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The Relationship between Thyroid Hormones, Metabolic Syndrome and HOMA-IR in People with Obesity or Overweight

ABSTRACT

Objective: In the literature the data about the relationship between thyroid hormone (TH) levels and Metabolic Syndrome (MetS) components are conflicting. Our aim was to evaluate the associations between THs and MetS as well as individual components of MetS and homeostatic model assessment of insulin resistance (HOMA-IR) in euthyroid people with obesity and overweight.

Materials and methods: Adult patients who presented to Family Medicine Outpatient Clinics of a tertiary hospital between May 2019 and December 2019 with the intention of weight loss were enrolled in this cross-sectional, descriptive study. The data including height, weight, waist circumference, hip circumference, blood pressure (BP), fasting blood glucose (FBG), total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglyceride, thyroid stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), insulin, HOMA-IR, and HbA1c were analyzed.

Results: A total of 175 patients, 135 (77.1%) female, 40 (22.9%) male (mean age: 40.8 ± 13.1 years), without known thyroid dysfunction were included. A total of 86 were overweight and 89 were obese. Fifty-nine (33.7%) of the study participants were diagnosed with MetS. Subjects with MetS had significantly higher level of fT3 even within the normal range (p = 0.039). When TSH, fT4 and fT3 values were compared with other metabolic components in the group with MetS, a significant positive correlation was found only between fT4 level and HOMA-IR (Rho = 0.316, p = 0.026).

Conclusions: MetS was associated with high normal fT3 suggesting differential thyroid hormone metabolism in people with MetS. (Clin Diabetol 2022; 11; 5: 333–339)

Keywords: thyroid hormones, metabolic syndrome, overweight, obesity, insulin resistance

Introduction

Metabolic syndrome (MetS), a well-known cluster of cardiovascular risk factors, is a major public health concern worldwide [1]. The risk of cardiovascular disease, diabetes mellitus and certain types of cancer are increased in patients with MetS [1, 2]. Weight gain, sedentary lifestyle and genetic predisposition pave the way for MetS [1, 3].

Thyroid hormones (TH) are essential for cellular energy homeostasis and regulation. These actions are mediated both through the central nervous system and the direct interaction of TH with peripheral target organs [4]. Abnormal levels of THs alter metabolism and these alterations cause a MetS-like picture [1, 4]. Studies suggest an association between a high thyroid stimulating hormone (TSH) and (individual components of) the MetS [1, 4–7]. Both MetS and hypothyroidism are independent risk factors for cardiovascular disease (CVD) and presence of both conditions may

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increase the risk of CVD with a synergistic effect [8, 9]. Determination of the relationship of thyroid dysfunction with CVD and MetS led the researchers to conduct studies for analyzing the associations of THs with MetS components [10, 11]. Some of these researchers reported the association between thyroid stimulating hormone (TSH) levels and metabolic risk factors, whereas others observed that high-normal free triiodothyronine (fT3) levels and fT3-fT4 ratio were related to MetS] [5–12]. It was also suggested that insulin resistance (IR) and MetS were associated with low serum free thyroxine (fT4) levels in euthyroid patients [11]. While it has not been confirmed by all studies, higher serum TSH concentrations were found in children and adults with obesity compared with lean individuals [5–7, 12, 13].

As a result, the literature about the issue is controversial. Because of the differing results regarding the issue, we aimed to evaluate the association between THs, MetS and individual components of MetS, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in euthyroid patients with overweight or obesity in this study.

Materials and methods

Study design

This study was designed as a cross-sectional, descriptive, retrospective study. Adult patients who presented to Health Sciences University, Ankara Diskapi Training and Research Hospital Family Medicine Outpatient Clinic between May 2019 and December 2019 with the intention of weight loss constituted the target population of this study.

Study population

Approximately 300 patients per year apply to the Family Medicine outpatient clinic in order to lose weight. It was aimed to reach a total of 169 patients with a 95% confidence interval and 5% margin of error. Eighteen of the 230 patients who came in the relevant period, whose data were missing, were excluded. Patients older than 80, younger than 18, patients who were under treatment for a thyroid disorder and/or hyperlipidemia, and patients who were on medications known to interact with thyroid function were not included in the study cohort. In addition, participants with diabetes mellitus, chronic lung disease, cancer, renal failure, autoimmune disease, pregnancy or other conditions that might affect TH concentrations or basal metabolic rate were excluded. A total of thirty-seven patients were excluded because of those comorbidities and medications. The data of the remaining 175 patients were included in analysis.

The collected patient data included: height (cm), weight (kg), waist circumference (WC) (cm), hip circumference (HC) (cm), blood pressure (BP) (mmHg), fasting blood glucose (mg/dL), total cholesterol (TC) (mg/dL), HDL-cholesterol (HDL-C) (mg/dL), low density lipoprotein cholesterol (LDL-C) (mg/dL), triglyceride (TG) (mg/dL), TSH (mIU/L), free thyroxine (fT4) (ng/dL), free triiodothyronine (fT3) (ng/L), insulin (mU/L) HbA1c (%) and HOMA-IR.

BP and anthropometric measurements were obtained using a standardized protocol. BP was measured every minute during a period of 10 min with an automated OMRON Monitor (M3 Comfort HEM-7155-E, Japan). The average of the final three readings was recorded for systolic and diastolic BP. Height, weight and waist and hip circumference were measured with the participant in light clothing and without shoes.

Biochemical measurements

Blood samples were collected between 8 and 10 a.m. after at least 8 h of overnight fasting, directly into tubes containing heparin and centrifuged. Serum lipid parameters were examined using the enzymatic colorimetric method (Beckman Coulter AU, USA). Fasting blood glucose was determined through the enzymatic UV test (Beckman Coulter AU, USA). Levels of thyroid stimulating hormone (TSH), as well as free thyroxine (fT4) and free triiodothyronine (fT3) were assayed by chemiluminescence immunoassay method (Beckman Coulter, Access 2, USA). Normal values (the reference range) for the THs: 2–4.4 ng/L for fT3, 0.9–1.7 ng/dL for fT4, 0.3–.4.2 mIU/L for TSH. The general Turkish population is iodine sufficient.

Body mass index (BMI) was calculated by division of the total body weight (kg) to the square of height (m^2). As per 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease, the study participants were categorized as overweight if the BMI was in the range of 25–29.9 kg/m^2 or obese in the case that BMI was 30 kg/m^2 or above [14]. Insulin resistance was assessed using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) scores [15]. HOMA-IR was calculated according to the following formula: FPG (mg/dL) × fasting insulin (mU/mL)/405. Patients with HOMA-IR scores higher than 2.33 were accepted to have IR [16]. MetS was diagnosed based on the National Cholesterol Education Programs Adults Treatment Panel III (NCEP ATPIII) criteria [17]. The MetS was diagnosed in the presence of three or more of the following factors: waist circumference of more than 40 inches (102 cm) in male and 35 inches (89 cm) in female patients, a serum triglyceride level of 150 milligrams per deciliter (mg/dL) or higher, a serum high-density lipoprotein (HDL) level

Table 1. Baseline Characteristics of the Participants*

Variable	MetS (+) (n = 59)	MetS (–) (n = 116)	P
Gender (female/male), n	38/21	97/19	**0.007**
Age [years]	43 ± 12.6	40.4 ± 13.3	0.215
TSH [mIU/L]	2.1 ± 0.9	1.9 ± 0.9	0.189
fT4 [ng/dL]	0.9 ± 0.2	0.9 ± 0.1	0.810
fT3 [ng/L]	3.7 ± 0.5	3.5 ± 0.5	**0.039**
Systolic blood pressure [mmHg]	127.1 ± 16.9	115.9 ± 14	**0.001**
Diastolic blood pressure [mmHg]	84 ± 14	77.7 ± 11	**0.001**
Pulse rate [/min]	77.3 ± 8.3	79.3 ± 9	0.168
Fasting glucose [mg/dL]	90.8 ± 13.1	83.5 ± 9.4	**0.001**
Insulin [mU/L]	13.9 ± 12	10.1 ± 13.2	**0.071**
HbA1c [%]	5.7 ± 0.4	5.6 ± 0.3	0.139
Insulin resistance (HOMA-IR)	3.2 ± 3.2	2.1 ± 3.2	**0.046**
Triglycerides [mg/dL]	192.7 ± 92	120.7 ± 56.8	**0.001**
HDL-C [mg/dL]	39.6 ± 7.4	49.7 ± 10.1	**0.001**
LDL- C [mg/dL]	129.1 ± 31.6	132.2 ± 28.8	0.515
BMI [kg/m^2]	32.3 ± 4.3	29.9 ± 3.5	**0.001**
Overweight/Obese (n)	18/41	68/48	**0.001**
Waist circumference [cm]	107.9 ± 12.8	100.1 ± 13.1	**0.001**
Hip circumference [cm]	114.7 ± 7.6	111.1 ± 7.5	**0.004**

*Data presented as mean ± SD
BMI — body mass index; fT3 — free triiodothyronine; fT4 — free thyroxine; HbA1c — glycated hemoglobin; HDL-C — high density lipoprotein cholesterol; HOMA-IR — Homeostatic Model Assessment of Insulin Resistance; LDL-C — low density lipoprotein cholesterol; TSH — thyroid stimulating hormone

of lower than 40 mg/dL in men or 50 mg/dL in women, a fasting blood glucose level of 100 mg/dL or above, a systolic blood pressure of 130 mmHg or higher and/or diastolic blood pressure of 85 mmHg or higher.

Outcome measures

The primary endpoint of this study was to evaluate the presence of MetS affects TH levels in euthyroid patients with obesity or overweight. The second endpoint was to examine whether there is a relationship between MetS components and some clinical and laboratory parameters and THs in euthyroid individuals with obesity or overweight.

Statistical analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS version 21.0, IBM®, Chicago, IL, US). Descriptive statistical methods in the evaluation of demographic data: frequency, percentage, mean, standard deviation were used. Normal distribution of the data was tested by the Shapiro-Wilks test. Quantitative variables were stated as mean ± standard deviation (SD) and median (min–max), and categorical variables as number (n) and percentage (%). In the examination of a statistically significant difference between the groups the Student's *t*-test was used for quantitative variables and Chi-Square test was used for categorical variables. The correlations between TH levels and other parameters were assessed by Spearman's correlation analyses. The differences were considered statistically significant when p value was lower than 0.05.

Ethical considerations

This study was designed and conducted in accordance with the principles stated by the Declaration of Helsinki of 1975, as revised in 2013. The study was reviewed and approved by the local ethic committee of Ankara Diskapi Training and Research Hospital (Date-number: 2019-75/10).

Results

In total, 175 patients participated in this study. The study population consisted of 135 (77.1%) female and 40 (22.9%) male patients. Mean patient age was 40.8 ± 13.1 (18–80). Among the study patients, 49.1% were overweight and 50.9% were obese. Fifty-nine (33.7%) of the study participants were diagnosed with MetS. Data regarding the comparison between the groups with and without MetS are presented in Table 1. Of these, considering that approximately 77% of the study participants are female, MetS was found to be more common in men (p = 0.007). Subjects with MetS had

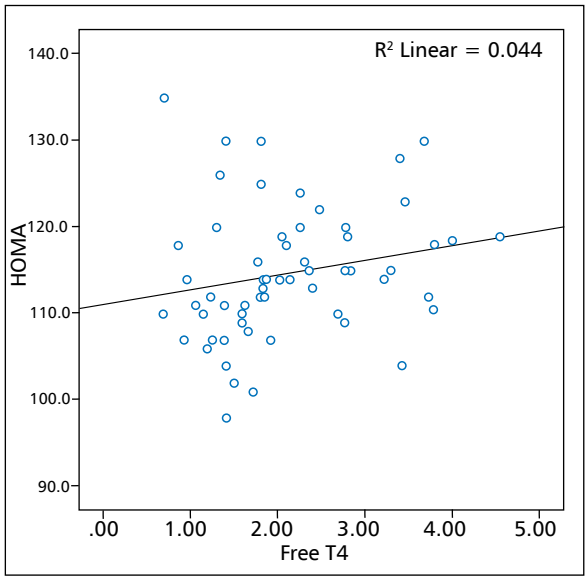

Figure 1. Correlation Between Homeostatic Model Assessment of Insulin Resistance and Free Thyroxine in MetS (+) Group

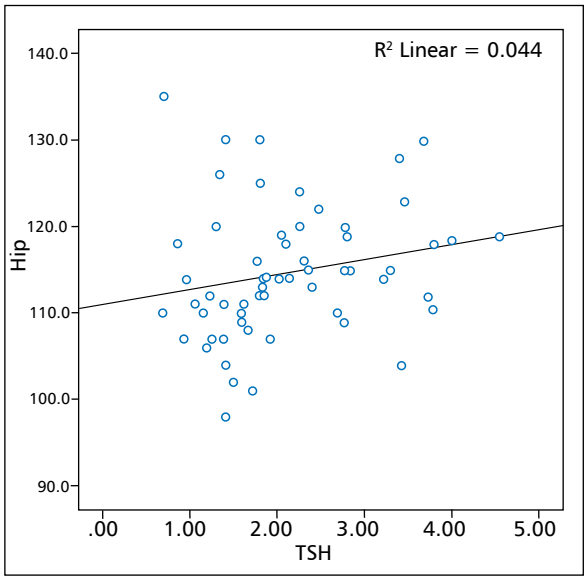

Figure 2. Correlation Between Hip Circumstances Thyroid Stimulating Hormone Levels in MetS (+) Group

significantly higher level of fT3 (even within the normal range), BP, glucose, triglyceride, LDL-C, HOMA-IR, BMI, WC, and HC. The prevalence of MetS was higher in obese compared to overweight ones.

This analysis revealed that considering THs, there was a significant difference for only the levels of fT3 of these two groups ($p = 0.039$). There was no significant difference between the two groups in terms of other THs.

On the other hand, while there was no difference between the insulin levels of both groups, the HOMA index was higher in those with MetS ($p = 0.046$).

When TSH, fT4 and fT3 values were compared with other metabolic components in the group with MetS, a significant positive correlation was found only between fT4 level and HOMA index ($p = 0.026$) and between TSH level and HC ($p = 0.015$) (Figs.1 and 2). (Tab. 2).

Discussion

In recent years, the relationship between THs and metabolic risk markers has been widely discussed [2–12]. This study aimed to assess the relationship between THs and MetS and its components in healthy euthyroid adults with overweight or obesity. Our analysis revealed that there were no significant associations between fT4, TSH and MetS. However increased fT3 level was observed in MetS patients with overweight or obesity

In a study done in China in 2018, the rate of MetS was calculated as 17.7% and authors reported that TSH and fT4 levels were not associated with the rates of MetS and its individual components, but increased serum fT3 level was an indicator for developing MetS in euthyroid subjects [4]. Our findings were in line with this study. In our study, the rate of MetS was 33.7%. However, it should be considered that our study population consisted of patients who presented to our outpatient clinic with the intention of losing weight. In another study, authors assessed the relationship between serum TSH levels and MetS and they found no significant association [9]. It is similar to our results. In a study conducted with 26719 patients, MetS was diagnosed in 20.7% of men and 11.8% of women. It has been determined that the highest quartiles of fT3 and fT3/fT4 ratio predicted a 49% and 67% higher prevalence of MetS in men, and a 62 and 80% higher prevalence in women [10]. These results were consisted with the results of our study, except for MetS rates. Our interpretation of the higher incidence of MetS in our study was given above. In another study which evaluated 44196 euthyroid patients, it was found that the association between serum fT4 levels and MetS components were age- and gender-dependent, but there was no relationship between serum fT4 levels and MetS in age-adjusted analysis [11]. Similarly, we did not find a relationship between fT4 and MetS components. Our investigation regarding the association between THs and MetS components revealed that increased fT3 level was observed in MetS patients with overweight or obesity. This finding was consistent with the findings reported in a study conducted with 16975 patients in China [18]. In that study, the authors found that participants with overweight or obesity had a high serum concentration of T3, high fT3/fT4 ratio and a low concentration of fT4 [18]. We have demonstrated an association between fT4 levels within the normal reference range and increased

Table 2. Associations of Thyroid Hormones with Clinical Parameters in MetS (+) Group

Variable	fT3	fT4	TSH
Fasting glucose [mg/dL]			
Rho	–0.144	0.007	–0.203
p	0.3	0.960	0.124
Triglycerides [mg/dL]			
Rho	0.029	–0.076	0.032
p	0.834	0.573	0.809
HDL-C [mg/dL]			
Rho	–0.157	–0.012	–0.247
p	0.256	0.932	0.060
LDL-C [mg/dL]			
Rho	–0.098	0.149	–0.218
p	0.479	0.268	0.096
Systolic blood pressure [mmHg]			
Rho	–0.201	–0.092	0.074
p	0.150	0.501	0.582
Diastolic blood pressure [mmHg]			
Rho	–0.012	–0.037	0.112
p	0.934	0.788	0.403
Pulse rate [/min]			
Rho	0.102	–0.110	0.145
p	0.469	0.422	0.286
HOMA-IR			
Rho	–0.047	**0.316**	–0.133
p	0.749	**0.026**	0.348
HbA1c [%]			
Rho	–0.026	0.054	–0.040
p	0.857	0.696	0.771
BMI [kg/m^2]			
Rho	–0.263	–0.057	0.079
p	0.055	0.672	0.550
Waist circumference [cm]			
Rho	–0.054	0.039	0.089
p	0.698	0.775	0.560
Hip circumference [cm]			
Rho	–0.100	–0.007	**0.315**
p	0.471	0.962	**0.015**

BMI — body mass index; fT3 — free triiodothyronine; fT4 — free thyroxine; HbA1c — hemoglobin A1C; HDL-C — high density lipoprotein cholesterol; HOMA-IR — Homeostatic Model Assessment of Insulin Resistance; LDL-C — low density lipoprotein cholesterol; TSH — thyroid stimulating hormone

insulin resistance. This finding was not consistent with the result of another study in which was found that an inverse correlation between serum fT4 level and HOMA-IR [19].

In the study of euthyroid adolescents with obesity, they revealed that fasting insulin and HOMA-IR positively correlated with fT3 and TSH and negatively with fT4 [20]. This study highlights that there is the association of higher levels of both fT3 and TSH with body adiposity, MetS and insulin resistance in euthyroid subjects. Similar to the results of this study, our findings showed a positive relationship between BMI and TSH and fT3 levels (p = 0.055, p = 0.055 respectively).

Our study participants include 46% obese population having MetS instead only around 20% overweight having Mets. This finding was consistent with the result of study which shows that both duration and severity of obesity are positively associated with incident MetS [21].

A meta-analysis on the association of thyroid dysfunction and MetS showed that there was a strong

overlap in these two diagnoses. However, the authors stated that cause and effect relation is not clear between two clinical entities. They also noted that some studies based on the previously defined criteria for diagnosing MetS, while some others considered cases with MetS-like clinical features as MetS. As per the cohort studies reported in 2020, it would not be reasonable to suggest that thyroid dysfunction leads to MetS or it is significantly related to MetS. In fact, the more popular opinion is that MetS can also impact the thyroid functions [22].

The result of our study supports that TH levels can be affected when MetS occurs in euthyroid individuals with obesity or overweight. Even if the TH levels of people with obesity and MetS are normal in the initial evaluations and they do not have other comorbidities, care should be taken in their follow-up, and they should be evaluated periodically in terms of type 2 diabetes mellitus or thyroid dysfunctions that may occur later.

There are some limitations of our study. Having worked with a larger number of patient's dataset would have helped obtain more reliable information. We are unable to infer causality, because this was a retrospective cross-sectional study.

Conclusions

We conclude that serum fT3 levels within the normal range were associated with MetS in individuals with overweight or obesity. Unlike many studies, there was no significant difference in serum insulin levels in groups with and without MetS, but a significant difference was found in HOMA-IR values, and a positive correlation was found between HOMA-IR and fT4 in those with MetS. These findings suggest that MetS may affect TH levels, especially fT3 and fT4.

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Conflict of interest

None declared.

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