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Evaluation of Cathelicidin (LL-37) Serum Levels Among Iraqi Psoriatic Patients and Its Association with Disease Severity and Complications

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ABSTRACT

Background: Psoriasis is a chronic skin condition distinguished by inflammation and the rapid proliferation of skin cells, leading to scaly, red patches. **Methods:** A case-control study was executed on 110 individuals, the patient's group, which included 60 psoriatic patients with a mean age of (37.23 ± 8.26) years old, and 50 volunteers without psoriasis were control group, with a mean age of (35.32 ± 7.53) years old. Study was implemented at Merjan Teaching Hospital in Hilla City, Babylon Province. The data were collected from October 2024 to January 2025. Blood specimens were obtained from all research participants after acquiring verbal permission. ELISA measured the concentration of LL-37 in serum from (Bioassay Technology Laboratory Co/China). **Results:** the mean levels of LL-37 were significantly elevated in psoriasis individuals compared to that of control subjects (p=0.001). Also, the mean levels of LL-37 were significantly associated with psoriatic severity (p=0.026). In contrast, the mean levels of LL-37 were non-significantly associated with complications. **Conclusion:** Serum level of LL-37 was significantly elevated in psoriasis patients and significantly associated with the severity; therefore, it could be used as a predictor of psoriasis progression and severity.

Keywords: Psoriasis, LL-37, and Disease Severity.

Article Information

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INTRODUCTION

Psoriasis, a prevalent persistent, recurring, and inflammatory dermatological disease, impacts around 2-3% of the global community (1). **First,** The condition often manifests as chronic, symmetrical, erythematous, scaling papules and plaques (2). often seen on the elbows, knees, lower back, and scalp.(3) **Second,** Globally, 125 million individuals are affected with psoriasis, with its incidence significantly ranging from 2.5% to 3% (4). The incidence of psoriasis condition in Iraqi society is 2.3%.(5). **Third,** Psoriasis significantly impacts patients' self-esteem and body image, and its severity is directly correlated with a diminished quality of life (6).

Clinically, psoriasis is categorized into mild, moderate, and severe based on the extent and intensity of skin involvement.(7) Psoriasis is linked to many complications, such cardiovascular disorders, obesity, diabetes mellitus, and metabolic syndrome.(8) Fourth, The etiology of the illness remains debatable; nonetheless, biochemical, genetic, and environmental variables are essential for its beginning and progression of disease (9). Furthermore, innate and adaptive immunity contributes to the progression of psoriasis as the IL-23/IL-17 axis serves a significant function in connecting innate and adaptive immunity since both T cells and innate immune cells secrete IL17 which is the main inflammatory player in disease pathogenesis immune (10).



Antimicrobial peptides (AMPs) are essential innate immunity components and studies proved their role in psoriatic lesion development and local inflammation process progression as they modulate immunity via interactions with diverse immune cells .(11)

Cathelicidin (also known as LL-37) is one of these antimicrobial peptides that is secreted by keratinocytes. It may attach to self-DNA and stimulate plasmacytoid dendritic cells via Toll-like receptors (TLRs)(12). These receptors mainly TLR7 and TLR9 when triggered and stimulated by RNA and DNA complexes which are usually composed from nucleic acids in conjunction with antimicrobial peptides such as LL37 in cases of psoriasis) resulting in synthesis of many inflammatory cytokines such as IL-23, which is a pivotal cytokine in the stimulation of Th17 cells and the IL-17 pathway that are fundamental in the inflammatory processes of psoriasis.(13)

The role of Cathelicidin has been examined in psoriasis by the assessment of their levels primarily in skin lesions, and their involvement in the immunopathogenesis of the disease has been well established (14). Other researchers attempt to quantify it in serum as a systemic inflammatory biomarker for the condition. Nevertheless, research linking its levels to disease severity and other comorbidities remains limited, and when conducted, the findings have been inconsistent across diverse groups investigated (15)(16). More researches are needed to clarify the role of cathelicidin in the severity and the complications related to the disease, and such research will open the door on the use an AMPs as diagnostic and therapeutic targets for psoriasis (17). Hence, the present study aims to evaluate cathelicidin (LL-37) serum levels among Iraqi psoriatic patients and its association with disease severity and complications.

METHODS

A case-control study was executed 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 psoriatic vulgaris, with a mean age of $(37.23 \pm$ 8.26) years old, and the control group, which included 50 randomly selected volunteers without psoriasis, with a mean age (35.32 \pm 7.53) years old. Control individuals match with psoriasis patients in concern of age and sex. The Enzyme-Linked Immunosorbent (ELISA) conducted by Bioassay Technology Lab Co. in China was used to assess the blood concentrations of LL-37 in both groups. Disease severity is categorized into mild, moderate, and severe according to .(7)

Ethical Approval

The University of Kufa Faculty of Medicine's ethics committee gave its approval to this study before it even began. All research participants were apprised of the study's objective, and verbal permission was obtained before collecting blood samples to evaluate various study parameters. Ethical approval number (2899 in 11\9\2024).

Inclusion Criteria

- 1- The study included psoriasis individuals older than 18 years.
- 2- All The patients of the current study receive topical treatment to overcome the modifying effect of systemic treatment on inflammatory markers.

Exclusion Criteria

- Patients less than 18 years old.
- Pregnant women .
- Individuals with other skin and inflammatory diseases.
- The patient has taken Biologics therapy for the last three months.



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 categorical percentages for variables. Disparities among both of these 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 determined at p-values < 0.05.

RESULTS

The current study contains 60 individuals with psoriasis and 50 control subjects. The demographic characteristics of psoriasis individuals and control subjects are displayed in Table (4-1). The mean age of patients was 37.23 \pm 8.26, and that of control subjects was 35.32 \pm 7.53 years. There was no significant difference among patients and control subjects according to mean age and according to age group (p =0.467, 0.779, respectively). The patients' group included 38 (63.3%) males and 22 (36.7%) females, in contrast the control group included 33 (66%) males and 17 (34%) females, with no significant difference in the frequency distribution of patients and control subjects based on sex (p = 0.771).

Serum level of cathelicidin LL-37 in Psoriatic patients and control subjects.

The comparison of serum cathelicidin LL-37 concentration between psoriatic individuals and the control group was indicated in Table (1) and Figure (1). Mean concentrations of serum cathelicidin LL-37 were (2.89 ± 0.92 and 1.67 ± 0.73) in psoriatic patients and control subjects, respectively; the concentrations were

significantly higher in the patients in comparison to controls (p = 0.001).

The analysis of cathelicidin LL-37 levels based on certain criteria has been conducted, yielding findings that were demonstrated in Table (2). The current results demonstrate a non-significant disparity in cathelicidin (LL-37) levels between males and females, (2.77 ± 0.63) and 3.01 ± 0.91) respectively, (P = 0.534). Mean levels of serum LL-37 were (2.68 \pm 0.79, 2.99 \pm 0.75) in patients with less than 30 years and patients with higher than 30 years respectively; the mean levels were elevated in individuals with more than 30 years compared to other groups, but the difference was non-significant (P = 0.405). Also, the present results show a non-significant difference in LL-37 levels according to family history (P = 0.171), occupation (P = 0.667), duration of disease (P =0.750), smoking (P = 0.417) and Response to treatment (P = 0.761).

Figure (2) revealed that the mean levels of serum LL-37 were $(2.35 \pm 0.66, 2.37 \pm 0.71)$, and 3.35 ± 0.72 in individuals with mild, moderate, and severe conditions, respectively; the mean levels were elevated in individuals with severe psoriasis compared to other two categories, and the difference was significant (P = 0.026). Additionally, figure (3) shows a significant positive correlation between PASI & LL37, p= 0.05.

Mean serum levels of cathelicidin LL-37 levels according to complications.

The comparison of LL-37 levels according to complications has been demonstrated in Table (3). The results demonstrated non-significant disparities in LL-37 among individuals with and without metabolic syndrome, cardiovascular disease, Obesity, diabetes mellitus, and psoriatic arthritis (p= 0.33, p= 0.347, p= 0.091, p=0.083, p= 0.177), respectively.



Table (1): Serum cathelicidin LL-37 level in psoriatic patients and control subjects.

	Patients <i>n</i> = 60	Healthy control $n = 50$	P		
cathelicidin LL-37 level(ng/ml)					
Mean ± SE	2.89 ± 0.92	1.67 ± 0.73	p < 0.001		
Range	0.28 - 5.93	0.16 – 4.95	Ť		

n: number of cases; **SD**: standard deviation; †: independent samples t-test; HS: Highly significant at P = 0.001.

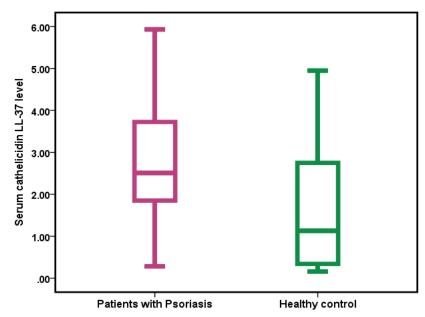


Figure (1): Mean Serum cathelicidin LL-37 of patients and controls.

Table (2): Mean serum levels of Cathelicidin(LL- levels according to some characteristics.

Characteristics		N	Mean ± SE	P
Age groups	< 30 years	26	2.68 ± 0.79	0.405
	≥ 30 years	34	2.99 ± 0.75	ľ
Sex	Male	38	2.77 ± 0.63	0.534
	Female	22	3.01 ± 0.91	†
Family history	Positive	22	2.52 ± 0.59	0.171

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Characteristics		N	Mean ± SE	P
	Negative	38	3.05 ± 0.78	†
Occupation	Housewife	15	2.94 ± 0.53	
	Employee	16	2.68 ± 0.65	0.667
	Student	13	2.64 ± 0.86	A
	Earner	13	2.93 ± 0.91	
	Retired	3	3.96 ± 1.01	
Duration	< 10 years	29	2.8 ± 0.67	0.750
	≥ 10 years	31	3 ± 0.71	† NS
Smoking	Smoking	34	2.73 ± 0.60	0.417
Smoking	Non-smoking	26	3.03 ± 0.68	†
Response to treatment	Poor	53	2.84 ± 0.73	0.761 †
	Good	7	3.01 ± 0.66	'

n: number of cases; **SD**: standard deviation; †: independent samples t-test; A: Anova test; NS: non-significant at P > 0.05.

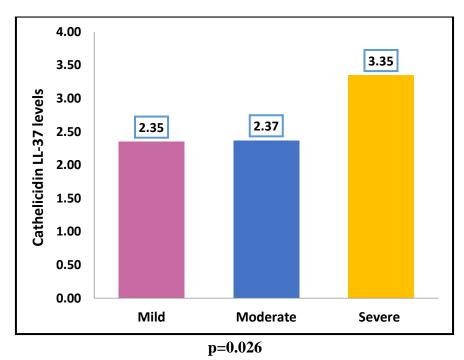


Figure (2): Frequency distribution of cathelicidin (LL-37) levels according to severity.

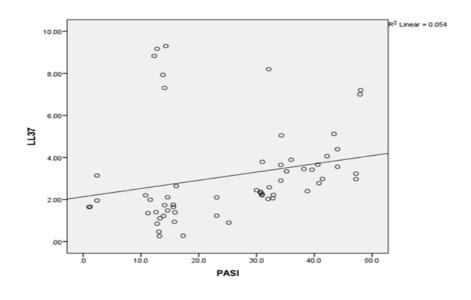


Figure (3): Pearson's correlation between the Mean serum level of cathelicidin (LL-37) and PASI.

Table (3): Mean serum levels of cathelicidin LL-37 levels according to complications.

Characteristics		N	Mean ± SE	P
Metabolic syndrome	Present	8	3.9 ± 0.83	0.33
	Absent	52	2.71 ± 0.57	'
Cardiovascular disease	Present	23	3.08 ± 0.62	0.347 †
	Absent	37	2.80 ± 0.53	Ť
Obesity	Obese	17	3.35 ± 0.61	0.091 †
	Non-obese	43	2.66 ± 0.84	
Diabetes mellitus	Present	15	3.41 ± 0.76	0.083 †
	Absent	45	2.67 ± 0.61	
Psoriatic Arthritis	Present	16	3.27 ± 0.83	0.177 *
	Absent	44	2.71 ± 0.57	†

n: number of cases; **SD**: standard deviation; †: independent samples t-test; A: Anova test; S: significant at P < 0.05.



DISCUSSION

The current study demonstrated a highly significant difference among cases and control subjects. The study corresponds with the study conducted by Al-Shibly & Al-Sultany (18), who demonstrated a significant difference in cathelicidin levels between psoriatic patients and control groups (P = 0.004). Also, Yuan et al. (19) reported that IgG autoantibodies targeting the LL-37 autoantigen have been detected in the sera of psoriasis individuals, correlating with the PASI score. It also indicates the development of illness in longitudinally obtained serum specimens from psoriasis persons.

The role of cathelicidin is acknowledged as an autoantigen by circulatory T cells. LL-37 stimulates dendritic cells through TLR7 and TLR9. Cathelicidin is associated with nucleic acids released from keratinocytes during injury, forming a complex that stimulates LL-37-specific dendritic cells. This action initiates the whole inflammatory cascade since stimulated dendritic cells create large quantities of IFN α , which may further stimulate conventional dendritic cells and other immune system cells in the dermis. LL-37 promotes the development of circulating CD3+ T cells, which secrete IL-17, and the ability for IL-17 production correlates with illness severity (20).

The mean serum level of cathelicidin is not statistically significant, regarding age, sex, family history, duration of disease, and smoking. However, Pavlov et al. (21), assumed that older patients may have elevated serum levels of LL-37, and he explained that increment by a vigorous inflammatory reaction in the elderly due to prolonged exposure environmental stimuli and increased inflammatory mediators.

Regarding sex, a study documented by Danielsen et al. (22) showed that females with psoriasis have an increased chance of developing metabolic syndrome compared to

males, which may impact the inflammatory indicators and consequently alter LL-37 expression. Also, Popa et al. (23) state that LL-37 is associated with inflammation in fat tissue and the onset of insulin resistance in obese females cathelicidin as may augment inflammation by stimulating pro-inflammatory genes and modulating the response that causes inflammation, and this in context with Lau et al. (24) observations who demonstrated that women elevated generally exhibit levels inflammatory indicators, including C-reactive protein (CRP), interleukin-6 (IL-6), adipokines.

The non-significant association of cathelicidin with demographic characteristics of patients may be clarified through the fact that cathelicidin has an intrinsic role in psoriasis development as it is released from damaged keratinocytes in response to_triggering external stimulants in genetically predisposed persons. This mechanism of disease is not influenced by age or sex but influenced by the interplay among genetic and environmental variables (25).

Additionally, researchers show that higher levels of LL-37 are associated with elevated levels of key inflammatory cytokines like IFN- γ , IL-17, and IL-22; this suggests that the inflammatory environment itself is the primary driver of LL-37 expression rather than demographic or historical influences (26).

The findings indicated that the mean concentration of LL-37 was not correlated with smoking. Smoking does not consistently influence LL37 levels across studies as this effect may be dependent upon additional factors, including genetic predisposition or disease severity. Consequently, although smoking is recognized as a risk factor for psoriasis, its specific impact on LL37 may be less significant or require further investigation for clarification (27).



Regarding severity: The study shows that the mean levels of LL-37 in individuals with severe psoriasis were significantly elevated (3.35 ± 0.72) than in mild and moderate cases (2.35 \pm 0.66, 2.37 ± 0.71 respectively, p= 0.026); this is in accord with the study of Lao et al.(26), who mentioned that increased level of the antimicrobial peptide LL-37 has been noted in individuals with psoriasis and a higher levels associated with greater illness severity. In addition, Lao et al. (26) found that LL-37 is recognized for its role in modulating immunological responses by interaction with self-DNA, resulting in the formation of complexes that stimulate plasmacytoid dendritic cells. This stimulation results in the synthesis of type I interferons, which subsequently enhance T-helper cell responses, namely the Th1, Th17, and Th22 pathways. These pathways are linked to the release of pro-inflammatory cytokines, including IFN-γ, IL-17, and IL-22, which motivate more inflammatory milieu in psoriasis.

Research indicates a significant correlation between blood levels of LL-37 and the above cytokines, indicating that elevated LL-37 levels may enhance inflammatory reactions, worsening disease severity. LL-37 functions not only to continuously stimulate innate immune cells but is also acknowledged as an autoantigen, with circulating T lymphocytes present in up to 75% of individuals with moderate-to-severe psoriasis (28).

The mean levels of LL-37 are increased in metabolic syndrome individuals, patients with cardiovascular disease, obesity, DM, and psoriatic arthritis, with non-significant differences. This finding corresponds with the results of Popa et al. (23), which showed that the LL-37 is associated with inflammation in fat tissue and the onset of insulin resistance in obesity.

Cathelicidin may amplify inflammation by pro-inflammatory triggering and genes modulating the response that causes inflammation. The causes of insulin resistance involve the triggering of intricate signaling pathways that provoke inflammation and diminish insulin signaling in adipocytes. Stimulating Toll-like receptors (TLRs) by cathelicidin induces the release of proinflammatory cytokines that impair insulin action in adipose cells, and this inflammatory pathway related to metabolic syndrome is likely to cause cardiovascular disease (23).

The results regarding cardiovascular complications are consistent with those Nakamura et al. (29), who displayed that LL-37 levels are correlated with a higher chance of developing cardiovascular disease. increased LDL absorption in macrophages via the LDL receptor (LDLR), scavenger receptor class B member 1 (SR-B1), and CD36. This interplay resulted in elevated cytosolic levels cholesterol in macrophages alterations in the expression of lipid metabolism genes indicative of enhanced cholesterol absorption (29).

Increased levels of LL37 have been noticed in individuals with psoriatic arthritis, owing to LL37 release from neutrophils infiltrating the affected joints. LL37 can undergo irreversible specifically changes, citrullination or carbamylation; subsequently, autoantibodies developed against citrullination carbamylation LL37 lead to immune deposition in joints that enhances arthritis (30). Cathelicidin has an immunomodulatory action through the activation of several different types of immune cells, and it links to self-DNA and acts as an autoantigen induce dendritic cells to release type I interferon and other pro-inflammatory cytokines that leads to the autoimmune inflammatory reaction like that seen in of PsA



The current study showed elevated LL37 levels in patients with specific complications but with the lack of a statistically significant relationship, and this could be due to confounding from other co-occurring complications because patients without the complication of interest may have had other complications that influenced LL37 levels and obscure the real effect of the specific complication. This may affect the results and make the results not statistically significant.

CONCLUSION

The serum concentrations of LL-37 are significantly higher among Iraqi psoriasis individuals, and the concentrations of LL-37 are significantly correlation with psoriasis severity. Additionally, the levels of LL-37 elevated in the complications among psoriasis patients, but the difference was non-significant.

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Ethical approval

The present study Which is conducted by authors (Rasool Moussa Bader) was approved by the local Department of Medical Microbiology, Faculty of Medicine, University of Kufa, Najaf, Iraq committee.

Statement of Permission and Conflict of Interests

The others declare that there is no Conflict of Interest.

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