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Ischemia-modified albümin and malondialdehyde levels in patients with overt and subclinical hyperthyroidism: effects of treatment on oxidative stress

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Abstract. The main purpose of this study was to evaluate the levels of ischemia-modified albumin (IMA) and malondialdehyde (MDA) in patients with OHyper and SHyper, to assess the effects of antithyroid drug (ATD) therapy on the oxidative stress (OS) parameters. Forty-five untreated patients with overt hyperthyroidism (OHyper), 20 untreated patients with subclinical hyperthyroidism (SHyper) and 30 age-and sex-matched healthy controls were prospectively included in the study. Biochemical and hormonal parameters were evaluated in all patients before and after treatment. Compared with the control subjects, the levels of MDA, glucose and TG were significantly increased in patients with SHyper ($p<0.05$), whereas LDL-C levels were significantly decreased ($p<0.01$). Patients with OHyper showed significantly elevated MDA and glucose levels ($p<0.001$) and significantly decreased LDL-C and HDL-C levels compared with the controls ($p<0.01$). In patients with Graves' disease, serum TSH levels were inversely correlated with plasma MDA levels (r: -0.42, $p<0.05$). Plasma MDA levels significantly decreased and levels of TC, LDL-C and HDL-C significantly increased in the groups of OHyper and SHyper after treatment. Serum IMA levels did not significantly change at baseline and with the therapy in all subjects. In conclusion, increased MDA levels in both patient groups represent increased lipid peroxidation which might play an important role in the pathogenesis of the atherosclerosis in these patients. Increased oxidative stress in patients with SHyper and OHyper could be improved by ATD therapy. Also, MDA can be used as a reliable marker of OS and oxidative damage, while IMA is considered to be inappropriate.

Key words: Ischemia-modified albumin, Malondialdehyde, Oxidative stress, Biomarker, Overt and subclinical hyperthyroidism

OVERT HYPERTHYROIDISM (OHyper) has been associated with an increased risk of cardiovascular mortality and morbidity [1-3]. The causes of increased cardiovascular risk associated with OHyper are dysrhythmias, especially atrial fibrillation [AF] [4], systolic hypertension [5], heart failure [6], pulmonary hypertension [7], angina pectoris [8], and abnormalities in blood coagulation/fibrinolytic system [9-12]. On the other hand, subclinical hyperthyroidism (SHyper) is defined biochemically by a low serum thyrotropin (TSH) concentration but normal serum free thyroxine (T_4) and triiodothyronine (T_3) concentrations [13-15]. These patients typically have few or no symptoms of hyperthyroidism. Patients with SHyper also have an increased risk of AF [16], nonfatal cardiovascular disease (CVD) [17], and heart failure [18]. However, it is unknown whether there is an increase in mortality. In a meta-analysis of 10 prospective cohort studies that included only patients with endogenous SHyper, there was an increased risk of both total and cardiovascular mortality in the patients. The risk of cardiovascular mortality was higher for TSH concentrations <0.1 mU/L compared with concentrations between 0.1 and 0.44 [16].

Oxidative stress (OS) is defined as the imbalance between the generation of reactive oxygen species (ROS) as a consequence of incompleted reduction of oxygen and antioxidant defense system [19]. Increased ROS generation and the consequent oxidative damage are believed to contribute to the development of several diseases including cardiovascular, endocrine and neoplastic [20]. Thyroid hormones accelerate the basal

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metabolic rate and oxidative metabolism by mitochondrial enzyme induction [21]. OHyper and SHyper are associated with increased markers of lipid peroxidation, oxidative stress and oxidative damage in central and peripheral tissues [22-25]. Oxidative damage of cellular membranes can lead to cell death and to production of toxic and reactive aldehyde free radical metabolites [24]. Among these metabolites, malondialdehyde (MDA) is the most important lipid peroxidation marker. In addition, OS has been shown to decrease after treatment of hyperthyroidism [25, 26].

Ischemia-modified albümin (IMA) is a sensitive and ideal biochemical marker of ischemia and oxidative stress [27]. In the early 1990s, it was first discovered that exposure to ischemic tissue changes the N-terminus of the serum albümin, decreasing its binding capacity for metals (such as cobalt, copper, and nickel) and resulting in the formation of IMA [28, 29]. Proposed mechanisms for the IMA formation include endothelial and extracellular hypoxia, acidosis, free radical injury, energy-dependent membrane disruption and exposure to free iron and copper [28, 30]. The albümin cobalt binding (ACB) test is a clinical chemistry colorimetric assay that indirectly detects IMA determinig the decreased binding capacity of albümin for cobalt [28]. The pathologies and diseases associated with an increase in IMA include acute coronary syndromes, acute myocardial infarction, cerebrovascular accidents, peripheral vascular disease, end-stage renal disease, advanced liver cirrhosis, acute infections, malignancies, systemic sclerosis, obesity, type 2 diabetes mellitus, and metabolic syndrome [27, 28, 31].

To our knowledge, although there are few studies regarding serum IMA levels in OHyper [23, 32, 33] and MDA levels in SHyper [34, 35], serum IMA levels have not been investigated in patients with SHyper. Therefore, in a prospective study, we determined the levels of IMA and MDA and the effect of antithyroid drug (ATD) therapy on OS parameters in patients with OHyper and SHyper. We also investigated the relationships serum thyroid hormones and IMA and MDA in these patients. A high oxidative stress might predispose to an increased prevalence of CVD.

Design and Methods

Patients and study design

The study was performed at Department of Internal Medicine, Faculty of Medicine, Karadeniz Technical University. We prospectively evaluated 45 untreated patients with OHyper (33 women and 12 men; mean age, 50.5±18.0 yr) and 20 untreated patients with SHyper (17 women and 3 men; mean age, 56.1±13.3 yr). The diagnosis of OHyper and SHyper was based on clinical assessment and biochemical findings. OHyper patients were clinically and biochemically hyperthyroid, defined as having increased serum thyroid hormone levels, a suppressed TSH concentrations (<0.1 mU/L). The causes of OHyper were Graves' disease (GD) (n=25) and toxic nodular goiter (TNG) (17 toxic multinodular and 3 toxic adenoma). The diagnosis of Graves' disease was based on the additional presence of a smooth goiter, increased thyroid autoantibodies [anti-thyroglobulin (anti-Tg), anti-thyroid peroxidase (anti-TPO) and anti-TSH receptor], or specific eye signs. The diagnosis of toxic multinodular goiter was based on the presence of thyroid nodules at palpation and an irregular distribution and/or multiple hyperactive and/or hypoactive nodules of technetium-99m pertechnetate on a thyroid scan. Toxic adenoma was defined as OHyper in the presence of solitary nodule at palpation and a solitary hyperactive nodule and suppression in the rest of the thyroid on a thyroid scan. SHyper patients had normal FT_3 and FT_4 concentrations and suppressed TSH concentration (<0.1mU/L). The causes of SHyper were early Graves' disease (n=8), autonomous adenoma (n=3), and multinodular goiter (n=9). Early GD was defined as the presence of biochemical SHyper (normal serum free T_4 and free T_3 concentrations and suppressed TSH) together with the presence of two of the following: a palpable diffuse goiter, a significant titer of TPO, Tg autoantibodies and/or TSH receptor antibodies, and/or the presence of ophthalmopathy. The diagnosis of multinodular goiter was based on the presence of thyroid nodules at palpation and an irregular distribution and/or multiple hyperactive and/or hypoactive nodules of technetium-99m pertechnetate on a thyroid scan. Autonomous adenoma was defined as SHyper in the presence of solitary nodule at palpation and a solitary hyperactive nodule and suppression in the rest of the thyroid on a thyroid scan.

The SHper and OHper patients were treated with methimazole (an initial dose of 15 and 30 mg/day) or propylthiouracil [PTU] (an initial dose of 150 and 300 mg/day). The daily ATD dose was gradually reduced or increased till it reached a dose to provide and maintain authyroid state. During the treatment, the patients were regularly checked to record the moment of hor-

monal normalization. Maximal effective dose was 60 mg/day for methimazole and 600 mg/day for PTU. Maintenance dose was 10-15 mg/day for methimazole and 100-150 mg/day for PTU.

Clinical examination included height and body weight measurements. Body mass index (BMI) was calculated as weight (kilograms) divided by the square of height (meters squared). Systolic (SBP) and diastolic (DBP) blood pressures were measured thrice in sitting position after 15 minutes rest, and the mean was taken for all cases. Participants were advised to avoid alcohol, caffeinated beverages, and exercise for at least 30 min before their blood pressure measurement. Antithyroid drug treatment were performed in all patients. Euthyrodism was achieved in patients with OHyper and SHyper.

Patients neither received any medical treatments nor had any known diseases (*e.g*. active infection, known diabetes mellitus, metabolic syndrome, polycystic ovary syndrome, morbid obesity, familial hyperlipidemia, coronary heart disease, cerebrovascular disease, peripheral vascular disease, collagen diseases, inflammatory diseases, liver cirrhosis, malignancy, atrial fibrillation, or renal disease) that might affect OS markers at the time of the study. Thirty healthy age-and-sex-matched subjects (21 women and 9 men, mean age 51.6±17.4 yr) were used as controls. Their biochemical values were within normal ranges. None of the controls were taking any drugs affecting the levels of serum thyroid hormones, OS parameters and serum lipid concentrations. Informed consent was obtained in all cases and the study was approved by the local ethics committee of Karadeniz Technical University (No: 2011/129).

Biochemical and hormonal parameters including IMA and MDA were evaluated in patients with OHyper and SHyper just before and one month after the maintenance of euthyroidism.

Laboratory analysis

Blood was collected in the morning between 0800-0900 h after an overnight fast to avoid the differences of diurnal variation, especially for hormonal and OS parameters. Serum free T_3 (FT_3), free T_4 (FT_4) and TSH concentrations were immediately measured by automated electrochemiluminescence system (Beckman Coulter, DxI-800, USA) before and every 4 weeks after the initiation of treatment until the euthyroid stage was reached. Normal ranges are 2.5-3.9 pg/mL for FT_3, 0.61-1.12 ng/dL for FT_4, and 0.34-5.6 μU/mL for TSH. Anti-TPO and anti-Tg autoantibodies were measured by a chemiluminescence immunoassay (Immulite 2000, 5700 West 96th. Street, Los Angeles, USA). TSH R Ab was measured by radioimmunoassay (Brahms, Germany). Normal ranges are <34 IU/mL for anti-TPO antibodies, <40 IU/mL for anti-Tg antibodies and 0-10 U/L for anti-TSH receptor Ab. Serum total cholesterol (TC) was measured using a cholesterol oxidase enzymatic method; triglycerides (TG), by an enzymatic method; high density lipoprotein cholesterol (HDL-C), by a cholesterol oxidase enzymatic method in a reaction with specific antibodies directed to HDL particles. These routine analyses were carried out by autoanalyzer (Beckman Coulter, USA). Low density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald's formula.

For IMA and MDA analyses, a venous blood samples was collected into Vacutainer tubes (Becton Dickinson, Mountain View, CA) without anticoagulant. Serum samples were obtained by centrifugation 3500 × *g* at 10°C for 20 min. Aliquots of serum were transferred into plastic tubes without delay and frozen at –80 ºC until assays for determination of IMA. Ischemia-modified albümin levels were determined by using the rapid colorimetric method developed by Bar-Or et al. [36]. Two hundred microliters of patient serum was placed into glass tubes and 50 μL of 0.1% cobalt chloride (Sigma, St. Louis, MO, $CoCl_2 \cdot 6H_2O$ was added. After gentle shaking, the mixture was left for 10 min, in order to ensure sufficient cobalt albumin binding. Fifty microliters of dithiothreitol (DTT) (Sigma, 1.5 mg/mL H_2O) was added as a colorizing agent and the reaction was stopped 2 min later by adding 1.0 mL of 0.9% NaCl. A colorimetric control was prepared for serum samples. For the colorimetric control samples, 50 μL of distilled water was substituted for 50 μL of 1.5 mg/mL DTT. Sample absorbances were analyzed at 470 nm by a spectrophotometer (Shimadzu UV1601, Japan). The color of the DTT containing samples was compared with that of the colorimetric control tubes. IMA levels were given as absorbance units (ABSU).

Lipid peroxidation in samples was determined as MDA concentration using the spectrophotometric method defined by Yagi [37]. This method relies on the reaction of lipid peroxidation with MDA and thiobarbituric acid (TBA). Briefly, 2.4 mL of N/12 H_2SO_4 was mixed with 0.3 mL of serum, and 0.3 mL of 10% phosphotungstic acid was added. After being

allowed to stand at room temperature for 5 minutes, the mixture was centrifuged at 1,600 × g for 10 minutes. Supernatant was discarded, and the sediment was suspended in 4 mL of distilled water. Subsequently, 1 mL of 0.67% thiobarbituric acid was added, and the mixture was heated in boiling water for 60 minutes. The formed color was extracted into n-butanol. The mixture was centrifuged at 1,600g for 10 minutes. The absorbance of the organic layer was read at 532 nm. Tetramethoxypropane was used as a standard, and the MDA levels were calculated as nanomoles per milliliter. All the samples were assayed at the same time.

Statistical analysis

Data were analyzed using SPSS for windows (version 13.0, SPSS, Chicago, IL, USA). Results are expressed as mean ± standard deviation or as the median. ANOVA test-Sheffe's F test were used for the comparison of groups. Tukey test or Bonferroni corrections were used for *post-hoc* analysis. Mann–Whitney U test with Bonferroni corrections were used for the comparison of three groups for the data which were not normally distributed. Paired *t*-test (two sided) for normally distributed data and Mann–Whitney U test for nonparametric distributions were used to evaluate differences in the same group. Multivariate logistic regression anaysis was done to correct some demographic factors (age, gender, blood pressures and BMI) and laboratory parameters (glucose, lipid parameters, thyroid hormones, anti-TPO and anti-Tg). In patient group, correlations among biochemical parameters and thyroid hormones were carried out using Pearson (normal distribution data) and Spearman (not normal distribution data) correlation analysis. Significance was defined as $p < 0.05$.

Results

Controls and patients: clinical description

Clinical characteristics of the patients and controls are presented in Table 1. There were no significant differences between the groups for mean age, gender, duration of disease, cigarette smoking, BMI, SBP and DBP.

Baseline thyroid functions and oxidative stress parameters in the study groups

Data are given in Table 2, Fig. 1.

Compared with the control subjects, the levels of glucose, TG and MDA were significantly increased in patients with SHyper ($p<0.05$), whereas LDL-C levels were significantly decreased ($p<0.01$). Patients with OHyper showed significantly elevated glucose and MDA levels ($p<0.001$) and significantly decreased LDL-C and HDL-C levels compared with the controls ($p<0.01$ for all of them). MDA levels were higher in the patients with OHyper when compared with the patients with SHyper ($p=0.01$) (Table 2). Serum IMA levels did not significantly change in patients with OHyper and SHyper compared with the controls. We did not find a significant difference between Graves' disease and toxic nodular goiter for biochemical and oxidative parameters including IMA and MDA. In the multivariable analysis, demographic factors and laboratory parameters did not affect OS parameters.

In patients with untreated Graves' disease (n=25), serum TSH levels were inversely correlated with plasma MDA levels ($r= -0.42$, $p< 0.05$) (Fig. 1). We did not find any significant correlation between serum thyroid hormones and the other biochemical parameters that we measured.

Table 1 Clinical characteristics of control subjects and patients with subclinical and overt hyperthyroidism. Results are given as either means±S.D. or median (range).

Parameter	Control	Subclinical hyperthyroidism	Overt Hyperthyroidism	*P* value
No. of subjects	30	20	45	
Age (years)	51.6±17.04	56.1±19.33	50.49±17.98	0.311
Gender	9M (30%) 21F (70%)	3M (15%) 17F (85%)	12M (31.6%) 33F (73.3%)	0.635
SBP (mmHg)	115.17±9.1	116.75±9.4	117.56±10.4	0.060
DBP (mmHg)	73.67±7.87	76.25±6.46	77.44±7.35	0.076
BMI (kg/m^2)	26.53±3.2	26.65±3.63	25.04±3.54	0.111
Smoking	5 (16.7%)	2 (10%)	9 (20%)	0.693
Duration of disease (years)	-	2.50	2.43	0.173

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; M, male; F, female

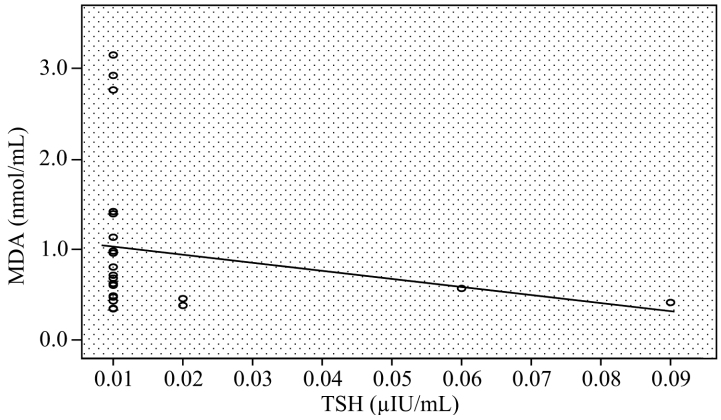

Fig. 1 Correlation between serum TSH levels and MDA in patients with Graves' disease (r= -0.419, p= 0.037).

Table 2 Baseline biochemical and hormonal parameters of the control subjects and patients with subclinical and overt hyperthyroidism. Results are given as either means±S.D. or median (range).

Parameter	Control (n=30)	SHyper (n=20)	OHyper (n=45)	*P* value
FT_3 (pg/mL)	3.13±0.33	3.31±0.57	9.07±5.75	<0.001
FT_4 (ng/dL)	0.85±0.10	0.97±0.27	2.84±1.55	<0.001
TSH (μU/mL)* (Min–Max)	1.29 (0.41-4.22)	0.03 (0.01-0.09)	0.01 (0.01-0.09)	<0.001
Glucose (mg/dL)	81.2±9.0	87.85±8.07	89.07±8.90	0.001
T-C (mg/dL)	182±33.62	177.9±28.8	173.64±26.9	0.416
LDL-C (mg/dL)	125.6±26.6	101.6±22.2	104.7±25.3	0.001
HDL-C (mg/dL)	54.04±7.71	49.95±9.16	47.4±7.7	0.003
TG (mg/dL)	90.97±41.24	119.80±30.10	123.23±46.61	0.046
IMA (ABSU)	0.438±0.071	0.447±0.074	0.422±0.122	0.598
MDA(nmol/mL)* (Min–Max)	0.375 (0.306-1.474)	0.453 (0.317-1.377)	0.687 (0.348-3.15)	<0.001

* = median value (range).

Changes in parameters after ATD treatment

Overt hyperthyroidism

Plasma MDA levels significantly decreased (p=0.001; p<0.05 for GD and p=0.001 for TNG) and levels of TC, LDL-C and HDL-C significantly increased (p<0.001 for all them) in the OHyper group after treatment (Table 3).

Subclinical hyperthyroidism

Statistical significant decreases in the MDA levels (p<0.05) and significant increases in the levels of TC, LDL-C and HDL-C (p<0.05, p<0.01 and p<0.01, respectively) were found in the SHyper group after treatment (Table 4). Serum IMA levels did not significantly change with the therapy in all patient groups.

Discussion

In this study, the most important findings are that patients with OHyper and SHyper have elevated MDA levels and unchanged IMA levels which play a role on OS. No reports are available in the literature to comment on the simultaneous measurement of these parameters in hyperthyroidism.

Thyroid hormones are asssociated with the oxidant and antioxidant status of the human organism. The findings obtained from in vitro and in vivo studies show that thyroid hormones have a strong impact on OS [33]. Untreated hyperthyroidism is associated with an increase of parameters of OS in serum/plasma compared with euthyroid subjects including lipid peroxides, hydrogen peroxide, and MDA [20-22]. Treatment with ATD is followed by a decline in the levels of these parameters, which may related to the euthyroidism and antioxidant properties of these drugs [20].

Ischemia-modified albümin, as measured using the ACB test, is currently the most promising biomarker for early detection of ischemic conditions [27, 28]. Also, IMA generation depends strongly on the high

Table 3 Biochemical and hormonal parameters in patients with overt hyperthyroidism before and after antithyroid drug treatment. Results are given as either means±S.D. or median (range).

Parameter	Before treatment	After treatment	*P* value
ST_3 (pg/mL)	9.07±5.75	3.14±0.60	<0.001
ST_4 (ng/dL)	2.84±1.55	1.01±0.25	<0.001
TSH (μU/mL)* (Min–Max)	0.01 (0.01-0.09)	0.89 (0.17-4.05)	<0.001
T-C (mg/dL)	173.6±26.9	192.0±30.1	<0.001
LDL-C (mg/dL)	104.7±25.3	118.5±28.7	<0.001
HDL-C (mg/dL)	47.4±7.7	52.8±6.9	<0.001
TG (mg/dL)	123.2±46.6	110.3±28.8	0.309
IMA (ABSU)	0.422±0.122	0.393±0.116	0.282
MDA(nmol/mL)* (Min–Max)	0.687 (0.348-3.15)	0.445 (0.295-1.11)	<0.001

* =median value (range).

Table 4 Biochemical and hormonal parameters in patients with subclinical hyperthyroidism before and after antithyroid drug treatment. Results are given as either means±S.D. or median (range).

Parameter	Before treatment	After treatment	*P* value
ST_3 (pg/mL)	3.31±0.57	2.90±0.39	0.008
ST_4 (ng/dL)	0.97±0.27	0.84±0.12	0.016
TSH (μU/mL)	0.03±0.029	0.74±0.79	0.001
T-C (mg/dL)	177.9±28.8	187.7±22.37	0.039
LDL-C (mg/dL)	101.6±22.2	111.1±19.9	0.007
HDL-C (mg/dL)	49.95±9.2	54.7±6.8	0.005
TG (mg/dL)	119.8±30.1	112.2±37.0	0.057
IMA (ABSU)	0.447±0.074	0.427±0.095	0.465
MDA (nmol/mL)* (Min–Max)	0.453 (0.317-1.377)	0.411 (0.195-0.786)	0.028

* =median value (range).

oxidative stress state such as obesity, hypercholesterolemia, type 2 diabetes, metabolic syndrome, and higher amounts of free fatty acids in the body [27, 28, 31, 38]. Therefore, IMA appears to play the role of an oxidative stress biomarker.

To the best of our knowledge, this is the first study to evaluate IMA in association with SHyper. On the other hand, there are only two reports evaluating the relation between IMA levels and OHyper [32, 33]. Ma *et al*. reported that serum IMA levels are higher in patients with OHyper (n= 35) compared to control subjects (n= 35) [32]. Basal IMA levels were reduced after treatment in patients. Also, in these patients, serum IMA levels were positively correlated with FT_3 (r= 0.424, p=0.011) and FT_4 (r= 0.567, p<0.001) levels. They suggested that OHyper has a significant impact on the OS status. In an other recent study, Oncel *et al*. have demostrated that serum IMA levels were markedly higher in patients with OHyper (n=27) compared to controls (n=27) [33]. In that study, IMA was negatively correlated with TSH levels (r= -0.473, p<0.001) and positively correlated with FT_3 (r= 0.275, p=0.01) and FT_4 (r= 0.496, p<0.001) levels. In our study, serum IMA levels did not significantly differ between the groups in pre-or post-treatment periods. In addition, we did not observe a correlation between IMA and thyroid hormones. Our results are different from previous these two reports. This finding might indicate only a limited role for serum IMA as a marker of ischemia or oxidative stress in this patient population. Also, we suggested that IMA may not be an appropriate marker for OS.

To our knowledge, there are only two studies to evaluate MDA levels in patients with SHyper in the literature [34, 35]. But, there is no study evaluating the MDA levels after ATD treatment. Cetinkaya *et al*. measured plasma MDA levels in total of 30 untreated patients with SHyper and 30 euthyroid control subjects [34]. MDA levels were higher in patients with SHyper than the control subjects (p<0.01). They suggested that increased OS associated with SHyper may play an important role in the systemic effects and progression to OHyper. In the other study, Rybus-Kalinowska et al. measured MDA levels in women with non-autoimmunological SHyper (n=20) and euthyroid controls (n=15) [35]. They reported that MDA significantly increased in the patient group compared with the controls (p<0.05). It was concluded that increased MDA concentration may indicate enhancement of lipid peroxidation in patients with SHyper. In our study, MDA levels were significantly higher in SHyper patients compared to the control group. This abnormality improved during the euthyroid period after ATD therapy. We suggest that increased OS in the patients normalizes after treatment. The thyroid function was normalized after treatment in two groups of patients, but MDA does not return to a level same as the control group. Reason of this controversion may be explained by time of the treatment of 4 weeks after reaching to euthyroid state. If we would take blood samples after 8-12 weeks, MDA levels would reach to those of control values. Our results regarding MDA are consistent with the previous two studies.

Multiple prospective studies have identified an association between plasma MDA levels and OHyper [25, 39, 40-42]. Increased plasma MDA levels were reported in OHyper patients and were observed to decrease to

normal levels in the patients who became euthyroid after ATD treatment [21, 40-43]. Researchers stated that the patients with OHyper experience abnormal oxidative status of the organism, and induction of euthyroidism after treatment with ATD results in resolution of these abnormalities. In other some studies, it was reported that increased MDA levels did not change in patients with OHyper after treatment leading to euthyroidism [25, 40]. In addition, Aliciguzel et al. detected a positive correlation between thyroid hormone levels and MDA levels [42]. Lassoued et al. did not observe between the OS markers including MDA and the antithyroid antibody levels in GD patients [39]. In the present study, our results concerning OHyper confirmed the previous reports showing increased MDA levels. This condition in the patients may be contribute to tendency to cardiovascular events seen in hyperthyroidism. In addition, MDA levels were higher in patients with OHyper than in SHyper patients. This finding suggests that hyperthyroid patients display a progressive deterioration in oxidative status depending on the severity of the disease. Interestingly, in the present study, there was no significant difference between patients with GD and TNG for MDA levels. Thus, oxidative damage in hyperthyroidism may be related to thyroid hormones regardless of the etiology of the disease. However, we found an inverse relationship between MDA and TSH levels only in patients with GD (Fig. 1). This finding may contribute to the relationship between autoimmunity and oxidative damage in these patients. Also, the normalization of the MDA levels with ATD therapy shows that oxidative damage is reversible.

Thyroid hormones regulate all aspects of lipid metabolism including synthesis, mobilization, and degradation [44, 45]. They are induce LDL receptor gene expression in the liver, explaining the decreased LDL-C levels observed in the hyperthyroidism [44, 46]. In addition, decreased or unaltered TC, TG, HDL-C, apoAI, apoB, and Lp(a) levels have been found in patients with SHyper and OHyper compared with the euthyroid controls [47-49]. The impact of treatment of hyperthyroidism on the lipid levels is not clear. ATD therapy has been associated with increased TC and LDL-C levels in some but not all studies [44, 47, 50-52]. Triglycerides are not changed with ATD therapy [47, 53]. HDL-C levels have been found to be increased or unchanged after treatment compared to the control group [47, 49, 54]. In the present study, in pre-treatment period, SHyper patients showed increased TG and decreased LDL-C levels. Patients with OHyper showed also decreased LDL-C and HDL-C levels. In post-treatment euthyroid period, patients with SHyper and OHyper showed increased TC, LDL-C and HDL-C levels. The alterations in lipid profile in pre-treatment period may influence the tendency to increased CVD seen in these patients.

In conclusion, we found some important differences in the OS parameters and lipid profile between the patients with SHyper and OHyper and healthy controls. Increased MDA levels in both SHyper and OHyper groups represent increased lipid peroxidation which might play an important role in the pathogenesis of the atherosclerosis in the patients. Increased OS could be improved by ATD therapy in patients with SHyper and OHyper. Also, MDA can be used as a reliable marker of OS and oxidative damage, while IMA is considered to be inappropriate. However, further prospective studies are needed to explain the association between hyperthyroidism and IMA.

Declaration of Interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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