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ORIGINAL ARTICLE

Oxidative stress in patients with thyroidectomy and thyroparathyroidectomy under replacement therapy

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Abstract Several studies have demonstrated an imbalance between free radicals and the antioxidative system in individuals with thyroid dysfunction. However, oxidative stress has not been evaluated in patients with thyroidectomy and thyroparathyroidectomy, who are under replacement therapy. The objective of this study was to evaluate the oxidative stress using malondialdehyde, nitric oxide, and catalase levels in patients with thyroidectomy and thyroparathyroidectomy. Nineteen patients with thyroidectomy, 20 patients with thyroparathyroidectomy, and 20 controls with no history of thyroid or parathyroid disease or surgery were included in the study. Serum malondialdehyde, nitric oxide, and catalase levels were examined. Levels of nitric oxide and malondialdehyde were elevated, and catalase levels decreased in patients with thyroidectomy and thyroparathyroidectomy compared with controls (p value for all the parameters: $p < 0.001$). Free tetraiodothyronine was a potential predictor of malondialdehyde in the patient groups (p: 0.002). Catalase was negatively correlated with nitric oxide ($p < 0.01$) and malondialdehyde ($p < 0.01$). The results of the current study demonstrated that oxidative stress increased in patients with thyroidectomy and thyroparathyroidectomy despite the application of replacement therapies.

Keywords Thyroidectomy · Parathyroidectomy · Oxidative stress · Malondialdehyde · Nitric oxide · Catalase

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Introduction and objective

Reactive oxygen species (ROS) are defined as molecules with one or more uncoupled electrons, a short lifespan, an unstable character, and a low molecular weight and those that are highly active and disrupt the chemical structure of other molecules [1]. ROS are formed continuously during normal physiological events of the mitochondrial respiratory chain. These ROS might impair the structure of lipids, proteins, and nucleic acids and cause oxidative injury to a certain degree. The organism attempts to fight the detrimental effects of ROS via anti-oxidative defense mechanisms [2]. However, this balance is impaired in several pathological processes, including diseases, and the resulting oxidative stress causes oxidative injury in cellular membranes or intracellular molecules [3]. In addition to these pathological conditions, oxidative stress can be explained by the aging process. There is a lack of knowledge about the effect of oxidative stress on the aging of the endocrine system and the induction of age-related endocrine diseases [4]. However, the thyroid gland and thyroid hormones seem to have a role in the modulation of oxidative stress.

Thyroid hormone synthesis requires a potent oxidative and antioxidative system [5]. Nevertheless, the most common causes of hyperthyroidism and hypothyroidism

are autoimmune thyroid diseases and oxidative stress, which are mediated by free radicals and have been demonstrated to play a role in the etiopathogenesis of several autoimmune diseases [6, 7]. It has been demonstrated that the balance between free radicals and the antioxidative system is impaired in many thyroid diseases, including overt hypothyroidism, subclinical hypothyroidism, and hyperthyroidism [8–10]. In addition, oxidative stress has been shown to decrease following medical treatment of both hypothyroidism and hyperthyroidism [11, 12]. Total thyroidectomy is performed to treat certain thyroid diseases, including multinodular goiter, thyroid cancer, or Basedow–Graves' disease. Hypoparathyroidism is a potential complication of these surgical procedures. Current guidelines recommend the use of levothyroxine in the follow-up of total thyroidectomy cases and levothyroxine, calcium, and calcitriol in the follow-up of total thyroidectomy plus surgical hypoparathyroidism cases [13, 14]. In the management of hypothyroidism with levothyroxine replacement, current guidelines recommended that the therapeutic target for TSH should be within the normal range [15]. Serum T4 concentrations peak 2–4 h after an oral dose and remain above normal for ~6 h in patients receiving daily levothyroxine replacement therapy [16]. Although TSH levels can reach target levels by means of replacement therapy in cases with thyroidectomy and thyroparathyroidectomy, free T4 levels fluctuate during the day. The effect of this replacement therapy, which cannot exactly mimic physiological release, on oxidative stress has not been studied before.

The objective of the current study was to evaluate oxidative stress using malondialdehyde, nitric oxide, and catalase levels in patients with thyroidectomy and thyroparathyroidectomy.

Materials and methods

This study was performed between August 2013 and October 2013 at the Department of Endocrinology and Metabolism of the Yuzuncu Yil University Medical Faculty. A total of 59 subjects were included in the study. Nineteen patients with thyroidectomy for multinodular goiter were receiving levothyroxine replacement therapy, and 20 patients with thyroidectomy for multinodular goiter and concomitant hypoparathyroidism were receiving levothyroxine, calcium, and calcitriol replacement therapy. Of these 39 patients who underwent thyroidectomy because of multinodular goiter, none had thyroid cancer. The control group consisted of 20 subjects with a similar age and gender distribution, who had no history of thyroid or parathyroid diseases or surgery.

The subjects were grouped as controls, thyroidectomy cases, and thyroparathyroidectomy cases who had developed hypoparathyroidism due to with thyroidectomy.

Calcium levels, phosphorus levels, spot urine calcium/creatinine ratios, thyrotropin (TSH), free tetraiodothyronine (fT4), and parathormone (PTH) were examined in all study subjects. All biochemical tests were performed according to the photometric method using a Modular P800 device, and hormonal tests were performed according to the microparticle chemiluminescence method using an Architect i2000SR device.

Oxidative malondialdehyde (MDA) was determined by the spectrophotometric method defined by Yagi. This method relies on the reaction of lipid peroxidation with MDA and thiobarbituric acid (TBA). MDA forms a pink-colored complex with TBA, and the absorbance of this solution is determined by spectrophotometry at 532 nm [17]. Serum antioxidative catalase activity was determined by the Aebi method [18]. Serum nitric oxide levels were measured according to the Griess method [19].

The study data were entered from forms into SPSS 16 computer statistical analysis software, and statistical analyses were performed. Three group comparisons were performed with the analysis of variance (ANOVA) test. Variables potentially affecting the oxidative and antioxidative parameters were analyzed with covariance analysis. The correlation between variables was evaluated with Spearman correlation analysis. The results were expressed as the mean ± standard deviation, and a p value of <0.05 was considered statistically significant.

Results

A total of 59 subjects were included in the study. Thirty-nine of the subjects had undergone thyroidectomy, and 20 were controls of similar age and gender with no history of thyroid or parathyroid diseases or surgery. Nineteen patients with a history of thyroidectomy performed 4.3 ± 3.1 years previously for multinodular goiter were on levothyroxine replacement therapy. They regularly used 1.63 μg/kg levothyroxine. Twenty patients with a history of thyroidectomy and concomitant hypoparathyroidism performed 5.1 ± 4.2 years previously for multinodular goiter were on levothyroxine, calcium, and calcitriol replacement therapy. They regularly used 1.64 μg/kg levothyroxine. There was no significant difference between the thyroidectomy and thyroparathyroidectomy cases in terms of duration of postoperative follow-up or levothyroxine replacement dosage. (p: 0.475, p: 0.777, respectively).

The mean ages were 46.9 ± 7, 50.5 ± 12.4, and 51 ± 8.8 years in the thyroidectomy, thyroparathyroidectomy,

Table 1 Descriptive statistics and comparison results for studied traits

	Group 1 Control (20)	Group 2 Thyroparathyroidectomy (20)	Group 3 Thyroidectomy (19)	*p*
Age	51 ± 8.80	50.55 ± 12.40	48.95 ± 7.05	0.371
BMI (kg/m^2)	25.85 ± 2.81	24.80 ± 2.35	23.89 ± 2.78	0.151
Calcium (mg/dL)	9.46 ± 0.41	8.27 ± 0.98[a]	9.11 ± 0.47[c]	<0.001
Phosphorus (mg/dL)	3.32 ± 0.49	4.41 ± 0.69[a]	3.39 ± 0.56[c]	<0.001
Parathyroid Hormone (pg/mL)	84.05 ± 21.65	11.78 ± 8.03[a]	75.26 ± 34.52[c]	<0.001
Urinary Calcium/ reatinin	0.08 ± 0.04	0.17 ± 0.17	0.13 ± 0.12	0.078
TSH (μIU/mL)	1.88 ± 0.99	1.33 ± 1.32[b]	3.19 ± 3.65[db]	0.041
FT4 (ng/dL)	1.07 ± 0.17	1.39 ± 0.26[a]	1.28 ± 0.22[a]	<0.001
Catalase (EU/mL)	10.77 ± 1.2	4.72 ± 0.55[a]	5.11 ± 0.59[a]	<0.001
Nitric oxide (μmol/L)	11.29 ± 1.36	21.12 ± 2.66[a]	20.97 ± 2.85[a]	<0.001
Malondialdehyde (μmol/L)	9.78 ± 0.78	22.16 ± 2.37[a]	21.67 ± 1.44[a]	<0.001

Comparison with group 1, [a] $p < 0.001$, [b] $p < 0.05$, Comparison with group 2, [c] $p < 0.001$, [d] <0.05

and control groups, respectively. In total, 90 % (18) of subjects in the control group, 85 % (17) of subjects in the thyroparathyroidectomy group, and 94.7 % (18) of subjects in the thyroidectomy group were female. There was no significant difference between patients and controls in terms of age or gender distribution (*p*: 0.371, *p*: 0.603, respectively).

In the comparison of the three groups, significant differences in calcium ($p < 0.001$), phosphorus ($p < 0.001$), parathyroid hormone ($p < 0.001$), free T4 ($p < 0.001$), TSH (*p*: 0.041), catalase ($p < 0.001$), nitric oxide ($p < 0.001$) and MDA ($p < 0.001$) were detected among the groups (Table 1).

Serum calcium ($p < 0.001$) and parathormone levels ($p < 0.001$) were significantly lower and serum phosphorus ($p < 0.001$) levels were higher in patients in the thyroparathyroidectomy group compared with control and thyroidectomy groups.

Serum TSH levels were significantly lower in the thyroparathyroidectomy group compared with the thyroidectomy and control groups (*p*: 0.041). Serum TSH levels were significantly higher in the thyroidectomy group compared with the thyroparathyroidectomy and control groups (*p*: 0.041).

Serum catalase levels were lower and nitric oxide and malondialdehyde levels were higher in patients with thyroparathyroidectomy and in the thyroidectomy group compared with the control group ($p < 0.001$ for all parameters).

Spearman correlation analysis showed significant positive correlations between catalase and calcium and parathyroid hormone ($p < 0.01$ for all parameters). Catalase was negatively correlated with nitric oxide ($p < 0.01$), MDA ($p < 0.01$), phosphorus ($p < 0.01$), and urinary calcium/creatinine ratio ($p < 0.05$). NO was positively correlated with phosphorus, fT4 and MDA and negatively correlated with calcium, parathyroid hormone and catalase ($p < 0.01$ for all parameters). MDA was correlated positively with NO, fT4 and phosphorus and negatively correlated with calcium, parathyroid hormone and catalase ($p < 0.01$ for all parameters) (Table 2).

Factors (age, BMI, calcium, phosphorus, spot urine calcium/creatinine ratio, TSH, fT4, PTH, using levothyroxine dose per kg) that might affect MDA, NO, and catalase levels in the patient and control groups were analyzed in a covariance analysis, and fT4 and levothyroxine dose per kg were found to be potential predictors of MDA (*p*: 0.002, *p*: 0.029, respectively) (Table 3).

Discussion

In this study, nitric oxide, malondialdehyde, and catalase levels were examined in 39 patients with total thyroidectomy for multinodular goiter and 20 controls. Twenty of the 39 cases had hypoparathyroidism that developed following the operation. The patients with thyroidectomy were receiving levothyroxine therapy, and the patients with thyroparathyroidectomy were receiving levothyroxine, calcium, and calcitriol replacement therapy. Calcium and thyroid hormone levels were within the target range with replacement. However, nitric oxide and malondialdehyde levels were higher and catalase levels were lower in both the thyroidectomy and thyroparathyroidectomy cases compared with controls ($p < 0.001$ for all parameters).

Thyroid hormone synthesis in the thyroid gland during normal physiological processes requires hydrogen peroxide, a strong oxidative substance [20]. Thyroid tissue has its own

Table 2 Spearman correlation coefficients among the traits

	Age	BMI (kg/m^2)	Calcium (mg/dL)	Phosphorus (mg/dL)	Parathyroid Hormone (pg/mL)	Urinary calcium/creatinin	TSH (μIU/mL)	FT4 (ng/dL)	Catalase (EU/mL)	Nitric oxide (μmol/L)	Malondialdehyde (μmol/L)
Age	1										
BMI (kg/m^2)	0.374**	1									
Calcium (mg/dL)	−0.034	0.220	1								
Phosphorus (mg/dL)	0.154	0.105	−0.352**	1							
Parathyroid hormone (pg/mL)	−0.100	−0.085	0.431**	−0.691**	1						
Urinary calcium/creatinin	0.003	0.100	0.116	0.086	−0.373**	1					
TSH (μIU/mL)	−0.016	−0.156	0.071	−0.040	0.256	−0.114	1				
FT4 (ng/dL)	−0.114	−0.010	−0.280*	0.338**	−0.383**	0.212	−0.228	1			
Catalase (EU/mL)	0.129	0.247	0.433**	−0.345**	0.529**	−0.302*	−0.027	−0.452**	1		
Nitric oxide (μmol/L)	−0.027	−0.154	−0.388**	0.379**	−0.469**	0.170	0.084	0.346**	−0.845**	1	
Malondialdehyde (μmol/L)	−0.092	−0.264	−0.436**	0.406**	−0.521**	0.220	0.092	0.380**	−0.929**	0.916**	1

* Correlation is significant $p < 0.05$

** Correlation is significant $p < 0.01$

antioxidative system, consisting of peroxiredoxin, glutathione peroxidase, thioredoxin, and catalase, for protection against oxidation [5]. The balance between oxidative and antioxidative systems may be disrupted in diseases with impaired thyroid hormone synthesis either due to the impairment of this oxidative–antioxidative system of the thyroid tissue itself or due to the effects of thyroid hormones on metabolism. Thyroid hormones are a major factor controlling metabolic and respiratory rates in virtually all cell types in mammals. The general metabolic effect of thyroid hormones is a relative acceleration of the basal metabolism that includes an increase in the rate of both catabolic and anabolic reactions. Because of these metabolic activities and mechanisms, thyroid hormones are thought to be related to oxidative stress [21]. However, one in vitro study demonstrated that macrophage-induced low-density lipoprotein oxidation was reduced with thyroid hormone components [22].

Autoimmune thyroid disease is the most common cause of both hyperthyroidism and hypothyroidism, and oxidative stress mediated by free radicals has been shown to have a role in the etiopathogenesis of several autoimmune diseases [6]. In addition, toxic multinodular goiter and thyroid cancer have been shown to cause oxidative stress [23, 24]. Increases in reactive oxygen radicals (ROS) in the case of severe oxidative stress cause lipid peroxidation. Malondialdehyde is one of the aldehyde products of lipid peroxidation [25]. Malondialdehyde levels were higher in patients with thyroidectomy and thyroparathyroidectomy compared with controls in the current study ($p < 0.001$ for both groups). Several studies have demonstrated that malondialdehyde levels increase in the active phase of autoimmune hyperthyroidism and decrease with the establishment of euthyroidism with medical therapy [6, 11, 26, 27]. All of the patients in the current study had a history of thyroidectomy performed to treat multinodular goiter, and none had autoimmune thyroid disease or thyroid cancer. The mean TSH levels and fT4 levels of the subjects were within the target range with levothyroxine replacement therapy. However, fT4 levels were close to the upper range of the normal and higher than those in controls in both the thyroidectomy and thyroparathyroidectomy cases. In addition, fT4 was a potential predictor of MDA (p: 0.002). Elevated MDA levels in both thyroidectomy and thyroparathyroidectomy cases were possibly associated with increases in peroxy and hydroxyl radicals secondary to supraphysiological fT4 levels resulting from levothyroxine replacement.

Nitric oxide levels were higher in the patient group compared with the control group in the current study. Nitric oxide is a free radical gas that is synthesized endogenously in the body and has a short half-life. It is synthesized by the nitric oxide synthetase enzyme and is

Table 3 Covariance analysis results for malondialdehyde, catalase, and nitric oxide

Covariate variables	Malondialdehyde (μmol/L) *p* value	Catalase (EU/mL) *p* value	Nitric oxide (μmol/L) *p* value
Age	0.192	0.244	0.383
BMI (kg/m^2)	0.427	0.805	0.699
Calcium (mg/dL)	0.845	0.613	0.519
Phosphorus (mg/dL)	0.496	0.168	0.606
Parathyroid hormone (pg/mL)	0.100	0.788	0.777
Urinary calcium/creatinin	0.277	0.643	0.271
TSH (μIU/mL)	0.128	0.919	0.970
FT4 (ng/dL)	0.002	0.119	0.358
Levothyroxine dose (μg/kg)	0.029	0.380	0.911

an important signaling molecule of several physiological or pathological processes [28]. Thyroid hormones affect the neuronal and endothelial nitric oxide synthetase activity [29]. Clinical or subclinical hypothyroidism decreases nitric oxide levels [30, 31]. However, several animal studies have demonstrated that vascular nitric oxide synthesis increases with 3–4 months of triiodothyronine (T3) therapy [32]. In the current study, NO was positively correlated with fT4 ($p < 0.001$). Subjects in the patient groups had been receiving levothyroxine therapy, and their fT4 levels were significantly higher compared with controls, which was likely the cause of the discrepancy in NO levels in the patient and control groups. In addition, NO was positively correlated with MDA and negatively correlated with catalase ($p < 0.01$ for all parameters). Elevated oxidative stress was related to rising levels of NO. The effects of oxidative stress on endothelial dysfunction and NO were studied. MDA levels were found to be significantly higher and nitrate levels were found to be significantly lower in patients with overt hypothyroidism compared with a control group in the study by Tejovathi et al. [33]. However, in this study, MDA showed increased oxidative stress and was not negatively correlated with NO. Therefore, decreased NO may be a sign of hypothyroidism in this study.

Another study finding was lower catalase levels in the patient groups compared with the control group. MDA levels were negatively correlated with catalase levels ($p < 0.001$). The lower levels of catalase enzyme in the patient group may be explained by increased MDA. Matsunami et al. [34] examined the gene expression of antioxidant enzymes (cytosolic superoxide dismutase, cytosolic glutathione peroxidase, and catalase) in streptozotocin-induced DM model rats under hyperbaric oxygen (HBO) treatment, which increased the formation of ROS. They suggested that DM induction and HBO exposure might be synergistically increased because of an oxidative stress state and decreased because of cytosolic superoxide dismutase and catalase gene expression. Similarly, Duarte et al. [35] demonstrated SOD activity that was lower in hypercholesterolemic patients with a superoxide dismutase gene polymorphism. In addition, catalase levels were lower but not significantly so in patients with thyroparathyroidectomy compared with patients with only thyroidectomy. Although both parathormone and catalase are products of the same chromosome (short arm or chromosome 11), the exact effects of parathormone on the oxidative and antioxidative systems have not been investigated extensively [36]. In a case report, Tanaka et al. [37] demonstrated that parathyroidectomy results in a reduction in oxidative stress. In the current study, we determined that the positive correlation between parathormone and catalase was a reflection of this condition. However, one study on rats demonstrated that early thyroparathyroidectomy does not have any effect on catalase levels [38]. In addition, the current subjects were evaluated while receiving calcitriol and calcium replacement therapies. This current medication regimen may have influenced the results. Hamden et al. [39] also demonstrated that calcitriol lowers catalase levels in diabetic rats.

Consequently, the current results demonstrated that oxidative stress increased in patients with thyroidectomy and thyroparathyroidectomy, despite the use of replacement therapies. These conditions seem to be related to the elevation of thyroid hormone exposure to tissue level because replacement treatment cannot exactly mimic physiological release.

Conflict of interest The authors stated that there are no conflict of interest regarding the publication of this article.

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