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Association of serum proprotein convertase Subtilisin/Kexin Type 9 (PCSK9) level with thyroid function disorders

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Abstract. – OBJECTIVE: We aimed at demonstrating the effect of thyroid function status on proprotein convertase subtilisin kexin type 9 (PCSK9) and determining the effect of thyroid hormones on lipid metabolism by comparing the PCSK9 levels of patients with subclinical hypothyroidism, overt hypothyroidism, and hyperthyroidism.

PATIENTS AND METHODS: 124 patients with thyroid disorders, aged between 18 and 65 years, were included in this study. The participants were divided into 3 groups. Group 1 comprised 52 patients with subclinical hypothyroidism, Group 2 comprised 40 patients with overt hypothyroidism, and Group 3 comprised 32 patients with hyperthyroidism. In all of these groups, the thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, total cholesterol, fasting serum glucose, antithyroid peroxidase antibody, antithyroglobulin antibody, and PCSK9 levels were measured.

RESULTS: No significant difference was found between the 3 groups in terms of age, gender, and body mass indices. Median PCSK9 measurements were 14.55 ng/mL in Group 1, 14.895 ng/mL in Group 2, and 9.775 ng/mL in Group 3. There was a significant difference in the PCSK9 levels between Group 1-Group 3 and Group 2-Group 3 (p <0.0001 and p <0.0001, respectively). A positive correlation between PCSK9 and the TSH levels (r = 0.211, p= 0.019), and a negative correlation (r = -0,239, p = 0.009 and r = -, 0.218, p = 0.015) between the fT3 and fT4 levels were found.

CONCLUSIONS: The serum PCSK9 levels were shown to be associated with thyroid dysfunction. However, no relationship was observed between the serum PCSK9 level and thyroid autoantibody positivity, and obesity in this study.

Key Words:
PCSK9, TSH, Thyroid dysfunction.

Introduction

Thyroid hormones (THs) have important and complex roles in the regulation of lipid metabolism. THs have known effects in several steps of the cholesterol metabolism, such as inducing 3 hydroxy 3-methylglutaryl-coenzyme A reductase, the first step of cholesterol biosynthesis, stimulating intestinal cholesterol absorption, and hepatic lipase[1,2]. Dyslipidemia is also common in cases of thyroid dysfunction[3].

The proprotein convertase subtilisin kexin type 9 (PCSK9) gene was first identified in 2003 by Abidafel et al[4]. This gene is located on chromosome 1p32.3 and comprises 12 exons encoding a 692 amino acid protein. PCSK9 is mainly expressed in the liver, small intestine, and kidney[5]. The main function of PCSK9 is to mature proteins such as secreted hormones, cytokines, growth factors and cell surface receptors through proteolysis[6].

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PCSK9 binds to epidermal growth factor–A domain of the LDL receptor, and stimulates the degradation of LDL receptors[7,8]. Thus, recycling of LDL-R on the hepatic cell surface is prevented, and the capacity of LDL-receptors to remove LDL cholesterol from the bloodstream is reduced[9,10]. This results in an increase in plasma LDL-C levels. It has been shown that gain of function mutations in the PCSK9 gene were associated with autosomal dominant familial hypercholesterolemia[4].

There are some factors that correlate with the PCSK9 levels, such as the plasma apolipoprotein B, and LDL-C levels. It has been known that PCSK9 levels were associated with the severity of coronary heart disease[11]. Another factor that is correlated with PCSK9 levels is the sterol regulatory element-binding protein transcription factor 2 (SREBP2), which stimulates intracellular cholesterol synthesis, and supports LDL-R gene expression. SREBP2 is a molecule with the up-regulating properties of PCSK9[12].

It was reported that TH was effective on LDL-R expression via SERBP2 in a study published by Shin et al[13] in 2003. Considering the SREBP2-PCSK9 and the TH-SREBP2 interactions, we can hypothesize that there may be a relation between TH and PCSK9 levels. In recent years, several studies reported the relationship between TH and PCSK9 levels. Bonde et al[3] reported that TH plays a role in the formation of low plasma LDL-C levels in hyperthyroidism by means of reducing circulating PSCK9 levels. Furthermore, they suggested that LDL-C levels may also be lowered by stimulation of bile acid synthesis by TH, which was not considered to be a critical pathway for the LDL-C metabolism.

In a study published in 2015, short-term overt hypothyroidism was shown to increase the serum PCSK9 levels[14]. Kwakernaak et al[2] suggested that even the level of thyroid stimulating hormone (TSH) in the euthyroid range correlated positively with serum PCSK9 levels.

In this study, we aimed to compare the serum PCSK9 levels of patients with subclinical hypothyroidism, overt hypothyroidism, and hyperthyroidism, and investigate the effect of thyroid status on the LDL-C metabolism.

Patients and Methods

We recruited 150 patients, with newly diagnosed thyroid dysfunction who were referred to the Internal Medicine or Endocrinology and Metabolic Diseases outpatient clinics of the Kecioren Education and Research Hospital (n = 150, aged between 18 and 65 years). Those who received antithyroid therapy (propitiouracil/methimazole), TH replacement, antihyperlipidemic medications (statin/fibrate), pregnant women, and puerperant women, and patients who had a family history of hyperlipidemia, diabetes mellitus (DM) were excluded from the study. According to these exclusion criteria, 36 patients were excluded from the study, and the study was completed with a total of 124 patients (n = 124) (Figure 1). The participants were divided into 3 groups, such as Group 1: subclinical hypothyroid (n = 52), Group 2: overt hypothyroid (n = 40), and Group 3: hyperthyroid (n = 32). Patients with serum TSH <l0 μIU/mL, and free thyroxine (fT4) levels within the normal range were assigned to the subclinical hypothyroid group, patients with TSH ≥l0 μIU/mL were assigned to the overt hypothyroid group, and those with serum free TSH levels below and free triiodothyronine (fT3)/free thyroxine (fT4) levels above normal reference range were assigned to the hyperthyroid group. Definition of subclinical

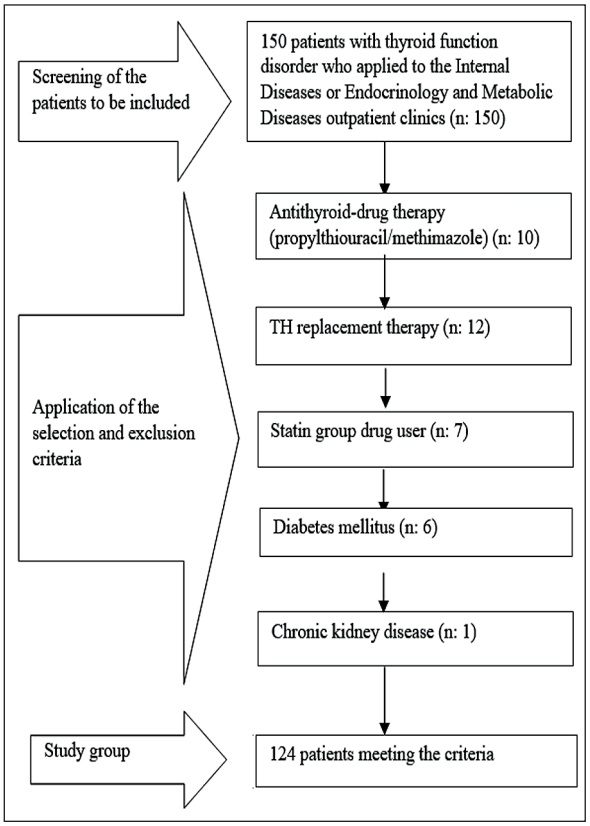

Figure 1. Determination of the patient groups.

and overt hypothyroidism was made according to the 2012 ATA AACE Clinical Practice Guidelines for Hypothyroidism. The 2011 ACE Hyperthyroidism Guideline was consulted for the selection of the patients for the hyperthyroidism group.

Detailed physical examinations of all of the participants were performed, history of the symptoms were recorded, and height and weight measurements were also recorded. The fT3, fT4, TSH, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), total cholesterol (TC), antithyroid peroxidase antibody (anti-TPO), antithyroglobulin antibody (anti-TG), and fasting serum glucose levels of all of the participants were measured. Fasting blood samples were also taken for PCSK 9 analysis. After storing the samples for 2 h, they were centrifuged and kept at –80°C, and all of the samples were studied in the same session.

Thyroid function tests were measured from peripheral venous blood taken between 08:00 and 09:00 h after at least 10 h of fasting. Serum TSH, fT3, and fT4 measurements were performed using chemiluminescence on an automatic Unicel DXI 800 Access Immunassay autoanalyzer (Beckmann Coulter Inc. Brea, CA, USA). The TSH reference interval was 0.27-4.3 mIU/L, the fT3 reference interval was 2.3-4.2 pg/mL, and the fT4 reference interval was 0.93–1.7 ng/dL.

PCSK9 levels were studied using an ELISA kit (USCN Life Science Inc. Wuhan, Hubei, China) with double antibody sandwich technique. Serum PCSK9 levels were expressed as ng/mL. The concentration of acylated ghrelin was measured using enzyme-linked immunosorbent assay (ELISA) method. The procedure for the ELISA method was performed according to the instructions provided by the manufacturer. Absorbance was measured at a wavelength of 450 nm using the ELISA reader. The PCSK9 levels were presented as ng/mL. The intra-assay coefficient was 10% and inter-assay coefficient of variations was < 12%. In this method, values were calculated quantitatively by drawing graphs with standards. Values above 20 were diluted.

Ethics Committee Approval was obtained from the Clinical Research Ethics Committee of the Health Sciences University Kecioren Education and Research Hospital (Project No: 717). Written and oral informed patient consent was obtained from all the participants.

Statistical Analysis

The data obtained in this study were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA) software. Normally distributed continuous variables were expressed as the mean and standard deviation, and skewed-distributed continuous variables were expressed as the median (minimum–maximum). When analyzing the differences between the groups, the Mann-Whitney U and Kruskal-Wallis H tests were used due to the lack of normal distribution of variables. Chi square analysis was used to compare the differences between the groups of nominal variables. The Spearman correlation coefficient was used to compare the relationships between variables. The results were evaluated in a confidence interval of 95% and at a significance level of $p < 0.05$.

Results

This study was completed with a total of 124 participants, who were divided into 3 groups: subclinical hypothyroidism (Group 1), overt hypothyroidism (Group 2), and hyperthyroidism (Group 3).

Among the participants, 84 were female. There were 38 females in Group 1, 28 in Group 2 and 18 in Group 3. There was no significant difference in gender between the groups ($p = 0.259$). The median ages were 41 years (26-61) for Group 1, 44 years (21-63) for Group 2, and 46.5 years (21-64) for Group 3. There was no significant difference in age between the groups ($p = 0.304$).

The median body mass index (BMI) values in Groups 1, 2 and 3 were: 26 kg/m^2 (17.58-32.45 kg/m^2), 29.4 kg/m^2 (19.53-42.97 kg/m^2), and 25.95 kg/m^2 (17.72-44.92 kg/m^2), respectively. There was a significant difference between the Groups in terms of BMI ($p < 0.0001$).

There was a significant difference in the PCSK9 levels when Group 1 was compared to Group 3, and Group 2 was compared to Group 3 ($p<0.0001$ and $p<0.0001$). However, there was no difference between Group 1 and Group 2 in terms of the PCSK9 levels ($p = 0.013$) (Table I; Figure 2). Twenty-eight of the participants (n:2 in Group 1, n:21 in Group 2, and n:5 in Group 3) were obese (BMI ≥30 kg/m^2). In the analysis performed by excluding obese patients, a significant difference was found between the PCSK9 levels ($p = 0.006$). Similarly, there was no difference when Group 1 was compared to Group 2, and there was a significant difference when Group 1 was compared to Group 3 ($p = 0.001$), and

Table I. Basic laboratory results of the subclinical hypothyroidism, overt hypothyroidism, and hyperthyroidism groups.

	Group 1 (subclinical hypothyroidism) (n = 52)	Group 2 (overt hypothyroidism) (n = 40)	Group 3 (hyperthyroidism) (n = 32)
PCSK9 (ng/mL)	14.55 (7.09-131.28)	14.895 (5.38-131.28)	9.775 (4.10-33.89)
fT3 (pg/mL)	3.19 (2.21-4)	2.86 (1.0-4.11)	1.90 (2.64-32.0)
fT4 (ng/dL)	0.91 (0.8-1.46)	0.75 (0.18-0.79)	1.90 (0.97-7.97)
TSH (µIU/mL)	6.19 (5.0-8.4)	14.05 (9.67-100)	0.021 (0.001-0.1)
Anti-TPO (IU/mL)	6.38 (0.06-2000)	343 (0.25-2000)	34.73 (0.19-2000)
Anti-TG (IU/mL)	20.90 (0.49-6250.9)	46.225 (0.96-1000)	13.37 (0.60-1000)
HDL-C (mg/dL)	50.500 (27.0-82.0)	46.00 (24.0-64.0)	45.0 (22.0-68.0)
LDL-C (mg/dL)	106 (55.0-188.6)	121 (67-261)	83.0 (38.0-136)
Triglyceride (mg/dL)	98.0 (40.0-372)	130.50 (49.0-506)	99.5 (53.0-318)
Total cholesterol (mg/dL)	179.5 (54.0-316)	203.50 (126-379)	154.5 (78-216)

fT3: free triiodothyronine, fT4: free thyroxine, TSH: thyroid stimulating hormone, PCSK9: proprotein convertase subtilisin kexin type 9, antiTPO: thyroid peroxidase antibody, anti-TG: thyroglobulin antibody, HDL-C: high density lipoprotein, LDL-C: low density lipoprotein.

Group 2 was compared to Group 3 (p = 0.049) by excluding obese patients. It was observed that there was no correlation between serum TSH and PCSK9 in the analysis in which obese patients were included.

There was a significant difference in the LDL-C, TG, and TK levels between all of the groups (p <0.0001, p = 0.006, and p <0.0001, respectively). However, there was no difference in the HDL-C levels between the groups (Table I). A positive correlation was found between the PCSK9 level and LDL-C (r = 0.245, p = 0.007), TSH (r = 0.211, p = 0.019), TK (r = 0.184, p = 0.043) levels, and a negative correlation was found between the PCSK9 levels and fT3 (r = –0,239, p = 0.009), and fT4 (r = –0.218, p = 0.015) levels (Figure 3).

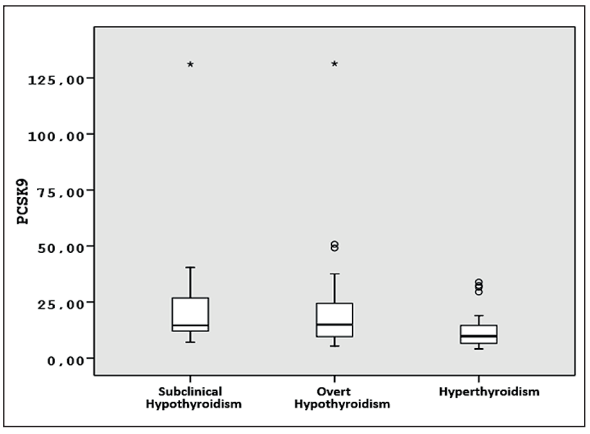

Figure 2. Schematic view of the PCSK9 levels of the subclinical hypothyroidism, overt hypothyroidism, and hyperthyroidism groups.

There was no correlation between the PCSK9 levels, and anti-TPO, and anti-TG levels. There was a total of 65 participants, 24 in Group 1, 23 in Group 2, and 18 in Group 3, that were anti-TPO and/or anti-TG positive. When a subgroup analysis was performed in patients with antibody positivity, there was no significant difference between the PCSK9 levels.

Discussion

To our knowledge, this is the first study in the literature investigating serum PCSK9 levels in patients with overt hypothyroidism, subclinical hypothyroidism, and hyperthyroidism. In this study, it was shown that patients with subclinical hypothyroidism and overt hypothyroidism had higher PCSK9 levels than patients with hyperthyroidism. In addition, a positive correlation was found between the PCSK9 and TSH levels (r = 0.211, p = 0.019), and a negative correlation was found between the fT3 and fT4 levels (r = –0.239, p = 0.009 and r = –0.218, p = 0.015).

The mechanisms of action of THs on lipoprotein metabolism were elusive until Kuusi et al[1] reported that THs stimulated lipoprotein lipase and hepatic lipase in 1980. The theory of the relationship between PCSK9 and THs was first reported in 2013 by Kwakernaak et al[2]. In the current study, it was also shown that there was a relationship between PCSK9 and TSH levels in euthyroid individuals. In 2014, Gagnon et al[15] found that acute TSH stimulation did not change serum PCSK9 levels in 14 patients who had thy-

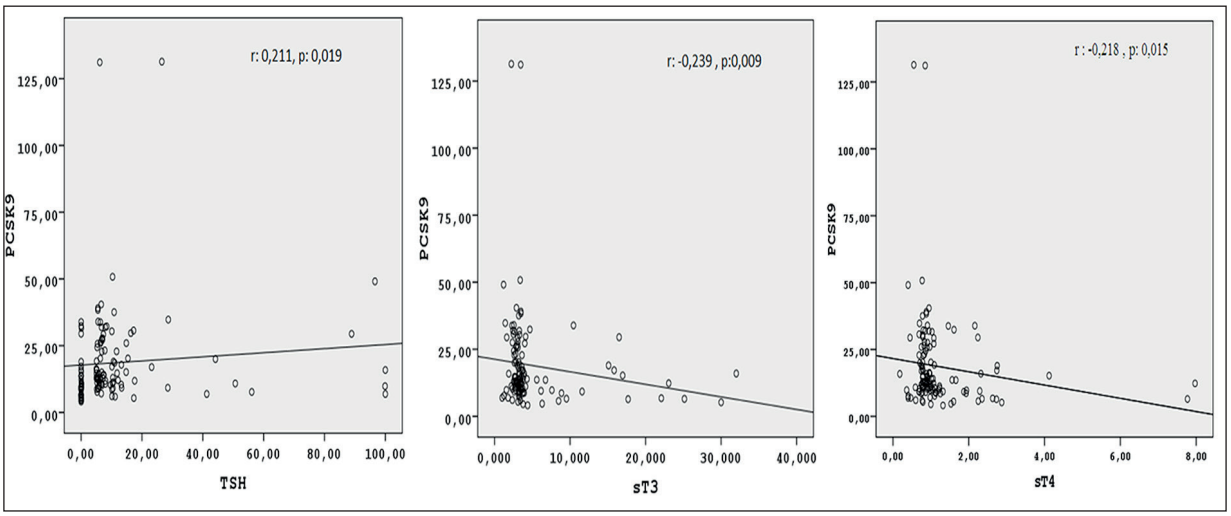

Figure 3. Correlations of the PCSK9 levels with the serum TSH, fT3, and fT4 levels.

roidectomy due to thyroid cancer or radioiodine therapy. Bonde et al[3] found that patients with hyperthyroidism had low PCSK9 and bile acid levels when compared to euthyroid patients. In their study, healthy volunteers were given the liver selective TH agonist, eprotirome, and it was shown that there was a decrease in serum lipoprotein, triglyceride, and PCSK9 levels. In a recent study, serum PCSK9 levels were increased in patients with subclinical hypothyroidism[16]. Gong et al[17] showed stimulated PCSK9 expression by increasing mRNA expressions of SREBP1 and SERBP2 using recombinant TSH, which was an important step towards clarifying the TSH-PCSK9 relationship. These findings may explain the positive correlation between serum the PCSK9 and TSH levels, and the negative correlation between PCSK9 and the fT3 and fT4 levels in our study.

Obesity was associated with increased PCSK9 levels (18, 19). As a result of the study of Kwakernaak et al[2], it was suggested that a positive relationship between serum TSH and PCSK9 levels was not detected in patients with obesity, and the increase in adipose tissue disrupted the positive relationship between PCSK9-TSH. Gagnon et al[15] reported that the PCSK9 levels did not affect TSH stimulation in patients with obesity. In parallel with the results of these studies, it was observed herein that the correlation between serum TSH and PCSK9 levels disappeared in patients with obesity.

Studies have shown that basal PCSK9 levels in women were lower than in men[2,3]. In the current study, PCSK9 levels were comparable among genders. Although there have been studies showing the opposite of these findings, it is our belief that the result was not statistically significant due to the limited number of participants in the study[20].

It can be said that the relationship between thyroid autoantibodies and PCSK9 is still in the dark considering previous studies. Low PCSK9 levels have been found to be beneficial in reducing inflammation in non-autoimmune diseases[21,22]. In a recent study, a positive correlation was found between the insulin and PCSK9 levels in type 1 diabetic patients[23]. Low levels of PCSK9 have also been observed in rheumatoid arthritis, another autoimmune disease[24]. In the present study, no correlation was found between anti-TPO, and anti-Tg and PCSK9 levels. We believe that autoimmune diseases can also affect PCSK9 levels and, thereby disrupting the TSH-PCSK9 relationship.

Herein, it was found that the PCSK9 levels had a positive correlation with LDL-C and TK, in accordance with the literature[12,20]. There was no correlation between serum PCSK9 levels, and serum TG and HDL-C levels, which were also similar to the results obtained in the study of Kotowski et al[25].

The positive correlation between the PCSK9 and TSH levels found in the current study, was similar to the findings in previous studies[2,3]. It was shown herein that there was a negative correlation between fT3 and fT4 levels and PCSK9 levels, contradicting previous data. This difference was attributed to the relatively higher number of participants and the lack of ethnic differences that could have an effect on PCSK9 mutations.

Serum PCSK9 levels, similar to cholesterol synthesis, have shown a diurnal rhythm, which are high in the morning and low in the evening (26). In the current study, fasting serum samples were taken in a certain time in the morning to minimize the possibility of the diurnal variations in the PCSK9 levels.

Limitations

This study has some limitations. First of all, there was no control group with a euthyroid condition. Second, since the number of participants was relatively low, we cannot generalize these results to various ethnic populations. In addition, since this study was designed cross-sectionally, it was not possible to evaluate whether there was a change in the serum PCSK9 level after thyroid function improvements.

Conclusions

In addition to supporting the publications in the literature revealing the relationship between TSH and PCSK levels, our study also suggests that thyroid hormones may also be associated with PCSK9. It is known that thyroid hormones affect lipid metabolism in many steps. On the other hand, we think that our study is also important in terms of presenting an innovative perspective on to these mechanisms. Considering that thyroid dysfunction causes a significant change in serum PCSK9 levels, TH levels should be reviewed in patients with hyperlipidemia before treatment, and thyroid dysfunction may be considered in patients with persistent hyperlipidemia in spite of treatment. Further studies are needed to clarify the relationship between thyroid dysfunction and PCSK9.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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