Type of the Paper (Systematic Review)

Assessment of Serum Interleukins in Acne Vulgaris

Salwa M. M. Abdel-Hameed[1]*, Nesreen M. M. Abo-Raia[1], Olfat G. Shakir[2], Shereen A. A. Ahmed[1]

[1] Dermatology Department, National Liver Institute, Menoufia University, Menoufia, 39111 Egypt.

[2] Advanced GI Endoscopy Unit, Ahmed Maher Teaching Hospital, Cairo, 11617, Egypt.

[3] Biochemistry Department, Cairo University, Giza, 12613 Egypt.

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Abstract:

Introduction: Acne vulgaris (AV) is a chronic inflammatory skin disorder characterized by an interplay of hyperkeratinization, sebaceous gland activity, microbial colonization, and immune dysregulation. Among the many mediators implicated, interleukin (IL)17 and IL-6 have emerged as key players, particularly in driving the chronic inflammation characteristic of more severe acne.

Aim of the study: To determine the relationship among levels of IL-17 and IL-6 in the serum of individuals with AV.

Methods: We searched Cochrane, Web of Science, PubMed, and SCOPUS for relevant articles. We utilized a strategy for our search by combining these keywords: (‘’ IL-6’’ OR ‘’ interleukin-6’’) AND (‘’ interleukin-17’’ OR ‘’ IL-17’’) AND (‘’ Acne ‘’ OR ‘’ Vulgaris ‘’ OR ‘’ dermatological diseases ‘’). Quality evaluation of the involved studies was assessed regarding to Cochrane’s risk of bias tool.

Results: We found that patients showed significantly higher serum IL-17 and 6 levels than healthy individuals ($P < 0.001$). Additionally, significantly higher levels of IL-17 and 6 in the serum were detected in individuals with severe AV lesions than those with moderate and mild lesions ($P < 0.001$).

Conclusions: IL-17 and IL-6 have a central role in the pathogenesis of AV by driving neutrophil recruitment, amplifying inflammation, and contributing to tissue damage and scarring. Elevated levels of IL-17 and IL-6, systemically in serum, correlate with disease severity and resistance to standard treatments.

*Correspondence: Salwa M. M. Abdel-Hameed, sm1317@fayoum.edu.eg, Tel: (002) 01020806307.

1. Introduction

AV is a prevalent skin condition that affects millions globally, primarily during adolescence, although it can persist into adulthood. Multiple non-inflammatory lesions are the disease's initial manifestation, such as comedones, and inflammatory lesions, involving nodules, pustules, and papules, which can lead to scarring and psychological distress in affected individuals [1]. The pathogenesis of AV is multifactorial, involving a complex interplay of factors such as hormonal changes, increased sebum production, follicular hyperkeratinization, and the colonization of the hair follicles by Cutibacterium acnes (formerly known as Propionibacterium acnes). Among these factors, inflammation has emerged as a critical component, with recent research indicating that acne is, fundamentally, an inflammatory disease even at its earliest stages [2].

Cytokines, small proteins that play a crucial role in cell signaling during immune responses, are key mediators in the inflammatory process. Two cytokines, IL-17 and IL-6, have garnered attention in the context of AV due to their potential role in the disease's pathophysiology. IL-6 is a pro-inflammatory cytokine involved in both acute and chronic inflammatory processes. It is produced by various cells, including T-cells, macrophages, and keratinocytes, and has been shown to play a role in systemic inflammation [3]. IL-6 stimulates the production of other inflammatory mediators, such as C-reactive protein (CRP), and acts on various immune cells to perpetuate the inflammatory response. Elevated levels of IL-6 have been detected in several inflammatory skin conditions, and emerging evidence suggests it may also be implicated in AV [4].

IL-17, on the other hand, is produced predominantly by T helper 17 (Th17) cells, a subset of T-cells involved in autoimmune and inflammatory responses. IL-17 is known for its role in recruiting neutrophils to sites of inflammation and activating other pro-inflammatory cytokines, which contribute to the amplification of inflammatory processes.

Th17 cells and IL-17 have been associated with chronic inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, and psoriasis, highlighting IL-17's role in sustaining inflammation. In AV, the presence of IL-17 may exacerbate inflammation by activating keratinocytes and promoting the infiltration of neutrophils and other immune cells into acne lesions [4, 5].

Research has shown that individuals with AV may exhibit raised levels of IL-17 and IL-6 in the serum, which correlate with the severity of the disease. These results suggest that ILs 17 and 6 may serve as biomarkers for the inflammatory activity in acne and underscore the potential role of these cytokines in acne pathogenesis. By contributing to both the initiation and maintenance of inflammation in acne, IL-17 and IL-6 may facilitate the formation and persistence of inflammatory lesions, thereby influencing the clinical course of the disease [4, 6].

The study of IL-6 and IL-17 in AV offers valuable insights into the inflammatory mechanisms underlying this condition. This knowledge not only enhances our understanding of acne pathophysiology but also opens potential avenues for therapeutic intervention. By targeting these cytokines with specific inhibitors or anti-inflammatory agents, it may be possible to reduce the inflammatory burden in acne patients, providing a more focused approach to treatment that goes beyond traditional therapies aimed at reducing sebum production or bacterial load. Further research into the levels of IL-17 and IL-6 in the serum of individuals with AV could thus pave the way for novel therapeutic strategies, particularly for individuals with moderate to severe inflammatory acne that are resistant to conventional treatments (6). This study aims to determine the relationship among levels of IL-17 and IL-6 in the serum of individuals with AV.

2. Methods

2.1. *Information Sources and Search Strategy*

We performed this study based on the PRISMA guidelines and recommendations [7]. We utilized a strategy

for our search by combining these keywords: (‘’ interleukin-6’’ OR ‘’ IL-6’’) AND (‘’ interleukin-17’’ OR ‘’ IL-17’’) AND (‘’ Acne ‘’ OR ‘’ Vulgaris ‘’ OR ‘’ dermatological diseases ‘’). Regarding the sources of data, we utilized the Web of Science, Cochrane Library, PubMed, and SCOPUS databases in the search process. We searched these databases till November 2024.

2.2. *Study selection*

We started by screening the titles and abstracts. We then carried out a full-text screening. Finally, we chose the qualifying articles by the following eligibility requirements: Case cohort: Adult individuals suffering from AV, Control cohort: Healthy individuals without skin diseases, Intervention: Assessing the levels of IL-6 and IL-17, and Outcome: levels of serum IL-17 in the controls and patients.

2.3. *Subjects*

Inclusion criteria

We included papers that met our eligibility criteria, which were recent studies above 2010, studies that included both males and females, studies that evaluated the levels of IL-6 and IL-17, double-arm studies that had case and control cohorts, and articles in English. We chose observational studies and blind or non-blind and non-randomized or randomized controlled clinical trials (RCTs).

Exclusion criteria

We excluded reviews, surveys, abstracts, and meta-analyses. Also, we excluded single-arm studies that assessed only one group and studies in languages other than English.

2.4. *Quality evaluation*

Since we involved five observational studies, we used the Cochrane risk of bias (ROB) assessment that evaluates 14 categories in each clinical study [8]. Each study got a score from 1 to 14, and the overall average score was calculated.

2.5. *Data extraction*

Two different categories of data were taken from the included papers. The first type includes the demographic information about the patients involved and the data of baseline data for our results. The second type was data on quality assessment. Microsoft Excel was used to carry out the data collection process [9].

3. Results

3.1. *Summarization of the involved studies*

The results of our search are demonstrated in the PRISMA flow chart (Figure 1). In this systematic review, we involved six studies (10-15) that met the inclusion criteria of our systematic review. Our study involved 770 individuals divided into two cohorts: the case cohort, which involved 419 patients and the control cohort, which involved 351 healthy individuals. The average age of the included individuals in the case cohort was 22.8 years, while that of the control cohort was 23.5 years. **Table 1** declares the baseline features of the involved individuals and studies.

Table 1: The baseline features of the involved individuals and studies.

Study ID	**Country**	**Study design**	**Sample size**		**Age, years (mean)**		**Male (N)**		**Female (N)**	
			Case	Control	Case	Control	Case	Control	Case	Control
Abd-Elmaged 2019	Egypt	Cross-sectional	135	150	21±2.8	23.1±4.6	54	78	81	72
Ebrahim 2019	Egypt	Case-control	80	80	20.2±4.4	22.1±4.1	34	42	46	38
Singh 2021	India	Cross-sectional	50	30	22.4±3.1	24±4.2	39	21	11	9
Singh 2023	India	Cross-sectional	60	30	22.4±5.3	21.9±3.8	21	10	39	20
Stańkowska 2020	Poland	Case-control	47	41	23.1±3.7	23.6±2.3	10	20	37	21
Triatmakusuma 2024	Indonesia	Cross-sectional	47	20	26.4±7.8	25.3± 9.3	12	5	35	15

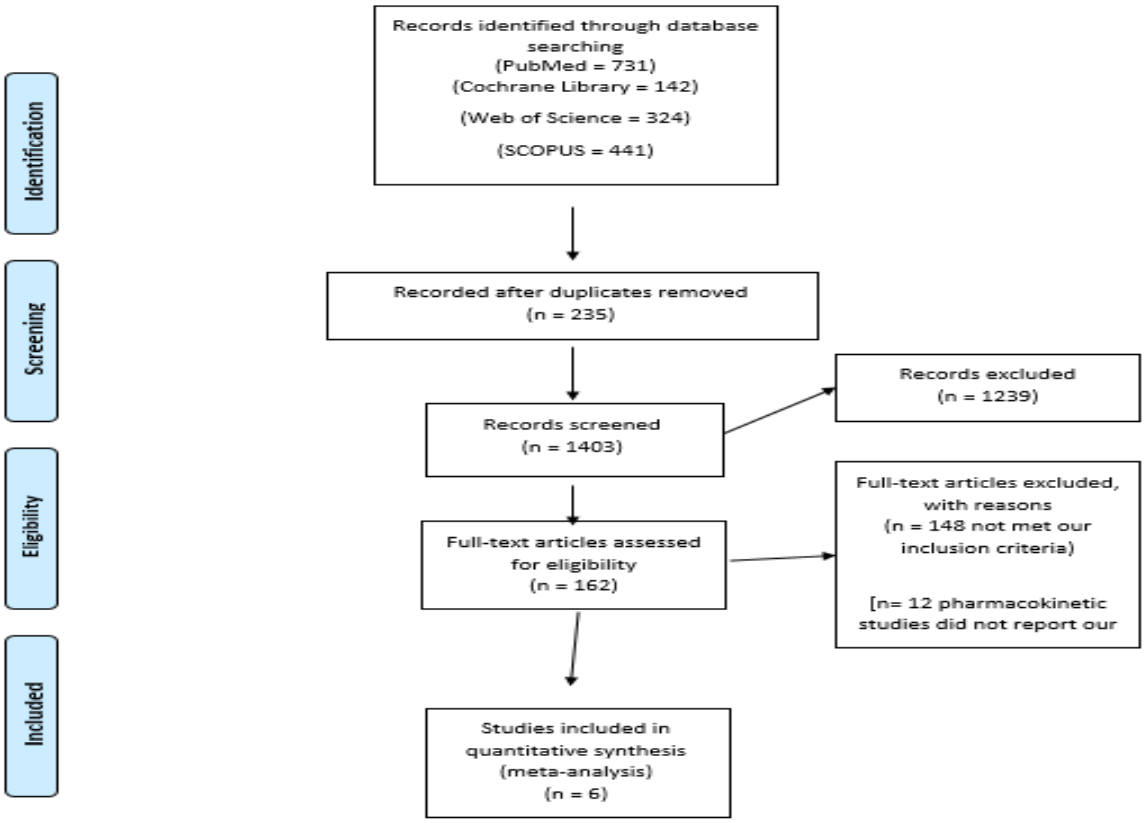

Figure 1: Literature search's PRISMA flow diagram.

3.2. *Results of quality assessment*

Since we included six observational studies [10-15], we assessed their quality using Cochrane's tool. Cochrane's tool indicated that the observational studies' mean score was 10.3 out of 14. The quality evaluation of the observational studies is shown in detail in **Table 2**.

Table 2: The quality evaluation of the involved studies.

	Abd-Elmaged 2019	Ebrahim 2019	Singh 2021	Singh 2023	Stańkowska 2020	Triatmakusuma 2024
1. Was this paper's goal or research question made clear??	1	1	1	1	1	1
2. Was the target population for the study well-defined and specified?	1	1	1	1	1	1
3. Was at least 50% of the eligible individuals participating?	1	1	1	0	1	1

4. Did all the participants come from the same or comparable populations, and did they all participate over the same period?	0	1	1	1	1	1
5. Was there a power description, an explanation for sample size, or estimates of effect and variance?	0	0	0	0	0	0
6. Were the exposure(s) wanted to be measured before the outcome(s) were determined for the analysis in this paper?	1	1	1	1	1	1
7. Was the duration such that, if a relationship between outcome and exposure existed, one could fairly anticipate seeing it?	1	1	1	1	1	1
8. Was the relationship between different exposure levels and outcomes for exposures that can change in quantity or degree (such as exposure categories or exposure measured as a continuous variable) examined in the study?	1	1	1	1	1	1
9. Were the independent variables, or exposure measurements, well specified, valid, trustworthy, and applied uniformly to each study participant?	1	1	1	1	1	1
10. Was there a repeated evaluation of the exposure(s) throughout time?	0	0	0	0	0	0
11. Were the dependent variables, or outcome measurements, properly defined, dependable, valid, and applied similarly to every study participant?	1	1	1	1	1	1
12. Were the people evaluating the results blinded to the participants' exposure status?	*	*	*	*	*	*
13. Was the follow-up loss 20% or less of the baseline?	1	1	1	1	1	1
14. Has the impact of important potential confounding variables on the link between outcome(s) and exposure(s) been quantified and statistically adjusted?	1	1	0	1	0	0
Total score (out of 14)	10/14	11/14	10/14	10/14	10/14	10/14

Key: 0 = No, 1 = Yes, N/A = Not applicable, * = Not reported

Table 3: The changes in IL-17 and IL-6 levels in AV.

Author	Interleukin	Results
Abd-Elmaged 2019 [10]	IL-17	Using ELISA tests, the mean levels of IL-17 in the serum (pg/mL) were 42.2±8.1 and 544.2±477.4 for the controls and patients, respectively. The case cohort had significantly higher levels. Levels of IL-17 in the serum significantly increased as the severity of acne increased.
Ebrahim 2019 [11]	IL-17	Serum IL-17 levels were substantially greater in the patients than in the control cohort ($p < 0.001$). Participants with severe AV lesions had substantially higher levels of IL-17 in the serum than those with moderate and mild lesions ($p <0.001$).
Singh 2021 [12]	IL-17	Acne individuals' mean serum IL-17 levels were 8.2±5.3 pg/mL, substantially higher ($p <0.001$) than those of controls (2.5±2.1 pg/mL). Acne severity was shown to be significantly correlated with elevated IL-17 levels ($p <0.001$).
Singh 2023 [13]	IL-6 and IL-17	Levels of IL-17 and IL-6 in the serum were 0.193±0.082 and 0.152±0.0174 pg/ml in the case cohort, respectively, and 0.131±0.0033 and 0.132±0.0095 pg/ml in the control cohort, respectively. The IL-17 level variation between controls and patients was considerable, but the IL-6 level difference was not noticeable. The degree of illness was positively correlated with both IL-17 and IL-6 levels in a highly significant way.
Stańkowska 2020 [14]	IL-6	The difference between the case and control cohorts' serum IL-6 concentrations is statistically substantial ($p = 0.0319$). AV patients had elevated IL-6 levels. While the range in healthy individuals is 1.00 to 14.24 pg/ml, the amount in the patients is from 1.39 to 67.41 pg/ml. There was a positive correlation ($p < 0.0001$) between the severity of lesions on the skin in AV and the level of IL-6.
Triatmakusuma 2024 [15]	IL-6	Those with AV had mean serum IL-6 levels that were 110.2±88.3 pg/ml greater than those without acne, which had mean values of 26.7±23.7 pg/ml. Levels of IL-6 in the serum and the severity of AV are strongly positively correlated, with a significant positive correlation.

4. Discussion

IL-6, a multifunctional cytokine, plays a central role in initiating immune responses and promoting Th17 cell differentiation, which is the primary synthesis of IL-17. IL-17, in turn, acts as a potent pro-inflammatory cytokine that amplifies local and systemic inflammation. These cytokines, individually and in synergy, drive the recruitment of immune cells, sustain chronic inflammation, and contribute to tissue damage observed in severe acne cases [16]. This interplay between IL-6 and IL-17 not only exacerbates the severity of AV but also

provides a deeper understanding of its pathophysiology. Exploring their serum levels offers valuable insights into their systemic involvement in acne and potential utility as biomarkers or therapeutic targets. This discussion delves into the relation between IL-17 and IL-6 in AV, highlighting their roles in disease progression and clinical implications [17].

In our systematic review, our results revealed that patients showed significantly higher serum IL-17 and IL-6 levels than healthy individuals ($p < 0.001$). Additionally, significantly higher levels of IL-17 and IL-6 in the serum were detected in individuals with severe AV lesions than those with moderate and mild lesions ($p < 0.001$).

IL-17 induces the synthesis of chemokines such as CXCL1, CXCL2, and IL-8 (CXCL8), which attract neutrophils to the site of infection or inflammation. Neutrophils secrete reactive oxygen species (ROS) and neutrophil extracellular traps (NETs), contributing to tissue damage and pustule formation. IL-17 amplifies the local inflammatory response by stimulating keratinocytes, sebocytes, and fibroblasts to produce other pro-inflammatory cytokines like IL-6, TNF-α, and IL-1β. This creates a feedback loop that perpetuates inflammation in acne lesions [18].

Although a small number of recent Egyptian studies have demonstrated elevated intralesional and serum IL-17 levels, some earlier publications have indicated elevated tissue IL-17 levels in acne patients. Elevated IL-17 secretion at the illness site is probably the cause of elevated serum IL-17 levels. This cytokine's significance in the pathophysiology of acne is highlighted by the elevated serum levels that arise from a condition that is restricted to a tiny area of skin. Additionally, Murlistyarini et al. observed a noteworthy increase in IL-17 levels as acne severity increased [19].

IL-6 directly affects sebaceous gland activity, promoting sebum production and secretion. Sebocytes, the primary cells of sebaceous glands, express IL-6 receptors and are sensitive to inflammatory mediators. Increased sebum production contributes to the lipid-rich microenvironment necessary for C. acnes proliferation, perpetuating inflammation. Hyperkeratinization of follicular epithelium is a hallmark of AV

[20]. IL-6 stimulates keratinocyte proliferation and inhibits apoptosis, leading to the accumulation of keratinocytes in the pilosebaceous unit. This process promotes comedogenesis, the initial lesion in acne. Elevated levels of IL-6 in the serum of patients with moderate to severe acne indicate a systemic inflammatory component. This systemic involvement may explain the association between severe acne and comorbid conditions like insulin resistance and metabolic syndrome, where IL-6 is also implicated [21].

Several studies have demonstrated a connection between IL-6 levels and the severity of acne. They found that IL-6 levels are substantially elevated in the skin of acne lesions compared to non-lesional skin, with higher concentrations in nodulocystic and inflammatory acne. Also, they reported that serum IL-6 levels are elevated in individuals with moderate to severe acne, suggesting a systemic inflammatory response that parallels local skin inflammation. Additionally, Elevated IL-6 may drive the transition from non-inflammatory lesions (comedones) to inflammatory lesions (papules, pustules, and nodules), marking disease progression [22].

5. Conclusion

IL-17 and IL-6 have a central role in the pathogenesis of AV by driving neutrophil recruitment, amplifying inflammation, and contributing to tissue damage and scarring. Elevated IL-17 and IL-6 levels, systemically in serum, correlate with disease severity and resistance to standard treatments. Future research into the role of IL-17 and IL-6 in acne and its broader systemic implications will enhance our ability to manage this chronic and often debilitating condition.

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