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Prevalence of metabolic syndrome in hypothyroid patients under Levothyroxine therapy

Levotiroksin tedavisi altındaki hipotiroidi hastalarında metabolik sendrom prevalansı

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ABSTRACT

Aim: *Since thyroid hormones have an impact on lipid and glucose metabolism, thyroid dysfunction is a risk factor for cardiovascular diseases. Metabolic syndrome (MS) is related to higher risk of cardiovascular disease, diabetes mellitus, and all-cause mortality. Studies have demonstrated that thyroid dysfunction corresponds to a higher prevalence of MS. Additionally, some studies have showed patients with MS had a higher prevalence of hypothyroidism. We aimed to investigate whether hypothyroid patients being treated with levothyroxine still have a higher prevalence of metabolic syndrome or not.*

Methods: *One hundred and eighty-six hypothyroid patients (175 female, 11 male) using levothyroxine treatment were included in the study. Demographic, anthropometric and laboratory measures were recorded. International Diabetes Federation (IDF) criteria were used for diagnosis of MS.*

Results: *The prevalence of MS was 52% in hypothyroid patients using levothyroxine. Mean age was 48.44±14.90 years. Mean TSH was 1.94±1.11 uIU/L and mean free T4 was 1.06±0.20 (ng/dL). Mean weekly levothyroxine dose was 537.01 mcg. Weekly levothyroxine dose was positively correlated with weight (r^2:0.188, p:0.010), BMI (r^2:0.227, p:0.026) and waist circumference (r^2:0.164, p:0.026). Weekly levothyroxine dose was also positively correlated with LDL-cholesterol (r^2:0.167, p:0.031) and HbA1c (r^2:0.180, p:0.034) levels. Weekly levothyroxine dose was not correlated with other cardiometabolic risk factors (p>0.05).*

Conclusions: *The prevalence of metabolic syndrome is still high in hypothyroid patients under levothyroxine treatment. Moreover, more comprehensive studies should be performed in a larger-scale population to enlighten this association.*

Keywords: *Metabolic syndrome, hypothyroidism, levothyroxine treatment*

ÖZ

Amaç: *Tiroid hormonlarının lipid ve glukoz metabolizması üzerinde etkileri olduğundan, tiroid disfonksiyonu kardiyovasküler hastalıklar için bir risk faktörüdür. Metabolik sendrom (MS) artmış kardiyovasküler hastalık ve tip 2 diyabetes mellitus riski ile birlikte artmış tüm nedenlere bağlı ölümle ilişkilidir. Çalışmalar tiroid disfonksiyonunun artmış MS prevalansı ile ilişkili olduğunu göstermiştir. Bunun yanında, MS'lu hastalarda daha fazla hipotiroidi görülmektedir. Bu çalışmada, levotiroksin tedavisi altındaki hastaların hala daha yüksek metabolik sendrom prevalansına sahip olup olmadıklarını araştırdık.*

Method: *Çalışmaya levotiroksin tedavisi altında olan hipotiroid 186 hasta (175 kadın, 11 erkek) alındı. Demografik, antropometrik ve laboratuvar verileri dosyalarından kaydedildi. International Diyabetes Federation (IDF) kriterleri metabolik sendrom tanısında kullanıldı.*

Bulgular: *Hipotiroidi hastalarında metabolik sendrom sıklığı %52 idi. Ortalama yaş 48,44±14,90 yıl idi. Ortalama TSH düzeyleri 1,94±1,11 uIU/L iken ortalama serbest T4 1,06±0,20 ng/dL idi. Ortalama haftalık levotiroksin dozu 537,01 mcg idi. Ortalama haftalık levotiroksin dozu ağırlık (r^2:0,188, p:0,010), vücut kitle indeksi (r^2:0,227, p:0,026) ve bel çevresi (r^2:0,164, p:0,026) ile pozitif korrele idi. Ortalama haftalık levotiroksin dozu aynı zamanda LDL-kolesterol (r^2:0,167, p:0,031) ve HbA1c (r^2:0,180, p:0,034) düzeyleri ile de pozitif korrele idi. Ortalama haftalık levotiroksin dozu diğer kardiyometabolik risk faktörleri ile ilişkili değildi (p>0,05).*

Sonuç: *Levotiroksin tedavisi altında ötiroid olan hipotiroidi hastalarında hala artmış metabolik sendrom prevalansı mevcuttur. Bununla birlikte daha büyük hasta grubu içeren daha geniş kapsamlı çalışmalar yapılmalıdır.*

Anahtar kelimeler: *Metabolik sendrom, hipotiroidi, levotiroksin tedavisi*

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INTRODUCTION

Hypothyroidism is characterized by insufficient production of thyroid hormones or lack of any effect of thyroid hormone on target organs. It is a very common endocrinologic disorder[1]. Since metabolisms of lipid and glucose are affected by thyroid hormones; thyroid dysfunction is accepted as a cardiovascular risk factor[2]. Metabolic syndrome (MS) is defined as a group of specific cardiovascular (CV) risk factors such as central obesity, hypertension, hyperglycemia, and dyslipidemia. Inflammation, and dysfunction of endothelium, hypercoagulability, and atherosclerosis are other important features of MS which are related to increased risk of cardiovascular disorders, diabetes mellitus, and all-cause mortality[3,4]. Lifestyle, demographic, socio-economic, and genetic factors affect the prevalence of MS that varies by region and ethnic group[5]. According to previous studies, frequency of MS in Turkey ranges between 23.7% and 32.2% in males and 38.6% and 45.0% in females[6].

The association between hypothyroidism and MS has become a popular topic of discussion in recent years. Studies have demonstrated that thyroid dysfunction is related to an increased prevalence of MS[7,8]. Additionally, some studies showed patients with MS had a higher prevalence of hypothyroidism[9,10]. Lee et al.[11] have demonstrated a higher prevalence of MS in patients with high- normal TSH levels. We aimed to investigate whether hypothyroid patients being treated with levothyroxine still have an increased prevalence of MS or not.

MATERIAL and METHODS

Participants

One hundred and eighty-six hypothyroid patients using levothyroxine were enrolled in the study. Local ethics committee approval was obtained and all participants were provided with written informed consent forms. Fourteen patients diagnosed with thyroid cancer, and sixty patients who were not euthyroid were excluded from the study. Finally, one hundred and eighty-six hypothyroid patients under levothyroxine treatment, in whom euthyroidism was achieved, were enrolled in the study. All individuals were older than 18 years. Patients with pregnancy, heart failure, renal failure, liver failure, infectious disease, rheumatologic disease were also excluded from the study.

Euthyroidism was described as a condition with normal TSH (reference range: 0.35-4.94 uIU/L) and free T4 (reference range: 0.7-1.48 ng/dL) levels. TSH and free T4 levels were measured using a chemiluminescent immunoassay method.

Blood pressures (BP) were measured from both arms with the patient in a sitting position following a minimum of 10 minutes of rest with a suitable mercurial blood pressure monitors. Body weight, waist circumference (WC), height, and body mass index (BMI) were measured by the same person using standard measurement tools.

International Diabetes Federation (IDF) criteria were used for the diagnosis of MS. Diagnosis of MS was made in consideration of the following criteria: waist circumference >94 cm for males or >80 cm for females plus the presence of at least two of the below criteria: BP ≥130/85 mmHg (or current treatment with antihypertensive drug); fasting blood glucose ≥100 mg/ dL (or current treatment with hypoglycemic drug); fasting triglyceride (≥150 mg/ dL or current treatment for elevated triglyceride; high-density lipoprotein cholesterol <40 mg/dL (for males) or <50 mg/dL (for females) or current treatment for reduced HDL-C[12].

Statistical analysis

All statistical analyses were performed using the JMP 13.0.1 software (SAS Institute, Cary, NC, USA). Mean ± standard deviation was used for expression of quantitative data and numerical values and proportions were used for expression of categorical data. Normality of distribution was examined by using the Kolmogorov-Smirnov or Shapiro-Wilk W test. The chi-square or Fisher's exact test was used when for

categorical variables. Student's t-test was used for normally distributed continuous variables and the Mann-Whitney U test was used for those that did not fit to a normal distribution. Correlations were assessed using Pearson's and Spearman's correlation tests. A p-value of less than 0.05 was accepted as statistically significant.

RESULTS

One hundred and eighty-six hypothyroid patients (175 female, 11 male) using levothyroxine were included in the study. Mean age was 48.30±14.89. Mean TSH value was 1.94±1.11 uIU/L and mean free T4 was 1.06±0.20 (ng/dL). Demographic, anthropometric and laboratory characteristics of patients are shown in table 1.

Mean age, body mass index, waist circumference, systolic blood pressure, triglyceride, fasting plasma glucose, Hba1c, HOMA-IR (for all p<.0001), GGT (p<.001), creatinine (p<0.005), and diastolic blood

Table 1. Demographic, anthropometric and laboratory investigations of patients.

	Mean	SD
Age (years)	48.30	14.89
Gender (female), n(%)	175	94
Height (cm)	161.91	7.25
Weight (kg)	75.62	17.99
BMI (kg/m^2)	29.30	6.38
Waist circumference (cm)	93.05	14.44
Systolic Blood Pressure (mmHg)	123.63	18.17
Diastolic Blood Pressure (mmHg)	80.35	10.38
Levothyroxine dose (weekly)	537.02	239.53
TSH uIU/L	1.90	1.08
Free T4 (ng/dL)	1.06	0.20
Anti-TPO (IU/mL)	162.18	264.41
Anti-TG (IU/mL)	91.04	244.82
Total Cholesterol (mg/dL)	206.59	41.46
HDL-Cholesterol (mg/dL)	53.01	15.59
LDL-Cholesterol (mg/dL)	128.38	35.05
Triglyceride (mg/dL)	128.74	63.40
Fasting plasma glucose (mmol/L)	96.83	23.33
Hb-A1C (%)	5.93	1.06
Insulin mU/L	8.19	4.42
HOMA-IR	2.06	1.60
25-OH Vitamin D (ng/mL)	26.99	13.90
Creatinin (mg/dL)	0.76	0.13
AST (UI/L)	18.93	7.75
ALT (UI/L)	20.52	13.34
CRP (mg/L)	0.82	1.60

Table 2. Demographic, anthropometric and laboratory investigations of patients with and without metabolic syndrome.

	Metabolic syndrome (-)		Metabolic syndrome (+)		
	Mean	SD	Mean	SD	
Age (years)	42.73	13.80	54.07	14.37	<.0001
BMI (kg/m^2)	26.30	5.17	32.48	6.01	<.0001
Waist circumference (cm)	84.75	11.95	101.14	11.88	<.0001
Systolic Blood Pressure (mmHg)	117.90	13.78	130.13	20.10	<.0001
Diastolic Blood Pressure (mmHg)	78.14	9.95	82.56	10.51	0.0051
Levothyroxine dose (weekly)	502.29	219.33	563.56	254.26	0.0908
TSH uIU/L	1.75	0.99	1.97	1.11	0.1793
Free T4 (ng/dL)	1.06	0.19	1.08	0.21	0.5808
Anti-TPO (IU/mL)	194.13	288.59	131.42	242.22	0.2822
Anti-TG (IU/mL)	77.98	157.90	110.07	321.88	0.5792
Total Cholesterol (mg/dL)	202.23	41.70	209.35	40.52	0.2674
HDL-Cholesterol (mg/dL)	59.36	15.35	46.95	13.41	<.0001
LDL-Cholesterol (mg/dL)	125.56	31.54	130.05	37.85	0.4083
Triglyceride (mg/dL)	88.87	25.49	162.91	63.47	<.0001
Fasting plasma glucose (mmol/L)	87.65	7.42	105.59	29.39	<.0001
Hb-A1C (%)	5.46	0.49	6.32	1.25	<.0001
HOMA-IR	1.36	0.56	2.91	2.01	<.0001
25-OH Vitamin D (ng/mL)	26.98	15.32	26.56	12.54	0.8477
Creatinin (mg/dL)	0.73	0.08	0.79	0.17	0.0011
AST (UI/L)	17.83	5.20	19.94	9.56	0.0756
ALT (UI/L)	18.05	9.87	22.72	15.79	0.0213
GGT(UI/L)	14.69	9.63	22.69	18.66	0.0009
CRP (mg/L)	0.60	1.25	1.00	1.85	0.2228

pressure levels (p<.01) were significantly higher in patients with MS when compared to those patients without MS while HDL cholesterol levels were significantly lower (p<.0001) (Table 2).

Mean age, BMI, systolic and diastolic BP, WC, triglyceride, fasting plasma glucose, Hba1c, HOMA-IR, creatinine, and GGT levels were higher in patients with MS when compared to those of the patients without MS. HDL cholesterol levels were lower in patients with MS (Table 2).

Mean weekly levothyroxine dose was 537.01±239.53 mcg. Weekly levothyroxine dose was positively correlated with weight (r^2:0.188, p:0.010), BMI (r^2:0.227, p:0.026) and waist circumference (r^2:0.164, p:0.026). Weekly levothyroxine dose was also positively correlated with LDL-cholesterol (r^2:0.167, p:0.031) and HbA1c (r^2:0.180, p:0.034) levels. Weekly levothyroxine dose was not correlated with other cardiometabolic risk factors (p>0.05) (Table 3).

Table 3. Correlation analysis of weekly levothyroxine dose with cardio-metabolic risk parameters.

	Correlation coefficient	p
Age (years)	0.044	0.547
Height (cm)	0.010	0.891
Weight (kg)	0.188	0.010
BMI (kg/m2)	0.227	0.026
Waist circumference (cm)	0.164	0.026
Systolic Blood Pressure (mmHg)	0.044	0.549
Diastolic Blood Pressure (mmHg)	-0.045	0.540
Total Cholesterol (mg/dL)	0.131	0.089
HDL-Cholesterol (mg/dL)	-0.068	0.382
LDL-Cholesterol (mg/dL)	0.167	0.031
Triglyceride (mg/dL)	0.104	0.182
Fasting plasma glucose (mmol/L)	0.112	0.139
Hb-A1C (%)	0.180	0.034
HOMA-IR	0.122	0.165
CRP (mg/L)	0.043	0.683

DISCUSSION

In our study, MS was seen in 52% of hypothyroid patients using levothyroxine. The frequency of MS was higher among hypothyroid patients treated with levothyroxine relative to general population. These results suggest that metabolic syndrome was more frequently seen even among treated hypothyroid patients.

Thyroid hormones modulate basal metabolism, thermogenesis and have a significant role in lipid and glucose metabolism, food intake and oxidation of fatty acids[13]. Hypothyroidism leads to mild hypertension due to low cardiac output, a decrease in ventricular filling, and cardiac contractility and an increase in systemic vascular resistance[14]. Thyroid hormones have an impact on the synthesis, metabolism, and mobilization of lipids by regulating the activities of key enzymes in lipoprotein metabolism[15]. Hypothyroidism may lead to accelerated atherosclerosis and coronary heart disease, probably as a result of hypercholesterolemia and hypertension[14]. Increased TSH concentrations are related to increased body weight[16].

Even small variations in TSH could result in an increase in body weight[17]. Hypothyroidism is considered to be a risk factor for insulin resistance. Hypothyroidism leads to a decrease in the rate of intestinal glucose absorption, a decrease in liver and muscle glycogenolysis by lowering the adrenergic activity and a reduction in gluconeogenesis and basal insulin secretion. Nevertheless, insulin secretion and free fatty acids levels increase postprandially with a decreased glucose uptake and increased glucose oxidation[18]. Handisurya et al.[19] showed that levothyroxine treatment improved insulin tolerance in hypothyroid patients.

Hypothyroidism has negative effects on total cholesterol, LDL, Apo AI, Apo B, and lipoprotein (a) levels[20-22]. Caron et al.[23] reported that hypothyroidism was associated with lower HDL-C levels that increased with levothyroxine treatment.

Thyroid hormones have an adverse effect on all parameters of MS including lipid and glucose metabolism, BP and weight; hence thyroid dysfunction may lead to the onset of MS[24].

Shantha et al.[25] reported that hypothyroidism was re-

lated to MS, with higher risk in females. Erdogan et al. considered that hypothyroidism had a major impact on the development of MS as a result of increasing waist circumference and insulin resistance[7]. Roos et al.[26] associated free T4 levels with components of MS in individuals with normal thyroid function.

Various studies have evaluated the impact of levothyroxine treatment on metabolic parameters. Bakiner et al.[27] could not find any decrease in body weight and body fat percentage with levothyroxine treatment. Efstathiadou et al.[20] notified that patients with subclinical hypothyroidism have elevated concentrations of the atherogenic lipids (mainly LDL-C and Lp(a)), however, levothyroxine treatment did not improve dyslipidemia in these patients. In a study conducted in hypercholesterolemic patients, the liver-selective thyromimetic eprotirome was shown to decrease serum levels of atherogenic lipoproteins[28].

BMI, WC, BP, triglyceride, fasting plasma glucose, Hba1c, HOMA-IR levels were higher and HDL cholesterol levels were lower in our patients with MS as expected[4]. Hu W et al.[29] showed that MS was independently related to a mildly reduced glomerular filtration rate. We found higher creatinine concentrations in patients with MS. Elevated serum GGT level predicts the onset of MS. We found higher GGT levels in patients with MS.

MS is described as a pandemic affecting 20 to 30% of adult population worldwide[30], while 9.2 million adult people aged ≥ 30 years and 53% of the patients with coronary artery disease suffered from MS according to TEKHARF study conducted in 2000[31]. METSAR (Türkiye Metabolik Sendrom Araştırması) study reported the prevalence of MS as 33.9% among adults in Turkey[32]. Gundogan et al.[6] reported the prevalence of MS in Turkey as 44% according to IDF criteria. According to data of PURE (Prospective Urban Epidemiological Study) Turkey study conducted with 4057 adults; the prevalence rates of MS in women and men were 43.5% and 41.4% respectively. Additionally, the prevalence of MS increases as the population ages. As a matter of fact the prevalence of MS in adults 60-64 years old was 57.7%[33]. We aimed to investigate whether hypothyroid patients under levothyroxine treatment still have a higher prevalence of MS or not. We evaluated the prevalence and parameters of MS in these euthyroid patients. We found that the prevalence of MS is 52% in these patients. These results may show that the prevalence of MS is still high in hypothyroid patients even if they are using levothyroxine treatment. Therefore, MS should be considered in these patients even they are euthyroid. The prevalence of MS found in our study was higher than the results of these mentioned studies conducted in Turkey. These findings could be explained by slightly older patients included in our study.

A cross-sectional design, being a single-center trial, relatively small sample size are limitations of our study.

In conclusion, the prevalence of metabolic syndrome is still high in hypothyroid patients under levothyroxine treatment. Moreover, more comprehensive studies should be performed in a larger population to enlighten this association.

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