Original Article

Interleukin-16 Serum Levels and Gene Polymorphism in Patients with Acne Vulgaris

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Abstract

Aim: Interleukin-16 (IL-16), a cytokine that promotes inflammation, affects immune system cells in a variety of ways. The biological characteristics of IL-16, including its ability to activate CD4+ T-cell migration and proliferation, as well as stimulate the production of proinflammatory cytokines, suggest that it may be a key player in the pathophysiology of several illnesses associated with immunological disorders. The purpose of the study was to evaluate serum levels and gene polymorphism (rs4072111) of IL-16 in acne vulgaris (AV).

Materials and Methods: Forty AV cases and forty controls who were matched for age and sex participated in this cross-sectional study. To assess the severity of acne, the Global Acne Grading System was utilized; serum IL-16 was evaluated using ELISA; and real-time polymerase chain reaction was used to evaluate *IL-16 (rs 4072111)* gene polymorphism.

Results: IL-16 serum levels were considerably greater in acne cases than in controls, according to this study. Additionally, severe cases had a much higher level of IL-16 than mild and moderate cases. Concerning *IL-16* gene polymorphism (rs 4072111), CC genotypes were substantially more in cases than in controls, and significantly enhanced the risk of the occurrence of acne *(P* = 0.025). Compared to variant T, the presence of allele C raises the risk of acne (*P* -value = 0.035).

Conclusion: Compared to the T allele, the presence of the allele C raised the possibility of developing acne.

Keywords: Acne, gene polymorphism, interleukin-16, rs4072111

Introduction

Acne vulgaris (AV), a chronic inflammatory skin disorder of the pilosebaceous follicles, affects people worldwide. It ranks eighth among skin conditions, affecting about 9% of the world's population.[1] The distinct clinical picture of AV can be either inflammatory (papules, pustules, nodules, and cysts) or non-inflammatory (closed/white and open/black comedones), causing skin discoloration and scarring and requiring continuous, long-term care. Lesions are seen on the chest, upper back, face, and neck.[2]

Acne can be attributed to the interaction of several genes and environmental variables, or it might be impacted by polygenic inheritance. Many genes have been studied in acne patients.[3]

Inflammation is a key factor in the pathophysiology of AV. Adaptive and innate immune systems work together to trigger the immune response during inflammation. Proinflammatory cytokines, including interleukin-16 (IL-6), TGF-β, and IL-1β, are produced by antigen-presenting cells resident in the skin, sebocytes, and keratinocytes in response to changes in the follicular microenvironment. Macrophages generate

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proinflammatory cytokines and phagocytose oxidized lipids. The first cells to produce IL-17 were mast cells (MCs), which were followed by innate lymphoid cells and Th cells. Multiple T helper 17- and Th1-derived cytokines are expressed, and the adaptive Th-mediated response is crucial in the early stages of acne.[4]

IL-16 (a multifunctional cytokine) was initially described in 1982. According to the early findings for triggering the chemotaxis of CD4+ T-cells, the factor was initially referred to as lymphocyte chemoattractant factor. Since then, evidence has shown that IL-16 can attract and stimulate a wide variety of other cells expressing the CD4 molecule, such as dendritic cells, eosinophils, and MCs.[5]

Because of its association with CD4+ T-cells and pleiotropic effects on immune system cells, IL-16 may be involved in the pathogenesis of acne. This study is the first to be published in the literature on the role of IL-16 in this illness.[6,7]

The purpose of this study was to evaluate serum levels of IL-16 and its gene polymorphism (rs4072111) in AV and its correlation with acne severity.

Materials and Methods

This cross-sectional case-control study was conducted on patients with varying degrees of AV who visited the dermatology, andrology, and sexually transmitted diseases clinic between March 2024 and August 2024, and on a community-based control group of sex- and age-matched healthy volunteers without prior AV in their medical history.

Sample Size Justification

The sample was determined based on all patients attending the dermatology outpatient clinic in our institution during the defined 6-month period. Therefore, an a priori sample size calculation was not performed since the study aimed to include the maximum available number of AV patients during that timeframe.

Ethical Consideration

Before sample collection, this study was approved by the Menoufia University Faculty of Medicine Research Ethics Committee (approval number: DERMA/2, date: 3/2024) and all participants provided written informed consent.

Exclusion criteria:

1. Patient with any other cutaneous disorders.

2. Patients with any systemic or cutaneous immune-mediated skin diseases.

3. Patients who have used any kind of topical acne therapy over the last month.

4. Patients using any systemic treatment for acne in the previous 3 months.

Every patient was subjected to:

1. Complete medical history, including name, age, sex, acne onset, course (stationary or progressive), duration, and family history.

2. Comprehensive general examination.

3. Thorough dermatological examination to identify the site of AV (shoulders, back, and/or face) and the kind of lesions which may be non-inflammatory (comedones) or inflammatory (papule, pustule, or nodule), and the Global Acne Grading System (GAGS), which depend on the location and the quantity of lesions that were categorized into mild (1-8), moderate (19-30), severe (31-39), and extremely severe (> 39) categories, assesses the severity of acne.[8]

Laboratory Assessment

Blood Sampling

Venipuncture was used to collect seven milliliters (mL) of venous blood under strict aseptic conditions. The blood was processed as follows: For measuring complete blood count, DNA extraction, and genotyping of *IL-16* gene (rs4072111), 2 mL was collected in EDTA tubes. 3 mL was collected into a plain tube and underwent centrifugation for ten minutes at 4000 rpm. The serum was kept cold at -80 °C until additional investigations were carried out.

DNA Extraction Step

The DNA was extracted from whole blood using the GeneJET Genomic DNA Purification Kit (Thermo Scientific, Lithuania; cat. #K0721). Using the Nanophotometer N-60 (Implen, Germany), DNA concentration, quality, and purity were evaluated. The assessment of the purity of DNA-extracted samples by spectrophotometry involves detecting other contaminants and absorbance from 230 nm to 320 nm. DNA will have a A260/A280 ratio of 1.7 to 2.0, indicating good quality.

Real-time PCR Step

***IL-16* gene polymorphism detection:** Single-nucleotide polymorphism (SNP) of the *IL-16* gene (rs4072111) was assessed by the real-time polymerase chain reaction (PCR) technique using a TaqMan probe. The primers, Master Mix II (2x), and probes were supplied by Thermo Fisher Scientific. The probe sequences were marked with [VIC/FAM] fluorescent dyes. The sequences of specific primers were:

IL-16 Gene (rs4072111)

Forward primer: 5'-CACTGTGATCCCGGTCCAGTC-3',Reverseprimer: 5'-GCTCAGGTTCACAGAGTGTTTC CATA-3', and the sequence of the probe was TGCAG TAGG GAATGGTTTGCTTGG[T/C]CTGAGTACAGCA GTGTTGGTGTGTG. Add 12.5 µL of the master mix to 1.25 µL of the genotyping assay of primer/probe mix and 6.25 µL of DNase-free water for each sample. Use 5 microliters of genomic DNA extract, and for the negative control reaction, use 5 microliters of DNase-free water. The cycling conditions were 4 minutes of initial denaturation at 94 °C, 40 cycles of denaturation at 94 °C for 30 seconds, primer annealing and extension at 60 °C for 40 seconds, and the final extension at 72 °C for 3 minutes. The Real-Time PCR Instrument, Applied Biosystems® 7500, with software version 2.0, was used to complete the data analysis.

Human IL-16 ELISA kit: Assayed by Elabscience®

Statistical Analysis

IBM SPSS software version 20.0 was utilized to analyze the data statistically (Armonk, NY: IBM Corp, released 2011). Percentages and numbers were used to summarize categorical data. Using the Shapiro-Wilk test, normality was evaluated for continuous data. Quantitative data were described using the following metrics: mean, standard deviation (SD), median, range (minimum and maximum), and interquartile range. The tests used were: for categorical data, the chi-square test was used to compare groups. For quantitative data that are normally distributed, the Student's t-test is used to compare the two groups under study. For quantitative variables that are not normally distributed, the Mann-Whitney test is used to compare the two groups under study. The equilibrium of the Hardy-Weinberg equation was determined by examining the population of the sample under study.

A *P* -value of less than 0.05 was deemed statistically significant.

Results

Forty AV patients and forty controls who were matched for age and sex participated in this cross-sectional case-control study.

The age of cases ranged from 14 to 35 years, with 20.80±5.82 as the mean ± SD value. Thirteen (32.5%) were female, and 27 (67.5%) were male. The control subjects' ages varied from 15 to 39 years, and their mean ± SD value was 22.47±6.95; (80%) of the controls were men, and 8 (20%) were women. Age and gender did not significantly differ between the cases and controls.

Concerning clinical data, the age of disease onset varied from 12 to 32 years, with 15.83±3.71 years (mean ± SD). The course of the disease was stationary in 20 (50%) cases and progressive in 20 (50%) cases. The mean ± SD value for the disease duration is 4.43±4.21, with a range of 1 to 17 years. Nineteen patients (47.5%) had a positive family history, whereas twenty-one patients (52.5%) had a negative one Table 1.

The acne was detected in the face in 26 (65%) of patients, in the back in 6 (15%), and in the face and back in 8 (20%) of patients Table 1.

As for acne severity, 18 (45%) of the cases were mild, 14 (35%) were moderate, and 8 (20%) were severe; the acne score ranged from 6 to 36, with a mean ± SD value of 20.18±8.69. Of the cases, 26 (65%) had inflammatory acne, 6 (15%) had comedonal acne, and 8 (20%) had both inflammatory and comedonal acne: Table 1.

Given that the average serum level of IL-16 was higher in patients (mean ± SD 17.22±13.10) than in controls (mean ± SD 7.90±7.56), there was a significant difference between the two groups ($P = 0.001$) Table 2.

Concerning the relation between serum concentrations of IL-16 and various clinical parameters within the AVgroup, there was a noteworthy correlation found between the acne severity and IL-16 serum levels, with severe cases exhibiting markedly higher values in comparison to mild and moderate cases ($P = 0.005$), Table 3. Furthermore, IL-16 levels were positively correlated with GAGS scores, as shown in Figure 1.

Regarding the *IL-16 rs4072111* gene, the genotype TT was absent in both cases and controls, while the control group had a noticeably higher prevalence of the TC genotype (30%) when compared with the AV group (10%), with a statistically significant $P = 0.025$. Similarly, the C allele was predominant in both groups but was more frequent in the acne group (95% vs. 85%), with a *P* -value of 0.035, as shown in Table 4. No statistically significant relationship was detected between rs4072111 genotypes, or allele, and different parameters in the AV group.

Discussion

AV is a persistent cutaneous inflammation of the upper pilosebaceous unit, and is among the most prevalent skin conditions with a complicated etiology. A crucial element in the pathophysiology of AV is inflammation. The immune system's innate and adaptive components work in tandem to elicit immunological reactions during the inflammatory phase of acne.[4]

IL-16 belongs to a class of cytokines known as chronic inflammatory cytokines, which also includes TNFα and β, Eotaxin, and IL-1, IL-6, IL-8, IL-11 and IL-17. These cytokines mediate either tissue-specific or systemic inflammation.[9]

Contrary to the majority of other precursor molecules, it has been discovered that both IL-16's mature and pro-molecule forms are biologically active.[10] The precursor protein's N-terminal domain (pro-IL-6) translocates into lymphocytes' nuclei and acts as a transcriptional repressor with cell cycle-regulating properties, while the cytoplasmic C-terminal domain of mature IL-16, which is secreted from the cell, binds to CD4 and can serve as a growth factor, chemoattractant, and differentiation factor on a range of hematopoietic cell types that are implicated in an inflammatory response.[10]

The pro-inflammatory cytokine IL-16 is produced and secreted by CD8+ cells, including MCs, eosinophils, peripheral lymphocytes, and epithelial cells, in response to mitogen or antigen activation. The CD4 molecule, found on macrophages, monocytes, T-cells, and dendritic cells, is the primary receptor for IL-16.[5]

IL-16 has been thoroughly outlined in numerous studies as an immunomodulatory cytokine that aids in the regulation of CD4+ cell activation and recruitment at inflammatory locations, including atopic dermatitis (AD)[11], pemphigoid[12], systemic lupus erythematosus (SLE)[13], cutaneous T-cell lymphomas.[14] However, no data exist about the association between AV and IL-16.

A total of 40 patients with different types of AV and 40 community-based healthy participants, matched in age and sex, participated in the current investigation as a control group.

The outcome of this investigation showed that the IL-16 serum levels of acne cases and controls differed significantly, with acne cases having greater levels. the fact that IL-16 was produced and secreted by T-cells, MCs, eosinophils, monocytes, fibroblasts, dendritic cells, and epithelial cells may account for the elevated blood level of IL-6 in AV patients.[5]

Table 1. Clinical data of cases under the study (n = 40)

	n	%
Age of onset (years)		
Minimum-maximum	12.00-32.00	
Mean ± SD	15.83±3.71	
Median (IQR)	15.00 (13.00-17.00)	
Course		
Stationary	20	50.00
Progressive	20	50.00
Duration in years		
Minimum-maximum	1.00-17.00	
Mean ± SD	4.43±4.21	
Median (IQR)	2.50 (2.0-6.0)	
Family history		
No	19	47.5
Yes	21	52.5
Site		
Face	26	65.0
Back	6	15.0
Face and back	8	20.0
Type of acne		
Inflammatory	26	65.0
Comedonal	6	15.0
Both	8	20.0
Severity		
Mild	18	45.0
Moderate	14	35.0
Severe	8	20.0
GAGS score		
Minimum-maximum	6.00-36.00	
Mean ± SD	20.18±8.69	
Median (IQR)	19.50 (11.50-28.0)	

IQR: Interquartile range, SD: Standard deviation, GAGS: Global Acne Grading System

Table 2. Comparison of interleukin 16 serum levels among acne cases and controls

	Acne vulgaris (n = 40)	Control (n = 40)	U	*P*
IL16 serum levels by ELISA				
Min.-max.	2.14-66.63	1.93-26.76	320.00*	< 0.001*
Mean ± SD	17.22±13.10	7.90±7.56		
Median (IQR)	16.50 (9.33-20.98)	4.56 (9.33-20.98)		

P: *P* -value for comparing between groups
*: Statistically significant at $P \leq 0.05$
IQR: Interquartile range, SD: Standard deviation, U: Mann Whitney test, Min.: Minimum, Max.: Maximum

Each of these cells contributes to the pathophysiology of acne. IL-16 can increase the synthesis of many cytokines that promote inflammation by mononuclear cells, including IL-1β, tumor necrosis factor-alpha (TNF-α), and IL-6.[15] These cytokines have an important role in acne pathogenesis.

IL-1β promotes keratinocyte proliferation, which leads to clogging of the follicular opening and microcomedone development.[16]

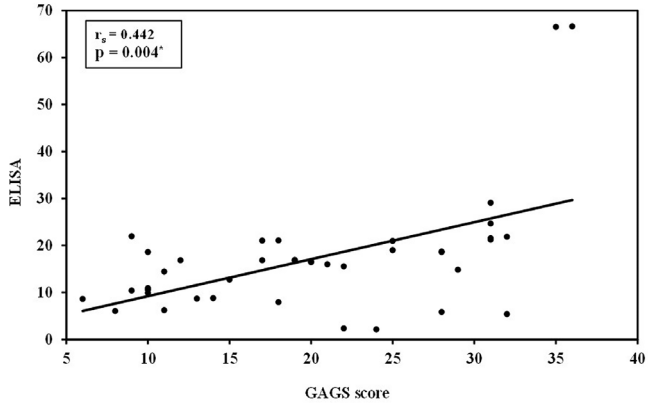

Figure 1. Correlation between IL-16's serum levels by ELISA and GAGS score in acne vulgaris group (n = 40)
IL: Interleukin, GAGS: Global Acne Grading System

The study of Triatmakusuma et al.[17], demonstrated a positive correlation between serum IL-6 levels and the severity of AV. IL-6's role in acne is illustrated by its ability to facilitate the production of various cytokines, proteases, and free radicals. IL-6, induces T-cell differentiation, B-cell maturation, and immunoglobulin production.

IL-16 promotes Th2 and Th17 cytokine production.[18] IL-17 is a crucial cytokine that aids in the pathophysiology of AV. IL-17 can target keratinocytes, endothelial cells, monocytes, and fibroblasts to produce pro-inflammatory mediators and recruit neutrophil infiltration. Th17 cell activation is also influenced by the elevated expression of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α, which are induced by IL-16.[19]

Thus, IL-16 may contribute to the pathophysiology of acne.

Additionally, our results demonstrated that serum IL-16 levels increased in proportion to the severity of AV, with a statistically significant difference between moderate and severe cases and between mild and severe ones.

Similar to our results, AD patients showed elevated serum levels of IL-16 in association with the disease severity (as determined by SCORAD score)[11], The SLE disease activity index score showed a correlation between IL-16 and SLE

Table 3. Relation between serum levels of IL-16 and different clinical parameters in acne vulgaris group (n = 40)

	n	Serum levels of IL-16 by ELISA		Test of significance	*P*
		Mean ± SD	Median (minimum-maximum)		
Gender					
Male	27	19.38±14.75	16.85 (5.40-66.63)	U = 127.500	0.168
Female	13	12.71±7.32	10.48 (2.14-24.64)		
Site					
Face	26	19.31±15.43	17.57 (2.34-66.63)	H = 2.618	0.270
Back	6	11.46±6.11	13.57 (2.14-16.92)		
Face and back	8	14.73±5.23	15.83 (7.92-21.22)		
Course					
Stationary	20	20.69±17.04	17.66 (2.34-66.63)	U = 149.500	0.174
Progressive	20	13.74±6.04	15.63 (2.14-21.83)		
Type of acne					
Inflammatory	26	19.22±15.37	16.59 (2.14-66.63)	H = 1.140	0.566
Comedonal	6	13.67±5.39	13.62 (7.92-21.22)		
Both	8	13.38±6.97	12.62 (5.40-21.83)		
Severity (GAGS grade)					
Mild	18	12.85±5.28	10.69 (6.03-21.93)	H = 10.590*	0.005*
Moderate	14	14.32±6.16	16.50 (2.14-20.94)		
Severe	8	32.10±22.33	23.24 (5.40-66.63)		
Family history					
No	19	14.35±5.47	15.54 (6.03-24.64)	U = 173.500	0.486
Yes	21	19.81±17.11	16.75 (2.14-66.63)		

P: *P* -value for the relation between ELISA and different clinical parameters
SD: Standard deviation, U: Mann-Whitney test, H: Kruskal-Wallis test, GAGS: Global Acne Grading System, IL: Interleukin
*: Statistically significant

Table 4. Comparing the IL-16 genotypes of patients and controls

	Acne vulgaris (n = 40)		Control (n = 40)			
	No.	%	No.	%	χ^2	*P*
Genotypes						
TT	0	0.0	0	0.0	5.0*	0.025*
TC	4	10.0	12	30.0		
CC	36	90.0	28	70.0		
$^{HW}p_0$	0.739		0.264			
Allele						
T	4	5.0	12	15.0	4.444*	0.035*
C	76	95.0	68	85.0		

χ^2: Chi-square test
$^{HW}p_0$: *P* value for χ^2 for goodness of fit for Hardy-Weinberg equilibrium (HWE) (If $P < 0.05$-not consistent with HWE)
P: P -value for comparison between the two studied groups
*: Statistically significant
IL: Interleukin

activity.[20] Furthermore, Richmond et al.[14] showed that IL-16 closely matches the Sézary syndrome disease stage.

Considering the important roles recognized for cytokines in the process that regulates the immune response, potential alterations in cytokine expression or genes may have traceable consequences on a person's vulnerability to inflammation. Numerous studies have demonstrated that genetic changes can either increase or decrease the likelihood of developing acne.[3]

The human genome's chromosome 15q26.3 contains the gene that codes for the cytokine IL-16, which has eight exons and spans about 17 kb. The SNP rs4072111 is located at position 434 of the longer isomorph's second PDZ domain. The IL-16 protein exists in two different forms, known as isoforms 1 and 2: leukocyte IL-16 and neuronal IL-16, respectively.[21]

The coding and regulatory regions of the *IL-16* gene contain polymorphisms that may affect gene transcription and result in individual differences in IL-16 production.[22]

Numerous autoimmune, neurological, viral, inflammatory, and cardiovascular disorders have been linked to functional polymorphisms in the *IL-16* gene.[23]

To our knowledge, this research is the first to look at the possible impact of *IL16* gene variants (rs4072111) in AV patients.[3]

The results of our study demonstrated that the frequency of the genotype (CC) was substantially greater in patients than in controls and significantly enhanced the risk of acne occurrence. additionally, compared to variant T, the presence of allele C raises the risk of acne.

Polymorphisms in the *IL-16* gene could be connected to a higher risk of developing inflammatory and autoimmune disorders, according to several studies. According to Xue et al.[13], the T allele of rs4072111 was commonly found in patients with SLE, suggesting a genetic link between polymorphisms in the *IL-16* gene and SLE vulnerability. Furthermore, Chen and Chen[24] found that the risk of peri-implantitis in the Chinese population was linked to the CT genotype of the *IL-16* gene, rs4072111 SNP.

More rs4072111 CT genotype carriers were found in those with periodontitis than in the healthy control group, according to a study conducted in the Brazilian population.[25]

Glas et al.[26] observed a relationship between Crohn's disease and the IL-16-295 SNP. Furthermore, IL16 polymorphisms may be involved in the pathogenesis of alopecia areata (AA) or the manifestation of AA symptoms in the Korean population, according to Lew et al.[27] likewise, Reich et al.[28] demonstrated that individuals with polysensitized allergic contact dermatitis had a much higher prevalence of the IL-16-295 CC genotype in contrast to healthy controls. Given that inflammation has a key role in acne pathogenesis, this could account for our findings.

In contrast to our findings, some researchers discovered a non-significant correlation between a variation in the *IL-16* gene and certain allergy disorders, such as atopy or asthma.[29]

Additionally, our research's findings contradicted those published by Purzycka-Bohdan et al.[30], who did not notice variations in psoriasis genotype and allele frequencies of patients for the -295 T/C *IL-16* gene polymorphism. This difference may result from variations in the ethnic backgrounds of the populations under study, as well as variations in the SNPs within the *IL-16* gene that were investigated in these illnesses.

Since IL-16 may be linked to the pathophysiology of acne, an inflammatory disease, blocking its effects with monoclonal antibodies would likely be a suitable treatment for cases of AV. This is because blocking IL-16 may attenuate inflammatory responses, reduce recruitment of target cells to the inflammatory sites, and decrease the secretion of pro-inflammatory cytokines.

Additionally, the increased IL-16 levels in proportion to AV severity suggest that IL-16 may be used as a marker for acne severity.

Study Limitations

This study has some limitations. First, the small sample size may limit the statistical power and generalizability of the findings. Second, as this is a single-center study conducted on

Egyptian patients, the results may not be representative of other populations or ethnic groups. Finally, other environmental and clinical factors that may contribute to acne pathogenesis were not evaluated in the present study. Therefore, further large-scale, multicenter studies are needed to validate and expand our findings.

Conclusion

Our study's results indicate a strong correlation between AV and the *IL-16* gene polymorphism (rs4072111), with AV patients more likely to have the CC genotype and C allele than healthy controls. Furthermore, AV patients had considerably higher IL-16 levels, which were also related to the severity of the condition, suggesting that this cytokine may play a role in the pathophysiology of acne. These findings demonstrate the immunological and genetic components of AV and imply that IL-16 could be a useful biomarker for the severity and susceptibility of the condition.

Ethics

Ethics Committee Approval: This study was approved by the Menoufia University Faculty of Medicine Research Ethics Committee (approval number: DERMA/2, date: 3/2024).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.M.Y., A.M., N.T., O.M.M., B.A.E.N.M., Concept: A.M.Y., A.M., N.T., O.M.M., B.A.E.N.M., Design: A.M.Y., A.M., N.T., O.M.M., B.A.E.N.M., Data Collection or Processing: A.M.Y., A.M., N.T., O.M.M., B.A.E.N.M., Analysis or Interpretation: A.M.Y., A.M., N.T., O.M.M., B.A.E.N.M., Literature Search: A.M.Y., A.M., N.T., O.M.M., B.A.E.N.M., Writing: A.M.Y., A.M., N.T., O.M.M., B.A.E.N.M.

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