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Relationship of Thyroid Function with Metabolic Parameters in Euthyroid Adults

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Abstract

Objective: Thyroid hormones have a significant effect on carbohydrate, lipid metabolism disorders, and insulin resistance (HOMA-IR) development. Vitamin D (25(OH)D) has been shown also can affect not only the musculoskeletal system, but also almost all tissues in the body, including the thyroid in recent years. In the study, we aim of this study is to investigate the relationship between the levels of thyroid-stimulating hormone (TSH) within the reference range and metabolic parameters in adults.

Methods: 561 adult outpatients were divided into 2 groups low normal range (0.27-2.5 mIU/mL) and high normal range (2.5-4.2 mIU/mL) according to TSH, and HOMA-IR, 25(OH)D, and lipid levels were compared.

Results: A statistically significant positive correlation was found between TSH and HOMA-IR in both the low normal range group (r = 0.123, p = 0.041) and the high normal range group (r = 0.196, p = 0.001). In the high normal range group, the relationship between TSH with vitamin D (r =-0.200, p =0.003), cholesterol (r =0.143, p =0.024), LDL cholesterol (r =0.154, p =0.018), non-HDL cholesterol (r = 0.134, p = 0.035) levels was statistically significant.

Conclusion: Our study shows that high normal TSH levels in euthyroid adults are related to higher insulin resistance and lower 25(OH)D levels, and this interaction is a major contributor to dyslipidemia. Thyroid hormones explain the metabolic disorder in the early stages of T2DM. Therefore, we believe that screening TSH levels and determining the optimal TSH target will be beneficial.

Keywords: Euthyroidism, insulin resistance, lipid profile, vitamin D

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INTRODUCTION

Insulin resistance is a metabolic disorder in which cells fail to respond adequately to normal or increased insulin levels, causing impaired glucose uptake and utilization (1). Insulin resistance may occur with hypertriglyceridemia, hypercholesterolemia, glucose intolerance, obesity, Type 2 DM, and cardiovascular diseases. Thyroid hormones are also one of the important determinants involved in glucose homeostasis (2). Contrary to a general opinion that insulin is the main hormone responsible for blood glycemic control, there is reported that the synergistic effects of insulin and triiodothyronine affect glucose and lipid metabolism (3). In studies, it has been shown that patients with overt hypothyroidism and hyperthyroidism are more likely to develop insulin resistance and dysglycemia (2). However, it has also been stated that thyroid hormones are associated with insulin resistance in individuals with subclinical hypothyroidism and hyperthyroidism with mild thyroid dysfunction (4). This shows that abnormal thyroid hormones and thyroid-stimulating hormone (TSH) levels are effective on glucose metabolism and insulin resistance. The seriousness of the illness picture is proportional to the seriousness of the disorders. The development of insulin resistance in hypothyroidism is related to decreased blood flow, gluconeogenesis, lipolysis, and basal insulin secretion in peripheral tissues (2).

Overt hypothyroidism is also identified as a possible risk factor for increased risk of coronary artery disease (CAD) and death, it is often related to hyperlipidemia (5). Similarly, asymptomatic subclinical hypothyroidism, characterized by serum free T4 concentrations at normal levels and slightly elevated serum TSH concentrations are also accompanied by a risk of CAD, increased cholesterol, and LDL cholesterol levels (6). It has been indicated that the total cholesterol and LDL cholesterol levels of these individuals can be reduced by thyroxine treatment (7).

Vitamin D is involved in bone mineral homeostasis. However, high expression of Vitamin D receptors (VDR) has been shown in many tissues, including the thyroid gland in recent years (8). It has been shown that vitamin D is an effective hormone not only in the skeletal system but also in many target tissues and also affects the secretion of pituitary hormones (9). In addition, it has also been stated that vitamin D has anti-proliferative effects on thyrocytes in vitro. In the studies conducted, the correlation between low Vitamin D levels and subclinical hypothyroidism was drawn attention (10).

In the levels of thyroid hormones and TSH are observed differences which are documented with little individual variation within the normal range (11). Similarly, substantial

variation in thyroid function can be seen between populations. Such variations are due to a combination of genetics and environmental factors, for which the level of iodine intake is of great importance. Studies have conducted an increased risk of developing thyroid dysfunction in people with high normal TSH levels (12). It has been shown that the TSH value has above 2.5 mIU/L in about 9% of the population and the risk of developing hypothyroidism in the future is high. Therefore, although the optimal level for serum TSH levels is not clear, the general trend in recent years is to narrow the optimal TSH range (13).

TSH levels harm insulin resistance and cardiovascular risk factors. In addition, in euthyroid individuals, even small differences in thyroid function have a possible contribution to these negative effects. Therefore, the question of whether there is an **association** between TSH levels in the normal range with metabolic parameters and vitamin D levels will allow the identification of early new markers of cardiovascular risk. This study was conducted to investigate the potential relationship of TSH levels in the reference range with insulin resistance, serum 25(OH)D, and lipid levels in healthy, euthyroid adults.

METHODS

Study design and participants

This study was approved by the ethics committee of Istanbul Başakşehir Çam and Sakura City Hospital (No.2021.06.120). Due to the retrospective and observational character of the study design, the requirement for informed consent has been waived.

The records of 561 healthy, euthyroid adult patients who applied to the Internal Medicine Outpatient Clinic of Başakşehir Çam and Sakura City Hospital in Istanbul between September 2020-December 2020 were retrospectively analyzed. Those with diabetes mellitus, thyroid dysfunction, pregnancy, infection, and cardiovascular disease were not included in the study. The normal ranges of TSH are between 0.3-2.5 mIU/mL in 95 percent of the population (13). According to the TSH levels, the cases were divided into 2 groups as group 1 (low normal range (0.27-2.5 mIU/mL), (n=285) and group 2 (high normal range (2.5-4.2 mIU/mL), (n=276)). Fasting glucose, insulin, HOMA-IR, 25(OH)D levels, and lipid levels were compared between individuals with high normal and low normal TSH levels.

Data collection and analysis

Age, gender, body mass index (BMI), and biochemical data obtained retrospectively from the hospital information system of the patients who had simultaneous measurements of fasting glucose, insulin, TSH, 25(OH)D, and lipid profile were analyzed and compared. All tests were analyzed in Istanbul Başakşehir Çam and Sakura City Hospital Central Laboratory. The analysis of biochemical tests was carried out with serum obtained. Serum glucose concentrations with enzymatic reference

hexokinase, urea level with kinetic urease and glutamate dehydrogenase, creatinine level with kinetic colorimetric, cholesterol and triglyceride with the enzymatic colorimetric method, HDL with homogeneous enzymatic colorimetric method were measured on the Roche Cobas 8000 (Roche Indianapolis/America) analyzer. Serum TSH and insulin concentrations quantitatively with sandwich principle, fT4 and 25 (OH) D concentrations with competition principle method were measured on the Roche Diagnostics Cobas 8000 (Roche Indianapolis/America) analyzer. Serum LDL cholesterol levels were calculated. Evaluation of insulin resistance is based on simultaneous measurements of glucose and insulin. HOMA-IR= fasting glucose (mmol/L) x fasting insulin (µu/ml)/22.5 **(**4).

Statıstıcal Analysıs

In calculating the sample size of this study a Power analysis was determined by taking at least 80% and Type-1 error of 5 % for each variable. Kolmogorov-Smirnov and Skewness-Kurtosis tests were determined to check whether the continuous measurements in the study were normally distributed, and Parametric tests were applied because the measurements were distributed normally. The ”Independent T-test“ was used to compare continuous measurements according to the ”TSH groups". Pearson correlation coefficients were calculated to determine the relationships between continuous measurements. The chi-square test was used to determine the relationships between categorical variables. The SPSS (IBM SPSS for Windows, ver.26) statistical package program was used for analysis, and the statistical significance level was taken as 5 % in the calculations.

RESULTS

Basic and metabolic characteristics of groups formed according to TSH levels

A total of 561 adult participants were included in this study. TSH levels of all individuals were within normal limits (0.27–4.2 ml/mL). 285 patients had low normal TSH levels and 276 patients had high normal TSH levels. The mean age was 37.47±12.43 years in the low normal TSH group and 37.89 ± 12.84 years in the high normal TSH group. 73.7% and 75.7% of the patients were women, while 26.3% and 24.3% were men, respectively. There was no statistically significant relationship between the groups in terms of gender (p<0.05) (Table 1).

Table 1. The relationship and distribution of gender and TSH groups

Gender	TSH (0.27-2.5mIU/mL)			TSH (2.5-4.2 mIU/mL)			
	N	*Row %*	*Column %*	*N*	*Row %*	*Column %*	**p.*
F	210	50,1%	73,7%	209	49,9%	75,7%	,578
M	75	52,8%	26,3%	67	47,2%	24,3%	

** Significance level according to Chi-square test results,F: female, M: male*

In the table below; The biochemical measurements of the patients "according to

TSH groups" were compared and the results were given (Table 2).

Table 2: Comparison results of metabolic data according to TSH groups

	TSH (0.27-2.5 mIU/mL) Mean± SD	TSH (2.5-4.2 mIU/mL) Mean± SD	*p
Age, years	37.47±12.43	37.89±12.84	*0.691*
Glucose (mg/dL)	94.91±9.40	97.41±11.76	***0.005***
Insulin, uIU/mL	12.68±6.74	18.12±11.27	***0.001***
HOMA-IR	3.02±1.74	4.50±3.15	***0.001***
BMI, kg/m²	27.12±5.43	31.62±7.81	***0.001***
FT4, ng/dL	1.26±.17	1.09±0.12	***0.001***
25 (OH) D, ng/mL	21.06±11.36	16.39±7.99	***0.001***
Urea, mg/dL	23.96±7.05	24.56±10.70	*0.435*
Creatinine, mg/dL	0.74±0.16	0.77±0.54	*0.427*
Triglyceride, mg/dL	111.65±62.93	148.54±115.48	***0.001***
Cholesterol, mg/dL	185.17±40.34	195.06±38.98	***0.005***
HDL, mg/dL	53.02±14.83	49.93±13.08	***0.014***
LDL, mg/dL	110.31±33.59	116.50±30.90	***0.036***
Non-HDL Cholesterol, mg/dL	134.09±40.06	146.34±39.65	***0.001***

** Data are presented as mean ± standard deviation (SD), BMI = Body mass index. Significance levels according to Independent T-test results*

The fasting, insulin, glucose, and HOMA-IR levels of the patients changed according to the groups and were found to be statistically significantly higher in group 2 than in group 1 ($p<0.05$) (Figure 1 a, b, c). The BMI value of the patients was found to be statistically significantly increased while Vitamin D, and HDL significantly decreased in group 2 ($p<0.05$) (Figure 1 d, e). Similarly, the triglyceride, cholesterol, LDL, and non-HDL cholesterol levels of the patients were found to be significantly increased in group 2 compared to group 1 ($p<0.05$) (Figure 1 e).

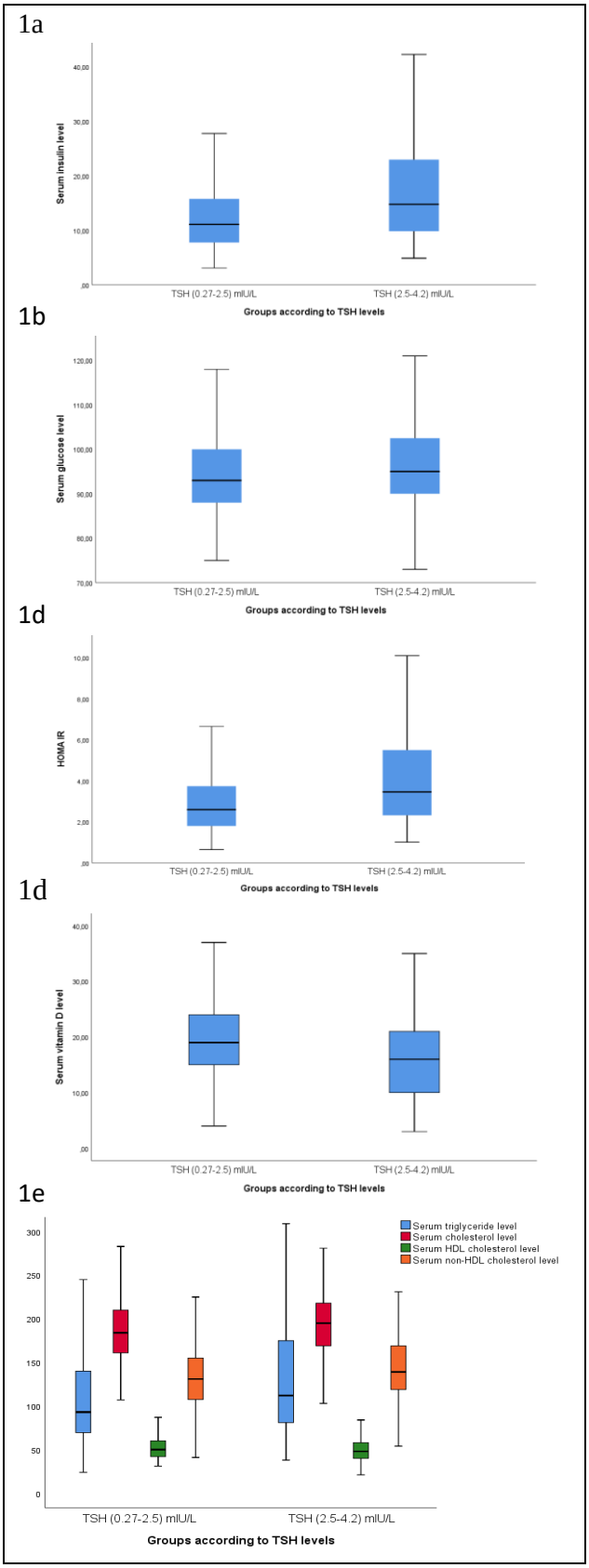

Figure 1 (a-e): Serum insulin, glucose, HOMA-IR, Vitamin D and Lipid levels according to TSH levels

Correlation analysis

TSH and insulin resistance

In the table below; the results of correlation analysis between "TSH" and "HOMA-IR" measurements were shown separately in the groups (Table 3). Accordingly; a statistically significant positive correlation (12.3%) was found between the "TSH" and "HOMA-IR" measurements in the "low normal range" group ($p<0.05$) (Figure 2 a). Similarly; a statistically significant positive correlation (19.6%) was found between "TSH" and "HOMA-IR" measurements in the "high normal range" group ($p<0.05$) (Figure 2 b).

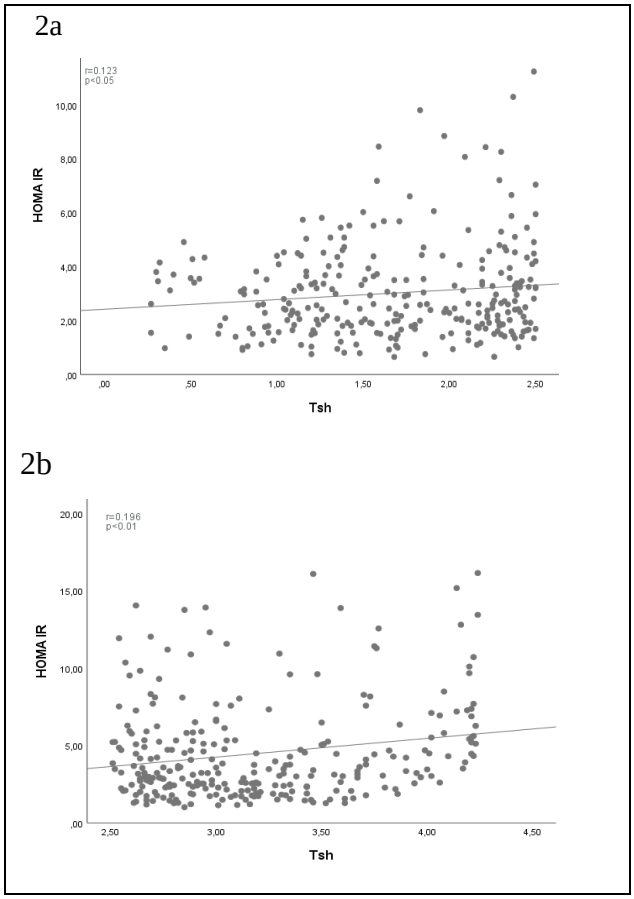

Figure 2 (a, b): Relationship between "TSH" and "HOMA-IR" in the low normal and high normal range group

Table 3: Correlation analysis between "TSH"and "HOMA-IR" measurements in groups

HOMA-IR	(0.27-2.5 mIU/mL)	(2.5-4.2 mIU/mL)	(0.27-4.2 mIU/mL)
	TSH	TSH	TSH
r	0.123	0.196	0.314
p.	***0.041***	***0.001***	***0.001***

** Pearson correlation*

TSH and other data

There was a significant positive correlation between TSH and HOMA-IR (r =0.123, p = 0.041), fT4 (r = -0.404, p =0.040) in the low normal range group. The relationship between vitamin D and cholesterol (r =0.141, p =0.045), LDL cholesterol (r =0.162, p =0.025), non-HDL cholesterol (r =0.157, p =0.027), HOMA-IR and glucose (r =0.443, p <0.001), BMI (r =0.329, p <0.001), insulin (r =0.982, p <0.001), HDL cholesterol (r =-0.203, p =0.001), non-HDL cholesterol (r =0.132, p = 0.040), triglyceride (r = 0.405, p <0.001) levels was statistically significant. There was a positive correlation between glucose and insulin (r =0.295, p <0.001), triglyceride (r =0.168, p =0.007), non-HDL cholesterol (r =0.141, p =0.025), BMI (r =0.289, p =0.001) levels was also statistically significant.

The relationship between TSH and glucose (r =0.231, p <0.001), insulin (r =0.165, p =0.006), HOMA-IR (r =0.196, p <0.001), fT4 (r =-0.477, p =0.025), vitamin D (r =-0.200, p =0.003), cholesterol (r =0.143, p =0.024), LDL cholesterol (r =0.154, p =0.018), non-HDL cholesterol (r = 0.134, p = 0.035) levels was statistically significant in the high normal range group. There was a significant positive

correlation between HOMA-IR with glucose (r =0.560, p <0.001), insulin (r =0.979, p <0.001), BMI (r =0.426, p <0.001), triglyceride (r =0.276, p <0.001), HDL cholesterol (r =-0.291, p <0.001), non-HDL cholesterol (r =0.159, p =0.013) levels was statistically significant. The relationship between glucose and insulin (r =0.413, p <0.001), triglyceride (r =0.231, p <0.001), HDL cholesterol (r =-0.224, p <0.001), non-HDL cholesterol (r =0.185, p =0.003) levels was also statistically significant.

DISCUSSION

As far as we know, this is the first study aimed at assessing whether TSH levels within the reference range are simultaneously related to insulin resistance, lipid profile, and vitamin D levels. In our study, the mean serum TSH level of all our patients was within the normal range. Our results showed that the increase in serum TSH levels within the reference range was positively associated with insulin resistance and BMI. The correlation between TSH and HOMA-IR was better in the high normal TSH group than in the low normal TSH group. In addition, cholesterol, LDL, and non-HDL cholesterol levels were found to be positively correlated with TSH levels, and fT4 and vitamin D were negatively associated. These data suggest that thyroid hormones are associated with metabolic status and may lead to increased insulin resistance and related diseases. Our data are similar to several studies showing that TSH levels in adults may be associated with insulin resistance (12,14).

Serum TSH concentrations were found to be positively correlated with fasting and post-loading insulin levels and negatively correlated with insulin sensitivity in euthyroid individuals (15). Ping Zhu et al. reported that TSH levels in 447 euthyroid individuals were positively and linearly related to HOMA-IR in both diabetic and nondiabetic groups (16). Mueller et al. also in a study, found a correlation between insulin resistance with TSH in polycystic ovary syndrome, independent of age and BMI (14). In our study, we found that increases in TSH levels in the reference range were positively associated with HOMA-IR, as reported by Vaia Lambadiari et al. (17). Studies suggest that even small deviations in thyroid hormone levels in the physiological range can lead to insulin resistance (2). Thyroid hormones control metabolic rate, core body temperature, appetite, and sympathetic activity as well as regulate insulin secretion and destruction (17). Studies conducted showed that thyroid hormones may affect insulin sensitivity by affecting the activation or expression of β adrenergic, and gamma receptors (18). Brenta et al. have reported that patients with hypothyroidism showed much lower glucose utilization during intravenous insulin tolerance tests (19). Thyroid hormone therapy has been reported to increase insulin sensitivity in obese diabetic rodents (20). In tissue cultures from rats, pose

to the thyroid hormone has been shown to cause raised GLUT 4 expression and glucose transport rate in the precursor cells of brown adipocytes. As a result, even mild hypothyroidism can trigger insulin resistance by causing reduced transcription of glucose transporters such as GLUT4 (18).

It has been stated that thyroid function is positively related to insulin resistance in obese individuals (21). Insulin resistance is determined by adipose tissue and associated inflammatory changes. As a possible key factor in the development of IR, it has also been suggested that leptin, which causes obesity, may be related to TSH (14). Studies conducted on euthyroid individuals have shown a positive relationship between serum TSH and BMI (12). Even minor changes in thyroid function have possible implications for the risk of developing obesity. Our results are consistent with the results of Mueller et al., in which BMI is positively correlated with TSH levels in the reference range (14). TSH receptors are found in a variety of body cells, including adipocytes. TSH mediates leptin secretion by binding to receptors on adipocytes (16). Leptin also has a possible role in the regulation of thyroid function through the stimulation of TRH. Moreover, thyroid hormones, and their metabolites also cause adiposity and weight gain. Mechanisms are related to adenosine triphosphate utilization, synthesis, direct impact on mitochondrial biogenesis, and its inotropic and chronotropic effects (22). This condition the idea that changes in the thyroid function are the main ones, and changes in BMI through changes in energy expenditure are secondarily effective. The increase in BMI and fat mass can also subsequently cause an increase in serum leptin (12). Since ectopic fat has a critical role in the formation of insulin resistance, fat cells may be an important factor in the relationship between TSH and insulin resistance (16). Our data confirm the results of some studies showing a close relationship between BMI and HOMA-IR and that development of obesity is a risk factor for the formation of IR (23,24).

Thyroid hormones are associated with dyslipidemia as they act as stimulators in the synthesis and destruction of lipids (25). Asvold et al. in a study conducted with people without known thyroid disease; reported that TSH increases in the normal range were positively, and significantly correlated with serum cholesterol, triglyceride, LDL, and non-HDL cholesterol levels (26). In our study, as in some studies conducted in individuals without significant thyroid dysfunction, increases in TSH showed an association with total cholesterol (27, 28) LDL cholesterol (27, 28) non-HDL cholesterol (27), and TG (28) levels. Thyroid hormones induce lipolysis in adipocytes and thus rise fatty acid levels in vivo. It also stimulates the re-esterification of free fatty acids to triacylglycerol, fatty acid

oxidation in the liver, and de novo lipogenesis from glucose metabolism (22). The higher total cholesterol and LDL cholesterol levels we detected may be due to less cell surface receptor expression for LDL leading to a reduction in LDL catabolism (26). Decreased lipoprotein lipase activity and impaired clearance of lipoproteins due to less LDL receptor function may also outcome in high triglycerides in patients with high TSH (18). Increased accumulation of triglyceride in muscle tissue of type 2 diabetics and obese has been related to IR (29). It is also known that insulin resistance is accompanied by high hepatic cholesterol, very low-density lipoprotein production, precursor LDL particles, and increased HDL cholesterol clearance. Since LDL particles have a lower affinity than the LDL receptor, there is a retardation in their clearance (30). Studies have shown that thyroid hormone replacement reduces total serum cholesterol and LDL cholesterol levels in persons with TSH in the upper limit of the reference range (31).

Data on the direct interactions among circulating TSH and vitamin D levels are still insufficient. Tamer et al. found the frequency of vitamin D deficiency to be higher in those with obvious hypothyroidism (94%) or subclinical hypothyroidism (98%) than in those with euthyroidism (86%) (32). Our results showed that TSH levels at the upper limits of the normal range were related to lower vitamin D. Barchetta et al. in his study, which examined the relationship of TSH levels with the seasons in euthyroid adults, revealed for the first time that vitamin D deficiency was related with higher TSH levels, and showed that the relationship between serum TSH levels with vitamin D status was independent of the season (33). Liu et al. found that mice that received intraperitoneal injection of calcitriol before sensitization with porcine thyroglobulin did not show signs of inflammation of the thyroid, and reported that vitamin D had a protective role against the formation of thyroiditis (34). Gelbard et al. VDRs have been detected in the pituitary gland and it has been shown that vitamin D regulates the secretion of pituitary hormones in experimental studies (35). Vitamin D levels can affect the hypothalamus-pituitary-thyroid axis exerting a direct effect on thyrocytes as well as VDR expression in hypothalamic and thyrotropic pituitary cells. Vitamin D insufficiency may result in decreased sensitivity of thyrocytes to TSH stimuli and increased serum TSH levels (33).

There is concurrence that many persons with high normal TSH are probably to have early signs of thyroid dysfunction**.** Some authors state that the reference range for TSH must keep as 0.4 -4.0 mIU/l, as there is not sufficient cause for lowering the upper limit of the reference range for TSH (36). Mueller et al. in their study, associated the 2 mIU/l TSH threshold for IR detection with the best sensitivity and specificity in women with PCOS (14). Some

studies suggest that individuals with a TSH value above 2.5 mIU/L are at risk in terms of thyroid disorders (13). Studies in euthyroid individuals have detected that increased thyroid antibodies correlate with TSH levels (31). In addition, the results of the 20-year follow-up of study also showed that TSH elevations greater than 2 mU/l were related to an increased hypothyroidism risk (37). The American Society of Clinical Endocrinologists stated that it would be appropriate to change the upper limit of the TSH reference range for adults to 3.0 mIU/L (38).

Our study has some limitations. The sample size of the study was relatively small, retrospective, and cross-sectional. Our findings indicate that multicenter, larger prospective studies are needed for the relationship between insulin resistance, hyperlipidemia, and vitamin D in people with TSH levels within the normal range.

In conclusion, our study showed that increased TSH levels within the reference range were positively correlated with insulin resistance and cholesterol, LDL cholesterol, and non-HDL cholesterol levels, and negatively correlated with vitamin D and fT4 levels. These data suggest that even TSH levels showing clinically normal thyroid function may be associated with low vitamin D levels and may conduce to the development of IR and dyslipidemia, which are effective in the formation of Type 2 DM and CAD. Therefore, we believe that determining the optimal TSH target and regularly reviewing serum TSH levels with thyroid status can reduce cardiometabolic risk and related morbidity and mortality.

Ethics Committee Approval: This study was approved by the ethics committee of Istanbul Başakşehir Çam and Sakura City Hospital (No.2021.06.120). Due to the retrospective and observational character of the study design, the requirement for informed consent has been waived.

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