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ORIGINAL ARTICLE

EFFECT OF METHIMAZOLE ON SERUM CONCENTRATIONS OF OXIDATIVE STRESS MARKERS IN PATIENTS WITH HYPERTHYROIDISM IN THE POPULATION OF KUTAHYA CITY, TURKEY

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ABSTRACT

Background: In hyperthyroidism, oxidative stress is produced due to an increase in the production of reactive oxygen species as a result of the hypersecretion of thyroid hormone. The objectives of this study were to determine the effect of methimazole on three oxidative stress markers in patients with hyperthyroidism in the population of Kutahya City, Turkey.

Materials & Methods: This quasi-experimental study was conducted in Faculty of Medicine, Kutahya Health Sciences University, Kutahya, Turkey from August 2020 to September 2021. Thirty newly diagnosed hyperthyroidism patients were included. Methimazole treatment was given to all patients for three months. Two patients were dropped due to allergic reactions. Total antioxidant status (TAS) and total oxidant status (TOS) were measured, and oxidative stress index (OSI) was calculated at the time of diagnosis and after three months of methimazole treatment. All data was analyzed by mean and SD with 95%CI. Three hypotheses were verified by paired samples t test.

Results: In a sample of 30 hyperthyroidism patients, mean TAS level was 1.52 mmol Trolox Eq/L before treatment. It increased significantly to 1.58 with methimazole treatment (p=.013). Mean TOS level was 10.40 µmol H_2O_2 Eq/L before treatment. It decreased significantly to 6.79 with methimazole treatment (p=<.0001). Mean OSI level was 0.68 arbitrary units before treatment. It decreased significantly to 0.44 with methimazole treatment (p=<.0001).

Conclusion: Methimazole drug treatment for three months for hyperthyroidism increased total antioxidant status, while decreased total oxidant status and oxidative stress index in population of Kutahya City, Turkey.

KEY WORDS: Hyperthyroidism; Total Oxidant Status; Total Antioxidant Status; Oxidative Stress Index; Methimazole; Oxidative Stress; Graves' Disease; Goiter; Thyroiditis.

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1. INTRODUCTION

1.1 Background: Thyroid hormones affect the oxidant and antioxidant status of the organism. They regulate oxidative metabolism and affect free radical production. Findings obtained from in vitro and in vivo studies showed that thyroid hormones had a prominent effect on oxidative stress (OS).[1] In hyperthyroidism, basal metabolic rate and oxidative metabolic rate increase as a result of mitochondrial enzyme induction.[2]

OS is defined as the deterioration of the balance between the oxidative system and the antioxidant defense system depending on the increase of reactive oxygen species.[3] Elevated reactive oxygen species activity and related oxidative damage may contribute to the development of various disorders like cardiovascular, endocrine, and neoplastic diseases.[4] The increased reactive oxygen species production is the cause of the OS mechanism in hyperthyroidism.[5] In manifest and subclinical hyperthyroidism, it has been shown that the

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increased lipid peroxidation markers in the tissues are related to OS and damage to DNA.[6]

1.2 Research Objectives (ROs)

RO 1-3: To determine the effect of methimazole drug treatment on serum concentrations of OS markers; TAS, TOS, and OSI in patients with hyperthyroidism in the population of Kutahya City, Turkey.

1.3 Research (Null) Hypotheses (RHs)

H_{01}: Methimazole drug treatment has no effect on the serum concentration of TAS in patients with hyperthyroidism in the population of Kutahya City, Turkey...

H_{02}: Methimazole drug treatment has no effect on the serum concentration of TOS in patients with hyperthyroidism in the population of Kutahya City, Turkey.

H_{03}: Methimazole drug treatment has no effect on OSI in patients with hyperthyroidism in the population of Kutahya City, Turkey.

2. MATERIALS & METHODS

2.1 Design, Duration & Setting: This quasi-experimental study with pre-test and post-test evaluation was conducted in the Department of Internal Medicine, Faculty of Medicine, Kutahya Health Sciences University, Kutahya, Turkey from August 2020 to September 2021. Kütahya Health Science University's Clinical Research Ethics Committee approved the study protocol (No. 2017-14/9). Written informed consent from the patients was obtained before inclusion in the study.

2.2 Population & Sampling: According to 2020 estimates, Kutahya city had population of 576,688 people. Thirty adult patients with hyperthyroidism with age 18-65 years were included. Patients with chronic diseases (malignancy, history of cerebrovascular disorder, rheumatological disorders, diabetes mellitus, hypertension, chronic kidney failure, chronic liver disease, coronary artery disease, etc.), active infection, pregnancy, smoking and alcohol consumption habits, and use of vitamin or antioxidant supplements were excluded. Two patients were dropped from the study due to allergic reactions to methimazole and 28 patients were continued with. Hyperthyroidism was related to Graves' disease in 23 (82%) patients, toxic multinodular goiter (MNG) in three (11%) patients, and thyroiditis in two (7%) patients.

2.3 Procedure & Intervention: The diagnosis and etiology of hyperthyroidism were evaluated with the serum levels of thyroid-stimulating hormone (TSH), free thyroxin (fT4), and thyroid-stimulating hormone receptor antibody (TRAb). Also, all patients underwent ultrasonographic thyroid examinations (Siemens Acuson Sequoia, Germany) by an experienced radiologist, and nodules were diagnosed in four patients. Regarding the antithyroid treatment, methimazole was started in all patients according to the Guidelines for the Management of Graves' Hyperthyroidism of the European Thyroid Association.[7] The mean dose of methimazole used in the study was 23.3±18.1 mg and the range was 5-60 mg per day. A follow-up plan was applied to the patients at one-month intervals until they completed three months of methimazole treatment. TAS, TOS levels were measured, and OSI values were calculated before methimazole treatment and then three months after starting treatment.

2.4 Collection of blood samples and analysis of laboratory parameters

2.4.1 Blood sample collection: After overnight fasting, venous blood samples were collected. Blood samples were centrifuged to obtain serum samples. The serum samples were kept at -80 °C until the biochemical measurements were performed.

2.4.2 Measurement of serum TAS and TOS levels: TAS and TOS levels were measured using a Beckman Coulter AU680 analyzer (Beckman Coulter, Miami, FL, USA) with commercial reagents (Rel Assay Diagnostic, Gaziantep, Turkey). The method was based on novel automated measurement methods developed by Erel.[8,9]

2.4.3 Calculation of OSI: The percent ratio of TOS to TAS was accepted as the OSI, an indicator of the degree of OS. [(TOS, μmol H_2O_2 Eq/L)/ (TAS, mmol Trolox Eq/L) x 100] was used to calculate OSI, and results were expressed as arbitrary units.[8,9]

2.4.4 Measurement of serum fT4, TSH, and TRAb levels: Serum fT4, TSH, and TRAb levels were determined on a Beckman Coulter UniCel® DxI 800 immunoassay system (Beckman Coulter, Miami, FL, USA) using original reagents. In healthy subjects, the reference ranges were as follows: TSH 0.34-5.6 mIU/mL, and fT4 7.85-14.41 pmol/L.

2.5 Data collection and data analysis plan

2.5.1 Normality of data: The skewness, kurtosis, coefficient of variation percent (CV percent), and Shapiro-Wilk (SW) tests were used to determine normality. SW test statistics (W) and p-values are presented with interpretation.

2.5.2 Descriptive statistics and estimation of parameters: Three research variables were serum TOS, TAS concentrations, and OSI values on ratio scale. Since all data were normally distributed, data were described by mean, minimum, maximum, range, and standard deviation for each group separately for the sample with 95% CI.

2.5.3 Hypotheses testing: Since all data were normally distributed; a parametric paired samples t-test was used for comparison, giving sample size, mean, standard deviation (SD), mean difference, and CI of mean difference, t-value with significance (p-value). SPSS v.16.0 (SPSS Inc., Chicago, IL, USA) for Windows was used for data analysis.

3. RESULTS

3.1 Tests of normality: The results are shown in Table 3.1, with interpretations based on the five tests. All variables are interpreted as normally distributed.

3.2 Descriptive statistics & estimation of parameters: The mean age of the sample was 35.9±11.2 (18-60, range 42) years. The sample of 28 patients included 24 (85.7%) women and four men (14.3%). Before the treatment, median (Q2), (Q1-Q3) [IQR] values for TSH were 0.07 (0.00-0.10) [0.10] mIU/mL, for fT4 were 1.77 (1.26-2.95) [1.69] ng/dL, and for TRAb were 4.85 (1.61-16.30) [14.69] U/L.

Table 3.2 shows serum concentrations of OS markers before and after the treatment. The mean serum level of TOS and the value of OSI are decreased after treatment, while the mean serum level of TAS is increased after treatment.

3.3 Hypotheses Testing

3.3.1 Effect of methimazole treatment on TAS levels (H_{01}): The difference in the mean levels of TAS before and after treatment was analyzed by paired t-test. The difference was statistically significant with a p-value of 0.013. Serum TAS concentration was increased after treatment. (Table 3.3.1)

3.3.2 Effect of methimazole treatment on TOS levels (H_{02}): The difference in the mean level of TOS before and after treatment was analyzed by paired t-test. The difference was statistically significant with

Table 3.1: Tests of normality for oxidative stress markers in individuals with hyperthyroidism in Kutahya City, Turkey

Variables	Observation	Skewness	Kurtosis	CV %	W	p-value	Data distribution
TAS	Before treatment	0.570	0.485	12.47	0.957	0.334	Normal
	After treatment	0.770	1.138	12.59	0.961	0.414	Normal
TOS	Before treatment	0.902	0.483	29.97	0.933	0.091	Normal
	After treatment	-0.070	-0.566	22.89	0.952	0.252	Normal
OSI	Before treatment	0.450	-0.203	24.87	0.965	0.492	Normal
	After treatment	0.400	-0.336	26.62	0.964	0.484	Normal

TAS=Total antioxidant status, TOS=Total oxidant status, OSI=Oxidative stress index, CV%=Coefficient of variation %, W=Shapiro-Wilk statistics

Table 3.2: Effect of methimazole treatment on serum concentrations of TAS, TOS, and OSI values in patients with hyperthyroidism in Kutahya city, Turkey (n=28)

Variables	Observation	Sample Statistics					95% CI of Mean	
		Mean	Min.	Max.	Range	SD	Lower	Upper
TAS (mmol Trolox Eq/L)	Before treatment	1.52	1.21	2.02	0.81	0.19	1.442	1.595
	After treatment	1.58	1.24	2.14	0.90	0.20	1.501	1.662
TOS (μmol H_2O_2 Eq/L)	Before treatment	10.40	6.23	18.62	12.39	3.12	9.140	11.657
	After treatment	6.79	4.21	9.60	5.39	1.55	6.166	7.422
OSI (Arbitrary Unit)	Before treatment	0.68	0.42	1.09	0.67	0.17	0.613	0.750
	After treatment	0.44	0.24	0.67	0.43	0.12	0.390	0.484

TAS=Total antioxidant status, TOS=Total oxidant status, OSI=Oxidative stress index, n=Sample size, SD=Standard deviation, CI=Confidence interval

Table 3.3.1: Effect of methimazole treatment on TAS levels in patients with hyperthyroidism in the population of Kutahya City, Turkey (n=28)

Observation	Sample size	Mean	SD	Difference of means	95% CI of difference		t value	d.f.	p-value (2-tailed)
					Lower	Upper			
Before treatment	28	1.52	0.19	0.06	0.026	0.127	3.182	27	.013
After treatment	28	1.58	0.20						

SD= Standard deviation, CI= Confidence interval, d.f.= Degree of freedom

Table 3.3.2: Effect of methimazole treatment on TOS levels in patients with hyperthyroidism in the population of Kutahya City, Turkey (n=28)

Observation	Sample size	Mean	SD	Difference of means	95% CI of difference		t value	d.f.	p-value (2-tailed)
					Lower	Upper			
Before treatment	28	10.4	3.12	-3.61	-4.528	-2.130	5.602	27	<.0001
After treatment	28	6.79	1.56						

SD= Standard deviation, CI= Confidence interval, d.f.= Degree of freedom

Table 3.3.3: Effect of methimazole treatment on OSI values in patients with hyperthyroidism in the population of Kutahya City, Turkey (n=28)

Observation	Sample size	Mean	SD	Difference of means	95% CI of difference		t value	d.f.	p-value (2-tailed)
					Lower	Upper			
Before treatment	28	0.68	0.17	-0.24	-0.289	-0.150	6.560	27	<.0001
After treatment	28	0.44	0.12						

SD= Standard deviation, CI= Confidence interval, d.f.= Degree of freedom

a p-value of <0.0001. Serum TOS concentration was decreased after treatment. (Table 3.3.2)

3.3.3 Effect of methimazole treatment on OSI values (H_{03}): The difference in the mean values of OSI before and after treatment was analyzed by paired t-test. The difference was statistically significant with a p-value of <0.0001. Serum OSI value was decreased after treatment. (Table 3.3.3)

4. DISCUSSION

4.1 Effect of methimazole treatment on TAS levels (H_{01}): In our study, treatment with methimazole increased the TAS levels. Several clinical and experimental studies focused on the effects of hyperthyroidism on OS have been conducted.

In a study by Andryskowski and Owczarek[10] from Łódź city, Poland, including 27 patients with hyperthyroidism and 12 healthy persons; a significant oxidation-reduction imbalance was observed in hyperthyroid patients compared to healthy subjects. TAS levels were lower in hyperthyroid patients compared to healthy individuals.

Similar to our study, Kocak, et al.[11] from Turkey demonstrated that TAS levels decreased significantly in patients treated with methimazole and propylthiouracil in 60 cases with Graves' disease in hyperthyroid state. Serum samples were taken just before the onset of treatment and then later on in the third month of the treatment.

Saleh AAS, from Cairo city, Egypt, compared TAS levels in control (euthyroid), hypothyroid, and hyperthyroid rat groups; each with 10 rats.[12] Compared to euthyroid rats, TAS values were found to be lower in hypothyroid rats, but no significant difference was found for hyperthyroid rats.

Komosinska-Vassev et al.[13] from Poland, investigated 30 patients with hyperthyroidism due to untreated Graves' disease and 30 age-matched healthy subjects before and after thiamazole treatment for superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and TAS levels. They observed that hyperthyroidism resulted in a marked increase in intracellular antioxidant enzymes, i.e., superoxide dismutase, catalase, and glutathione peroxidase activities as compared to the controls. Treatment with thiamazole resulted in normalization of the free radical and antioxidant activity indices. TAS levels increased significantly with thiamazole treatment.

4.2 Effect of methimazole treatment on TOS levels (H_{02}): In our study, TOS levels after the methimazole treatment were decreased significantly.

In a study by Aslan, et al.[14] conducted in Turkey, serum TAS, TOS, and OSI levels of 36 patients with hyperthyroidism and 30 healthy controls were compared. Graves' disease was diagnosed in 21 and toxic MNG in 15 of the hyperthyroid patients. Compared with the control group, TAS levels were decreased while TOS levels and OSI values were increased in hyperthyroid patients. There were no differences in TAS levels, TOS levels, and OSI values for Graves' disease and toxic MNG groups. The authors suggested that there was no correlation between OS and the etiology of hyperthyroidism.

Erdamar, et al.[15] from Turkey investigated the influence of hypothyroidism, hyperthyroidism, and their treatments on the metabolic state of OS, and antioxidant status markers. A total of 20 newly diagnosed patients with overt hypothyroidism due to Hashimoto's thyroiditis, 20 patients with overt hyperthyroidism due to Graves' disease, and 20 healthy subjects as control were enrolled. Malondialdehyde levels and myeloperoxidase activities, which are OS markers,

were found to be higher in the hyperthyroid group than in the control group. Antithyroid treatment with propylthiouracil caused a significant decrease of myeloperoxidase activity.

Bednarek et al.[16] from Poznan city, Poland, investigated the effect of methimazole treatment on oxidation products and antioxidant markers in plasma of patients with Graves' disease and toxic MNG. Twenty-five newly diagnosed and untreated Graves' disease patients and 24 patients with toxic MNG were included. Extracellular OS parameters-hydrogen peroxide, plasma lipid hydroperoxides, and thiobarbituric acid reacting substances levels were significantly increased in both hyperthyroid patient groups. Methimazole treatment produced normalization of all analyzed indices of increased oxidation in both hyperthyroid patient groups.

4.3 Effect of methimazole treatment on OSI values (H_{03}): OSI values after the methimazole treatment were found to be significantly decreased.

In a study by Guerra, et al.[17] from Buenos Aires city, Argentina, an antioxidant mixture was evaluated in the treatment of Graves' disease. Fifty-six hyperthyroid patients were treated with methimazole, antioxidant mixture, or methimazole plus antioxidant mixture. Normal controls (euthyroid subjects) of similar age and sex were also studied. Hyperthyroid patients had increased malondialdehyde content and superoxide dismutase activity and decreased catalase activity compared to controls. After methimazole treatment, malondialdehyde content and superoxide dismutase activity were decreased, and catalase activity was increased.

In another study by Abalovich, et al.[18] from Buenos Aires city, Argentina, the authors evaluated the antioxidant/ oxidant balance in active Graves' disease and the effects of treatment with methimazole and iodine-131. Sixty-nine hyperthyroid patients with Graves' disease and 19 healthy adult volunteers as controls were evaluated. Catalase activity, superoxide dismutase activity, and total glutathione content were found to be decreased in patients with Graves' disease compared to control group.

Leo, et al.[19] carried out a randomized clinical trial in Pisa city, Italy, between January 2014 and December 2015. The study aimed to evaluate the efficacy of the combined treatment (methimazole plus selenium) in the treatment of hyperthyroidism as compared to methimazole alone in 30 Graves' disease untreated patients. Fifteen of them received methimazole, and the remaining 15 received selenium in addition to methimazole. The authors found that serum malondialdehyde was similar in the two groups and decreased significantly with treatment, with no difference between groups. This result suggested that selenium combined with the antithyroid treatment did not contribute to reduction in OS.

5. CONCLUSION

Methimazole drug treatment for hyperthyroidism increased total antioxidant status, while decreased total oxidant status and oxidative stress index in population of Kutahya City, Turkey. Methimazole reduced oxidative stress and enhanced the oxidant-antioxidant balance in hyperthyroid individuals, favoring antioxidant status.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	SYS, TPK
Acquisition, Analysis or Interpretation of Data:	SYS, TPK, FEK
Manuscript Writing & Approval:	SYS, TPK, FEK

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.