Dermatology Practical & Conceptual

Evaluation of Thiol Disulfide Homeostasis and Ischemia-Modified Albumin Levels as an Indicator of Oxidative Stress in Acne Vulgaris

Zeynep Büşra Balık[1], Ahmet Rıfat Balık[2], Esra Fırat Oğuz[3], Özcan Erel[3], Mustafa Tunca[1]

1 Health Sciences University Gulhane Training and Research Hospital Department of Dermatology, Ankara, Turkey
2 Health Sciences University Gulhane Training and Research Hospital Department of Medical Biochemistry, Ankara, Turkey
3 Ankara City Hospital Department of Medical Biochemistry, Ankara, Turkey

Key words: acne vulgaris, oxidative stress, thiols, IMA

Citation: Balık ZB, Balık AR, Oğuz EF, Erel Ö, Tunca M. Evaluation of Thiol Disulfide Homeostasis and Ischemia-Modified Albumin Levels as an Indicator of Oxidative Stress in Acne Vulgaris. *Dermatol Pract Concept.* 2023;13(4):e2023280. DOI: https://doi.org/10.5826/dpc.1304a280

Accepted: July 4, 2023; **Published:** October 2023

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Zeynep Büşra Balık: Health Sciences University Gulhane Training and Research Hospital Department of Dermatology, Ankara/Turkey, E-mail: zeynepbusrakucuker@gmail.com

ABSTRACT

Introduction: Acne vulgaris (AV) is the most common skin disease. AV is a skin disease often associated with oxidative stress. Thiols and ischemia modified albumin (IMA) analysis are used as oxidative stress markers.

Objectives: In this study, it was aimed to evaluate the blood levels of thiols and IMA, which are accepted as oxidative stress markers, and to determine the severity of the disease in AV patients whose severity is determined by the global acne score rate (GAS).

Methods: Thiol parameters and IMA values were measured spectrophotometrically in blood samples taken from patients and controls. Determine GAS values in AV patients. The thiol and IMA values obtained were compared between the patient and control groups and their correlation with the patient's GAS values was evaluated.

Results: In our study, in acne patients, native thiol (NT), total thiol (TT) and index 3 (I3=NT/TT*100) were significantly lower than the control group, disulfide (SS), index 1 (I1=SS/NT*100), index 2 (I2=SS/TT*100) and IMA values were found to be significantly higher. GAS values, which are accepted as an indicator of the degree and severity of acne disease, and SS, I1 and I2 showed a positive correlation, while I3 showed a negative correlation.

Conclusions: Our study suggests that oxidative stress associated with AV disease pathogenesis may occur through mechanisms dependent on thiol and IMA levels. Therefore, in AV, oral supplementation or topical application of antioxidants may be a good way to increase drug efficacy or prevent potential harm.

Introduction

Acne vulgaris (AV) is the most common skin disease. In general, AV is a time-varying disease of the skin. It can also cause years of physical (wound growth) and psychological discomfort [1]. In addition to other causes such as hyperkeratosis, increased sebum secretion and immune system, recent research has linked oxidative stress to AV diseases [2-5]. It has been reported that sebum oxidation and oxidative stress in the pilosebaceous unit provide an environment that can cause some acne-causing bacteria [6]. An imbalance in the production of oxygen-derived prooxidants, also known as reactive oxygen species (ROS), is thought to cause oxidative stress and the potency of ROS [7].

It is well documented that oxidative stress is involved in the pathogenesis of many diseases, including skin diseases. Various markers are available to measure oxidative stress. Recent studies have shown that ischemia modified albumin (IMA) is not only an indicator of ischemia, but also a marker of oxidative stress. The N-terminal region of the albumin molecule binds divalent heavy metals such as nickel, copper, cobalt. Hydroxylated radicals damage the N-terminal region of the albumin molecule and albumin cannot bind divalent heavy metals [8].

Another indicator of exposure to oxidative stress is thiols. Thiols are susceptible to oxidation due to "-SH" groups. Thiols are evaluated under three groups. The first of these are native thiols (NT). Native thiols oxidize to a second thiol group called disulfides (SS) when exposed to ROS. Therefore, the decrease of native thiol groups and increase of disulfide groups after oxidation is considered as an indicator of strong oxidative stress. The sum of the native thiols and disulfides forms the third thiol group called total thiols (TT) [9].

Global Acne Score (GAS) is an index that aims to determine the severity of pain in patients by measuring AV disease [10]. In this measure to determine severity of acne, the face is divided into upper chest and lower back sections and a coefficient is given for each area, including the width of the area where dense pilosebaceous units are found [11].

Objectives

Many studies have been conducted on Thiol and IMA [9,12]. However, until now, the effects of oxidative stress in AV patients have not been evaluated by simultaneous measurement of thiol and IMA levels. In this study, we aimed to evaluate the oxidative stress level in AV patients using biochemical parameters. In addition, we aim to determine the severity of AV disease with the GAS method and evaluate it according to its correlation with the indicators.

Methods

Study Population

A total of 43 patients were identified at the beginning of the study. One patient was excluded because he used benzoyl peroxide for acne and six patients used the topical agents. Six patients were excluded from the study because they were taking medication for different types of acne. Another 30 patients completed the study. In addition, those under the age of 18 and over the age of 65, those with metabolic disease, those with severe or chronic diseases, those with blood diseases, those with malignancies, those who are pregnant and breastfeeding, and those who received medical treatment for diseases other than acne were excluded from the study.

Thirty healthy individuals were included in the study as the control group. Demographic characteristics of all participants were recorded. This study was approved by the Ethics Committee (approval number: 19/369) and written informed consent was obtained from all participants in accordance with the principles of the Declaration of Helsinki.

Determination of Global Acne Scores (GAS)

To determine the severity of acne, it is divided into facial and upper chest and under-back sections, and a coefficient is given for each area, including the width and density of the area and the distribution of pilosebaceous units (forehead, right cheek and left cheek = 2, nose and chin = 1, chest and upper back = 3). Acne lesions were also graded 0-4 according to their type (no lesion = 0, ≥1 comedones = 1, ≥1 papules = 2, ≥1 pustules = 3, ≥1 nodules = 4). Each region was analyzed separately, and the global acne score was calculated by multiplying the region coefficient by the maximum number of lesions in that region to determine the score of each region. Acne severity was determined by the total number of acne scars (0 = no acne, 1-18 = mild acne, 19-30 = moderate acne, 31-38 = severe acne, >39 = severe acne) [11].

Sample Collection and Measurement of Parameters

After a 12-hour fast, take venous blood from the participants in the vein. Blood collected for analysis was centrifuged at 3500xg for 10 minutes. The separated sera were divided into Eppendorf dishes and stored in a deep freezer at -80°C until analysis. On the day of examination, all blood samples were simultaneously removed from the refrigerator and thawed at room temperature for 20 minutes. Then the blood is homogenized and prepared for analysis using the vortexing technique.

Blood samples from patients and controls were tested spectrophotometrically for IMA and Thiols (NT, TT and SS)

Table 1. Comparison of parameters between patient and control groups.

Parameters	Patient Group (Mean±SD)	Control Group (Mean±SD)	P
Native Thiol	332.89±51.62	372.58±34.43	0.001
Total Thiol	378.29±48.33	411.93±37.06	0.004
Disulfide	22.70±7.64	19.68±2.05	0.041
Index 1	7.10±3.22	5.30±0.46	0.005
Index 2	6.09±2.32	4.78±0.38	0.004
Index 3	87.82±4.65	90.43±0.76	0.005
IMA	0.624±0.010	0.618±0.012	0.034

IMA = Ischemia-modified Albumin; SD = Standard Deviation.

Index 1: Disulfide/Native Thiol*100, Index 2: Disulfide/Total Thiol*100, Index 3: Native Thiol/Total Thiol*100.

Table 2. Correlation data of Global Acne Score (GAS) values with measured parameters.

		Disulfide	Index 1	Index 2	Index 3
GAS	r	0.406	0.369	0.369	(-) 0.371
	P	0.026	0.045	0.045	0.044

GAS = Global Acne Score.

Index 1: Disulfide/Native Thiol*100, Index 2: Disulfide/Total Thiol*100, Index 3: Native Thiol/Total Thiol*100.

on a Siemens Advia 1800 automated analyzer under the same conditions and all results were closed (13,14). Calculate and record indicators for the thiol index (Index 1 = I1: SS/NT*100, Index 2 = I2: SS/TT*100, Index 3 = I: NT/TT*100).

Statistical Analysis

IBM SPSS Statistic V.22 program was used for all statistical analyses. Shapiro-Wilk test was used for normality test. Results are shown as mean ± SD as they are parametric data. Student's t test was used for statistical analysis. Correlations between statistical variables were made using the Pearson test. The significance value was accepted as $P < 0.05$ in all tests.

Results

In the study, there were no gender (P 0.601) and age (P 0.134) difference between the patient group (age; 22.93 ±5 .13, 11 men/29 women) and the control group (age; 24.4 0± 4.37, 13 men/27 women). It was determined that stress in 5 patients, fatty food in 8 patients, menstruation in 2 patients, epilation in 1 patient and laser application in 1 patient caused acne.

According to GAS data (19.83 ± 6.103), 12 cases of mild acne, 17 cases of moderate acne, and 1 case of severe acne. It was found that NT, TT and I3 values in patient group were lower than the control group (P values 0.001, 0.004, 0.005, respectively).

The SS, I1, I2 and IMA patient groups were higher than the control group (P values 0.041, 0.005, 0.004, 0.034, respectively) (Table 1).

While GAS values in the patient group were positively correlated with SS, I1 and I2, they were negatively correlated with I3 (Table 2).

Conclusions

In our study, NT, TT and I3 decreased in AV patients compared to controls, while SS, I1, I2 and IMA values increased. GAS values showed a positive correlation with SS (Figure 1), I1 and I2, while I3 showed a negative correlation. These results clearly demonstrate a change from NT (-SH) to SS (-S-S-) due to oxidative stress in AV patients. This change increases as acne progresses. At the same time, albumin oxidation increases in acne patients, causing IMA levels to increase.

AV is a chronic disease of the pilosebaceous glands that affects young people. The main mechanisms of acne are altered keratinization of pilaris, hypersebum secretion, inflammation, and colonization of pilosebaceous ducts by Cutibacterium acnes [15]. In all its stages, there is an inflammatory process. AV is now recognized as a primary inflammatory disease. Healthy skin in acne patients refers to subclinical inflammation before lesions appear [16].

ROS are toxic molecules that play an important role in many skin diseases [17,18]. Oxidative stress is known to affect many aspects of the skin [19]. According to recent studies, tissue damage with reactive oxygen species is one of the main factors affecting the pathogenesis of acne. Protein oxidation, lipid peroxidation, and nitrosative stress increase in acne patients and are associated with disease activity [3].

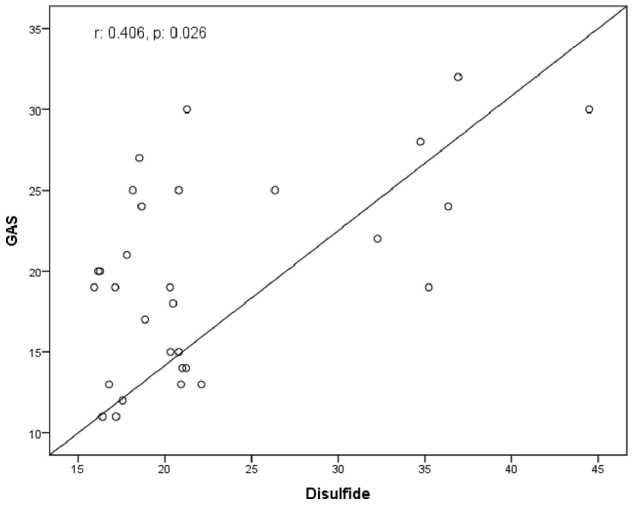

Figure 1. Correlation of Global Acne Score (GAS) values with disulfide results.

Propionibacterium acnes is involved in the pathogenesis of acne, secretes some chemokines to stimulate the accumulation of neutrophils, and releases some bacteria such as lysosomal enzymes through phagocytosis, causing inflammation of fur cover follicle epithelial cells. ROS is released by active neutrophils in inflamed tissues. These oxidants attack and damage DNA and/or membrane lipids, including those in healthy tissues [17,20,21]. Reactive oxygen species synthesized by neutrophils are closely related to the pathogenesis of many skin diseases [2,22,23]. Squalene, unique to human sebum, protects the skin surface from lipid peroxidation, ie substances that cause comedogenic effects, and is present in high concentrations in open or closed comedones [21]. In addition, sebocytes and keratinocytes secrete proinflammatory cytokines (IL-1alpha, IL-8, TNF-alpha) in response to lipopolysaccharide in the Bacillus acnes test. Thus, the inflammatory process contributes to the formation of acne lesions. Kart et al have been suggested that oxidative stress plays a role in the pathogenesis of acne vulgaris through various pathways such as PPAR, TLR and mTOR [24].

Arican et al. spectrophotometric measurement of oxidative stress such as catalase (CAT), glucose-6-phosphate dehydrogenase (G6PD), superoxide dismutase (SOD) and malondialdehyde (MDA) in acne patients and determination of oxidative stress in acne patients [23]. Basak et al. decreased leukocyte antioxidant levels and increased lipid peroxidation in AV patients [25]. ElAkawi et al found that antioxidant levels, such as vitamin A and vitamin E, were reduced in patients with AV [26]. Awad et al found that although acne patients had higher MDA levels than controls, total antioxidant capacity was lower [27]. Saric et al found that serum MDA and xanthine oxidase (XO) were higher in AV patients compared to controls [28]. In another study, acne patients had higher levels of MDA and nitric oxide (NO) and lower levels of SOD and GSH compared to healthy controls [3]. Moazen et al MDA levels were found to be higher in acne patients [29]. Perryhan et al increased levels of antioxidant enzymes found in scraping samples from acne patients. They think this may be the body's local response to increased oxidative stress. They also found that oxidative stress increased with disease severity [4]. In another study, it was noted that oxidative stress biomarkers were higher in AV lesions and showed a positive correlation with acne severity. In addition, a decrease in antioxidant enzymes (SOD, CAT) has been observed in acne [24]. In one study, Al-Shobaili found that acne patients had higher plasma MDA levels and lower levels of the antioxidant enzymes SOD and CAT compared to controls. In addition, it was found that the total antioxidant capacity (TAC) in acne patients was lower than in controls. Although higher MDA levels were observed in the severe acne group compared to the mild and moderate groups, there was a negative correlation between MDA and CAT in the severe acne group [2]. All these studies using different levels of oxidative stress in AV patients support our results and clearly show that oxidative stress is present in acne and may play an important role in their disease.

Dynamic thiol-disulfide homeostasis has been studied for different organisms. It found that the prevalence of SS was higher in people with obesity, lung disease, and inflammatory diseases such as diabetes [14]. Doru et al NT levels were found to be lower in patients with ankylosing spondylitis [30]. In another study, Kundi et al found a relationship between disease severity and thiol levels in patients with atherosclerosis and found that mortality was higher in patients with low thiol levels [31]. Kaplan et al were determined that celiac patients had lower TT and NT levels and higher SS, I1 and I2 rates compared to controls [32]. It is also the study of thiol-disulfide homeostasis, skin diseases such as psoriasis, seborrheic dermatitis, atopic dermatitis, leukoplakia, lichen planus and rosacea. A unique aspect of these findings is the implication of thiol-disulfide homeostasis as an indicator of oxidative stress [33]. On the other hand, Güler et al in their study, they found that AV patients had a lower TT and I2 ratio, similar to our results, and concluded that the antioxidant defense of AV, an inflammatory disease, was low [34]. These studies show that oxidative stress plays an important role in the development of acne and can be used as a biomarker to evaluate the disease and monitor its treatment.

High IMA levels are associated with infections, tumors, cirrhosis, etc associated with [35]. In previous studies, IMA levels were evaluated in some skin diseases. High IMA levels in hidradenitis suppurativa, leukoplakia, acute and chronic urticaria and Behçet's disease compared to controls suggest that IMA may be a marker of oxidative stress in these diseases [12]. Guler et al found that IMA was higher in AV patients and suggested that IMA might be a marker of oxidative stress in

AV patients [36]. Ebrahim et al stated that since IMA levels are elevated in AV patients, serum IMA levels can be considered as an independent predictor of AV susceptibility and function [37]. Akyurek et al found that citrulline and vitamin A levels in AV patients were lower than in controls. They also found that IMA plasma levels increased with disease severity. As the disease progresses, plasma levels of L-arginine, citrulline and vitamin A decrease [38]. According to all these studies, our results show that AV patients have higher IMA levels. However, there was no correlation between the GAS values we used to determine the severity of the disease and the IMA values. This may be due to the low number of educated people.

In a previous study, thiol testing and IMA were examined separately in AV patients. However, our study is simultaneously evaluate two important aspects of oxidative stress in AV patients. The small size of our study population can be considered as a limitation of our study.

AV-related oxidative stress may occur through mechanisms dependent on thiol and IMA levels. Given the diverse nature of AV, many combinations can have a synergistic effect. Decreased antioxidant activity due to disruption of oxidation-antioxidant balance in AV is another possibility. Therefore, future studies with larger patient populations may better understand the role of thiols and IMA in the pathogenesis of AV. Our study showed that oxidative stress plays an important role in the development of AV disease. Therefore, oral supplementation or topical application of antioxidants may be a good way to increase the effectiveness of drugs or prevent their harm.

References

1. Zouboulis CC. Acne as a chronic systemic disease. *Clin Dermatol*. 2014;32(3):389-396. DOI: 10.1016/j.clindermatol.2013.11.005. PMID: 24767186.
2. Al-Shobaili HA. Oxidants and anti-oxidants status in acne vulgaris patients with varying severity. *Ann Clin Lab Sci*. 2014;44(2):202-207. PMID: 24795060.
3. Al-Shobaili HA, Alzolibani AA, Al Robaee AA, Meki ARMA, Rasheed Z. Biochemical Markers of Oxidative and Nitrosative Stress in Acne Vulgaris: Correlation With Disease Activity. *J Clin Lab Anal*. 2013;27(1):45-52. DOI:10.1002/jcla.21560. PMID: 23325743. PMCID: PMC6807565.
4. Perihan O, Ergul KB, Neslihan D, Filiz A. The activity of adenosine deaminase and oxidative stress biomarkers in scraping samples of acne lesions. *J Cosmet Dermatol*. 2012;11(4):323-328. DOI:10.1111/jocd.12011. PMID: 23174057.
5. Yang YS, Lim HK, Hong KK, et al. Cigarette Smoke-Induced Interleukin-1 Alpha May Be Involved in the Pathogenesis of Adult Acne. *Ann Dermatol*. 2014;26(1):11. DOI:10.5021/ad.2014.26.1.11. PMID: 24648681. PMCID: PMC3956775.
6. Bowe WP, Logan AC. Clinical implications of lipid peroxidation in acne vulgaris: old wine in new bottles. *Lipids Health Dis*. 2010;9(1):141. DOI:10.1186/1476-511X-9-141. PMID: 21143923. PMCID: PMC3012032.
7. Kardeh S, Moein SA, Namazi MR, Kardeh B. Evidence for the Important Role of Oxidative Stress in the Pathogenesis of Acne. *Galen Med J*. 2019;8:e1291. DOI:10.31661/gmj.v0i0.1291. PMID: 34466486. PMCID: PMC8344136.
8. Sbarouni E, Georgiadou P, Voudris V. Ischemia modified albumin changes – review and clinical implications. *Clin Chem Lab Med*. 2011;49(2):177-184 DOI:10.1515/CCLM.2011.037. PMID: 21083441.
9. Erel Ö, Erdoğan S. Thiol-disulfide homeostasis: an integrated approach with biochemical and clinical aspects. *Turk J Med Sci*. 2020;50(7):1728-1738. DOI:10.3906/sag-2003-64. PMID: 32233181. PMCID: PMC7672356.
10. Bilaç C, Şahin MT, Öztürkcan S. Disease severity scoring systems in dermatology. *TURKDERM*. 2016;50(2):42-53. DOI:10.4274/turkderm.67799.
11. Doshi A, Zaheer A, Stiller M. A comparison of current acne grading systems and proposal of a novel system. *Int J Dermatol*. 1997;36(6):416-418. DOI:10.1046/j.1365-4362.1997.00099.x. PMID: 9248884.
12. Tampa M, Mitran CI, Mitran MI, Amuzescu A, Matei C, Georgescu SR. Ischemia-Modified Albumin-A Potential New Marker of Oxidative Stress in Dermatological Diseases. *Medicina (Kaunas)*. 2022;58(5):669. DOI:10.3390/medicina58050669. PMID: 35630086. PMCID: PMC9147831.
13. Bar–Or D, Lau E, Winkler J V. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia—a preliminary report. *J Emerg Med*. 2000;19(4):311-315. DOI:10.1016/S0736-4679(00)00255-9. PMID: 11074321.
14. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. *Clin Biochem*. 2014;47(18):326-332. DOI:10.1016/j.clinbiochem.2014.09.026. PMID: 25304913.
15. Tan JKL, Stein Gold LF, Alexis AF, Harper JC. Current Concepts in Acne Pathogenesis: Pathways to Inflammation. *Semin Cutan Med Surg*. 2018;37(3S):S60-S62. DOI:10.12788/J.SDER.2018.024. PMID: 30192343.
16. Kircik LH. Advances in the Understanding of the Pathogenesis of Inflammatory Acne. *J Drugs Dermatol*. 2016;15(1 Suppl 1):s7-s10. PMID: 26741394.
17. Briganti S, Picardo M. Antioxidant activity, lipid peroxidation and skin diseases. What's new. *J Eur Acad Dermatol Venereol*. 2003;17(6):663-669. DOI:10.1046/j.1468-3083.2003.00751.x. PMID: 14761133.
18. Öztas MO, Balk M, Ögüs E, Bozkurt M, Ögüs IH, Özer N. The role of free oxygen radicals in the aetiopathogenesis of rosacea. *Clin Exp Dermatol*. 2003;28(2):188-192. DOI:10.1046/j.1365-2230.2003.01179.x. PMID: 12653711.
19. Baek J, Lee MG. Oxidative stress and antioxidant strategies in dermatology. *Redox Report*. 2016;21(4):164-169. DOI:10.1179/1351000215Y.0000000015. PMID: 2602052. PMCID: PMC8900706.
20. Akamatsu H, Horio T, Hattori K. Increased hydrogen peroxide generation by neutrophils from patients with acne inflammation. *Int J Dermatol*. 2003;42(5):366-369. DOI:10.1046/j.1365-4362.2003.01540.x. PMID: 12755973.
21. Brown SK, Shalita AR. Acne vulgaris. *The Lancet*. 1998;351(9119):1871-1876. DOI:10.1016/S0140-6736(98)01046-0. PMID: 9652685.
22. Choi C, Lee D, Kim H, Kim B, Park K, Youn S. The clinical features of late onset acne compared with early onset acne in women. *J Eur Acad Dermatol Venereol*. 2011;25(4):454-461. DOI:10.1111/j.1468-3083.2010.03813.x. PMID: 20659307.

23. Arican O, Kurutas EB, Sasmaz S. Oxidative stress in patients with acne vulgaris. *Mediators Inflamm*. 2005;2005(6):380-384. DOI:10.1155/MI.2005.380. PMID: 20659307. PMCID: PMC1533901.
24. Kardeh S, Moein SA, Namazi MR, Kardeh B. Evidence for the Important ¬Role of Oxidative Stress in the Pathogenesis of Acne. *Galen Med J*. 2019;8:1291. DOI:10.31661/gmj.v8i0.1291. PMID: 34466486. PMCID: PMC8344136.
25. Basak PY, Gultekin F, Kilinc I. The Role of the Antioxidative Defense System in Papulopustular Acne. *J Dermatol*. 2001;28(3):123-127. DOI:10.1111/j.1346-8138.2001.tb00105.x. PMID: 11349462.
26. El-akawi Z, Abdel-Latif N, Abdul-Razzak K. Does the plasma level of vitamins A and E affect acne condition? *Clin Exp Dermatol*. 2006;31(3):430-434. DOI:10.1111/j.1365-2230.2006.02106.x. PMID: 16681594.
27. Awad SM, Morsy H, Sayed AA, Mohamed NA, Ezzat GM, Noaman MM. Oxidative stress and psychiatric morbidity in patients with facial acne. *J Cosmet Dermatol*. 2018;17(2):203-208. DOI:10.1111/jocd.12366. PMID: 28631890.
28. Sarici G, Cinar S, Armutcu F, Altınyazar C, Koca R, Tekin N. Oxidative stress in acne vulgaris. *J Eur Acad Dermatol Venereol*. 2009;24(7):763-767. DOI:10.1111/j.1468-3083.2009.03505.x. PMID: 19943837.
29. Moazen M, Mazloom Z, Jowkar F, Nasimi N, Moein Z. Vitamin D, Adiponectin, Oxidative Stress, Lipid Profile, and Nutrient Intakes in the Females with Acne Vulgaris: A Case-Control Study. *Galen Med. J*. 2019;8:1515. DOI:10.31661/gmj.v8i0.1515. PMID: 34466520. PMCID: PMC8343516.
30. Dogru A, Balkarli A, Cetin GY, et al. Thiol/disulfide homeostasis in patients with ankylosing spondylitis. *Bosn J Basic Med Sci*. 2016;16(3):187-192. DOI:10.17305/bjbms.2016.1001. PMID: 27186972. PMCID: PMC4978110.
31. Kundi H, Erel Ö, Balun A, et al. Association of thiol/disulfide ratio with syntax score in patients with NSTEMI. *Scand Cardiovasc J*. 2015;49(2):95-100. DOI: 10.3109/14017431.2015.1013153. PMID: 25658436.
32. Kaplan M, Ates I, Yuksel M, et al. Thiol/disulphide homeostasis in celiac disease. *World J Gastrointest Pharmacol Ther*. 2017;8(2):120. DOI:10.4292/wjgpt.v8.i2.120. PMID: 28533921. PMCID: PMC5421110.
33. Georgescu SR, Mitran CI, Mitran MI, et al. Thiol-Disulfide Homeostasis in Skin Diseases. *J Clin Med*. 2022;11(6);1507. DOI:10.3390/jcm11061507. PMID: 35329832. PMCID: PMC8954849.
34. Gürel G. Evaluation of thiol/disulfide homeostasis in patients with acne vulgaris. *J Clin Anal Med*. 2019;10(02);166-169. DOI:10.4328/JCAM.5852.
35. Sinha MK, Vazquez JM, Calvino R, Gaze DC, Collinson PO, Kaski JC. Effects of balloon occlusion during percutaneous coronary intervention on circulating Ischemia Modified Albumin and transmyocardial lactate extraction. *Heart*. 2006;92(12):1852-1853. DOI:10.1136/hrt.2005.078089. PMID: 17105887. PMCID: PMC1861307.
36. Gürel G, Karadöl M, Bal C, Neselioğlu S, Çölgeçen E. Evaluation of ischemia-modified albumin levels in acne vulgaris patients. *TURKDERM*. 2019;53(3):84-87. DOI:10.4274/turkderm.galenos.2019.71224.
37. Ebrahim AA, Mustafa AI, Abdel-Halim WA, Abo-Ghanema DM. Ischemic Modified Albumin as A Biomarker in Predicting Oxidative Stress in Patients With Acne Vulgaris. *Benha Journal of Applied Sciences*. 2020;5(8):205-209. DOI: 10.21608/bjas.2020.187209.
38. Tunçez Akyürek F, Saylam Kurtipek G, Kurku H, et al. Assessment of ADMA, IMA, and Vitamin A and E Levels in Patients with Acne Vulgaris. *J Cosmet Dermatol*. 2020;19(12):3408-3413. DOI:10.1111/jocd.13590. PMID: 32623816.