Serum Total Antioxidant Status, Lipid Profile, Malondialdehyde and Erythrocyte Superoxide Dismutase Levels in Hashimoto Thyroiditis Patients Treated with Levothyroxine

Levotiroksin Tedavisi Gören Hashimoto Tiroiditi Hastalarında Serum Total Antioksidan Kapasitesi, Lipit Profili, Malondialdehit ve Eritrosit Süperoksit Dismutaz Düzeyleri

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ABSTRACT Objective: To compare the serum level of total antioxidant status (TAS), malondialdehyde (MDA) and erythrocyte superoxide dismutase (SOD) levels in Hashimoto thyroiditis patients treated with levothyroxine and healthy control subjects and to assess possible correlations of these parameters with biochemical parameters such as glucose and lipid profile. **Material and Methods:** SOD, TAS, MDA, fasting glucose, lipid profile, thyroid hormones and body mass index (BMI) were measured in 30 Hashimoto thyroiditis patients treated with levothyroxine and 30 healthy control subjects. **Results:** Body Mass Index was increased in Hashimoto thyroiditis patients compared to control subjects. The biochemical parameters such as glucose, triglycerides, total cholesterol and low-density lipoprotein cholesterol (LDL-C) were higher and high-density lipoprotein cholesterol (HDL-C) was lower in the patient group than in control patients. TAS and MDA levels were significantly higher and erythrocyte SOD levels were lower in the patient group compared to the control group. **Conclusion:** Our study showed that lipid peroxidation was increased in hypothyroid patients compared to healthy controls, even though they were treated with levothyroxine. Erytrocyte SOD levels were lower and TAS was higher in the patient group compared to the control group. Thyroiditis patients treated with levothyroxine had normal thyroid homone ranges but treatment did not seem to improve dyslipidemia and oxidative stres. In conclusion, although the hypothyroid patients had normal thyroid hormone levels due to levothyroxine treatment, oxidative stress parameters seemed to contiue to increase. Thus, we suggest that antioxidant treatment may be continued even after the achievement of euthyroidism.

Key Words: Malondialdehyde; superoxide dismutase; Hashimoto disease; body mass index

ÖZET Amaç: Serum total antioksidan kapasitesi (TAK), malondialdehit (MDA) ve eritrosit süperoksit dismutaz (SOD) düzeylerinin, levotiroksin tedavisi gören Hashimoto tiroiditi hastaları ile sağlıklı kontroller arasında karşılaştırılması ve bu parametrelerin glikoz ve lipit profili gibi biyokimyasal parametreler ile olası ilişkilerinin değerlendirilmesi amaçlanmıştır. **Gereç ve Yöntemler:** Bu çalışmaya, levotiroksin tedavisi gören 30 Hashimoto tiroiditi hastası ve 30 sağlıklı birey dâhil edilmiştir. Bütün bireylerde SOD, TAK, MDA, açlık glikozu, lipit profili, tiroit hormonları ölçümleri yapılmış ve beden kitle indeksi (BKİ) hesaplanmıştır. **Bulgular:** Levotiroksin tedavisi gören Hashimoto tiroiditi hastalarında BKİ'nin ve glikoz, trigliserit, total kolesterol ve düşük yoğunluklu lipoprotein kolesterol (LDL-C) gibi biyokimyasal parametrelerin düzeyinin artmış olduğu saptanmıştır. Yüksek yoğunluklu lipoprotein kolesterol (HDL-C) düzeyinin ise hasta grubunda azalmış olduğu belirlenmiştir. TAK ve MDA düzeyleri hasta grubunda, kontrol grubuna göre istatistiksel olarak anlamlı ölçüde daha yüksek bulunmuştur. Levotiroksin tedavisi gören Hashimoto tiroiditi hastalarında eritrosit SOD düzeyinin ise kontrol grubundaki düzeye göre azalmış olduğu belirlenmiştir. **Sonuç:** Çalışmada, levotiroksin tedavisi gören hipotiroidi hastalarında lipit peroksidasyon düzeyinin kontrol grubuna göre arttığı gösterilmiştir. Eritrosit SOD değerleri hasta grubunda kontrol grubuna göre azalmış, TAK değerlerinin ise artmış olduğu tespit edilmiştir. Levotiroksin tedavisi gören hipotiroidi hastalarında, tiroit hormonları normal düzeye ulaşsa bile, oksidatif stres parametrelerindeki artışın devam ettiği gözlemlenmiştir. Bu hastalara antioksidan takviyesine, ötiroit duruma geçtikten sonra da devam edilmesi gerektiği kanısına varılmıştır.

Anahtar Kelimeler: Malondialdehid; süperoksid dismutaz; Hashimoto hastalığı; beden kitle indeksi

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Hashimoto thyroiditis is an autoimmune disease involving both humoral and cellular responses. The former mechanism is mediated by secretion of antibodies by sensitized cells that bind to the thyroid stimulating hormone receptor and block the action of thyroid stimulating hormone.[1]

Thyroid hormones control the growth of an organism thoroughly by modulating metabolic and energy homeostasis, thermogenesis and the transcription of genes that regulate cell proliferation and basal metabolic rate. Thyroid hormones are also implicated in the regulation of oxidative metabolism and thereby play an important role in reactive oxygen species generation.[2] Any variation in circulatory hormones is suspected to modulate in vivo cellular oxidative stress. The main pathway of this physiological/pathological change is conceived to be an indirect result of enhancement of mitochondrial respiration, which is a source of reactive oxygen species generation.[3]

Accumulating evidence has suggested that hypermetabolic state in hyperthyroidism is associated with increases in free radical production and lipid peroxide levels, whereas the hypometabolic state induced by hypothyroidism is associated with a decrease in free radical production and lipid peroxidation products. However, it is not clear whether thyroid hormone induced increase in lipid peroxidation is confined to some tissues.[4,5] Conflicting results have been reported in studies carried out using different tissues.[4] Besides, the response of antioxidant systems to both hyperthyroidism and hypothyroidism is unclear.

The cell contains a variety of substances capable of scavenging the free radicals, protecting it from their harmful effects. Superoxide dismutase (SOD) is an important antioxidant defense in nearly all cells exposed to oxygen. It outcompetes damaging reactions of superoxide thus protecting the cell from superoxide toxicity. Red cells are known to produce hydrogen peroxide by various mechanisms such as the reaction between ascorbic acid and oxyhemoglobin and the decomposition of oxygen anion by superoxide dismutase. Superoxide dismutase catalyzes the reaction between the two superoxide radicals to yield one molecule each of oxygen and hydrogen peroxide.[6]

Total antioxidant status (TAS) reflects the overall antioxidant state of the organism. Lipid peroxidation is the oxidative degradation of lipids, which enhances with the increase in reactive oxygen species. Malondialdehyde (MDA) is a breakdown product of lipid peroxidation, which is used as a marker to assess lipid peroxidation.[7]

In this study, we investigated the serum MDA, TAS and erythrocyte SOD levels in Hashimoto thyroiditis patients treated with levothyroxine, attending the Endocrinology Department in Dr. Burhan Nalbantoğlu Government Hospital. We also evaluated the lipid profile in order to assess the possible relationship between lipid peroxidation and antioxidant parameters.

MATERIAL AND METHODS

This prospective study examines patients who attended the outpatient clinic of the Endocrinology Department in Dr. Burhan Nalbantoğlu Government Hospital in Cyprus between April 2010 and August 2010. The study population consisted of 60 subjects divided into two groups. The first group included 30 Hashimoto thyroiditis patients treated with levothyroxine and the second group comprised 30 healthy control subjects. The subjects in the control group did not have any history of thyroid disease. Patients had a history of Hashimoto thyroiditis disease and were treated with levothyroxine. All subjects provided written informed consent before enrollment in the study, and the study was approved by the Local Research Ethical Committee. General health characteristics such as age, sex, smoking status, menopausal status and alcohol consumption were investigated by a self-administered questionnaire. The height (m), weight (kg), and waist circumference (cm) of each subject were recorded and body mass index (BMI) was calculated (kg/m^2).

Blood samples were drawn from the antecubital vein after overnight fasting and were centrifuged at 4000 rpm for 10 minutes for serum separation. The serum samples were stored at -80°C

until they were analyzed for MDA and TAS. The erythrocytes were washed three times with physiological saline. A known volume of erythrocytes was lysed with hypotonic phosphate buffer (0.01 M phosphate buffer, pH 7.0). The hemolysates were then aliquoted and stored at -80°C until use for SOD level determination.

Laboratory Analysis

The levels of serum glucose, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were determined using a fully automated clinical chemistry analyzer (Abbott Architect C8000). Thyroid stimulating hormone (TSH), free T3 (FT3) and free T4 (FT4) levels were measured by electrochemiluminescent immunometric assay test method with an Elecsys 2010 Analyzer (Roche Diagnostics, Mannheim, Germany). Serum TAS levels were measured with TAS kit (Randox Labs, Crumlin, UK) and were expressed as mmol/l. Erythrocyte SOD activity was measured with SOD kit (Randox Labs, Crumlin, UK) and was expressed as U/mL. Serum MDA was measured according to the method of Buege and Aust (1978) and was expressed as nmol/l.[8]

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS version 15.0 for Windows, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. All results were expressed as mean±standard deviation. The laboratory characteristics in both groups were compared with the Student's t-test. Differences were considered significant when $p<0.05$.

RESULTS

This study was run between April 2010 and August 2010 with 60 voluntary participants at the Dr. Burhan Nalbantoğlu Government Hospital. The study group consisted of 30 Hashimoto thyroiditis patients treated with levothyroxine (10 males, 20 females) and 30 healthy control subjects (10 males, 20 females). The demographic characteristics of the study population were shown in Table 1. The mean age of Hashimoto thyroiditis patients treated with levothyroxine was 44.83±10.27 and that of control subjects was 36.53±10.03 years. Hashimoto thyroiditis patients treated with levothyroxine had an increased BMI and waist circumference compared to control subjects. Smoking percentage for Hashimoto thyroiditis patients and healthy controls was 66.67% and 60%, respectively.

TABLE 1: Demographic characteristics of the study groups.

	Hashimoto Thyroiditis Group (n=30)	Control Group (n=30)	p
Male/Female	10/20	13/17	0.292
Age (years)	44.83±10.27	36.53±10.03	0.002
BMI (kg/m^2)	27.10±3.38	24.53±3.41	0.671
Waist circumference (cm)	87.27±7.62	85.10±9.38	0.330
Smoking (%)	66.67	60	0.387

BMI: Body Mass Index.
Age, BMI and waist circumference are present as mean±SD.

Table 2 indicates the general biochemical profile, lipid peroxidation and antioxidant status of both groups. The levels of fasting glucose, TG, TC and LDL-C levels were significantly higher in the Hashimoto thyroiditis group than in those in the control group ($p<0.001$). HDL-C levels were signif-

TABLE 2: Biochemical profile of the groups.

	Hashimoto Thyroiditis Group (n=30)	Control Group (n=30)	p
Fasting glucose (mg/dL)	101.30±19.78	89.47±7.20	<0.001
Triglyceride (mg/dL)	142.67±50.56	100.63±28.57	<0.001
Total cholesterol (mg/dL)	234.97±46.45	149.33±37.66	<0.001
HDL cholesterol (mg/dL)	31.67±10.98	33±7.39	0.019
LDL cholesterol (mg/dL)	152.33±29.65	118.03±21	<0.001
TSH (µIU/mL)	2.5±0.65	2.35±0.75	0.411
FT4 (pmol/L)	15±2.14	16±1.92	0.062
FT3 (pmol/L)	6±1.87	7±2.18	0.061
Total antioxidant status (TAS)(mmol/L)	2.42±0.39	1.48±0.16	<0.001
Malondialdehyde (MDA) (nmol/mL)	9.26±0.90	5.08±0.83	<0.001
SOD (U/mL)	129.97±15.04	193±13.67	<0.001

HDL: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol; TSH: Thyroid stimulating hormone; FT3: Free T3; FT4: Free T4; SOD:Superoxide dismutase. Data are presented as mean±SD. Hashimoto Thyroiditis patient compared with control. $p<0.05$.

icantly lower in the patient group when compared to the control group. No significant difference was observed between the two groups in terms of TSH, FT3 and FT4 levels, as the patient group was treated with levothyroxine.

Total antioxidant status was significantly higher in the patient group compared to the control subjects. MDA levels in the Hashimoto thyroiditis group (9.26±0.90 nmol/mL) was higher than the levels of the controls (5.08±0.83 nmol/mL) and the difference was significant ($p<0.001$). Mean erythrocyte SOD level was significantly lower in the Hashimoto thyroiditis patient group (129.97±15.04 U/mL) than in the control group (193±13.67 U/mL).

DISCUSSION

Thyroid hormones are effective in nearly all cells of the body and they have profound effects on many physiological processes such as growth and metabolism. Thyroid hormones tend to increase basal metabolic rate; thus, they alter metabolic oxygen consumption, which leads to an increase in free radical production. It is thus not surprising that changes in thyroid hormone levels affect the mitochondrial free radical generation, as was previously shown in some animal models.[9,10] Thyroid hormones have been shown to affect the synthesis and degradation of the antioxidant proteins, vitamins and enzymes. Because of an associated lower metabolic rate, hypothyroidism is expected to slow the free radical generation, as shown in several studies.[11] In contrast; some studies have shown an increased oxidative stress in hypothyroidism.[12]

Thyroid hormones are predominantly considered hormones involved in the catabolic processes of lipids.[13] Increased thyroid hormone levels stimulate fat mobilization leading to increased concentration of fatty acids in plasma. Plasma concentration of lipids is inversely correlated with thyroid hormone levels. In our study, we found LDL-C, TG and TC levels to be significantly higher and HDL-C levels to be significantly lower in the Hashimoto thyroiditis group treated with levothyroxine than in the control group. Our findings in hypothyroid patients are similar to those in recent studies.[13-15] Decreased cholesterol clearance seems to be the most likely mechanism leading to elevated cholesterol level in hypothyroidism.[16] The inactivation of thyroid gland leads to an increase in BMI. Both BMI and waist circumference were increased in Hashimoto thyroiditis patients treated with levothyroxine in our study.

There were no significant differences in TSH, FT3, and FT4 levels between the patient group compared to the control group, as the Hashimoto thyroiditis patients were treated with levothyroxine.

Thyroid hormones are the most important factors involved in the regulation of the basal metabolic condition as well as the oxidative metabolism. Thyroid dysfunction brings about pathological changes in various organs of the body.[17] Data on the oxidative status in hypothyroidism are limited and controversial. MDA, which is a terminal product of lipid peroxidation and which can be used to estimate the extent of lipid peroxidation, was elevated in our study in the patient group. Pereira et al. found that lipid peroxidation decreased in lymphoid tissues of hypothyroid rats.[11] In contrast, Dimitriu et al. found increased lipid peroxidation in hypothyroid patients.[18] Venditti et al. evaluated different tissues of hypothyroid rats, and found that MDA levels were similar to the levels of the control group.[5] Lassoued et al. found that the plasma MDA level significantly increased in Hashimoto thyroiditis patients.[19] Torun et al. found elevated lipid peroxidation in both overt hypothyroidism and subclinical hypothyroidism patients.[7] All data on MDA and Hashimato thyroidits reported in the literature cited above were derived from Hashimoto thyroiditis patients who were not on levothyroxine treatment and knowledge on MDA and Hashimoto thyroiditis patients treated with levothyroxine is limited in the literature. Only Baskol et al. studied Hashimoto thyroiditis patients both before and after levothyroxine treatment and reported that MDA was higher in hypothyroid patients and still remained higher than the control groups even after being treated with levothyroxin.[20] Our findings on increased MDA, which is a marker for increased oxidative stress are in agreement with the results of Baskol et al.[20]

Free radicals are produced as a consequence of normal metabolism and SOD is an important antioxidant defense in nearly all cells, which is known to catalyze the SOD into oxygen and hydrogen peroxide.[21,22] Thyroid hormones are involved in combatting the toxicity of oxidative stress in animals and humans.[23,24] However, hypothyroidism is characterized by impairment in the redox potential; and the mechanism linking hypothyroidism to oxidative stress and antioxidants is unknown. This leads to free radical chain reactions and to metabolic suppression of antioxidant capacity.[24] Pasupathi et al. found significantly decreased SOD levels in hypothyroid patients.[25] Lassoued et al. found that plasma SOD levels significantly increased in Hashimoto thyroiditis patients.[19] All the findings mentioned above were derived from studies carried out in Hashimoto thyroiditis patients who were not on treatment. Only Baskol et al., Gerenova and Gadjeva reported on the differences in SOD levels both before and after levothyroxine treatment.[20,26] Although Gerenova and Gadjeva found an insignificant decrease in SOD levels in hypothyroid patients treated with levothyroxine, our results suggested significant decreases in the SOD levels.[26] On the contrary, Baskol et al. found significant increases in SOD levels in Hashimoto thyroiditis patients treated with levothyroxine.[20]

Total antioxidant status measurement is informative about the total cellular antioxidant defense system against active oxygen and lipid peroxidation. It consists of a network of antioxidant enzymes and low molecular weight non-protein sulfhydryls that cooperate to keep the concentration of active oxygen species within acceptable levels.[27] TAS has not been studied yet in hypothyroid patients either before or after treatment with levothyroxine. Only Torun et al. found TAS to be significantly higher in subclinical hypothyroid patients when compared with patients with overt hypothyroidism.[7] We also found TAS levels to be significantly higher in Hashimoto thyroiditis patients although they were treated with levothyroxine when compared to the control group.

The relationship between lipid peroxidation and aging was investigated extensively. In our previous study carried out with 140 healthy subjects divided into three groups-young (21-40 years), mature (41-60 years) and elderly (61-85 years)-while we did not find any significant difference in MDA levels, antioxidant activity and lipid profile between the first two groups, they were increased in the elderly group (61-85 years).[28] Thus, the significant differences in those parameters do not seem to be due to age differences.

In conclusion, we found increased oxidative stress in Hashimoto thyroiditis patients treated with levothyroxine compared to the control group. Erythrocyte SOD levels were lower and TAS levels were increased in Hashimato patients when compared to those of the control group. Although hypothyroid patients had normal thyroid homone levels due to levothyroxine treatment, they had increased oxidative stress. Our purpose in this study was to emphasize the importance of prooxidant status in hypothyroidism in order to monitor the pathological status in hypothyroid patients. Our finding need to be confirmed with large-scale studies with a longer duration of levothyroxine treatment.

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