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Patients with thyroid disease observational analysis of serum levels of Retinol Binding Protein 4 (RBP4) and Visfatin: focus on thyroid cancer

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ABSTRACT

Background: Retinol Binding Protein 4 (RBP4) is a transport protein responsible for carrying vitamin A (retinol) from the liver to peripheral tissues. Visfatin, also known as Nicotinamide Phosphoribosyl Transferase (NAMPT), is an adipokine involved in glucose metabolism and has pro-inflammatory properties. Our core hypothesis suggests a potential link between thyroid diseases and distinct serum level of RBP4 and visfatin. The study aims to discern any significant differences in these protein levels between individuals with thyroid disorders and healthy control.

Methods: Conducted as a case-control study at multiple centers in Baghdad, Iraq from November 2022 to May 2023, this research assessed 150 serum samples across five groups: Hyperthyroidism, Hypothyroidism, Thyroid cancer, Thyroid Goiter, and healthy controls. Parameters included BMI, Serum RBP4 and Visfatin., and thyroid hormones (T3, T4, TSH). Assessment utilized ELISA kits and Tosoh AIA 360 Analyzer.

Results: Significant differences in serum RBP4 and Visfatin levels were discovered across thyroid conditions and between genders. Elevated RBP4 levels were predominantly seen in Hypothyroidism, Thyroid Cancer, and Thyroid Goiter cases, while Visfatin levels were notably higher in hypothyroid patients. Additionally, varying BMI levels across thyroid conditions were observed, promoting further investigation.

Conclusion: The results corroborate our hypothesis, suggesting that RBP4 and Visfatin could be potential markers for thyroid dysfunction. However, the complexity and hormone-specific interactions necessitate caution in their diagnostic application. Future studies should explore the diagnostic and prognostic value of these adipokines for specific thyroid conditions and further examine variables affecting BMIA.

Keywords: retinol binding protein, NAMPT, thyroid cancer

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INTRODUCTION

Thyroid diseases like hypothyroidism and hyperthyroidism are common endocrine disorders affecting million globally. The thyroid gland regulates metabolism, and its dysfunction can cause various physiological changes. According to WHO, it's the second most common endocrine disorder after diabetes. About 2% and 1% of people are affected by hyperthyroidism and hypothyroidism, respectively., with women being eight times more susceptible [1]. Thyroid diseases also include cancer, goiter, and autoimmune conditions such as Grave's disease and Hashimoto's thyroiditis [2].

Thyroid dysfunction can arise from issues in the pituitary gland, hypothalamus, or from iodin deficiency, leading to conditions like goiter [3, 4]. Research focuses on identifying markers for thyroid function, such as Retinol Binding Protein 4 (RBP4). Part of the lipocalin protein family, RBP4 plays a key role in Vitamin A regulation and is mainly produced in the liver but also in adipose tissues [5]. It is influenced by thyroid hormones, affecting insulin resistance and inflammation [6].

Visfatin, an *adipocytokine* mainly produced by visceral adipose tissue, has roles in regulation and inflammation [7]. While Chu C.-H *et al*., in 2008 reported reduced visfatin concentrations in hyperthyroidism, Caixàs et al., in 2019 observed elevated levels in hyperthyroid patients [8, 9]. Its involvement in various malignancies is established, but its diagnostic value in thyroid cancer is unconfirmed [10]. Recent research indicates that visfatin is not a reliable serum indicator for papillary thyroid cancer or ongoing structural issues [11].

The relationship between RBP4, visfatin, and thyroid diseases could have significant diagnostic and therapeutic implications. Elevated RBP4 levels in patients with subclinical hyperthyroidism were found to be linked to Coronary Heart Disease (CAD) risk [12]. RBP4 and adiponectin levels were the focus in a study of 150 patients with thyroid disorders and 28 controls. They found elevated RBP4 levels in clinical hypothyroid patients that normalized after thyroid hormone

treatment, whereas adiponectin levels remained stable [13]. These studies suggest that RBP4 could serve as an indicator for both CAD in subclinical hypothyroidism and metabolic shifts in thyroid disorders. Understanding these associations could improve early diagnosis and management of thyroid diseases and may offer new avenues for therapeutic interventions.

Examining serum levels of RBP4 and visfatin may offer new diagnostic tools for thyroid diseases, complementing traditional measures like thyroid hormone and TSH levels. Significantly higher levels of RBP4 and visfatin were found in hyperthyroid patients in a case-control study involving 60 participants, suggesting these proteins could enhance diagnostic accuracy [14].

Study objectives

Our study aims to address several key objectives to shed light on the role of Retinol Binding Protein (RBP4) and visfatin in thyroid disorders. Firstly, we aim to compare the serum levels of RBP4 and visfatin between individuals with thyroid disorders and a healthy control group. Secondly, we will investigate if there is any correlation between the levels of these proteins and the severity or nature of the thyroid conditions. Lastly, we aim to assess the viability of using RBP4 and visfatin serum levels as potential biomarkers for diagnosis and monitoring thyroid disorders. Through these objectives, we hope to uncover new insights that could redefine diagnostic and treatment strategies in endocrinology.

Study hypothesis

The central hypothesis of our study posits that there will be a notable difference in the serum levels of RBP4 and visfatin between individuals with thyroid disorders and those without. Specifically, we hypothesize that individuals with thyroid diseases might have distinct levels of RBP4 and visfatin in their serum compared to a healthy control group. This points to a potential link between these proteins and thyroid function, a discovery that could have significant implications for diagnosis and treatment in endocrinology.

MATERIALS AND METHODS

Study participants

This case-control study involved 150 individuals----120 diagnosed with various thyroid diseases and 30 serving as healthy controls. Specialized physicians made diagnoses based on symptoms, medical history, and lab tests, which included T3, T4, and TSH levels. Serum levels of RBP4 and Visfatin were also assessed. The study was conducted between November 2022 and May 2023 at multiple medical centres in Baghdad, Iraq. Ethical approval was obtained from the Iraqi Ministry of Health, as confirmed by a letter dated December 4, 2022, with reference number 51158. All participants provided verbal consent.

Collection of data

Data was collected through face-to-face interviews using a structured questionnaire that covered demographic details, medical history, lifestyle factors, and nutritional habits. Participants, primarily those with thyroid diseases, provided information on personal characteristics, symptom duration, and family medical histories. The aim was to identify correlations between participants' backgrounds and serum levels of RBP4 and Visfatin. Ethical standards were maintained, ensuring confidentiality. The questionnaire also noted conditions like hypertension and diabetes, as well as factors like iodine intake and medication use, given their potential impact on thyroid function.

Inclusion and exclusion criteria for the case-control study

Participants were within a specified age range and had confirmed thyroid conditions like Hyperthyroidism or Hypothyroidism. They were on stable medications, provided informed consent, and offered adequate serum samples. Pregnancy, acute illnesses, and other endocrine disorders were among the exclusion criteria. The study included only those who gave informed consent for both patient and healthy control groups. Individuals with conditions or treatments that could affect RBP4 and Visfatin levels, as well as pregnant or lactating women, were excluded. The control group also excluded people with chronic ailments like diabetes or hypertension and those on medications that could interfere with the study.

Determination of Body Mass Index (BMI) in the case-control study

Methodology:

BMI was calculated for each participant using the standard formula: weight in kilograms divided by the square of height in meters $BMI=\text{weight (Kg)}/\text{height (m)}^2$.

Limitations:

It is acknowledged that BMI does not distinguish between muscle and fat. However, it has a strong correlation with overall body fat and is frequently employed as a risk predictor for various health conditions.

Reference ranges:

In this study, the BMI ranges were categorized as follows [15]:

- Normal weight: BMI of 18.5 Kg/m^2 -24.9 Kg/m^2
- Overweight: BMI of 25 Kg/m^2 -29 Kg/m^2
- Obesity: BMI of ≥ 30 Kg/m^2

Contextual Relevance: The assessment of BMI was pivotal in this study to contextualize its effects on thyroid disorders and how these disorders, in turn, might influence the serum levels of proteins such as RBP4 and Visfatin.

Collection and processing of specimens in the case-control study

In this case-control study, blood samples were collected from each participant using a standardized venipuncture technique to minimize both discomfort and the risk of contamination. Approximately 5 mL of blood was collected per participant. To allow for differential clotting methods in the laboratory analysis, samples were immediately placed in either plain (red-top) tubes or serum separator (tiger-top or gold-top) tubes.

Upon collection, each sample was carefully sealed and labeled with a unique identifier to mitigate the risk of contamination and misidentification. Samples were transported to the laboratory as expediently as possible.

In the laboratory, the samples underwent centrifugation at a standardized speed of approximately 1500 rpm-2000 rpm for a duration of 10 min-15 min to separate the serum from cellular components. The extracted serum was then stored in Eppendorf tubes and was earmarked for subsequent analyses of T3, T4, TSH, RBP4, and Visfatin levels.

Quality assurance protocols were rigorously followed throughout the collection and processing stages to ensure the reliability of test results. This included calibration of equipment and validation of analytical methods.

If there were any unavoidable delays in sample transport, temperature control was strictly maintained. Samples were stored at temperatures between 2°C and 8°C to preserve their biological integrity until they could be processed.

Thyroid hormone analysis in serum specimens for the case-control study

In this case-control study, serum T3, T4, and TSH levels were quantified using the Tosoh AIA 360 Analyzer. TSH was measured via a two-site immune-enzymonometric assay using AIA-PACK TSH test cups and specific antibodies. T3 and T4 levels were determined through competitive enzyme immunoassays using AIA-PACK T4 test cups. In the TSH assay, hormone concentration was directly proportional to enzyme-antibody binding, while in T3 and T4 assays, it was inversely proportional. All assays adhered to strict quality control protocols, and results were displayed on the Tosoh AIA 360 alongside established normal ranges.

Methods for evaluating RBP4 and Visfatin concentrations in serum samples

In this case-control study, serum levels of RBP4 and Visfatin were analyzed using ELISA, selected for its accuracy, specificity, cost-effectiveness, and high-throughput capabilities. Serum samples were thawed to the appropriate assay temperature and any required dilutions were made. These steps were in line with the study objectives and available lab methods. All assays were conducted in compliance with quality control protocols to ensure reliable results.

Evaluation of RBP concentrations using ELISA

In this case-control study, RBP4 concentrations were quantified using a two-antibody sandwich ELISA, as outlined by the My BioSource Human RBP4 ELISA Kit protocol. Samples were exposed to anti-RBP antibodies for initial capture, followed by the introduction of HRP-conjugated secondary antibodies. Post wash, a chromogenic substrate 3,3',5,5'-tetramethylbenzidine (TMB), was added to assess the bound enzyme amount, which directly correlated with RBP4 levels in the sample. Absorbance was measured at 450 nm, calibrated using a standard curve. This method was consistently applied to both patient and control samples and all assays adhered to quality assurance protocols.

Analysis of visfatin concentrations through competitive ELISA

In this case-control study, Visfatin (VF) concentrations were assessed using a competitive enzyme immunoassay with the My BioSource Human VF ELISA Kit (USA), in compliance with manufacturer protocol. A pre-coated anti-VF plates was used for incubation with samples, VH-HRP conjugate, and buffer. Following a wash, an HRP substrate was added to initiate a color reaction, which was terminated with a stop solution. The color's optical density, inversely proportional to VF concentration, was spectrophotometrically quantified at 450 nm. VF levels were then determined through interpolation from a standard curve. The assay involved a defined sequence of standard loading, conjugate addition, washing and incubation, ensuring methodological consistency across samples.

Statistical analysis

In this case-control study, data analysis was performed using SPSS version 26.0 (2019). Data were tabulated as complex frequency distribution tables and quantitatively described by mean and standard deviation. The analytical techniques implemented include independent sample t-tests, the Monte Carlo test (MCP), ANOVA and Post Hoc Bonferroni tests for multiple comparisons. The level of statistical significance was determined based on p-value. Specifically, p-value >0.05 were considered non-significant p-values ≤ 0.05 were regarded as statistically significant (S), and p-values ≤ 0.01 were deemed Highly Significant (HS).

RESULTS

Baseline characteristics across thyroid conditions and control group

Table 1 provides an overview of the demographic characteristics of the study participants across different thyroid disease categories and a control group. The cohorts were comparable in size, each consisting of 30 participants. While age was similarly distributed across all groups, indicated by a non-significant P-value of 0.52, the gender distribution was marginally different, but also not statistically significant with a p-value of 0.0549.

Tab. 1. Basic attributes of the examined cohorts

Variables	Thyroid diseases				Control	p-value
	Hyperthyroidism	Hypothyroidism	Thyroid Cancer	Thyroid Goiter		
Age (years)	28.14-54.20	33.92-57.54	33.54-58.12	28.14-54.2	29.94-46.26	0.52
Range						
Mean ± SD	41.17 ± 13.03	45.73 ± 11.81	45.83 ± 12.29	41.17 ± 13.03	38.10 ± 8.16	
Male No. (%)	14 (47%)	9 (30%)	6 (20%)	8 (27%)	13 (43%)	0.0549
Female No. (%)	16=53%	21=70%	24=80%	22=73%	17=57%	
Total	30	30	30	30	30	

Gender-specific variations in body mass index across thyroid conditions

Table 2 outlines the mean Body Mass Index (BMI) and its Standard Deviation (SD) for males and females across different thyroid conditions and a control group. Statistically significant differences in BMI were observed among males, indicated by a P-value of 0.0001. Although the table offers a detailed numerical breakdown, it is noteworthy that the BMI values vary markedly, especially among males with different thyroid conditions.

Tab. 2. Mean Body Mass Index (BMI) and Standard Deviation (SD) by Gender across different thyroid conditions and control group

Gender	Study Group	Mean (BMI)	SD (BMI)	p-value
Male	Control	22.65	1.86	0.0001
	Hypothyroidism	35.89	2.37	
	Thyroid Cancer	23.87	2.99	
	Thyroid Goiter	32.45	3.18	
	Hyperthyroidism	23.49	1.7	
Female	Control	22.99	1.92	
	Hypothyroidism	29.59	4.82	
	Thyroid Cancer	24.25	2.68	
	Thyroid Goiter	27.85	4.88	
	Hyperthyroidism	20.07	2.22	

Hormonal variances in thyroid conditions

Table 3 presents the mean and standard deviation of thyroid hormone levels—T3, T4, and TSH—across various study groups, including hyperthyroidism, hypothyroidism, thyroid cancer, thyroid goiter, and a control group. The hormone levels differ significantly across the groups, with each condition exhibiting unique thyroid hormone profiles when compared to the control.

Tab. 3. . Thyroid Hormone Levels Across Study Groups

	Mean ± SD		
Group	**T3**	**T4**	**TSH**
Hyperthyroidism	0.81 ± 0.12	3.438 ± 0.80	10.4 ± 3.35
Hypothyroidism	1.19 ± 0.29	8.39 ± 3.06	2.27 ± 1.95
Thyroid Cancer	1.07 ± 0.18	7.69 ± 1.69	3.21 ± 1.43
Thyroid Goiter	1.73 ± 0.41	5.54 ± 1.44	0.29 ± 0.24
Control	1.12 ± 0.14	7.94 ± 1.18	2.05 ± 0.622
Post Hoc	Control –thyroid diseases 0.000 (H.S)	Control –thyroid diseases 0.0001 (H.S)	Control –thyroid diseases 0.0001 (H.S)
Bonferroni	Control-UC 0.0001 (H.S)		Control-UC 0.0001 (H.S)

Concentrations of RBP4 according to gender and thyroid conditions

Table 4 reports the mean Retinol Binding Protein 4 (RBP4) concentrations and their standard deviations across different

thyroid conditions and a control group, separated by gender. The data reveals statistically significant differences in RBP4 concentrations, further corroborated by highly significant Post Hoc Bonferroni test results between certain conditions. These variations in RBP4 concentrations are notable across both males and females within various thyroid conditions when compared to the control group.

Tab. 4. Gender-specific RBP4 levels in various thyroid conditions

Gender	Study Group	Mean RBP4 (µg/ml)	SD RBP4 (µg/ml)	p-value
Male	Control	11.84	3.476	0.001
	Hypothyroidism	28.81	4.042	
	Thyroid Cancer	26.25	5.764	
	Thyroid Goiter	27.17	5.376	
	Hyperthyroidism	23.46	2.828	
Female	Control	12.25	3.102	
	Hypothyroidism	22.72	3.806	
	Thyroid Cancer	29.36	4.448	
	Thyroid Goiter	21.99	6.12	
	Hyperthyroidism	18.32	3.867	
Post Hoc Bonferroni	Hyperthyroidism vs. Hypothyroidism		Thyroid Cancer vs. Thyroid Goiter	0.0001

Visfatin concentrations across gender and thyroid conditions

Table 5 presents the mean levels of Visfatin and their standard deviations in males and females across different thyroid conditions and a control group. The data indicates a statistically significant difference in Visfatin levels, supported by a p-value of 0.001. Further delineation by Post Hoc Bonferroni tests between Hyperthyroidism and Hypothyroidism as well as between Thyroid Cancer and Thyroid Goiter confirms highly significant differences, reflected in a p-value of 0.0001. These variations in Visfatin levels are noteworthy across both genders in various thyroid conditions when compared to the control group.

Tab. 5. Gender-specific visfatin levels in various thyroid conditions

Gender	Study Group	Mean Visfatin (ng/ml)	SD Visfatin (ng/ml)	p-value
Male	Control	3.9	0.8	0.001
	Hypothyroidism	19.09	5.35	
	Thyroid Cancer	7.38	5.9	
	Thyroid Goiter	19.35	6.97	
	Hyperthyroidism	4.02	0.79	
Female	Control	3.86	0.67	
	Hypothyroidism	10.16	6.15	
	Thyroid Cancer	8.04	4.86	
	Thyroid Goiter	10.49	8.94	
	Hyperthyroidism	2.32	1.05	
Post Hoc Bonferroni	Hyperthyroidism vs. Hypothyroidism		Thyroid Cancer vs. Thyroid Goiter	0.0001

DISCUSSION

Our study specifically evaluated RBP4 and visfatin levels in thyroid conditions. We observed significant variations in RBP4, supporting previous finding by Azo Najeeb H. et al., [16]. The variations hint at the proteins' potential as thyroid disorder indicators, a notion backed by Dadej D. *et al*., [5]. This data underlines the need for further research to substantiate these proteins as reliable biomarkers for thyroid dysfunction.

Our study found significant BMI variations in thyroid conditions, especially among males with hypothyroidism and thyroid goiter. This contradicts findings by Ríos-Prego M *et al.,* who reported no inherent BMI correlation with untreated thyroid dysfunction. The discrepancies suggest additional

variables influencing BMI in thyroid patients and call for further investigation [17].

Significant differences in RBP4 levels were identifies in our study across thyroid conditions and genders, notably higher in hypothyroidism, thyroid cancer, and goiter groups compared to controls. Post Hoc tests indicated marked variations particularly between hyperthyroidism and hypothyroidism, and thyroid cancer and goiter. These findings align with Zhang et al.'s study suggesting RBP4's potential role in thyroid disorders [18].

In the current study, it was observed that elevated RBP4 levels in thyroid dysfunction echo Kokkinos et al.'s study, which showed a decrease in RBP4 after hormone normalization, reinforcing RBP4's role in thyroid-related metabolic imbalances [19].

Significant variations in visfatin levels were observed, particularly in hypothyroid males and females, compared to control group. These changes, especially between hyperthyroidism and hypothyroidism, and between thyroid cancer and goiter, highlight visfatin's potential role in thyroid disorders. This is consistent with Caixàs A et al.'s study, which showed increased visfatin levels after thyroid function normalization, suggesting that visfatin may operate independently of other variables like inflammation or insulin resistance [9].

Elevated visfatin levels in both hyperthyroid and hypothyroid patients were confirmed by a study by M. Farazandeh Mher *et al.*, consistent with our findings. Their research also found these elevations to be independent of BMI, bolstering the notion that visfatin could serve as a diagnostic marker for thyroid dysfunction [20].

Our findings align with Shafeeq N.K.'s study, which also noted increased visfatin levels in hyperthyroid patients, accompanied by elevated lipid parameters. The study adds complexity by revealing that these hyperthyroid patients were also Familial Hypercholesterolemia heterozygotes. This suggests that visfatin could play multiple roles in metabolic processes beyond thyroid function, supporting our call for further exploration, especially regarding lipid abnormalities [21].

Chen D. *et al.* study revealed elevated RBP-4 and BPA levels in pregnant females with subclinical hypothyroidism, aligning with our findings of increased visfatin in thyroid dysfunction. Their work suggests that factors like RBP-4 and BPA may serve as risk factors and potential biomarkers for thyroid conditions and associated disorders [22].

Alshaikh EM *et al.* study found altered levels of adipokines like chemerin, visfatin, and omentin in hyperthyroid female patients compared to controls. These changes were correlated with thyroid hormones, supporting the idea that thyroid conditions can affect adipokine levels [23].

Our study suggests that elevated levels of visfatin, also known as extracellular Nicotinamide Phosphoribosyltransferase (eNAMPT) when in its extracellular form, could be an indicator of thyroid dysfunction. This finding contrasts with the work of Sawicka-Gutaj et al., who investigated visfatin and eNAMPT levels in the context of recurrent Papillary Thyroid Cancer (PTC). They found no significant difference in visfatin/eNAMPT levels between PTC patients and controls, and also concluded that eNAMPT has no prognostic value in PTC. This discrepancy between the two studies underscores the need for further, more targeted research to clarify the diagnostic and prognostic utility of visfatin in various thyroid conditions [24].

Sawicka-Gutaj *et al*. found that visfatin levels increased after restoring thyroid function in hypothyroid women, and were linked to fat mass and insulin levels. Their study also noted that thyroid treatment didn't improve body composition, particularly in hyperthyroid females. This suggests that visfatin's relationship with thyroid conditions may be influenced by treatment [25].

CONCLUSION

Our study revealed significant variations in serum levels of RBP4 and visfatin among individuals with different thyroid conditions, supporting the idea that these adipokines may serve as potential markers for thyroid dysfunction. Elevated RBP4 level were particularly observed in cases of hypothyroidism, thyroid cancer, and goiter; visfatin levels were also higher in hypothyroid individuals. Additionally, we noted variations in Body Mass Index (BMI) across thyroid conditions, suggesting other influencing variables that warrant further investigation. While our findings indicate the potential diagnostic utility of RBP4 and visfatin, caution should be exercised due to the complexities uncovered, such as their interaction with specific thyroid hormones. Future research should aim for a more nuanced understanding of these markers, investigating other variables affection BMI in thyroid patients and exploring the specific diagnostic value of RBP4 and visfatin in various thyroid disorders.

SUMMARY

What is already known:

- Adipokines like RBP4 and visfatin have been investigated in relation to various medical conditions, including metabolic disorders.
- Thyroid disorders often come with metabolic imbalances, which may interact with adipokines.
- Limited research has been done to examine the serum levels of RBP4 and visfatin specifically in individuals with different thyroid conditions.

New findings:

- This study shows significant variations in RBP4 and visfatin levels were found across different thyroid disorders and between genders, highlighting their potential as markers for thyroid dysfunction.
- From our results, elevated RBP4 levels were particularly associated with hyperthyroidism, thyroid cancer, and thyroid goiter.
- In the current study, notable variations in Body Mass Index (BMI) were observed across thyroid conditions, suggesting additional variables affecting BMI in these patients.

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