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ORIGINAL CONTRIBUTIONS

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HMGB1-RAGE-moesin axis may be indicted for acne vulgaris

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Abstract

Background: High-mobility group box 1 (HMGB1)-receptor for advanced glycation end (RAGE)-moesin axis could be implicated in induction of inflammation. However, there is a scarcity in literature discussing the role of this axis in inflammatory skin disorders.

Aims: The aim of the present study was to evaluate the serum levels of HMGB1 and moesin in patients with inflammatory acne vulgaris.

Patients/Methods: This comparative cross-sectional study included 66 inflammatory acne vulgaris patients classified according to Global Acne Grading System (GAGS) into three groups (22 patients each): mild, moderate, and severe acne vulgaris. In addition, 82 acne-free individuals were included as a control group. Serum HMGB 1 and moesin levels were measured using enzyme-linked immunosorbent assay kits.

Results: High-mobility group box 1 and moe sin serum levels in acne patients were significantly higher than the levels in control subjects (p = 0.04, 0.0005 respectively). Serum levels of both markers in severe acne patients and in those with post-acne scarring were elevated when compared to the levels in the other groups, and however, this elevation was significant only for moesin levels. There was a significant positive correlation between the serum levels of HMGB1 and moesin in the studied patient's sample (r = 0.3079, p = 0.011).

Conclusion: High-mobility group box 1-receptor for advanced glycation end-moesin axis may be implicated in acne vulgaris pathogenesis, and it may be a promising therapeutic target.

KEYWORDS
acne, HMGB 1, moesin

1 | INTRODUCTION

Acne vulgaris is the most common skin disorder which affects more than 80% of people in their second or third decades. It occurs due to the interplay between multiple factors: excessive sebum production with changes in its composition, hormonal changes, follicular hyperkeratinization, and induction of an inflammatory process comprising multiple inflammatory mediators.[1]

High-mobility group box 1 (HMGB1) is an intra-cellular highly conserved protein that presents in almost all body cells. It exerts a regulatory role on different vital physiological processes in the body via controlling gene transcription.[2]

Under certain circumstances such as sepsis, inflammation, or injury, HMGB1 can be released extracellularly from the affected cells under the effect of inflammatory molecules, for example, tumor necrosis factor (TNF)-α. It also may be released to the extracellular environment following cell necrosis.[3] Extracellular HMGB1 has pro-inflammatory properties by binding to Toll-like receptors 2 or 4 or the receptor for advanced glycation end products (RAGE).[4] HMGB1 has been implicated in the pathogenesis of various inflammatory and autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, and ankylosing spondylitis.[5–7]

Moesin (membrane-organizing extension spike protein) is a member of the ERM protein family which includes ezrin, radixin,

and moesin. It is expressed physiologically in many cell types mainly macrophages, lymphocytes, fibroblasts, epithelial cells, and neuronal cells. It also can be found in certain neoplasms.[8]

Moesin is supposed to modify inflammatory responses especially the lipopolysaccharides-induced inflammatory response. Moesin functions as an independent lipopolysaccharide receptor on human monocytes.[9] It also plays a role in maintaining cytoskeleton (actin remodeling) and controlling cell locomotion (endothelial cells migration).[10] Moesin is required in HMGB1-mediated activities including F-actin remodeling, hyperpermeability, and inflammation. Lee et al[11] reported that HMGB1-RAGE-moesin axis could be implicated in induction of inflammation. However, there is a scarcity in literature discussing the role of this axis in different inflammatory skin disorders.

The aim of the present study was to evaluate the serum levels of HMGB1 and moesin in patients with inflammatory acne vulgaris.

2 | SUBJECTS AND METHODS

A total of 66 inflammatory acne vulgaris patients were enrolled in this comparative cross-sectional study. Patients were recruited from the outpatient clinic of Dermatology and cosmetology during the period from January to July 2020. Patients were classified according to Global Acne Grading System (GAGS)[12] into 3 groups (22 patients each): mild, moderate, and severe acne vulgaris. In addition, 82 acne-free individuals were included as a control group.

The study was approved by the local ethics committee on research involving human subjects of Faculty of Medicine. Informed consent was obtained from each individual before sample collection.

Subjects suffering from other inflammatory skin diseases, for example, psoriasis, alopecia areata, and subjects with any infectious disease or systemic serious condition, for example, cardiac, hepatic, or renal disorders were not included in the current work. Acne patients using systemic or topical anti-acne therapy during the month preceding sample collection were excluded from this study. Pregnant and lactating women, subjects with malignancy, and those with metabolic syndromes were also excluded.

All patients gave full history about their condition, and all of them were examined to evaluate the type and distribution of acne lesions.

2.1 | LABORATORY INVESTIGATIONS

All participants were tested for evaluation of serum of Serum level of HMGB1and Moesin using ELISA technique.

I. Sampling

Five milliliters of venous blood was collected from each participant under complete aseptic conditions by clean venipuncture using disposable plastic syringe and put into a plain sterile tube (without anticoagulant) for serum separation. The tube was left at room temperature for 30 min till coagulation and then was centrifuged for 10 min at 1000 *g*. The separated serum was stored at −20°C until analysis.

II. Methods

Serum levels of HMGB1 were measured using Human HMGB1 ELISA Kit prepared for research use only (Cat #: 201-12-1636, Sun Red Bio, China). Assay detection range was 0.8–13 ng/ml, and sensitivity was 0.3 ng/ml.

Serum levels of HMGB1 were measured using Human HMGB1 ELISA Kit prepared for research use only (Cat #: 201-12-1636, Sun Red Bio, China). Assay detection range was 1.0–25 ng/ml, and sensitivity was 0.1 ng/ml. All methods were performed according to the manufacturer's instructions.

2.2 | Statistical methods

The collected data were revised, coded, tabulated, and analyzed using Statistical package for Social Science (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Data were presented, and suitable analysis was done according to the type of data obtained for each parameter.

2.3 | Sample size calculation

MedCalc software version 16.1(© 19932016 MedCalc Software bvba) was used to calculate the required sample size using the AUC of serum irisin in detection of severe acne vulgaris according to Mustafa and El-Shimi,[13] where the following parameters were entered in the program: The level of significance (type I error) = 0.05, Type II error (1-level of power) = 0.2, AUC = 0.873, null hypothesis value of 0.5, ratio of sample size in mild and moderate-to-severe cases (negative/positive groups) = 2.33. Accordingly, the total sample size of the patient's group is at least 20 patients.

As the studied markers were not investigated in acne vulgaris before (to the best of our knowledge), irisin values were used for estimation of the sample size and the current researchers increased the sample size to 66 patients and 82 controls instead of 20 subjects in each group.

3 | RESULTS

There was insignificant difference between patients and control subjects regarding sex, age, and BMI (p = 0.65, 0.1, and 0.42 respectively) (Table 1).

Family history of acne vulgaris was positive in 40 (60.6%) patients. The mean duration of acne was 3.46 ± 1.83 years. The study included mild, moderate, and severe acne patients in equal groups (22 patients each). Face was affected in all cases, while back was affected in 37 (56.06%) patients only. Fifty patients (78.78%) of the current sample had post-acne scars.

TABLE 1 Demographic data of the studied groups

Variable	Patients (n = 66)		Control (n = 82)		Test	p
	No.	%	No.	%		
Sex						
Male	21	31.81	29	35.36	$\chi^2 = 0.2$	0.65
Female	45	68.18	53	64.63		
Age (years)	21.47 ± 2.53		22.13 ± 2.42		$t = 1.616$	0.1
BMI (Kg/m^2)	23.44 ± 1.80		23.67 ± 1.72		$t = 0.792$	0.42

Note: $p < 0.05$ is significant.

Abbreviations: Kg, Kilogram; m, meter; t, Student t-test; χ^2, chi-square test.

TABLE 2 HMGB 1 and Moesin serum levels in the studied groups

Serum levels	Patients (n = 66)	Control (n = 82)	t	p
HMGB1 (ng/ml)	32.42 ± 20.48	19.56 ± 47	−2.069	0.04
MSN (ng/ml)	3.94 ± 4.76	0.86 ± 5.64	−3.537	0.0005

HMGB1, High-mobility group box 1; MSN; moesin; t, Student's test, statistically significant at $p < 0.05$.

TABLE 3 Relation between HMGB1 and moesin serum levels and acne severity and post-acne scarring

Variables		HMGB1 (ng/ml) Mean ± SD	Moesin (ng/ml) Mean ± SD
Acne severity	Mild	28.55 ± 7.4	2.22 ± 1.4
	Moderate	33.87 ± 17.7	3.209 ± 3.8
	Severe	34.82 ± 30.37	6.38 ± 6.7
	ANOVA teat	0.58	5.07
	p Value	0.56	0.009
Post-acne scarring	Positive	33.32 ± 23.22	4.6 ± 5.3
	Negative	29.6 ± 8.6	1.8 ± 1.6
	t-test	−0.6	−2.07
	p Value	0.5	0.04

Note: HMGB1, High-mobility group box 1. $p < 0.05$ is significant.

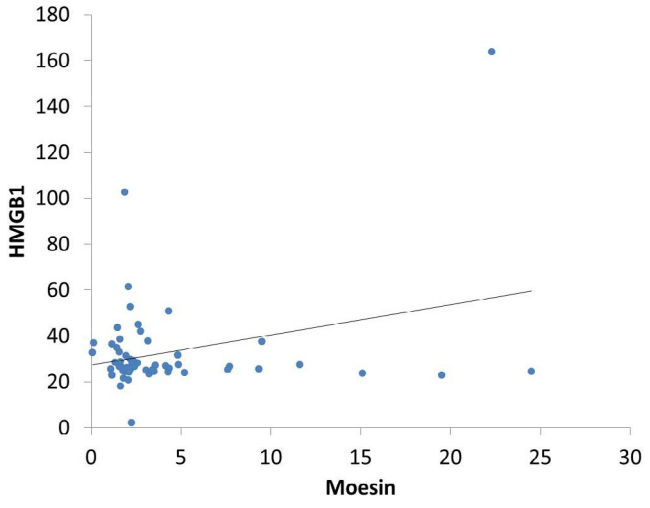

FIGURE 1 The correlation between serum HMGB 1 and moesin in acne patients

High-mobility group box 1 and moesin serum levels in acne patients were significantly higher than the levels in control subjects (p = 0.04 and 0.0005, respectively) (Table 2). Serum levels of both markers in severe acne patients and in those with post-acne scarring were elevated when compared to the levels in the other groups, and however, this elevation was significant only for moesin levels (Table 3). There was a significant positive correlation between the serum levels of HMGB1 and moesin in the studied patients sample (r = 0.3079, p = 0.011) (Figure 1).

4 | DISCUSSION

To the best of our knowledge, this is the first study to propose the role of HMGB1 and moesin in the inflammatory process of acne vulgaris.

In the present study, HMGB1 serum levels in acne patients were significantly higher than the levels in control subjects. Although it has been considered as a pro-inflammatory cytokine in the pathogenesis of dermatological inflammatory and autoimmune diseases such as psoriasis [14] and alopecia areata,[15] it was not evaluated in acne vulgaris, the commonest inflammatory skin disorder.

In fact, the mode of action of HMGB 1 resembles that of conventional inflammatory cytokines. The pro-inflammatory properties of HMGB 1 may be based on its role in inducing the cytokine production, promoting chemotaxis, and activating various cells involved in the inflammatory process such as immune and endothelial cells as well as fibroblasts.[16] This would explain the elevated HMGB 1 levels in inflammatory acne patients.

Despite the higher mean serum levels of HMGB 1 in severe acne when compared to the other two groups, this difference was insignificant. This marker has failed to reflect acne severity although it was sensitive to psoriasis severity and correlated significantly with PASI scores in a previous study.[3]

We detected also a significant elevation in serum moesin levels in acne vulgaris patients when compared to the control group.

Moreover, moesin serum levels were sensitive to the degree of the disease severity. Its levels in severe acne were significantly higher than the levels in moderate and mild acne patients. From these results, the current workers suggest that moesin may have a role in the pathogenesis of acne vulgaris and may be even used as an inflammatory marker in this disease.

Moesin may contribute to the inflammatory reaction in acne vulgaris in many ways. Firstly, moesin is found on human monocytes where it acts as a lipopolysaccharides receptor. Lipopolysaccharide, a glycolipid found in the outer membranes of gram-negative bacteria, induces the secretion of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and IL-6 by monocytes/macrophages.[17] The binding between p. acnes lipopolysaccharides with moesin on the monocytes receptors might be a way for monocytes activation in acne vulgaris with the subsequent release of various inflammatory cytokines.[18] Secondly, ERM may regulate cell motility through its association with membrane-type 1 matrix metalloproteinase (MT1-MMP).[19] Matrix metalloproteinases (MMP) are among the key players in the inflammatory process and matrix remodeling in acne vulgaris.[20] Membrane type 1 (MT1)-MMP is the most predominant form regulated by cytokines and growth factors, and it can also activate proMMP-2.[21] This regulatory effect on the matrix metalloproteinase besides the link between both HMGB 1 and moesin with the cellular cytoskeletal dynamics and their relation with increased collagen deposition [22,23] can explain the elevated serum levels of both markers in patients with post-acne scarring when compared to those who healed without post-acne scars.

A significant positive correlation between serum levels of HMGB 1 and moesin in the current sample was detected. The interplay between HMGB 1 and moesin (HMGB1-RAGE-moesin axis) was previously proposed. The involvement of this axis in inflammatory reactions was suggested by Lee et al[11] who discovered that many HMGB 1 inflammatory actions are mediated by moesin. The significant elevation of HMGB 1 and moesin in inflammatory acne patients in the current study, together with the significant correlation between their levels suggest that this axis might be implicated in the pathogenesis of acne.

Although acne is generally not considered as a serious disorder, it may be associated with severe psychological distress and it also can impair all quality of life aspects in its active form and after healing with post-acne scarring.[24,25] Moreover, some variants of acne may be severe and life-threatening such as acne fulminans.[26] For these reasons, discovery of new molecules which may be indulged in acne pathogenesis and targeting them may be promising in managing many challenging cases.

The inflammatory reaction in acne vulgaris has been considered as a completely local cutaneous reaction.[27] However, recent research showed that acne vulgaris changes significantly the serum levels of many inflammatory mediators.[28,29] Better understanding of the disease nature can suggest new molecules as a potential therapeutic targets.

Targeting moesin may result in suppressing inflammation markedly.[11] Targeting HMGB 1 also has sown to be promising in ameliorating inflammation and stopping cellular damage in sterile and infection-induced inflammatory scenarios.[30] This may pave the road for targeting this axis in different inflammatory conditions including acne vulgaris.

CONFLICT OF INTEREST

No Conflict of interest to declare.

ETHICAL APPROVAL

The study was approved by the local ethics committee on research involving human subjects of Faculty of Medicine. An informed consent was obtained from each individual before sample collection.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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