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Increased Serum Levels of Nesfatin-1 in Hyperthyroid and Hypothyroid Disorders

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ABSTRACT

Background and Objective: Thyroid disease has been associated with alterations in nesfatin-1 levels in some studies; however, the available data regarding nesfatin-1 levels and their relationship with thyroid disorders are limited and contradictory. Therefore, the aim of this study was to determine the relationship between nesfatin-1 and several factors, including thyroid hormones, thyroid-stimulating hormone (TSH), anti-thyroperoxidase (TPO), and anti-thyroglobulin (Tg) antibodies, in patients with these disorders.

Methods: In this cross-sectional study, conducted in Baqubah, Iraq, from January to May 2024, 40 patients aged 29-65 years were divided into two groups—hyperthyroid and hypothyroid—and compared with 20 healthy individuals serving as controls. Blood samples were collected. Serum nesfatin-1 levels were measured using enzyme-linked immunosorbent assay (ELISA), while anti-TPO and anti-Tg antibodies were assessed via electrochemiluminescence immunoassay (COBAS e 411). Additionally, T3, T4, and TSH were quantified using enzyme-linked fluorescence assay (ELFA) and subsequently compared across groups.

Findings: The results showed a significant increase in serum nesfatin-1 (16.21±0.89 vs. 4.24±0.96), T3 (3.61±0.60 vs. 1.37±0.20), T4 (171.34±4.75 vs. 89.16±3.15), anti-TPO (137.25±8.85 vs. 19.62±1.96), and anti-TG (131.44±3.58 vs. 65.34±2.29) in hyperthyroid patients compared to healthy controls. In contrast, serum TSH (0.06±0.008 vs. 3.02±0.26) and BMI (22.16±0.89 vs. 24.52±1.32) were significantly decreased in the hyperthyroid group ($p<0.05$). In hypothyroid patients, there was a significant increase in TSH (19.36±1.22 vs. 3.02±0.26), anti-TPO (225.23±9.24 vs. 19.62±1.96), anti-TG (169.45±5.28 vs. 65.34±2.29), and BMI (28.11±0.92 vs. 24.52±1.32), along with a significant decline in serum T3 (0.64±0.09 vs. 1.37±0.20) and T4 (54.53±2.31 vs. 89.16±3.15) relative to healthy controls ($p<0.05$).

Conclusion: The findings of the present study demonstrated that nesfatin-1 levels were increased in patients with either hyperthyroidism or hypothyroidism, suggesting that this peptide could function as a useful indicator in the context of thyroid pathology.

Keywords: *Nesfatin-1, Hypothyroid, Hyperthyroid, Thyroid Antibodies*.

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Introduction

Thyroid hormone plays a vital role in human metabolism. All bodily processes, including growth and development, metabolism, energy homeostasis, and temperature regulation, depend on it. Peripheral thyroid hormone exerts a strong influence on pituitary hormone levels. Large population-based studies have revealed prevalences ranging from 2% to 6% for thyroid function abnormalities, which are frequently diagnosed. Thyroid diseases, which result from either an overactive or underactive thyroid gland, are very common worldwide (1-3).

The N-terminal portion of the precursor protein NEFA/nucleobindin-2 (NUCB2) contains the peptide nesfatin-1, which is found in the hypothalamus, particularly in the paraventricular nucleus (PVN) (4). Thyroid function control is intimately linked to nesfatin-1, which has been found to colocalize with thyrotropin-releasing hormone (TRH) and to influence the membrane potential of TRH neurons in the PVN (5, 6). Interestingly, nesfatin-1 and ghrelin have been demonstrated to be co-expressed in gastric X/A-like endocrine cells, and Sawicka et al. observed that abnormal thyroid hormone levels are associated with altered ghrelin expression (7, 8). These results suggest that thyroid function and nesfatin-1 may maintain an intimate association. The findings of other investigations regarding alterations in nesfatin-1 levels in cases of thyroid dysfunction have been inconsistent (9-17).

The most common thyroid-related autoimmune disease is Hashimoto thyroiditis. Few investigations have examined the relationship between nesfatin-1 levels and thyroid autoimmunity (14). The anorexigenic peptide nesfatin-1 is responsible for regulating glucose homeostasis and suppressing appetite (4, 5, 18, 19). Thyroid hormones also influence metabolism and satiety, and there are some similarities between their mechanisms of action (5-7, 20). Therefore, it is plausible to consider the possibility that alterations in thyroid autoimmunity or changes in thyroid hormone status could result in altered nesfatin-1 levels. Thyroid diseases have been linked to variations in nesfatin-1 levels in some studies, but not in others.

Xu et al. demonstrated that among depressed patients with subclinical hypothyroidism, there was a positive correlation between nesfatin-1 and TSH. This may suggest a mechanism linking hypothalamic–pituitary–thyroid (HPT) axis dysfunction to the comorbidity of depression and subclinical hypothyroidism (17). Nesfatin-1 levels did not change significantly in another investigation involving patients with overt and subclinical hyperthyroidism (11); however, Tohma et al. (16) found that hyperthyroidism has a notable impact on nesfatin-1 levels. Nesfatin-1 exhibited a positive correlation with FT3 and FT4 and a negative correlation with TSH. After euthyroidism was restored, they noted a decrease in nesfatin-1 levels (16). The present investigation aimed to evaluate serum nesfatin-1 levels in patients with hypothyroidism and hyperthyroidism.

Methods

This cross-sectional study was approved by the scientific and ethical committees of the College of Medicine, University of Diyala, Iraq. The research was certified as compliant with the guidelines for ethical scientific research and was approved by the Institutional Review Committee (Code No.: 2025ESM918; 28 April 2025). The present study was conducted at Al-Ebtehal Private Laboratory between January 2024 and May 2024. The study population consisted of patients and healthy subjects aged 29 to 65 years. Forty individuals with thyroid disorders were divided into two groups: 20 patients with a known diagnosis of hyperthyroidism and 20 patients with a known diagnosis of hypothyroidism, who were matched with 20 healthy controls.

Individuals presenting with other medical conditions, including diabetes mellitus, hepatic disorders, renal disease, or cardiovascular disease, were excluded from participation in the study to minimize potential confounding effects on the measured parameters. For each participant, a 5-mL peripheral blood sample was collected. The blood samples were then subjected to centrifugation at 3000 rpm for 15 minutes, and the resulting serum was stored at -80°C until the time of analysis. Serum levels of nesfatin-1 were measured using the enzyme-linked immunosorbent assay (ELISA) technique. Anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies were quantified using electrochemiluminescence technology on a COBAS e 411 analyzer. Serum concentrations of triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH) were determined using an enzyme-linked fluorescent assay (ELFA).

Statistical analysis was performed using SPSS software (version 24) with the ANOVA test, and statistical significance was defined as a two-tailed $p<0.05$. All data were expressed as mean ± standard deviation (SD).

Results

Sixty participants were recruited for this case-control investigation. The mean age of hypothyroid patients was 38.87±1.51 years, that of hyperthyroid patients was 37.89±1.57 years, and that of controls was 38.71 ± 0.81 years. The participants were divided into three groups: a hyperthyroid group (n=20; 7 males and 13 females), a hypothyroid group (n=20; 6 males and 14 females), and a healthy control group (n=20; 7 males and 13 females). The findings showed no significant differences in age, whereas significant differences in BMI were observed between hypothyroid and hyperthyroid patients and healthy individuals, as shown in Table 1.

Table 1. Anthropometric measurements and serum levels of nesfatin-1, T3, T4, TSH, anti-TPO, and anti-TG in patient groups and healthy control subjects

Variables	Control (n=20)	Hypothyroid (n=20)	Hyperthyroid (n=20)
	Mean±SD	Mean±SD	Mean±SD
Age (year)	38.71±0.81	38.87±1.51	37.89 ±1.57
Nesfatin-1 (ng/dl)	4.24±0.96	10.82±1.07[a]	16.21±0.89[a, b]
T3 (nmol/l)	1.37±0.20	0.64±0.09[a]	3.61±0.60[a, b]
T4 (nmol/l)	89.16±3.15	54.53±2.31[a]	171.34±4.75[a, b]
TSH (µIU/ml)	3.02±0.26	19.36±1.22[a]	0.06±0.008[a, b]
Anti-TPO (U/L)	19.62±1.96	225.23±9.24[a, b]	137.25 ±8.85[a]
Anti- TG (U/L)	65.34±2.29	169.45±5.28[a, b]	131.44±3.58[a]
BMI (Kg/ m^2)	24.52±1.32	28.11±0.92[a]	22.16 ±0.89[a, b]

[a] p<0.05 versus control, [b] p<0.05 versus hypothyroid group

Table 1 also presents the findings for all patients with hyperthyroidism and hypothyroidism, in addition to the healthy subjects. According to the findings, nesfatin-1 levels were significantly higher in patients with hyperthyroidism and hypothyroidism than in healthy subjects ($p<0.05$), as shown in Figure 1.

Additionally, serum levels of T3, T4, anti-TG, and anti-TPO were significantly elevated, while a significant decline in TSH and BMI values was observed in the hyperthyroid group relative to the control group ($p<0.05$). Conversely, serum levels of TSH, anti-TG, anti-TPO, and BMI were all significantly increased, whereas serum levels of T3 and T4 were significantly decreased in the hypothyroid group compared with the control group ($p<0.05$).

Serum nesfatin-1 levels showed a significant negative association with serum TSH and BMI in the hyperthyroid group, while significant positive correlations with T3, T4, anti-TG, and anti-TPO were observed. In contrast, serum nesfatin-1 levels were positively and significantly correlated with TSH, anti-TG, anti-TPO, and BMI in the hypothyroid group, whereas notable negative associations were found between nesfatin-1 and T3 and T4, as shown in Table 2.

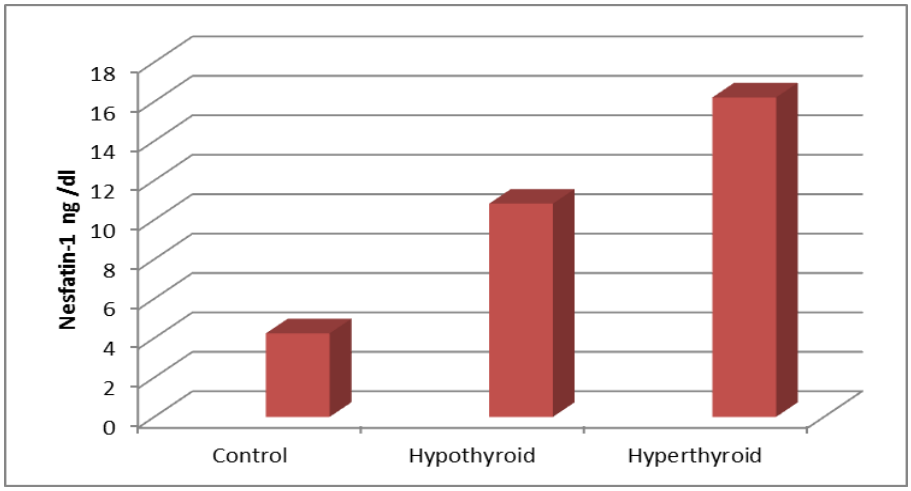

Figure 1. Differences in nesfatin-1 levels among hypothyroid patients, hyperthyroid patients, and controls

Table 2. Correlation between serum nesfatin-1 levels and all measured parameters

Variables	Hypothyroid	Hyperthyroid
T3 (nmol/l)	-0.86	0.91
T4 (nmol/l)	-0.88	0.92
TSH (µIU/ml)	0.95	-0.93
Anti-TPO (U/L)	0.86	0.97
Anti-TG (U/L)	0.85	0.95
BMI (Kg/ m^2)	0.69	-0.51

Discussion

The results demonstrated a significant elevation in serum nesfatin-1 levels among patients with hyperthyroidism and hypothyroidism relative to healthy control participants.

In the current investigation, patients in the hyperthyroid group demonstrated significantly elevated serum levels of nesfatin-1, T3, T4, anti-TPO, and anti-TG, while TSH and BMI values were significantly lower compared with the healthy control subjects. In contrast, when the hypothyroid group was compared with the healthy control group, a significant increase was observed in TSH, anti-TPO, anti-TG, and BMI, accompanied by a significant reduction in both T3 and T4. These findings are in agreement with those of a prior study conducted on hyperthyroidism (15). However, the literature contains conflicting evidence: one investigation reported that circulating nesfatin-1 levels were suppressed in hyperthyroid patients (9), whereas another study found that serum nesfatin-1 levels remained unchanged (11). Additionally, Sahin et al. reported that nesfatin-1 levels exhibited almost no alteration in individuals with hypothyroidism when compared with an age- and BMI-matched healthy control group (14).

Metabolic alterations that influence fat mass are commonly observed in patients with thyroid disease. Hypothyroidism is typically associated with reduced thermogenesis and metabolic rate, as well as a modest increase in body weight. In the present study, BMI differed significantly between the two patient groups and the healthy controls. These findings are in conflict with those of a previous study that compared healthy subjects with hypothyroid patients (14).

In the current study, nesfatin-1 demonstrated a significant negative correlation with BMI in the hyperthyroid group, a finding corroborated by Tsuchiya et al. (21). Nesfatin-1 levels were also significantly positively correlated with T3 and T4, while TSH exhibited a significant negative correlation in hyperthyroid patients. These results are consistent with previous studies (11, 16).

In this study, nesfatin-1 levels were markedly influenced by both hyperthyroidism and hypothyroidism. The findings suggest that nesfatin-1 plays a key role in the body's metabolic regulatory systems and may represent a potential therapeutic target for metabolic disorders, particularly in patients with thyroid conditions. The relationship between nesfatin-1 and thyroid autoimmunity warrants further investigation with larger sample sizes.

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