

Thiol/Disulfide Homeostasis in Patients with Telogen Effluvium: Is Oxidative Stress Important in the Pathogenesis of Telogen Effluvium?

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Abstract

Objective: The aim of this study was to assess the correlation between telogen effluvium (TE) with the new oxidative stress (OS) indicator of thiol/disulfide balance and to research the role of OS in the pathogenesis of TE. **Methods:** Our study included 101 patients with TE diagnosis and 39 healthy individuals. Serum thiol/disulfide was measured with a new automated spectrometric method developed by Erel and Neselioglu, and results were compared statistically. **Results:** Among the six thiol/disulfide parameters, there were statistically significant differences for native thiol, total thiol, disulfide, disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol studied in the patient and control groups ($P = 0.042, 0.044, <0.001, 0.013, 0.026,$ and $< 0.001,$ respectively). **Conclusions:** Based on the results of this study, it can be said that OS is closely associated with TE pathogenesis. There is a need for new studies that will show the possible effects of OS on TE pathogenesis and research different OS markers in addition to thiol/disulfide parameters.

Keywords: Alopecia, diffuse hair loss, disulfide, oxidative stress, telogen effluvium, thiol

INTRODUCTION

Diffuse and nonscarring hair shedding is called telogen effluvium (TE).^[1] The definite prevalence of TE is unknown; however, it has been reported as a common disorder. A large percentage of adults experience TE attacks at some point. TE may develop in both genders; however, there is a greater tendency to experience this situation in women due to hormonal changes after birth.^[2]

The life cycle of a hair follicle follows three phases of the anagen (growth period), catagen (regression causing apoptosis), and telogen (resting period) phases.^[3] A functional stress condition causes TE, by inducing a large amount of hair from anagen phase to suddenly enter the telogen phase. Accrual of telogen hair terminates after 1–6 months (mean 3 months); however, this disruption of growth is rarely noticed by patients. When hair enters the growth phase again (anagen), hair in the

resting phase (telogen) falls from the follicle and is observed as hair loss.^[2]

Headington defined five mechanisms for TE as anagen phase occurring immediately due to fever, stress and medication, delayed anagen phase linked to birth, short anagen phase causing chronic TE, sudden telogen phase with topical minoxidil treatment, and the theoretically possible delayed telogen phase.^[4] Although it is known that TE is a reactive process that may be triggered by metabolic stress, hormonal changes or medications, the pathogenesis is not clear. It is associated with common trigger events such as acute fever diseases, severe infection, major surgery, severe trauma, hormonal changes after birth, especially reduced estrogen,

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hypothyroidism, cessation of medications containing estrogen, strict diets, low protein intake, heavy metal intake, and iron deficiency.^[2,5]

Recent studies have revealed significant correlations between oxidative stress (OS) and certain diseases. There are various biochemical markers used with the aim of identifying OS and inflammation. One of these markers is dynamic thiol/disulfide balance. Dynamic thiol/disulfide level has crucial functions in regulation of transcription factors, apoptosis, antioxidant protection, cell signal mechanisms, detoxification, signal transduction, and enzyme activities.^[6]

In addition, there is increasing evidence showing that abnormal thiol/disulfide homeostasis situations play a role in pathogenesis of a variety of diseases such as rheumatoid arthritis,^[7] diabetes,^[8] cancer,^[9] cardiovascular disease,^[10] acquired immunodeficiency syndrome,^[11] chronic kidney disease,^[12] Parkinson disease,^[13] Friedreich's ataxia,^[14] liver disorder,^[15] and Alzheimer disease.^[16]

Thiols, forming a significant proportion of total antioxidants in the body, are compositions containing sulfur and play a substantial role in aiding the body's defense versus reactive oxygen species. Plasma thiols scavenge free radicals through a variety of mechanisms and are commonly accepted as playing a physiologic role by acting as antioxidants.^[17]

Recent reports have identified that the thiol/disulfide balance plays an important role in the pathogenesis of many skin diseases such as vitiligo,^[18] psoriasis,^[19] basal cell carcinoma,^[20] urticaria,^[21] and rosacea.^[22]

The goal of this study was to evaluate thiol/disulfide balance as a novel marker of OS in TE patients and to investigate the importance of OS in TE pathogenesis. To the best of our knowledge, there is one study in the literature related to OS in TE patients.^[23]

METHODS

Other diseases causing hair loss such as trichotillomania, alopecia areata, and androgenetic alopecia were excluded in the patients. Diagnosis was placed with more than 100 days of hair shedding in the patient's history, detailed physical examination, and a positive hair pull test (more than four hairs shedding when lightly pulled). The control group had no complaints of hair loss and abided by the same exclusion criteria as the TE patient group, encompassing individuals over the age of 18 years attending the dermatology clinic as outpatients.

For the patient and healthy control group, those with chronic and systemic diseases, history of surgical operations, pregnancy, breastfeeding, irregular menstruation, excessive weight loss, low-calorie diet, receiving iron supplements, active smoking habit, and medication use that may cause hair loss were excluded from the study. Venous blood samples were collected from the two groups after at least 8–10 h fasting.

Samples were centrifuged at 1500 g for 10 min and serum was obtained. The separated serum was immediately placed in Eppendorf tubes and left in a freezer at -80°C .

Thiol/disulfide homeostasis evaluation had performed by a fully-automatic method, developed by Erel and Neselioglu.^[6] Disulfide bonds are first reduced with sodium borohydride to create functional thiol groups. Unused reducing agent, sodium borohydride, was removed with formaldehyde to prevent reduction of 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB). All thiol groups, including reduced and native thiol groups, were later fixed by reactions with DTNB. Half of the difference between total thiol and native thiol determined the dynamic disulfide amount. After determining native and total thiols, disulfide levels, disulfide/total thiol, disulfide/native thiol, and native thiol/total thiol ratios were calculated.

Statistical analysis

Statistical analysis was completed using IBM SPSS 23.0 (SPSS for Windows, SPSS Inc., Chicago, IL, USA). The Shapiro–Wilks test was used for normality testing of native thiol, total thiol, disulfide level, disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol ratios. The groups displayed normal distribution. The independent samples *t*-test, among parametric tests, was used to investigate whether there were considerable differences between the groups. The differences between the sociodemographic characteristics of gender and age among the patient and control groups were investigated with the Pearson–Chi-square and Student's *t*-test. $P < 0.05$ was accepted as statistically significant.

RESULTS

The current study was completed in accordance with the Helsinki Declaration and all patients and healthy controls provided written consent. It was also approved by the Ethics Committee of Tokat Gaziosmanpaşa Medicine Faculty with the number of 19-KAEK-003. This research included 101 patients (91 females and 10 males) older than 18 years attending the dermatology clinic with TE diagnosis and 39 healthy volunteers (34 females and 5 males). The mean age of the patient group was 31.49 ± 13.14 years, with mean age of the control group 34.38 ± 13.15 years. There were no statistically significant differences between the groups in terms of age and gender ($P = 0.246$ and 0.454 , respectively). Among the six thiol/disulfide parameters, there were statistically significant differences for native thiol, total thiol, disulfide, disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol studied in the patient and control groups ($P = 0.042$, 0.044 , <0.001 , 0.013 , 0.026 and <0.001 , respectively). The statistical correlations between demographic characteristics and thiol/disulfide parameters are shown in Table 1.

DISCUSSION

TE is a disease characterized by hair thinning or shedding as a result of the early entry of hair into the telogen phase. Increased or synchronized telogen shedding occurs linked to

the disruption in the hair follicle cycle in TE. The trigger may frequently be found in the patient's history.^[24]

The plasma thiol pool mainly comprises albumin thiols and protein thiols, followed by smaller amounts of low-molecular-weight thiols such as cysteine (Cys), cysteinyl glycine, glutathione, homocysteine, and γ -glutamyl Cys.^[6] Thiols protect keratinocytes against the results of oxidative changes in the stratum corneum and regulate intracellular redox metabolism.^[25] The main source of thiols in skin are mature dendritic cells, and thiols are the first antioxidants consumed in OS conditions. Measurement of plasma total thiol levels and identification of thiol/disulfide homeostasis is a good marker of excessive free radical formation in many diseases, and it also provides important clues about the dimension of free radical-mediated oxidation causing protein damage.^[17,26]

Erel and Neselioglu developed a new fully-automated method to determine thiol/disulfide homeostasis by measuring native thiol, total thiol, and disulfide levels. Thiol parameters determined with this method may be good markers of antioxidant capacity in human metabolism. Erel and Neselioglu used this method to show higher plasma disulfide levels in degenerative diseases such as obesity, pneumonia, bronchiolitis, and diabetes mellitus compared to healthy groups; in other words, the thiol/disulfide homeostasis had slid toward disulfide. However, they showed that in proliferative diseases such as renal cancer, colon cancer, urinary bladder cancer, and multiple myeloma, this balance slid toward the thiol side.^[6]

To date, thiol/disulfide homeostasis has been researched in many studies with this new method.^[27] However, in the literature, there are few studies researching thiol/disulfide homeostasis in certain dermatologic diseases such as vitiligo, psoriasis, basal cell carcinoma, urticaria, rosacea, and tinea versicolor.^[18-22,28]

Studies by Akbas *et al.* researching thiol/disulfide balance in vitiligo patients identified that serum thiol/disulfide levels were similar in patient and control groups and that vitiligo did not affect thiol/disulfide balance.^[23] Kilinc *et al.* in a study assessing thiol/disulfide homeostasis in patients with tinea versicolor by measuring thiol and disulfide levels in serum reported no statistically significant difference between patient

and control groups.^[28] Yazici *et al.* detected that serum thiol levels in psoriasis patients were significantly low compared to a healthy group.^[19] Demirseren *et al.* showed that thiol/disulfide balance in patients with basal cell carcinoma changed with reduced disulfide and elevated thiols, and there was a statistically significant difference compared to the healthy group.^[20] In another study, Akbas *et al.* reported thiol/disulfide levels did not change in patients with acute urticaria compared to a healthy group, while thiol/disulfide levels significantly changed in patients with chronic spontaneous urticaria.^[21]

Akbas *et al.*, in their TE study, indicated that native thiol has not been changed but disulfide decreased. Since disulfide decreased, total thiol decreased and the ratio of native thiol/total thiol also decreased. Thorough their findings, there were no significant differences between patients and control group statistically in terms of native thiol, total thiol, and disulfide ($P > 0.05$).^[23]

Reactive oxygen species forming as a result of chronic exposure of skin to both endogenous and environmental pro-oxidant materials may harm cellular components such as nucleic acids, proteins and cell membranes, and disrupt the antioxidant/oxidant balance. In addition, excessive production of free radicals and weak antioxidant defense contributes to formation of OS.^[29]

In our study, the novel oxidative markers of thiol/disulfide parameters and thiol/disulfide balance were compared in TE patients and a healthy control group. There were statistically significant decreases observed between native thiol, total thiol, disulfide, disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol values in patient and control groups ($P < 0.05$). The results of our study support the relationship between TE and OS. Akbas *et al.*, reported that thiol/disulfide homeostasis is effected in TE, but the balance is not damaged.^[23] Our findings are contrary to this study; thiol/disulfide homeostasis and balance are both effected.

A limitation of this study is that body mass index was not calculated in the patient and control groups.

CONCLUSIONS

To the best of our knowledge, our study is the second clinical research investigating the role of OS in TE pathogenesis using

Table 1: Thiol/disulfide homeostasis parameters and demographic features of patient and control groups

Parameter	Control (n=39)	Patients (n=101)	P
Age (years), mean±SD	34±13	31±13.1	0.246
Gender (male/female)	5/34	10/91	0.454
Native thiol (SH) (μmol/l), mean±SD	347.5±47.8	328.5±48.2	0.042
Total thiol (μmol/l), mean±SD	388.5±53.4	368.0±51.9	0.044
Disulphide (SS) (μmol/l)	21.8±3.7	18.6±4.3	<0.001
Disulfide/native thiol (%)	6.4±1.1	5.78±1.7	0.013
Disulfide/total thiol (%)	5.65±0.87	5.1±1.3	0.026
Native thiol/total thiol (%)	88.7±1.7	89.72±2.6	0.001

SD: Standard deviation

thiol/disulfide parameters. Based on the results of the study, it can be said that OS plays a key role in TE pathogenesis. In addition, there may be an important inspiration that antioxidant treatment would be beneficial in TE. There is a need for novel studies supporting our findings by showing the possible effects of OS on TE pathogenesis and researching different OS markers in addition to thiol/disulfide parameters.

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Conflicts of interest

There are no conflicts of interest.

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