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Altered visfatin and adiponectin levels and their interaction with HEGF in the metabolic dyslipidemia of overt hypothyroidism: A case-control study

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ABSTRACT

Background: Hypothyroidism is a common endocrine disorder associated with significant metabolic dysregulation, including dyslipidemia. Adipokines such as visfatin and adiponectin are key regulators of metabolism, but their specific roles and potential as markers of metabolic dysfunction in overt, treatment-naive hypothyroidism require further elucidation.

Objectives: This study aimed to investigate the association between visfatin and adiponectin levels with hypothyroidism, assess their potential utility for metabolic risk assessment, and explore their associations with metabolic parameters and human epidermal growth factor (HEGF).

Materials and methods: This case-control study included 71 hypothyroid patients and 71 frequency-matched euthyroid controls. All patients were newly diagnosed and therapy-naive. Serum levels of adipokines (visfatin, adiponectin), HEGF, thyroid hormones, and lipids were assessed. Statistical analyses included ROC curves, Spearman's correlation, multivariate regression, and ANCOVA to adjust for BMI and age.

Results: After adjusting for BMI and age, hypothyroid patients had significantly lower visfatin (adjusted LS mean: 11.04±1.56 vs 19.36±1.59 ng/mL, $p<0.001$) and adiponectin (10.77±2.04 vs 23.61±2.09 ng/mL, $p<0.001$) compared to controls and exhibited atherogenic dyslipidemia (all $p<0.001$). A strong positive correlation was observed between visfatin and adiponectin ($\rho=0.533$ and $p<0.001$). Regression analysis revealed significant interactions in the hypothyroid group: visfatin×HEGF was associated with an increased LDL-C ($\beta=0.1306$, $p=0.0188$), while adiponectin×HEGF was associated with decreased LDL-C (=-0.0919, $p=0.0062$). Adiponectin showed a good screening for metabolic risk in hypothyroidism (AUC=0.80) compared to visfatin (AUC=0.68).

Conclusion: Hypothyroidism is associated with altered adipokine levels and a specific interplay with HEGF that influences LDL-C. Adiponectin shows promise as adjunctive marker for assessing metabolic dysfunction severity in hypothyroidism, and the HEGF-adipokine network represents a potential pathophysiological mechanism worthy of further investigation.

Introduction

Hypothyroidism is one of the most common endocrine conditions associated with an increased risk of hyperlipidemia, hypertension, atherosclerosis, and low-grade inflammation.[1] Fatigue, lethargy, weight gain, and sensitivity to cold are cardinal features of hypothyroidism; however, these symptoms are indicators, and serum thyroid function tests are often

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used to diagnose the condition based on biochemical criteria.[2] Thyroid hormones affect many aspects of lipid metabolism, including synthesis, mobilization, and degradation.[3] However, the precise mechanisms linking thyroid dysfunction to metabolic disturbances, particularly through adipokine-mediated pathways, remain incompletely understood.

Thyroid hormones act through both genomic and non-genomic pathways to modulate the expression and activity of key enzymes and receptors. Crucially, it upregulates the activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), cholesteryl ester transfer protein (CETP), hepatic lipase (HL), and lecithin-cholesterol acyltransferase (LCAT), furthermore, simultaneously increasing the expression of LDL receptors (LDL-R) via the activation of sterol regulatory element-binding protein 2 (SREBP-2), enhancing cholesterol clearance.[4] Thyroid hormone is critical for enhancing β-oxidation via the induction of hepatocyte autophagy.[5] Consequently, in primary hypothyroidism the level of thyroid hormones is reduced or deficient; thus, many enzymes and receptors that are involved in the metabolism of lipids are decreased. TSH stimulates lipolysis in adipocytes via phosphorylation of perilipin and hormone-sensitive lipase (HSL), increasing circulating FFAs.[6] In hepatocytes, TSH promotes triglyceride synthesis through the THR/cAMP/PKA/PPARγ and SREBP1C pathways. It also stimulates the production of apolipoprotein B.[7] These disturbances create a pro-atherogenic lipid profile, but the contribution of adipose tissue-derived factors-particularly adipokines-to this metabolic dysregulation is an emerging area of interest.

Adipokines can affect numerous processes, including the regulation of energy and appetite, lipid and glucose metabolism, insulin sensitivity, endothelial cell function, inflammation, angiogenesis, blood pressure, hemostasis, and the onset of atherosclerosis and metabolic syndrome.[9] Owing to their pro- and anti-inflammatory properties, adipokines play a vital role in coordinating the immune response and systemic metabolism.[9] The balance between pro- and anti-inflammatory adipokines is maintained in individuals with normal metabolic functions. However, when adipose tissue accumulates in obese individuals, this balance shifts towards pro-inflammatory mediators.[10] Given the well-established link between hypothyroidism and altered adipose tissue function.

Visfatin, a pro-inflammatory adipokine, is most likely generated and released by white adipose tissue, namely the visceral white adipose tissue (vWAT). Visfatin exists in two forms: intracellular and extracellular visfatin, also known as nicotinamide phosphoribosyltransferase (NAMPT). Both intracellular (iNAMPT), which is crucial for the biosynthesis of nicotinamide adenine dinucleotide (NAD^+), and extracellular (eNAMPT) pathways are linked to numerous hormone-like signaling pathways and intracellular signaling cascades.[11] According to previous studies, plasma visfatin levels are high in both hyperthyroid and hypothyroid conditions, but significantly normalize once euthyroid is achieved.[12] This implies that visfatin can dynamically react to changes in thyroid hormone levels. Research suggests that visfatin may help stabilize the effects of thyroid hormones without affecting anthropometric or inflammatory factors.[12]

Adiponectin is an adipokine secreted by white adipose tissue and has pleiotropic effects on several physiological processes.[13] After therapy, adiponectin levels in hypothyroidism patients have been shown to drop noticeably, which may indicate a connection between thyroid function and adiponectin alterations.[14] Due to possible feedback pathways between adiponectin and thyroid hormones, adiponectin may be a candidate for monitoring metabolic disturbances associated with hypothyroidism. This variability highlights the complexity of adipokine regulation and the need for studies that account for potential modulating factors. HEGF and its receptor (EGFR) have been implicated in various metabolic processes beyond cell growth. Preclinical studies suggest that EGFR signaling can influence adipocyte differentiation and may modulate hepatic lipid metabolism.[15] Moreover, there is emerging evidence linking thyroid status to the expression of epidermal growth factors.[16,17] Thyroid hormones modulate both the production of EGF and the expression of its receptors in various tissues. T3 has been shown to potentially down-regulate EGF receptor mRNA, thereby altering cellular sensitivity to growth factors.[18] Conversely, long-term exposure to EGF can attenuate thyroid hormone responses by decreasing the concentration of specific nuclear thyroid hormone receptors.[19] This interplay suggests that EGF may mediate some of the developmental and metabolic actions of thyroid hormones. We hypothesized that HEGF may be involved in the relationship between adipokines and dyslipidemia in the hypothyroid state. Adipokines are thought to mediate metabolic disorders associated with hypothyroidism, such as dyslipidemia and insulin resistance. Elevated TSH levels are linked to enhanced insulin resistance, and alterations in adipokines may be associated with these effects.[20] Clinical investigations have connected adipokine level alterations to lipid disorders among individuals with hypothyroidism, indicating that they play a role in their pathogenesis. Despite growing evidence, the direct causal involvement of adipokines in metabolic diseases associated with thyroid dysfunction remains unclear. In contrast, adiponectin and visfatin levels in hypothyroidism reflect systematic variance, which is complicated by an overlap with obesity, inflammation, insulin resistance, and possible differences in local versus systemic adipokine effects.[12]

To address these gaps, this study focuses on two main objectives. Primary (confirmatory) aims were 1) to compare circulating levels of visfatin and adiponectin

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between patients with overt, treatment-naive hypothyroidism and age- and sex-matched euthyroid controls, and 2) to characterize the lipid profile (total cholesterol, LDL-C, HDL-C, triglycerides, VLDL) in hypothyroid patients compared to controls. Secondary (exploratory) aims were 1) to investigate whether HEGF levels differ between groups and whether HEGF interacts with visfatin and adiponectin to associate with lipid parameters, particularly LDL-C, and 2) to assess the potential of adipokines as adjunctive markers for metabolic dysfunction.

Materials and methods

Study population

This case-control study recruited participants (aged 16 to 65 years) who were then classified into two groups based on their thyroid function status: a hypothyroid group (N=71) and a euthyroid control group (N=67). The hypothyroid group (N=71) consisted of patients newly diagnosed with primary hypothyroidism (confirmed by elevated TSH (>5 mIU/L) and low T3 and T4 levels), who were recruited before the initiation of levothyroxine replacement therapy. The euthyroid control group (N=67) was recruited from individuals attending routine health check-ups, who were confirmed to have TSH and thyroid hormone levels within the reference range (TSH between 0.5-5.0 mIU/L and total T4 between 60-135 nmol/L) and had no personal or family history of thyroid disease, autoimmune disorders, or use of medications known to affect thyroid function. The controls were frequency-matched to the case group by age and sex.

Biochemical assays

Serum adiponectin (SunLong Biotech, SL0068Hu), visfatin (SL0325Hu), and Human Epidermal Growth Factor HEGF (SL0666Hu) were quantified using sandwich ELISA. The intra- and inter-assay coefficients of variation (CVs) were <10% and <12 % for all assays, respectively. Thyroid hormones (TSH, T3, T4) were measured using a Chemiluminescent Immunoassay (CLIA) on an SNIBE Maglumi 800 analyzer, and lipids (Total Cholesterol, BIOLABO 80106; Triglycerides, LP80019) were assayed by enzymatic methods. HDL was measured directly; LDL and very low-density lipoprotein (VLDL) levels were calculated using the Friedewald formula (LDL=Total Cholesterol-HDL-(Triglycerides/5), and VLDL=Triglycerides/5).

Statistical framework

All statistical analyses were performed using GraphPad Prism 10.5 for descriptive statistics, non-parametric tests, correlation analyses, and ROC curve analysis. Data were assessed for normality using the Shapiro-Wilk test. Normally distributed data are represented as mean±SD. Non-normally distributed data are presented as median (range). Categorical variables are presented as counts (percentages). Group comparisons for continuous variables were made using the independent t-test or Mann-Whitney U test. To account for significant differences in BMI between groups, we additionally performed Analysis of Covariance (ANCOVA) with group as the fixed factor and BMI and age as covariates. Adjusted least-squares means (LS means) with standard errors were calculated, along with adjusted mean differences (β), 95% confidence intervals, and partial eta-squared (η^2) effect sizes. To control for multiple comparisons, False Discovery Rate (FDR) adjustment was applied using the Benjamini-Hochberg procedure. The Chi-square test was used for categorical variables. Correlations were assessed using Spearman's rank correlation coefficient (ρ) adjusted for potential confounders (BMI and age) in the correlation between visfatin and adiponectin, a partial correlation analysis was conducted. The strength of correlations was interpreted as: |ρ| <0.3 (weak), 0.3-0.5 (moderate), >0.5 (strong). The diagnostic performance of biomarkers was evaluated using the Receiver Operating Characteristic (ROC) curve analysis. The area under the curve (AUC) is reported with 95% confidence intervals (CI). The optimal cut-off value was determined by maximizing the Youden Index. Pairwise comparisons of AUCs were performed using DeLong's test.

To investigate effect modification, multiple linear regression models were constructed with LDL-C as the dependent variable. Models included main effects and their two-way interaction terms, with adjustment for age, sex, and BMI. A $p<0.05$ was considered significant.

Results

Baseline characteristics and thyroid hormone profiles

The clinical characteristics of the study participants are shown in Table 1. The control group was frequency-matched to the hypothyroid group for age and sex, as confirmed by the non-significant differences in these variables ($p>0.05$), However, Body Mass Index (BMI) was significantly higher in the hypothyroid group (25.95±4.63 kg/m^2) compared to the control group (24.20±3.36 kg/m^2, $p=0.027$). Therefore, all subsequent group comparisons were adjusted for BMI and age using ANCOVA to isolate the effects of thyroid status from those of adiposity.

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Table 1. Demographic and clinical characteristics of participants.

Variable	Hypothyroid patients (N=71)	Healthy controls (N=67)	*p* value*	95% CI
Age (years) Median (IQR)	43 (35-52.5)	36(33-46.2)	0.078	
Sex			0.857	
• Male	15	15		
• Female	56	52		
BMI (Mean±SD)	25.95 ±4.63	24.20±3.36	0.027	0.198-3.287

Note: *Data are presented as median (IQR) for non-normally distributed variables (age), mean±SD for [illegible]ally distributed variables (BMI), and counts (%) for categorical variables (sex). The p values were calculated using Mann-Whitney U test for age, the unpaired t-test for BMI, and the Chi-square test for sex.*

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The detailed distribution of thyroid hormone levels is provided in Table 2. As expected, the hypothyroid group had significantly higher median [IQR] of TSH levels (22.00 [11.00-43.00] mIU/L) and significantly lower Mean±SD of T4 levels 31.38±19.49 nmol/L [illegible] compared to [illegible] control group (TSH median [IQR]: (1.80 [1.2[illegible]3.00] mIU/L), T4 [illegible]n±SD 10[illegible]6±17.86 nmol/L, all $p<0.0001$) [illegible]nfirming the distinct biochemical profile[illegible] of the two groups. T3 results are shown in Table [illegible]

Table 2. Comparison of thyroid hormone profiles between the cont[illegible] and hypothyroidism group.

Hormone	Healthy co[illegible]ols (N=67) Median [illegible]QR] or Mean±SD	[illegible]ypothyroid p[illegible]ients (N=71) [illegible]edian [illegible]QR] or Mean±SD	[illegible]ue
TSH (mIU/L)	1.80 (1.23-3.00)	[illegible]0 (11.00-43.00)	<0.0001
T4 (nmol/L)	102.6±[illegible]86	31.38±19[illegible]	<0.0001
T3 (n[illegible]/L)	[illegible](1.00-[illegible])	0.96[illegible]0-1.20)	<0.0001

[illegible]: Data are present[illegible]as me[illegible]±SD or [illegible]dian (IQR). TSH: thyro[illegible]stimulating hormone, T3: triiodothyronine, T4: thvroxine. The [illegible].0001 for all [illegible]mparisons between grou[illegible]Mann-Whitney U test).

[illegible]sex-strati[illegible]ana[illegible]sis [illegible]nfirmed that the significant reduct[illegible]ns in vi[illegible]ti[illegible]nd a[illegible]nectin were pr[illegible]nt in both males [illegible]nd fe[illegible]les with hypoth[illegible]oidism compared to their [illegible]x-matched control[illegible](all $p<0.05$, Table 3). Vi[illegible]atin levels in males s[illegible]wed a median of 13.0 ng/mL ([illegible]4-33.7) in healthy control versus 10.5 ng/mL (7.2-16.[illegible] in hypoth[illegible]oid patients ($p=0.0268$); in females, values [illegible]f vi[illegible]tin were 15.4 ng/mL (6.6-88.9) versus 10.25 ng/mL (6.1-28.1) ($p=0.0002$), in controls and patients respectively. Similarly, adiponectin levels were reduced in patients: males had 14.7 ng/mL (6.8-36.1) versus 9.1 ng/mL (5.8-25.8) ($p=0.0464$); females showed 19.2 ng/mL (6.0-135.8) versus 8.6 ng/mL (2.3-80.7) ($p<0.0001$). In contrast, no significant differences in adipokine levels were observed between males and females within either the hypothyroid or control groups ($p>0.7$, our unpublished data), indicating that the hypothyroid state, not biological sex, was the primary factor associated with adipokine dysregulation. Sex-stratified analysis using unadjusted data showed similar patterns in both males and females. After adjusting for BMI and age in the main ANCOVA models (Table 4), the overall differences between groups remained significant, though the study was not powered for sex-stratified adjusted analyses.

Table 3. Sex-stratified analysis of adipokine levels.

Biomarker	Sex	Healthy controls (N=67) Median (range)	Hypothyroid patients (N=71) Median (range)	*p* value
Visfatin (ng/mL)	Male (N=15/15)	13.0 (7.4-33.7)	10.5 (7.2-16.3)	0.0268
	Female (N=52/56)	15.4 (6.6-88.9)	10.25 (6.1-28.1)	0.0002
Adiponectin (ng/mL)	Male (N=15/15)	14.7 (6.8-36.1)	9.1 (5.8-25.8)	0.0464
	Female (N=52/56)	19.2 (6.0-135.8)	8.6 (2.3-80.7)	<0.0001

Note: *Data are presented as median (range). The p values were calculated using the Mann-Whitney U test with $p<0.05$ compared to same-sex controls. No significant differences were observed between males and females within the same group (all $p>0.05$).*

Comparative analysis of biomarkers and lipid profiles

To account for the significant difference in BMI between groups, we performed ANCOVA adjusting for BMI and age. The fully adjusted results are presented in Table 4. After adjustment, the hypothyroid group maintained significantly lower levels of both visfatin and adiponectin. Hypothyroid patients had an adjusted least-squares (LS) mean visfatin concentration of 11.04±1.59 ng/mL compared to 19.36±1.59 ng/mL in controls (adjusted mean difference [β]=-8.32, FDR-adjusted p<0.001). Similarly, adiponectin remained significantly lower in the hypothyroid group (10.77±2.04 vs. 23.61±2.09 ng/mL; β=-12.84, FDR-adjusted p<0.001). The partial η^2 values (0.092 and 0.124, respectively) indicate moderate effect sizes, suggesting that thyroid dysfunction itself, rather than differences in adiposity, is a primary driver of these adipokine alterations. Interestingly, HEGF levels were modestly but significantly elevated in the hypothyroid group after adjustment (47.96±2.10 vs. 41.73±2.14 pg/mL, β=6.23, FDR-adjusted p=0.043). The lipid profile remained markedly atherogenic in hypothyroid patients even after controlling for BMI and age. Compared to controls, the hypothyroid group showed significantly higher adjusted LS means for total cholesterol (202.84±6.58 vs 148.63±6.73 mg/dL, β=54.22, FDR-adjusted p<0.001), triglycerides (186.45±8.34 vs 106.75±8.53 mg/dL, β=79.69, FDR-adjusted p<0.001), LDL-C (137.89±6.10 vs 92.12±6.24 mg/dL, β=45.7[illegible], FDR-adjusted p<0.001), and VLDL (37.30±1.67 vs 21.35±1.71 mg/dL, β=15.95, FDR-adjusted p<0.001), together with significantly reduced HDL-C (27.65±1.10 vs 35.15±1.12 mg/dL, β=-7.50, FDR-adjusted p<0.001).

Table 4. ANCOVA-adjusted comparison of biomarkers between hypothyroid and control groups.

Parameter	Control group LS Mean±SE⁺ (N=67)	Hypothyroid group LS Mean±SE⁺ (N=71)	Adjusted mean difference (β)*	t-value*	p-value*	Partial $\eta^{2‡}$	FDR adjusted p-value†
Adipokines and growth factors							
Visfatin (ng/mL)	19.36±1.59	11.04±1.56	-8.319	2.266	<0.001	0.092	<0.001
Adiponectin (ng/mL)	23.61±2.09	10.77±2.04	-12.838	2.965	<0.001	0.124	<0.001
EGF (pg/mL)	41.73±2.14	47.96±2.10	6.229	3.046	0.043	0.030	0.043
Lipid profile							
Total cholesterol (mg/dL)	148.63±6.73	202.84±6.58	54.218	9.565	<0.001	0.195	<0.001
Triglycerides (mg/dL)	106.75±8.53	186.45±8.34	79.694	12.117	<0.001	0.245	<0.001
HDL-C (mg/dL)	35.15±1.12	27.65±1.10	-7.500	1.593	<0.001	0.143	<0.001
LDL-C (mg/dL)	92.12±6.24	137.89±6.10	45.768	8.859	<0.001	0.167	<0.001
VLDL (mg/dL)	21.35±1.71	37.30±1.67	15.951	2.423	<0.001	0.246	< 0.001

Note: *LS Mean±SE: Least-squares mean and standard error from ANCOVA, adjusting for age and BMI. *β, SE, and p value. Adjusted mean difference, its standard error, and raw significance for the group effect. ‡Partial η^2: Effect size (proportion of variance associated with thyroid status independent of covariates). †FDR-adjusted p value: False discovery rate q-value via Benjamini-Hochberg procedure (significance at<0.05), LS: least-squares, SE: standard error, FDR: false discovery rate, TSH: thyroid-stimulating hormone, HEGF: human epidermal growth factor, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, VLDL: very low-density lipoprotein, BMI: body mass index, ANCOVA: analysis of covariance.*

Correlation analysis

After adjusting for BMI and age using partial correlation, a strong positive association was observed between circulating visfatin and adiponectin concentrations (Spearman's p=0.533, p<0.001) in the hypothyroid group (Table 5). This alignment suggests concurrent alteration of these adipokines during thyroid dysfunction. No significant correlations were detected between TSH and any of the investigated adipokines or HEGF (all p>0.05). HEGF itself showed no significant correlation with other biomarkers (all p≥0.071), suggesting its signaling pathways operate independently within the adipokine-thyroid axis in this context.

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Table 5. Correlation matrix of study variables in the hypothyroid group (N=71).

Variable	TSH	Visfatin	HEGF	Adiponectin	Age
TSH	-				
Visfatin	0.140 (0.245)	-			
HEGF	-0.145 (0.220)	0.176 (0.141)	-		
Adiponectin	-0.030 (0.805)	0.533* (<0.001)	0.107 (0.376)	-	
Age	0.060 (0.618)	-0.126 (0.295)	-0.167 (0.163)	0.010 (0.934)	

Note: *Values represent Spearman's correlation coefficient (ρ) with the corresponding p value in parentheses.*

As shown in Table 6, TSH demonstrated significant positive correlations with atherogenic lipid parameters, total cholesterol (ρ=0.243, p=0.041), and LDL-C (ρ=0.298, p=0.012). A distinct inverse relationship emerged between visfatin and triglyceride-rich lipoproteins, including triglycerides (ρ=-0.271, p=0.021) and VLDL (ρ=-0.270, p=0.022). This inverse association suggests a potential link between lower visfatin levels and higher triglyceride-rich lipoproteins in hypothyroidism. Adiponectin showed similar, near-significant inverse trends with triglycerides (ρ=-0.229, p=0.054) and VLDL (ρ=-0.226, p=0.057).

Table 6. Correlations of biomarkers and lipid markers in hypothyroid patients (N=71).

Variables	Cholesterol	Triglyceride	HDL-C	LDL-C	VLDL
TSH	ρ 0.243	0.028	-0.015	0.298	-0.027
	p value 0.041*	(0.814)	(0.898)	0.012*	(0.822)
Visfatin	ρ -0.133	-0.271	-0.182	0.008	-0.270
	p value (0.269)	0.022*	(0.128)	(0.945)	0.022*
HEGF	0.155	0.067	0.031	0.119	0.067
	p value 0.196	(0.575)	(0.795)	(0.321)	(0.574)
Adiponectin	ρ -0.151	-0.229	0.025	-0.094	-0.226
	p value (0.208)	(0.054)	(0.832)	(0.432)	(0.057)
Age	ρ 0.251	0.140	0.063	0.187	0.138
	p value 0.034*	(0.243)	(0.599)	(0.117)	(0.248)

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Diagnostic performance (ROC analysis)

The discriminative ability of adiponectin and visfatin for differentiating hypothyroid patients from euthyroid controls is presented in Table 7. Adiponectin demonstrated the highest overall discriminative ability, with an Area Under the Curve (AUC) of 0.80 (95% CI: 0.72-0.87, *p*<0.0001) (Figure 1). At its optimal cut-off value of <14.50 ng/mL, determined by maximizing the Youden Index, adiponectin achieved a sensitivity of 81.69% and a specificity of 68.66%. Visfatin exhibited more modest discriminative power with an AUC of 0.68 (95% CI: 0.59-0.77, *p*<0.001). At its optimal cut-off of 12.35, visfatin achieved a sensitivity of 75.00% and a specificity of 62.69%.

Table 7. ROC analysis for adipokine discriminative ability

Biomarker	AUC	Optimal Cut-off	Sensitivity	95% CI	Specificity	95% CI	Youden Index
Adiponectin	0.80	<14.50	81.69%	71.15%-88.98%	68.66%	56.80%-78.49%	50.35
Visfatin	0.68	12.35	75%	0.6345-0.8332	62.69%	0.5072-0.7328	37%

Note: *AUC values are interpreted as: 0.90-1.00=excellent; 0.80-0.90=good, 0.70-0.80=fair, 0.60-0.70=poor; <0.60=fail. Adiponectin demonstrated good discriminative ability (AUC=0.80), while visfatin showed poor discriminative ability (AUC=0.68).*

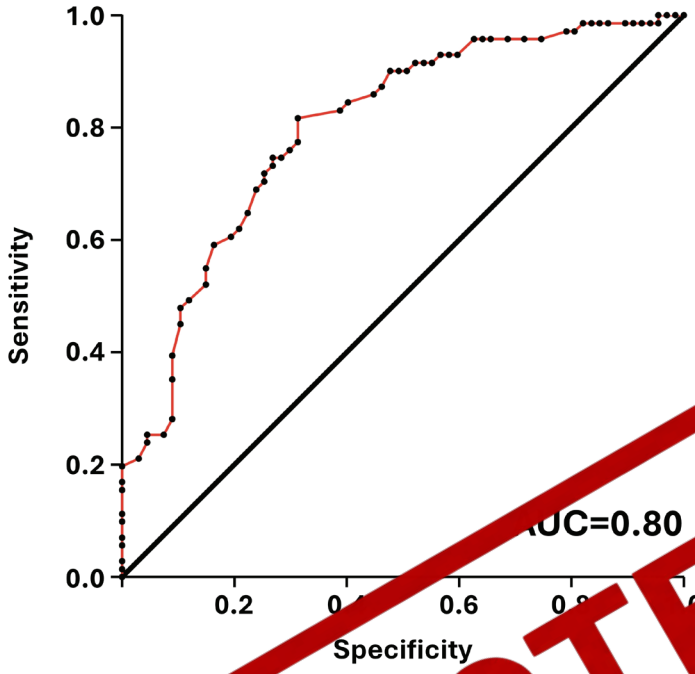


Figure 1. *ROC Curve for Adiponectin. The area under the curve (AUC) is 0.80 (p<0.0001). The optimal cut-off value is <14.50 ng/mL, yielding a sensitivity of 87% and a specificity of 68.7%.*

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Multivariate regression and interaction analysis

To investigate the interplay between adipokines and HEGF on lipid metabolism, this study conducted multiple linear regression models with LDL-C as the dependent variable, adjusting for age, sex, and BMI. The results are detailed in Table 8. Significant interaction effects between specific adipokines and HEGF on LDL-C levels were observed exclusively in the hypothyroid group and not in the euthyroid controls. The Visfatin×HEGF interaction term demonstrated a positive β-coefficient (β=0.1306, p=0.0188), indicating that the combination of higher levels of both factors associated with increased LDL-C concentrations. Conversely, the Adiponectin×HEGF interaction term showed a negative β-coefficient (β=-0.0919, p=0.0062), suggesting that this combination is associated with reduced LDL-C levels. Visfatin also independently and positively predicted adiponectin levels across all subjects (β=0.0328, p<0.0001), reinforcing the strong association observed in the correlation analysis. The absence of these significant interactions in the control group (all p>0.05) underscores the disease-specific nature of this novel signaling network in hypothyroidism (Table 8).

Table 8. Multiple linear regression and interaction analyses for adipokines and lipid parameters

Analysis type	Group	Predictor/interaction	Outcome	β-coefficient (SE)	p value	95% CI for β
Multivariate regression	Combined†	TSH	Adipokines		NS	-
Linear regression	Combined†	Visfatin	Adiponectin	0.328 (0.096)	<0.0001	0.121 to 0.045
Interaction analysis	Combined†	Visfatin×HEGF	Adiponectin	-	NS	-
Interaction analysis	Hypothyroidism	Visfatin×HEGF	LDL-C	0.1306 (0.052)	0.0188	0.028 to 0.233
Interaction analysis	Hypothyroidism	Adiponectin×HEGF	LDL-C	-0.0919 (0.032)	0.0062	-0.155 to -0.029
Interaction analysis	Control	Visfatin×HEGF	LDL-C	-	NS	-
Interaction analysis	Control	Adiponectin×HEGF	LDL-C	-	NS	-

Note: *Values represent unstandardized regression coefficients (β) with standard errors (SE) in parentheses, p values, and 95% confidence intervals (CI) for statistically significant associations. All models were adjusted for age, sex, and BMI unless otherwise specified. Interaction terms were created by multiplying the centered values of the two variables of interest. Statistical significance was set at p<0.05. NS (non-significant) indicates p≥0.05. †Combined group includes both hypothyroid patients and euthyroid controls (N=138), with adjustment for group status in the model.*

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Discussion

This case-control study examined the associations of visfatin and adiponectin with metabolic dysfunction in overt, treatment-naive hypothyroidism. Our main observations are threefold. Firstly, patients with hypothyroidism had significantly lower circulating levels of both visfatin and adiponectin than euthyroid controls, accompanied by a pronounced atherogenic lipid profile (elevated total cholesterol, LDL-C, triglycerides, and VLDL, and reduced HDL-C). Secondly, we observed a strong positive correlation between visfatin and adiponectin specifically in the hypothyroid group, contrasting with the inverse relationship typically reported in obesity and diabetes. Thirdly, exploratory interaction analyses revealed disease-specific associations between HEGF and both adipokines in relation to LDL-C metabolism: the visfatin×HEGF interaction was positively associated with LDL-C, while the adiponectin×HEGF interaction was negatively associated with LDL-C. These findings provide new insights into the complex adipokine-HEGF-lipid axis in hypothyroidism.

Our observation of reduced adiponectin in hypothyroidism aligns with some reports but contrasts with others that found increased or unchanged levels.[21-23] Similarly, our finding of decreased visfatin is consistent with Bekaya *et al.*,[24] but differs from Caixàs *et al.*[25] who reported elevated in thyroid dysfunction. These discrepancies might be the consequence of different study populations, methods, and definitions of hypothyroidism (overt vs subclinical). In milder or subclinical hypothyroidism, the body may mount a compensatory or stress-related response, leading to an initial increase in certain adipokines like visfatin. This biphasic response to elevation in early or mild dysfunction, followed by suppression in advanced or severe dysfunction, may reconcile the conflicting literature. According to Sawicka *et al.*, visfatin levels in hypothyroid patients are influenced by both the presence of autoimmune diseases and the levels of free thyroid hormones.[25]

In hypothyroidism, changes in visfatin and adiponectin levels are associated with metabolic dysfunction (dyslipidemia), which is shown by elevated total cholesterol, triglycerides, LDL, VLDL, and reduced HDL levels in hypothyroid individuals. Low visfatin levels could adversely affect NAD^+ dependent energy metabolism, aggravating lipid buildup, whereas reduced adiponectin impairs high-density lipoprotein(HDL) production and fatty acid oxidation.[11] Adiponectin decreases plasma triglyceride (TG) level by promoting the breakdown of triglyceride-rich lipoproteins by upregulating the expression of very low density lipoprotein (VLDL) receptors and skeletal muscle lipoprotein lipase (LPL), which in turn results in very low density lipoprotein and triglyceride catabolism.[26] This mechanism aligns directly with our findings in the hypothyroid group; the ANCOVA-adjusted results (Table 4) confirmed that hypothyroid patients have significantly higher triglycerides and VLDL alongside reduced visfatin and adiponectin, independent of BMI and age. The negative correlation we observed between adiponectin and both TG and VLDL further supports this relationship, although it did not reach statistical significance, possibly due to sample size limitations. Similarly, visfatin showed a significant negative correlation with both TG and VLDL ($p<0.05$, Table 6), suggesting that reduced levels of both adipokines may contribute to the atherogenic dyslipidemia characteristic of hypothyroidism.

TSH was correlated significantly but with weak positive correlations with LDL-C (ρ=0.298, p=0.012) and total cholesterol (ρ=0.243, p=0.041), but not with adipokines (Table 6). Our finding is consistent with many studies, such as that reported by Wang *et al.*,[27] who found that lipid abnormalities emerge even with TSH values at the upper end of the normal range, becoming more pronounced in subclinical and overt hypothyroidism. The biochemical mechanism involves decreased LDL receptor activity, resulting in the reduced catabolism of LDL and intermediate-density lipoproteins(28). Moreover, thyroid hormones influence cholesterol production through hepatic HMG-CoA reductase regulation.[29] The absence of direct correlations between TSH and adipokines suggests that the adipokine alterations in hypothyroidism may not be directly driven by TSH itself, but rather by broader metabolic disturbances associated with the hypothyroid state, including changes in adipose tissue biology and insulin sensitivity. In contrast to the negative association commonly found in patients with obesity and type 2 diabetes.[30] Our hypothyroid group showed a significant positive correlation between visfatin and adiponectin levels (ρ=0.533, $p<0.001$). This is counterintuitive, as visfatin is largely considered pro-inflammatory while adiponectin is anti-inflammatory; they are often inversely correlated.[31] However, coordinated reduction and strong correlation suggest a potential common upstream regulator. This finding suggests that in the unique metabolic environment of hypothyroidism, these two adipokines may be subject to common regulatory influences rather than existing in a simple pro-inflammatory or anti-inflammatory.

Notably, this regulator is unlikely to be TSH itself, given the absence of significant correlations between TSH and either adipokine. We hypothesize that the profound metabolic derangements of overt hypothyroidism, including altered adipose tissue biology, insulin sensitivity, and energy metabolism, may shift the relationship between visfatin and adiponectin towards coordinated regulation. Similar coordinated responses have been observed in other distinct physiological states, such as normal pregnancy.[32] The BMI-adjusted nature of our analysis suggests that this finding is not merely a consequence of adiposity differences between groups.

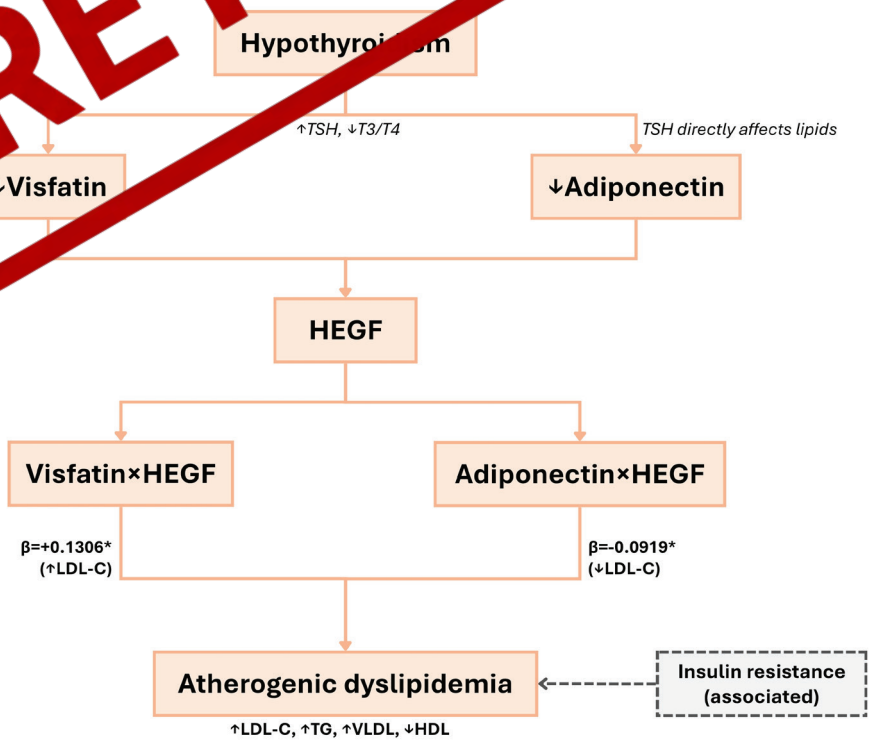
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Adiponectin emerged as the highest discriminative ability among the biomarkers studied, with an area under the curve (AUC) of 0.80 (Table 7 and Figure 1). Evaluating the diagnostic utility of these adipokines, our results demonstrated a moderate sensitivity of 81.7% and a modest specificity of 68.7%. While the sensitivity suggests these markers are reasonably capable of identifying metabolic alterations in hypothyroid patients, the specificity of 68.7% warrants cautious clinical interpretation. Crucially, this specificity translates to a false-positive rate of approximately 31.3%. In a practical clinical setting, utilizing adiponectin as a standalone diagnostic tool would result in nearly one-third of euthyroid individuals being incorrectly flagged for metabolic dysregulation. It should be utilized as part of a broader, comprehensive screening panel to aid in metabolic risk stratification alongside standard thyroid and lipid profiles. Its value likely lies in its ability to integrate information about thyroid dysfunction with downstream metabolic sequelae, including insulin resistance and inflammation.[33,34]

Regression analysis revealed significant interaction effects between specific adipokines and HEGF on LDL-C levels exclusively in the hypothyroid group. A statistically significant positive interaction was observed between visfatin and HEGF (β=0.1306, *p*=0.0188), indicating that high levels of this combination are associated with increased LDL concentrations. Conversely, a negative interaction was identified between adiponectin and HEGF (β=-0.0919, *p*=0.0062), signifying that this combination was correlated with reduced LDL-C levels (Table 8). A key finding of our study is the significant, disease-specific interaction between adipokines and HEGF on LDL-C levels. The significant interaction terms suggest that HEGF may influence the relationship between adipokines (both visfatin and adiponectin) and LDL-C metabolism, but only in the context of hypothyroidism. This raises the possibility that HEGF or the pathways it represents may function as a contextual factor in this setting.[35] In the euthyroid state, adipokine-HEGF interactions are quiescent. In the hypothyroid state, however, this axis becomes active, with HEGF potentially influencing both the visfatin-associated and adiponectin-associated effects on LDL-C.

Based on these findings, we propose a schematic mechanism summarizing the complex interplay between thyroid status, adipokines, and HEGF in hypothyroidism-associated dyslipidemia (Figure 2). In this proposed model, the hypothyroid state initiates reductions in both visfatin and adiponectin, which, together with HEGF, influence LDL-C metabolism through opposing interaction effects. This framework integrates our key observations and provides a visual hypothesis for how HEGF may act as a contextual influencing of adipokine function in the hypothyroid state, ultimately contributing to the observed atherogenic lipid profile.

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*p<0.05; interaction effects from multiple linear regression (adjusted for age, sex, BMI).

Figure 2. *Proposed schematic mechanism of adipokine-HEGF interactions in hypothyroidism-associated dyslipidemia.*

Limitations

There are several limitations of this study. Firstly, the case-control design precludes any conclusions about causality. Secondly, the BMI difference between groups to address this, we performed ANCOVA adjusting for BMI and age in all group comparisons (Table 4), and the significant differences persisted after adjustment. However, residual confounding cannot be entirely excluded, and future studies with BMI-matched controls would provide stronger evidence. Third, unmeasured confounders (insulin resistance, inflammation, lifestyle factors). Fourthly, the lack of interaction analyses for total cholesterol, triglycerides, and VLDL. Fifthly, the single-center design and modest sample size. Sixthly, the modest specificity of adiponectin and its implications; and finally, the exploratory nature of the HEGF findings and the need for validation in prospective studies.

Conclusion

In conclusion, this study demonstrates that overt, treatment-naive hypothyroidism is associated with significant metabolic dysregulation characterized by atherogenic dyslipidemia and marked reductions in serum visfatin and adiponectin levels even after controlling for differences in BMI and age. Furthermore, our findings highlight a potential interplay between altered HEGF expression and adipocyte dysfunction in the hypothyroid state, though these findings should be considered hypothesis-generating and require validation. However, given the modest sensitivity and modest specificity of visfatin and adiponectin should not be considered standalone diagnostic tools for metabolic complications.

Rather, a more cautious interpretation suggests they may serve as valuable adjunctive biomarkers, aiding in the broader metabolic risk stratification of hypothyroid patients. Future longitudinal and interventional studies are warranted to fully elucidate the prognostic value of these adipokines and to clarify the exact mechanistic pathways linking thyroid status, HEGF, and lipid metabolism.

Ethical approval

This study was approved by the Research Committee of the Thi-Qar Health Directorate, Training and Human Development Center (Approval No. 2025/20, dated January 14, 2025). The Committee confirmed compliance with ethical and scientific standards mandated by the Iraqi Ministry of Health and the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment. The fieldwork was authorized at Al-Rifae Teaching Hospital (Ref. No. 1642, dated January 14, 2025).

Conflict of interests

The authors have no conflicts of interest to declare relevant to the content of this article.

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CRediT authorship contribution statement

Murtadha Kareem Najim: conceptualization, methodology, investigation, formal analysis, writing: original draft, review and edit; **Abtisam Faris Al-Shukry**: investigation, resources, supervision, writing: review and edit.

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