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RESEARCH

Chemerin and Sfrp5 levels in subclinical hypothyroidism

Subklinik hipotiroidizmde chemerin ve Sfrp5 düzeyleri

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Abstract

Purpose: This study aimed to investigate the impact of subclinical hypothyroidism on chemerin and Sfrp5 levels.
Material and Methods: Forty-six individuals with subclinical hypothyroidism were enrolled in the patient group, and 49 healthy individuals were included as controls. Serum levels of chemerin and Sfrp5 were measured using the ELISA method. LDL cholesterol, total cholesterol, triglycerides, HDL cholesterol, insulin, and glucose levels were simultaneously measured in blood samples and obtained from patients' medical records.
Results: In the patient group, a statistically significant positive correlation was found between chemerin and Sfrp5 levels in the Spearman correlation analysis (r = 0.704). When both the patient and control groups were evaluated together, a significant positive correlation was observed between chemerin and Sfrp5 levels (r = 0.814). Additionally, negative correlations were found between Sfrp5 and LDL cholesterol, total cholesterol, triglycerides, body mass index, diastolic blood pressure, and systolic blood pressure (r = -0.320, r = -0.341, r = -0.278, r = -0.383, r = -0.230, and r = -0.206, respectively).
Conclusion: In subclinical hypothyroidism, chemerin, an inflammatory marker, tended to be elevated, while Sfrp5, an anti-inflammatory marker, tended to be reduced; however, these changes were not statistically significant. Further studies with larger sample sizes are needed to clarify the role of adipokines and inflammation in the development of subclinical hypothyroidism and to assess whether these parameters could serve as potential biomarkers.
Keywords:. Chemerin, Sfrp5, subclinical hypothyroidism

Öz

Amaç: Bu çalışmanın amacı subklinik hipotiroidizmin chemerin ve Sfrp5 düzeyleri üzerindeki etkisini araştırmaktır.
Gereç ve Yöntem: Subklinik hipotiroidi tanısı alan 46 birey hasta grubu, 49 sağlıklı birey ise kontrol grubu olarak çalışmaya katıldı. Serum Chemerin ve Sfrp5 düzeyleri ELISA yöntemiyle çalışıldı. Bireylerin eş zamanlı olarak alınan kanda çalışılan LDL kolesterol, total kolesterol, trigliserid, HDL kolesterol, insülin, glukoz düzeyleri ise hasta dosya bilgisinden alındı.
Bulgular: Hasta grubunda yapılan Spearman korelasyon analizinde Chemerin ve Sfrp5 düzeyleri arasında istatistiksel olarak anlamlı pozitif korelasyon tespit edildi (r = 0,704). Hasta ve kontrol grupları birlikte değerlendirilerek yapılan Spearman korelasyon analizinde ise, Chemerin ve Sfrp5 düzeyleri arasında anlamlı pozitif korelasyon bulunurken (r = 0,814) ; Sfrp5 ile LDL kolesterol, total kolesterol, trigliserid, vücut kitle indeksi, diyastolik kan basıncı ve sistolik kan basıncı değerleri arasında negatif korelasyonlar tespit edildi (r = -0,320, r = -0,341, r = -0,278, r = -0,383, r = -0,230, and r = -0,206, respectively).
Sonuç: Subklinik hipotiroidizmde inflamatuvar belirteç olan Chemerin düzeyinde artış, antiinflamatuvar belirteç olan Sfrp5 düzeyinde azalma olmasına rağmen bu değişiklik istatistiksel olarak anlamlı bulunmadı. Subklinik hipotiroidizm gelişiminde adipokinlerin ve inflamasyonun etkilerini ortaya koymak ve bu iki parametrenin biyobelirteç olarak kullanılıp kullanılmayacağını anlamak için daha fazla katılımcı ile yeni çalışmalara ihtiyaç vardır.
Anahtar kelimeler: Chemerin, Sfrp5, subklinik hipotiroidi

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INTRODUCTION

Thyroid gland disorders are among the most common endocrine abnormalities encountered by physicians. Patients with thyroid dysfunction often experience changes in weight, body temperature and adipose tissue. Thyroid hormones influence, and are influenced by, body weight, body fat mass, body temperature, insulin resistance, and glucose and lipid metabolism[1]. Subclinical hypothyroidism (SH) is the most common thyroid dysfunction[2]. This condition is characterized by elevated serum thyroid-stimulating hormone (TSH) levels above 4 mIU/L, with free T3 (FT3) and free T4 (FT4) levels remaining within reference ranges[3,4]. The prevalence of SH varies between 4-10%, depending on age and gender, and increases with age[5]. Women are affected twice as often as men[6]. While iodine deficiency is the most common cause of SH, other factors such as Hashimoto's thyroiditis, thyroid surgery, thyroid ablation, radiotherapy, and certain medications (e.g., lithium, amiodarone) are identified as underlying causes in individuals with adequate iodine intake[7]. Subclinical hypothyroidism is classified into two categories: mild SH (TSH levels between 4 and 10 mIU/L) and severe SH (TSH levels >10 mIU/L)[8]. Symptoms are often absent in patients with SH; however, potential consequences include cardiac dysfunction, atherosclerotic disease, increased LDL cholesterol levels, systemic hypothyroid symptoms, neuropsychiatric symptoms[13], and progression to overt hypothyroidism[9-15].

Chemerin, a recently discovered adipokine released from adipose tissue, has gained attention due to its metabolic effects. It binds to the G-protein coupled receptor CMKLR1, also known as Chem R23 or GPCR-DEZ. Chemerin is expressed in various organs, including adipose tissue, liver, kidney, pancreas, lungs, ovaries, and the pituitary gland[16]. Synthesized by adipose tissue, chemerin exerts both autocrine and paracrine effects. It promotes lipolysis and metabolic pathways through autocrine signaling, while also participating in the chronic low-grade inflammation associated with obesity via paracrine effects[17]. Chemerin's CMKLR1 receptor is present on neutrophils, activated macrophages, and dendritic cells and was initially identified as a chemotactic protein. Chemerin has been linked to adipogenesis, osteoclastogenesis, angiogenesis, metabolic syndrome (MetS), type 2 diabetes, arthritis, and Crohn's disease[18].

Secreted frizzled-related protein 5 (Sfrp5), another adipokine with anti-inflammatory properties, is produced by adipose tissue and has beneficial effects on metabolic functions. Initially discovered in retinal pigment epithelial cells and the pancreas, Sfrp5 is highly abundant in white adipose tissue, particularly in visceral fat[19,20]. In healthy individuals, Sfrp5 exerts anti-inflammatory effects by suppressing Wnt signaling through Wnt5a. In obese individuals, this balance is disrupted, leading to an increased Wnt5a/Sfrp5 expression ratio[21]. Metabolic dysfunction caused by Sfrp5 deficiency is associated with macrophage accumulation in adipose tissue and increased production of pro-inflammatory cytokines such as TNF and IL-6, while Sfrp5 overexpression inhibits the phosphorylation of JUN N-terminal kinase 1, a target of non-canonical Wnt signaling in adipocytes. Furthermore, Sfrp5 has been shown to inhibit macrophage-induced production of pro-inflammatory cytokines[22,23].

Given these findings, the relationship between adipokine release and thyroid dysfunction has attracted considerable attention. Although many studies have explored the connection between thyroid hormones and various adipokines, there is limited research investigating the relationship between Sfrp5 and chemerin levels and thyroid diseases. Therefore, this study aims to examine the role of the anti-inflammatory adipokine Sfrp5 and the inflammation marker chemerin in the pathogenesis of thyroid disorders.

MATERIALS AND METHODS

Sample

A power analysis was conducted based on data from a similar study, assuming a 5% Type I error rate and 80% study power. The calculated required sample size was 80 individuals (40 healthy controls and 40 patients)[24].

A total of 46 newly diagnosed SH patients, whose treatment had not yet started, and 49 individuals constituting the healthy control group, who were admitted to the Department of Internal Medicine, Division of Endocrinology and Metabolism Diseases at Ondokuz Mayıs University Faculty of Medicine between January 1 and December 31, 2020, were included in the study. Since SH is more commonly observed in women, only female individuals were included in our study[6]. The names, age, gender, date of diagnosis, blood pressure, waist circumference,

height, weight, and body mass index (BMI) of the participants were recorded on forms. Medical histories were obtained, and systemic physical examinations were performed on all participants.

The inclusion criteria for the study were that all participants should be women aged 18-65, the patients should have been diagnosed with subclinical hypothyroidism but not yet started treatment, and the control group should consist of healthy individuals without any thyroid dysfunction. Individuals under 18 or over 65 years of age, those with diseases that could cause inflammation (such as acute infectious diseases, malignancies, inflammatory rheumatic diseases), pregnancy, chronic kidney disease, diabetes mellitus, hypertension, acute or chronic liver diseases, those using medications such as glucocorticoids or non-steroidal anti-inflammatory drugs, and individuals who smoke or consume alcohol were excluded from the study.

Procedure

Ethical approval for this study was obtained from the Ondokuz Mayıs University (OMU) Faculty of Medicine Clinical Research Ethics Committee (OMU KAEK 2020/98) on February 28, 2020. The study materials and kits were funded by OMU BAP (PYO.TIP.1904.20.005). Informed consent was obtained from all participants.

The study was conducted in the Medical Biochemistry Laboratory of OMU Faculty of Medicine Hospital. All laboratory analyses were performed by the same team in accordance with standard procedures. The patient data used in the study were obtained from patient files by the relevant clinical physicians in accordance with the approval of the Ethics Committee of OMU Medical Faculty Hospital. All data were evaluated within the framework of confidentiality and ethical rules.

Blood samples were collected between 09:00 and 11:00 AM after a minimum of 12 hours of fasting to assess the biochemical parameters. Venous blood was drawn into gel biochemistry tubes, centrifuged at 4000 rpm for 5 minutes, and the serum was transferred to 1.5 ml microtubes. The samples were stored at -80°C in the Department of Medical Biochemistry, OMU Hospital, until the analysis was conducted.

Serum insulin, glucose, FT3, FT4, TSH, and lipid profile (total cholesterol, triglycerides, HDL cholesterol) were measured using the electrochemiluminescence method on the ROCHE COBAS 8000 device (e602 module) at the OMU Hospital Biochemistry Laboratory. Insulin was measured by chemiluminescence on the Immulite 2000 XPI device, and HOMA-IR was calculated using the formula: $\mathrm{HOMA-IR} = \frac{\text{Glucose (mg/dl)} \times \text{İnsülin (µU/mL)}}{405}$ [25].

Measurement of chemerin and Sfrp5 levels

Chemerin and Sfrp5 protein levels were determined using the ELISA method with commercial kits (Human Chemerin - BT LAB, Cat No: E1435Hu, Zhejiang, China; Sfrp5 - BT LAB, Cat No: E2186Hu, Zhejiang, China) and measured on a Synergy 4 spectrophotometric ELISA plate reader (BioTek Instruments Inc., USA) at a wavelength of 450 nm. Chemerin levels were expressed in ng/L and Sfrp5 levels in ng/mL.

Subclinical hypothyroidism classification

SH patients were classified based on their TSH levels: those with TSH levels between 4 and 10 mIU/L were placed in the mild SH group, while those with TSH levels >10 mIU/L were categorized in the severe SH group. All patients in our study were in the mild SH group[8].

Statistical analysis

The distribution of variables was assessed using the Shapiro-Wilk test**.** The Mann-Whitney U test was used for nonparametric variables (Sfrp5, Chemerin, Total cholesterol, HDL cholesterol, LDL cholesterol, TSH) while the Student's t-test was employed for parametric variables (FT3, FT4, triglycerides, glucose, insulin, HOMA-IR). Results outside the 95% confidence interval were excluded from the study. Data are presented as mean ± SD and median (range). A p-value <0.05 was considered statistically significant. All analyses were performed using SPSS 21.0 software**.** Correlations between serum Chemerin, Sfrp5 levels, and other parameters were analyzed using Spearman's correlation analysis, as the variables were nonparametric.

RESULTS

There was no statistically significant difference in the demographic data shown in Table 1 between the two groups ($p > 0.05$). When thyroid function tests were compared between the groups, a significant increase in TSH levels and a significant decrease in sT4 levels

were observed in the patient group ($p < 0.001$) (Table 2).

Serum Chemerin levels were 379 ± 206 ng/L in the SH group and 431 ± 246 ng/L in the control group. No statistically significant difference was observed between the SH and control groups in terms of serum Sfrp5 levels ($p = 0.248$) (Table 4) (Figure 1).

Serum Sfrp5 levels were 17±13 ng/mL in SH and 26±24 ng/mL in the control group. No statistically significant difference was observed between SH and control groups in terms of serum Sfrp5 levels ($p=0.248$) (Table 4) (Figure 2).

When the biochemical parameters (lipid panel, glucose, insulin levels, and HOMA-IR values were compared between the patient and control groups, no significant difference was found ($p > 0.05$) (Table 3).

The relationship between Chemerin and Sfrp5 levels and demographic and biochemical parameters was investigated in the patient group. A statistically significant positive correlation was found between Chemerin and Sfrp5 parameters in the patient group ($r=0.704$, $p<0.01$). However, the correlation between these adipokines and other parameters was not statistically significant (Table 5).

In the overall study group (patient + control), a strong positive correlation was found between Sfrp5 and Chemerin levels ($r = 0.814$, $p < 0.01$). In addition, statistically significant negative correlations were found between Sfrp5 and LDL cholesterol, total cholesterol, triglycerides, BMI, age, diastolic blood pressure, systolic blood pressure, and waist circumference ($r = -0.320$, $p < 0.01$; $r = -0.341$, $p < 0.01$; $r = -0.278$, $p < 0.01$; $r = -0.383$, $p < 0.01$; $r = -0.366$, $p < 0.01$; $r = -0.230$, $p < 0.05$; $r = -0.206$, $p < 0.05$, respectively). A statistically significant negative correlation was found between Chemerin and age in the overall study group ($r = -0.210$, $p < 0.05$) (Table 6).

Table 1. Demographic characteristics of the patient and control groups

Parameters	Patient (n=46) Mean ± SD	Control (n=49) Mean ± SD	Total (n=95) Mean ± SD
Age (year)	39.69 ± 13.69	39.26 ± 13.31	39.47 ±13.43
Height (cm)	162.65 ± 5.32	161.75 ± 6.91	162.18 ± 6.17
Weight(kg)	72.8 ± 16.08	68.3 ± 13.98	70.5 ± 15.12
BMI (kg/m²)	27.55 ± 6.17	26.31 ± 6.14	26.91 ± 6.15
WC (cm)	86.15 ± 14.2	80.4 ± 14.47	83.18 ± 14.57
SBP (cmHg)	11.95 ± 1.26	11.79 ± 1.20	11.87 ± 1.23
DBP (cmHg)	7.7 ± 0.8	7.75 ± 0.8	7.73 ± 0.8

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, WC: Weist circumference
SD: Standart Deviation

Table 2. Thyroid Function Test Values of Patient and Control Groups

	Patient (n=46)		Control (n=49)		P
	Median (min-max)	Mean±SD	Median (min-max)	Mean±SD	
TSH[2] (μIU/mL)	5.38 (4.30-9) [2]	5.9±1.43	1.98 (0.6-3.8) [2]	2.1 ± 0.85	<0.001
FT3[1] (pg/ml)	3 (1.42-4.17)	3.13±0.6 [1]	3.06 (2.1-4.2)	3.1 ± 0.5 [1]	0.82
FT4[1] (ng/dL)	1.13 (0.93-1.6)	1.16±0.2 [1]	1.31(0.16-1.3)	1.3 ± 0.16 [1]	<0.001

[1]: parametric [2]: nonparametric
HDL: High Density Lipoprotein, LDL: Low density lipoprotein SD: Standart Deviation, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance

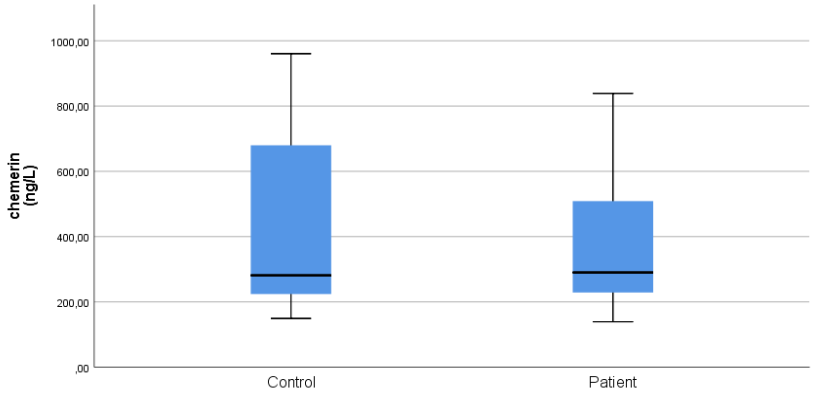

Figure 1. Chemerin levels in the patient and control groups

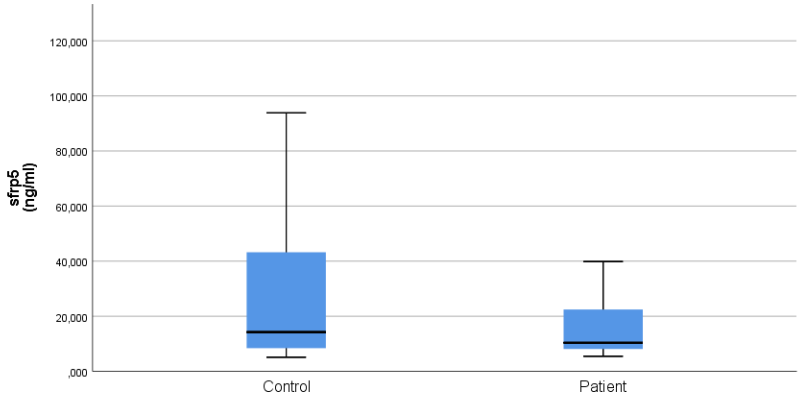

Figure 2. Sfrp5 levels in the patient and control groups

Table 3. Biochemical parameters of patient and control groups

	Patient (n:46)		Control (n:49)		
	Median (min-max)	**Mean±SD**	**Median (min-max)**	**Mean±SD**	
Total Cholesterol 2 (mg/dL)	187(116-328) [2]	196.4±48.3	177(79-288) [2]	179.9±46.6	0.09
HDL Cholesterol 2 mg/dL)	54.1(26.7-92) [2]	55.9±13.29	51.7(28-78) [2]	51.77±13	0.13
LDL Cholesterol 2 (mg/dL)	104(44-232) [2]	115 ± 43	100(20-203) [2]	106±38.2	0.29
Triglyceride1 (mg/dL)	109(43-405)	128±73 [1]	89(45-278)	110±55 [1]	0.24
Glucose1 (mg/dL)	94(56-118)	92±13 [1]	92(59-119)	92±12 [1]	0.68
İnsülin1 (µU/mL)	7(2-32)	8.7±5.9 [1]	7(2-64)	10.84±7.2 [1]	0.94
HOMA-IR1 (mg/dL)	1.75(0.28-8.13)	2±1.4 [1]	1.7(0.36-15)	2.44±1.55 [1]	0.98

1: parametric, 2: nonparametric HDL: High Density Lipoprotein, LDL: Low density lipoprotein SD: Standart Deviation, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance

Table 4. Sfrp5 and chemerin levels in the patient and control groups

	Patient (Chemerin n=45 Sfrp5 n=46)		Control (Chemerin=48 Sfrp5=49)		P
	Median (min-max)	**Mean±SD**	**Median (min-max)**	**Mean±SD**	
Chemerin[1] (ng/L)	290(139-838) [1]	379±206	281(149-960) 1	431±246	0.518
Sfrp5[1] (ng/mL)	10 (5-57) [1]	17±13	14(5-115) [1]	26±24	0.248

Sfrp5: secreted frızzled-related protein 5, SD: Standart Deviation[1]: nonparametric

Table 5. Patient group: correlation analysis of Sfrp5 and chemerin with other data

Parameters (Patient group)	**Chemerin(n=45)**	**Sfrp5(n=46)**
	r	**r**
Sfrp5	**0.704***	-
TSH	-0.101	0.033
FT3	0.023	0.147
FT4	-0.004	-0.104
BMI	-0.018	-0.289
HOMA-IR	-0.217	-0.18
Glucose	-0.109	-0.142
Insuline	-0.171	-0.148
Triglyceride	0.067	-0.171
Total cholesterol	0.058	0.226
HDL Cholesterol	0.13	0.184
LDL Cholesterol	-0.023	-0.211
Age	0.04	-0.185
SBP	0.215	0.059
DBP	-0.028	-0.245

TSH: Throid Stimulating Hormone, FT3: Free T3, FT4: Free T4, Sfrp5: secreted frızzled-related protein 5, HDL: High Density Lipoprotein, LDL: Low density lipoprotein, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure; *p<0.01

Table 6. Total study group: correlation analysis of sfrp5 and chemerin with other data

Parameters (Study Group)	**Chemerin (n=93)**	**Sfrp5 (n=95)**
	r	**r**
Sfrp5	**0,814****	-
TSH	-0.113	-0.121
FT3	0.065	-0.007
FT4	0.063	0.069
BMI	-0.162	**-0.383****
HOMA-IR	-0.16	-0.117
Glucose	-0.04	-0.045
Insuline	-0.139	-0.094
Triglyceride	-0.11	**-0.278****
Total Cholesterol	-0.127	**-0.341****
HDL	-0.065	-0.019
LDL	-0.128	**-0.320****
Age	-0.210*	**-0.366****
SBP	-0.133	**-0.206***
DBP	-0.129	**-0.230***

TSH: Throid Stimulating Hormone, FT3: Free T3, FT4: Free T4, Sfrp5: secreted frızzled-related protein 5; HDL: High Density Lipoprotein, LDL: Low density lipoprotein; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure; **p<0.01, *p<0.05

DISCUSSION

The fT4 levels of patients diagnosed with subclinical hypothyroidism (SH) included in our study were found to be significantly lower compared to the control group ($p < 0.05$). Our findings suggest that although the fT4 levels in SH patients may remain within the reference range, they tend to be lower than those in healthy controls and should therefore be evaluated more carefully in clinical practice.

Chemerin and Sfrp5 proteins have been shown to be associated with various diseases in several studies[17,18,20,31-34]. However, there are very few studies investigating the relationship between Chemerin and Sfrp5 and thyroid hormones, as well as their pathophysiological roles in subclinical thyroid disorders, and no consensus has been reached on this issue. Therefore, the aim of this study was to investigate the significance of these two parameters in subclinical hypothyroidism (SH), particularly due to the lack of studies on the role of Sfrp5 in thyroid diseases and the limited number of studies on Chemerin.

Although our study results showed an increase in Chemerin levels and a decrease in Sfrp5 levels in the SH group compared to the control group, these differences were not statistically significant. To summarize the findings of previous studies on this topic: Berta et al. reported that Chemerin levels in patients with Hashimoto's thyroiditis did not change significantly compared to the control group and that there was no significant correlation between Chemerin and TSH, FT3, or FT4 levels[26]. In a recently published study, similar to ours, serum Chemerin levels showed a statistically non-significant increase in subclinical hypothyroidism compared to healthy controls. In the same study, Chemerin levels in the subclinical hyperthyroidism group were found to be significantly lower than in the healthy control group[27]. In contrast to these findings, Alshaikh et al. reported that serum Chemerin levels were higher in patients with hyperthyroidism than in healthy controls, and they found a positive correlation between Chemerin and FT3, and a negative correlation with TSH and FT4[28]. In a separate study conducted on rats with experimentally induced thyroid dysfunction, a significant increase in Chemerin levels was observed in hypothyroidism, and a decrease in hyperthyroidism, along with a significant positive correlation between Chemerin and TSH[29,30].

Chemerin and Sfrp5 levels may be influenced by factors such as age, lipid abnormalities, the presence of insulin resistance, and gender[31-33]. Furthermore, evaluating the circulating levels of these two proteins is considered highly important, as they have been associated with many disease parameters linked to MetS, diabetes mellitus, and obesity[20,33,35-38]. In our study, the exclusion of obese individuals from both the patient and control groups, the lack of differences in lipid parameters, glucose levels, and HOMA-IR indices between the groups, the similar age distribution of participants, and the inclusion of only female subjects helped eliminate the influence of these confounding factors on the levels of the two proteins. Therefore, although Chemerin and Sfrp5 did not show statistically significant changes in SH which was the focus of our study the observed trends suggest that this topic warrants further investigation.

Indeed, the presence of a significant positive correlation between Chemerin and Sfrp5 levels in both the overall study group and the patient group supports our hypothesis. While Chemerin is known as a pro-inflammatory protein, Sfrp5 acts as an anti-inflammatory counterpart. Although this correlation did not reach statistical significance, the coexistence of elevated Chemerin and reduced Sfrp5 levels in the patient group suggests a potential cause-and-effect relationship. It is plausible that an increase in Chemerin may trigger a compensatory rise in Sfrp5 as an anti-inflammatory response. The combination of high Chemerin and low Sfrp5 levels in SH may reflect a pro-inflammatory state. Supporting this, Yong et al. reported elevated Chemerin levels in thyroid cancers and proposed that Chemerin could serve as a marker of inflammation associated with cancer progression[35]. Therefore, monitoring Chemerin levels in patients diagnosed with SH may help predict potential pathological developments and inform treatment strategies.

Our study gains importance as it represents the first investigation of the Sfrp5 protein in thyroid diseases. Whether Sfrp5 can serve as a biomarker in thyroid disorders remains unclear. As noted above, there was no statistically significant difference in Sfrp5 levels between the two groups. However, several studies have investigated the significance of Sfrp5 outside the context of thyroid diseases. In an experimental study on mice, Sfrp5 was identified as an anti-inflammatory adipokine whose expression was impaired in models of obesity and type 2 diabetes[20]. Another study reported significantly lower Sfrp5 levels in newly

diagnosed MetS patients compared to healthy controls. Additionally, Sfrp5 was found to be negatively correlated with markers of adiposity such as waist-to-hip ratio, BMI, and free fatty acids. The same study also demonstrated correlations between Sfrp5 levels and fasting insulin, fasting glucose, HbA1c, and HOMA-IR, suggesting that Sfrp5 may play a role in the pathogenesis of MetS in humans[33]. In a study by Hu et al., Sfrp5 levels were significantly lower in individuals with impaired glucose tolerance and newly diagnosed type 2 diabetes mellitus compared to those with normal glucose tolerance. Furthermore, overweight/obese individuals had significantly lower Sfrp5 levels than lean individuals, and women exhibited higher Sfrp5 levels compared to men[34]. In our study, Sfrp5 levels showed statistically significant negative correlations with LDL cholesterol, total cholesterol, triglycerides, BMI, diastolic blood pressure, systolic blood pressure, and waist circumference. These findings are consistent with previous literature indicating an association between Sfrp5 and MetS parameters[33,34].

The limitations of our study include the fact that it consisted solely of female patients, the limited sample size, and the exclusion of inflammatory and anti-inflammatory markers. Although Chemerin levels were measured in 95 individuals, the results of 45 patients and 48 healthy controls were included for the analysis of Chemerin levels due to the exclusion of 2 individuals whose results were outside the 95% confidence interval.

In conclusion, our study results revealed that there were no significant changes in the levels of Sfrp5 and Chemerin in subclinical hypothyroidism (SH). However, our study is important as it is the first investigation into Sfrp5 levels in SH. The selected patient group consisted of newly diagnosed and mild SH patients. Although there were no statistically significant changes between these two parameters, we believe that the presence of a change could be attributed to the fact that our study consisted of patients in the early stages of the disease, and factors that could affect the levels of these two parameters were eliminated. Our results suggest that Chemerin and Sfrp5 may serve as markers in thyroid hormone disorders. However, our study needs to be supported by different studies with more participants, including parameters that indicate inflammation.

Author Contributions: Concept/Design : KŞ, BB; Data acquisition: KŞ, AA; Data analysis and interpretation: KŞ, BB; Drafting manuscript: KŞ, LT; Critical revision of manuscript: BB, SA, AA; Final approval and accountability: KŞ, BB, SA, LT, AA; Technical or material support: KŞ, SA; Supervision: BB, LT; Securing funding (if available): n/a.
Ethical Approval: Date of 28.02.2020 and B from the Clinical Research Ethics Committee of Ondokuz Mayıs University.30.2.ODM.ethical approval was obtained with the decision numbered 0.20.08/109.
Peer-review: Externally peer-reviewed.
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REFERENCES

1. Korbonits M. Leptin and the thyroid - a puzzle with missing pieces. Clin Endocrinol. 1998;49:569-72.
2. Knudsen N, Jorgensen T, Rasmussen S, Christiansen E, Perrild H. The prevalence of thyroid dysfunction in a population with borderline iodine deficiency. Clin Endocrinol. 1999;51:361-7.
3. Biondi B, Palmieri EA, Klain M, Schlumberger M, Filetti S, Lombardi G. Subclinical hyperthyroidism: clinical features and treatment options. Eur J Endocrinol. 2005;152:1-9.
4. Ross D. Subclinical hypothyroidism. In: Braverman LE, Utiger RD (eds). Werner and Ingbar's the thyroid: a fundamental and clinical text. 8th ed: 1070-1078. Philadelphia, Lippincott Williams & Wilkins. 2005.
5. Hollowell J, Staehling N, Flanders W, Hannon W, Gunter E, Spencer C. Serum tsh, t4, and thyroid antibodies in the United States population: National health and nutrition examination survey. J Clin Endocrinol Metab. 2002;87:489-99.
6. Cooper DS. Clinical practice. Subclinical hypothyroidism. N Engl J Med. 2001;345:260-65.
7. Vanderpump MP, Tunbridge WM. Epidemiology and prevention of clinical and subclinical hypothyroidism. Thyroid. 2002;12:839-47.
8. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004;291:228-38.
9. Biondi B, Palmieri EA, Lombardi G, Fazio S. Effects of subclinical thyroid dysfunction on the heart. Ann Intern Med. 2002;137:904-14.
10. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam study. Ann Intern Med. 2000;132:270-78.
11. Danese MD, Ladenson PW, Meinert CL, Powe NR. Effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. J Clin Endocrinol Metab. 2000;85:2993-3001.

12. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160:526-34.
13. Kong WM, Sheikh MH, Lumb PJ, Naoumova RP, Freedman DB, Crook M et al. A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. Am J Med. 2002;112:348-54.
14. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham survey. Clin Endocrinol (Oxf). 1995;43:55-68.
15. Huber G, Staub JJ, Meier C, Mitrache C, Guglielmetti M, Huber P et al. Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve and thyroid antibodies. J Clin Endocrinol Metab. 2002;87:3221-6.
16. Wittamer V, Franssen JD, Vulcano M, Mirjolet JF, Poul E, Migeotte I et al. Specific recruitment of antigen-presenting cells by chemerin, a novel processed ligand from human inflammatory fluids. J Exp Med. 2003;198:977-85.
17. Booth A, Magnuson A, Fouts J, Foster M. Adipose tissue, obesity and adipokines: role in cancer promotion. Horm Mol Biol Clin Investig. 2015;21:57-74.
18. Rourke JL, Dranse HJ, Sinal CJ. Towards an integrative approach to understanding the role of chemerin in human health and disease. Obes Rev. 2013;14:245-62.
19. Chang JT, Esumi N, Moore K, Li Y, Zhang S, Chew C et al. Cloning and characterization of a secreted frizzled-related protein that is expressed by the retinal pigment epithelium. Hum Mol Genet. 1999;8:575-83.
20. Ouchi N, Higuchi A, Ohashi K, Oshima Y, Gokce N, Shibata R et al. Sfrp5 is an antiinflammatory adipokine that modulates metabolic dysfunction in obesity. Science. 2010;329:454-7.
21. Satoh W, Matsuyama M, Takemura H, Aizawa S, Shimono A. Sfrp1, sfrp2, and sfrp5 regulate the Wnt/β-catenin and the planar cell polarity pathways during early trunk formation in mouse. Genesis. 2008;46:92-103.
22. Cho YK, Kim HJ, Park JY, Ro H, Chang JH, Lee HH et al. Effect of sfrp5 (secreted frizzled-related protein 5) on the wnt5a (wingless-type family member 5a)-induced endothelial dysfunction and its relevance with arterial stiffness in human subjects. Arterioscler Thromb Vasc Biol. 2018;38:1358-67.
23. Liu W, Wang X, Gong L, Zhang Y, Li J, Chen Y et al. Sfrp5 mediates downregulation of the wnt5a/caveolin-1/jnk signaling pathway. J Endocrinol. 2020;247:263-72.
24. Assiri AMA, Kamel HFM, Hassanien MFR. Resistin, visfatin, adiponectin, and leptin: risk of breast cancer in pre- and postmenopausal saudi females and their possible diagnostic and predictive implications as novel biomarkers. Dis Markers. 2015;2015:253519.
25. Balkau B, Charles MA. Comment on the provisional report from the who consultation. European group for the study of ınsulin resistance. Diabet Med. 1999;16:442-3.
26. Berta E, Harangi M, Varga VE, Lőrincz H, Seres I, Nagy EV et al. Evaluation of serum chemerin level in patients with hashimoto's thyroiditis. J Atherosclerosis. 2016;252:e168.
27. Tamer S, Turan T, Taşkan T, Karakoç MA, Arslan İE, Gönenç A. Serum chemerin, vaspin, oxidative stress and inflammation markers in subclinical hypothytoidism/hyperthyroidism. JBACHS. 2004;8:296-307.
28. Alshaikh EM, Omar UM, Alsufiani HM, Alzahrani OA, Al-Hussein KA, Al-Amri AM et al. The potential influence of hyperthyroidism on circulating adipokines chemerin, visfatin, and omentin. Int J Health Sci. 2019;13:44-7.
29. Lehrke M, Becker A, Greif M, Stark R, Laubender RP, Ziegler FV et al. Chemerin is associated with markers of inflammation and components of the metabolic syndrome but does not predict coronary atherosclerosis. Eur J Endocrinol. 2009;161:339-44.
30. Chen X, Gao C, Gong N, Wang Y, Tian L. The change of left ventricular function in rats with subclinical hypothyroid and the effects of thyroxine replacement. Int J Endocrinol. 2018;2018:2968670.
31. Goralski KB, McCarthy TC, Hanniman EA, Zabel BA, Butcher EC, Parlee SD et al. Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. J Biol Chem. 2007;282:28175-88.
32. Bozaoglu K, Bolton K, McMillan J, Zimmet P, Jovett J, Collier G et al. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology. 2007;148:4687-94.
33. Xu Q, Wang H, Li Y, Zhang Y, Liu Y, Chen X et al. Plasma sfrp5 levels correlate with determinants of the metabolic syndrome in Chinese adults. Diabetes Metab Res Rev. 2017;33:e2904.
34. Hu W, Li L, Yang M, Luo X, Ran W, Liu D et al. Circulating sfrp5 is a signature of obesity-related metabolic disorders and is regulated by glucose and liraglutide in humans. J Clin Endocrinol Metab. 2013;98:290-8.
35. Gao Y, Sheng M, Zhao Y, Jiang H, Zhang Y. Serum chemerin and thyrotropin expression levels in patients with thyroid cancer and roles in predicting survival. Int J Clin Exp Med. 2019;12:7561-8.
36. Yang M, Yang G, Dong J, Liu Y, Zong H, Liu H et al. Elevated plasma levels of chemerin in newly diagnosed type 2 diabetes mellitus with hypertension. J Investig Med. 2010;58:883-6.
37. Li Y, Shi B, Li S. Association between serum chemerin concentrations and clinical indices in obesity or metabolic syndrome: a meta-analysis. PLoS One. 2014;9:e113915.

38. Stejskal D, Karpisek M, Hanulova Z, Svestak M. Chemerin is an independent marker of the metabolic syndrome in a Caucasian population – a pilot study. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2008;152:217-21.