RESEARCH ARTICLE

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Serum Biomarkers in Thyroid Malignancies: Evaluating Thyroid-Stimulating Hormone Receptor (TSHR) and Vascular Adhesion Protein-1 (VAP-1) as Potential Diagnostic Biomarker

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Abstract

Background: Thyroid cancer is a prevalent endocrine malignancy, and identifying reliable molecular markers is crucial. This study evaluates the diagnostic potential of the thyroid-stimulating hormone receptor (TSHR) and vascular adhesion protein-1 (VAP-1). **Materials and Methods:** A total of 90 patients with thyroid disorders including malignant tumors, benign tumors, and hyperthyroidism were recruited from the Al-Amal National Hospital for Cancer Management in Baghdad (March–June 2022). Twenty-five age-matched healthy individuals served as controls. Serum levels of T3, T4, TSH, and thyroglobulin (Tg) were measured along with TSHR and VAP-1 using commercial sandwich ELISA kits. **Results:** Patients with thyroid cancer exhibited significantly elevated levels of T3 and T4, as well as markedly increased Tg concentrations, compared to controls. In contrast, TSH levels were significantly reduced ($P < 0.001$). Notably, VAP-1 levels were significantly lower in thyroid cancer patients when compared with both healthy controls and patients with other thyroid disorders ($P < 0.001$), while TSHR levels did not differ significantly among the groups. **Conclusion:** The distinct hormonal profile observed characterized by increased T3, T4, and Tg, alongside a significant reduction in VAP-1 suggests that low serum VAP-1 may serve as a useful diagnostic marker for thyroid cancer. These findings underscore the complex interplay between thyroid function and tumor biology and warrant further investigation into the molecular mechanisms underlying these alterations.

Keywords: Thyroid cancer- TSHR- VAP-1- Diagnostic biomarkers- Serum hormonal profiles

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Introduction

Thyroid cancer represents one of the most common endocrine malignancies, with its incidence steadily increasing worldwide. Accounting for roughly 3% of all human cancers, thyroid cancer predominantly affects women, often with a female-to-male ratio as high as 3:1. The disease encompasses a spectrum of histological subtypes including differentiated thyroid cancers—such as papillary and follicular carcinomas—which generally have favorable outcomes, as well as more aggressive variants like medullary and anaplastic thyroid carcinomas [1, 2]. Despite progress in treatment, early detection remains critical for optimizing patient prognosis and survival, thereby emphasizing the need for reliable molecular biomarkers [3].

The normal function of the thyroid gland is tightly regulated by the hypothalamic-pituitary-thyroid axis. In this system, the anterior pituitary secretes thyroid-stimulating hormone [4], which binds to the thyroid-stimulating hormone receptor (TSHR) located on thyroid follicular cells. TSHR, a G-protein-coupled receptor characterized by its leucine-rich repeats, is pivotal in promoting thyroid hormone synthesis and regulating cellular proliferation [5]. Activation of TSHR leads to the production of the thyroid hormones triiodothyronine (T3) and thyroxine (T4), which are essential for maintaining metabolic homeostasis. In the context of thyroid neoplasms, TSHR signaling has been implicated in driving both benign and malignant cellular proliferation, thereby contributing to tumor progression [6].

Moreover, thyroglobulin, a glycoprotein exclusively synthesized by thyroid follicular cells, serves as an important clinical biomarker. Under normal circumstances, thyroglobulin is processed within the thyroid to facilitate hormone production; however, its elevated serum levels following thyroidectomy may indicate residual tissue or recurrence of malignancy. Thus, thyroglobulin remains a key tool in monitoring disease status post-treatment [7, 8].

In addition to traditional hormonal markers, vascular adhesion protein-1 (VAP-1) has recently garnered attention as a potential biomarker in cancer. VAP-1 is a

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170-kDa glycoprotein with semicarbazide-sensitive amine oxidase activity, predominantly expressed on endothelial cells. It is actively involved in leukocyte adhesion and migration during inflammatory responses. Alterations in VAP-1 expression have been linked to the modulation of the tumor microenvironment, including changes in immune cell infiltration and angiogenesis, both of which are critical in tumor development and metastasis [9, 10].

Given these multifaceted roles, the present study aims to assess the expression of thyroid-stimulating hormone receptor and vascular adhesion protein-1 in patients with thyroid cancer in comparison to benign thyroid disorders and hyperthyroidism. By correlating these markers with thyroid hormone profiles and thyroglobulin levels, this investigation seeks to evaluate the diagnostic utility of serum VAP-1, TSHR and provide deeper insights into the molecular underpinnings of thyroid tumor biology in an Iraqi patient cohort.

Materials and Methods

Study Design and Participants

This case-control study was conducted at Al-Amal National Hospital for Cancer Management in Baghdad, Iraq, from March to June 2022. A total of 90 patients with thyroid disorders were enrolled, consisting of three groups: those with malignant thyroid tumors, benign thyroid nodules, and hyperthyroidism. An additional 25 age-matched healthy individuals with no history of thyroid dysfunction or chronic illness served as controls. All participants were aged between 40 and 54 years. Written informed consent was obtained from each subject, and the Institutional Research Ethics Committee approved the study protocol.

Inclusion and Exclusion Criteria

Patients were included if they had a confirmed clinical and, when applicable, histopathological diagnosis of thyroid malignancy, benign thyroid tumor, or hyperthyroidism. Subjects with chronic diseases such as diabetes, hypertension, chronic kidney disease, or arthritis, as well as those on medications or special diets, were excluded from the study. Healthy controls were selected based on the absence of any known endocrine or chronic conditions.

Sample Collection and Processing

Venous blood samples (approximately 5 mL) were collected from each participant using standard aseptic techniques. The blood was drawn into serum-separating tubes and immediately centrifuged at 3000 rpm for 5 minutes to isolate the serum. The serum samples were then aliquoted and stored at –20°C until further analysis to ensure the preservation of biomarkers.

Biochemical and Immunological Assays

Serum levels of thyroid hormones, including total triiodothyronine (T3), total thyroxine (T4), and thyroid-stimulating hormone [4], were measured using established immunoassays. Additionally, serum thyroglobulin (Tg) concentration was assessed as a marker of thyroid tissue function. The expression levels of thyroid-stimulating hormone receptor (TSHR) and vascular adhesion protein-1 (VAP-1) were quantified using commercial sandwich enzyme-linked immunosorbent assay (ELISA) kits supplied by Ela Science (USA). All assays were conducted according to the manufacturers' protocols, and each sample was analyzed in duplicate with the mean value recorded.

Statistical Analysis

Data analysis was performed using SPSS version 26. Descriptive statistics for each group were reported as the mean ± standard deviation (SD) or standard error (SE), as appropriate. One-way analysis of variance (ANOVA) was employed to compare differences between groups, and post hoc tests were applied when necessary to identify specific group differences. Pearson's correlation coefficient was used to examine relationships among the study parameters. Statistical significance was determined at $P < 0.05$. All tables and figures were prepared under standard guidelines for scientific reporting.

Results

Demographic Analysis

A total of 90 individuals participated in the study: 65 patients with thyroid disorders and 25 healthy controls. The patient cohort was subdivided into three groups: those with hyperthyroidism (n = 25; mean age: 45.64 ± 0.56 years), benign thyroid nodules (n = 25; mean age: 48.56 ± 0.62 years), and malignant thyroid tumors (n = 15; mean age: 46.27 ± 0.64 years). The control group (n = 25) had a mean age of 46.52 ± 0.67 years. Demographic analysis revealed statistically significant differences in age distribution among the groups ($P \leq 0.01$). Additionally, gender differences were significant ($P \leq 0.05$), as shown in Table 1.

Thyroid Hormone Profiles

Serum levels of total triiodothyronine (T3) and total thyroxine (T4) were assessed in all participants. The

Table 1. Distribution of Sample Study According Difference Factors in Moderate and Severe Groups

Factors		Hyper No. (%)	Benign No. (%)	Malignant No. (%)	Control No. (%)	P-value
Gender	Male	8 (32.00%)	7 (28.00%)	4 (26.67%)	8 (32.00%)	0.0294 *
	Female	17 (68.00%)	18 (72.00%)	11 (73.33%)	17 (68.00%)	
Age (year)	<50 yr.	23 (92.00%)	16 (64.00%)	14 (93.33%)	20 (80.00%)	0.0062 **
	≥50 yr.	2 (8.00%)	9 (36.00%)	1 (6.67%)	5 (20.00%)	

** (P≤0.01).

Table 2. Summary of the mean ± standard Deviation (S.D) for T3, T4, and TSH Levels Across Different Groups (Control, Benign, Hyperthyroidism, and Malignant), including P values indicating statistical significance of differences among groups.

Parameter	Groups	Mean ± S.E	P value Control	P value Benign	P value Hyperthyroidism	P value Malignant
T3	Control	0.91 ± 0.03	-	<0.001**	<0.001**	<0.001**
	Benign	1.59 ± 0.04	<0.001**	-	<0.001**	0.2 NS
	Hyperthyroidism	1.11 ± 0.05	<0.001**	<0.001**	-	<0.001**
	Malignant	1.67 ± 0.05	<0.001**	0.2 NS	<0.001**	-
T4	Control	8.8 ± 0.11	-	<0.001**	<0.001**	<0.001**
	Benign	14.84 ± 0.19	<0.001**	-	<0.001**	<0.001**
	Hyperthyroidism	13.30 ± 0.17	<0.001**	<0.001**	-	<0.001**
	Malignant	16.35 ± 0.22	<0.001**	<0.001**	<0.001**	-
TSH	Control	1.95 ± 0.15	-	<0.001**	<0.001**	<0.001**
	Benign	3.56 ± 0.07	<0.001**	-	<0.001**	0.3 NS
	Hyperthyroidism	0.09 ± 0.01	<0.001**	<0.001**	-	<0.001**
	Malignant	3.40 ± 0.08	<0.001**	0.3 NS	<0.001**	-

Table 3. Levels of TG between Patients' Group and Healthy Control

Parameter	Groups	Mean+S.D	P value			
			Control	Benign	Hyperthyroidism	Malignant
TG	Control	7.89±0.26	-	<0.001**	0.9 NS	<0.001**
	Benign	17.01±0.27	<0.001**	-	<0.001**	<0.001**
	Hyperthyroidism	7.91±0.28	0.9 NS	<0.001**	-	<0.001**
	Malignant	103.12±0.90	<0.001**	<0.001**	<0.001**	-

malignant group exhibited significantly elevated T3 levels (1.67 ± 0.05) compared to controls (0.91 ± 0.03) and hyperthyroidism (1.11 ± 0.05) ($P < 0.001$ for all comparisons). Similarly, T4 levels were markedly higher in the malignant group (16.35 ± 0.22) compared to controls (8.80 ± 0.11), benign (14.84 ± 0.19) and hyperthyroidism groups (13.30 ± 0.17; $P < 0.001$). In contrast, TSH displayed distinct patterns: the hyperthyroidism group showed a profoundly suppressed TSH level (0.09 ± 0.01), while both benign (3.56 ± 0.07) and malignant cases (3.40 ± 0.08) had significantly higher TSH concentrations compared to controls (1.95 ± 0.15; $P < 0.001$). Notably, the difference in TSH between benign and malignant patients did not reach statistical significance ($P = 0.3$) Table 2.

Thyroglobulin (Tg) Levels

Serum thyroglobulin (Tg) was measured as an important marker reflecting thyroid tissue burden. Tg levels were dramatically elevated in patients with malignant thyroid tumors (103.12 ± 0.90 ng/mL)

Table 4. Levels of TSH R between Patients' Group and Healthy Control

Parameter	Groups	Mean+S.D	P value			
			Control	Benign	Hyperthyroidism	Malignant
TSH RE	Control	1.34±0.02	-	<0.001**	<0.001**	0.6 NS
	Benign	0.98±0.005	<0.001**	-	0.09 NS	<0.001**
	Hyperthyroidism	1.02±0.01	<0.001**	0.09 NS	-	<0.001**
	Malignant	1.32±0.03	0.6 NS	<0.001**	<0.001**	-

Table 5. Variants of VAP-1 between Patients' Group and Healthy Control

Parameter	Groups	Mean+S.D	P value			
			Control	Benign	Hyperthyroidism	Malignant
VAP-1	Control	670.22±5.61	-	<0.001**	<0.001**	<0.001**
	Benign	635.86±2.71	<0.001**	-	<0.001**	<0.001**
	Hyperthyroidism	610.20±1.62	<0.001**	<0.001**	-	<0.001**
	Malignant	347.99±4.29	<0.001**	<0.001**	<0.001**	-

Table 6. Pearson correlation between Patients' Group and Healthy Control

Parameter		T3	T4	TSH	TG	VAP-1	TSH RE
T3	Pearson Correlation (r)	1					
	Sig. (2-tailed)						
T4	Pearson Correlation (r)	0.730**	1				
	Sig. (2-tailed)	0.001					
TSH	Pearson Correlation (r)	0.606**	0.343**	1			
	Sig. (2-tailed)	0.001	0.001				
TG	Pearson Correlation (r)	0.545**	0.580**	0.466**	1		
	Sig. (2-tailed)	0.001	0.001	0.001			
VAP-1	Pearson Correlation (r)	-0.51**	-0.624**	-0.282**	-0.961**	1	
	Sig. (2-tailed)	0.001	0.001	0.007	0.001		
TSH RE	Pearson Correlation (r)	-0.268*	-0.426**	0.151	0.370**	-0.290**	1
	Sig. (2-tailed)	0.011	0.001	0.156	0.001	0.006	

**, Significant differences

compared to benign cases (17.01 ± 0.27 ng/mL) and healthy controls (7.89 ± 0.26 ng/mL) (P < 0.001). The hyperthyroidism group, however, showed Tg levels (7.91 ± 0.28 ng/mL) similar to those observed in the control group Table 3.

Thyroid-Stimulating Hormone Receptor (TSHR) Expression

Serum expression levels of the thyroid-stimulating hormone receptor were quantified by ELISA. The mean TSH receptor concentration in the malignant group (1.32 ± 0.03 pg/mL) was similar to that in healthy controls (1.34 ± 0.02 pg/mL), with no statistically significant difference observed (P > 0.05). Conversely, patients with benign thyroid nodules and hyperthyroidism showed slightly lower TSH receptor levels (0.98 ± 0.005 and 1.02 ± 0.01 pg/mL, respectively), although the differences were only significant when comparing benign cases to controls (P < 0.001) Table 4.

Vascular Adhesion Protein-1 (VAP-1) Levels

A striking finding was observed for VAP-1. Healthy controls exhibited the highest serum VAP-1 levels (670.22 ± 5.61 pg/mL), while significantly lower levels were detected in benign (635.86 ± 2.71 pg/mL) and hyperthyroidism groups (610.20 ± 1.62 pg/mL). Most notably, patients with malignant thyroid tumors had dramatically reduced VAP-1 concentrations (347.99 ± 4.29 pg/mL), with differences being highly significant across all comparisons (P < 0.001) Table 5.

Correlation Analysis

Pearson's correlation analysis demonstrated strong positive correlations between T3 and T4 (r = 0.730, P = 0.001) and significant positive relationships among TSH and Tg levels. In contrast, VAP-1 levels were inversely correlated with T3 (r = –0.51, P = 0.001), T4 (r = –0.624, P = 0.001), TSH (r = –0.282, P = 0.007), and Tg (r = –0.961, P = 0.001). The thyroid-stimulating hormone receptor showed weaker and mostly non-significant correlations with the other parameters Table 6.

Discussion

In this study, we evaluated the expression profiles of key thyroid biomarkers thyroid hormones (T3, T4), thyroid-stimulating hormone [4], thyroglobulin (Tg), thyroid-stimulating hormone receptor (TSHR), and vascular adhesion protein-1 (VAP-1) across various thyroid disorders, including malignant tumors, benign nodules, and hyperthyroidism, using a cohort of Iraqi patients. Our results demonstrate a distinct hormonal and protein expression pattern in malignant thyroid cancer compared to benign thyroid disorders and healthy controls.

The malignant group exhibited significantly elevated levels of T3 and T4 relative to the control group, which is consistent with the notion that thyroid hormone synthesis and release are upregulated in thyroid neoplasms. Concurrently, we observed markedly increased serum Tg in the malignant cohort. Elevated Tg levels post-thyroidectomy has been recognized as a sensitive indicator for residual thyroid tissue or early recurrence of malignancy [11-13]; thus, our findings reinforce the clinical utility of Tg as a prognostic marker in thyroid cancer management.

Conversely, TSH was significantly reduced in the hyperthyroidism group, which aligns with the well-established negative feedback mechanism inherent to the hypothalamic-pituitary-thyroid axis. In malignant cases, while TSH was also lower than in healthy controls, the differences between benign and malignant groups did not reach statistical significance. These observations suggest that TSH levels, although reflective of overall thyroid function, may not offer sufficient discriminatory power on their own for differentiating between various thyroid pathologies [14, 15].

The evaluation of TSHR, a critical mediator of thyroid hormone signaling, revealed no significant differences among the study groups. This finding implies that TSHR expression may remain relatively stable across different thyroid conditions or that its role in tumorigenesis may be more related to downstream signaling events rather than changes in receptor quantity [16, 17]. Further investigation into post-receptor signaling pathways could provide

additional insights into the role of TSHR in thyroid cancer progression.

A particularly striking finding was the significant decrease in serum VAP-1 levels in patients with malignant thyroid tumors compared to all other groups. VAP-1, an endothelial adhesion molecule with amine oxidase activity, is integral to leukocyte trafficking and inflammatory responses. Its reduced expression in thyroid cancer may reflect alterations in the tumor microenvironment—such as diminished recruitment of immune effector cells—which could contribute to tumor progression and metastasis [9, 18]. Our results are consistent with previous studies reporting that decreased VAP-1 expression is associated with more aggressive tumor phenotypes in various malignancies [19, 20]. Thus, low serum VAP-1 emerges as a promising diagnostic marker that warrants further validation in larger, independent cohorts.

Overall, our findings suggest that a comprehensive evaluation of thyroid function including traditional markers such as T3, T4, and Tg—alongside novel biomarkers like VAP-1, may enhance the diagnostic accuracy and provide deeper insights into the tumor biology of thyroid cancer [21, 22]. The apparent stability of TSHR expression across the groups raises questions regarding its precise role in tumor pathophysiology, calling for future studies to explore potential alterations in its signaling cascade [23, 24].

Limitations of this study include the cross-sectional design and the relatively modest sample size, which may restrict the generalizability of the findings. Future research should focus on longitudinal studies with larger populations to better elucidate the prognostic value of these biomarkers and to explore the molecular mechanisms underlying the observed alterations in VAP-1 levels.

In conclusion, our study underscores the potential of reduced serum VAP-1 as a useful diagnostic adjunct in thyroid cancer, while affirming the complex interplay between thyroid hormone regulation and cancer biology. These insights not only contribute to the refinement of current diagnostic strategies but also open avenues for targeted therapeutic interventions in thyroid malignancies.

Author Contribution Statement

All authors contributed equally in this study.

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