

Diagnostic potential of circulating Meteorin-like protein in Graves' disease with subclinical hyperthyroidism subgroup analysis

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ABSTRACT

Background: Meteorin-like protein (Metrl) is an adipokine mostly produced and secreted by adipose tissue. Metrl is an adipokine that enhances insulin sensitivity, promotes the browning of adipose tissue, and increases energy expenditure.

Objectives: This study aimed to investigate alterations in serum Metrl levels in patients with Graves' disease (GD) and subclinical hyperthyroidism (SCH), with the objective of assessing its potential as a diagnostic biomarker.

Materials and methods: This case-control study was matched for age, sex, and BMI and included 40 patients with GD, 40 with SCH, and 80 controls. The average ages of the participants ranged from 22 to 59 years. Samples were obtained from July 2025 to January 2026. Metrl levels were measured using a sandwich enzyme-linked immunosorbent assay. T4 and TSH levels were evaluated using the VIDAS system (bioMérieux), whereas thyroid-stimulating hormone receptor antibodies (TRAb) were detected using the Roche Cobas e411 Analyzer. The Roche Cobas c111 Analyzer was employed to evaluate lipid profiles.

Results: The mean serum Metrl levels in the control group were 11.7 ± 1.9 ng/mL. In contrast, patients with GD had a significantly elevated mean Metrl level of 22.1 ± 2.3 ng/mL ($p < 0.001$). The SCH group had a markedly elevated mean concentration of 22.4 ± 2.8 ng/mL ($p < 0.001$) compared to the control group. Serum concentrations of TSH, total cholesterol, triglycerides, LDL, and VLDL were markedly reduced in both GD and SCH relative to controls ($p < 0.001$). T4 and TRAb levels were significantly elevated in GD and SCH compared with controls ($p < 0.001$).

Conclusion: Elevated levels of Metrl in Graves' disease suggest its potential as a new biomarker for diagnosis and evaluation of metabolic risks, alongside conventional thyroid function tests.

Introduction

Thyroid hormones are essential regulators of metabolism, growth, and development, and thyroid dysfunction can disrupt multiple physiological systems.¹ Graves' disease (GD) is the most common cause of hyperthyroidism and is an autoimmune disorder characterized by stimulation of the thyroid gland and excessive thyroid hormone production, with potential involvement of extra-thyroidal tissues such as the eyes and skin.² It is more common in women aged 30-60 years and results from genetic and environmental

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factors, with immune-related (T-cell) genes playing a key role.³ Subclinical hyperthyroidism (SCH) is defined by suppressed TSH levels with normal free T4 and free T3 concentrations, often with minimal or absent clinical symptoms. Both conditions represent important stages of thyroid dysfunction with clinical and metabolic significance.⁴

Meteorin-like protein (Metnrl) is an adipokine mostly synthesized and released by adipose tissue. Metnrl was first recognized in an early study as an adipokine, demonstrating pleiotropic effects on glucose homeostasis. These results included enhanced insulin sensitivity, increased browning of adipose tissue, and elevated energy expenditure.⁵ Metnrl, which is encoded by 936 base pairs and contains 311 amino acids, is located in regions of human chromosome 17q25.3. The small (~27 kDa) secreted protein is encoded by a gene called Meteorin-like (*METRNL*).⁶ Thyroid hormone is a vital regulator of energy balance, plays a key role in regulating basal metabolic rate, enables adaptive thermogenesis, and manages body weight through modulating food intake and energy expenditure.⁷ Excess thyroid hormone induces a hypermetabolic state marked by increased lipid mobilization, diminished cholesterol levels, weight loss, heat intolerance, and heightened energy expenditure. Thyroid hormones predominantly regulate metabolism by binding to thyroid hormone receptors α or β , thereby affecting white and brown adipose tissue. Moreover, research involving both humans and animals has demonstrated that elevated levels of thyroid hormone increase the expression of the uncoupling protein-1 (UCP-1) gene, thereby augmenting brown adipose tissue activity and facilitating the browning of adipose tissue.⁸

Recent studies have indicated that there is a complex link between adipokines, such as the newer adipokine Metnrl, and thyroid hormones in regulating metabolism. Thyroid hormones are known to control thermogenesis and basal metabolic rate, while adipokines are endocrine mediators that connect the liver, skeletal muscle, and adipose tissue to energy homeostasis.⁹ Accumulating evidence suggests that thyroid dysfunction may influence circulating Metnrl concentrations, potentially contributing to the metabolic alterations associated with hyperthyroidism. Metnrl is predominantly expressed in skeletal muscle and adipose tissue, and its secretion is regulated through several transcriptional pathways, particularly peroxisome proliferator-activated receptor gamma (PPAR γ) and PPAR γ coactivator-1 alpha (PGC-1 α). In hyperthyroid states, elevated thyroid hormone activity may stimulate PGC-1 α and PPAR γ signaling pathways, thereby promoting a hypermetabolic and catabolic state characterized by increased energy expenditure, enhanced lipid mobilization, and altered metabolic homeostasis. These metabolic adaptations may contribute to increased Metnrl expression.¹⁰ At the tissue level, thyroid hormone excess induces thermogenic

programming via upregulation of uncoupling protein-1 (UCP-1) and type 2 iodothyronine deiodinase (DIO2), leading to browning of white adipose tissue. This process increases mitochondrial density and enhances fatty acid oxidation, thereby accelerating whole-body energy turnover. Although these adaptations are generally associated with improved glucose utilization, persistent metabolic stress and altered adipokine signaling, including changes in Metnrl activity, may contribute to variability in insulin sensitivity.¹¹ Metnrl exerts several metabolic effects that may contribute to adipose tissue remodeling and energy homeostasis. Experimental evidence suggests that Metnrl enhances glucose uptake, promotes fatty acid oxidation, and improves insulin sensitivity in skeletal muscle through activation of peroxisome proliferator-activated receptor delta (PPAR δ)-dependent pathways and upregulation of AMP-activated protein kinase (AMPK), a key regulator of cellular energy metabolism. These metabolic actions share similarities with the physiological effects of thyroid hormones, which are known to increase thermogenic activity, stimulate oxidative phosphorylation, and enhance mitochondrial biogenesis.¹²

The relationship between thyroid hormone and Metnrl functions indicates a potential feedback or synergistic interaction, wherein changes in Metnrl expression and activity may partially regulate or enhance the thermogenic processes linked to hyperthyroidism. The weight loss commonly seen in hyperthyroid patients is due to increased energy expenditure and the associated stimulation of adipose tissue browning.¹³ However, persistent activation of these metabolically demanding pathways may aggravate protein-energy disequilibrium, thereby sustaining the hypermetabolic state characteristic of hyperthyroidism and promoting progressive catabolism of both skeletal muscle and adipose tissue. Within this metabolic context, the elevated circulating Metnrl concentrations observed in hyperthyroid conditions may reflect a compensatory adaptive response intended to mitigate metabolic stress and preserve insulin sensitivity. This interpretation is supported by experimental evidence demonstrating that Metnrl enhances insulin signaling, improves glucose homeostasis, and attenuates insulin resistance, as evidenced by favorable modulation of surrogate indices, such as the homeostatic model assessment of insulin resistance (HOMA-IR), in metabolic disease models.

Furthermore, Metnrl has been implicated in the regulation of lipid metabolism through stimulation of fatty acid oxidation and enhancement of lipid utilization pathways, suggesting a mechanistic association between thyroid hormone excess, altered lipid handling, and insulin resistance-related metabolic disturbances. Nevertheless, the precise molecular mechanisms underlying thyroid hormone-mediated regulation of Metnrl expression and

secretion remain insufficiently elucidated and require further mechanistic investigation.^{5,15} Thyroid hormone receptor-mediated transcriptional regulation and the indirect modulation of upstream regulators, such as PGC-1 α and inflammatory cytokines, are two potential mechanisms through which thyroid affects tissues that produce Metrnl. The elevation in metabolism may also arise from circulating catecholamines and heightened sympathetic nervous system activity associated with hyperthyroidism, both of which are recognized to enhance thermogenic gene expression.¹⁶

Serum levels of TSH, thyroid hormones, and TRAb serve as the mainstays for diagnosing GD and SCH; however, these biomarkers primarily reflect thyroid functional status instead of immune-metabolic alterations during disease development. In addition, measuring thyroid hormones is susceptible to physiological variation, hypothalamic-pituitary-thyroid feedback regulation, and analytical interference such as from high-dose biotin supplementation. Consequently, there is an increasing interest in identifying complementary circulating biomarkers that more accurately reflect disease-specific alterations in metabolism and inflammation. Metrnl, an immunometabolic adipokine may well be a potential candidate to supplement standard thyroid function tests and further elucidate the growing field of autoimmune thyroid disease.

Therefore, this study aims to comprehensively evaluate serum Metrnl levels in patients with Graves' disease and subclinical hyperthyroidism compared with healthy controls, to determine its association with thyroid function parameters, and to assess its diagnostic performance, as a supportive diagnostic indicator, in differentiating Graves' disease from healthy individuals using regression-based analysis. Additionally, the study explores its potential involvement in the early metabolic alterations observed in subclinical hyperthyroidism.

Materials and methods

Study design and participants

This case-control study was conducted following approval from the Institutional Review Board (IRB) of a medical college (Date: 10 March 2025; Ref. No. 217/3/2). All procedures were performed in accordance with institutional ethical standards and the principles of the Declaration of Helsinki. Verbal informed consent was obtained from all participants prior to enrollment. Sample collection was carried out at a tertiary care medical center, and laboratory analyses were performed in an academic biochemistry laboratory between July 2025 and January 2026. Participants were aged 22-59 years. The study included 40 patients diagnosed with Graves' disease and 40 patients with subclinical hyperthyroidism, recruited by an endocrinologist. Additionally, 80 age- and gender-matched individuals were enrolled as a control group.

Inclusion criteria

Participants were eligible for inclusion if they matched the following criteria:

1. GD was diagnosed based on suppressed TSH levels, elevated total thyroxine (T4), and positive TRAb. Only patients presenting with overt hyperthyroidism at the time of evaluation were included. All cases were newly diagnosed and had not received any prior treatment.
2. SCH is characterized by suppressed TSH levels with total T4 within the laboratory reference range and clinical signs and symptoms. In the present study, SCH was classified based on TSH and total T4 due to resource limitations and the unavailability of free thyroid hormone measurements. All included patients were newly diagnosed and had not received any prior treatment at the time of enrollment.
3. The control group exhibited normal thyroid function testing, with TSH and T4 levels within reference limits, and no known thyroid disease.

Exclusion criteria

Participants were excluded if they had diabetes mellitus, obesity, or other endocrine disorders; autoimmune diseases excluding thyroid disorders; chronic inflammatory, pulmonary (e.g., COPD), cardiac, renal, or hepatic diseases; malignancy or a history of thyroid cancer; pregnancy; current use of antithyroid, immunosuppressive, or anti-inflammatory medications, or mineral supplements; or an inability to provide informed consent.

Sample size calculation

The sample size was calculated a priori using G*Power software (version 3.1.9.4; Heinrich Heine University Düsseldorf, Germany).¹⁷ A one-way ANOVA (fixed effects, omnibus) was conducted, considering a modest effect size ($f=0.30$) in accordance with Cohen's guidelines.¹⁸ The required minimum sample size, with a significance level of 0.05 and 90% statistical power, was 144 people. To account for any dropouts and missing data, an extra 10% was included, giving a final target sample of 160 participants.

Calculation of body mass index

Body mass index (BMI) is a widely used measure of weight-for-height, calculated as weight (kg)/height (m^2) and classified according to WHO criteria.¹⁹

Sample collection and biochemical analysis

Morning fasting venous blood samples (5 mL) were obtained from each participant and then placed into gel tubes. Samples were centrifuged at 3,000 rpm for 10 minutes to isolate serum. One mL of serum was used for lipid profile analysis, while 1.5 mL was allocated to thyroid function testing, including TSH, T4, and TRAb.

The residual serum was divided into microcentrifuge tubes and stored at -20 °C until analysis. TSH and total T4 were selected because they represent the routine thyroid function tests available in our institution during the study period.

Serum Metrnl concentrations were measured using a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kit (MyBioSource, USA) according to the manufacturer's instructions. The standard calibration curve range was 0.05-15 ng/mL, with a minimum detectable concentration (analytical sensitivity) of 0.023 ng/mL. To ensure measurement accuracy and assay linear range, serum samples exceeding the upper limit of the standard curve were appropriately diluted and re-measured. Final concentrations were calculated by applying the corresponding dilution factors. All samples were analyzed in duplicate, and internal quality control procedures recommended by the manufacturer were followed to ensure assay precision and reproducibility.

TSH and T4 were assessed using the VIDAS automated immunoassay system (bioMérieux, France), based on a solid-phase enzyme-linked fluorescent immunoassay (ELFA) with fluorescence signal detection following antigen-antibody binding. TRAb levels were measured using the Roche Cobas e411 Analyzer (Roche Diagnostics, Germany), which employs a chemiluminescent immunoassay (CLIA) with signal generation through chemiluminescent reaction.

Lipid profile parameters, including total cholesterol (TC), triglycerides (TG), HDL-C, and LDL-C, were analyzed using enzymatic colorimetric methods on the Roche Cobas c111 Analyzer (Roche Diagnostics, Germany).

VLDL-C was estimated using the Friedewald-derived formula ($VLDL-C = TG/5$, mg/dL).

Statistical analysis

Statistical analysis was conducted using the IBM SPSS statistical software program (version 25.0; IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was applied to evaluate the normality of data distribution. Descriptive statistics were employed to summarize the data. Comparisons between the three study groups (GD, SCH, and control) were performed using one-way analysis of variance (ANOVA) for normally distributed variables, followed by Tukey's post hoc test for multiple comparisons. Spearman's correlation coefficient (r) was determined to assess the relationships between variables. Statistical significance was established at $p < 0.05$.

Results

No significant differences were seen in age, sex distribution, or BMI among the GD, SCH, and control groups (all $p > 0.05$), providing suitable baseline comparability between the groups. Serum T4 and TRAb levels were significantly higher in both GD and SCH patients than in healthy controls (both $p < 0.001$), whereas TSH levels were significantly decreased in the patient groups ($p < 0.001$). Regarding lipid metabolism, total cholesterol (TC), triglycerides (TG), HDL-C, LDL-C, and VLDL-C levels were significantly lower in patients with GD and SCH than in controls (all $p < 0.001$). Metrnl levels were significantly elevated in both the GD and SCH groups compared to controls ($p < 0.001$). No significant difference was seen between GD and SCH patients ($p = 0.812$) (Figure and Table 1).

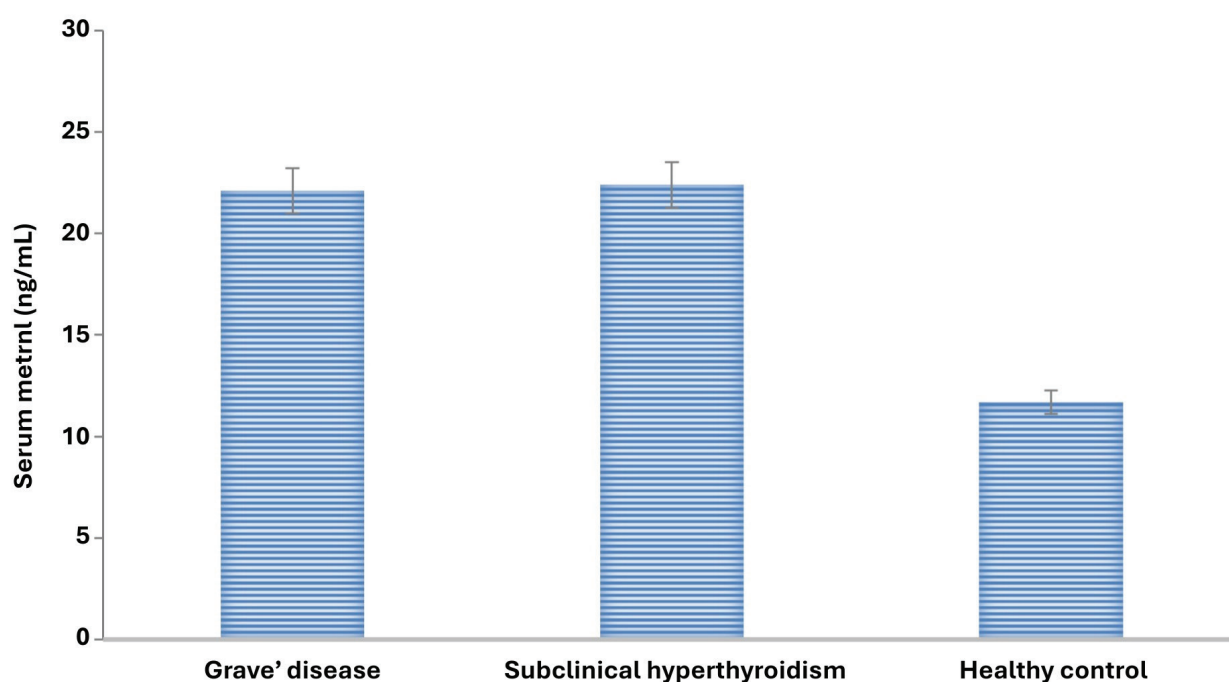


Figure 1. Serum Metrnl concentrations in GD, SCH, and control groups.

Table 1. Demographic, biochemical parameters and serum Metrnl levels in GD, SCH, and control groups.

Parameter	GD (N=40)	SCH (N=40)	Control (N=80)	p value
Sex (M/F)	19/21	18/22	34/46	0.980
Age (years)	39.20±8.10*	41.40±8.30*	39.80±10.80**	0.975
BMI (kg/m ²)	23.90±2.80*	24.20±3.10**	23.70±2.90*	0.680
T4 (nmol/L)	204.00±17.20*	147.50±10.20**	81.50±9.10***	<0.001
TSH (mIU/L)	0.02±0.01*	0.15±0.04**	2.28±0.73***	<0.001
TRAb (IU/L)	11.78±5.76*	2.33±0.52**	0.54±0.33***	<0.001
TC (mg/dL)	160.60±8.90*	166.80±6.70**	194.00±17.40***	<0.001
TG (mg/dL)	92.60±11.30*	98.40±6.10**	114.70±16.70***	<0.001
HDL-C (mg/dL)	38.70±4.00*	41.50±3.10**	51.80±5.80***	<0.001
LDL-C (mg/dL)	105.30±12.20*	108.10±7.70*	124.20±8.30**	<0.001
VLDL-C (mg/dL)	13.80±1.00*	19.60±1.30**	23.00±3.40***	<0.001
Metrnl (ng/mL)	22.10±2.30*	22.40±2.80*	11.70±1.90**	<0.001

Note: Data are presented as mean±SD or number (N). Group comparisons were performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for continuous variables and the chi-square test for categorical variables. *, **, ***statistically significant differences between groups ($p<0.05$). A $p<0.05$ was considered statistically significant. BMI: body mass index, T4: thyroxine, TSH: thyroid-stimulating hormone, TRAb: thyroid-stimulating hormone receptor antibodies, TC: total cholesterol, TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, VLDL-C: very-low-density lipoprotein cholesterol, Metrnl: meteorin-like protein.

Spearman correlation analysis showed no statistically significant associations between serum Metrnl and thyroid function tests (all $p>0.05$), indicating that Metrnl reflects the hyperthyroid state independently of hormonal levels.

Serum Metrnl levels showed no statistically significant association with SCH (OR=1.13, 95% CI: 0.99-1.31, $p=0.081$). However, Metrnl showed a significant positive association with GD, with an Odds Ratio of 1.706 (95% CI: 1.35-2.15, $p<0.001$), as shown in Table 4.

Table 4. Logistic regression analysis of serum Metrnl and thyroid function markers as predictors of subclinical hyperthyroidism and Graves' disease.

Variable	SCH		GD	
	OR (95% CI)	p value	OR (95% CI)	p value
Metrnl (ng/mL)	1.13 (0.99-1.31)	0.081	1.706 (1.35-2.15)	<0.001
T4 (nmol/L)	1.10 (1.06-1.14)	<0.001	1.745 (1.35-2.25)	<0.001
TSH (mIU/L)	0.09 (0.03-0.32)	<0.001	2.40 (1.62-3.55)	<0.001
TRAb (IU/L)	4.77 (2.05-11.08)	<0.001	1.186 (1.10-1.28)	<0.001

ROC curve analysis showed that serum Metrnl differentiated Graves' disease patients from healthy controls more clearly than SCH patients (Figures 2 and Figure 3). In Graves' disease, the AUC was 0.989 (95% CI: 0.950-0.999, $p<0.0001$), with a sensitivity of 100%

and specificity of 97.5% at a cutoff value of >14.82 ng/mL. In SCH patients, the AUC was 0.913 (95% CI: 0.847-0.957, $p<0.0001$), with a sensitivity of 92.5% and specificity of 85.0% at a cutoff value of >14.50 ng/mL.

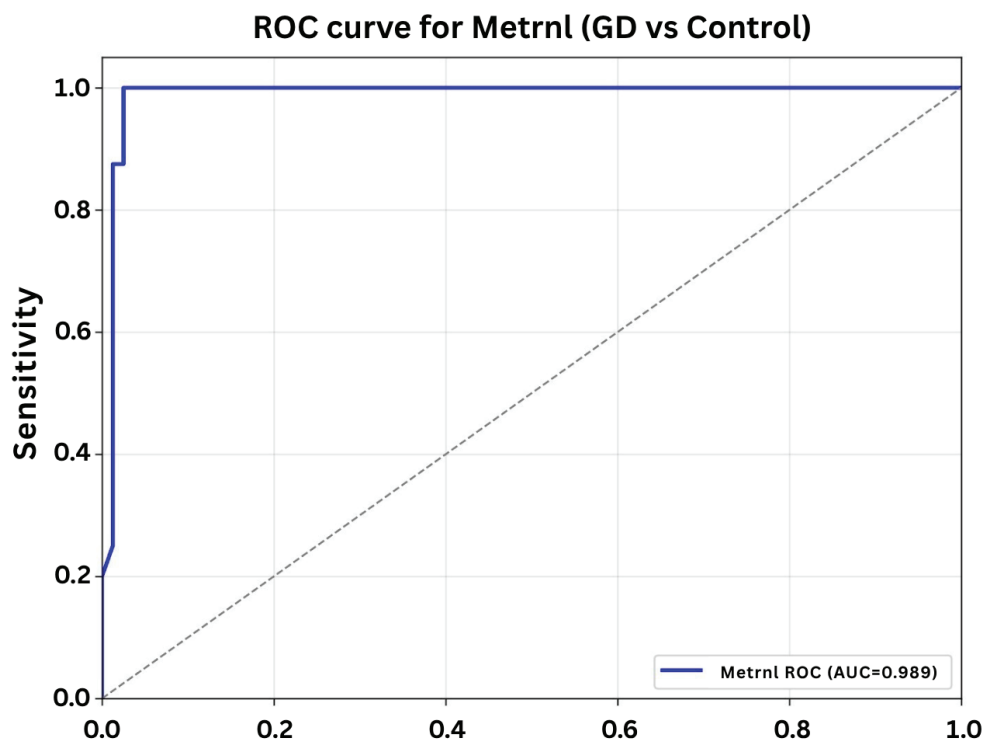


Figure 2. ROC curve of Metrnl for discrimination between GD and control groups.

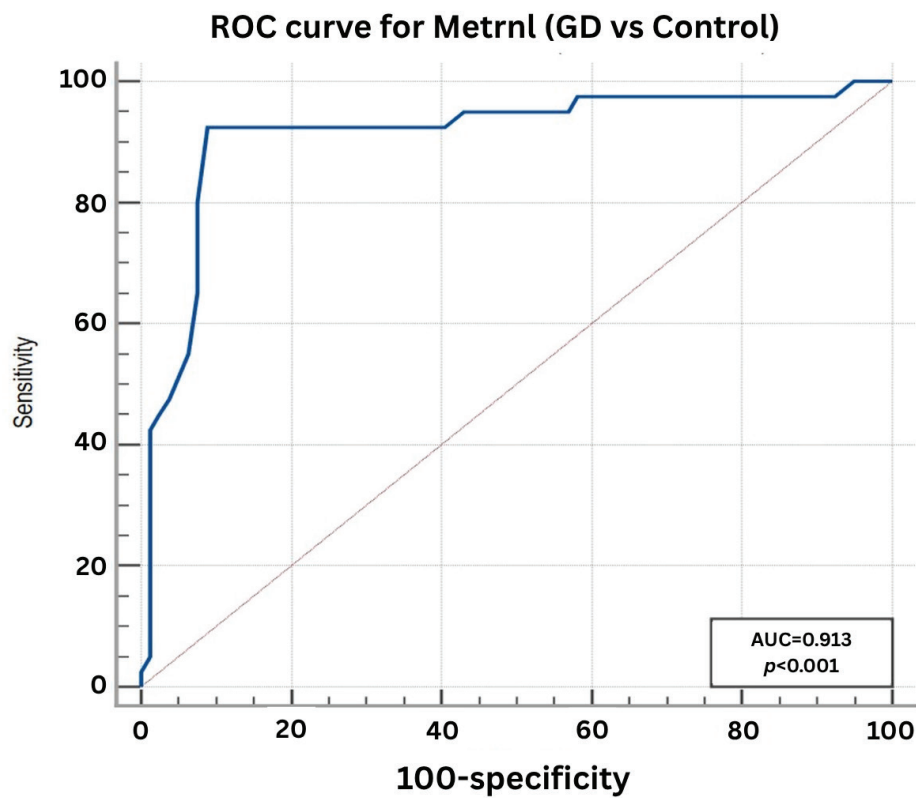


Figure 3. ROC curve of Metrnl for discrimination between SCH and control groups.

Discussion

The present study shows that circulating Metrnl levels are significantly elevated in patients with Graves' disease and subclinical hyperthyroidism compared to healthy controls. Significantly, no significant difference was detected between GD and SCH, indicating that Metrnl increase can appear early in thyroid overactivity and isn't just affected by the autoimmune aspect of Graves' disease.

These findings largely agree with those of Wen *et al.*, who observed elevated circulating Metrnl levels in newly diagnosed, untreated hyperthyroid patients, showing strong correlations with FT3 and FT4 and an inverse relationship with TSH.¹³ In contrast to their findings, the present study did not identify significant relationships between Metrnl and thyroid function markers (T4, TSH, or TRAb). This gap might result from methodological variations, specifically the inclusion of total T4 instead of free thyroid hormone fractions, which more closely represent biologically active hormone levels. Differences in study demographics, disease severity, sample size, and uncontrolled contributing factors could clarify the varying findings.

The absence of significant correlations in the current study indicates that Metrnl does not directly represent circulating thyroid hormone levels. It could indicate metabolic or inflammatory changes associated with hyperthyroidism, especially in Graves' disease. Additional research is required to explain the conditions under which Metrnl and thyroid function parameters may be mechanistically associated.

The lack of direct associations between Metrnl and circulating thyroid hormones in the present study suggests that Metrnl may not directly reflect hormonal excess, but rather a secondary metabolic and inflammatory response associated with hyperthyroid states. The elevated circulating Metrnl levels observed in GD and SCH may therefore be attributed to metabolic and inflammatory alterations induced by thyroid hormone excess. Thyroid hormones are key regulators of thermogenesis, mitochondrial function, and lipid metabolism, and may enhance the activation of PGC-1 α and PPAR-related signaling pathways that regulate Metrnl expression in skeletal muscle and adipose tissue. Moreover, thyroid hormone excess promotes adipose tissue browning and adaptive thermogenesis through increased mitochondrial biogenesis and upregulation of thermogenic mediators, processes in which Metrnl has also been implicated. In addition, the chronic low-grade inflammatory milieu characteristic of GD may further contribute to altered Metrnl secretion through immune-metabolic interactions.

The observed elevation of Metrnl in SCH further suggests that these metabolic alterations may occur during the early stages of thyroid overactivity, even prior to the development of overt clinical manifestations. Nevertheless, the precise molecular mechanisms underlying thyroid hormone-mediated regulation of

Metrnl expression and secretion remain incompletely elucidated and warrant further investigation.

This interpretation is supported by the comprehensive conceptual framework described by Dong *et al.*, which focuses on the relationship among Metrnl signaling, thyroid hormone pathways, and the hypothalamic-pituitary-thyroid axis in the regulation of thermogenesis and systemic energy expenditure.²⁰

Gong *et al.* demonstrated significantly reduced Metrnl levels in patients with Graves' disease compared to healthy controls, making it the only study to report an inverse trend.²¹ Variations in immunological activity, treatment status, demographic variables, or test variability could be responsible for this variance. Considering the dual metabolic and immunomodulatory characteristics of Metrnl, it is likely that its circulating levels are affected by the fluctuating equilibrium between metabolic activity and autoimmune-mediated inflammation in thyroid disease.

Collectively, the present findings suggest that circulating Metrnl levels are altered in hyperthyroid states and may reflect broader metabolic and inflammatory disturbances rather than thyroid hormone excess alone. The elevation of serum Metrnl observed in both Graves' disease and subclinical hyperthyroidism may indicate that alterations in Metrnl secretion occur during the early phases of thyroid overactivity. Given the recognized role of Metrnl in energy homeostasis and lipid metabolism, the observed changes in circulating Metrnl may represent an adaptive metabolic response to the hypermetabolic and inflammatory milieu associated with thyroid overactivity.

Therefore, serum Metrnl may serve as a complementary biomarker for distinguishing patients with Graves' disease from healthy individuals, while also providing additional insight into the metabolic and inflammatory alterations associated with subclinical hyperthyroidism.

Limitations

Several limitations must be considered. The limited sample size and cross-sectional design prevent causal inferences between circulating Metrnl levels and hyperthyroid conditions, such as Graves' disease. The assessment of longitudinal changes in Metrnl post-treatment was not conducted. Another limitation of the present study is that free thyroid hormones (fT4 and fT3) were not measured due to laboratory and resource constraints, and only total T4 was available for analysis. This may have reduced the precision of thyroid functional assessment, particularly in identifying isolated T3-toxicosis or mild thyrotoxic states. Nevertheless, the diagnosis of Graves' disease and subclinical hyperthyroidism was established based on clinical evaluation in combination with TRAb measurements and suppressed TSH levels, which strengthened the diagnostic classification of the study groups. Body composition measures, such as body fat percent-

age, were not assessed, despite Metrnl acting as an adipomyokine and potentially being affected by metabolic tissue distribution. The single-center design may restrict the generalizability of these results. Consequently, extensive multicenter longitudinal investigations with thorough metabolic and hormonal assessments are necessary to confirm these findings.

Conclusion

The results of this study indicate that circulating Metrnl may serve as a potential biomarker for differentiating patients with Graves' disease and subclinical hyperthyroidism from healthy individuals. The observed variations in circulating Metrnl levels in these conditions indicate a possible association between thyroid dysfunction and Metrnl regulation. Due to its established involvement in energy metabolism, adipose tissue function, and inflammatory signaling, Metrnl may indicate underlying metabolic and immunological changes associated with thyroid hormone dysregulation. However, larger prospective and mechanistic studies are required to further validate its diagnostic utility and to clarify the biological pathways linking Metrnl to thyroid dysfunction.

Ethical approval

The study was performed according to the ethical standards of the Declaration of Helsinki and received approval from the Research Ethics Committee/ Institutional Review Board (IRB) of a medical college (Date: 10 March 2025; Ref. No. 217/3/2). All participants provided verbal informed consent prior to their involvement in the study.

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Data availability

Data can be provided upon request from the authors.

Declaration of generative AI and AI-assisted technologies

In the writing of this paper, the authors utilized Gemini (Google LLC, Mountain View, CA, USA) to enhance language and readability. The tool was used exclusively in the introduction and discussion phases. After utilizing this tool, the authors checked and updated the content as required and accepted full responsibility for the finished article.

Conflict of interest

The authors declare that they personally have no competing interests, whether financial or otherwise.

CRedit authorship contribution statement

Sajjad Kadhim Ashour: conceptualization, methodology, formal analysis, investigation, data curation, visualization, writing: original draft, review and edit; **Mohammed Imran Hamzah:** supervision,

conceptualization, methodology, validation, writing: review and editing; **Mahmood Shakir Khudhair:** clinical supervision, patient diagnosis, investigation, resources, and writing: review and edit.

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