

Role of InterLeukins in acne: a systematic review and meta-analysis

Gehad M. Elhanboli

M.B.B.CH, Dermatology, STDs and Andrology department, Faculty of Medicine – Fayoum University

Abstract

- **Background**

Multiple factors have been attributed to acne vulgaris predisposition and individual variations in the severity of skin symptoms, and interleukins stood out as one of the major factors.

- **Methods**

I performed a systematic review on the interleukins that have been investigated for association with acne presentation and severity. This included a subset data of 497 acne cases and 295 controls .

- **Results**

Systematic review of 8 articles found 10 interleukins implicated in acne. The studied interleukins were IL6, 8, 10, 12, 17, 19, 31, 36, 37 and 38. This meta-analysis showed that all of these interleukins increase their serum level significantly in acne cases compared with control group, except IL-8, which did not show significant difference in its serum level between case and control groups. Majority of them, their serum level increase significantly with the severity of the disease.

- **Conclusion**

This systematic review and meta-analysis suggest that interleukins influencing inflammatory responses, have potential risk variants for acne presentation and severity across populations. Understanding the

susceptibility factors and biological pathways involved in the pathogenesis of acne will help us to gain insights into developing effective acne treatments.

- **Keywords**

Acne, Interleukins.

Introduction:

Acne vulgaris (acne) is a highly prevalent, chronic inflammatory skin disease affecting the pilosebaceous unit, mainly at the face, neck, upper trunk and back (1). The severity of acne is characterized by the number of non-inflammatory closed and open comedones, inflammatory pustules and papules, as well as residual pathology like nodules and cysts (1,2). Chronic acne inflammatory symptoms like scars, erythema and hyperpigmentation, lead to psycho-social consequences such as depression, anxiety (3) and unemployment (4).

The etiology of acne is a complex interplay between androgen-induced sebum production, follicular keratinization, inflammation, and colonization of pilosebaceous follicles by *Cutibacterium acnes* (formerly *Propionibacterium acnes*) (1). Acne is a multifactorial disease, and we have recently reviewed that the epidemiological risk factors for acne and acne severity include demographics, genetics/hormonal, dietary habits and lifestyle factors (5).

Since the discovery of IL-1 in 1977, approximately 360,000 published scientific articles have referred to interleukins. Secreted proteins that bind to their specific receptors and play a role in intercellular communication among leukocytes are named interleukins (6).

IL-6 is a member of the IL-6-type family of cytokines (7). It is a multifunctional pleiotropic cytokine involved in regulation of immune responses, acute-

phase responses, hematopoiesis, and inflammation (8).

IL-8 was identified as a neutrophil-specific chemotactic factor and later classified as a member of the CXC chemokine family (9). The receptors for IL-8 are CXCR1 (IL-8RA) and CXCR2 (IL-8RB) (10).

The major effector functions of IL-8 are activation and recruitment of neutrophils to the site of infection or injury. In addition to neutrophils, IL-8 also attracts NK cells, T cells, basophils, and GM-CSF- or IL-3-primed eosinophils (11).

IL-10 is an anti-inflammatory interleukin produced mainly by monocytes, T cells, B cells, a small fraction of NK cells, macrophages, and DCs (12).

Mast cells can also produce IL-10, which limits the rate of leukocyte infiltration, inflammation, and skin disorders. IL-10 directly affects APC functions by down regulating the expression of MHC class II and costimulatory molecules on the surfaces of macrophages and monocytes. IL-10 inhibits the expression of many proinflammatory cytokines, chemokines, and chemokine receptors (13).

IL-12 is produced by activated monocytes, macrophages, neutrophils, microglia, and DCs (14). Bioactive IL-12 mediates the development and maintenance of T_H1 cells by inducing IFN- γ production by T_H1 and NK cells. In addition, it plays an important role for the induction of ILC1s (15).

IL-12 indirectly activates the antimicrobial, antiparasitic, and antitumor activity of macrophages and promotes cytolytic activity of NK cells and lymphokine-activated killer cells (16).

IL-17A, also called IL-17 in some studies, is the founding member of this

structurally distinct cytokine family. It binds as a homodimer or a heterodimer with IL-17F to its receptor, IL-17RA (17). IL-17A is expressed by activated CD4⁺ T_H17 cells (18), but its expression has also been detected in CD8⁺ T cells, $\gamma\delta$ T cells, NK cells, and neutrophils (17).

Consistent with the broad expression pattern of its receptor, IL-17A acts on a variety of cells, which respond by upregulating expression of proinflammatory cytokines, chemokines, and metalloproteases. By inducing cells to produce chemokines, IL-17A attracts neutrophils to mediate defenses against different pathogens. IL-17A and T_H17 cells are involved in several inflammatory disorders (19).

IL-19 is expressed by LPS-stimulated monocytes, and low levels have been observed in B cells (20).

Mouse IL-19 stimulates production of IL-6 and TNF- α and induces apoptosis and production of reactive oxygen species in monocytes, indicating a role in proinflammatory responses. IL-19 might promote T_H2 cell responses because it induces IL-4, IL-5, IL-10, and IL-13 expression by activated T cells (21).

IL-31 is expressed by activated CD4⁺ T cells (mostly by T_H2 cells) and at lower levels by CD8⁺ T cells. IL-31 signals through a heterodimeric receptor complex that consists of the IL-31RA and oncostatin M receptor β ; this receptor is expressed mainly by keratinocytes but also by epithelial cells, dorsal root ganglia, eosinophils, basophils, and monocytes. IL-31 is induced by IL-4 and promotes T_H2-driven inflammation (22).

IL-36 is another proinflammatory family member of IL-1 and a common mediator

of innate and adaptive immune responses. It is inhibited by IL-36Ra (23) and uses mitogen-activated protein kinase and nuclear factor κ B pathways, exerting proinflammatory effect *in vivo* and *in vitro*. IL-38 binds to IL-36 receptor, as does IL-36Ra, and has similar biological effects on immune cells. Both IL-38 and IL-36Ra have anti-inflammatory biological effects (24).

IL-37 was originally defined as IL-1 family member 7, which is found in monocytes, tonsil plasma cells, and breast carcinoma cells (25).

Recently, IL-1R8 was found to act as the coreceptor for IL-37–IL-18R α , and this interaction was required for the anti-inflammatory function of IL-37 (26).

IL-38 is also a member of the IL-1 cytokine family and shares some characteristics of IL-1Ra, binding the same IL-1 receptor type I. IL-38 is highly homologous to IL-36Ra and IL-1Ra, suggesting that it might act as an IL-1 family antagonist. IL-38 expression was reported in skin, tonsil, thymus, spleen, fetal liver, and salivary glands (27).

IL-38 plays a role in the pathogenesis of inflammatory diseases, exerting a protective effect in some autoimmune diseases. The effects of IL-38 might resemble those of IL-36Ra because it binds to the IL-36 receptor and inhibits its effects, particularly the T_H17 response (28).

Methods:

• Literature search

The articles reviewed were retrieved from searches conducted on the Web of Science database on June 2021. In the first search, the search criteria used were:

document type ‘article’, search terms ‘acne’ in the topic and ‘pathogenesis’ in the title. Additional searches using the following criteria—document type ‘article’ and either the search terms ‘acne’ and ‘predisposition’ in the topic or search terms ‘acne risk’ and ‘interleukins’ in the topic—were also conducted. The searches aimed to garner articles about interleukins associated with acne presentation (presence/absence of acne vulgaris, severe acne, or teenage acne) and acne severity (mild, moderate, severe grades), thus more general search terms were chosen.

- **Criteria for meta-analysis**

Studies were included in the meta-analysis if they satisfied the following inclusion criteria: 1. Interleukins that were involved in case–control studies that evaluated acne presentation and/or acne severity; 2. No restriction regarding country, patient race or occupation; 3. Studies of acne targeting age group from 15-30 years; 4. Studies that have provided an estimation of serum level of different types of interleukins in acne cases and healthy controls and in different acne stages. Of 34 search results found, a total of 9 articles were chosen based on selection criteria.

Results

A total of 8 articles; including 464 acne cases and 264 controls, were chosen from 34 results in searching the role of interleukins in pathogenesis of acne by estimating their serum level. All of studies found a significant association with acne alone or both acne and acne severity, but some studies found insignificant associations with acne severity alone.

The first article which estimate the serum level of IL-6 and IL-8 included 47 acne

patients and 41 healthy control individuals showed that the serum level of interleukin 6 of acne vulgaris patients was higher than in the control group. A statistically significant correlation was demonstrated between the interleukin-6 level and severity of skin lesions in the course of the disease. Serum levels of interleukin-8 of volunteers from both groups did not show a statistically significant difference (29).

The second one estimated the serum level of IL-10, included 33 acne patients and 31 control found that there was an association between serum levels of IL-10 with the severity of acne vulgaris (30).

The 3rd article estimated serum and tissue level of IL-31, included 40 patients and 40 control persons result in the mean tissue and serum levels of IL-31 were significantly higher in patients than in controls ($P < 0.001$). The tissue level of IL-31 was significantly higher in patients with severe AV in comparison with its levels in moderate AV ($P = 0.001$) (31).

The 4th article was about estimating serum level of IL-19, including 120 subjects divided into 4 groups; 30 patients with severe acne, 30 patients with moderate acne, 30 patients with mild acne and 30 healthy control individuals. Its results showed significant difference in serum IL-19 levels between acne patients and controls, being higher in the former group (P value is < 0.001). Moreover, the rise in serum IL-19 levels was significantly proportional to the increased acne severity (P value < 0.001) (32).

The 5th article evaluating also serum level of IL-19; including 36 patients and 12 controls, resulted in serum Interleukin 19 level is highly significant increased in

patients with acne compared to controls. Serum IL-19 level was statistically significant with age of patients, disease duration and site of lesion (33).

The 6th article estimating serum level of IL-36 and IL-38; including 70 acne patients with different degrees and 30 healthy controls. The study relieved that IL36 and IL38 mRNA level was fundamentally higher in Correlation to seriousness of skin inflammation (34).

The 7th article was about serum IL-12, IL-17 and IL-37 in acne patients; included 68 acne patients divided into 4 groups; 38 patients with mild acne, 24 patients with moderate acne, 5 patients with severe acne and only one patient with very severe acne. Its results showed that IL-17 is associated with severity of acne vulgaris, while no-association was found between the severity of the disease and IL-12 or LL-37 (35).

The last article included in my study was evaluating serum level of IL-17 in acne patients; was included 80 patients and 80 controls. This study showed that serum IL-17 level was significantly higher in acne vulgaris patients than control group ($P < 0.001$). Moreover, it was increasing significantly with the increase in disease severity and in patients with scarring lesions ($P < 0.001$ each) (36).

Discussion

A total of 8 articles; including 464 acne cases and 264 controls, were chosen from 34 results in searching the role of interleukins in pathogenesis of acne by

estimating their serum level. All of studies found a significant association with acne alone or both acne and acne severity, but some studies found insignificant associations with acne severity alone.

Meta-analysis of this study revealed that:

- Significant increase of serum level of IL-6, IL-10, IL-12, IL-17, IL-19, IL-31, IL-36, IL-37 and IL-38 in acne cases group than healthy control group.
- Significant increase in serum level of IL-6, IL-10, IL-17, IL-19, IL-31, IL-36 and IL-38 in patients with severe acne in comparison with moderate and mild degrees of acne.
- Significant increase of serum level of IL-19 with increase of patient age and with chronicity of the disease and site of lesion.

Conclusion

In conclusion, this review summarizes the literature on interleukins implicated in the risk of acne presentation and severity and possible mechanisms by which these interleukins may affect acne pathogenesis. Notably, a large majority of the interleukins identified are suggested to have roles in the function and activity of sebaceous glands or immune and inflammatory responses—in line with the literature that describes acne as a chronic inflammatory disease of the pilosebaceous unit. Understanding the interleukin actions and biological pathways involved in the pathogenesis of acne will help us to gain insights into developing effective acne treatments.

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