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Evaluation the Salivary levels of Interleukin-23 in Individuals with Thyroid Disorders

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Abstract:

Background: The study investigates the role of IL-23 in autoimmune thyroid disorders, focusing on patients with hypothyroidism and hyperthyroidism .

Material and Methods: This case-control research was conducted at Baghdad Teaching Hospital from January to May 2023. Saliva samples were collected from 87 participants, including 29 with hypothyroidism, 29 with hyperthyroidism, and 29 healthy controls. Saliva samples were analyzed for IL-23 levels using ELISA assays, while thyroid function tests (FT3, FT4, TSH) were conducted using the cobas c 111 colorimetric method .

Results: The study found a significant difference in IL-23 levels between the hyperthyroid group and the control group ($P<0.01$). However, no significant difference in IL-23 levels was observed in the hypothyroid group compared to controls ($P>0.05$). The age distribution showed no significant differences across patient groups ($P>0.05$), while gender distribution indicated a higher prevalence of thyroid disorders in females.

Conclusion: IL-23 serves as a significant marker for hyperthyroidism diagnosis, but further research is needed to explore its role in hypothyroidism. The study supports IL-23's involvement in autoimmune responses and its potential as a diagnostic tool for thyroid disorders.

Keywords: IL-23, thyroid disorders, hyperthyroidism, hypothyroidism, autoimmune response, saliva.

1 .Introduction:

The thyroid gland is the biggest endocrine organ and matures earliest throughout foetal development (Aboud, 2011; OZGÜNER, 2014). The butterfly-shaped gland has two rounded lobes on either side and a small isthmus in the middle (Maitra, 2010; Mescher, 2010). Thyroid gland encircles the front of the trachea in the neck, below the larynx, between the fifth cervical vertebra (C5) and the first thoracic vertebra (T1). Adult glands are 5 cm tall and wide and weigh 20–30 g. Women have a larger thyroid gland than men, (Mescher,2010). Thyroid diseases are common

worldwide, however iodine deficiency or supplementation affects their prevalence (Suleiman et al., 2009). Typical glands have numerous follicles covered with fibrous material. This covering divides functional tissue into lobules with septae-based blood vessels and nerve supply (Maitra, 2010; Mescher, 2010; Rosai, 2011). Colloid—a viscous material made of thyroglobulin, a thyroid hormone precursor—is found in follicles (Mescher, 2010).

Thyroid follicular cells generate metabolism-regulating T3 and T4. Hormone production and secretion are controlled by the hypothalamic-pituitary-thyroid axis (Mescher, 2010; Al.Meshaikhly and AlRawi, 2020; Taha, 2019). The anterior pituitary gland produces TSH after the hypothalamus releases TRH (Mescher, 2010; Costanzo, 2010). Afterward, this hormone causes thyroid follicular cells to generate thyroglobulin, an inactive protein discharged as "colloid." Thyroid peroxidase oxidises iodine to iodinate tyrosine residues in the follicle via sodium-iodide cotransporters. T3 and T4 are formed by oxidative coupling of iodinated tyrosine residues (Mescher, 2010). The lysosome protease in the follicular cell releases T3 and T4 into the capillaries from iodinated thyroglobulin. Thyroxin-binding protein binds thyroid hormones in circulation (Costanzo, 2010).

T3 and T4 increase basal metabolic rate. They regulate mitochondrial ATP synthesis. In hyperthyroidism, increased thyroid hormone production may improve organ system function to fulfil sickness requirements. Due to thyroid hormone stimulation, hyperthyroidism symptoms often suggest increased metabolic activity. (Ali et al. 2013). By negative feedback, thyroid hormone inhibits hypothalamus and first pituitary gland TSH and TRH release (Ouyang et al., 2012). T4 has 60-150 nmol/L plasma concentration, whereas T3 has 1.0-2.9. These hormones boost foetal growth, basal metabolic rate, cardiac output, and CNS development. These hormones fulfil other critical tasks. The negative feedback process between thyroid hormones, TSH, and TRH maintains hormone production and release equilibrium, according to Costanzo (2010).

Thyroid hormones impact almost every organ. Growth hormones aid osteogenesis. They increase basal metabolic rate, gluconeogenesis, lipolysis, proteolysis, thermogenesis, glucose absorption, and oxygen utilisation. Ouyang et al. identified the most frequent thyroid symptoms in 2012. Thyroid disease and joint problems affect salivary function (Harbi and Mahmood, 2024).

Goitre is thyroid enlargement that may or may not produce hormone abnormalities. Hyperthyroidism is caused by elevated T3 and T4. Graves' disease rules. (Ali, 2013) Due to thyroid hormone overproduction. Hypothyroidism is thyroid hormone deficiency. Hypothyroidism causes weariness, a swollen face, cold sensitivity, joint and muscle discomfort, constipation, dry skin, reduced sweating, weight gain, impaired fertility, constipation, heavy or irregular menstrual cycles, depression, and slower heart rate (Naji et al,.2013).

Previously thought to be associated with TH1, interleukin (17, 21, and 22) have a role in some autoimmune disorders. Patients suffering from severe Grave's disease had a higher abundance of peripheral TH17 cells compared to those in a state of remission (14). T-lymphocytes that are activated secrete cytokines that initiate the autoimmune response. These cytokines promote the development of TH17 cells rather than TH1 or TH2 cells. IL-6 is well-known for its involvement in this process, however, new studies have shown that IL-23 is crucial for maintaining immunological equilibrium. The cytokine IL-23 contains two protein subunits, a unique p19 subunit and a shared p40 subunit with IL-12. Both cytokines are produced by APCs such macrophages and dendritic cells. Normally, Th1

immune responses need it. T cells and macrophages release anti-inflammatory IL-10 (Mohamed et al., 2018).

The two cytokines work differently. IL-12 promotes interferon-producing TH1 cells, whereas IL-23 is needed for TH17 cell proliferation (Parham et al., 2002; Cua et al., 2003). A recent research found that IL-23 controls autoimmune inflammation in mice. Antibodies that target the p40 subunit may be therapeutic (Brok et al., 2002; Chen et al., 2006; Huber, 2008). Many autoimmune diseases, including Graves' disease, are linked to the IL-23 receptor gene. Zheng et al. (2013) found that IL-23 contributes to autoimmune thyroid disorders. A reduction in salivary pH, insufficient salivary flow rate, and increased usage of carbonated drinks and sugary meals may contribute to caries prevalence (Al.Anbari & Al. Ani, 2021). Serum components are in saliva. Systemic inflammatory diseases may influence saliva indicators (Nsaif and Hassan 2023). Most research have examined Grave's disease (Figueroa-Vega et al., 2010). This research examines HT-affected patients' saliva IL-23 levels, both euthyroid and untreated.

2. Subjects, materials and methods:

This case-control research was carried out at Baghdad Teaching Hospital from January to May 2023. Saliva samples were obtained from a total of eighty-seven patients with thyroid disorders, including 29 with hypothyroidism, 29 with hyperthyroidism, and 29 healthy individuals serving as controls. The specific case sheet necessitates the inclusion of the individual's name, age (ranging from 30 to 60 years old), year, and gender (either "male" or "female"). The subjects in this study had thyroid insufficiency for a minimum duration of six months. Individuals with systemic diseases, chronic disease medications, tobacco use, previous periodontal interventions, and pregnant women were not included .

After the collection and separation of saliva, a part was placed in sterile, labelled, and sealed containers within a refrigerated box, where it would be kept until further analysis in the laboratory. Additional saliva samples were stored at a temperature of -20°C until IL23 (ELK Biotechnology, USA) was quantified using an ELISA assay. Meanwhile, FT3, FT4, and TSH (Roche, Germany) were assessed using a colorimetric method called cobas c 111.

2.1 Ethical approval

The University of Baghdad Medical Ethics Committee granted approval (Ref. number 796, February 2, 2023), and all participants in the research supplied informed permission in accordance with the Helsinki Declaration.

2.2 Statistical Analysis:

The study's findings were analysed using SPSS 22.0 and other statistical methods. Kruskal-Wallis H compares factors between groups. Mann-Whitney U evaluates group differences. Spearman's rank correlation coefficient test for within-group variables. The relationship between nominal variables is measured by C.C. Finding significant relationships between variables using chi-square test. One-Sample Kolmogorov-Smirnov: analyse theoretical and observable distributions. The binomial test distributes two nominal/ordinal groups with no 50% cutoff.

3. Results and Discussion:

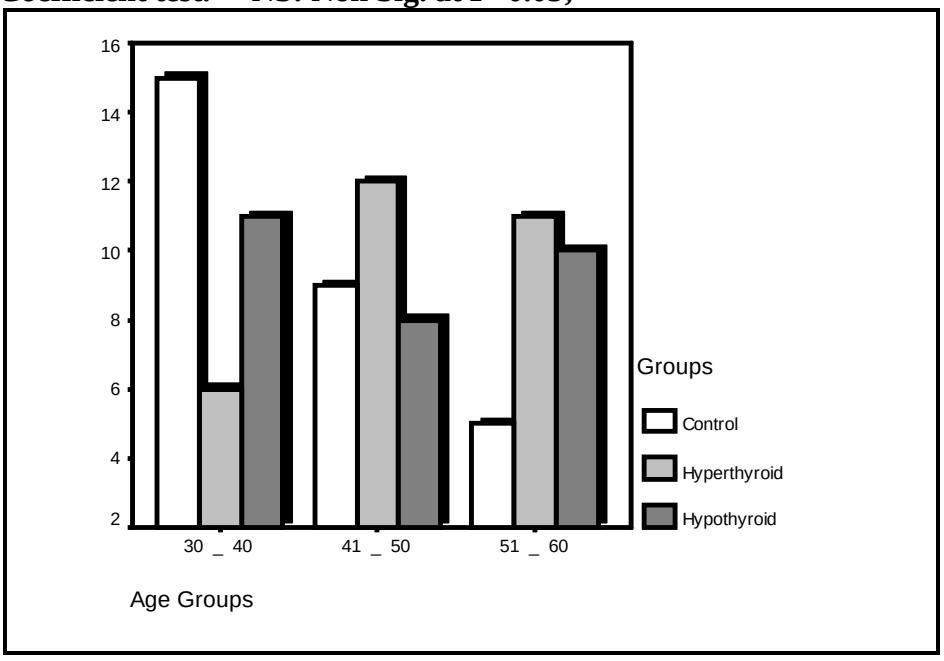
Age and gender demographics are shown in Table 1 and Figure 1. The mean age values were highest in patients over 40, especially among patient groups. Additionally, the groups exhibited no

significant difference at P>0.05. The observed age frequencies across classes did not vary significantly at P>0.05 within any group. The gender distribution in the 'Hyperthyroid' group showed a significant difference (P<0.05), with almost 75% of patients being female. In contrast, 'Hypothyroid' individuals had no gender difference at P>0.05. P=0.063 was the significance threshold.

Table 1: Frequency and percentages of Demographical Characteristics variables for Age and Gender in the studied groups

	Groups	Control		Hyperthyroid		Hypothyroid		C.S.
	Classes	No.	%	No.	%	No.	%	
Age	30 _ 40	15	51.7	6	20.7	11	37.9	
	41 _ 50	9	31	12	41.4	8	27.6	
	51 _ 60	5	17.2	11	37.9	10	34.5	
	Total	29	100	29	100	29	100	
	Mean ± SD	40.66 ± 7.97		45.93 ± 8.16		43.90 ± 8.02		
	C.S.	P=0.073 NS		P=0.343 NS		P=0.786 NS		P=0.131 NS
Gender	Male	12	41.4	7	24.1	9	31.0	
	Female	17	58.6	22	75.9	20	67.8	
	Total	29	100	292	100	29	100	
	C.S.	P=0.458 NS		P=0.009 HS		P=0.063 NS		P=0.368 NS

Testing based on Chi-Square test for one sample; Binomial test for the nominal scales, and a Contingency Coefficient test. (*) NS: Non Sig. at P>0.05;



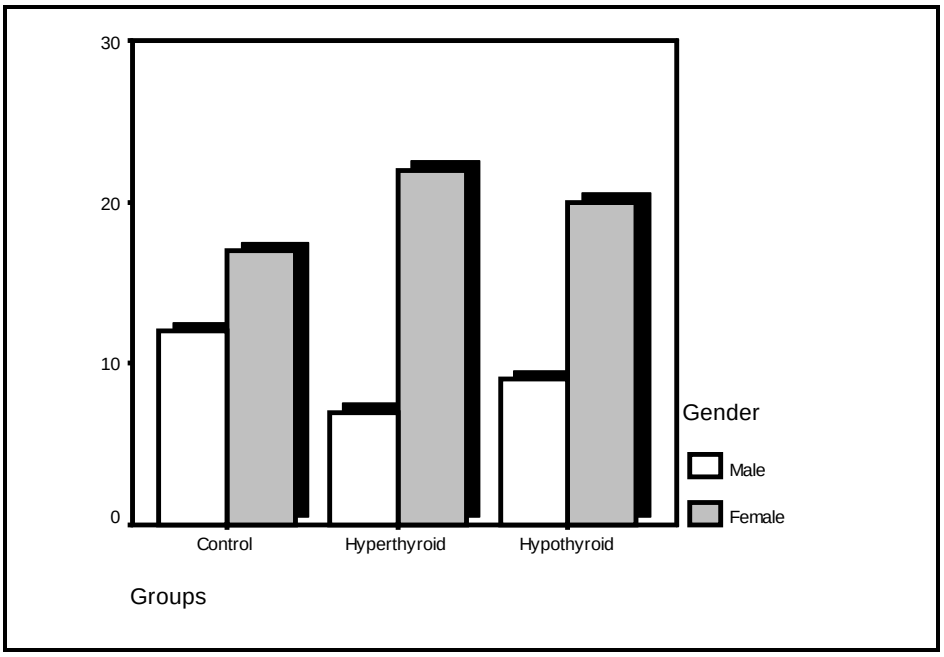


Figure 1: Cluster Bar Chart concerning frequency distribution of Demographical Characteristics variables of Age and Gender in studied groups

Regarding the IL-23 marker, the results indicate that the highest average value was observed in the hyperthyroid patient group (36.09 ± 9.83), followed by the hypothyroid patient group, which showed the second highest mean value (32.49 ± 16.28). The control group, consisting of healthy individuals, exhibited the lowest average value (27.38 ± 13.72). However, statistical analysis revealed non-significant difference (p=0.053) among the study groups, as detailed in (Table 2)

Table 2: Descriptive Statistics of (IL-23) Marker for studied groups

Marker	Group	No.	Mean	SD	SE	Min.	Max.	F-test	*p.value*
IL-23	Control	29	27.38	13.72	2.55	8.46	55.48	3.034	0.053
	Hyperthyroid	29	36.09	±9.83	1.83	19.62	47.51		
	Hypothyroid	29	32.49	16.28	3.02	12.69	54.96		

The result of Normality test is shown in (Table 3) by the One-Sample Kolmogorov-Smirnov Test, indicating that the variables conform to normal distribution with p-values ($p<0.05$) among IL-23 (pg/ml) and SFR (ml/min), while non-normal distribution among thyroid function biomarker.

Table 3: Tests of Normality

Variable	Groups	One-Sample Kolmogorov-Smirnov Test				
		Statistic	Df	p-value	Sig.	
IL-23 (pg/ml)	Control	1.210	29	0.107	NS	Test Distribution of studied markers are Normal
	Hyperthyroid	1.304	29	0.067	NS	
	Hypothyroid	1.129	29	0.157	NS	
SFR (ml/min)	Control	1.318	29	0.062	NS	
	Hyperthyroid	1.051	29	0.220	NS	
	Hypothyroid	1.156	29	0.138	NS	
TSH (µIU/ml)	Control	0.805	29	0.536	NS	Test Distribution of studied markers are non-normal
	Hyperthyroid	1.492	29	0.023	S	
	Hypothyroid	1.302	29	0.068	NS	
FT3 (pmoI/L)	Control	1.059	29	0.212	NS	
	Hyperthyroid	2.408	29	0.000	S	
	Hypothyroid	0.619	29	0.838	NS	
fT4 (pmoI/L	Control	1.126	29	0.159	NS	
	Hyperthyroid	1.221	29	0.101	NS	
	Hypothyroid	0.599	29	0.865	NS	

Table 4 illustrates the estimated area of cut-off between sensitivity and specificity by plotting sensitivity against the complement of specificity to examine this cut-off, known as the Receiver Operating Characteristic (ROC) curve. It also includes significant levels for testing the area under the curve against the guideline of fifty percent, with a 95% confidence interval for all probable combinations among patient groups and controls, in the context of the studied IL-23 marker.

The results indicate that "IL-23" has recorded a significant area at P=0.007 for hyperthyroid patients compared to the control group, as represented by the Receiver Operating Characteristic (ROC) curve. This suggests that the IL-23 marker could be considered an excellent indicator for the diagnosis of the studied disease. Furthermore, the area under the curve (AUC) could reach an estimated value of up to 0.846 in the study of a diseased sampling population, as indicated by the upper bound of the 95% confidence interval. However, for other test markers (IL-23), no significant area was observed at P>0.05, indicating that they may not be as effective as indicators for the diagnosis in this context. As shown in (Table 5) and

Table 3-17: ROC curve outcomes of Patients Groups & Controlled for IL-23 Marker

IL-23 Marker	Area	Cutoff Pint	Sen.	Spec.	p-value
Hyper. X Con.	**0.707**	**19.467**	**1.000**	**0.414**	**0.007**
Hypo. X Con.	**0.587**	**44.461**	**0.414**	**0.862**	**0.256**
Hyper. X Hypo.	**0.553**	**18.807**	**1.000**	**0.345**	**0.489**

(*)Significant at P< 0.05; NS: Non-Significant at P> 0.05;

The present study found that the mean values of age were focused on patients older than forty years and especially on patient groups over and above; no statistically significant difference (P > 0.05) was observed among the groups studied, and distribution of observed frequencies of age across different classes had no significant differences at P>0.05 in each Previous research found the largest sample size in the 40-49 age bracket (Al.Mashaykhi, 2020). These findings corroborate numerous studies that revealed most thyroid issues among 30–50-year-olds (Al.hinawi et al., 2017 Other studies reveal that older adults have the greatest thyroid difficulties (Veltri, 2017). These age group data suggest that ageing alters TSH secretion set point. Vanderpump (2005) reported that women outweighed men in recent studies. Hypo and hyperthyroidism affect women more. Women and the elderly are more prone to hypo and hyperthyroidism. Golden et al. found thyrotoxicosis was more common in women in 2009. Meng et al. (2015) identified greater thyroid problems in women.

A substantial difference (P<0.01) in IL23 levels was identified in the "Hyperthyroid" patient group compared to the control group, as evidenced by the ROC curve. The findings indicate that the previous marker may be a valid illness diagnosis indication. The upper limit of the 95% confidence interval of the region suggests it may estimate 0.846 in the sick population. However, at P>0.05, the residual test marker (IL-23) has no statistically significant area.

This study confirms Zheng et al. (2012) and Kimura et al. (2007) results that IL-23 is essential for Th17 differentiation and IL-17 production. IL-23 is essential for autoimmune diseases. IL-23 may increase Th17 cells in inflamed tissues. Maloy (2008) states that IL-23 deficiency reduces Th17 cell and cytokine output. IL-23 helps Th17 cells adapt to the internal environment and produce cytokines. Compared to the control group, hyperthyroidism increased significantly. Additionally, investigations have shown a tight relationship between Graves' disease (hyperthyroidism) and IL-23 receptor gene polymorphisms (Huber et al., 2008). Furthermore, the study revealed that Hypothyroidism exhibited a statistically significant mean value, while the healthy group had a comparatively lower mean value.

IL-23 plays a vital role in the development of several inflammatory and autoimmune diseases, primarily by facilitating the proliferation of Th17 cells (OZGÜNER, 2014). Although there is literature evidence supporting the considerable involvement of Th17 cells in autoimmune thyroid illnesses, there is a lack of studies specifically investigating IL-23 levels in these individuals, with the majority of research focusing on Graves' disease. Although there is literature evidence supporting the considerable involvement of Th17 cells in autoimmune thyroid diseases (AITD), there is a lack of research specifically investigating the levels of IL-23 in these individuals. Most existing studies mostly concentrate on Graves' disease (GD). The studies conducted by Ruggeri et al in 2013 and Kim et al in 2012. A solitary study has evaluated the blood concentrations of IL-23 in persons diagnosed with Hashimoto's Thyroiditis (HT) and other autoimmune thyroid diseases (AITD). The study found that people with HT had increased levels of T cells that produce IL-17 and IL-22 in their bloodstream. The study also discovered that the levels of IL-6 and IL-15 were considerably elevated, although the levels of IL-23 showed a tendency to be greater in the blood samples of patients with HT (Huber et al., 2008).

4. Conclusion:

According to this research, IL-23 has been shown to be an outstanding diagnostic tool for hyperthyroid patients. The study followed a controlled group and found that IL-23 had a 100% sensitivity rate for diagnosing the ailment. However, it fell short of reaching the minimal threshold for diagnosing hypothyroid individuals.

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