ORIGINAL ARTICLE

Evaluation of Thiol/Disulfide Homeostasis and İschemia-modified Albumin Levels in Symptomatic Dermographism

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Abstract

Background: Symptomatic dermographism (SD) is the most common chronic inducible urticaria (CIndU) type. Thiol/disulfide homeostasis (TDH) and ischemia-modified albumin (IMA) levels are indicators of oxidative stress. **Aim:** Our study aims to investigate the role of thiol/disulfide balance and IMA levels in the pathogenesis of SD. This focus guides our research and helps us to better understand the disease. **Materials and Methods:** This cross-sectional study, conducted with utmost care and precision, included 50 SD patients and 50 healthy volunteers. The patients and controls were meticulously evaluated regarding IMA, native thiol, total thiol, and disulfide levels and disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol ratios, ensuring a thorough and reliable understanding of the data. **Results:** In our study, the patient group demonstrated significantly higher levels of native thiol, total thiol, disulfide, and IMA values than the control group ($P < 0.05$). **Conclusions:** In patients with SD, impaired TDH and increased IMA suggest that oxidative stress may play a significant role in the disease pathogenesis, underscoring the importance of our findings.

Key Words: *Artificial urticaria, ischemia-modified albumin, oxidative stress, symptomatic dermographism, thiol-disulfide homeostasis*

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Introduction

Urticaria is categorised as acute or chronic based on the duration of the lesions. Chronic urticaria (CU) is further classified into two groups: 'spontaneous' and 'inducible' urticaria.[1] Chronic inducible urticaria (CIndU) involves the development of hives and angioedema due to specific triggers or stimuli.[2] The most common form of CIndU is symptomatic dermographism (SD) (dermographic urticaria and artificial urticaria). SD following scratching or rubbing the skin with swelling accompanied by itching and burning sensation is characterised.[3] Blisters form on the skin without itching after a strong stimulus. This is known as simple dermographism. It is called SD if it is accompanied by itching.[4] The average disease in SD is 6.5 years. Diagnosis is established through patient history and provocation tests. The treatment includes pharmacological treatment and avoiding trigger factors.[5,6] Oxidative stress happens when cells are imbalanced due to increased free radicals or decreased antioxidants. Free radical chain reactions in the body produce reactive oxygen species (ROS) and lipid peroxides, which can cause tissue damage. This imbalance plays a role in the development of various diseases, such as cancer and aging.[7] Multiple markers are available to measure oxidative stress. Ischemia-modified albumin (IMA) is a marker for ischemia in heart diseases and indicates oxidative stress in various conditions. The N-terminal end of albumin is where metals such as cobalt, copper, and nickel bind. When the body experiences ischemic or oxidative stress, the structure of the N-terminal end of albumin changes, resulting in a variant of IMA.[8] Thiols are a crucial indicator of exposure to oxidative stress. They contain 'SH' groups that are prone to oxidation. Thiols fall into three groups: native thiols (NTs), which can oxidise into disulfides (SS) when exposed to ROS, and total thiols (TT), which is the sum of NTs and SS. A decrease in NT groups and an increase in SS groups after oxidation strongly indicate oxidative stress.[9]

SD is a common dermatological problem, but its etiopathogenesis has not been fully revealed. The effects of oxidative stress in SD patients have yet to be evaluated by simultaneous measurement of thiol and IMA

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Quick Response Code:

Website: https://journals.lww.com/ijd

DOI: 10.4103/ijd.ijd_770_24

How to cite this article: Metin MS, Tehçi T, Kolukırık İ, Akoğul S, Öner Ü, Metin Z. Evaluation of thiol/disulfide homeostasis and ischemia-modified albumin levels in symptomatic dermographism. Indian J Dermatol 2025;70:246-51.

Received: August, 2024. **Accepted:** January, 2025.

levels. This study aims to investigate whether plasma antioxidant status is effective in disease pathogenesis in SD patients.

Materials and Methods

Study design and patients

This cross-sectional study included patients with SD attending the dermatology OPD clinic between July 2022 and August 2023 and a control group without any dermatological or systemic conditions. The diagnosis of SD was established through patient history and clinical examination and confirmed by provocation tests. People who had accompanying cutaneous or systemic disorders, who smoked or consumed alcohol, who were pregnant, and who used topical or systemic medications in the last three months were excluded from the study. They were asked to complete a questionnaire detailing sex, age, family history, any history of allergic rhinitis, asthma and eczema, drug and food reactions, duration of illness, duration of wheals, skin areas involved, and associated symptoms. Medications, insect bites, *Helicobacter pylori* infection or infestation (e.g., scabies and *Fasciola hepatica*) were ruled out as triggers. The patients' oxidative stress markers, age, and gender were assessed.

Sampling and measurements

After obtaining an informed consent form from the patient, venous blood samples were secured in biochemistry tubes following overnight fasting. The samples were centrifuged at 1300 g for 10 minutes. After centrifugation, the sera were separated and stored at −80°C until analysis. TDH was measured using the automated spectrometric technique developed by Erel and Neselioğlu.[10] Thiol and SS values were represented as mmol/L, while SS/TT, SS/NT, and NT/TT rates were described as percentages. After the determination of native and TTs, SS amounts, index-1: ([SS]/[NT]) × 100, index-2: ([SS]/[TT]) × 100, and index-3: ([NT]/[TT]) × 100 were calculated. Serum IMA levels were measured using a colorimetric method developed by Bar-Or *et al*.[11] IMA exhibits a low affinity for cobalt, which can be measured through an indirect technique, albumin cobalt-binding (ACB) assay. The data obtained are shown as absorbance units (ABSU).

Statistical analysis

Statistical analyses were conducted using the IBM SPSS Statistics 29 software package. Frequency tables and descriptive statistics were used to analyse the findings. Continuous variables were presented as mean ± standard deviation, and categorical variables were presented as frequency and percentage. We utilised Chi-square analysis to examine categorical data and the Shapiro-Wilk test to assess data normality. When comparing two independent groups, we employed the independent *t*-test for normally distributed data; otherwise, we used the Mann-Whitney U test. We conducted a Spearman correlation analysis to establish the relationship between the two variables. A *P* value of <0.05 was considered statistically significant.

Results

Fifty patients with SD and 50 healthy subjects participated in the study. The mean ages of the patients (23 males and 27 females) and controls (21 males and 29 females) were 34.48 ± 10.36 and 28.96 ± 6.16, respectively ($P > 0.05$). Table 1 provides descriptive statistics and statistical test results for age, NT, TT, SS, index-1 (SS/NT%), index-2 (SS/TT%), index-3 (NT/TT%), and IMA parameters of both the patient group and the control group. According to Table 1, the NT, TT, SS, and IMA values were significantly lower in the control group than in the patient group ($P < 0.05$, Figures 1–4). No statistically significant difference was found between the control and patient groups regarding age, Index-1, Index-2, and Index-3 levels ($P > 0.05$). A statistically significant difference was found between genders in the values of NT and TT ($P < 0.05$), with these values being significantly higher in women. However, there was no statistically significant difference between genders in SS, Index-1, Index-2, Index-3, and IMA values ($P > 0.05$). The study examined the relationships between SD patients' IMA values and parameters such as NT, TT, SS,

Table 1: Descriptive statistics and statistical test results on the relevant parameters

Parameters	Control group (*n*=50)	SD patients (*n*=50)	Test statistic* and *P*
Native thiol, µmol/L	290.69±49.30	316.78±45.60	*t*=2.746
			P=0.007
Total thiol, µmol/L	328.79±54.58	358.76±51.34	*t*=2.828
			P=0.006
Disulfide, µmol/L	19.05±3.14	20.99±3.28	*t*=3.023
			P=0.003
(Disulfide/native thiol) ×100	6.59±0.65	6.64±0.56	*t*=0.382
			P=0.704
(Disulfide/total thiol) ×100	5.82±0.51	5.86±0.43	*t*=0.399
			P=0.691
(Native thiol/ total thiol) ×100	88.36±1.02	88.29±0.87	*t*=-0.399
			P=0.691
IMA, ABSU	0.56±0.06	0.78±0.19	*Z*=6.936
			P<0.001
Age	28.96±6.16	34.48±10.36	*Z*=1.598
			P=0.110

n: Number of objects; Data were expressed as mean±standard deviation * The independent *t*-test (*t*) was calculated for data where the assumption of normal distribution was met, and the Mann-Whitney *U* test (*Z*) was calculated in cases where the assumption was not met

Index-1, Index-2, and Index-3 by using the statistical test results provided in Table 2.

A negative and moderately statistically significant relationship was found between IMA and the values of NT, TT, and SS in patients with SD ($P < 0.05$). As the patients' IMA values increase, the NT, TT, and SS values decrease. However, no statistically significant relationship could be detected between the patients' IMA values and Index-1, Index-2, and Index-3 ($P > 0.05$).

Discussion

SD significantly impacts patients' quality of life and requires advanced treatment. It is reported that 2%–5% of the general population has SD.[5] Urticaria is a mast-cell-driven disease, and mast cell (MC) degranulation initiates the inflammatory process. In CU, there is an activation of basophils or MCs causing the release of histamine and other mediators. It has also been seen that there is an intradermal infiltration characterised by MCs, CD4 T lymphocytes, monocytes, neutrophils, eosinophils, and basophils.[12,13] These inflammatory cells, chronically activated, produce large amounts of free oxygen radicals.[14] Skin, the largest organ in the human body, is exposed to air pollutants, including diesel exhaust fumes, ultraviolet rays, food, xenobiotics, drugs, and cosmetics, which promote the production of ROS.[15] In particular, mechanical trauma and solar radiation in SD are the main factors that trigger the formation of ROS.[16]

This study is the first to demonstrate that oxidative stress increases in patients with SD by examining the thiol-SS balance and IMA values. In our research, NT and TT levels, essential antioxidants in the body, were

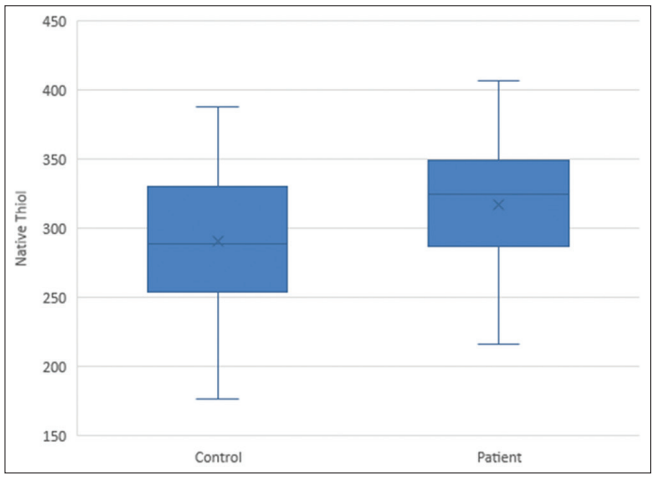

Figure 1: Mean values of native thiol levels in the patient and control groups

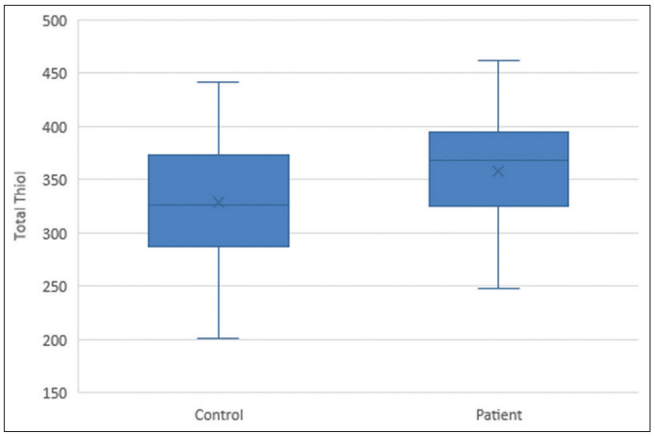

Figure 2: Mean values of total thiol levels in the patient and control groups

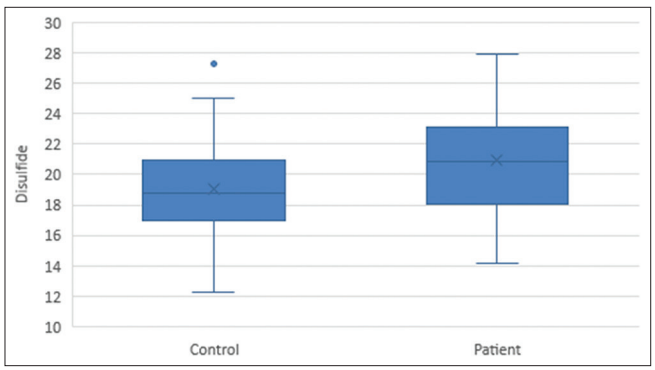

Figure 3: Mean values of disulfide levels in the patient and control groups

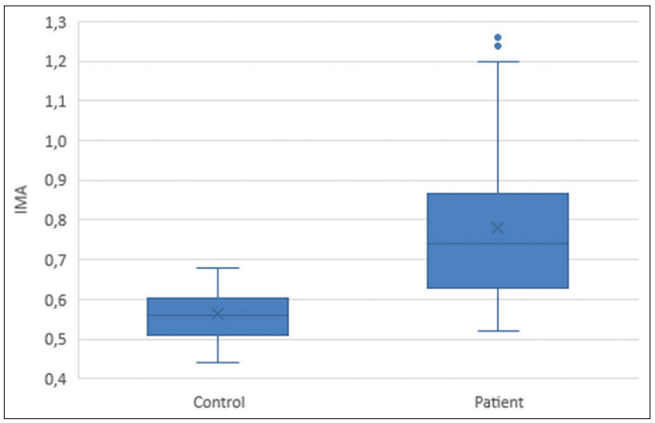

Figure 4: Mean values of IMA levels in the patient and control groups

Table 2: Relationships between patients' IMA values and relevant parameters

Ischemia-Modified Albumin	Native Thiol	Total Thiol	Disulfide	Index-1	Index-2	Index-3
Spearman Coefficient	ρ=–0.433	ρ=-0.418	ρ=-0.333	ρ=0.102	ρ=0.102	ρ=-0.102
P	0.002	0.003	0.018	0.480	0.480	0.480

*Pearson (r) correlation coefficient was calculated for the relationship between normally distributed data, and Spearman (ρ) correlation coefficient was calculated if the assumption was unmet

significantly higher in SD patients than in healthy controls. This imbalance in thiol-SS levels suggests that oxidative and antioxidative mechanisms are involved in the development of SD. Thiols play a crucial role in antioxidant defence. A balance exists between thiols and their oxidised forms, SS, referred to as dynamic TDH. The skin is continually exposed to oxidative stress. Thiols are the initial antioxidants to be used in an oxidising environment. They regulate the redox status inside cells and shield keratinocytes from ROS. It appears that mature dendritic cells are the primary origin of thiols in the skin. The physiological processes of keratinocyte differentiation and cell apoptosis are strongly linked to thiols.[17] Maintaining a balance between free radical generation and the antioxidant system prevents excess ROS.[18] The imbalance between ROS generation and the oxidant-antioxidant system can affect cellular processes, gene expression, inflammation, and apoptosis, contributing to the development of cutaneous inflammatory disorders.[14,19] Thiol SS levels have been studied in various dermatological conditions, including psoriasis vulgaris, seborrheic dermatitis, atopic dermatitis, vitiligo, cutaneous lichen planus, acne vulgaris, pityriasis rosea, tinea versicolor, and onychomycosis.[20-28] Previous studies have shown that specific enzyme systems associated with oxidative stress play a role in developing urticaria in adults.[29,30] On the contrary, particular reports indicate no variation in oxidative stress markers among patients with CU.[31,32] A study conducted on paediatric patients with CU demonstrated increased oxidative stress. There is a positive correlation between oxidative stress and disease activity. This was investigated by analysing the total oxidant state (TOS), total antioxidant state (TAS), and oxidative stress index (OSI).[33] In another study involving paediatric patients, Akdag *et al*.[34] discovered that children with a family history of autoimmune disease have higher levels of oxidative stress. Akbas *et al*.[35] studied TDH in acute urticaria (AU) and CU patients. They found no change in TDH in the AU group, but TDH shifted towards SS in the CU group. Aydin *et al*.[36] stated in their study that low NT and TT levels could be used as oxidative stress markers in patients with AU. Matei *et al*.[37] investigated the impact of H1-antihistamine treatment on TDH in patients with chronic spontaneous urticaria (CSU). They discovered that treatment with H1-antihistamines increases thiol levels and decreases SS levels. The TDH parameters could help monitor therapy with H1-antihistamines in urticaria. IMA is a type of serum albumin with a modified structure. Its plasma levels increase following acute ischemia or in cases of oxidative stress in various diseases.[38,39] Previous studies have evaluated IMA levels in several skin diseases. Elevated IMA levels in psoriasis, acne vulgaris, hidradenitis suppurativa, vitiligo, alopecia areata, and Behçet's disease compared to controls suggest that IMA could be a marker of oxidative stress in these conditions.[40] Otal *et al*.[41] discovered elevated serum IMA levels in their study on patients with AU. They suggested that IMA could be a marker of oxidative stress in AU. In their study, Akdag *et al*.[34] found elevated serum IMA levels in patients with CU. They believe that oxidative stress plays a role in the development of CU. Our study observed that the IMA level in patients in the SD group was significantly higher compared to the control group, consistent with existing literature. When we considered the irregularity in thiol levels, this result provided additional evidence supporting the role of oxidative stress in the development of SD. In our study, there was no significant correlation between the parameters and the patient's age. In line with existing literature, we observed a 56% female predominance.[34] When comparing gender, a statistically significant difference was found in NT and TT values, significantly higher in women.

The pathogenesis of CIndU is the focus of several recent and ongoing studies. Pathogenic mechanisms that are involved in CSU appear to also play an important role in CIndU.[42] MC activation and degranulation, together with the subsequent release of histamine and other inflammatory mediators, are the key drivers of CIndU skin lesion development. A recent study confirmed that MCs are indispensable for the development of SD and cold urticaria (ColdU). A single treatment with barzolvolimab, an anti-KIT monoclonal antibody (mAb) that depletes MCs, completely abolished symptoms in SD and ColdU patients.[43] Findings from this study show that MCs are indispensable for the development of SD and ColdU.

There are many studies investigating oxidative stress in patients with CSU and showing its relationship.[16,18,33,35,37,44-46] From this perspective, if adequate studies are carried out in cases of CIndU, the effect of ROS on the pathogenesis of these urticaria will be better understood.

Vitamin C (ascorbate) (VC) is one of the most effective aqueous-phase antioxidants in human blood plasma for protection against oxidative stress. Vollbracht C *et al*.[47] provided observational evidence for the use of high doses of intravenous VC in daily practice for the treatment of respiratory and cutaneous allergic diseases (eczema, urticaria, psoriasis, etc.). Johnston *et al*.[48] showed that VC supplementation lowered blood histamine levels by 38%. Adjunctive treatment with over-the-counter VC 1000 mg daily is thought to help degrade histamine and increase removal, diminishing the triple response of Lewis. In a study of vitiligo, another skin condition thought to be related to oxidative stress, VC levels were found to be low in 30 patients. In another study, a combination of a cream containing 0.05% clobetasol propionate and oral VC and B12 was shown to be effective.[49,50] Based on these examples, although there

are mixed results in the literature, we believe that VC supplements can be used in the treatment of SD, where we believe oxidative stress plays a role in the pathogenesis.

We should mention some limitations in our study. The small sample size limits generalisations from the results. More evidence is needed to understand these specific observations in depth. Additionally, as our study is cross-sectional, it limits the ability to judge the temporal order of relationships and makes it difficult to establish causality.

Conclusion

High thiol and IMA levels may be involved in the development of SD and associated with increased MC proliferation, serum histamine, and IgE levels in the disease. Our study is the first to investigate thiol/SS balance and IMA levels in patients with SD. Oxidative stress plays a role in SD pathogenesis. Serum IMA levels could be a potential biomarker of oxidative stress in SD. In addition, our study may be useful in the development of new treatments, including the use of antioxidants, in CU patients, including SD. Further research should focus on evaluating vitamin supplements, including vitamins C and E, and drugs, including corticosteroids and calcineurin inhibitors, in relation to levels of oxidative stress markers. In the context of dermographism, the results of our study will pave the way for new clinical trials and treatments that reduce oxidative stress.

Declaration of patient consent

All patients gave informed written consent to participate in the study.

Ethical approval

The study protocol was performed following the Helsinki Declaration. Ethics committee approval was obtained for the present study from Ahi Evran University (REF number: 2022-15/133).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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