The Egyptian Journal of Hospital Medicine (April 2023) Vol. 91, Page 5081- 5087

# Assessment of Serum Interleukin-36γ Level in Patients with Acne Vulgaris and Post -Acne Scars

**Radwa El-Sayed Mahmoud[1], Kholoud Tarek EL-Emam[2], Hagar Ahmed Kamal Eldin[3], Hesham Ahmed Nada[1]**

[1] Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

[2] Department of Dermatology, Ministry of Health and Population, Nasr Hospital, Portsaid, Egypt

[3] Department of Clinical Pathology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

*** Correspondence:** Radwa El-Sayed Mahmoud Marie, **E-mail:** rivercruise84@gmail.com, http://orcid.org/0000-0002-8144-0926, Address: Po box 112 Ismailia 41511, Mobile**:** 00201147776399

## ABSTRACT

**Background:**

Acne vulgaris (AV) is a typical inflammation-related condition of the pilosebaceous apparatus that has extremely detrimental impact on one's quality of life & mental health. Interleukin (IL)-36 cytokines (α, β, γ) promote the activation of T-helper 1 and T-helper-17 cells, which then secrete tumor necrosis factor-, interferon-γ, IL-17, IL-22 in addition to other inflammatory mediators. These cytokines stimulate epithelial cells for producing numerous growth factors and inflammatory mediators, thereby exacerbating the inflammation. IL-36 cytokines have been associated with various conditions that are inflammation-related. **Aim:** Its objective was to evaluate IL-36γ serum levels among AV participants and healthy controls, and to look into any possible connection among IL-36 & the severity of AV.

**Patients and methods:** 45 participants were enrolled in this study after they presented with AV, along with 45 controls who did not have AV. Enzyme-linked immunosorbent assay (ELISA) was utilized to evaluate serum levels of IL-36γ in AV patients and controls. **Results:** The study revealed that cases with AV had significantly higher IL-36γ serum levels than controls ($p < 0.001$). IL-36γ serum levels correlated positively with AV severity (P=0.002). Cases with severe acne had higher levels than those with mild & moderate acne (p=0.005). Moreover, IL-36γ serum levels were significantly higher among cases with positive family history of AV (p=0.019).

**Conclusion:** Individuals with AV had significantly greater serum IL-36γ levels in contrast to controls and they were related to AV severity and post acne scarring**.** IL-36γ may therefore show a significant function in AV inflammatory reactions and the induction of post acne scarring.

**Keyword:** Acne vulgaris, Interleukin-36γ, Propionibacterium acnes, Pilosebaceous unit, Global acne grading system.

## INTRODUCTION

AV is a widespread inflammatory skin condition of the pilosebaceous apparatus impacting 47% to 90% of adolescents and has a substantial -ve influence on quality of life and mental health. Propionibacterium acnes (P. acnes) colonization, enlarged sebum production & pilosebaceous duct hypercornification are the primary etiological reasons causing acne **(1)**.

Colonization of P. acnes results in activation of inflammatory mediators. Pathogen-associated molecular patterns (PAMPS) released by P. acnes induce activation of Toll-like receptors (TLR) present on sebocytes, keratinocytes, and immune cells especially TLR2, TLR1 and TLR6. TLR activation triggers the release of proinflammatory cytokines mainly interleukin (IL)-1, IL-8, IL-12, interferon-ɣ (INF-ɣ) & tumor necrosis factor-α (TNF-α). These cytokines cause chemoattraction of various immune cells such as neutrophils, natural killer cells, macrophages & dendritic cells **(2)**. Moreover, human sebocytes release antimicrobial peptides as a result of P. acne. Cathelicidin and human β-definsin-2 were found in cultured human sebocytes & their expression levels were induced when acne-causing P. acnes was present causing the development of perifollicular abscesses, follicular rupture and the infra-infundibular inflammatory process **(3)**. Furthermore, P. acnes has been reported to promote T-helper (TH) 1 and TH17 immune responses **(4)**. INF-ɣ secreting TH1 cells specific to P. acnes were isolated from inflammatory lesions of 100% of AV patients **(5)**. High expression of Interleukin -17A was observed in acne lesions. Peripheral blood circulatory P. acnes specific TH1 and TH17 have been detected in AV patients **(6)**.

IL-36γ is one of Interleukin-36 agonists cytokines. IL-36 agonists cytokines are mostly demonstrated in keratinocytes & monocytes/macrophages. IL-36 agonists act as proinflammatory cytokines that enhance the innate immune responses. They stimulate keratinocyte production of antimicrobial peptides, IL-1β, TNF-α also chemokines, as well as plasmacytoid dendritic cell production of INF-ɣ, and myeloid cell production of IL-1β, IL-6 & IL-23 **(7)**.

These mediators make TH1 and TH17 polarization causing the revealing of IL-17, IL-6, IL-1β & TNF-α **(8)**.

These cytokines in turn synergize the production of IL-36 agonists **(7)**. The expression of IL-36 cytokines agonists in AV patients has only been evaluated in few earlier studies **(9)**. Among these cytokines, acne lesions have been identified to express IL-36 at the highest levels **(7)**. Therefore, in order to highlight its potential role in the inflammatory reactions encountered in AV, the purpose of this trial was to contrast Interleukin-36γ levels in the blood of individuals with AV to those of healthy controls, and to look into a connection among IL-36 levels as well as the severity of AV.



Received: 12/12/2022
Accepted: 12/02/2023

## PATIENTS AND METHODS

45 individuals with AV who visited the Dermatology Outpatient Clinic at Suez Canal University Hospitals and were diagnosed by a trained dermatologist were enrolled in this case-control research. The study also comprised age and gender-matched control individuals without AV, cancer, active infections and inflammatory or auto-immune illnesses.

**Inclusion criteria:** Patients suffering from AV, aged 14 years or more and of both genders were involved.

**Exclusion criteria:** Pregnant patients, patients with active infections, inflammatory or autoimmune skin or systemic diseases, patients on systemic treatment for AV for three months before the investigation or on systemic steroids or immunosuppressive treatment or diagnosed with cancer were excluded.

The sample size was determined via the prevalence/proportion of interleukin-36γ in the study group =80% & in the control group = 20% [(10)]. So, by calculation, the sample size was equal to 40 AV patients and 40 controls. For possibility of drop out (10%), the sample size was estimated to be 45 AV patients and 45 controls. The Dermatology Outpatient Clinic included eligible patients who presented with AV for 2-month period, and patients were chosen at random from the list by simple random selection. Enrolled patients with acne vulgaris were subjected to full history taking that comprised name, age & sex and present history which included disease onset, course, duration, aggravating factors, and family history of AV.

Moreover, full Clinical examination was done, which included general examination, dermatologic examination such as types of acne lesions, distribution, presence of pigmentation, and scarring. Evaluation of AV severity was carried out using the Global acne grading system as presented in table (1) [(11)]

**Table (1):** The global acne grading system [(12)]

| Location | Factor x Grade (0-4) = Local score | Grade | Global score |
|---|---|---|---|
| **Forehead** | 2 x Grade (0-4) | **0** (no lesions) | (0) **None** |
| **Right cheek** | 2 x Grade (0-4) | **1** (≥ one comedone) | (1-18) **Mild** |
| **Left cheek** | 2 x Grade (0-4) | **2** (≥ one papule) | (19-30) **Moderate** |
| **Nose** | 1 x Grade (0-4) | **3** (≥ one pustule) | (31-38) **Severe** |
| **Chin** | 1 x Grade (0-4) | **4** (≥ one nodule) | (>39) **Very severe** |
| **Chest and upper back** | 3 x Grade (0-4) | | |

Assessment of interleukin-36γ serum level: Serum levels of Interleukin-36γ were detected using ELISA kit (Human Interleukin-36 Gamma ELISA kit, China, Cat 850, E4404Hu). Laboratory tests were carried out at Clinical Pathology Department, Suez Canal University Hospital.

About 5 milliliters of venous blood sample were withdrawn from patients also controls then centrifuged to separate the serum. Test principle was competitive binding enzyme immunoassay approach.

The microtiter plate (solid phase) was pre-coated with an antibody specific to IL-36γ and then the samples and standards were added. The standard or sample was in constant competition with a known concentration of biotin-labeled IL-36γ for binding sites on a monoclonal antibody specific for interleukin-36 that had been coated on the wells. After the microplate wells were washed, avidin conjugated to horseradish peroxidase was included in every one & after an incubation period, a solution of tetramethylbenzidine was added as a substrate to each well. After applying sulphuric acid-based stop solution, we observed the resulting color shift in a spectrophotometer set to a wavelength of 450 nm ± 2 nm. Specimen concentration was identified through comparison of optical density readings to those from a reference curve. The kit's included standards were used to create the standard curve.

**Ethical Approval: The study was approved by the Ethics Board of Suez Canal University (No. 4340 at 22/10/2020). The patients were given all the information they need about the trial. An informed written consent was taken from each participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.**

### *Statistical Analysis*

The collected data were performed by statistical program for social science version 22.0 (SPSS Inc. USA). Explanation of qualitative parameters was given as numbers and percentages, while description of quantitative variables was given as mean, SD & range. To compare significance between two means, the Man Whitney U test was utilized as non-parametric test and student t test was used as a parametric test. The chi-square test was utilized to examine the difference among many proportions at the level of 95%. Pearson correlation was applied to evaluate the relation amongst quantitative data. Spearman rank correlation was applied for qualitative data. P-value ≤ 0.05 was regarded significant.

## RESULTS

Table (2) showed that AV cases and controls had comparable age & sex.

**Table (2):** Demographic data of participants with AV (n=45) in addition healthy controls (n=45).

| | Patients with acne (n = 45) | | Controls (n = 45) | | Test of Sig. | P |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| **Sex** | | | | | | |
| Male | 22 | 48.9 | 21 | 46.7 | $\chi^2$= 0.05 | 0.833 |
| Female | 23 | 51.1 | 24 | 53.3 | | |
| **Age** | | | | | | |
| Min. – Max. | 15.0 – 25.0 | | 15.0 – 26.0 | | | |
| Mean ± SD. | 20.58 ± 2.8 | | 20.84 ± 3.1 | | t= 0.422 | 0.674 |
| Median (IQR) | 21.0 (18.5 – 23.0) | | 21.0 (18.0 – 23.5) | | | |

Table (3) showed that 31 (68.9%) patients had AV in a single site, 27 (60%) patients in the face, and 4 (8.9%) patients in the back. 14 (31.1%) patients had AV in multiple sites. Regarding severity, 25 (55.6%) patients presented with mild acne, 15 (33.3%) patients presented with moderate acne and 5 (11.1%) patients presented with severe acne. Twenty patients (55.6%) had positive family history of AV. 24 (53.3%) patients presented with post-acne scars.

**Table (3):** Clinical characteristics of patients with AV (n=45)

| | No. | % |
|---|---|---|
| **Single site** | | |
| Face | 27 | 60 |
| Back | 4 | 8.9 |
| **Multiple site** | | |
| No | 31 | 68.9 |
| Yes | 14 | 31.1 |
| **Severity** | | |
| Mild | 25 | 55.6 |
| Moderate | 15 | 33.3 |
| Severe | 5 | 11.1 |
| **Family history** | | |
| Negative | 20 | 44.4 |
| Positive | 25 | 55.6 |
| **Scaring** | | |
| Absent | 21 | 46.7 |
| Present | 24 | 53.3 |
| **Duration (months)** | | |
| Min. – Max. | 3.0 – 72.0 | |
| Mean ± SD. | 22.18 ± 22.58 | |
| Median (IQR) | 18.0(9.0 – 36.0) | |

In table (4), cases with AV had significantly increased serum levels of IL-36γ (mean: 8.54 ± 1.60) than controls (mean: 2.01 ± 0.62) (p<0.001).

**Table (4):** Serum levels of Interleukin -36γ in cases with AV (n=45) relative to healthy controls (n=45).

| IL-36γ levels (ng/ml) | Patients with acne (n = 45) | Controls (n = 45) | t | P |
|---|---|---|---|---|
| Min. – Max. | 6.0 – 13.0 | 1.0 – 3.0 | | |
| Mean ± SD. | 8.54 ± 1.60 | 2.01 ± 0.62 | 25.52* | <0.001* |
| Median (IQR) | 8.6 (7.4 – 9.5) | 2.0(1.5 – 2.6) | | |

Serum levels of Interleukin -36γ had a significant direct association with the duration of AV (Table 5 and figure 1).

**Table (5):** Correlation between IL-36γ serum levels and different clinical characteristics of patients with AV

| | IL-36γ levels ng/ml | |
|---|---|---|
| | **r** | **P** |
| **Age** | 0.123[1] | 0.420 |
| **Severity** | 0.846 [2]* | **<0.001** |
| **Duration (months)** | 0.68 [1]* | **<0.001** |

IL: Interleukin. 1: Pearson coefficient, 2: Spearman rank correlation.

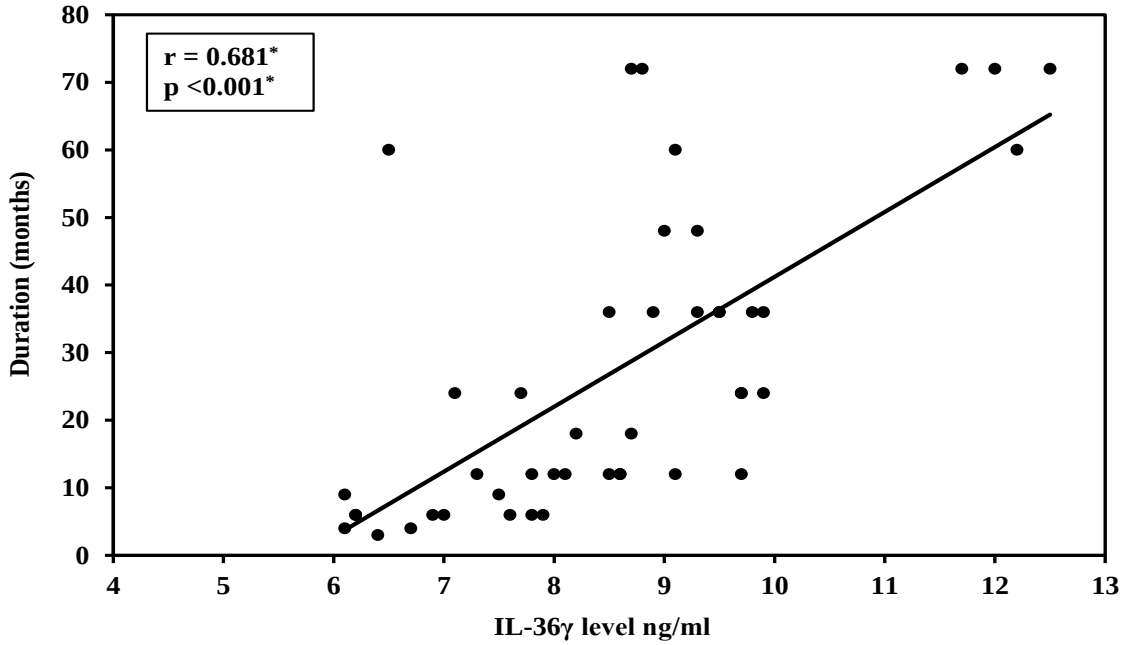


**Figure (1):** Correlation amongst Interleukin -36γ serum levels in addition duration (months) in cases with AV

Also, there was a significant relationship among serum levels of IL-36γ and AV severity as individuals with severe acne vulgaris had higher levels than those with moderate & mild AV (p=0.005). IL-36γ serum levels had a significant direct correlation with AV severity (Figure 2).

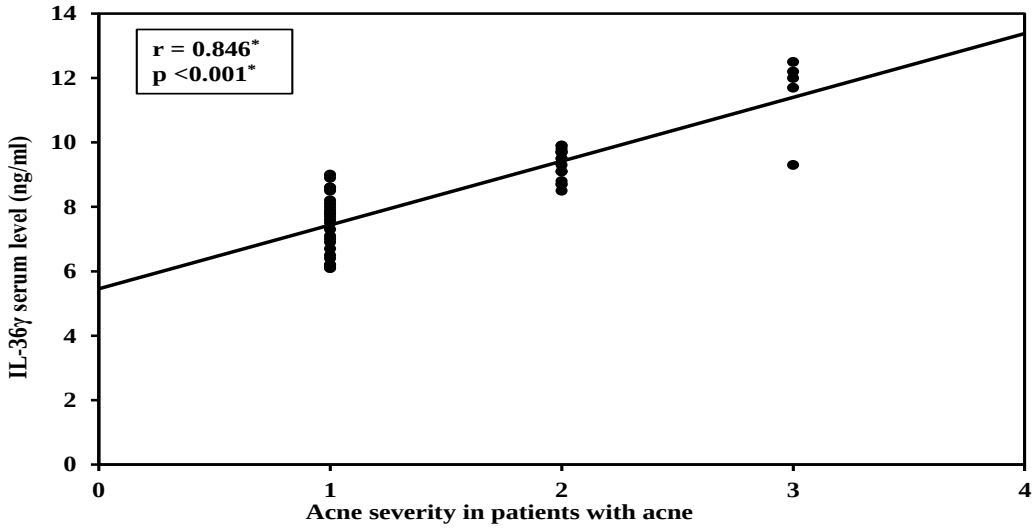


**Figure (2):** Scatter plot showing relation among IL-36γ serum levels (ng/ml) & acne severity in patients with acne (n=45).

IL-36γ serum levels were significantly greater in people who have positive family history of acne ($p \leq 0.001$). Moreover, patients with scarring had significantly larger serum levels of IL-36γ than patients without scarring ($p \leq 0.001$). Otherwise, IL-36γ serum levels didn't vary significantly with patients' age, gender or site of AV (Table 6).

**Table (6):** Relation among serum IL-36 levels as well as the clinical features of cases with acne (n=45).

| | N | IL-36γ levels (ng/ml) | | | Test of Sig. | P |
|---|---|---|---|---|---|---|
| | | Min. – Max. | Mean ± SD. | Median | | |
| **Sex** | | | | | | |
| Male | **22** | 6.0 – 10.0 | 8.21 ± 1.29 | 8.55 | t=1.35 | 0.184 |
| Female | **23** | 6.0 – 13.0 | 8.85 ± 1.83 | 8.6 | | |
| **Single site** | | | | | | |
| Forehead | **4** | 6.0 – 12.0 | 8.27 ± 1.66 | 8.5 | | |
| Face | **23** | 6.0 – 10.0 | 7.85 ± 1.37 | 7.65 | F=0.334 | 0.719 |
| Back | **4** | 8.0 – 9.0 | 8.75 ± 0.80 | 9.05 | | |
| **Multiple site** | | | | | | |
| No | **31** | 6.0 – 12.0 | 9.80 ± 1.08 | 8.50 | t=1.432 | 0.224 |
| Yes | **14** | 7.0 – 13.0 | 10.40 ± 1.91 | 9.0 | | |
| **Severity** | | | | | | |
| Mild | **25** | 6.0 – 9.0 | 7.47± 0.91 | 7.6 | | |
| Moderate | **15** | 8.5 – 10 | 9.33 ± 0.48 | 9.50 | F=58.35* | <0.001* |
| Severe | **5** | 9.0 – 13.0 | 11.54 ± 1.29 | 12.0 | | |
| **Family history** | | | | | | |
| Negative | **20** | 6.0 – 8.0 | 7.15 ± 0.73 | 7.20 | t=8.231* | <0.001* |
| Positive | **25** | 9.0 – 13.0 | 9.65 ± 1.19 | 9.30 | | |
| **Scarring** | | | | | | |
| Absent | **21** | 6.10 – 9.70 | 7.41 ± 1.03 | 7.50 | t=5.881 | <0.001* |
| Present | **24** | 7.30 – 13.0 | 9.53 ± 1.34 | 9.30 | | |

---

## DISCUSSION

The pathophysiology of AV is greatly influenced by the immune system. The inflammation in AV is linked with P. AV, which release PAMPs that stimulate both keratinocytes and sebocytes via TLRs to produce proinflammatory cytokines, including IL-1 [(13)]. Moreover, multiple investigations have shown the importance of T-helper-1 & TH17 in AV inflammatory responses [(5, 6)]. The pathophysiology of AV also includes follicular canal hyperkeratinization, which causes follicular occlusion [(1)].

In this study, serum levels of IL-36γ were significantly more in AV participants in comparison with controls. In addition, a significant association exists amongst these levels & AV severity. These results may confirm the possible role of IL-36γ in AV pathophysiology. IL-36γ induces the stimulation & retention of innate immune system cells, along with their production of proinflammatory cytokines [(10)]. Furthermore, acanthosis and hyperkeratosis have been observed in the skin of transgenic mice that overexpress IL-36γ in their epidermal basal cell layer indicating that IL-36γ may contribute to follicular canal hypercornification, the initial step of AV [(11)]. It has also been demonstrated that IL-36γ signaling promotes T-cell propagation. Additionally, it benefits polarizing naïve T-helper cells toward TH 1 and TH17 cells by inducing their stimulatory cytokines [(7)].

In agreement with our results, the gene expression of IL-36α, I-36β & IL-36γ in AV lesions, in addition to their serum levels in persons were significantly higher in contrast to controls. Notably, IL-36γ had the highest level of expression [(9)]. **Mohamed *et al.*** [(14)] exposed that the gene expression of IL-36γ was significantly higher in AV lesions related to healthy skin of normal controls, and it was significantly related to AV severity. **Shahin *et al.*** [(15)] reported a significant more in IL-36 serum levels in individuals with AV versus controls. However, in contrast to our findings, no correlation was found between these levels and disease severity, duration, or family history of AV. Moreover, **El-Esawy *et al.*** [(16)] noticed that the gene expression of IL36 was significantly higher in AV persons than in controls, and it was significantly related to AV severity. Nonetheless, neither studies demonstrated which IL-36 agonist cytokine was evaluated.

To our knowledge, this is the 1st trial to reveal that IL-36γ serum levels were significantly higher in patients with post acne scars than in patients without scarring. This finding may shed light on the function of IL-36γ in inducing post acne scars. Interestingly, all IL-36 agonists were found to stimulate lung fibroblasts [(17)]. Individuals pulmonary fibroblasts activated by granulocyte colony stimulating factor, IL-36γ expressed inflammatory mediators including IL-6, granulocyte macrophage colony stimulating factor & the neutrophil chemokines IL-8 and CCL20 [(18)]. Neutrophils are known to induce fibrosis via their proteolytic enzymes, especially elastase [(19)]. All IL-36 agonist cytokines have been linked to neutrophil accumulation and collagen

deposition [20, 21]. Furthermore, neutrophil-derived elastase is essential for activation of IL-36 cytokine resulting in a feedback circuit of neutrophil chemoattraction, elastase release, and fibrosis [17]. In fact, **Ebrahim *et al*.** [22] observed that AV people with post acne scars had significantly more serum IL-17 levels than AV patients without scarring. This high IL-17 level in patients with post-acne scars may be explained by our finding that those cases have higher IL-36γ levels, which increases TH17 polarization and IL-17 release [8].

Notably, the expression of IL-36 cytokines has been extensively studied in immune-mediated diseases and inflammatory dermatological disorders. The gene expression of the entire IL-36 family cytokines was higher in psoriasis vulgaris, especially IL-36α and IL-36γ [23]. **Chen *et al*.** [24] have demonstrated that individuals with psoriasis had significant greater serum levels of IL-36γ than controls & these levels were linked with PASI score. Furthermore, the expression of IL-36α, IL-36β in addition IL-36γ was increased in allergic contact dermatitis skin lesions with positive patch tests [25]. Also, in patients with intrinsic atopic dermatitis, IL-36 was discovered to be very active in acute lesions & even more expressed in chronic eczematous lesions [26, 27].

Due to measurement issues and a limited sample size, other IL-36 agonists cytokines are among the study limitations. Additional research evaluating the tissue expression of IL-36γ besides other IL-36 agonists cytokines in inflammatory acne lesions, as well as in post acne scars are required to establish the work of these cytokines in AV inflammatory reactions and the development of post acne scars. Furthermore, future studies assessing the expression and serum levels of these cytokines before and after different AV systemic treatments are recommended.

## CONCLUSION

Serum IL-36γ levels in AV persons were significantly enlarged than in controls. As well, IL-36γ serum levels were related to AV severity and post acne scarring. IL-36γ may therefore show a significant importance in AV inflammatory reactions and the induction of post acne scarring. These findings may also shed light on the therapeutic potential of targeting this cytokine in the care of inflammatory acne and the stoppage of acne scarring.

## DECLARATIONS

**Consent for publication:** I attest that all authors agreed to submit the work.
**Availability of data and material:** Available
**Competing interests:** None
**Funding:** No fund
**Conflicts of interest:** no conflicts of interest.

## REFERENCES


1- **Goodarzi A, Mozafarpoor S, Bodaghabadi M *et al.* (2020):** The potential of probiotics for treating acne vulgaris: A review of literature on acne and microbiota. Dermatol Ther., 33 (3): e13279. doi: 10.1111/dth.13279.
2- **Platsidaki E, Dessinioti C (2018):** Recent advances in understanding Propionibacterium acnes (Cutibacterium acnes) in acne. doi:10.12688/f1000research.156591.
3- **Lee D, Yamasaki K, Rudsil J *et al.* (2008):** Sebocytes express functional cathelicidin antimicrobial peptides and can act to kill propionibacterium acnes. J Invest Dermatol., 128 (7): 1863-6. doi: 10.1038/sj.jid.5701235.
4- **Yu Y, Champer J, Agak G *et al.* (2016):** Different Propionibacterium acnes Phylotypes Induce Distinct Immune Responses and Express Unique Surface and Secreted Proteomes. J Invest Dermatol., 136 (11): 2221-2228. doi: 10.1016/j.jid.2016.06.615.
5- **Mouser P, Baker B, Seaton E *et al.* (2003):** Propionibacterium acnes-reactive T helper-1 cells in the skin of patients with acne vulgaris. J Invest Dermatol., 121 (5): 1226-8. doi: 10.1046/j.1523-1747.2003.12550 6.x.
6- **Kistowska M, Meier B, Proust T *et al.* (2015):** Propionibacterium acnes promote Th17 and Th17/Th1 responses in acne patients. J Invest Dermatol., 135 (1): 110-118. doi: 10.1038/jid.2014.290.
7- **Sachen K, Arnold Greving C, Towne J (2022):** Role of IL-36 cytokines in psoriasis and other inflammatory skin conditions. Cytokine, 156: 155897. doi: 10.1016/j.cyto.2022. 155897.
8- **Buhl A, Wenzel J (2019):** Interleukin-36 in Infectious and Inflammatory Skin Diseases. Front Immunol., 10: 1162. doi:10.3389/fimmu.2019.01162.
9- **Di Caprio R, Balato A, Caiazzo G *et al.* (2017):** IL-36 cytokines are increased in acne and hidradenitis suppurativa. Arch Dermatol Res., 309 (8): 673-678. doi: 10.1007/s00403-017-1769-5.
10- **Mantovani A, Dinarello C, Molgora M *et al.* (2019):** Interleukin-1 and Related Cytokines in the Regulation of Inflammation and Immunity. Immunity, 50 (4): 778-795. doi:10.1016/j.immuni.2019.03.012.
11- **Blumberg H, Dinh H, Trueblood E *et al.* (2007):** Opposing activities of two novel members of the IL-1 ligand family regulate skin inflammation. J Exp Med., 204 (11): 2603-2614. doi:10.1084/jem.20070157.
12- **Doshi A, Zaheer A, Stiller M (1997):** A comparison of current acne grading systems and proposal of a novel system. Int J Dermatol., 36 (6): 416-8. doi: 10.1046/j.1365-4362.1997.00099.x.
13- **Kircik L (2016):** Advances in the Understanding of the Pathogenesis of Inflammatory Acne. J Drugs Dermatol., 15 (1 Suppl 1): s7-s10.
14- **Mohamed F, Ali S, Nasar E *et al.* (2022):** Environmental, inflammatory, and anti-inflammatory squad in acne vulgaris pathogenesis: AhR, IL-36, and IL-38. J Cosmet Dermatol., 21 (7): 3038-3045. doi: 10.1111/jocd.14542.
15- **Shahin M, Ahmed M, Mahmoud E (2021):** Evaluation of Serum Interleukin 36 in Egyptian Acne Vulgaris Patients versus Controls. QJM: An International Journal of Medicine, 114 (1): hcab093. doi: 15. 10.1093/qjmed/hcab093.015.
16- **El-Esawy F, Elhabak D, Mohamed S *et al.* (2020):** Evaluating the role of Interleukin-36 and Interleukin-38

in acne vulgaris patients. Benha Journal of Applied Sciences, 5 (7 part 1-2): 49-54.

17- **Elias M, Zhao S, Le H *et al*. (2021):** IL-36 in chronic inflammation and fibrosis - bridging the gap? J Clin Invest., 131 (2): e144336. doi: 10.1172/JCI144336.

18- **Borthwick L (2016):** The IL-1 cytokine family and its role in inflammation and fibrosis in the lung. Semin Immunopathol., 38 (4): 517-534. doi:10.1007/s00281-016-0559-z.

19- **Barnes T, Anderson M, Edwards S *et al*. (2012):** Neutrophil-derived reactive oxygen species in SSc. Rheumatology (Oxford), 51 (7): 1166-1169. doi:10.1093/rheumatology/ker520.

20- **Ramadas R, Ewart S, Medoff B *et al*. (2011):** Interleukin-1 family member 9 stimulates chemokine production and neutrophil influx in mouse lungs. Am J Respir Cell Mol Biol., 44 (2): 134-145. doi:10.1165/rcmb.2009-0315OC.

21- **Sun Y, Mozaffarian A, Arnett H *et al*. (2013):** IL-36 induces inflammation and collagen deposition in the lung. Cytokine, 63 (3): 303. doi:10.1016/j.cyto.2013.06.256.

22- **Ebrahim A, Mustafa A, El-Abd A (2019):** Serum interleukin-17 as a novel biomarker in patients with acne vulgaris. J Cosmet Dermatol., 18 (6): 1975-1979. doi:10.1111/jocd.12934.

23- **Boutet M, Bart G, Penhoat M *et al*. (2016):** Distinct expression of interleukin (IL)-36α, β and γ, their antagonist IL-36Ra and IL-38 in psoriasis, rheumatoid arthritis and Crohn's disease. Clin Exp Immunol., 184 (2): 159-173. doi:10.1111/cei.12761.

24- **Chen J, Du J, Han Y *et al*. (2021):** Correlation analysis between IL-35, IL-36γ, CCL27 and psoriasis vulgaris. J Dermatolog Treat, 32 (6): 621-624. doi:10.1080/09546634.2019.1689226.

25- **Mattii M, Ayala F, Balato N *et al*. (2013):** The balance between pro- and anti-inflammatory cytokines is crucial in human allergic contact dermatitis pathogenesis: the role of IL-1 family members. Exp Dermatol., 22 (12): 813-819. doi:10.1111/exd.12272.

26- **Martel B, Litman T, Hald A *et al*. (2016):** Distinct molecular signatures of mild extrinsic and intrinsic atopic dermatitis. Exp Dermatol., 25 (6): 453-459. doi:10.1111/exd.12967.

27- **Tsoi L, Rodriguez E, Stölzl D *et al*. (2020):** Progression of acute-to-chronic atopic dermatitis is associated with quantitative rather than qualitative changes in cytokine responses. J Allergy Clin Immunol., 145 (5): 1406-1415. doi:10.1016/j.jaci.2019.11.047.