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Research Article

Serum Level of High Mobility Group Box1 Protein Among Iraqi Psoriatic Patients and its Relationship with Disease Severity and Comorbidities

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Abstract

Background: Psoriasis is a persistent, inflammatory skin condition characterized by distinct clinical and histological features. The disease is linked to systemic inflammation and immune system dysregulation. High Mobility Group Box 1 (HMGB1) is one of the innate immunity components that have been implicated in disease development and severity. ***Objective***: Evaluate the mean serum levels of High Mobility Group Box1 Protein (HMGB1) in Iraqi patients with psoriasis and analyze its potential association with disease severity and complications. ***Methods***: A case-control study was conducted on 110 individuals. The patient group included 60 randomly selected patients with a mean age of 37.23±8.26 years old, and the control group included 50 randomly selected volunteers (35.32±7.53 years). Blood specimens were obtained from all participants after acquiring verbal permission. The ELISA technique was used to measure the serum levels of HMGB1. ***Results***: the mean level of HMGB1 was 7.21±0.75 ng/ml in patients compared to 6.42±0.69 ng/ml in controls, although the difference was non-significant (p=0.451). The mean level of HMGB1 was significantly associated with response to treatment. Also, the mean level of HMGB1 was significantly higher in individuals with metabolic syndrome. In contrast, the mean level of HMGB1 was non-significantly associated with other complications and disease severity. ***Conclusions***: HMGB1 serum level was elevated non-significantly in psoriasis patients, but it was significantly correlated with metabolic syndrome and good treatment response, so it could be used as a predictor for metabolic syndrome and good management.

Keywords: Comorbidities, Disease Severity, HMGB1, Psoriasis.

مستوى مصل بروتين المجموعة عالية الحركة Box1 لدى مرضى الصدفية العراقيين وعلاقته مع شدة المرض والأمراض المصاحبة

الخلاصة

الخلفية: الصدفية هي حالة جلدية التهابية مستمرة تتميز بسمات سريرية ونسيجية مميزة. يرتبط المرض بالالتهاب الجهازي وخلل تنظيم الجهاز المناعي. مجموعة الحركة العالية المربع 1 (HMGB1) هو أحد مكونات المناعة الفطرية التي كانت متورطة في تطور المرض وشدته. **الهدف**: تقييم متوسط مستويات المصل من بروتين مجموعة Box1 عالي الحركة (HMGB1) في المرضى العراقيين المصابين بالصدفية وتحليل ارتباطه المحتمل بشدة المرض ومضاعفاته. **الأساليب**: أجريت دراسة حالة وشواهد على 110 أفراد. تضمنت مجموعة المرضى 60 مريضا تم اختيارهم عشوائيا بمتوسط عمر 37.23±8.26 سنة، وضمت المجموعة الضابطة 50 متطوعا تم اختيارهم عشوائيا (35.32±7.53 سنة). تم الحصول على عينات الدم من جميع المشاركين بعد الحصول على إذن شفهي. تم استخدام تقنية ELISA لقياس مستويات مصل HMGB1. **النتائج**: كان متوسط مستوى HMGB1 7.21±0.75 نانوغرام / مل في المرضى مقارنة ب 6.42±0.69 نانوغرام / مل في الضوابط ، على الرغم من أن الفرق كان غير معتد به (p = 0.451). ارتبط متوسط مستوى HMGB1 ارتباطا كبيرا بالاستجابة للعلاج. أيضا ، كان متوسط مستوى HMGB1 أعلى بشكل ملحوظ لدى الأفراد المصابين بمتلازمة التمثيل الغذائي. في المقابل ، كان متوسط مستوى HMGB1 غير مرتبط بشكل كبير بمضاعفات أخرى وشدة المرض. **الاستنتاجات**: ارتفع مستوى مصل HMGB1 بشكل غير ملحوظ في مرضى الصدفية، ولكنه كان مرتبطا بشكل كبير بمتلازمة التمثيل الغذائي والاستجابة العلاجية الجيدة ، لذلك يمكن استخدامه كمؤشر على متلازمة التمثيل الغذائي والإدارة الجيدة.

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INTRODUCTION

Psoriasis is a persistent inflammatory dermatological condition that decreases the quality of life and is marked by excessive proliferation of keratinocytes and erythematous scaly plaques; it may manifest in any region of the body. Nonetheless, the most often impacted areas are those susceptible to recurrent injuries, such as the elbows, knees, or lower back [1]. Presently, more than 125 million individuals are affected by psoriasis, and this ratio is rising year by year [2]. The global incidence ranges from 0.14% in East Asia to 1.99% in Australasia, with elevated rates in high-income nations and areas with aging populations [3]. European and North American communities have greater incidences (2–3%) in comparison to Asian and African populations (≤1%) [4]. While in Iraq, the documented psoriasis spread is 2.3% [5]. The condition

considerably affects the quality of life and healthcare expenditures, with yearly costs varying from €500 to €15,000 per patient, depending upon severity [6]. Psoriasis can be categorized into mild, moderate, and severe by utilizing the psoriasis area and severity index (PASI) score [7]. The disease is linked to several comorbidities, such as cardiovascular illnesses, metabolic problems, mental health issues, diabetes, and others [8]. The disease is characterized by a multifaceted etiology encompassing genetic, immunological, and external factors [9]. The interaction between innate and adaptive immune systems, including dendritic cells, mast cells, neutrophils, and different cytokines (such as TNF-α and IL-17), facilitates psoriasis progression [10]. One of the innate mediators considered as an alarmin in psoriasis development is High Mobility Group Box 1 protein (HMGB1), which functions as a damage-associated molecular pattern (DAMP) molecule that is secreted from keratinocytes in the affected skin, intensifying inflammation by stimulating immunological responses. It interacts with various receptors, including Toll-like Receptor 2 (TLR2), Toll-like Receptor 4 (TLR4), and Receptor for Advanced Glycation End-product (RAGE), resulting in the activation of inflammatory pathways. HMGB1 facilitates the recruitment of immune cells, including T cells and neutrophils, and enhances the IL-23/IL-17 axis, which is essential to psoriasis inflammation [11]. The role of these mediators has been investigated in psoriasis patients by measuring their level mainly in skin lesions, and their role in the immunopathogenesis of the disease has been well established [12,13]. Other researchers try to measure it in serum as a systemic inflammatory marker for the disease. However, studies correlating its level with disease severity and different comorbidities are still few, and when done, the results were controversial among different diversities of studied populations [14,15]. Concomitant with the development of psoriasis treatment by using immune modulator drugs, more clinical research data are required to substantiate the development of DAMPs like HMGB1 as a diagnostic and treatment target for psoriasis. Researchers concluded that the significance of DAMPs in psoriasis should not be overlooked, and more investigations are required to assess their potential as therapeutic targets thoroughly [11]. This study aims to assess the levels of HMGB1 in Iraqi patients with psoriasis compared to control subjects and try to associate this innate mediator with disease severity and different comorbidities.

METHODS

Study design and setting

A case-control study was conducted at Merjan Teaching Hospital in Hilla City, Babylon Province. The data were collected from October 2024 to January 2025. The study was conducted on 110 individuals and categorized into two groups: the patients group, which included 60 randomly selected patients with psoriasis vulgaris, a mean age of 37.23±8.26 years old, and the control group, which included 50 randomly selected volunteers without psoriasis, with a mean age of 35.32±7.53 years old. Control individuals match those with psoriasis patients in concern of age and sex. Disease severity is categorized into mild, moderate, and severe according to criteria stated by Fredriksson and Pettersson (1979) [16].

Outcome measurement

The Enzyme-Linked Immunosorbent Assay (ELISA) conducted by BT Lab Co. in China was used to assess the blood concentrations of HMGB1 in both groups.

Ethical considerations

All research participants were apprised of the study's objective, and verbal permission was obtained before collecting blood samples to evaluate various study parameters. The project was approved by the local research ethics committee of the College of Medicine, University of Kufa (No.1663 in 16/10/2024).

Statistical analysis

Data were collected, summarized, analyzed, and presented using SPSS (version 26). Descriptive statistics included means and standard deviations (or standard errors) for numerical variables and frequencies and percentages for categorical variables. Differences between the two groups were analyzed with t-tests, while ANOVA was used to compare three groups. Chi-square tests and graphs visualized categorical data. Correlations between markers were assessed using Pearson's correlation coefficient. Statistical significance was considered at $p< 0.05$.

RESULTS

The mean level of HMGB1 was increased in patients (7.21±0.75 ng/ml) compared to that of controls (6.42±0.69 ng/ml), and the difference was non-significant ($p= 0.451$) (Table 1).

Table 1: Mean serum levels of HMGB1 in psoriatic patients and control

HMGB1 level (ng/ml)	Patients (n = 60)	Healthy control (n = 50)	*p*-value
Mean ± SE	7.21±0.75	6.42±0.69	0.451
Range	0.70 – 21.50	0.60 – 16.10	

In Table 2, the HMGB1 level was increased in patients aged more than 30 years old compared to those less than 30 years old, with a mean of 7.75±1.0 and 6.48±1.14, respectively, but the difference was non-significant ($p= 0.408$). Also, females had slightly elevated HMGB1 serum levels compared to males (7.51±1.32 versus 7.03±0.91); however, the difference was non-significant ($p= 0.766$).

Table 2: Mean serum levels of HMGB1 according to some characteristics

Characteristics		*n*	HMGB1 level	*p-value*
Age groups	< 30 years	26	6.48±1.14	0.408
	≥ 30 years	34	7.75±1.0	
Sex	Male	38	7.03±0.91	0.766
	Female	22	7.51±1.32	
Family history	Positive	22	6.61±1.11	0.549
	Negative	38	7.55±1.0	
Occupation	Housewife	15	7.22±1.58	0.942
	Employee	16	8.20±1.51	
	Student	13	6.94±0.87	
	Earner	13	6.34±1.28	
	Retired	3	6.70±1.67	
Duration	< 10 years	29	7.24±1.17	0.962
	≥ 10 years	31	7.17±0.96	
Smoking	Smoking	34	7.10±0.88	0.871
	Non-smoking	26	7.35±1.30	
Response to treatment	Poor	53	6.66±0.76	0.045
	Good	7	11.33±2.55	

Values were expressed as mean±SE.

Regarding other characteristics, results show a non-significant difference in HMGB1 levels according to family history (p= 0.549), occupation (p= 0.942), duration of disease (p= 0.962), and smoking (p= 0.871) with the exception of response to treatment that was significant, as the mean serum levels in those patients with good response to treatment was 11.33±2.55 compared to 6.66±0.76 in patients with poor response, p= 0.045. In Table 3, the mean levels of HMGB1 were significantly elevated in patients with metabolic syndrome compared to patients without metabolic syndrome (13.8±3.58 *vs*. 6.99±1.0), respectively (p= 0.023). In contrast, the mean levels of HMGB1 had a non-significant association with complications (p> 0.05).

Table 3: Mean serum levels of HMGB1 according to the disease comorbidities

Comorbidity		n	HMGB1 levels	*p*-value
Metabolic syndrome	Present	8	13.8±3.58	0.023
	Absent	52	6.99±1.0	
Cardiovascular Disease	Present	23	7.83±1.25	0.518
	Absent	37	6.82±0.94	
Obesity	Obese	17	8.74±1.51	0.200
	Non-Obese	43	6.59±0.85	
Diabetes mellitus	Present	15	8.61±1.63	0.285
	Absent	45	6.74±0.83	
Psoriatic Arthritis	Present	16	4.80±0.58	0.053
	Absent	44	8.08±0.92	

Values were expressed as mean±SE.

According to disease severity, Figure 1 showed that the mean levels of HMGB1in mild cases seem to be higher than in moderate and severe cases (10.85, 7.48, 6.48 ng/l, respectively), and the difference is not significant (p= 0.356).

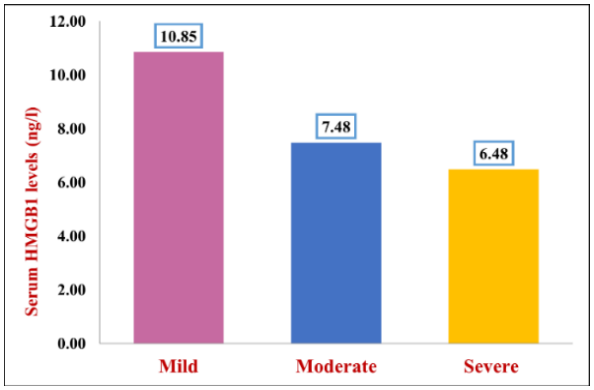

Figure 1: Mean serum levels of HMGB1 according to severity groups.

DISCUSSION

The study demonstrated that the mean levels of HMGB1 were increased in psoriatic patients compared to control subjects, but there were no significant differences. This study is consistent with Bergmann *et al*. and Borsky *et al*. [17,14], who showed that levels of HMGB1 significantly increase in individuals with psoriasis vulgaris. The researcher stated that HMGB1 in normal skin is mainly inside the nucleus. In contrast, psoriatic lesions show a notable movement of HMGB1 from the nucleus to the cytoplasm, then its release into the extracellular space. The modified distribution and release of HMGB1 enhance the inflammatory responses seen in psoriasis [18]. The research suggested that HMGB1 might change the type of chronic inflammation found in psoriasis, which could have an effect on Treg and Th17 cells [19]. HMGB1 may influence the pathophysiology of psoriasis by modulating Th17 cell development via the HMGB1-TLR4-IL-23-RORγt pathway in the inflammatory response [20]. Patients

older than 30 years old show higher levels of HMGB1 than those younger than 30 years old. However, the results are not statistically significant. The study is consistent with the finding of Haynes (2020) [21], who stated that elevated AMPs were linked to age-related immune system change, involving persistent low-grade inflammation and immunosenescence. Senescence influences many immune cells, such as T cells, B cells, and myeloid cells, resulting in alterations in immunological functionality. Senescent immune cells, especially CD8+ T lymphocytes, have a unique gene expression profile that includes making more inflammatory cytokines, which may indirectly boost AMP expression. Moreover, age-associated B lymphocytes (ABC) release pro-inflammatory cytokines such as IFN-γ and TNF-α, exacerbating this reaction. The buildup of senescent cells results in heightened production of antimicrobial molecules as part of the senescence-associated secretory phenotype (SASP), which encompasses antimicrobial peptides (AMPs) to mitigate the diminished immune response in the elderly [22]. Regarding sex, the mean levels of HMGB1 were higher in females than in males, with no significant difference. This result corresponds with the study conducted by Ortona *et al*. [23], which showed that estrogen specifically enhances the production of antimicrobial peptides in females. Generally, females have more robust innate and adaptive immune responses than men. Females often have elevated expression of specific pattern recognition receptors (PRRs) on immune cells, resulting in a more vigorous innate immune response. This amplified reaction may lead to elevated antimicrobial peptide (AMP) synthesis [24]. The study demonstrates that serum levels of HMGB1 are not related to disease duration, and this could be explained by the chronic nature of the disease that is characterized by a stage of flare and remission through the whole period of the disease and the flare stages associated with increased inflammation while the remission is associated with diminished inflammation, and thus the duration of disease seems to be not influencing the inflammatory mediators of disease, but the clinical course of the disease is associated with levels of inflammatory mediators [25]. The study didn't find a significant link between HMGB1 levels in the blood and treatment response. This might be because treatment only affected psoriatic skin lesions and didn't have an effect on these mediators throughout the body [26]. The study also did not find a statistical association between HMGB1 serum levels and smoking, although the latter had a well-known role in psoriasis progression and severity due to the effect of smoking on the systemic inflammation process involved in psoriasis development [27], while HMGB1 locally acting in disease pathogenesis and serum level may not reflect the actual activity of HMGB1 [28]. The present results demonstrated high levels of HMGB1 in psoriasis individuals with metabolic syndrome (p=0.023). Metabolic diseases, including obesity and diabetes, are significantly associated with psoriasis via exact inflammatory mechanisms. In obese patients, adipose tissue secretes pro-inflammatory cytokines such as TNF-α and IL-6, which may increase HMGB1 levels, exacerbating psoriasis symptoms. Furthermore, lifestyle variables such as nutrition and physical activity might affect HMGB1 expression and the course of illness [29]. The current results demonstrated elevated mean levels of HMGB1 in CVD among psoriatic patients in comparison to those without CVD. These results are consistent with the study of Singh and Agrawal [30], who indicated that HMGB1 is integral to inflammatory processes that aggravate cardiovascular disease (CVD). HMGB1 is a pro-inflammatory molecule that engages with receptors such as RAGE (Receptor for Advanced Glycation End-products) to promote systemic inflammation, which can lead to atherosclerosis and cardiovascular problems [30]. In terms of obesity and DM, the average levels seen in obese (8.74±1.51) and DM (8.61±1.63) psoriatic patients compared to those who were not obese or diabetic are similar to what Wang *et al*. [31] found. They said that people who are overweight and have type 2 diabetes have higher plasma HMGB1 levels, which are linked to insulin resistance and inflammation. Additionally, this is consistent with the study conducted by Kamel *et al*. [32], who demonstrated that HMGB1 level was elevated in psoriatic individuals with metabolic syndrome compared to those without. The present studies demonstrated that levels of HMGB1 decreased in psoriatic arthritis among psoriasis individuals compared to non-PsA individuals, but there were non-significant differences. This result disagrees with another study, which found serum HMGB1 levels are markedly elevated in PsA patients [15]. However, in the current study, psoriasis patients who do not have psoriatic arthritis may have other psoriasis complications like metabolic syndrome and cardiovascular diseases, which may cause confounding results in HMGB1 concentration. Regarding severity, our study showed that the mean levels of HMGB1 were higher in patients with mild cases (10.85) than in moderate cases (7.48) and severe cases (6.48), and this result aligns with another study that found elevated levels of HMGB1 in psoriatic patients with no significant association with PASI that reflect severity [14]. Psoriasis is influenced by a mix of innate and adaptive immune responses, namely the IL-17 and TNF-α pathways. Although AMPs are higher in psoriatic lesions, their function seems to initiate and sustain inflammation rather than directly correlate with disease severity, so one can find that the level in the mild initial state is higher than in the severe state [28]. The level of HMGB1 did not reflect its activity and effect because Chen *et al*. [33] stated that HMGB1 undergoes structural changes when released, like phosphorylation and acetylation, and these changes relate to its biological effects on disease. The coexistent

comorbidities in patients can affect the results. Additionally, researchers assumed that the half-life of saliva and serum HMGB1 proteins is about 17 min, so the time the sample was taken was beyond this time, which may have affected the results [34].

Conclusions

Iraqi psoriatic patients had higher serum levels of HMGB1 than non-psoriatic individuals, but the difference wasn't significant enough to make it a reliable diagnostic marker for psoriasis. However, the increased levels of HMGB1 were significantly associated with metabolic syndrome and response to treatment in psoriasis patients, and these findings might shed light on the usefulness of HMGB1 use as a prognostic or therapeutic biomarker, particularly for patients who also have metabolic conditions.

Recommendations

Conducting multi-center studies is highly recommended to collect more Iraqi psoriasis patients with different psoriasis subtypes, such as pustular, inverse, and Guttate psoriasis. Also, longitudinal follow-up of this marker throughout the disease course and management to validate its role in psoriasis.

Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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