micro particles are held magnetically on the electrode's face. Pro Cell/Pro Cell M is then used to remove whichever unrestricted compounds. When a voltage is applied to the electrode, chemiluminescent emission is induced, which is detected by a photomultiplier. Results are obtained using a calibration curve generated by 2point calibration on the device and a master curve provided by the reagent barcode. Calibration and a master curve provided via the reagent barcode.

3.4.5 Estimation of human IL-6 and TNF

This ELISA kit was used the Sandwich-ELISA principle (Alexhaller *et al*. 2016)

Assay Procedure:

1. Prepare all reagents, standard solutions, and specimen depending on the directive. Before using any reagents, bring them to room temperature. The test is occurring at room temperature.
2. Count the number of strips needed for the test. for using, the strips set in the frames. We should be keepunused strips at 2-8°C.
3. Fill standard well with 50 µL standard. Because the standard solution contains biotinylated antibody, Anti body don’t add on standard well.

4. Pour 40 μL of material into sample wells, followed by 10 μL of anti-IL-6 or TNF antibody. 50 μL streptavidin-HRP should be added to the sample and control wells (Not blank control well) Mix.

5. Remove the sealant and wash the plate with wash buffer 5 times. Per wash, dowse wells in at the minimum 0.35 mL wash buffer for 30 seconds to 1 minute. All wells should be aspirate plus washing for 5 times with wash buffer, excess filling wells with wash buffer, for automatic washing. By using filter paper or another absorpetive substance, seal the plate.

6. Pour 50 μL of substrate solution A into each well, following that 50 μL of substrate solution B. The plate must be incubated in the dark with in 10 minutes at 37°C with a fresh sealer.

7. Add 50 μL Stop Solution for everywell, the blue color will quickly convert to yellow.

8. Using a microplate reader set, at once determine the optical density (OD value) for every well.

3.4.6 Estimation of lipid profile

Cholesterol and HDL and LDL were used for the quantitative measurement of cholesterol in the serum of individuals under study by using (Hitac Cobas C111) (Rochel) full automated. The basic principle of this measurement is the (Enzymatic colorimetric methods). Triglycerides were used of the quantifiable (T.G) in the study using Rochel / HitachCobas C111 device full automated the quantitative analysis of triglyceride (Mohammad *et al*. 2017).

4. RESULTS

4.1 Biochemical Characteristics between Patient's vs Controls

4.1.1 Biochemical characteristics of TSH receptor Ab

The results of our study which was presented in Figure 4.1 and Table 4.1 show a significant increase (P< 0.01) in TSH-receptor Ab levels of patients (17.04 ± 5.10 vs. 1.15 ± 0.25 U/L) when compared with controls.

4.1.2 Biochemical characteristics of free T4

Our data in Figure 4.1 and Table 4.1 have also showed that a significant increase (P< 0.01) in FT4 levels patients (3.16 ± 0.62 vs. 1.40 ± 0.24 ng/dL) vs control.

4.1.3 Biochemical characteristics of free T3

The FT3 level in our study, which was presenting in Figure 4.1 and Table 4.1 shows a significant increase (P< 0.04) of patients (0.81 ± 0.20 vs. 0.32 ± 0.07 ng/dL) vs control.

4.1.4 Biochemical characteristics of TSH

The results of our study which was presenting in Figure 4.1 and Table 4.1 clearly shown a significant decrease (P< 0.01) in TSH levels of patients (0.19 ± 00.6 vs. 3.19 ± 0.58 µIU/L) vs control.

4.1.5 Biochemical characteristics of Tg

Figure 4.1 and Table 4.1 have also showed that a significant increase (P< 0.04) in thyroglobulin levels of patients (40.41 ± 9.62 vs. 22.16 ± 6.80 ng/mL).

4.1.6 Biochemical characteristics of lipid profile

Our study results that recorded in Figure 4.1 and Table 4.1 show no significant variatin in the concentration of serum HDL among patients and controls groups ($p < 0.28$). While in cholesterol, TG and LDL show a significant decrease ($P< 0.02, 0.03, 0.02$ respectively) in cholesterol levels of patients (80.82± 12.72 vs. 129.48 ± 19.04 mg/dL) as control, T.G (95.28 ± 15.28 vs 123.72 ± 14.21 mg/dL) as control and LDL (41.65 ± 12.16 vs 54.79 ± 17.66 mg/dL) as control.

Table 4.1 Biochemical characteristics between patient's vs controls

PARAMETER	CONTROL		PATİENT		P-VALUE
	MEAN	S.D.	MEAN	S.D.	
TRAB ab U/L	1.15	0.24	17.04	5.10	0.01
FT4 ng/dL	1.40	0.24	3.16	0.62	0.01
FT3 ng/dL	0.32	0.07	0.81	0.20	0.04
TSH µIU/L	3.19	0.58	0.19	0.06	0.01
Tg ng/dL	22.16	6.80	40.14	9.62	0.04
S.Cholestrol mg/dL	129.48	19.04	80.82	12.72	0.02
S. TG mg/dL	123.72	14.21	95.34	15.28	0.03
HDL mg/dL	54.14	4.58	54.36	3.82	0.28
LDL mg/dL	54.79	17.66	41.65	12.16	0.02

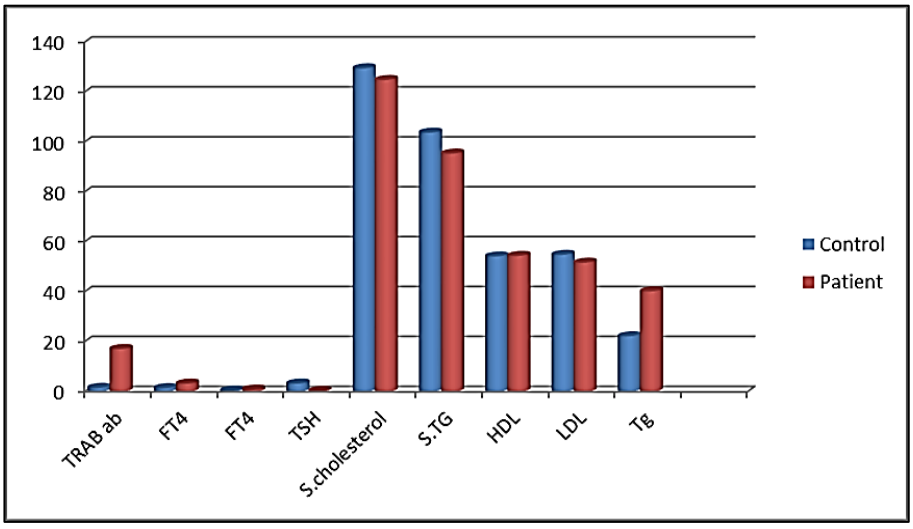

Figure 4.1 Biochemical parameters between patient's vs controls

4.2 Immune Characteristics Between Patient's vs Controls

4.2.1 Immune characteristics of IL-6 between patient's vs controls

The results of our study which was presented in the Figure 4.2 and Table 4.2 show a significant increase (P< 0.01) in IL-6 levels of patients (28.03 ± 2.80 vs. 18.14 ± 1.29 ng/dL) when compared with controls.

4.2.2 Immune characteristics of TNF between patient's vs controls

Our data in the Figure 4.2 and Table 4.2 have also showed that a significant increase (P< 0.01) in TNF levels patients (18.78 ± 3.95 vs. 8.63 ± 0.80 ng/mL) vs control.

Table 4.2 IL-6 and TNF characteristics between patient's vs controls

PARAMETER	CONTROL		PATİENT		P-VALUE
	MEAN	S.D.	MEAN	S.D.	
IL-6	18.14	1.29	28.03	2.80	0.01
TNF	8.63	0.80	18.78	3.95	0.01

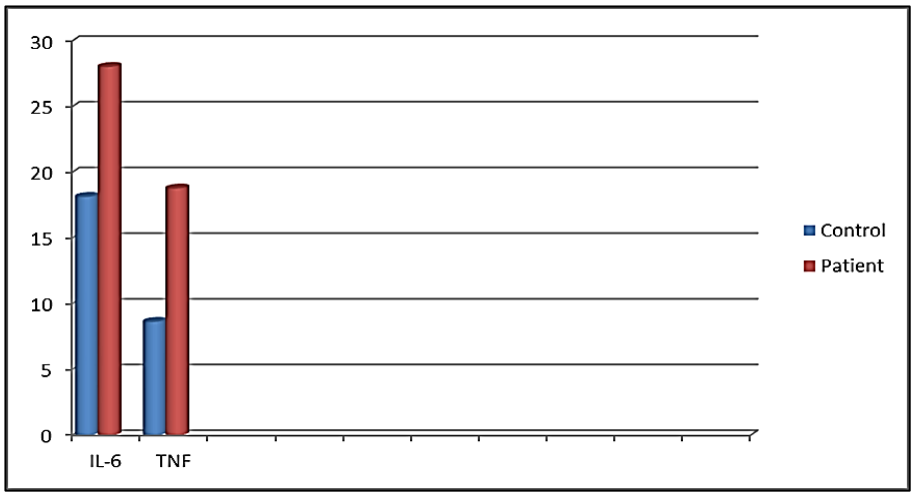

Figure 4.2 Immune parameters between patient's vs controls

4.3 Biochemical Characteristics Related to Gender

4.3.1 Biochemical characteristics of TSH-receptor Ab

The results of our study which was presented in the Table 4.3 show a significant increase (P< 0.01) in TSH-receptor Ab levels of thyroid male's patients (15.36 ± 5.12 vs. 1.03 ± 0.23 U/L) and for females (17.98 ± 6.89 vs. 1.26 ± 0.17 U/L).

4.3.2 Biochemical characteristics of free T4

Our data in the Table 4.3 have also showed that a significant increase (P< 0. 01) in free T4 levels of thyroid male's patients (3.31 ± 0.81 vs. 1.35 ± 0.29 ng/dL) and for females (3.08 ± 0.47 vs. 1.46 ± 0.23 ng/dL) when compared with controls.

4.3.3 Biochemical characteristics of free T3

The free T3 level in our study, which was presenting in the Table 4.3 shows a significant increase (P< 0. 01) of FT4 male patients (2.78 ± 0.21 vs. 0.33 ± 0.08 ng/dL) and for females (3.75 ± 0.22 vs. 0.31 ± 0.07 ng/dL).

4.3.4 Biochemical characteristics of TSH

The results of our study which was presenting in the Table 4.3 clearly shown a significant decrease (P< 0. 01) in TSH levels of thyroid male patients (0.20 ± 0.06 vs. 3.32 ± 0.49 µIU/L) and for females (0.18 ± 0.04 vs. 3.03 ± 0.64 µIU/L).

4.3.5 Biochemical characteristics of Tg

The results of our study which was presenting in the Table 4.3 clearly shown a significant increase (P< 0.02) in thyroglobulin levels of thyroid male patients (36.62± 11.64 vs. 21.58± 6.78 ng/mL) and for females (42.11 ± 12.07 vs. 23.15 ± 7.44 ng/mL).

4.3.6 Biochemical characteristics of lipid profile

Our study results that recorded in Table 4.3 show a decrease significant in the concentration of serum HDL between male patient's vs male controls (33.89 ± 4.19 vs. 53.08 ± 4.87 mg/dL) and female patients vs female controls (33.63 ± 3.62vs. 55.20 ± 4.10 mg/dL). The same results with cholesterol and LDL show a significant decrease in male patient's vs male controls groups (S.C 92.00 ± 12.66 vs. 125.88 ± 21.79 mg/dL) and (LDL-C 44.47 ± 13.55vs. 54.07 ± 20.45 mg/dL) and female patients vs female controls (S.C 102.46 ± 12.32 vs. 130.92 ± 20.32 mg/dL) and (LDL-S 47.81 ± 10.41 vs. 53.36 ± 19.01 mg/dL).

And show no significant in the concentration of serum T.G between male patient's vs male controls (T.G 84±10.71 vs 99.16±14.77mg/dL) and female patients vs female controls (T.G 101.71±13.77 vs108.28 ±12.29mg/dL).

Table 4.3 Biochemical characteristics between males vs females

PARAMETER	GENDER	CONTROL		PATİENTS		P-VALUE
		MEAN	SD	MEAN	SD	
TRAB ab U/L	Male	1.03	0.23	15.36	5.12	0.01
	Female	1.26	0.17	17.98	6.89	0.01
FT4 ng/dL	Male	1.35	0.29	3.31	0.81	0. 01
	Female	1.46	0.23	3.08	0.47	0.01
FT3 ng/dL	Male	0.33	0.08	2.78	0.21	0. 01
	Female	0.31	0.07	3.75	0.22	0.01
TSH µIU/L	Male	3.32	0.49	0.20	0.06	0.02
	Female	3.03	0.64	0.18	0.04	0.01
S. cholesterol mg/dL	Male	125.88	21.79	92.00	12.66	0.03
	Female	130.92	20.32	102.46	12.32	0.02
S.TG mg/dL	Male	99.16	14.77	84.00	10.71	0.15
	Female	108.28	12.29	101.71	13.77	0.61
HDL mg/dL	Male	53.08	4.87	33.89	4.19	0.04
	Female	55.20	4.10	34.63	3.62	0.04
LDL mg/dL	Male	54.07	20.45	44.47	13.55	0.02
	Female	53.36	19.01	47.81	10.41	0.02
Tg ng/dL	Male	21.58	6.78	36.62	11.64	0.02
	Female	23.15	7.44	42.11	12.07	0.02

4.4 Immune Characteristics Related to Gender

4.4.1 Immune characteristics of TNF between male and female

The TNF level in our study, which was presenting in the Table 4.4 shows a significant increase (P< 0.01) of TNF male patients (20.54 ± 4.62 vs. 8.62 ± 0.78 ng/dL) and for females (17.78 ± 3.18 vs. 8.64 ± 0.83 ng/dL).

4.4.2 Immune characteristics of IL-6 between male and female

The IL 6 level in our study, which was presenting in the Table 4.4 shows a significant increase (P< 0. 01) of IL 6 male patients (28.08 ± 2.51 vs. 18.35 ± 1.09 ng/dL) and for females (28.00 ± 2.99 vs. 17.93 ± 1.45 ng/dL).

Table 4.4 Immune characteristics between males vs females

PARAMETER	GENDER	CONTROL		PATİENTS		P-VALUE
		MEAN	SD	MEAN	SD	
TNF	Male	8.62	0.78	20.54	4.62	0.01
	Female	8.64	0.83	17.78	3.18	0.01
IL-6	Male	18.35	1.09	28.08	2.51	0.01
	Female	17.93	1.45	28.00	2.99	0.01

4.5 Correlation Between the Severity of Hyperthyroidism Disease and the Studied Parameters

From the results of our study, listed in the Table 4.1, Table 4.2, Table 4.3 and Table 4.4 which showed that TSH-R Ab is the better protein marker for hyperthyroidism disease, we can regard the severity of the disease is proportion to the TSH-R Ab levels, so we can make correlations between all the studied parameters and TSH-R Ab levels to understand the relationship between each parameters and the severity of the disease.

The correlation was done TSH-R Ab and the studied parameters by t-test, (P< 0.05) as significant correlation.

4.5.1 Correlation between TSH-R Ab and FT4

Our data in this study showed that a significant positive correlation between TSH-R Ab and FT4, (r= 0.32) and (P <0.05), as shown in the Figure 4.3 and Table 4.5.

Table 4.5 The correlation between TSH-R Ab and FT4

TRAB AB	R	P. VALUE	RESULTS
FT4	0.32	0.05	positive correlation

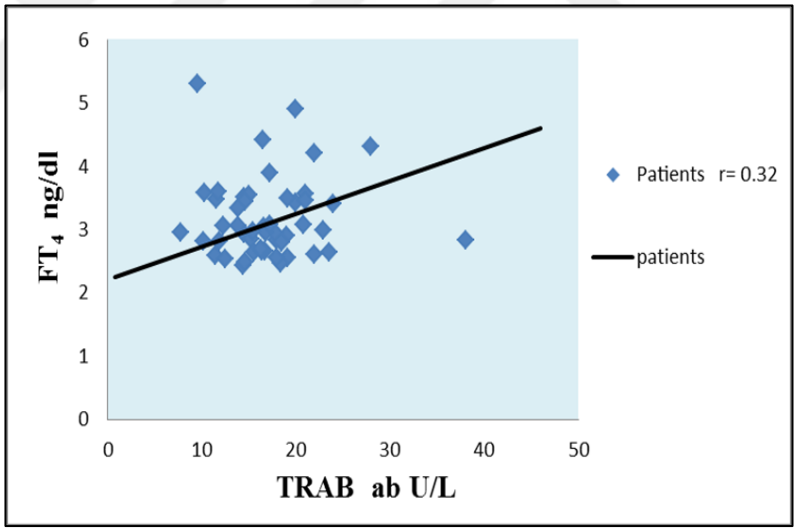

Figure 4.3 Diagram of correlation between TSH-R Ab and FT4

4.5.2 Correlation between TSH-R Ab and FT3

Clearly a significant positive correlation between TSH-R Ab and FT3 that showed in the Figure 4.4 and Table 4.6, (r= 0.31) and (P <0.05).

Table 4.6 The correlation between TSH-R Ab and FT3

TSH-R AB	R	P. VALUE	RESULTS
FT3	0.31	0.05	positive correlation

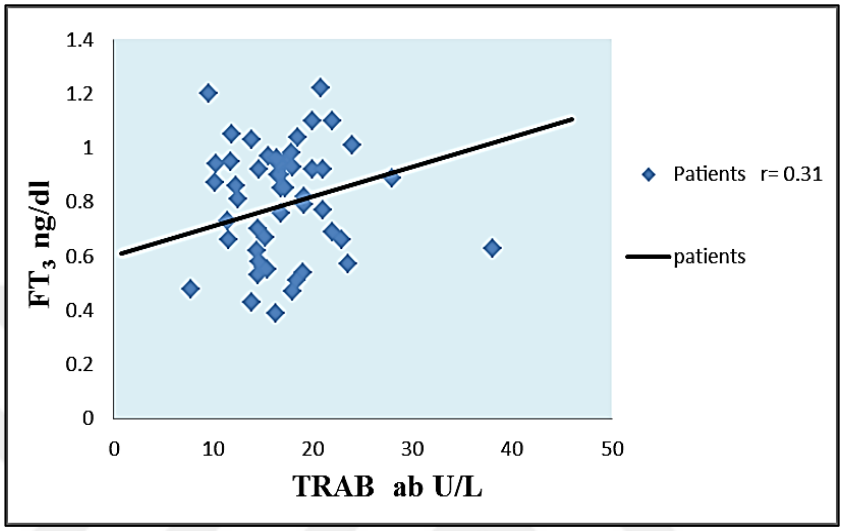

Figure 4.4 Diagram of correlation between TSH-R Ab and FT3

4.5.3 Correlation between TSH-R Ab and TSH

Our results show a significant positive correlation between TSH-R Ab and TSH in the Figure 4.5 and Table 4.7, (r= 0.37) and (P <0.05).

Table 4.7 The correlation between TSH-R Ab and TSH

TSH-R AB	R	P. VALUE	RESULTS
TSH	- 0.37	0.05	negative correlation

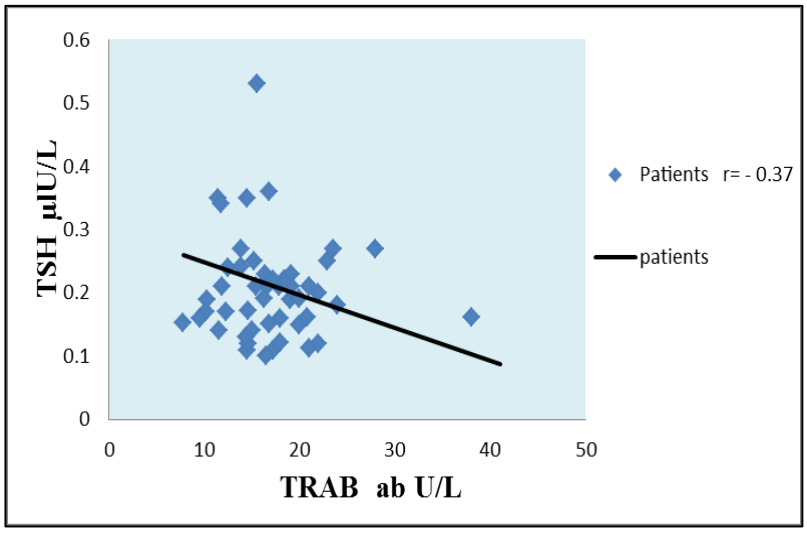

Figure 4.5 Diagram of correlation between TSH-R Ab and TSH

4.5.4 Correlation between TSH-R Ab and Tg

Our results show a significant positive correlation between TSH-R Ab and Tg in the Figure 4.6 and Table 4.8, (r= 0.46) and (P <0.05).

Table 4.8 The correlation between TSH-R Ab and Tg

TSH-R AB	R	P. VALUE	RESULTS
Tg	0.46	0.05	positive correlation

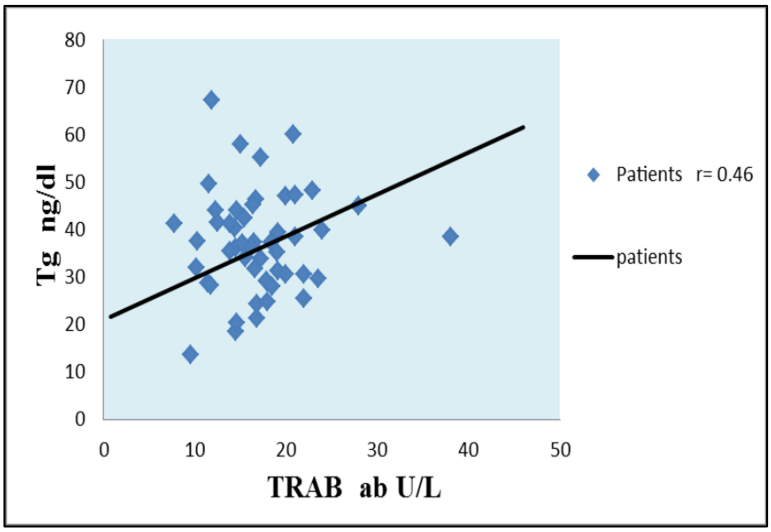

Figure 4.6 Diagram of correlation between TSH-R Ab and Tg

4.5.5 Correlation between TSH-R Ab and TNF

Our results show a significant positive correlation between TSH-R Ab and TNF in the Figure 4.7 and Table 4.9, (r= 0.55) and (P <0.05).

Table 4.9 The correlation between TSH-R Ab and TNF

TSH-R Ab	R	P. VALUE	RESULTS
TNF	0.55	0.05	positive correlation

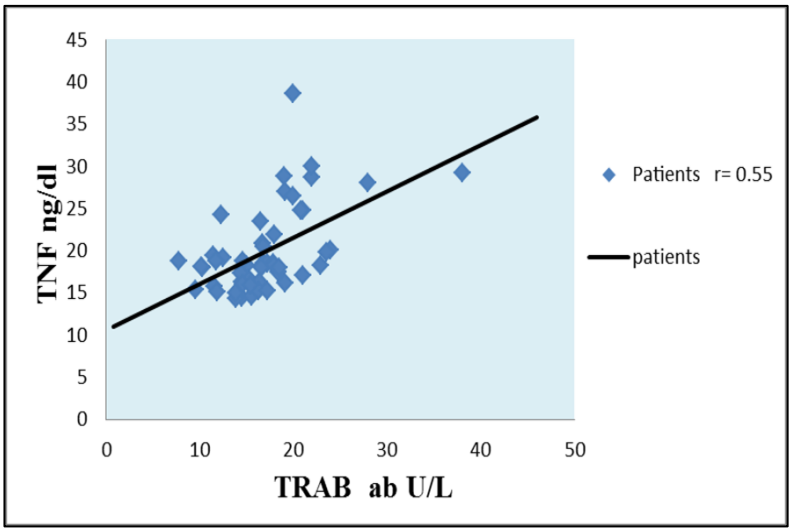

Figure 4.7 Diagram of correlation between TSH-R Ab and TNF

4.5.6 Correlation between TSH-R Ab and IL-6

Our results show a significant positive correlation between TSH-R Ab and IL-6 in the Figure 4.8 and Table 4.10, (r = 0.41) and (P <0.05).

Table 4.10 The correlation between TSH-R Ab and IL-6

TSH-R Ab	R	P. VALUE	RESULTS
IL-6	0.41	0.05	positive correlation

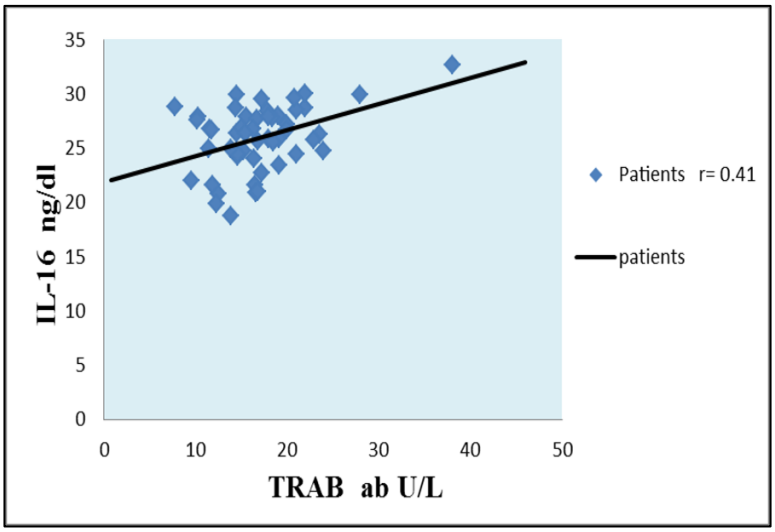

Figure 4.8 The correlation between TSH-R Ab and IL-6

5. DISCUSSION

5.1 Discussion of Biochemical Characteristics between Patients vs Controls

5.1.1 TSH-receptor Ab

This result may due to increase the immune response against thyroid gland by formation high level of IL-6 and TNF that may motor the immune system to made this auto Immune-Ab and this idea confirms us the disease is chronic clinical situation.

The results of our study are an agreement with Chaeng *et al*. (2021) that recorded, the presence of high titer of anti TSH-R Ab (52.35 ± 19.07 $p<0.01$) which stimulate excessive thyroid hormone production, Zhu *et al*. (2020) that showed increasing in TSH-R Ab (3.77 ± 18.4 $p<0.01$), Faawzi *et al*. (2018) whose showed high level of TSH-R Ab on thyroid gland surface that lead to increase thyroid mass an elevated it's production (12.11 ± 1.15 $p<0. 01$) and Mikoś *et al*. (2014) agree with With our study that showed TSH-R Ab reduce the functional activity of TSH and making a disease by attached with TSH receptor (> 10 U/L).

5.1.2 Free T4

We suggest this elevation in FT4 level is may be due to the increasing level of TSH R-AB that destroy the receptors of TSH hormone in thyroid gland surface, who stimulate the thyroid gland to stopped formation of T4, so T4 is level stay high.

We showed an agreement with Cheng *et al*. (2020) that reported elevated of FT4 (3.32 ± 3.44 ng/dL $p<0.01$) related for increasing TSH-R Ab, Zhu *et al*. (2020) FT4 (23.6 ± 6.15 ng/dL $p<0.001$), Diana *et al*. (2017) that showed increasing in FT4 (2.0 ± 1.2 ng/dL $p< 0.01$) and Elfadil *et al*. (2014) that showed a significant elevated in FT4 in Sudanese patients (32.61 ± 36.46 ng/dL $p< 0.01$).

5.1.3 Free T3

Influenced by FT4 concentration, the level of FT3 was elevating by forming TSH-R Ab as a result of immune response against thyroid gland surface.

The results of Zhu *et al*. (2020) are agreeing with our study results FT3 was (9.64 ± 3.07 pmol/L p< 0.01), Khamisi *et al*. (2021) was agreeing with our results that show increasing level of FT3 (34.0 ± 5.6 ug/L p< 0.01), the results of Diana *et al*. (2017) that showed increasing in FT3 (5.00 ± 1.50 ng/dL p< 0.01) and Elfadil *et al*. (2014) that showed a significant elevated in FT3 Ab in Sudanese patients (21.4 ± 20.6 pg/mL p< 0.01).

5.1.4 TSH

This result unequivocally indicates the TSH level was low because increase level of FT4 and FT3 hormones. The reflected relationship between them make the TSH level stay low when T4 and T3 higher.

Cheng *et al*. (2020) is agreeing with our results that show low level of TSH hormones effected with high FT4 (0.02 ± 0.03 P< 0.01), Khamisi *et al*. (2021) was agreeing with our results that show decreasing level of TSH (0.005 ± 0.004 ug/L p< 0.01) Faawzi *et al*. (2018) that showed low concentration of TSH because high activity of T4 (0.68 ± 0.14 P< 0.01) and Zhu *et al*. (2020) that showed decreasing in TSH (0.01 ± 0.02 p<0.01).

5.1.5 Tg

We suggested, lose the thyroid gland it's receptors by activation of auto Ab (TSH-R Ab) keep the activity of peroxidase enzyme that converted Tg into T4. So the manifestation of Tg stays high.

Khamisi *et al*. (2021) was agreeing with our results that show increasing level of Tg (132 ± 124 µg/L) is secreted from transport vesicles in thyrocytes into the extrafollicular space by a mechanism that is controlled by TSH or TRAb, El-Din *et al*. (2021) showed agreement with our stusy results Tg (412.88 ± 142.5 pg/L p< 0. 01) due to action of autoimmune antibody against og thyroid gland cells.

5.1.6 Lipid profile

We suggest that reducing cholesterol, T.G, HDL and LDL levels in hyperthyroidism patients due to an increased activity of T4 and T3 that cause elevated the clearance rate lipids or may due to increase rate of hepatic triglyceride lipase activity.

The result of our study agree with Rizos *et al*. (2011) levels of TC, T.G, LDL-C show a tendency to drop in patients who have clinical or subclinical hyperthyroidism and that because of rising in LDL receptor gene expression and decrease in HDL-C levels as well noted in hyperthyroidism, Chin *et al*. (2014) agree with our result that recorede hyperthyroid patients show lower level of TC, HDL-C and LDL-C and the agreement given with Iqbal *et al*. (2021)who show that, the concentration of cholesterol and LDL-C is reduced in hyperthyroid patients (TC= 101.8 ± 4:84 ng/dL p< 0.00l) and (LDL-C= 98.68 ± 2.51 ng/dL p< 0.0l).

5.2 Discussion of Immune Characteristics Between Patients vs Controls

5.2.1 Interlukine-6

This result may due to increase the self immune response that mes-presented thyroid gland cells for T-cell that lead to formation self Ab Mikoś *et al*. (2014). That recorded that high level of IL-6 elevated of thyroid follicular cell's prolfration, Slowik *et al*. (2012) agree with our data when recorded that, serum concentration of IL-6 increased in hyperthyroidism patients (3.82 ± 4.03 pg/mL p< 0.01) and Kumar *et al*. (2010) that recorded that adipogenesis is active inside tissue which is adipocytes themselves

possibly be a source for orbital IL-6. On athor hand, our study results are disagreement with Zhu *et al*. (2020) that showed no significant differences in IL-6.

5.2.2 Tumor necrosis factor

We suggest this elevation in TNF level is may be due to the mes translation for monocyte that motor the primary immune response, so it is attack the thyroid gland cell as self Ag then complete it's work by stimulate T-cell. The result of our study agree with Zhu *et al*. (2020) that associated between TNF as a primary immune stimulator with TSH-R Ab, Zhu *et al*. (2020) was showing that TNF (13.8 ± 3.87 pg/mL $p< 0.01$) was agree with our result that recorded that elevated of TNF play importet role in thyroid hyper activity and Mikoś *et al*. (2014) that appeared that TNF is inhibit the growth oan proliferation of thyroid cell.

5.3 Discussion Biochemical Characteristics Related to Gender

5.3.1 TSH-receptor Ab

We suggest the significant elevated of TSH-R Ab related for persistent false immune response those attacking thyroid follicular cells.

Diana *et al*. (2017) agree with our study when recorded that the TSH-R Ab increased in both euthyroid and hyperthyroid patients, Elfadil *et al*. (2014) that showed a significant elevated in TSH-R Ab in Sudanese patients (9.32 ± 7.71 U/ML $p< 0.01$), Leschik *et al*. (2013) that written that THS-R Ab mimic the receptors natural ligand by stimulation cyclic adenosine monophosphate and P Laurberg and Pedersen (2006) suggested that TSH-R Ab measurement is useful for diagnosis in hyperthyroid patients.

5.3.2 Free T4

We suggest this elevation in free T4 level is may be results of TSH-R Ab formation or may be for low level of TSH.

Chaeng *et al*. (2021) was agree with our result that recorded that elevated of FT4 effected with elevated of cytokines, Leschik *et al*. (2013) by showing high value of FT4 (2.3 ± 0.17 ng/dL P< 0.01) and Díez *et al*. (2002) was agree with our results when showed that, FT4 (49.34 ± 13.20 pmol/L p <0.01) is elevating by hyper level of TNF that leat to hyperthyroidism.

5.3.3 Free T3

As FT4 as, we suggest the elevation in FT3 is related to the same effect that causes increase in FT4.

Leschik *et al*. (2013) by showing high value of FT3 (10.71 ± 1.38 ng/dL P< 0.01), Kumar *et al*. (2010) that hypothesized that TSH-R Ab may act to catalyses IL-6 producing and secretion via mature adipocyte and Díez *et al*. (2002), Salvi *et al*. (2000) was agree with our study when insurance that patients with hyper thyrodisim have elevated of FT3 (12.85 ± 10.61 pmol/L p< 0.01).

5.3.4 TSH

There is no doubt the significant decreasing of TSH tightly related for elevation of thyroid secretion by action of immune attack.

The result of our study agree with Diana *et al*. (2017) that showed decreasing in TSH (1.6 ± 0.01 ng/dL p< 0.01), Elfadil *et al.* (2014) that showed a significant minimize in TSH in Sudanese patients (0.02 ± 0.01 U/L p< 0/00) and Díez *et al*. (2002) was agree

with our results when showed that, TSH (0.05 ± 0.05 μU/L p <0.001) is decreasing by hyper level of thyroid production.

5.3.5 Tg

We suggest the elevation of Tg linked with the high activation of thyroid gland that consume a lot amount of Tg as a precursor to thyroid hormones.

The result of our study agree with Diana *et al*. (2017) that showed increasing in Tg,

El-Din *et al*. (2021) showed agreement with our study results Tg (412.88 ± 142.5 pg/L p< 0.01) due to action of autoimmune antibody against thyroid gland cells.

5.3.6 Lipid profile

On anther hand, our results show no significant change in Triglyceride between both males and females when compared with controls.

The result of our data is agreeing with that suggested that total cholesterol, HDL-C and LDL in new cases were decreased in hyperthyroidism (TC= 107 ± 10.9 ng/dL p< 0.01), (HDL-C= 46.6 ± 10.4 ng/dL p< 0.0l) and (LDL-C= 35.6 ± 3.3 ng/dL p< 0.0l) while he disagreeing with our dated in triglycerides slightly increased (122 ± 14.6 ng/dL p< 0.0l), the result of our study agree with Duntas and Brenta (2012) that showed plasma levels of cholesterol are reduced in hyperthyroid patients and Iqbal *et al*. (2021) who show that, the concentration of cholesterol and LDL-C is reduced in hyperthyroid patients (TC= 101.8 ± 4:84 ng/dLp< 0.0l) and (LDL-C= 98.68 ± 2.51 ng/dL p< 0.0l).

5.4 Discussion Immune Characteristics Related to Gender

5.4.1 Tumar necrosis factor

We suggest that the elevation of TNF due to the persistence of the faully response of the immune system that attacked the follicular cells of the thyroid gland.

The result of our study agree with Mikoś *et al*. (2014) that appeared that TNF is inhibit the growth oan proliferation of thyroid cell, Diez (2002) was agree with our results when confirmed that, the activity of TNF (3.36 ± 1.21 pg/MLP< 0.01) relevance the patients with thyroid dysfunction and Salvi *et al*. (2000) was agreeing with our results when recorded that, hyper thyrodisim's patients have increased of TNF (4.4 ± 0.4 pg/mL p< 0.01).

5.4.2 Interleukin -6

We suggest the high level of IL-6 bonded with elevation of TNF as primary motor for immune response or due to increasing level of TSH-R Ab.

The result of our study agreement with Salvi *et al*. (2000) was agree with our study results when insurance that, patients with hyperthyroidism have elevated of IL-6 (3.2 ± 0.4 pg/ML p< 0.001) and Kute *et al*. (2021) agree with our data when recorded that serum concentration of IL-6 increased in hyperthyroidism patients (11.1±2.3pg/mL p< 0.01) and Kumar *et al*. (2010) that recorded that adipogenesis is active inside tissue which is the adipocytes themselves possibly be a source for orbital IL-6. On athor hand, our study results are disagreement with Chaeng *et al*. (2021) that showed no significant differences in IL-6.

5.5 Correlation Between TSH-R Ab and the Studied Parameters

We suggest that the affirmative relation among TSH-R Ab as well both FT4, FT3 and Tg that showed in the Figure 4.3, Figure 4.4 and Figure 4.5 respectively may due to persistence of falls immune response against thyroid follicular cell by action of elevation concentration of TNF and IL-6. The same reason for negative correlation between TSH-R Ab and TSH hormone. The correlation of our results' study in agreement with El-Din *et al*. (2021) that showed the results of TSH-R Ab level with serum FT4, FT3 and negative with TSH. This correlation could be explained by the action of TSH-R Ab on TSH receptors with subsequent stimulation of the thyroid cell to produce excessive amount of thyroid hormones, resulting in hyperthyroidisms and the correlation of our results' study in agreement with Zhu *et al*. (2020) we mentioned that positively correlated between TNF and TSH-R Ab.

6. CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

1. TSH-R Ab is the better hyperthyroidism marker specially with patients who suffer from elevation TNF and IL-6 even for males and females.
2. There is a tightly contact between elevation of TSH-R Ab and FT4, FT3 concentration in the patients with hyperthyroidism that effected with increase the activity of immune response which presented in TNF and IL-6 accompanying with decline of TSH concentration in both of general comparison or in case of males, females vs control.
3. There is no significant changes HDL between patients and controls groups and decrease significant with S.C, TG and LDL-C because hyperactivity for thyroid secretion. cholesterol, HDL and LDL levels in hyperthyroidism patients due to an increased activity of T4 and T3 that cause elevated the clearance rate lipids or may due to increase rate of hepatic triglyceride lipase activity in both genders. And show no significant in the concentration of serum T.G between male patient's vs male controls and female patients vs female controls. and The results with cholesterol, HDL and LDL show a significant decrease in male patient's vs male controls groups.

4. A significant positive correlation between TSH-R Ab with FT4, FT3, Tg, TNF and IL-6 while negative correlation with TSH.

6.2 Recommendations

1. Measurement of TSH-R Ab in hyperthyroidism patients and the role of T-cell in accumulation of cytokines.
2. Study the genetic ettection for HLA I and HLA II that may lead for formation and accumulation of cytokines against thyroid follicular cells.
3. Study the therapeutic supplement of thyrixin's limitation in the prevention of THS-R Ab accumulation in hyperthyroidism patients.

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