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Evaluation of Oxidative Stress with a New Method in Differentiated Thyroid Cancer Patients on Thyrotrophin Suppression Treatment

Tirotropin Süpresyon Tedavisi Alan Diferansiye Tiroid Kanserli Hastalarda Oksidatif Stresin Yeni Bir Metot ile Değerlendirilmesi

Abbas Ali TAM, Didem ÖZDEMİR, Nagihan BEŞTEPE, Afra ALKAN*, Sevgül FAKI, Özcan EREL**, Reyhan ERSOY, Bekir ÇAKIR

Department of Endocrinology and Metabolism, Ankara Yıldırım Beyazıt University Faculty of Medicine, Ankara, TURKEY
*Department of Biostatistics and Medical Informatics, Ankara Yıldırım Beyazıt University Faculty of Medicine, Ankara, TURKEY
**Department of Biochemistry, Ankara Yıldırım Beyazıt University Faculty of Medicine, Ankara, TURKEY

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Abstract

Objective: Thyroid hormone suppression treatment (THST) is an essential modality in treating differentiated thyroid cancer (DTC). This study aimed to evaluate thiol/disulfide homeostasis with a new method in patients on THST, which causes a state of subclinical hyperthyroidism. **Material and Methods:** Serum thyrotrophin (TSH), free triiodothyronine (fT3), free thyroxine (fT4), duration of disease, levothyroxine dose, and radioactive iodine (RAI) dose were evaluated along with native and total thiol and disulfide levels. **Results:** Data of 50 patients with DTC and 41 healthy subjects were analyzed. Though native thiol and total thiol were lower in patients with DTC, the difference was not statistically significant. Disulfide was found to be 18.25 μmol/L in DTC patients and 15.23 μmol/L in the control group. The ratios of native thiol to total thiol (N/T), disulfide to native thiol (D/N), and disulfide to total thiol (D/T) were similar in the 2 groups. Disulfide, D/N, and D/T were significantly higher, and N/T was lower in patients with overt thyrotoxicosis than patients with subclinical thyrotoxicosis and the control group. Disulfide, D/N, and D/T were both positively, and N/T was negatively correlated with fT4/fT3. **Conclusion:** Although the thiol/disulfide balance was maintained in patients with subclinical thyrotoxicosis, there was a shift of redox status toward disulfide in patients with overt thyrotoxicosis on THST. This suggests that the potency of oxidative stress is associated with the degree of thyrotoxicosis. Considering the potentially harmful effects of oxidative stress, overt thyrotoxicosis must be avoided in patients on THST.

Keywords: Differentiated thyroid cancer; thyroid hormone suppression treatment; thiol-disulfide homeostasis; oxidative stress; thyrotoxicosis

Özet

Amaç: Diferansiye tiroid kanserinin (DTK) tedavisinde, tiroid hormon süpresyon tedavisi (THST) önemli bir modalitedir. Bu çalışmada, bir subklinik hipertiroidi durumuna yol açan THST alan hastalarda, thiol/disülfid homeostazını yeni bir metot ile değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Nativ ve total tiol ve disülfid seviyelerinin yanı sıra serum tirotropin (TSH), serbest triiyodotironin (sT3), serbest tiroksin (sT4), hastalık süresi, levotiroksin dozu ve radyoaktif iyot (RAI) dozu değerlendirildi. **Bulgular:** DTK'li 50 hasta ve 41 sağlıklı birey analiz edildi. Nativ tiol ve total tiol, DTK'li hastalarda daha düşüktü fakat farklılık istatistiksel olarak anlamlı değildi. Disülfid, DTK'li hastalarda 18,25 μmol/L ve kontrol grubunda 15,23 μmol/L'ydi. Nativ tiolün, total tiole (N/T); disülfidin, nativ tiole (D/N) ve disülfidin, total tiole (D/T) oranı her 2 grupta da benzerdi. Aşikâr tirotoksikozlu hastalarda, subklinik tirotoksikoz ve kontrol grubuna göre disülfid, D/N ve D/T anlamlı olarak daha yüksek ve N/T daha düşüktü. sT4/sT3 oranı disülfid, D/N ve D/T ile pozitif ve N/T ile negatif olarak koreleydi. **Sonuç:** THST alan ve subklinik tirotoksikozu olanlarda, her ne kadar tiol/disülfid dengesi korunmuş olsa da aşikâr tirotoksikozu olan hastalarda, redoks durumunda disülfid yönünde kayma vardı. Bu oksidatif stres potensinin, tirotoksikozun derecesiyle ilişkili olduğunu göstermektedir. Oksidatif stresin zararlı etkileri düşünüldüğünde, THST alan hastalarda aşikâr tirotoksikozdan kaçınılmalıdır.

Anahtar kelimeler: Diferansiye tiroid kanseri; tiroid hormon süpresyon tedavisi; tiol disülfid homeostazı; oksidatif stres; tirotoksikoz

Address for Correspondence: Abbas Ali TAM, Department of Endocrinology and Metabolism, Ankara Yıldırım Beyazıt University Faculty of Medicine, Ankara, TURKEY
Phone: : +903122912525 **E-mail:** endoali@hotmail.com

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Introduction

Thyroid cancer is the most common endocrine malignancy (1). Total thyroidectomy followed by radioactive iodine (RAI) ablation and thyroid hormone suppression treatment (THST) forms the mainstay of the treatment for differentiated thyroid cancer (DTC) for years, in selected cases (2). It has been found that the suppression of serum thyrotrophin (TSH) reduces the recurrence rate and improves outcomes in some patients with DTC (3). This approach aims to create a state of subclinical thyrotoxicosis without significantly increasing serum-free triiodothyronine (fT3) and free thyroxine (fT4). Long-term suppression of TSH might cause untoward effects mainly related to the cardiovascular system and bone health (4). It is recommended to individualize THST, considering its potential benefits and harms (5).

Multiple intracellular adaptive mechanisms in the human body are activated with an increase in the intracellular reactive oxygen species (ROS). This primarily occurs as a defense mechanism to protect the tissues and prevent apoptosis. One of the agents that work against oxidative cell damage is thiols (6). The plasma thiols are composed of protein thiols, albumin thiols, and in small amounts, low molecular weight thiols such as cysteine, cysteinylglycine, glutathione, homocysteine, and γ-glutamylcysteine (7). Thiol-disulfide homeostasis is a dynamic process. Excessive electrons of the ROS are transferred to the thiols after oxidation, and disulfide bonds are formed. These disulfide bonds can, after that, become thiol groups again (8). They are involved in antioxidant protection, signal transduction, detoxification, and apoptosis. They also contribute to enzymatic activity, transcription factors, and cellular signaling mechanisms (7).

Thyroid hormones have an essential role in regulating mitochondrial respiration and oxidative metabolism, which further affects oxidative stress (OS). Therefore, OS levels might be affected by variations in thyroid hormones (9). Previous studies have shown that high serum fT3 and fT4 stimulate free radicals in mitochondria and cause an increase in OS (10,11). This study aimed to determine whether THST influences OS in DTC patients.

Material and Methods

This study was designed as a cross-sectional, case-control study. DTC patients on THST followed between January 2016 and December 2018 were recruited. Patients with unilateral resection, patients with TSH unresponsive thyroid neoplasms such as medullary and anaplastic thyroid cancer and thyroid lymphoma, and patients with a history of radiotherapy of the head and neck region were excluded from the study. Other exclusion criteria were defined as the presence of chronic diseases such as diabetes mellitus, hypertension, coronary heart disease, renal insufficiency, any chronic inflammatory disease, and smoking. Patients using antioxidant agents were excluded, as well. Thyroid functions were found to be normal in the control group. Ethical review board of Ankara Yıldırım Beyazıt University approved the study protocol. The local ethical committee approved the study based on Helsinki''s Declaration (Date of approval: 14/06/2017; decree no: 2017/132). All patients gave written informed consent.

Demographical features, serum TSH, fT3, fT4, and albumin were recorded. Chemiluminescence methods were used to measure TSH, fT3, and fT4 (Immulite 2000, Diagnostic Products Corp., Los Angeles, CA, USA and UniCel DXI 800, Beckman Coulter, Brea, CA). The normal ranges were as follows- for TSH: 0.4-4 μIU/mL, for fT3: 1.57-4.71 pg/mL, and for fT4: 0.85-1.78 ng/d. Disease duration, levothyroxine dose per week, and RAI treatment and dose were determined in DTC patients. All patients with DTC underwent total thyroidectomy. Patients with a serum TSH ≤0.1 μIU/mL were defined to have suppressed TSH.

Dynamic thiol/disulfide homeostasis was determined in the patient and control group using a new automatic and spectrophotometric method, defined by Erel and Neselioglu. (7). With this method, disulfide bonds are reduced by sodium borohydride ($NaBH_4$), and free functional thiol groups are formed. The unused reductant $NaBH_4$ was removed by formaldehyde. The aim was to inhibit the reduction of 5,5'-dithiobis-(2-nitrobenzoic) acid (DTNB). Reduced and native thiol groups were determined after reaction with DTNB. When native thiol is subtracted from total thiol, and the result is divided by

two, some amount of dynamic disulfide is obtained. The ratios of disulfide/total thiol percent (D/T), disulfide/native thiol percent (D/N), and native thiol/total thiol percent (N/TS) were calculated. This study compares the parameters between patients on THST and the healthy control group. The THST group was then classified as overt and subclinical thyrotoxicosis and a further analysis was made to compare the OS parameters in all three groups. The authors also tried to determine whether there is any correlation between some clinical features and OS measurements.

Statistical Analysis

All statistical analyses were done with IBM SPSS Statistics 22.0. Shapiro-Wilk test was used to find out whether continuous variables were distributed normally. All continuous variables (except the ratio of fT4/fT3 in patient and control groups) were assessed by median (minimum-maximum), while gender was summarized by frequency and percentage. fT4/fT3 was reported as "Mean±Standard Deviation (Mean±SD)". Independent sample t-test, Mann-Whitney U test, and Yates chi-square test were used to compare groups. The patient group was classified as overt and subclinical thyrotoxicosis in terms of the degree of hyperthyroidism. These groups and the control group were compared for the ratio of fT4/fT3 and OS measurements by the Kruskal-Wallis test followed by a stepwise step-down procedure to obtain homogeneous subsets. Spearman's rho correlation analysis was used to investigate the correlations between OS measurements and other clinical features. Statistical significance was accepted when the p value was <0.05.

Results

The data of 50 patients in the THST group and 41 patients in the control group were analyzed. The frequency of male patients was 10.0% in the control group and 29.3% in the patient group (p=0.038) (Table 1). Among DTC patients, 12 (24.0%) had extrathyroidal extension, 7 (14.0%) had lymph node metastasis, and 4 (8.0%) had vascular invasion. Median age, serum albumin, and fT3 levels did not differ in the two groups (p=0.088, p=0.125, and p=0.185,

Table 1. Demographic and clinical characteristics of patients on thyroid hormone suppression treatment and control group.

	Patients on THST (n=50)	Control (n=41)	
	Median (minimum-maximum)	Median (minimum-maximum)	p value
Age (year)	45 (24-66)	42 (18-68)	0.088
Gender* (Male)	5 (10.0)	12 (29.3)	**0.038**
Albumin (g/dL)	4.65 (4.07-5.20)	4.70 (4.20-5.90)	0.125
TSH (µIU/mL)	0.035 (0.001-0.101)	2.100 (0.439-4.000)	**<0.001**
fT4 (ng/dL)	1.69 (1.31-2.88)	1.28 (0.90-1.70)	**<0.001**
fT3 (pg/mL)	3.05 (2.30-4.97)	3.30 (2.20-4.20)	0.185
fT4/fT3** (ng/dL/pg/mL)	0.567±0.080	0.392±0.073	**<0.001**
Duration of treatment (years)	4 (1-18)	-	-
Levothyroxine dose (mcg/week)	875 (525-1,400)	-	-
Radioactive iodine	48 (96%)	-	-
Radioactive iodine dose (mCi)	100 (75-175)	-	-
Native thiol (µmol/L)	435.30 (347.30-554.80)	439.80 (333.20-836.70)	0.604
Disulfide (µmol/L)	18.25 (1.20-33.0)	15.30 (0.45-31.10)	0.096
Total thiol (µmol/L)	465.10 (353.00-601.60)	471.60 (353.60-859.80)	0.820
Disulfide/native thiol	0.042 (0.003-0.080)	0.033 (0.001-0.076)	0.068
Disulfide/total thiol	0.038 (0.003-0.069)	0.031 (0.001-0.066)	0.069
Native thiol/total thiol	0.922 (0.862-0.993)	0.938 (0.868-0.998)	0.067

THST: Thyroid hormone suppression treatment; TSH: Thyrotrophin; fT3: Free triiodothyronine; fT4: Free thyroxine.
*n (%); **Mean±SD.

respectively). Serum TSH was lower, and fT4 and fT4/fT3 were higher in the THST group than in the control group (p<0.001, for each). The median duration of levothyroxine treatment was four years (minimum 1-18) with a median dose of 875 mcg/week (minimum-maximum: 525-1,400 mcg/week). Forty-eight (96%) patients with DTC had received RAI treatment, and the median dose was 100 mCi (minimum-maximum: 75-175 mCi). THST group demonstrated higher disulfide and lower native and total thiol levels than the control group; however, the differences were not statistically significant. D/N, D/T, and N/T were similar in the control and THST groups (p=0.068, p=0.69, and p=0.067, respectively).

Patients on THST were further classified into overt and subclinical thyrotoxicosis groups (Table 2). Compared with each other and the control group, the lowest fT4/fT3 was observed in the control group, and the highest value was observed in the overt thyrotoxicosis group. The three groups differed significantly from each other concerning fT4/fT3 (p<0.001). Patients with overt and subclinical thyrotoxicosis had similar native and total thiol concentration (p=0.590 and p=0.421, respectively). Disulfide, D/N, and D/T were similar in subclinical thyrotoxicosis and control groups. However, all these parameters were significantly higher in patients with overt thyrotoxicosis than in the subclinical thyrotoxicosis and control groups. Patients with overt thyrotoxicosis presented lower N/T levels than the control group.

The correlation analysis revealed that OS parameters were not correlated with RAI dose, duration, and levothyroxine treatment dosage. fT4/fT3 was positively correlated with disulfide, D/N, and D/T, and was negatively correlated with N/T (Table 3).

Discussion

Stimulation of TSH receptors present on the membrane of DTC cells increases thyroid proteins such as thyroglobulin (Tg) and sodium-iodide symporter. This further increases the rate of cell growth. The current guidelines recommend suppressing TSH by levothyroxine treatment in some patients with DTC to prevent recurrence (12). However, this approach is also associated with some side effects, primarily related to the cardiovascular and skeletal system and cognitive and psychological status, quality of life, glucose metabolism, coagulation, and immunological function (13). Thus, the potential benefits and the possible side effects of THST should be interpreted carefully during the management of these patients (5).

Thyroid hormones play a role in regulating mitochondrial respiration and oxidative metabolism, affecting free radical production and OS. Accelerated basal metabolic rate and oxidative metabolism in hyperthyroidism lead to an increased free radical generation and OS (9). The literature re-

Table 2. Comparison of fT4/fT3 and oxidative stress measurements in overt thyrotoxicosis, subclinical thyrotoxicosis, and control groups.

	Overt thyrotoxicosis (n=21) Median (minimum-maximum)	Subclinical thyrotoxicosis (n=29) Median (minimum-maximum)	Control (n=41) Median (minimum-maximum)	p value
fT4/fT3 (ng/dL/pg/mL)	0.596 (0.49-0.78)[a]	0.535 (0.37-0.65)[b]	0.387 (0.22-0.59)[c]	**<0.001**
Native thiol (µmol/L)	445.9 (369.0-530.3)	432.9 (347.3-554.8)	439.8 (333.2-836,7)	0.590
Disulfide (µmol/L)	23.2 (2.55-33.0)[a]	15.1 (1.5-31.05)[b]	15.3 (0.45-31.1)[b]	**0.029**
Total thiol (µmol/L)	491.1 (393.4-353.0)	456.0 (353.0-601.6)	471.6 (353.6-859.8)	0.421
Disulfide/native thiol	0.052 (0.005-0.080)[a]	0.035 (0.003-0.065)[b]	0.033 (0.001-0.076)[b]	**0.029**
Disulfide/total thiol	0.047 (0.005-0.069)[a]	0.033 (0.003-0.058)[b]	0.031 (0.001-0.066)[b]	**0.030**
Native thiol/total thiol	0.906 (0.862-0.989)[a]	0.935 (0.885-0.993)[a,b]	0.938 (0.868-0.998)[b]	**0.031**

fT3: Free triiodothyronine; fT4: Free thyroxine.
Each superscript indicates a subset of the measurement.

Table 3. Correlation between oxidative stress measurements and clinical features.

	RAI Dose (mCI)	Duration of levothyroxine use (years)	Levothyroxine dose (mcg/week)	fT4/fT3
Native thiol (µmol/L)				
rS	0.127	-0.073	0.086	-0.043
p value	0.380	0.613	0.551	0.686
Disulfide (µmol/L)				
rS	0.072	-0.085	-0.026	0.247
p value	0.621	0.556	0.858	**0.018**
Total thiol (µmol/L)				
rS	0.156	-0.030	0.035	0.023
p value	0.279	0.837	0.809	0.831
Disulfide/native thiol				
rS	0.060	-0.082	-0.053	0.286
p value	0.681	0.573	0.713	**0.006**
Disulfide/total thiol				
rS	0.060	-0.082	-0.053	0.285
p value	0.681	0.573	0.713	**0.006**
Native thiol/total thiol				
rS	-0.061	0.080	0.054	-0.285
p value	0.673	0.580	0.707	**0.006**

RAI: Radioactive iodine treatment; fT3: Free triiodothyronine; fT4: Free thyroxine; rS: Spearman's correlation coefficient.

ports controversial results about the effects of thyrotoxicosis on the antioxidant defense system (14). Komosinska-Vassev et al. reported a marked increase in erythrocyte superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) activities that are responsible for intracellular antioxidant activity in hyperthyroid patients, as compared to the healthy subjects (15). Another study reported lower erythrocyte SOD and catalase activities in patients with Graves' disease than in the control group (16); though, erythrocyte GPx and total reactive antioxidant potential were similar. Andryskowski and Owczarek showed that sulfhydryl (SH) groups were 15% lesser in hyperthyroid patients than in euthyroid subjects (11).

The SH group in thiol plays a role in maintaining the level of the intracellular OS. Thiol concentration can differ at the cellular level during proliferation or apoptosis. SH groups of sulfur-containing amino acids are the main targets of oxygen radicals. Oxidation of these groups causes the formation of reversible disulfide bonds. The loss of these thiol groups is related to structural and functional changes in cellular proteins. Plasma and tissue levels of thiol groups can decrease during these processes to overcome the destructive effects of free radicals (6). Erel first introduced a method that could measure dynamic thiol/disulfide automatically (7). Only a small fraction of thiols-thiol and disulfide in low molecular weight compounds could be measured until this approach was developed. However, thiols of albumin and other proteins make up the major thiols in the body. The previous methods were insufficient in precisely measuring the body's thiol and disulfide levels (17).

The previous studies evaluating OS in thyrotoxicosis usually included patients with Graves' disease, with high or normalized thyroid hormones. The present study evaluated OS in DTC patients on THST with the help of a relatively new method. Patients on THST had lower native and total thiol and higher disulfide. Still, the differences were not statistically significant; thus, suggesting that the thiol/disulfide balance was maintained in these patients. A subgroup analy-

sis revealed that patients with overt thyrotoxicosis had higher disulfide levels than patients with subclinical thyrotoxicosis and control group; however, native and total thiols were similar. Additionally, D/T and D/N were increased, and N/T was decreased in the patients, demonstrating a shift of the thiol/disulfide status to the part of disulfide bond generation. Disease duration and levothyroxine dose did not affect these parameters. These findings suggest that oxidative balance is disturbed in relation to the severity of thyrotoxicosis in patients on THST. There is an association between the degree of thyrotoxicosis and the development and severity of adverse effects. In the study by Selmer et al., the risk of all-cause mortality was increased by 23% and 25% in subclinical and overt hyperthyroidism, respectively (18). They also found that patients with subclinical and overt hyperthyroidism were at an increased risk of major adverse cardiovascular events (9% and 16%, respectively). In another study, the risk of hip fractures was increased by 22% to 25% in euthyroid postmenopausal women with lower TSH and higher fT4, although within the reference range (19). In one more study involving 5,860 subjects over 65 years, fT4 was higher in patients with atrial fibrillation (20).

It is unclear whether there are differences in the cellular effects of exogenous and endogenous subclinical thyrotoxicosis. fT3 is generally higher in endogenous compared to exogenous thyrotoxicosis. In patients on THST, high serum fT4 rather than fT3 is more commonly encountered. Patients using levothyroxine after total thyroidectomy usually have significantly higher serum fT4 as compared to the presurgical levels. This increase is particularly prominent in patients on THST. It is known that 20% of circulating T3 is usually secreted directly by the thyroid gland. However, since this portion of T3 lacks in patients without a thyroid gland, higher serum T4 levels are required to maintain normal serum T3 levels (21). In the present study, fT3 was similar to the control group, while fT4 was significantly higher in patients on THST. The study also found that fT4/fT3 was the only parameter correlated with OS (positively with disulfide, D/T, and D/N and negatively with N/T).

This study also has some limitations. Designed as a single-center study, it involved a small sample size. Another limitation of the study was the lack of thiol/disulfide evaluation before thyroidectomy. Comparison of OS before surgery in euthyroid status and after surgery on THST would probably lead to more valuable inferences about OS in these patients.

Conclusion

In conclusion, to the best of the author's knowledge, this study was the first to evaluate thiol/disulfide balance in patients on THST. Although the thiol/disulfide balance seems to be preserved in these patients, redox status has shifted toward disulfide in patients with overt thyrotoxicosis. The OS potency in patients with THST appears to be related to the degree of thyrotoxicosis. Disturbed OS can be added to the well-known long-term complications of THST, and these findings can be considered a piece of evidence that fT4 levels should be maintained within normal limits in patients receiving THST.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Concept: Abbas Ali Tam, Bekir Çakır, Özcan Erel; Design: Didem Özdemir, Reyhan Ersoy; Data Collection and Processing: Afra Alkan, Sevgül Fakı, Nagihan Beştepe; Analysis or Interpretetion: Abbas Ali Tam, Didem Özdemir; Literature Search: Abbas Ali Tam, Didem Özdemir; Writing: Abbas Ali Tam, Didem Özdemir, Bekir Çakır, Özcan Erel.

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