

# Investigation of the Potential Roles of Thyroid Gland Hormones in the Pathogenesis of Thyroid Disorders.

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## Abstract

This study was designed to evaluate the roles of total Thyroxine T4, total T3, free Thyroxine FT4, free triiodothyronine FT3, and thyroid stimulating hormone TSH indicators in the pathogenesis of patients with thyroid diseases. Seventy patients with thyroid diseases and thirty healthy individuals (as a control group) were enrolled in this study from April to July 2024. An HSCL-5000MICRO Homogenous Chemiluminescence Immunoassay Analyzer was used to measure the markers. Most patients were females (82.9%) with age groups; 31-40 (32.9%) and 41-50 (40.0%) years. Significantly increased ( $p < 0.05$ ) levels of total T4 in patients than controls, while levels of FT4 were significantly ( $p < 0.05$ ) decreased in patients than controls. In contrast, our research reveals no significant difference ( $p > 0.05$ ) between levels of T3, FT3, and TSH indicators and study groups. ROC curve results showed the FT4 scored the highest sensitivity and specificity (77% and 72%), followed by T4 (68% and 68%) and then TSH (57% and 60%) at cut off values (13.42, 88.28 and 2.67) respectively in screening patients with thyroid diseases with significant difference ( $p < 0.05$ ). Our investigation mentions no significant differences ( $p > 0.05$ ) between levels of T4, T3, FT3 and TSH in males versus females and within age groups of patients. It was also noted that there was no significant correlation among thyroid hormones. In conclusion, this study proved that FT4 was more critical for detecting thyroid disease due to its high sensitivity and specificity.

## 1. Introduction:

The thyroid gland has a butterfly-like form and is situated anterior to the trachea and on either side of the larynx. It generates the hormone thyroxine, which controls the body's metabolic processes. The disorder known as hyperthyroidism (thyrotoxicosis) is characterized by excessive thyroid gland activity. happens when there is an overabundance of thyroid hor-

mone, which includes hyperthyroidism. The signs and symptoms can vary from person to person and include increased metabolism, weight loss, elevated body temperature, anxiety, and irritability. However, hypothyroidism (myxoedema), a common endocrine disorder caused by a lack of thyroid hormone or, less frequently, by their impaired activity at the tissue level, results in insufficient thyroid hormone production and a slowdown in metabolism [1].

Thyroid hormones accelerate the speed of cellular reactions in all organs and tissues of the body, which in turn leads to an increase in basic metabolic reactions such as accelerating growth and increasing oxygen consumption. In addition to their effects on some metabolic reactions, the decrease in



the work of thyroid hormones (whether practical or pathological) is reflected in a clear slowing of bodily processes as both body temperature and basal metabolic rates decrease. The decreased performance of thyroid hormones at or after birth is called infantile myxedema, while myxedema in adults refers to increased cholesterol in the blood. As for the case of increased activity of thyroid hormones, basal metabolic rates increase by an amount equivalent to about 30 to 60% of the normal limit [2], which results in a decrease in the level of cholesterol in the blood. Also, an increase or decrease in this hormone results in other pathological conditions such as Graves' disease, toxic goiter, and Hashimoto's thyroiditis, and therefore accuracy in measuring this hormone is of great importance. It requires knowing the normal rate for each within the community [3]. Thyroid disorders are the second most common endocrine problem and are regarded as the most important global public health concern [4]. Thyroid disorders affect 5% to 10% of the world's population [5]. According to Tahir et al. [6], the percentage of patients in Baghdad, Iraq, that were overt hypothyroid (3.2%), subclinical hypothyroid (14.1%), overt hyperthyroid (3%) and subclinical hyperthyroid (4%). It was shown that hypothyroidism was more common than hyperthyroidism in Nasiriya, Iraq, with the majority of patients being between the ages of 35 and 46 [7]. When comparing females to men and the elderly population to younger people, there is a higher prevalence of hypothyroidism and hyperthyroidism in the former group [8]. As for the United States, 1.3% of people had hyperthyroidism whereas 4.6% of people had hypothyroidism [4]. According to Shah et al. [9] the incidence of subclinical hypothyroidism and subclinical hyperthyroidism in Pakistan is 5.4% and 5.8%, respectively, whereas the incidence of hypothyroidism and hyperthyroidism is 4.1% and 5.1%, respectively.

Numerous metabolic processes, including bone formation, energy consumption, immune system function, neurological function, cardiovascular function, control of glucose and lipids, and coagulation, are influenced by thyroid hormones [10]. While hyperthyroidism (Hashimoto's Thyroiditis (HT)) is defined by a hypofunctioning thyroid gland and is associated with thyroid hormone reduce (a decline levels of (T3) and (T4) hormones, and boost TSH the amount), hyperthyroidism (Gravis disease (GD)) is an indication of hyperfunctioning thyroid gland and is referred to through multiple clinical signs that are linked to thyroid hormone excessive (a rise in quantities of (T3) and (T4) hormones, and minimize (TSH) amounts [11].

The FT4/TSH ratio has been proven to be a useful novel standard indicator for the multiple diagnoses of thyrotoxicosis, and thyroid hormones have played a vital role in the monitoring of individuals with thyroid illnesses [12]. Another investigation revealed that because Free T4 exhibits high diagnostic sensitivity and specificity compared to (TSH), it would be a better option for evaluating thyroid function [13].

Thyroid disorders are the second most common endocrine problem and are considered a major public health concern worldwide. Because of the importance of thyroid function in clinical diagnosis, the study aimed to measure the levels of total (T4), total (T3), (FT4), (FT3), and (TSH) in patients with hyperthyroidism and hypothyroidism in Baghdad.

## 2. Materials and Methods:

### 2.1 Samples Collection:

Current study was applied in Baghdad city/ Iraq on patients with thyroid diseases for period 1/4 to 30/7 -2024. Seventy (70) blood samples were collected from patients with thyroid diseases who visit the outpatient clinics after being examined by a specialist physician. Additionally, thirty (30) blood samples were taken from healthy individuals and were considered as the control group. The age groups of participants ranged from (30-60) years.

### 2.2 Methods:

Each participant had five milliliters of blood drawn, which was then split into gel tubes to create serum. Human blood was collected in gel tubes and spun for five minutes at 4000 rpm to create serum. Total T4, Total T3, Free T4, Free T3, and TSH indicators' serum concentrations were determined by HSCL-5000MICRO Homogenous Chemiluminescence Immunoassay Analyzer. This test was carried out in accordance with the manufacturer's procedures protocol, which was contained in the kit packaging.

### 2.3 Statistical Analysis:

Hormonal markers were appeared as Mean  $\pm$  SD. Student t test based to detected the differences between patients than controls groups. F test depended to reveal variations among mean levels of hormones. Personal characteristics were presented as frequencies and percentages. Pearson-Chi-square test was based to discover difference among percentages. Receiver operating characteristic (ROC) curve was used to discover area under the curve (AUC), cut off, sensitivity, and specificity of indicators. The standard significant level was  $P \leq 0.05$ . SPSS v. 19.0 and Prism v.6 programs were based on measuring current outcomes.

## 3. Results:

### 1- Personal Features of Participants:

After collecting patient samples, it was found that a higher percentage of patients were females than males in the Baghdad city community due to hormonal disorders in females. After that, samples of the control group are collected and are similar to the patient group in terms of age and gender, so the infection rate is compared between females and males within the patient group, as shown in the table below Table 1.

**Table 1.** Comparative personal features between thyroid diseases patients versus controls.

			Groups		Total	P value
			Patients (n=70)	Controls (n=30)		
<b>Gender</b>	Males	N	12	16	28	P<0.05*
		%	17.1%	53.3%	28.0%	
	Females	N	58	14	72	
		%	82.9%	46.7%	72.0%	
Age groups (years)	≤ 30	N	2	8	10	P<0.05*
		%	2.9%	26.7%	10.0%	
	31-40	N	23	10	33	
		%	32.9%	33.3%	33.0%	
	41-50	N	28	7	35	
		%	40.0%	23.3%	35.0%	
	51-60	N	17	5	22	
		%	24.3%	16.7%	22.0%	

**2- Mean Levels of Thyroid Hormones within Study Groups:**

Outcomes of our study showed there is a significant variation ( $P<0.05$ ) between levels of Total T4 and free T4 in patients versus controls, where it is found increased levels of Total T4 in patients ( $103.42 \pm 32.54$ ) than controls ( $85.77 \pm 14.37$ ), while levels of free T4 were decreases in patients ( $9.82 \pm 2.59$ ) than controls ( $16.30 \pm 3.15$ ). In contrast, our research reveals no significant difference ( $p>0.05$ ) between levels of Total T3, Free T3, TSH indicators, and study groups Table 2.

**Table 2.** Comparative personal features between thyroid diseases patients versus controls.

Groups		N	Mean	Std. Deviation	P value
Total T4 (nmol/l)	Patients	70	103.42	32.54	p<0.05*
	Controls	30	85.77	14.37	
Total T3 (nmol/l)	Patients	70	2.08	0.85	p>0.05
	Controls	30	2.03	0.54	
Free T4 (pmol/l)	Patients	70	9.82	2.59	p<0.05*
	Controls	30	16.30	3.15	
Free T3 (pmol/l)	Patients	70	2.75	1.32	p>0.05
	Controls	30	2.54	0.55	
TSH (uIU/ml)	Patients	70	2.52	1.09	p>0.05
	Controls	30	2.63	1.13	

**3- ROC Curve of Thyroid Hormones:**

ROC curve results showed that Free T4 scored the highest sensitivity and specificity (77% and 72%), followed by Total T4 (68% and 68%) and then TSH (57% and 60%) at cut off values (13.42, 88.28 and 2.67) respectively in screen-

ing patients with thyroid diseases with significantly different ( $p<0.05$ ) than another indicator that showed a little sensitivity and specificity Table 3.

**4- Relation of Thyroid Hormones with Gender Patients:**

The findings of the current investigation mention no significant differences ( $p>0.05$ ) between levels of Total T4, Total T3, Free T4, Free T3 and TSH in males versus females Table 4.

**5- Relation of Thyroid Hormones with Age Groups of Patients:**

Findings of current investigation mention no significant differences ( $p>0.05$ ) between levels of Total T4, Total T3, Free T4, Free T3 and TSH and age groups of patients Table 5.

**6- Correlation Relationship among Thyroid Hormones:**

Pearson correlation results showed there is a positive and negative correlation among thyroid hormones in patients with thyroid diseases, but these correlations are not significant ( $p>0.05$ ) Table 6.

**4. Discussion:**

Individuals seeking medical treatment for various reasons present with anomalies related to the structure or operation of the thyroid gland. They exhibit signs of hyperthyroidism or hypothyroidism, accordingly, which are physiological consequences of elevated or lowered thyroid hormone plasma concentrations. Additionally, they could exhibit signs of a localized or widespread expansion of the. These alterations might be the consequence of benign or malignant neoplasia, or functional problems [14]. The current investigation demonstrated the functions that thyroid hormones (TSH, free T4, total T3, and free T4) play in the etiology of thyroid disorders, Where he found that females were more affected than males

**Table 3.** Comparative personal features between thyroid diseases patients versus controls.

Test Result Variable(s)	AUC	Std. Error	P value	Cut off	Sensitivity %	Specificity %
Total T4	0.687	0.053	p<0.05*	88.28	68	68
Total T3	0.520	0.065	p>0.05	2.03	54	57
Free T3	0.493	0.058	p>0.05	2.56	46	44
Free T4	0.805	0.042	p<0.05*	13.42	77	72
TSH	0.584	0.060	p>0.05	2.67	57	60

**Table 4.** Comparative Thyroid Hormones Indicators between Males Versus Females' Patients.

Gender	N	Mean	SD	P value
Total T4 (nmol/l)	Males 12 Females 58	102.81 103.55	23.36 34.30	p>0.05
Total T3 (nmol/l)	Males 12 Females 58	2.10 2.08	0.50 0.91	p>0.05
Free T4 (pmol/l)	Males 12 Females 58	8.82 10.03	2.84 2.58	p>0.05
Free T3 (pmol/l)	Males 12 Females 58	3.66 2.56	1.74 1.15	p>0.05
TSH (uIU/ml)	Males 12 Females 58	2.49 2.53	1.09 1.11	p>0.05

in the age group above 30 years. These results are consistent with those obtained by Zhang et al. [15], who found that thyroid disorders were more common in older women. Furthermore, Hossain et al. [16] found that the majority of patients with thyroid disorders were female and were in the age group of 31-50. It may be due to autoimmune diseases being more common in females. This is partly due to the fact that autoimmune responses, which occur when the body's immune system begins targeting its own cells, often cause thyroid diseases [8].

It is considered Anaplastic thyroid tumors are far more prevalent in older adults, and thyroid lymphomas are more prevalent overall. The gland may expand and develop into a goiter if the thyroid is continuously stimulated to produce thyroid hormones. As people age, multinodular goiter becomes more prevalent [17]. An earlier study showed that in locations with enough iodine, hypothyroidism is widespread in the elderly. One age-related indication for hypothyroidism in older individuals is thyroid autoimmune disease (TAI). To learn more about how TAI affects thyroid health in elderly individuals, a long-term follow-up is required [12]. Another set of data showed a substantial correlation between Alzheimer's

disease (AD) and medical hypothyroidism, hyperthyroidism, and thyroiditis, albeit the underlying molecular processes are yet unknown. Additionally, our results suggest that treating these thyroid conditions may help avoid the beginning or progression of AD [18].

The results of the research indicated that while TSH and free T4 levels were lower in patients compared to controls, total T4, total T3, and free T3 levels were higher in cases compared in controls. The results obtained matched those of Zhang et al. [19] based on T4, total T3, free T3, and free T4 (boosted levels in individuals who had grave illnesses); however, there were variances based on TSH and free T4 (boosted levels in individuals with grave illnesses). These variations are associated with the kind of thyroid illness (hyperthyroidism or hypothyroidism), as demonstrated by the fact that in the current research, some of the participants had hypothyroidism (Hashimoto's thyroiditis) and others had hyperthyroidism (Graves disease).

The reason for the increase in the level of hormone T4 may be attributed to thyrotoxicosis which occurs as a result of hyperthyroidism due to an increase in thyroid hormone (T4) in the blood, and the reason for the increase may be due to Graves' disease which is an immune disease characterized by the formation of antibodies that bind to the cell wall of the thyroid follicles with hormone receptors [20] or the reason may be attributed to increased intake of iodine with food or to inflammation that affects the thyroid gland [21] and that thyroid hormones are necessary for the normal growth rate of the human body and given the importance of hormonal factors in the basic metabolic rate of the liver, kidneys, heart and brain [22]. While the reasons for the increase in T3 hormone are due to autoimmune diseases that include the body of the living organism forming antibodies against normal cells. These antibodies can stimulate the thyroid gland, increasing its activity or vice versa, in addition to thyroid hyperautonomus, as the thyroid gland can be affected by tumors in certain areas of it, and these areas have an autonomous function that is independent in their function and are not subject to the control of the thyroid-stimulating hormone as in the case of

**Table 5.** Comparative Thyroid Hormones Indicators among Age Groups of Patients.

Age groups (Years)	Total T4		Total T3		Free T4		Free T3		TSH	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
≤30	145.34	67.86	1.57	0.13	6.81	1.38	3.16	1.17	2.05	1.07
31-40	124.30	26.73	2.16	0.45	9.14	2.86	2.48	0.99	2.34	1.09
41-50	131.66	33.15	1.82	0.50	9.74	2.45	2.71	1.35	2.83	1.11
51-60	110.45	30.27	2.46	1.45	11.26	3.80	3.13	1.65	2.34	1.08
P value	P><0.05		P>0.05		P>0.05		P>0.05		P>0.05	

**Table 6.** Correlation Relationship among Thyroid Hormone Indicators in Patients with Thyroid Diseases.

Correlations				
		Total T4	Free T4	TSH
Total T4	Pearson coefficient (r)	1	-0.110	0.137
	Significant		0.366	0.256
Total T3	Pearson coefficient (r)	0.043	0.042	-0.039
	Significant	0.726	0.729	0.748
Free T3	Pearson coefficient (r)	-0.113	0.023	-0.046
	Significant	0.352	0.850	0.707
TSH	Pearson coefficient (r)	0.137	0.225	1
	Significant	0.256	0.061	

follicular tumors [23] T3 is more effective in the peripheral blood than T4 (3-5) times. It has a strong relationship with plasma proteins, which makes it spread outside the vessels more easily than T4. Accordingly, T3 is more important at the cellular level than T4. Therefore, it is believed that T3 is the only effective hormone and that T4 is the hormone generator, as it is converted in the cell to T3 after losing an iodine atom by the process of Deiodinase. Thus, T3 can be considered the biologically effective hormone [24]

Thyroid gland dysfunction is correlated with elevated or decreased amounts of thyroid hormone in thyroid condition patients. Excessive synthesis of T3 and T4 in conjunction with a compensating drop in TSH might be the outcome of problems with the thyroid gland. Furthermore, uncontrolled TSH production from thyrotroph adenoma might result in elevated synthesis of T3 and T4 [25] But since TSH is more dependable than plasma T3/T4 levels, which might vary, it consistently provides the best initial test. The levels of TSH are raised in primary hypothyroidism as a result of the anterior pituitary's absence of negative inhibition. On the other hand, TSH levels decrease with primary hyperthyroidism (11), The reason may be attributed to the thyroid-stimulating hormone, which is responsible for activating many proteins and thus

stimulating the darkness of the response, and the final result of the signal transmission process in the thyroid gland is the production of thyroid hormone. Therefore, any defect in the immune response leads to a disorder in the secretion of thyroid hormone [26], Comparing individuals who had hidden and determined hyperthyroidism to the control population of patients of identical age, a new investigation revealed that the circulating level of the hormone TSH decreases whereas the levels of FT3 and FT4 are raised. In hyperthyroidism and subclinical hyperthyroidism, the TSH concentration is lowered. In hyperthyroidism, there is an increase in the blood levels of FT3 and FT4, although in subclinical hyperthyroidism, these concentrations are within the reference range [27].

The results of the study demonstrated that the TSH and Free T4 indicators, which have excellent specificity (72 and 60%) and sensitivity (77 and 57%), respectively, are important tools for evaluating patients for thyroid disorders. These outcomes paled in comparison to those obtained by Zhang et al. [19], who demonstrated that the TSH and Free T4 indicators had sensitivity and specificity of 82% and 73% and 79% and 81%, respectively, in the differential diagnosis of subacute thyroiditis and Graves' illness. The author also highlighted that when it comes to evaluating thyroid function, Free T4 may be a more reliable and precise first diagnostic laboratory test versus TSH. Nonetheless, completing both at the same time improves the accuracy and dependability of determining the thyroid's functioning condition [13]. According to another research, monitoring for thyroid problems in older people receiving primary care may be enhanced by using FT4 rather than TSH or by modifying the TSH cutoff threshold. The potential cost savings from changing the screening technique may pique the attention of medical policymakers. By avoiding the diagnosis of Subclinical hypothyroidism (SCHT), patients may experience fewer medical issues and needless biochemical follow-up [28].

Because of its high sensitivity and specificity (81% and 78%), the serum-free T3 to Free T4 Ratio has been shown in previous studies to be a valuable indication for distinguishing



between Graves' disease and destruction-induced thyrotoxicosis [29]. According to a new study, the fT3/fT4 ratio can predict death in intensive care unit patients who have sepsis. Furthermore, it was discovered that fT3 was a predictor of death upon admission as well as 48 hours later [30].

Significantly, prior research indicates that a complete thyroid function panel may help clinicians diagnose older persons more accurately [31].

## 5. Conclusions:

Women were more affected by thyroid diseases than males due to increased hormonal disorder in women. Women >30 years were high risk for diseases than women <30 years. There is dysregulation in thyroid hormones in those patients due to thyroid damage. Free T4 indicator is very important in diagnosis patients with thyroid diseases than another indicators due to has this indicators highest sensitivity and specificity. There is no effect of gender and age on levels of thyroid hormones in patients with this diseases.

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**Data Availability Statement:** All of the data supporting the findings of the presented study are available from corresponding author on request.

## Declarations:

**Conflict of interest:** The authors declare that they have no conflict of interest.

**Ethical approval:** The manuscript has not been published or submitted to another journal, nor is it under review.

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## دراسة الأدوار المحتملة لهرمونات الغدة الدرقية في التسبب في اضطرابات الغدة الدرقية

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### الخلاصة

يهدف هذا البحث إلى تقييم أدوار المؤشرات لهرمون الثايروكسين الكلي  $T4$  وهرمون ثلاثي ايودو ثايرونين الكلي  $T3$  و الثايروكسين الحر  $FT4$  وهرمون ثلاثي ايودو ثايرونين الحر  $FT3$  وهرمون المحفز للغدة الدرقية  $TSH$  الذي يسبب اضطرابات الغدة الدرقية لدى مرضى، تضمنت الدراسة سبعين مريضاً مصاباً بأمراض الغدة الدرقية وثلاثين فرداً سليماً (كمجموعة السيطرة). تم جمع العينات الدراسة من أبريل إلى يوليو 2024. تم قياس جميع العلامات باستخدام اختبار محلل مقايصة المناعة الكيميائية المتجانس  $HSCL-5000MICRO$ . اظهرت نتائج الدراسة أن معظم المرضى كانوا من الإناث (82.9%) الذين تتراوح أعمارهم بين 31-40 (32.9%) و 41-50 (40.0%) سنة. كما وجد زيادة في مستويات  $T4$  الكلي في المرضى مقارنة بمجموعة السيطرة ( $p < 0.05$ )، بينما انخفضت مستويات  $FT4$  بشكل ملحوظ ( $p < 0.05$ ) لدى المرضى مقارنة بالضوابط. وعلى النقيض من ذلك لم يلاحظ فروق معنوية ( $p > 0.05$ ) بين مستويات هرمون  $T3$  الكلي، وهرمون  $FT3$ ، ومؤشرات هرمون  $TSH$ ، وبينت نتائج منحنى  $ROC$  أن هرمون  $FT4$  سجل أعلى حساسية وخصوصية (77% و 72%)، يليه  $T4$  الكلي (68% و 68%) ثم  $TSH$  (57% و 60%) عند قيم القطع (13.42 و 88.28 و 2.67) على التوالي في فحص المرضى المصابين بأمراض الغدة الدرقية مع وجود فروق معنوية ( $p < 0.05$ )، ومن ناحية الفئات العمرية للمرضى لم يلاحظ فروق ذات دلالة إحصائية ( $p > 0.05$ ) بين مستويات هرمون  $T4$ ،  $T3$ ،  $FT3$  وهرمون  $TSH$  في الذكور مقارنة بالإناث. أيضاً لوحظ عدم وجود ارتباط ذي دلالة إحصائية بين هرمونات الغدة الدرقية. وفي الختام، أثبتت هذه الدراسة أن  $FT4$  كان أكثر أهمية للكشف عن أمراض الغدة الدرقية بسبب حساسيته وخصوصيته العالية

الكلمات الدالة: أمراض الغدة الدرقية، هرمونات  $T3$ ،  $T4$ ،  $TSH$ .

التمويل: لا يوجد.

بيان توفر البيانات: جميع البيانات الداعمة لنتائج الدراسة المقدمة يمكن طلبها من المؤلف المسؤول.

اقرارات:

تضارب المصالح: يقر المؤلفون أنه ليس لديهم تضارب في المصالح.

الموافقة الأخلاقية: لم يتم نشر المخطوطة أو تقديمها لمجلة أخرى، كما أنها ليست قيد المراجعة.