Original Article

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Assessment of Serum Adropin Levels in Patients with Subclinical Hypothyroidism

Subklinik Hipotiroidili Hastalarda Serum Adropin Düzeyinin Araştırılması

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ABSTRACT

Objective: Subclinical hypothyroidism (SCH) is defined as elevated serum thyroid-stimulating hormone (TSH) levels with normal free thyroxine (FT4) and free triiodothyronine (FT3) levels. This study aimed to evaluate serum adropin levels in patients with SCH.

Methods: This prospective cross-sectional study included 41 patients with SCH and 43 euthyroid controls. Thyroid function tests, biochemical parameters, and serum adropin levels were measured using ELISA. The groups were statistically compared.

Results: No significant differences were observed between the groups regarding age, gender, or body mass index (p>0.05). Serum adropin levels were significantly lower in the SCH group compared to the control group (136.75±41.87 ng/mL vs. 220.65±64.93 ng/mL; p<0.001). A significant negative correlation was detected between adropin and TSH levels (r=-0.765; p<0.001), whereas no significant correlation was found with FT3 or FT4.

Conclusion: Serum adropin levels were significantly decreased in patients with SCH. Adropin may potentially serve as a biomarker for cardiometabolic risk assessment in SCH.

Keywords: Adropin, subclinical hypothyroidism, metabolic syndrome, insulin resistance

ÖZ

Amaç: Subklinik hipotiroidi (SKH), serum tiroid uyarıcı hormon (TSH) düzeylerinin yüksek, serbest tiroksin (FT4) ve serbest triiyodotironin (FT3) düzeylerinin ise normal olduğu bir durumdur. Bu çalışmanın amacı, SKH hastalarında serum adropin düzeylerini değerlendirmektir.

Yöntemler: Bu prospektif kesitsel çalışmaya 41 SKH hastası ve 43 ötiroid kontrol dahil edildi. Katılımcıların tiroid fonksiyon testleri, biyokimyasal parametreleri ve serum adropin düzeyleri ELISA yöntemi ile ölçüldü. Gruplar istatistiksel olarak karşılaştırıldı.

Bulgular: Gruplar arasında yaş, cinsiyet ve vücut kitle indeksi açısından anlamlı fark saptanmadı (p>0,05). SKH grubunda serum adropin düzeyi kontrol grubuna göre anlamlı olarak düşük bulundu (136,75±41,87 ng/mL'ye karşı 220,65±64,93 ng/mL; p<0,001). Adropin ile TSH arasında anlamlı negatif korelasyon saptandı (r=-0,765; p<0,001). FT3 ve FT4 ile anlamlı korelasyon izlenmedi.

Sonuç: SKH'li hastalarda serum adropin düzeyi anlamlı derecede düşüktür. Adropin, SKH'de kardiyometabolik riskin değerlendirilmesinde potansiyel bir biyobelirteç olabilir.

Anahtar Kelimeler: Adropin, subklinik hipotiroidi, metabolik sendrom, insülin direnci

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Introduction

The thyroid gland secretes thyroid hormones, which are crucial for the formation and growth of every physiological cell and for regulating metabolism (1). These metabolic effects at the tissue level are mediated by transmembrane transporters, deiodinases, and thyroid hormone receptors (2). Subclinical hypothyroidism (SCH) is characterized by normal peripheral free thyroxine (FT4) and free triiodothyronine (FT3) levels but an elevated serum concentration of thyroid-stimulating hormone (TSH). SCH affects approximately 4-20% of adults, with a higher prevalence in areas with iodine deficiency (3,4). The condition is found in 4-10% of the general population and 7-26% of the elderly, and it can progress to overt hypothyroidism (5-7). SCH is sometimes considered an early stage of hypothyroidism and has been associated with endothelial dysfunction, metabolic syndrome, insulin resistance, atherosclerosis, and cardiovascular diseases (CVD). By reducing nitric oxide (NO) synthesis and release, promoting the development of atheromatous plaque, and impairing endothelial function, research indicates that SCH may play a role in the development of ischemic heart disease (8). The liver and brain are the primary sites of expression for the peptide adropin, which is encoded by the *energy homeostasis-associated (ENHO)* gene. It is also generated in other organs, including the heart, kidneys, pancreas, and gastrointestinal tract (9). Adropin plays a key role in regulating endothelial function, reducing insulin resistance, limiting angiogenesis, and maintaining the balance of fats and carbohydrates. Low level of adropin levels have been linked to various metabolic and cardiovascular disorders, such as obesity, diabetes, hypertension, endothelial dysfunction, cerebrovascular diseases, and metabolic syndrome. Increased levels of adropin are associated with elevated NO levels that promote arterial stiffness via NO-dependent signaling (10,11). Given their associations with chronic conditions like diabetes, CVDs, and endothelial dysfunction, the possible link between SCH and serum adropin levels merits more research. There aren't many studies that look into this relationship. The principal objective of our research is to ascertain whether patients with SCH have changed serum adropin levels and whether adropin may be a valuable intermediate marker for the pathophysiology and clinical outcomes of this condition.

Methods

Study Group

This prospective, cross-sectional, case-controlled study received approval from the Bezmialem Vakıf University Faculty of Medicine Ethics Committee (decision no: 2/16; reference no: E-71306642-050.05.04-9611, date: 24.02.2021). Every participant who took part in the study gave written informed consent.

Inclusion and Exclusion Criteria

The study enrolled 41 adult patients with SCH and 43 age- and gender-matched euthyroid individuals (controls) from the outpatient clinic at Bezmialem Vakıf University. SCH was diagnosed based on elevated TSH levels above the upper normal limit, with normal FT4 levels. To account for potential TSH fluctuations, measurements were repeated within 1-3 months. Participants with normal thyroid function test results were assigned to the healthy control group.

For patients with SCH, the TSH reference range was defined as 4-10 mIU/L, while euthyroid individuals were considered to have TSH levels <4 mIU/L. The laboratory reference ranges were as follows; TSH: 0.35-4.94 mIU/L; FT4: 9-19 pmol/L; and FT3: 2.42-6 pmol/L. Individuals aged ≤65 years were included. Exclusion criteria comprised diabetes mellitus, hypertension, CVD, use of medications affecting thyroid function (including steroids, amiodarone, and lithium), pituitary disorders, familial hyperlipidemia, renal or hepatic dysfunction, infectious diseases (local or systemic), neoplasms, inflammatory conditions (acute or chronic), alcohol or tobacco consumption, pregnancy, lactation and morbid obesity.

Blood Assay

Venous blood samples for biochemical and adropin analyses were collected from all participants in gel tubes between 08:00 and 09:00 AM following a 12-hour fasting period. The process of acquiring serum involved centrifuging the samples at a rotational speed of 3600 revolutions per minute for a duration of 10 minutes. Subsequently, the obtained serum samples were transferred into Eppendorf tubes and preserved at a temperature of -80 degrees celsius until the time of analysis. The levels of adropin in the serum were determined utilizing the Human Adropin ELISA Kit, manufactured by BTLab, China (E3231Hy). All participants had their weight and height measured; weight was expressed in kilograms and height in centimeters. The following formula was used to calculate the body mass index (BMI):

$$\boxed{\text{BMI} = \frac{[\text{weight (kg)}]}{[\text{height}^2(\text{m}^2)]}}$$ (12).

Statistical Analysis

The analysis of the data was done with SPSS (IBM Statistics v. 22 points 0). The mean and standard deviation were computed as descriptive statistics. One-way analysis of variance was utilized to compare multiple variables. For data that were normally distributed, Pearson's correlation analysis was used, and for data that were not, Spearman's correlation analysis was used. The threshold for statistical significance was set at $p<0.05$, with a 95% confidence interval.

Results

The mean age of the 84 volunteers included in the study was 36.48±11.99 years in the SCH group (male: 8; female: 33) and 33.97±9.65 years in the control group (male: 9; female: 34). In the SCH and the control groups,

the mean BMI was 24.62±4.04 kg/m² and 23.50±2.52 kg/m², respectively. According to Table 1, there were no statistically significant differences between the groups in terms of age or BMI (p>0.05). The TSH level was significantly higher in the SCH group (6.47±1.36 mIU/L) than in the control group (2.02±0.86 mIU/L) (p<0.001). However, no significant difference was observed in mean FT4 and FT3 levels between the groups (SCH group: 11.73±1.32 pmol/L, 4.48±0.75 pmol/L; control group: 12.24±1.26 pmol/L, 4.42±0.50 pmol/L, respectively) (p>0.05) (Table 1).

A statistically significant negative correlation was observed between adropin and TSH levels in the regression analysis (p<0.001). However, adropin levels did not show significant correlations with FT3 or FT4 levels (p>0.05) (Figure 1). Additionally, adropin levels were not significantly associated with age, BMI, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), or triglyceride (TG) levels (p>0.05) (Table 1). Similarly, regression analysis demonstrated an inverse relationship between adropin and TSH levels, while no meaningful correlations were identified with FT3, FT4, age, BMI, TC, LDL-C, or TG levels (p>0.05) (Table 1).

A significant decrease in serum adropin levels was observed in the SCH group (136.75±41.87 ng/mL) relative to the control group (220.65±64.93 ng/mL) (p<0.001) (Figure 1). Adropin levels were found to be low in patients with SCH. In hypothyroidism, energy expenditure decreases, metabolic rate decreases, and adropin synthesis is suppressed.

In SCH, NO synthesis decreases. Adropin protects endothelial function, and low levels may be both a cause and a consequence of endothelial dysfunction.

Routine biochemical measures showed no significant differences between the groups (p>0.05), according to Table 2.

Table 1. Comparison of TSH, FT3, FT4, adropin and other biochemical parameters in SCH group and healthy control subjects

	Group 1 SCH group n=41 mean ± SD	**Group 2 healthy control group n=43 mean ± SD**	**p-value**
Age (year)	36.48±11.99	33.97±9.65	0.293
BMI (kg/m²)	24.62±4.04	23.50±2.52	0.130
Glucose (mg/dL)	91.92±10.85	91.34±9.86	0.799
Creatinine (mg/dL)	0.73±0.11	0.75±0.16	0.497
ALT (U/L)	18.85±9.59	17.83±11.01	0.654
AST (U/L)	27.29±48.33	17.79±4.56	0.203
GGT (U/L)	26.04±17.89	20.04±18.19	0.132
ALP (U/L)	76.00±24.87	67.86±18.87	0.094
CK (U/L)	63.82±26.97	70.69±36.81	0.334
Ca (mg/dL)	9.18±0.47	9.31±0.25	0.130
FT3 (pmol/L)	4.48±0.75	4.42±0.50	0.674
FT4 (pmol/L)	11.73±1.32	12.24±1.26	0.075
TSH (mIU/L)	6.47±1.36	2.02±0.86	**<0.001***
HbA1c (%)	5.01±0.38	5.14±0.31	0.100
HOMA-IR	2.10±1.23	2.63±2.61	0.240
TC (mg/dL)	180.29±46.3	193.65±46.25	0.190
LDL-C (mg/dL)	107.80±35.54	122.90±44.03	0.088
Triglyceride (mg/dL)	117.29±68.68	112.48±70.03	0.752
Fe (µg/dL)	70.80±33.63	63.79±30.13	0.317
TIBC	312.02±56.15	337.48±60.12	0.057
WBC (10³/µL)	7394.63±2007.48	7601.44±1967.82	0.635
Hg (gr/dL)	12.81±1.48	12.85±1.55	0.907
HCT (%)	39.63±3.94	38.83±4.01	0.362
PLT (10³/µL)	258.75±69.24	250.60±50.83	0.548
Adropin (ng/mL)	136.75±41.87	220.65±64.93	**<0.001***

*: Statistically significant, SD: Standart deviation, BMI: Body mass index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamagglutamyl transferase, ALP: Alkaline phosphatase, CK: Creatine kinase, Ca: Calcium, FT3: Free thyroiodothyronine, FT4: Free thyroxine, TSH: Thyroid-stimulating hormone, HbA1c: Glycosylated hemoglobin, HOMA-IR: Homeostatic model evaluation-insulin resistance, TC: Total cholesterol, LDL-C: Low density lipoprotein cholesterol, Fe: Iron, TIBC: Total iron binding capacity, WBC: White blood cell, Hg: Hemoglobin, HCT: Hematocrit, PLT: Platelet

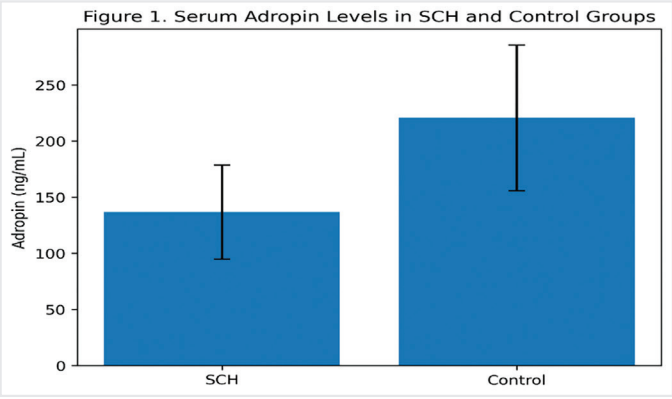

Figure 1. Adropin distribution according to groups
SCH: Subclinical hypothyroidism

Table 2. Evaluation of the relationship between adropin and age, BMI and laboratory results in the SCH and control groups

	Correlation coefficient (R)	p-value
Age	0.05	0.967
BMI	-0.141	0.202
Glucose (mg/dL)	0.015	0.891
Creatinine (mg/dL)	0.155	0.159
FT3 (pmol/L)	-0.033	0.765
FT4 (pmol/L)	0.075	0.496
TSH (mIU/L)	-0.765	**<0.001***
TC (mg/dL)	0.082	0.458
LDL-C (mg/dL)	0.118	0.284
Triglyceride (mg/dL)	-0.011	0.923
HOMA-IR	-0.089	0.419

*: Statistically significant; SCH: Subclinical hypothyroidism, BMI: Body mass index, FT3: Free thyroiodothyronine, FT4: Free thyroxine, TSH: Thyroid-stimulating hormone, TC: Total cholesterol, LDL-C: Low density lipoprotein cholesterol, HOMA-IR: Homeostatic model evaluation- insulin resistance

Discussion

This study evaluated serum adropin levels in patient with SCH and compared them with euthyroid controls. In addition, we investigated the relationship between adropin levels and anthropometric, metabolic, and biochemical parameters. To minimize potential confounding effects, the groups were closely matched in terms of age, gender, and BMI. No significant differences were observed between the groups regarding BMI, homeostatic model evaluation-insulin resistance, or HbA1c levels. Given the limited number of studies examining the association between SCH and adropin, our primary objective was to determine whether serum adropin levels differ in patients with SCH. We demonstrated a significant reduction in serum adropin levels in the SCH group, accompanied by a strong negative correlation between adropin and TSH levels. These findings suggest a potential interaction between thyroid function and adropin metabolism. Thyroid hormone receptors are present in vascular endothelial and myocardial tissues, indicating an important role of thyroid hormones in cardiovascular regulation. SCH has been associated with endothelial dysfunction, insulin resistance, dyslipidemia, and increased cardiovascular risk (13-17). Adropin, which regulates lipid and glucose homeostasis, has been shown to enhance endothelial nitric oxide synthase expression and support endothelial function. (9-11). Topuz et al. (18) found lower serum adropin levels in patients with type 2 diabetes mellitus (T2DM) with endothelial dysfunction, suggesting adropin as a marker for endothelial dysfunction. Similarly, Zang et al. (19) reported reduced adropin levels in overweight/obese patients with T2DM, linking it to insulin sensitivity and glucolipid homeostasis. Zheng et al. (20) found significantly lower adropin levels in patients with CAD, especially those with acute myocardial infarction or angina. Unlike previous studies, we focused on patients with SCH without chronic conditions such as hypertension, diabetes, or CAD. Serum adropin levels were 136 ng/mL in patients with SCH versus 229 ng/mL in controls, a significant difference consistent with prior findings. We propose that thyroid hormones influence *ENHO* gene expression in adropin-synthesizing tissues. Additionally, reduced adropin may contribute to CVD, insulin resistance, and endothelial dysfunction in SCH. Rezk and Atia (21) studied hypothyroid-induced rats and found significantly lower adropin levels in those that gained weight, along with increased LDL, very low-density lipoprotein (VLDL), and TGs. Adropin negatively correlated with LDL, VLDL, and TG, while positively correlating with HDL and FT3 (21). Unlike this study, our research focused on patients with SCH with similar BMI, finding no significant differences in lipid profiles, likely due to sample size limitations. Mogulkoc et al. (22) found lower adropin levels in both hypothyroid and hyperthyroid rats, suggesting thyroid dysfunction altered adropin metabolism. We hypothesize that SCH-related metabolic changes similarly affect adropin secretion through direct or indirect mechanisms. Akbaba et al. (23) compared adropin levels between patients with SCH, patients with overt hypothyroidism, and controls, finding lower adropin in hypothyroid groups, though not statistically significant. Overall, our findings support the hypothesis that thyroid function may influence adropin regulation through direct or indirect mechanisms. However, larger, multicenter studies are required to clarify the underlying molecular pathways and to determine whether adropin can serve as a reliable biomarker in patients with SCH.

Study Limitations

There are several limitations to our study. First, the study only included a small sample size and was carried out in one place, which might have limited how broadly the results could be applied. Second, there was an imbalance in gender distribution, with a higher number of female participants

compared to males. However, a strength of our study was that key demographic parameters, including age, gender, and BMI, were closely matched between the groups.

Conclusion

Patients with SCH had significantly lower serum adropin levels than the control group. This suggests that thyroid hormone levels may regulate adropin synthesis, possibly through direct or indirect effects on *ENHO* gene expression. Our hypothesis and objective is to determine whether adropin levels can be used as a marker for early detection of ischemic heart disease and metabolic heart disease in patients with SCH. Adropin can be useful in the early diagnosis and treatment of metabolic diseases that may develop as a precursor to hypothyroidism. Larger multicenter studies are needed to clarify the underlying mechanisms.

Ethics

Ethics Committee Approval: This prospective, cross-sectional, case-controlled study received approval from the Bezmialem Vakıf University Faculty of Medicine Ethics Committee (decision no: 2/16; reference no: E-71306642-050.05.04-9611, date: 24.02.2021).

Informed Consent: Every participant who took part in the study gave written informed consent.

Footnotes

Authorship Contributions

Design: T.Y.Y., M.Z., H.B., Data Collection or Processing: T.Y.Y., M.Z., Analysis or Interpretation: E.M.G., M.K., Literature Search: T.Y.Y., M.Z., E.M.G., Writing: T.Y.Y., M.Z.

Conflict of Interest: No conflict of interest was declared by the authors. This research is derived from the medical specialty thesis of Tuba Yılmaz Yıldırım.

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