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Novel Serum Oxidative Stress Biomarkers in Pemphigus Vulgaris: Clinical Insights and Implications for Pathogenesis

Naglaa M El Sayed[1], Dalia I Halwag[1], Nesrine A Helaly[2], Iman M Abdelmeniem[1]

1 Department of Dermatology, Venereology, and Andrology, Faculty of Medicine, Alexandria University, Egypt
2 Medical laboratory technology department, Faculty of Applied Health Sciences Technology, Pharos University, Alexandria, Egypt

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Corresponding Author: Naglaa M El Sayed, MD, Department of Dermatology, Venereology, and Andrology, Faculty of Medicine, Alexandria University, Alexandria, Egypt. ORCID ID: 0000-0002-2095-0615. E-mail: naglaasayed66@outlook.com

ABSTRACT

Introduction: Pemphigus vulgaris is an autoimmune disorder characterized by blistering of the skin and mucous membranes due to the loss of cohesion between keratinocytes. Oxidative stress, a condition caused by an excess of reactive oxygen species that overwhelms the body's antioxidant defenses, has been implicated in various autoimmune diseases, including pemphigus vulgaris.

Objectives: This study aimed to evaluate serum levels of advanced glycation end products and advanced oxidation protein products as novel biomarkers of oxidative stress in pemphigus vulgaris patients and to correlate these levels with disease activity.

Methods: Sixty participants were included, divided into three equal groups: 20 patients with active mucocutaneous pemphigus vulgaris not on systemic treatment, 20 patients in remission on minimal therapy, and 20 healthy controls. Serum levels of advanced glycation end products and advanced oxidation protein products were measured using the enzyme-linked immunosorbent assay.

Results: Serum levels of advanced glycation end products and advanced oxidation protein products were significantly higher in the active pemphigus vulgaris patient group compared to both the remission group and healthy controls ($P<0.001$). No significant correlation was found between the oxidative stress markers, desmoglein 3, and the Pemphigus Disease Activity Index.

Conclusions: The findings of the present study demonstrate that oxidative stress may not play a primary role in the pathogenesis or severity of pemphigus vulgaris but could instead be a secondary effect associated with tissue damage. Factors such as diet and ethnicity could have influenced the results, indicating the need for larger scale, population-specific studies.

Introduction

Pemphigus vulgaris (PV) is an autoimmune disease marked by blistering of the skin and mucous membranes due to the loss of cohesion between keratinocytes [1].This life-threatening condition is driven by pathogenic autoantibodies targeting keratinocyte surface antigens, primarily desmoglein 3 (Dsg3), and to a lesser extent, desmoglein 1 (Dsg1) [2]. Oxidative stress is a pathological condition caused by the generation of excessive reactive oxygen species (ROS) that overwhelm the body's antioxidant defenses [3]. There is substantial evidence linking oxidative stress to the development and progression of autoimmune skin diseases such as systemic lupus erythematosus (SLE), psoriasis, and Behçet disease (BD) [4-6]. Furthermore, increasing evidence suggests a similar role of oxidative stress (OS) in PV [3,7]. It has been hypothesized that PV-IgG targeting Dsg3 may induce OS in keratinocytes, resulting in elevated ROS production, which in turn compromises the integrity of intercellular junctions and leads to acantholysis, the hallmark of PV [8]. In this context, advanced glycation end products (AGEs) and advanced oxidation protein products (AOPPs) are emerging as novel markers of OS. These highly oxidant, biologically active compounds result from non-enzymatic glycation and oxidation of macromolecules, particularly proteins, that accumulate in tissues under conditions of oxidative stress and inflammation [9,10]. Importantly, these compounds are thought to bind to cell surface receptors on keratinocytes, initiating intracellular signaling pathways that may upregulate inflammation, increase ROS production, and disrupt desmosomal homeostasis, ultimately leading to acantholysis [11,12]. Advanced glycation end products and AOPPs have been thoroughly investigated in diseases where OS plays a significant role in disease pathogenesis or associated complications, such as diabetes, renal failure, and cardiopulmonary diseases [13-15].

Objective

Given this background, the present study aimed to evaluate the serum levels of AGEs and AOPPs as novel OS biomarkers in PV patients. Moreover, we sought to correlate these levels with the disease activity, with the goal of enhancing our understanding of the role OS plays in PV pathogenesis.

Methods

Participants

The present prospective cross-sectional case-control study involved 40 patients diagnosed with PV divided into two groups: 20 patients with active mucocutaneous type of PV not on systemic treatment and 20 in complete remission on minimal therapy (prednisone or the equivalent at ≤10 mg/d for at least two months) [16]. The patients were recruited from the Dermatology Outpatient Bullous Clinic at our main university hospital. The study received approval from the institute's ethics committee (serial number 0305991). All procedures were performed in accordance with the Helsinki Declaration of 1975, revised in 2013. Written informed consent was obtained from all participants.

Inclusion criteria encompassed confirmed cases of PV based on clinical presentation (active cases presented with three or more non-transient lesions for more than one week) and histopathological assessment (demonstrating suprabasal separation with acantholysis).

Exclusion criteria included specific systemic treatment for the group of active pemphigus patients and the use of antioxidant drugs or vitamins. Patients with other autoimmune and autoinflammatory diseases, malignancies, pregnancy, acute or chronic infections, uncontrolled diabetes, hypertension, or hyperlipidemia were also excluded.

The control group consisted of 20 healthy volunteers, matched by age and sex. The same exclusion criteria were applied to the control group.

Demographic data, comprehensive medical history, and drug history were recorded for all participants.

Clinical Assessment

Data collected included age, sex, and body mass index (BMI) as well as disease duration disease and comorbid conditions. The BMI was calculated according to the formula; BMI= kg/m^2. Skin, scalp, and mucus membrane examinations were conducted by the same expert dermatologist during the whole study to minimize interobserver bias. Disease severity was assessed using the pemphigus disease activity index (PDAI) [17]. The active patient group was classified as significant PV and extensive PV [18].

Sample Collection and Measurements

From all subjects, venous blood samples were taken after an overnight (10 hours) fasting, and samples were separated and stored frozen at –80° C until analysis.

Oxidative Stress Markers Assessment

For the analysis of oxidative stress markers, AGEs and AOPPs levels were measured in the collected sera of the participants using enzyme-linked immunosorbent assay (ELISA) kits from BT LAB (Jiaxing, Zhejiang, China), with catalog numbers E1266Hu and E0003Hu, respectively. All experiments were conducted according to the manufacturer's instructions. Pre-coated plates with wells pre-coated with human AGEs and AOPPs antibodies were used. Test standards and serum samples were added to the wells, followed by the addition of biotinylated Human AGEs and AOPPs

detection antibodies, which bind specifically to AGEs and AOPPs in the samples. Next, Streptavidin-HRP was introduced, binding to the biotinylated detection antibodies. After incubation, any unbound Streptavidin-HRP conjugates were washed away using a washing solution. Finally, substrate solutions A and B were added to complete the detection process. TMB substrate was used to visualize the enzymatic reaction of horseradish peroxidase (HRP), producing a blue-colored product that turned yellow upon the addition of the stop solution.

Finally, the optical density (OD) was measured from each well individually at a wavelength of 450 nm using ELISA reader, which was done within 10 minutes after adding the stop solution.

Measurement of Anti-Dsg3 Antibodies

Enzyme-linked immunosorbent assay technique was employed for the quantification of serum anti-Dsg3 anti bodies, (ELISA kit BT Lab; Bioassay technology laboratory, China, Cat. No E4590Hu), following the manufacturer's instructions. The concentration of anti-Dsg3 antibodies was determined by comparing the optical density (OD) of the samples to the standard curve.

Statistical Analysis of the Data

Data was fed into the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Categorical data are represented as numbers and percentages. Quantitative data are expressed as range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR).Chi-squared test was used for categorical variables to compare different groups fewer than 5. The Mann-Whitney test was applied for abnormally distributed quantitative variables to compare between two studied groups. F-test (ANOVA) was used for normally distributed quantitative variables to compare between more than two groups, and Post Hoc test (Tukey) for pairwise comparisons. The Kruskal-Wallis test was used for abnormally distributed quantitative variables to compare between more than two studied groups, and Post Hoc (Dunn's multiple comparisons test) for pairwise comparisons. The significance of the results obtained was judged at the 5% level.

Results

Sixty participants were included in this study, divided into three equal groups: 20 with active mucocutaneous PV, 20 in complete remission on minimal therapy, and 20 healthy controls. The demographic and clinical characteristics of the study population are summarized in Table 1. There were no statistically significant difference in age or sex among the three groups (P=0.988 and P=0.760, respectively). As for BMI, three patients in the active patient group were overweight, and 17 patients were obese, while in the remission group, three patients were of normal weight, four patients were overweight, and 13 patients were obese. In the control group, seven participants were overweight, and 13 participants were obese. A statistically significant difference in BMI was observed between the active PV cases and the control group (P=0.022).

As regards the comorbid conditions in the patient group (both active cases and those in remission), all comorbidities were well controlled. They included 16 patients with diabetes, 11 with hypertension, three with hyperlipidemia, and two with hypothyroidism, either occurring individually or in combination.

The active patient group was classified as significant PV in two patients and extensive PV in 18 patients. The mean PDAI for the active PV patients was 64.15 ± 11.38, compared to 10.55 ± 1.90 for the patients in remission, which was statistically significant (P< 0.001) (Table 1).

Correlation Between the Measured Serum Biomarkers in the Three Studied Groups

Serum levels of the measured biomarkers were significantly higher in the active PV group compared to the remission group and healthy controls (P<0.001). Detailed values and comparisons are provided in Table 2.

Correlation Between Oxidative Stress Markers and Different Clinical Parameters and Anti-Dsg3

Correlations between AGEs, AOPPs and the various clinical parameters are presented in Table 3. In summary, no statistically significant correlation was found between AGEs or AOPPs and the clinical parameters assessed among the three groups (P>0.05). Again, there was no statistically significant difference between measured AGEs or AOPPs and the PDAI score either in the active patient group (P= 0.496, 0.766) or patients in remission (P=0.238,0.752). Additionally, there was no significant correlation between AGEs or AOPPs levels and anti-Dsg3 levels in either the active PV group (P=0.198 and P=0.490, respectively) or the remission group (P=0.445 and P=0.061, respectively).

Discussion

The etiopathogenesis of pemphigus is complex. Although the pathogenic role of IgG antibodies is well established, antibody levels do not always correlate with disease severity; some patients in remission may still exhibit elevated antibody titers [19,20] suggesting that additional factors may be at play in the disease process. Considering this, it has been proposed that both environmental and genetic factors likely contribute to the development and progression of pemphigus

Table 1. Comparison between the Three Groups Studied according to Demographic and Clinical Data.

	Active cases (n = 20)	Remission (n = 20)	Control (n = 20)	Test of significance	p
Sex					
Male	9 (45.0%)	7 (35.0%)	9 (45.0%)	χ^2=0.549	0.760
Female	11 (55.0%)	13 (65.0%)	11 (55.0%)		
Age (years)					
Min. – Max.	31.0 – 55.0	35.0 – 60.0	30.0 – 62.0	F=0.012	0.988
Median (IQR)	45.0 (41.50 – 48.50)	44.50 (38.50 – 50.0)	45.0 (41.0 – 49.50)		
BMI (kg/m^2)					
Min. – Max.	23.56 – 39.06	23.68 – 37.50	25.0 – 35.40	F=3.777*	0.029*
Mean ± SD.	32.95 ± 4.26	31.19 ± 3.75	29.71 ± 3.06		
Significance between groups	p_1=0.305 p_2=0.022* p_3=0.425				
Comorbidities					
No	6 (30%)	8 (40%)	–	χ^2=0.440	p_1=0.507
Yes	14 (70.0%)	12 (60.0%)	–		
Duration (years)					
Min. – Max.	0.33 – 5.0	1.42 – 12.0	–	U=94.500*	p_1=0.004*
Mean ± SD.	2.17 ± 1.60	4.59 ± 2.96	–		
PDAI					
Min. – Max.	42.0 – 85.0	8.0 – 13.0	–	U=0.000*	p_1<0.001*
Mean ± SD.	64.15 ± 11.38	10.55 ± 1.90	–		

Abbreviations: IQR: Inter quartile range; SD: Standard deviation; U: Mann-Whitney test.

χ^2: Chi-squareD test; F: F for One-way ANOVA test, pairwise comparison bet. each two groups were done using post hoc test (Tukey); BMI: body mass index; PDAI: pemphigus disease activity index; p: p-value for comparing between the three studied groups; p_1: p-value for comparing between Active cases and Remission; p_2: p-value for comparing between Active cases and Control; p_3: p-value for comparing between Remission and Control; *: Statistically significant at $P \leq 0.05$.

Table 2. Correlation between the Three Groups Studied according to AGEs, AOPPs, and Anti-Dsg3.

Measured parameters ng/L	Active cases (n = 20)	Remission (n = 20)	Control (n = 20)	Test of Sig.	p
AGEs					
Min. – Max.	756.8 – 4204.5	344.2 – 592.3	134.3 – 352.9	H=51.941*	<0.001*
Mean ± SD.	1479.4 ± 880.4	431.5 ± 80.06	259.1 ± 56.50		
Significance between groups	p_1<0.001*, p_2<0.001*, p_3<0.001*				
AOPPs					
Min. – Max.	4.18 – 42.74	2.36 – 4.47	1.28 – 3.70	H=47.629	<0.001*
Mean ± SD.	12.83 ± 12.29	3.57 ± 0.59	2.28 ± 0.71		
Significance between groups	p_1<0.001*, p_2<0.001*, p_3=0.003*				
Anti-Dsg3					
Min. – Max.	321.98 – 903.23	203.5 – 336.8	–	U=4.000	p_1<0.001*
Mean ± SD.	612.66 ± 186.03	261.2 ± 48.42	–		

IQR: Interquartile range; SD: Standard deviation; U: Mann-Whitney test. H: H for Kruskal-Wallis test, pairwise comparison between each pair of groups were done using post hoc test (Dunn's for multiple comparisons test). Abbreviations: AGEs: advanced glycation end products; AOPPs: advanced oxidation protein products; Anti-Dsg3: anti-desmoglein 3 antibodies; p: p-value for comparing between the three studied groups; p_1: p-value for comparing between Active cases and Remission; p_2: p-value for comparing between Active cases and Control; p_3: p-value for comparing between Remission and Control. *: Statistically significant at $P \leq 0.05$.

Table 3. Correlation between AOPPs and AGEs with Different Parameters in Both Groups of Pemphigus Vulgaris Patients.

		AOPPs		AGEs	
		r_s	p	r_s	p
Active cases (n = 20)	Age (years)	0.181	0.446	0.017	0.942
	BMI (kg/m^2)	0.015	0.950	0.003	0.990
	Duration (years)	–0.131	0.583	0.288	0.218
	PDAI	0.071	0.766	–0.161	0.496
	Anti-Dsg3	–0.164	0.490	–0.301	0.198
	AGEs	–0.047	0.845	–	–
Remission (n = 20)	Age (years)	0.316	0.174	–0.029	0.903
	BMI (kg/m^2)	0.122	0.609	–0.109	0.647
	Duration (years)	–0.075	0.752	–0.276	0.238
	PDAI	0.046	0.848	–0.111	0.642
	Anti-Dsg3	–0.480	0.061	0.199	0.445
	AGEs	–0.171	0.470	–	–

r_s: Spearman coefficient; *: Statistically significant at $P \leq 0.05$. Abbreviations: BMI: body mass index; PDAI: pemphigus diseases activity index; Anti-Dsg3: anti-desmoglein 3 antibodies; AGEs: advanced glycation end products; AOPPs: advanced oxidation protein products.

[21]. Among these environmental factors, oxidative stress has garnered increasing interest in the pathogenesis of PV [3,8]. Building on this concept, our study aimed to evaluate oxidative stress markers that have not been previously investigated in PV, namely AGEs and AOPPs. These markers are significant because they serve as chemically stable indicators of oxidative stress, produced endogenously in response to reactive oxygen species (ROS) [12]. ROS production is heightened in PV due to several reasons, including the release of inflammatory mediators and mitochondrial damage caused by anti-mitochondrial antibodies in PV patients [22,23]. However, the most important source of ROS and OS in PV patients is the PV- IgG antibodies targeting Dsg3 [8].

Importantly, our findings revealed a significant elevation in both oxidative stress markers in patients with active disease compared to those in remission and in the control group. Furthermore, the difference between patients in remission and the control group was statistically significant. Taken together, these findings support the notion that oxidative stress may play a role in the pathogenesis of pemphigus vulgaris.

Various oxidative stress biomarkers have been previously evaluated in PV patients. For instance, one notable marker is lipid peroxidation product malondialdehyde, which was found to be significantly elevated in PV patients compared to controls, with a correlation to serum anti-Dsg3 levels [24].

Similarly, in a related study, Yesilova et al. [25] demonstrated an elevated oxidative stress index (OSI) in patients with PV. However, it is important to note that they did not find significant differences in total antioxidant capacity (TAC) between PV patients and healthy controls. Notably, elevated oxidative stress markers have also been detected in lesional, perilesional, and even normal skin of pemphigus patients as well as in red blood cells [26,7].

Interestingly, Shah and colleagues delineated that HLA allele status has a significant impact on oxidative stress. Specifically, HLA+ individuals had lower total antioxidant capacity (TAC) compared to those who were HLA-negative. They revealed a down regulation of genes that combat oxidative stress in HLA+ subjects [27]. However, when it comes to antioxidant activity, the findings have been somewhat conflicting. Javanbakht et al. [28] and Abida et al. [24] reported increased catalase activity in PV patients, correlating with disease duration and activity. In contrast, Naziroglu et al. [7] observed the opposite—a decrease in catalase activity in PV patients. A similar observation was made by Shah and colleagues, who found no correlation between total antioxidant capacity and disease activity or Dsg3 serum levels [27].

In general, the unbalanced production of ROS can alter the structure and function of various molecules, such as carbohydrates, lipids, DNA, and proteins, through processes like glycoxidation and peroxidation [28,29]. These oxidatively modified macromolecules may become targets for the immune system, potentially breaking B-cell tolerance [30]. Specifically, the effect of oxidative stress on intercellular junctions has been shown in multiple systems [31,32]. Inumaru et al. [31] demonstrated that oxidative stress can induce cell-cell dissociation through translocation of p120 catenin and internalization of cadherin to endosomal compartments from cell-to-cell adhesion sites. Similarly, Huang et al. [8],

in their experimental study, observed a dose-dependent reduction in Dsg3 and α-catenin in cells treated with H_2O_2. Moreover, these authors demonstrated that oxidative stress promotes pronounced cytoplasmic accumulation of yes-associated protein (YAP), mirroring the effects observed in cells treated with PV-IgG. YAP overexpression disrupts cell junction assembly through its impact on Dsg3 and α-catenin. Notably, this disruptive effect can be mitigated by antioxidants. These findings suggest that oxidative stress has a potential role, at least in part, in the process of pemphigus acantholysis.

It is widely accepted that various signaling pathways work together to modulate the structure and dynamics of desmosomes; AGEs and AOPPs may play a role in the pathogenesis of pemphigus by influencing these pathways [11]. Their effects can be initiated through binding to cell surface receptors on keratinocytes known as receptor for advanced glycation end products (RAGE)[12]. This binding activates a range of signaling molecules, including p38 mitogen-activated protein kinase (p38MAPK), heat shock protein (HSP) 27, and protein kinase-C, among others [33]. p38MAPK has been shown to mediate the internalization of Dsg3, leading to its depletion from endosomes [34,35] , retraction of keratin intermediate filaments, and actin reorganization [36-38], thereby disrupting the dynamics of desmosome assembly [39]. Furthermore, p38MAPK can activate various apoptotic pathways that have been implicated in pemphigus pathogenesis [11]. Additionally, the interaction between AGEs and RAGE can activate the nuclear factor kappa-B (NF-κB) signaling pathway, promoting the secretion of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [40]. This contributes to inflammation and increased production of ROS. The binding of AGEs to RAGEs not only disrupts signaling pathways but also enhances ROS production, which in turn increases the expression of RAGEs, creating a positive feedback loop that exacerbates pathological process [12].

Despite this compelling evidence regarding the role of oxidative stress in pemphigus pathogenesis, it remains debatable whether oxidative stress is a causative factor or merely a consequence of damage inflicted by pathogenic antibodies against desmoglein and non-desmoglein targets. This uncertainty is underscored by the absence of robust clinical evidence supporting the efficacy of antioxidants in treating pemphigus. Our study contributes to this ongoing debate by showing a statistically significant elevation in AGEs and AOPPs levels in active pemphigus patients. However, the lack of correlation between these oxidative stress markers and disease activity, duration, or anti-Dsg3 antibody levels supports the idea that oxidative stress may be more a consequence rather than a cause of the disease process. Although we controlled for factors like uncontrolled diabetes, hypertension, and hyperlipidemia, conditions known to affect oxidative stress markers, the influence of other environmental variables, such as diet, air pollution, or genetic predisposition, were not accounted for in our study. These factors could have contributed to the observed elevation in oxidative stress markers without showing a direct correlation with disease activity. Further research is needed to explore these additional variables and their impact on oxidative stress in pemphigus.

Limitations

The reliance on only two oxidative stress markers, AGEPs, and AOPPs, to evaluate OS in PV may have limited the comprehensiveness of our assessment. A larger sample size and the inclusion of additional or more diverse OS biomarkers could have strengthened our statistical power and provided a broader understanding of the role of OS in pemphigus. Additionally, the study was conducted at a single medical center and limited to patients with the mucocutaneous type of PV, which may restrict the generalizability of the results to other pemphigus subtypes or populations. Moreover, environmental and genetic factors which may affect OS levels were not evaluated in this study, limiting insight into their role.

Conclusions

The present study evaluated two novel OS biomarkers in patients with mucocutaneous PV. This study demonstrates a significant elevation in serum levels of AGEPs and AOPPs in patients with mucocutaneous PV, though no direct correlation with clinical or laboratory data was observed. These findings suggest that OS may not play a primary role in PV pathogenesis or severity but could instead be an associated byproduct rather than a causative factor in tissue damage. However, population-specific variables such as diet and ethnicity might have influenced these results, emphasizing the need for broader investigations.

A more comprehensive panel of oxidative stress markers could offer deeper insights into the complex role OS plays in PV. Future studies should prioritize larger, more diverse populations and account for environmental and genetic influences to clarify the clinical relevance of oxidative stress in PV. Until then, the utility of these markers as predictors of disease activity or therapeutic targets remains uncertain. Nonetheless, our findings add a crucial piece to the puzzle of PV pathogenesis, underscoring the importance of multifactorial approaches in unraveling its underlying mechanisms.

References

1. Schmidt E, Kasperkiewicz M, Joly P. Pemphigus. *Lancet* 2019; 394 (10201): 882–894. DOI:10.1016/S0140-6736(19)31778-7. PMID: 31498102.

2. Amagai M, Stanley JR. Desmoglein as a Target in Skin Disease and Beyond. *J Invest Dermatol*. 2012; 132 (3): 776–784. DOI:10.1038/jid.2011.390. PMID: 22189787.
3. Li WC, Mo LJ, Shi X, et al. Antioxidant status of serum bilirubin, uric acid and albumin in pemphigus vulgaris. *Clin Exp Dermatol*. 2018; 43(2):158-63. DOI:10.1111/ced.13289. PMID: 29067729.
4. Perl A. Oxidative stress in the pathology and treatment of systemic lupus erythematosus. *Nat Rev Rheumatol* 2013; 9(11): 67486. DOI: 10.1038/nrrheum.2013.147. PMID: 24100461
5. Gabr SA, Al-Ghadir AH. Role of cellular oxidative stress and cytochrome c in the pathogenesis of psoriasis. *Arch Dermatol Res* 2012; 304 (6): 451–457. DOI 10.1007/s00403-012-1230-8. PMID: 22421888.
6. Isik A, Koca SS, Ustundag B, Selek S. Decreased total antioxidant response and increased oxidative stress in Behcet's disease. *Tohoku J Exp Med* 2007; 212 (2): 133–41. DOI: 10.1620/tjem.212.133. PMID: 17548957.
7. Naziroğlu M, Kökçam I, Şimşek H, Karakılçık AZ. Lipid peroxidation and antioxidants in plasma and red blood cells from patients with pemphigus vulgaris. *J Basic Clin Physiol Pharmacol* 2003; 14 (1): 31–42. DOI:10.1515/JBCPP.2003.14.1.31. PMID: 12901444.
8. Huang Y, Jedličková H, Cai Y, et al. Oxidative stress-mediated YAP dysregulation contributes to the pathogenesis of pemphigus vulgaris. *Front Immunol*. 2021;12:649502. DOI: 10.3389/fimmu.2021.649502. PMID: 33968042
9. Najafizadeh SR, Amiri K, Moghaddassi M, et al. Advanced glycation end products, advanced oxidation protein products, and ferric reducing ability of plasma in patients with rheumatoid arthritis: a focus on activity scores. *Clin Rheumatol*. 2021; 40(10):4019-4026. DOI:10.1007/s10067-021-05771-y. PMID: 34050440.
10. Di Lorenzo G, Minciullo PL, Leto-Barone MS, et al. Differences in the behavior of advanced glycation end products and advanced oxidation protein products in patients with allergic rhinitis. *J Investig Allergol Clin Immunol*. 2013; 23(2):101-106. PMID: 23654076.
11. Sajda T, Sinha AA. Autoantibody signaling in pemphigus vulgaris: development of an integrated model. *Front Immunol*. 2018; 9: 692. DOI: 10.3389/fimmu.2018.00692 PMID: 29755451.
12. Chen CY, Zhang JQ, Li L, et al. Advanced glycation end products in the skin: Molecular mechanisms, methods of measurement, and inhibitory pathways. *Front Med*. 2022 11;9:837222. DOI: 10.3389/fmed.2022.837222. PMID: 35646963
13. Kalousova M, Skrha J, Zima T. Advanced glycation end-products and advanced oxidation protein products in patients with diabetes mellitus. *Physio Res*. 2002; 51(6):597-604. PMID: 12511184.
14. Witko-Sarsat V, Friedlander M, Khoa TN, et al. Advanced oxidation protein products as novel mediators of inflammation and monocyte activation in chronic renal failure1, 2. *J Immunol*. 1998;161(5):2524-2532. PMID: 9725252.
15. Hegab Z, Gibbons S, Neyses L, Mamas MA. Role of advanced glycation end products in cardiovascular disease. *World J Cardiol*. 2012; 4(4): 90. DOI: 10.4330/wjc.v4.i4.90. PMID: 22558488
16. Murrell DF, Dick S, Ahmed AR, et al. Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus. *J Am Acad Dermatol*. 2008;58(6):1043-1046. DOI: 10.1016/j.jaad.2008.01.012. PMID: 18339444
17. Rosenbach M, Murrell DF, Bystryn JC, et al. Reliability and convergent validity of two outcome instruments for pemphigus. *J Invest Dermatol*. 2009;129(10):2404-2410. DOI:10.1038/jid.2009.72. PMID: 19357707
18. Boulard C, Duvert Lehembre S, Picard-Dahan C, et al. Calculation of cut-off values based on the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) and Pemphigus Disease Area Index (PDAI) pemphigus scoring systems for defining moderate, significant and extensive types of pemphigus. *Br J Dermatol*. 2016;175(1):142-149. DOI: 10.1111/bjd.14405. PMID: 26800395.
19. Kwon EJ, Yamagami J, Nishikawa T, Amagai M. Anti-desmoglein IgG autoantibodies in patients with pemphigus in remission. *J Euro Acad Dermatol Venereol*. 2008; 22(9):1070-1075. DOI: 10.1111/j.1468-3083.2008.02715.x. PMID: 18410336.
20. Sardana K, Garg VK, Agarwal P. Is there an emergent need to modify the desmoglein compensation theory in pemphigus on the basis of Dsg ELISA data and alternative pathogenic mechanisms? *Br J Dermatol*. 2013; 168(3):669-74. DOI: 10.1111/bjd.12012. PMID: 22913529.
21. Moro F, Sinagra JL, Salemme A, et al. Pemphigus: trigger and predisposing factors. *Front Med*. 2023;10:1326359. DOI: 10.3389/fmed.2023.1326359. PMID: 38213911.
22. Marchenko S, Chernyavsky AI, Arredondo J, et al. Antimitochondrial Autoantibodies in Pemphigus Vulgaris: A missing link in disease pathophysiology. *J Biol Chem*. 2010 ; 285(6): 3695-3704. DOI: 10.1074/jbc.M109.081570. PMID: 20007702.
23. Kalantari-Dehaghi M, Chen Y, Deng W, et al. Mechanisms of mitochondrial damage in keratinocytes by pemphigus vulgaris antibodies. *J Biol Chem*. 2013;288(23):16916-16925. DOI: 10.1074/jbc.M113.472100. PMID: 23599429.
24. Abida O, Ben Mansour R, Gargouri B, et al. Catalase and lipid peroxidation values in serum of Tunisian patients with pemphigus vulgaris and foliaceus. *Biol Trace Elem Res*. 2012;150 (1-3):74-80. DOI: 10.1007/s12011-012-9497-3. PMID: 22907559.
25. Yesilova Y, Ucmak D, Selek S, et al. Oxidative stress index may play a key role in patients with pemphigus vulgaris. *J Euro Acad Dermatol Venereol*. 2013 ;27(4):465-467. DOI: 10.1111/j.1468-3083.2012.04463.x. PMID: 22324759.
26. Abida O, Gargouri B, Ben Mansour R, et al. Biomarkers of oxidative stress in epidermis of Tunisian pemphigus foliaceus patients. *J Euro Acad Dermatol Venereol*. 2013;27(3): e271-275. DOI: 10.1111/j.1468-3083.2012.04626.x. PMID: 22738420.
27. Shah AA, Dey-Rao R, Seiffert-Sinha K, Sinha AA. Increased oxidative stress in pemphigus vulgaris is related to disease activity and HLA-association. *Autoimmunity*. 2016;49(4):248-257. DOI: 10.3109/08916934.2016.1145675. PMID: 26911801.
28. Javanbakht MH, Djalali M, Daneshpazhooh M, et al. Evaluation of antioxidant enzyme activity and antioxidant capacity in patients with newly diagnosed pemphigus vulgaris. *Clin Exp Dermatol*. 2015;40(3):313-317. DOI: 10.1111/ced.12489. PMID: 25683954.
29. Mohammadi H, Djalali M, Daneshpazhooh M, et al. Effects of L-carnitine supplementation on biomarkers of oxidative stress, antioxidant capacity and lipid profile, in patients with pemphigus vulgaris: a randomized, double-blind, placebo-controlled trial. *Eur J Clin Nutr*. 2018;72(1):99-104. DOI: 10.1038/ejcn.2017.131. PMID: 28832573.
30. Rasheed Z, Ahmad R, Sheikh N, Ali R. Enhanced recognition of reactive oxygen species damaged human

serum albumin by circulating systemic lupus erythematosus autoantibodies. *Autoimmunity* 2007; 40 (4): 512–520. DOI: 10.1080/08916930701574331. PMID: 17966041.

31. Inumaru J, Nagano O, Takahashi E, et al. Molecular mechanisms regulating dissociation of cell-cell junction of epithelial cells by oxidative stress. *Genes Cells.2009*; 14(6):703–716. DOI: 10.1111/j.1365-2443.2009.01303.x. PMID: 19422420.
32. Van WS, Van Buul JD, Quik S, et al. Reactive oxygen species mediate Rac-induced loss of cell-cell adhesion in primary human endothelial cells. *J Cell Sci*. 2002; 115 :1837–1846 DOI: 10.1242 /jcs.115.9.1837. PMID: 11956315.
33. Egu DT, Schmitt T, Waschke J. Mechanisms causing acantholysis in pemphigus-lessons from human skin. *Front Immunol*. 2022;13:884067. DOI: 10.3389/fimmu.2022.884067. PMID: 35720332.
34. Jolly PS, Berkowitz P, Bektas M, et al. p38MAPK signaling and desmoglein-3 internalization are linked events in pemphigus acantholysis. *J Biol Chem*. 2010;285(12):8936-8941. DOI: 10.1074/jbc.M109.087999. PMID: 20093368.
35. Stahley SN, Warren MF, Feldman RJ, Swerlick RA, Mattheyses AL, Kowalczyk AP. Super Resolution Microscopy Reveals Altered Desmosomal Protein Organization in Tissue from Patients with Pemphigus Vulgaris. *J Cell Sci*. 2016;136(1):59-66 DOI: 10.1038/JID.2015.353. PMID: 26763424.
36. Berkowitz P, Hu P, Liu Z, et al. Desmosome signaling. Inhibition of p38MAPK prevents pemphigus vulgaris IgG-induced cytoskeleton reorganization. *J Biol Chem*. 2005;280(25):23778-23784. DOI: 10.1074/jbc.M501365200. PMID: 15840580.
37. Spindler V, Rotzer V, Dehner C, et al. Peptide-mediated desmoglein 3 crosslinking prevents pemphigus vulgaris autoantibody-induced skin blistering. *J Clin Invest*. 2013;123(2):800-811 DOI: 10.1172/JCI60139. PMID: 23298835.
38. Vielmuth F, Wanuske MT, Radeva MY, et al. Keratins Regulate the Adhesive Properties of Desmosomal Cadherins through Signaling. *J Invest Dermatol*. 2018b;138(1):121-31 DOI: 10.1016/j. jid.2017.08.033. PMID: 28899688.
39. Mao X, Sano Y, Park JM, Payne AS. p38 MAPK activation is downstream of the loss of intercellular adhesion in pemphigus vulgaris. *J Biol Chem*. 2011;286(2):1283-1291. DOI: 10.1074 /jbc.M110.172874. PMID: 21078676.
40. Yue Q, Song Y, Liu Z, Zhang L, Yang L, Li J. Receptor for advanced glycation end products (RAGE): a pivotal hub in immune diseases. *Molecules*. 2022;27(15):4922. DOI: 10.3390/molecules27154922. PMID: 35956875.