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ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2026;15(1):505-9

Investigation of ischemia modified albumin and dynamic thiol disulfide levels in patients with Chronic Spontaneous Urticaria

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Received 29 September 2025; Accepted 04 November 2025
Available online 27 February 2026 with doi: 10.5455/medscience.2025.09.253

Abstract

This study aims to assess ischemia-modified albumin (IMA) and thiol balance in Chronic Spontaneous Urticaria (CSU) patients. A total of 34 CSU patients were compared with 40 healthy controls. Erel et al. devised a new colorimetric approach to determine the dynamic thiol-disulfide balance. Bar-Or et al.'s albumin cobalt binding test was used to measure IMA levels. In comparison to controls, it was discovered that the CSU group had lower Total Antioxidant Status (TAS) levels and greater Total Oxidant Status (TOS) and Oxidative Stress Index (OSI) levels. Disulfide levels were higher in study subjects compare healthy subjects, although thiol levels were lower. The patient group's disulfide levels were greater than those of the control. IMA degrees were considerably divergent among the groups. Our findings suggest that increased disulfide formation reduces antioxidant defenses in individuals with CSU. The balance between thiols and disulfides could be a useful marker for assessing OS in these patients and for tracking conditions associated with it.

Keywords: Oxidative stress, ischemia-modified albumin, thiol- disulfide homeostasis, chronic urticaria

Introduction

Urticaria is a heterogeneous inflammatory skin disorder with a lifelong prevalence of approximately 20% worldwide [1]. The condition arises when mast cells in the skin become activated and release histamine along with various mediators [2]. These substances trigger sensory nerves, cause dilation of blood vessels, increase plasma leakage, and attract immune cells. As a result, the characteristic clinical findings such as itchy wheals, swelling, or both. Urticaria is categorized primarily by its duration, with cases persisting 6 weeks or less defined as acute (AU), while those continuing beyond 6 weeks are identified as chronic (CU).

Chronic spontaneous urticaria (CSU) is a subtype of chronic urticaria characterized by the spontaneous appearance of wheals, angioedema, or both, without an identifiable external trigger, persisting for more than six weeks [3]. It is thought to involve complex interactions between immune, inflammatory, and neurogenic pathways, with mast cell activation and histamine release playing central roles [4]. The condition can significantly impair quality of life due to persistent itching, swelling, and sleep disturbances [5]. Although the exact etiology is often unclear, autoimmune mechanisms, autoreactive antibodies, and dysregulation of intracellular signaling pathways have been implicated [1]. Management generally involves a stepwise approach, beginning with non-sedating H1-antihistamines and escalating to higher doses or advanced therapies, such as biologics, for refractory cases [6].

In CSU, histamine release is the primary driver of symptoms, although numerous additional mediators that are generated and secreted also contribute to the clinical picture [7]. The majority of patients develop wheals alone, while a smaller proportion experience both wheals and angioedema or angioedema without wheals [8]. Symptoms may arise unpredictably throughout the

CITATION
Erdal H, Gunaydin FE. Investigation of ischemia modified albumin and dynamic thiol disulfide levels in patients with Chronic Spontaneous Urticaria. Med Science. 2026;15(1):505-9.

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DOI: 10.5455/medscience.2025.09.253

day, though they tend to be more pronounced in the evening and at night, possibly related to circadian changes in mast cell activity and variations in disease mechanisms.

Oxidative stress (OS) has been increasingly recognized as an important factor in pathogenesis of CSU. Excessive production of ROS can disturb the delicate balance between oxidants and antioxidants, promoting inflammatory responses and mast cell activation. One of the key indicators of redox status is thiol–disulfide homeostasis, which reflects the dynamic balance between reduced thiol groups and their oxidized disulfide counterparts [9]. This reversible cycle is critical for preserving protein structure, regulating enzymatic activity, and ensuring proper cellular signaling. Disruption of this balance, characterized by diminished thiol reserves and increased disulfide formation, reflects an oxidative shift that has been associated with various diseases [10-15]. Thus, assessment of thiol–disulfide status provides valuable insight into oxidative stress–related pathophysiology of the disease.

Ischemia-modified albumin (IMA) is a biomarker that reflects OS and ischemic conditions. It is formed when the N-terminal region of serum albumin undergoes structural alterations, primarily as a result of exposure to Reactive Oxygen Species (ROS) and free radicals generated during ischemia and reperfusion [16]. These modifications reduce the metal-binding capacity of albumin, particularly for cobalt, which forms the basis of the commonly used albumin cobalt-binding test for IMA measurement. As a sensitive but non-specific marker of OS, IMA provides useful information about the underlying redox imbalance and tissue injury, and its evaluation may help in the early detection and monitoring of diseases where OS plays a pathogenic role. In this study, we sought to assess thiol balance and IMA grades in CSU.

Material and Methods

Study Groups

This prospective research was undertaken from June 2023 to June 2024. A total of 34 individuals affected by CSU and 40 healthy subjects took part in the study. Patients with active infection, cancer, diabetes mellitus, severe systemic disease, nutritional deficiency, malnutrition, hematologic disease, immunosuppressive therapy, or any urticaria treatments other than antihistamines were excluded from the current study. Medical consents of patients and controls were obtained.

Acquisition of Research Specimens

Venous blood specimens were collected in vacutainer tubes and centrifuged at 1500 rpm x for ten minutes. Then, samples were then split into Eppendorf and stored till the processing time.

Biochemical Assessments

IMA value

IMA concentrations were assessed through the assay established by Bar-Or et al [16]. Results were reported in absorbance units (ABSU).

Analysis of TAS and TOS values

Serum TOS and TAS values were quantified by a spectrophotometric method [17]. OSI was computed using the formula OSI (arbitrary unit)=TOS (μmol H2O2 Eq/L)/TAS (μmol Trolox Eq/L)×100.

Measurement of Thiol Values

Measurement of thiol/disulfide homeostasis was carried out using an automated spectrophotometric technique [18]. Disulfide concentration was calculated by taking the difference between total and native thiol values and dividing that value by two.

Statistical Analysis

Statistical analyses were performed using SPSS version 22. Data normality was assessed with the Shapiro–Wilk test. For variables not conforming to a normal distribution, comparisons were carried out with the Mann–Whitney U test. A p-value below 0.05 was accepted as statistically significant.

Ethics Considerations

This research was approved by Ethics Committee of Ordu University. (Date: 2023-04-28, Number: 2023/117).

Result

This study consisted of 74 people, including 34 chronic spontaneous urticaria (CSU) and 40 healthy subjects, were enrolled and no significant differences in age and sex were identified (Table 1). Demographic data are shown in Table 1. The biochemical parameters of the groups are shown in Table 2.

Table 1. Demographic features of study and control groups.

Parameters		CSU (n=34) Mean ± SD	Control (n=40) Mean ± SD	p
	Male	14 (41.2%)	**20 (50.0%)**	0.448*
	Female	20 (58.8%)	20 (50.0%)	
Age (year)		39.6 ± 11.4	39.9 ± 12.2	0.903¥

*Chi- Square test ¥ Student t –test; CSU: Chronic spontaneous urticaria

DOI: 10.5455/medscience.2025.09.253

Table 2. Biochemical parameters of study and control groups

Parameter	CSU (n=34) (min-max)	Control (n=40) (min-max)	p§
Hemoglobin (g/dL)	13.7 (10.3-17.1)	13.3 (10.4-16.6)	0.379
Neutrophile	4.53 (1.1- 9.1)	3.93 (2.4-6.9)	0.168
Lymphocyte	2.4 (0.73-3.6)	2.16 (1.2-3.6)	0.059
Monocyte	0.58 (0.24-0.99)	0.47 (0.26-0.75)	0.005
Platelet	258.3 (173-325)	262.9 (162-438)	0.665
White Blood Cell	7.56 (3.8-11.6)	7.4 (4.4-10.3)	0.618

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase; MCV: Mean Corpuscular Volume
§: Man-Whitney U test; CSU: Chronic spontaneous urticaria

The study group exhibited considerably lower levels of native and total thiols than the healthy subjects. Disulfide concentrations elevated in the patient group relative to healthy subjects. Additionally, we discovered that there was a significant difference in TAS values among study subjects ($p<0.001$). Furthermore, there was a significant difference ($p<0.001$) in TOS and OSI levels among study cases. Furthermore, Serum IMA levels differed significantly between the research individuals (Table 3).

Table 3. Thiol-disulfide homeostasis parameters of the study and control groups.

Parameter	CSU (n=34)	Control (n=40)	P*
Total thiol (µmol/L)	474.3 ± 53.4	513.3 ± 55.8	0.006
Native thiol (µmol/L)	417.9 ± 53.2	472.1 ± 54.2	<0.001
Disulfide (µmol/L)	28.2 ± 7.3	20.6 ± 5.9	<0.001
IMA (ABSU)	1.13 ± 0.28	0.85 ± 0.26	<0.001
TAS (nmol Troloks/L	2.7 ± 0.67	3.52 ±0.80	<0.001
TOS (µmol H2O2 Equiv./L	8.2 ± 1.15	5.14 ± 0.95	<0.001
OSI	0.32 ±0.11	0.15 ± 0.05	<0.001

IMA: Ischemia -modified albumin, TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index
*: Man-Whitney U test; CSU: Chronic spontaneous urticaria

Discussion

We indicated that thiol values were lower in CSU compare to the controls. However, S-S values were considerably higher in CSU than controls. We also demonstrated that IMA values were higher in CSU subjects than healthy subjects. This research indicated that TOS and OSI were markedly increased in patients relative to healthy participants, with statistical significance. However, TOS levels were higher in CSU compare to controls.

Akbas et al [19]. on patients with acute and chronic urticaria found that thiol levels were not statistically significance difference between the groups. They concluded that the results show a tendency for the thiol–disulphide system to favor disulphide generation, supporting the involvement of OS in CSU. They think that the increase in disulphide levels with the increase in urticaria activity score may play an important role in disease activation. This shows that the activation of urticaria has effects on thiol–disulphide but more detailed studies with a large sample set are needed to explain the mechanism of activation.

Otal et al [20]. showed that native and total values were lower in acute urticaria than the controls. Nevertheless, S-S values were expanded and statistically significant in patient groups than controls. They hypothesized that measurements of thiol–disulfide status may serve as indicators for monitoring therapeutic response in acute urticaria.

Dilet et al [21] in patients with CSU have elevated plasma TOS and OSI levels and reduced TAS levels compared to healthy controls. They indicate that OS is increase in children with CSU and is positively correlated with the disease activity. They thought that this information is valuable for both understanding the pathogenesis of CSU and finding targeted, more effective, and less toxic treatment alternatives

Matei and colleagues [22] reported increase in thiol values and a significant decrease in disulfide, and thiol ratios following H1 antihistamine treatment. They hypothesized that restoration of serum TDHP concentrations has been linked to improvement of clinical complaints, including decreased itching and fading of urticarial lesions. It has been proposed that thiol–disulfide balance contributes to protection against oxidative damage in chronic spontaneous urticaria, and that TDHPs could serve as markers for evaluating the effectiveness of H1-antihistamine treatment.

DOI: 10.5455/medscience.2025.09.253

In the study conducted by Aydin and his colleagues [23] on patients with acute urticaria, they indicate IMA levels were significantly greater in patient group than healthy subjects. Moreover, thiol and disulfide values were lower in SCU than healthy subjects. They asssumed that unchanged balance might be attributable to the transient nature of acute urticaria, which differs from a long-lasting inflammatory condition.

In the present study, our findings demonstrated markedly reduced thiol concentrations in patients than controls, whereas disulfide levels were elevated. The decline in thiols may reflect the ongoing consumption of sulfhydryl-based antioxidants in neutralizing reactive oxygen species. Additionally, TAS were lower in the study cases, while TOS and OSI were both increased, showing differences. IMA measurements also differed significantly between patients and controls. These results suggest that elevated IMA may be associated with OS and weakened antioxidant defenses.

Limitations of the study

This study has some limitations that should be noted when evaluating the findings. The very limited sample size and single-center methodology limit the findings' generalizability to larger groups. In addition, the cross-sectional nature of the study prevents conclusions about causality between oxidative stress markers and the clinical course of CSU. Although strict exclusion criteria were applied, residual confounding factors, including dietary habits, lifestyle influences, and unrecognized comorbidities, may still have affected oxidative stress levels. Furthermore, the evaluation was limited to a selected set of oxidative stress markers, and the inclusion of additional biomarkers could have strengthened the analysis. Despite these constraints, the study contributes valuable insight into the role of thiol balance and IMA in CSU and highlights the relevance of OS in its pathogenesis.

Conclusion

In conclusion, our findings indicate a disruption in the balance between oxidant and antioxidant systems. Patients with urticaria exhibited increased disulfide concentrations accompanied by decreased native and total thiol levels, suggesting that enhanced disulfide formation may weaken antioxidant defenses. The concurrent elevation in IMA levels further supports the presence of reduced antioxidant capacity and heightened OS, likely resulting from excessive reactive oxygen species (ROS) production. Therefore, evaluating the dynamic thiol–disulfide balance may serve as a valuable approach for assessing OS status in urticaria and related disorders.

Conflict of Interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical Approval

The present study was approved by the Ordu University Clinical Research Ethics Committee Date: 2023-04-28, No: 2023/117).

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DOI: 10.5455/medscience.2025.09.253

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