

The Relation Between Thyroid Function and Auto-Antibodies in Graves' Disease and Non-Autoimmune Hyperthyroidism Disease in AL-Najaf Province

العلاقة بين وظيفة الغدة الدرقية والأجسام المضادة الذاتية عند مرضى الدراق الجحوضي وإفراط الغدة الدرقية غير المناعي الذاتي في محافظة النجف

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الخلاصة:

الهدف: تقييم دور بعض المعلمات المناعية المرتبطة بالمرض والمقارنة مع غيرها من حالات فرط الغدة الدرقية غير المناعي. باتباع الخطوات التالية:
١- قياس هرمون T4, T3 وال TSH. ٢- تقييم مضاد مستلم الأجسام المضادة Anti-TSHR-antibody. ٣- تقدير Anti-TPO antibody.
المنهجية: شملت هذه الدراسة المقارنة على (73) مريضا تم تشخيصهم مع فرط نشاط الدرق و (20) شخصا من الاصحاء كمجموعة سيطرة، الذين يراجعون مدينة الصدر الطبية في النجف/ وحدة الهرمونات خلال الفترة ما بين مايو (2011) إلى أكتوبر (2011). ومن بين (73) مريض بفرط نشاط الدرق، كان هناك (48) مريض من الإناث و (25) مريض من الذكور تتراوح أعمارهم ما بين (15-50) سنة. جميع المرضى الذين يعانون من فرط نشاط الدرق تحت العلاج والنساء الحوامل تم استبعادهم من الدراسة تم التحليل الإحصائي باستخدام برنامج SPSS النسخة ٢٠ والمتضمن التالي:
١- استخدام (تحليل المتغيرات الانوفة "ANOVA") ٢- "r" persons correlation، عامل التكافؤ لقياس النتائج.
النتائج: وفقا لنتائج هذه الدراسة، فإن غالبية مرضى المرض المناعي الذاتي "GD" هم من الإناث (68.5%) أكثر من الذكور (17%) مع نسبة الإناث بالذكور كانت تتراوح (1:2.17) وأن متوسط العمر لمرض غريفز كان (38.88±8.17).
الفئة العمرية بين (36-50) سنة كانت هي الأكثر عرضة لمرض غريفز حيث سجلت (66.7%) من مجموع، تليها الفئة العمرية (26-35) سنة حيث سجلت (20.4%) من مجموع و (13%) من مجموع للفئة العمرية (15-25) سنة. ومع ذلك، كانت الاختبارات الهرمونية ل(T4, T3, TSH) قد أظهرت مستويات ذات فرق كبير للغاية ($P < 0.001$) بين مرضى غريفز والمجموع الأخرى المتضمنة فرط نشاط الدرق غير الذاتي والسيطرة. علاوة على ذلك، كانت مستويات الأجسام المضادة ل(TSHR) هامة للغاية ومترتبة بنسبة معنوية كبيرة بين مرضى غريفز ($P < 0.01$) "GD"، مقارنة بالمجموع الأخرى من مرضى فرط نشاط الدرق غير الذاتي والسيطرة، في حين لم يكن هناك اختلاف كبير بين مرضى فرط نشاط الدرق غير الذاتي ومجموعة السيطرة ($P > 0.05$). بالإضافة إلى ذلك، كانت مستويات مصل بيروكسيداز الغدة الدرقية (TPO- Ab) ذات فرق كبير جدا بين مرضى غريفز "GD" وفرط نشاط الدرق غير الذاتي ومجموعة السيطرة ($P < 0.001$)، في حين لا يوجد فرق كبير بين مرضى فرط نشاط الدرق غير الذاتية ومجموعة السيطرة ($P > 0.05$).
أضداد (Anti-TSHR-Ab) لها ارتباط إيجابي كبير للغاية ($P < 0.01$) مع (T4 و T3) هرمون، لكن أظهر علاقة سلبية مع هرمون TSH (-0.475).
الاستنتاج: فحص الأجسام المضادة (TSHR) يساعد في تشخيص مرضى غريفز "GD"، لأنها تستطيع الكشف عن أمراض المناعة الذاتية للغدة الدرقية "AITD" في وقت مبكر جدا. فإن وجودها في الأشخاص الذين يعانون من فرط الغدة الدرقية الغير متميز قد يتنبأ في نهاية المطاف الى حدوث مرض غريفز وهذا يجعلها علامة تشخيصية جيدة.
التوصيات: أفضل التوصيات للبالغين وضع فحوصات وظيفة الغدة الدرقية على لائحة العناية الصحية.

Abstract:

Objectives: The aim of presented study was evaluated the role of some immunological parameter associated with Graves' disease and comparison that with other non-autoimmune hyperthyroidism, by the following objectives: 1- measurement T3, T4 and TSH. 2- Evaluation of Anti-TSHR-antibody. 3- Estimation Anti-TPO antibody. **Methodology:** A case control study included patients with early diagnosis with thyrotoxicosis. Whole blood samples were collected from 73 cases from hormonal unite at Al-Sadder Medical City, Najaf, Iraq, in the period between May, 2011 to Oct., 2011. Out of the 73 hyperthyroidism patients, there were 48 females and 25 males, the patients' age range was between (15-50) years. All patients with hyperthyroidism under treatment and pregnant women excluded from the study. Statistical analysis was done by using SPSS version 20 in which include the followings: 1- ANOVA (analysis of variance) and LSD test (**F-test**). 2- persons correlation (**r**), coefficient for measurement data.

Results: According to the results of this study, the female: male ratio (2.17:1) in GD patients and (1.37:1) with non-autoimmune hyperthyroidism group, which detects more frequent in females (68.5% and 57.9%, respectively) than males (31.5% and 42.1%, respectively). The age group between (36-50) years with GD it is the most vulnerable age group was recorded (66.7%), followed (26-35) years age group (20.4%) and (13.0%) in age group (15-25) years. However, hormonal tests (T3, T4 and TSH) levels were highly significant difference ($P < 0.001$) between GD patients and other groups (non-autoimmune hyperthyroidism and healthy control). Furthermore, the levels of Anti-TSHR antibodies were highly significant between GD patients ($P < 0.001$), and both non-autoimmune hyperthyroidism patient and healthy control, while there was no significant difference between non-autoimmune hyperthyroidism and healthy control groups ($P > 0.05$). Additionally, the serum levels of thyroid peroxidase (TPO) was a highly significant difference between GD patients and (non-autoimmune hyperthyroidism and health control) ($P < 0.01$), while no significant difference between non-autoimmune hyperthyroidism and healthy control

($P>0.05$). Anti-TSHR antibodies have a highly significant positive correlation ($P<0.01$) with (T3 and T4) hormones (0.583 and 0.536, respectively) and a highly significant ($P<0.01$) but negative correlation with TSH hormone (-0.475). **Conclusion:** anti-TSHR antibodies assay is helpful in diagnosis of autoimmune GD, as they can be detected very early in AITD. They may predict the eventual development into AITD when founded in making them a good diagnostic marker.

Recommendation: For adults, the best recommendation may be to put thyroid function testing (TSH, T4, T3) on your list of health care provider.

Key word: Graves' disease (GD), T3, T4, TSH, Anti-TSHR-Ab, Anti-TPO-Ab.

INTRODUCTION:

Autoimmune thyroid Graves' Disease (GD) is one of the most common autoimmune diseases (AID), typified by hyperthyroidism and autoantibodies directed against the thyroid stimulating hormone receptor (TSHR), Thyroid peroxidase (TPO) and thyroglobin (Tg)^(1,2). The presence of thyroid autoantibodies substantially contributes to the pathogenesis of a number of thyroid disorders, such as Hashimoto's thyroiditis, primary myxoedema, Graves' disease⁽³⁾. They are also present in a smaller percentage of sera from other non- autoimmune thyroid disorders. Thyroid autoantibodies in autoimmune thyroid diseases have been reported to range from 1-40% but its prevalence in non-autoimmune diseases is unknown⁽⁴⁾. Graves' disease is one of the most common autoimmune diseases, affecting 13 million people and targeting women seven times as often as men, and people over the age of fifty who have hypertension or atherosclerosis are at risk for developing GD⁽⁵⁾.

OBJECTIVES: The aim of presented study was evaluated the role of some immunological parameter associated with Graves' disease and comparison that with other non-autoimmune hyperthyroidism, by the following objectives:

- 1- measurement T3, T4 and TSH.
- 2- Evaluation of Anti-TSHR-antibody.
- 3- Estimation Anti-TPO antibody.

METHODS:

1. Patients: Study population included patients were early diagnosed with thyrotoxicosis (with increased in T3 and/or T4 and decrease in TSH), "hyperthyroidism". Whole blood samples were collected from 73 cases from hormonal unite at Al-Sadder Medical City, Najaf, Iraq, in the period between May, 2011 to Oct., 2012. Out of the 73 hyperthyroidism patients, there were 48 females and 25 males, the patients age range was between (15-50) years. All hyperthyroidism patients were subdivided into two groups:

First group: patients with auto-antibodies "GD".

Second group: patients without auto-antibodies (non-autoimmune hyperthyroidism).

2. Control: twenty healthy control groups who had no history or clinical evidence of hyperthyroidism.

Study parameters: All hyperthyroidism patients and control group subjected to following serological studies:

I-Hormonal estimation including: T3, T4 and TSH.

II-Immunological study including: Anti-TSHR antibody and Anti-TPO antibody.

3. Collection of samples: Five ml of the whole blood were obtained by venipuncture from all study subjects after cleaning the skin with 70 % alcohol, then, the blood samples were divided into EDTA tubes and plain tubes. To separate the serum for serological studies, 3 ml of the blood samples allowed to clot for about 1 hr. at room temperature, then the clot loosed gently from the tube wall by means of a wooden stick. After that, the samples were centrifuged for 10 min at about 1200g and finally the serum transferred to other tubes for storage at - 20 °C ⁽⁶⁾.

Serological Test:

1. Hormonal Tests: Total Triiodothyronine (tT3), Total Thyroxine (tT4) and Thyrotropin (TSH), follow instructions of manufactured company ELISA kits, Monobind Inc./USA.

2. Anti-TSH Receptor Antibodies: Follow instructions of manufactured company, (IMTEC-TSH Receptor-Antibodies ELISA Kit, Human/ Germany).

3. Thyroidal Peroxidase- Ab (TPO-Ab): Follow instructions of manufactured company,(Thyroidal Peroxidase-Ab (TPO-Ab) ELISA Kit, Demeditec/Germany).

RESULTS:

Table(1): Comparison among groups regarding age and sex

Parameter	Control (N=20)	Graves' disease (N=54)	non-autoimmune hyperthyroidism (N=19)	P value
Mean Age(years)	40.75±3.8	38.88±8.71	37.89±9.54	0.530 NS
Female: male ratio	12:8= 1.5:1	37:17= 2.17:1	11:8= 1.37:1	1.8:1
(NS)=non-significant (P>0.05)				

LSD Test: The demographical distribution of studied groups was presented that no significant difference between Graves' disease (**38.88 ± 8.71**) and non-autoimmune hyperthyroidism group (**37.89 ± 9.54**) and healthy Control group (**40.75 ± 3.8**), regarding ageat (**P>0.05**).and also presented the female: male ratio with GD are 2.17:1

Table(2): Age distribution according to studied groups.

Groups		Control (n=20)	Graves' disease (n=54)	Non-autoimmune hyperthyroidism (n=19)	P value
Age					
Age/ years	15-25	0	7	3	0.208 NS
		0.0%	13.0%	15.8%	
	26-35	2	11	5	
		10.0%	20.4%	26.3%	
	36-50	18	36	11	
		90.0%	66.7%	57.9%	
Total		20	54	19	
		100.0%	100.0%	100.0%	
(NS)=non-significant (P>0.05)					

LSD Test: Showed that the age group between (**36-50**) years was the most vulnerable age group to GD (**66.7%)(n=36)**, followed by age group (**26-35**) years (**20.4%)(n=11)** and (**13.0%)(n=7)** in age group (**15-25**) years. While patients with non-autoimmune hyperthyroidism was most frequently in age group (**36-50**) years (**57.9%)(n=11)**. However, no significant difference between GD patients and patients with non-autoimmune hyperthyroidism age groups (**P>0.05**).

Table(3) :Relation between studied groups and sex

Groups Sex	Control (n=20)	Graves' disease (n=54)	Non-autoimmune hyperthyroidism (n=19)	P value
F	12	37	11	0.631

	60.0%	68.5%	57.9%	NS
M	8	17	8	
	40.0%	31.5%	42.1%	
Total	20	54	19	
	100.0%	100.0%	100.0%	

(NS)=non- significant ($P>0.05$)

LSD Test: Recorded (68.5%)(n=37) of the patients were females and (31.5%)(n=17) males, with ratio (2.17:1) female: male. In spite of the female sex was predominant among Graves' disease patients there was no significant ($P>0.05$) difference between studied groups.

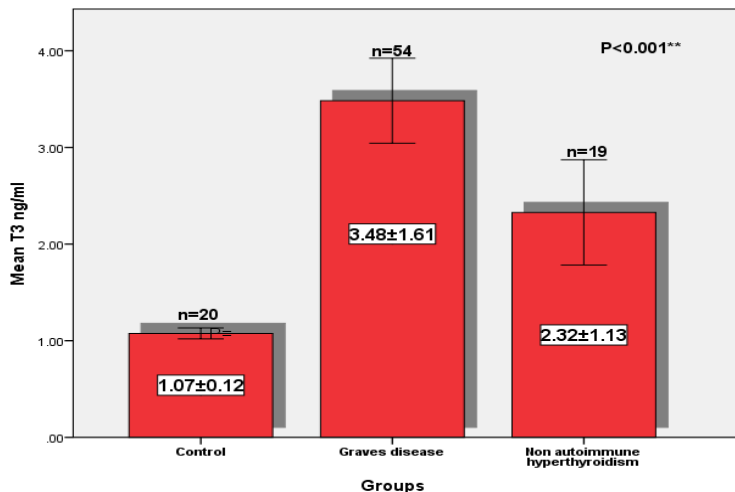
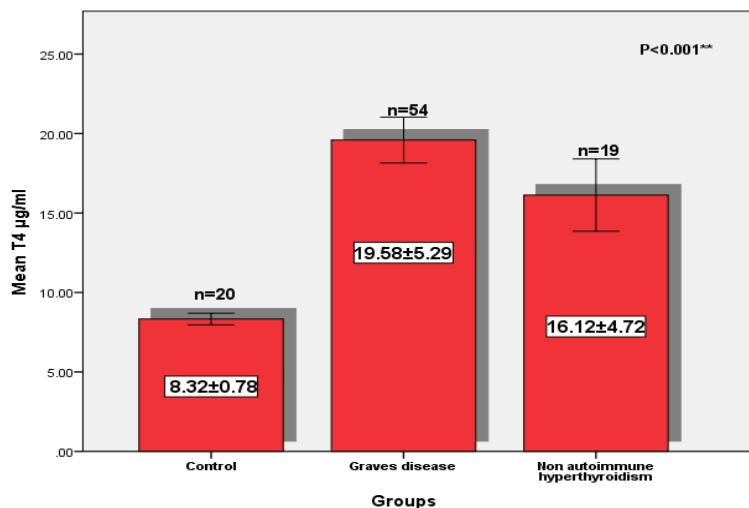


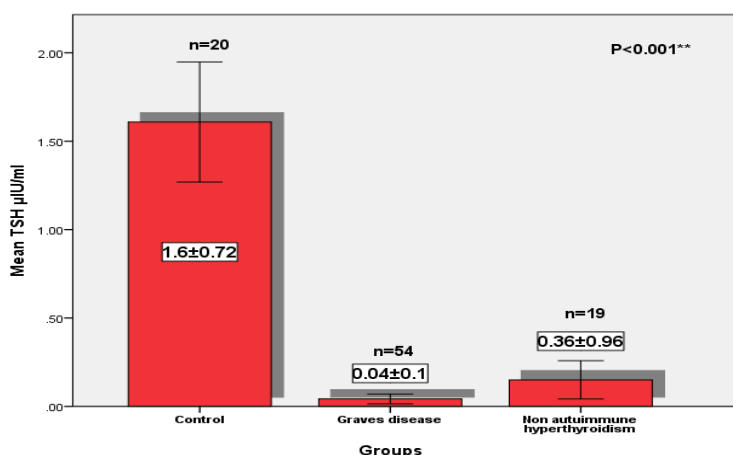
Figure (1): The level of "T3" hormone among studied groups. And revealed that the highest level of T3 hormone was among the GD patients (3.48 ± 1.61) while in non-autoimmune hyperthyroidism groups were (2.32 ± 1.13) and (1.07 ± 0.12) with healthy control groups. These results explain a highly significant differences ($P<0.01$), were observed between T3 hormone and among groups.

**= highly significant ($P<0.01$)



Figure(2): The level of hormone "T4" among studied groups. The present study revealed that the highest level of T4 hormone was found among the sera of Graves' disease patients (19.58 ± 5.29) as compared with non-autoimmune hyperthyroidism patients (16.12 ± 4.72) and healthy control groups (8.32 ± 0.78), with a highly significant ($P<0.01$) differences in among groups.

**= highly significant ($P<0.01$)



Figure(3): Evaluation of serum TSH hormone levels among studied groups. And showed that a highly significant difference ($P<0.01$) between

Graves' disease patients (0.04 ± 0.1) and patients with non-autoimmune hyperthyroidism groups (0.36 ± 0.96) and (1.6 ± 0.72) with healthy control.

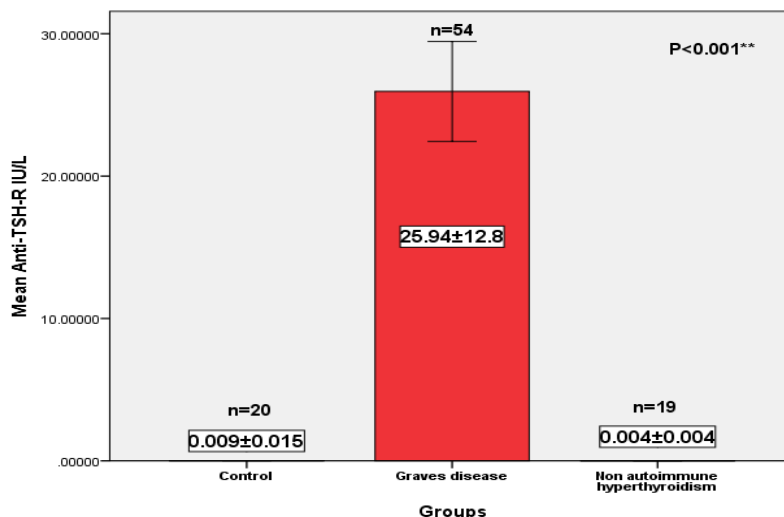
**= highly significant ($P < 0.01$)

Table(4): Relation between Anti-TSHR antibody among studied groups.

parameter	Cut-off Value	Groups			P value
		Control (20)	Graves' disease (54)	Non-autoimmune hyperthyroidism (19)	
Anti-TSHR-Ab IU/L	Normal (<=1)	20	6	19	<0.001**
		100.0%	11.1%	100.0%	
	High (>1.5)	0	48	0	
		0.0%	88.9%	0.0%	
Total		20	54	19	
		100.0%	100.0%	100.0%	
(**)=highly significance (P<0.01)					

(**)=highly significance ($P < 0.01$)

LSD Test: Serum anti-TSHR antibodies were significantly increased in patients with autoimmune Graves' disease ($n=48$) (88.9%) from a total number (73) patients of hyperthyroidism.



Figure(4): Serum levels of anti-TSHR antibodies in studied groups. Also showed that the levels of anti-TSHR antibodies were significantly increased at P value ($P < 0.001$) and significant difference between Graves' disease (25.94 ± 12.8) and non-autoimmune hyperthyroidism patients and healthy control group (0.004 ± 0.004 , 0.009 ± 0.015 , respectively), while there was no significant difference ($P > 0.05$) between healthy control and non-autoimmune hyperthyroidism groups.

**= highly significant ($P < 0.01$)

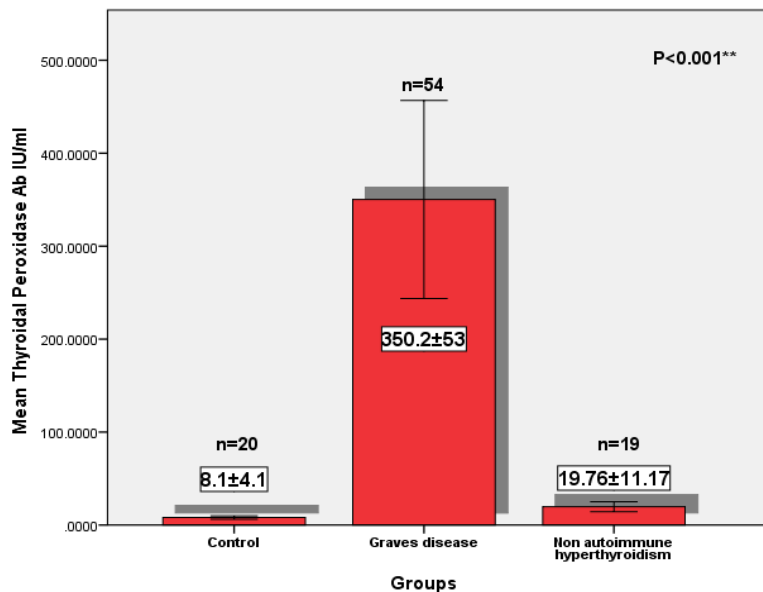
Table(5): Relation between thyroidal peroxidase Ab. level among studied groups

Parameter	Cut-off Value	Groups			P value
		Control	Graves' disease	Non-autoimmune hyperthyroidism	

Thyroidal peroxidase antibody IU/ml	Normal (<50)	20	14	19	<0.001**
		100.0%	25.9%	100.0%	
	Border line (50-75)	0	2	0	
		0.0%	3.7%	0.0%	
High (>75)		0	38	0	
		0.0%	70.4%	0.0%	
Total		20	54	19	
		100.0%	100.0%	100.0%	

(**)=high significance (P<0.01)

LSD Test: Serum thyroidal peroxidase (TPO) antibody were high significantly increased in patients with GD (n=38) (70.4%) than other studied groups.



Figure(5): Serum thyroid peroxidase antibodies level in studied groups. Presented a highly significant difference ($P<0.01$) between Graves' disease (350.2 ± 53) and non-autoimmune hyperthyroidism patients and healthy control groups (19.76 ± 11.17 and 8.1 ± 4.1 , respectively), but no significant difference ($P>0.05$) between patients of non-autoimmune hyperthyroidism and healthy control groups. And showed that the levels of anti-TSHR antibodies were significantly increased at P value ($P<0.001$).

**= highly significant ($P<0.01$)

Correlation between Graves' autoantibodies and (T3, T4 and TSH) hormone.

1. Anti-TSHR antibody and T3, T4, TSH:

Table(6): Correlation between Anti-TSH-R and (T3, T4 and TSH) hormone

Parameter	r	P value
T3	0.583	<0.001**
T4	0.536	<0.001**
TSH	-0.475	<0.001**

(**)= highly significant , (r) = relation, (-)= negative

LSD Test: Presented that a highly significant positive ($P<0.01$), correlation between Anti-TSHR Ab and T3, T4 ($r=0.583$, 0.536 , respectively). But highly significant negative correlation ($r=-0.475$), between Anti-TSHR antibody and TSH.

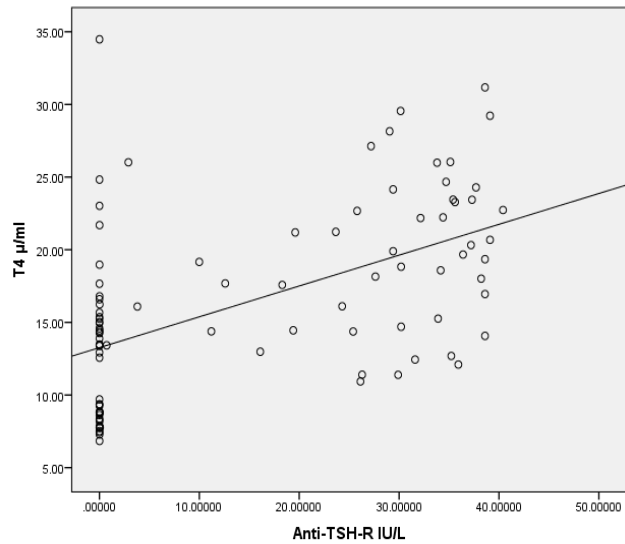
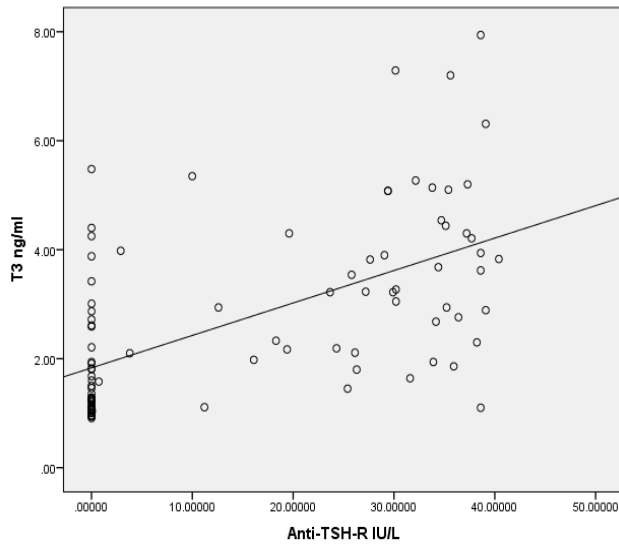


Figure (6): Correlation between T3 and Anti-TSHR-Ab IU/L
Figure (7): Correlation between T4 and Anti-TSHR-Ab IU/L

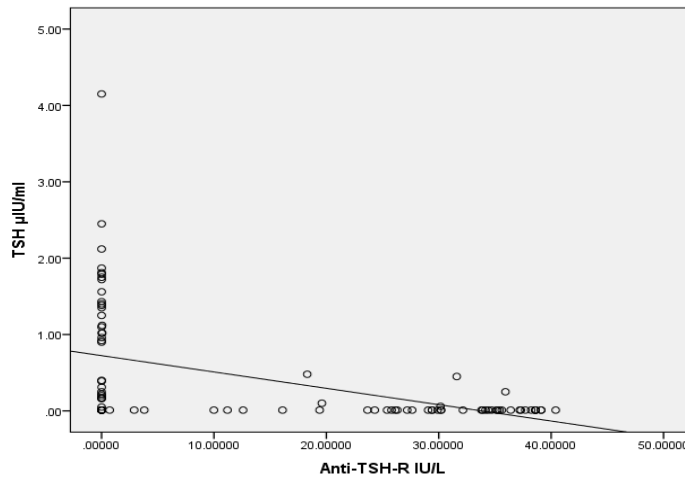


Figure (8): Correlation between TSH and Anti-TSHR-Ab

2. Correlation between Anti-TPO antibody and (T3, T4 and TSH) hormone:

Table (7): Correlation between Anti-TPO antibody with thyroid function tests

Parameter	R	P value
T3	0.373	<0.001**
T4	0.364	<0.001**
TSH	-0.307	<0.001**

(**)= highly significant , (r) = relation, (-)= negative, (*)= significant($P \leq 0.05$)

LSD Test: Presented that a highly significant ($P < 0.01$), positive correlation between Anti-TPO-Ab. and T3, T4 ($r = 0.373, 0.364$, respectively). While **Fig: (4-13)**, explain a highly significant ($P < 0.01$) negative correlation ($r = -0.307$), between Anti-TPO antibody and TSH.

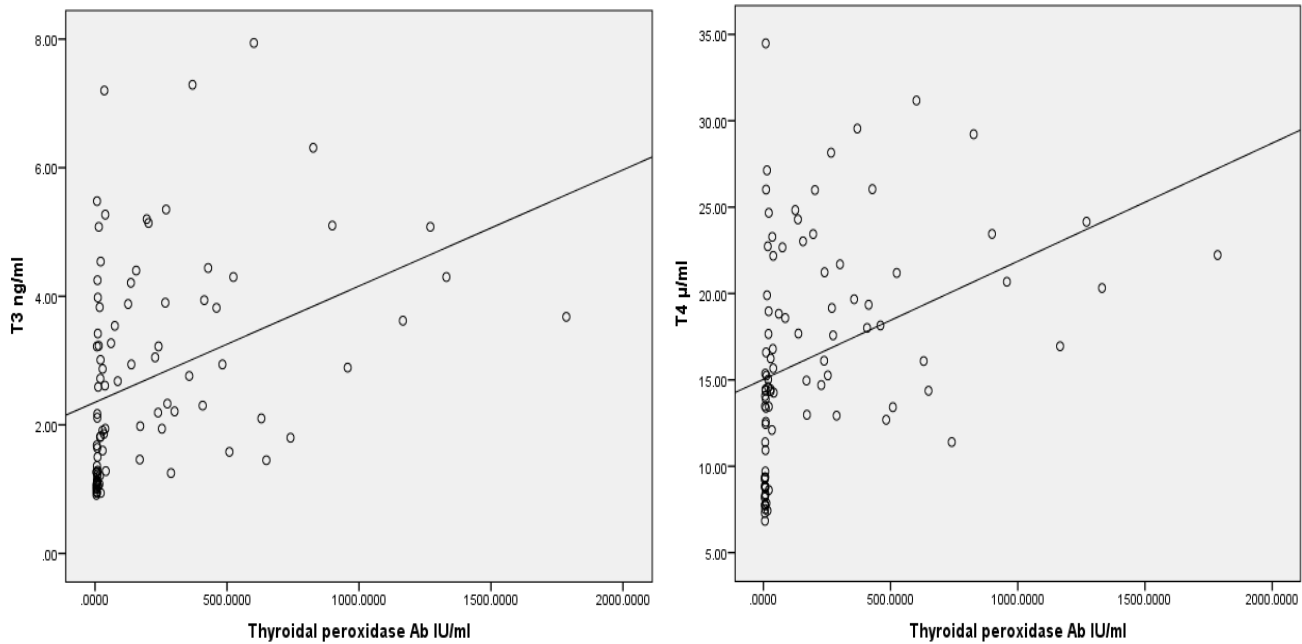


Figure (9): Correlation between T3 hormone and Anti-TPO-Ab IU/L and anti-TPO-Ab IU/L

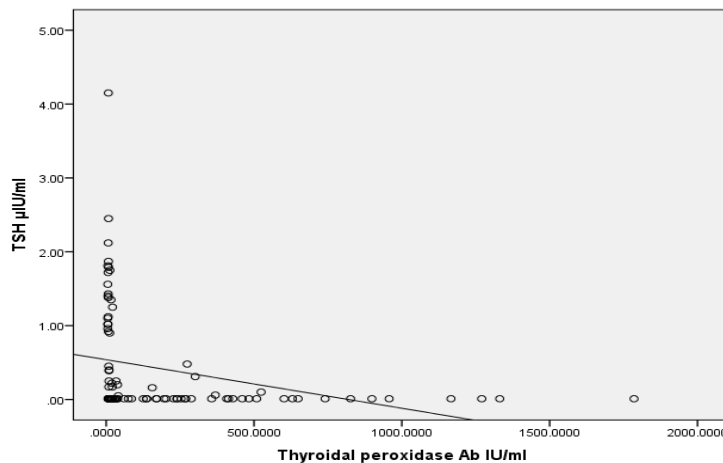


Figure (11): Correlation between TSH hormone and Anti-TPO-Ab IU/L

DISCUSSION:

The current study revealed that the majority of GD patients were at age group (36-50) years. Although GD may affect anyone, the prevalence was highest in those subjects aged 50 years, and this result was completely compatible with **Carléet al.**, when their findings were confirmed in multivariate models reporting age as a significant predictor for referral in GD patients ($p < 0.001$), among referred hyperthyroid patients, those aged up to 40 years (66.8%), Graves' disease was more common among women in/and before the age of 40 (27, 56%)⁽⁷⁾. Also our result was agreed with a recent study in Iraq country^(8, 4), when who presented the incidence of AITD "GD" was increased in (26-45) years age groups. Similar

observation was reported by⁽⁹⁾, they presented that the age of patients with hyperthyroidism was (15-61) years (38.63±10.03). The presented data also agreed with⁽¹⁰⁾, that the ratio of incidence was increased in females compared with males in all age groups.

The lower mean age among Iraq patients probably was due to the fact that the life spans of Iraqi patients were lower than that of European population. In addition the lower mean age years among graves' hyperthyroidism patients may be due to accumulative effects of environmental, psychological, and chemical agents of the last war occurred in Iraq.

In the presented study, the distribution of studied group according to the sex revealed that the majority of GD patients were females, **(68.5%)(n=37/54)** with female: male ratio **2.17:1**. Many study reported that the incidence of GD in women higher than in men, with a varying sex-ratio^(11, 12, 4). Thyroid disorders are prevalent worldwide, especially in women, and this is associated with sex hormones imbalance such as estrogen hormone, which is normally elevated in females during puberty and pregnancy and the X chromosome which affect the thyroid and immune system⁽¹³⁾.

The results obtained from this work were involved highly significant increase in levels of T3 and T4 associated with highly significant decrease of TSH levels of both males and females for patients with Graves' disease and non-autoimmune hyperthyroidism in comparison with control subjects. The explanations for the fact that excess production of T3 and T4 accompanied by low level of TSH was believed that the source of these antibodies is immune competent plasma cells, the antibodies bind with TSHR to initiate and increase T3 and T4 synthesis and production regardless of decrease level of TSH by negative feedback mechanism which exerted by T3 and T4 on pituitary and hypothalamic axis⁽⁹⁾. The level of T4, being an indicator of the severity of thyrotoxicosis, was also correlated with the Th1/Th2 and proinflammatory cytokines in Graves' disease patients^(14, 15). Therefore, a total T3/T4 ratio and TSH value, is a useful parameter for the rapid differentiation of Graves' disease^(16, 17). Among these hormones, serum TSH concentrations are considered the most reliable indicator of thyroid function abnormalities, because, the log/linear TSH/FT4 relationship dictates that an altered TSH will be the first abnormality to appear – as soon as the pituitary registers that FT4 has changed from its genetically-determined set point for that particular individual⁽¹⁸⁾. However, small changes in T4 concentration will provoke very large changes in serum TSH. The setting of the TSH reference range is critical for detecting mild (subclinical) hypo- or hyperthyroidism. Therefore, TSH measurement was appeared to be the first choice in selecting the hormone determination⁽¹⁹⁾.

Thyroid autoantibodies are the markers of autoimmunity in autoimmune thyroid diseases^(20, 4). Graves' hyperthyroidism disease which is an autoimmune disease where the antibodies to the thyroid stimulating hormone receptor (TSHR) make the thyroid gland produce too much hormone⁽¹⁰⁾. TSHR autoantibodies play a direct role in the pathogenesis of AITD. Therefore (TRAB) assay is helpful in diagnosis of Graves' disease when clinical features are not conclusive, and make as a golden diagnostic marker for Graves' disease.

In the current study the anti-TSHR antibody presented in a high number of GD patients with Anti-TSHR-Ab**(54.58%)**, out of total number patients hyperthyroidism **(73)**. This result agreed with other studied which conducted by⁽²¹⁾ who explained that the significant increase in mean of TRA in patients with graves when compared with both patients with hyperthyroidism and control group. **Amballi**, reported that elevation of TRAb in untreated Grave's disease 95% of patients were TRAb positive while 15% of patients diagnosed as nodular toxic goiter were TRAb positive⁽²²⁾. A study by **Pedersen**, reported that 90% of patients were TRAb positive due to hyperthyroidism of Graves' disease that was distinguished clinically from the presence of a painless diffuse goiter⁽²³⁾. These finding and our presented results was agreed with recent local study in Iraq⁽⁹⁾.

In the presented study, the results revealed significant differences in level of auto- antibodies TPO to the thyroid gland in patients with Graves' hyperthyroidism **(70.4%)** as compared with non-autoimmune hyperthyroidism and healthy control group **(0.0%)**. And this results were in agreement with a recent local study in Iraq^(8, 10). Other studied in Sudan by **Elmugadamet al.**, presented that the Anti-TPO antibody was positive in 66.7% of Graves' disease patients compared to 5% of control group, and 17.5% in patients with non-autoimmune hyperthyroidism disease⁽⁴⁾. Human TPO was found to bind to both IgG and IgM from patients with autoimmune thyroid diseases. The binding of IgG to microsomes is inhibited by TPO⁽²⁴⁾. TPO antibodies fix complement, and a complex of membrane and complement are formed, these complexes are present in autoimmune thyroid disease patients⁽²⁵⁾. Anti-TPO antibody, was founded in sera

typically have high affinities for an immune-dominant region of the intact TPO molecule. Estimates of TPO-Ab prevalence depend on the sensitivity and specificity of the method employed⁽²⁶⁾.

In this study, results revealed the highly significant positive correlation between Anti-TSH-R Ab and T3, T4 (**P<0.01**). While correlation between TSH and Anti-TSH-R Ab, was a significant negative (**R=-0.475**). Our observation was agreed with⁽²⁷⁾ who showed that the correlation between TRAB and degree of thyrotoxicosis (T4 at diagnosis) $P<0.01$. **Chen et al.**, was presented TSHR autoantibodies detected in more than 90% of untreated Graves patients, and TSHR Ab titer correlate closely with the severity of hyperthyroidism⁽²⁸⁾. The relationship between the TSH receptor antibodies and the excess production of thyroid hormones suggests the activation of B cells and dominance of humeral immune responses in patients with Graves' disease⁽²⁹⁾. In Graves' disease, autoantibodies bind to the receptor and mimic TSH action and stimulate thyroid cells. This leads to hyperthyroidism and abnormal overproduction of thyroid hormone^(30, 31). Mechanism of TSHR-autoantibodies production is more or less clear but a susceptibility gene, which is linked to their production, is still unknown. Genetic studies showed no linkage between the TSHR gene and Graves' disease⁽³⁰⁾. The primary cytokines secreted from Th1 cells include IL-2, IFN- γ , and TNF- β , overproduction of these cytokines from activated Th1 cells can induce excessive B-cell activation and autoantibody production⁽³²⁾.

Anti-TPO antibody in this study was founded to be highly significant (**P<0.01**) in positive correlation with T3 and T4 hormone, but negative correlation (**R=-0.307**) with a highly significant value with TSH hormone. **August and Cohen**, was recorded that the TPO-Ab, 70-80% has evidence of thyroid disease and showed a better correlation with thyroiditis⁽³³⁾. In some patients, the simultaneous production of antibodies that block the thyrotropin receptor reduces the stimulatory action of thyroid-stimulating antibodies. For these reasons there is no direct correlation between serum concentrations of thyroid-stimulating antibodies and serum thyroid hormone concentrations in patients with Graves' hyperthyroidism⁽³⁴⁾.

CONCLUSION:

- Assay of TRAB is helpful in diagnosis of Graves' disease when clinical features are not conclusive.
- Graves' hyperthyroidism occurs at a younger age with less exposure to environmental factors in subjects carrying susceptibility genotypes.

RECOMMENDATION:

- Everyone over 35 years of age should be screened for thyroid disorders, with women a particular concern. Get rechecked every 5 years or sooner if you have symptoms or concerns.
- For adults, the best recommendation may be to put thyroid testing (TSH, T4, T3) on your list of what to discuss with your health care provider.

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