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Evaluation of Serum IL 17 Level in Acne Vulgaris Patients

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ABSTRACT

Background: Acne vulgaris (AV) is a chronic inflammatory disorder, characterized by retention of desquamated keratinocytes within the pilosebaceous unit (PSU) forming a microcomedo. Interleukin (IL)-17A was seen in early AV lesions and is believed to have a role in AV development.

Aim: This study aimed to assess serum IL-17 level in cases with AV to assess its role in disease pathogenesis, its correlation with disease severity and its clinical significance.

Methods: This case control study was conducted on a total of 40 cases who were divided into two groups: AV group comprised 20 patients with AV, and the control group included 20 age- & sex-matched healthy controls (HC). The AV severity was graded using the Global Acne Grading System (GAGS). Also, serum IL-17 concentration was estimated in both groups.

Results: IL-17 level displayed significant increase in acne group compared to the control group. IL-17 displayed significant positive correlation with sex, smoking, family history, acne scars, acne grade & GAGS score. On the other hand, no correlation was noticed with disease duration and seborrheic dermatitis. At cut off 57.94 (pg/ml) IL-17 displayed significant AUC that could distinguish between AV cases and HC with sensitivity 95% and specificity 95%.

Conclusion: Serum IL-17 level can be used in diagnosis of patients with acne vulgaris. Moreover, it can be used as a predictor of disease severity and scarring& can be targeted as line of therapy.

Keyword: Acne vulgaris, Propionibacterium acne, Interleukin-17, Global acne grading system.

INTRODUCTION

Acne vulgaris (AV) is a frequent skin lesion from which millions of subjects throughout the world suffer. It is characterized by inflammation of the PSU. AV is stimulated by Propionibacterium acnes (P. acnes) in adolescence, under the effect of dehydroepiandrosterone. It frequently affects the face, however upper arms, trunk, chest, and back may also be affected [1, 2].

The increase in the level of AV biomarkers could be used in differential diagnosis and the proper choice of the optimum therapeutic agent. Of note, AV therapies differ according to the severity of the disease. Adipokines (irisin, adiponectin, visfatin, and ghrelin), cytokines (IL-1β, IL-6, IL-8, IL-17, and IL-19), and antioxidant enzymes (glutathione peroxidase, superoxide dismutase, and catalase) were demonstrated to be biomarkers of AV and have a strong association with disease severity [3].

Innate and adaptive immunity, in particular the Th17 pathway, might participate in the inflammatory response in AV. In addition, P. acne is considered a strong inducer of Th17 and Th1 in human PBMCs [4, 5].

Propionibacterium acnes stimulate expression of key Th17-related genes, such as IL-17A, RORα, and IL-17RC, and triggers IL-17 release from CD4+. Supernatants from P. acnes–stimulated PBMCs were adequate to encourage the differentiation of naive CD4+CD45RA T cells into Th17 cells. In addition, antibodies totally inhibit P.acnes–induced IL-17 formation. Essentially, it has been demonstrated that cellular IL-17 expression was detected in skin biopsies from AV cases.

In addition, IL-17 is a cytokine discharged by triggered T cells and is believed to have a central role in the pathogenesis of various skin lesions [5].

The current study is conducted to assess serum IL-17 level in patients with AV to evaluate its role in AV pathogenesis, its correlation with disease severity and its clinical significance.

PATIENTS AND METHODS

This case control study was conducted on 40 cases over one year at Dermatology Outpatient Clinic of Mansoura University Hospital (MUH), Egypt. The participants were divided into two groups: First group included 20 patients with acne vulgaris, and the second group included 20 age- & sex-matched healthy controls.

Inclusion criteria: Acne vulgaris patients aged between 12 to 25 years form the both genders.

Exclusion criteria: Patients with chronic inflammatory or autoimmune disorders, patients used topical or systemic treatment for AV which include hormonal therapy or isotretinoin one month before being enrolled in the study, and pregnants or lactating women.

Methods: All cases in the present study were subjected to full history taking comprising personal history (Age, sex, occupation, residence, marital status, dietary habits and past history of medical or surgical problems), present history (Onset, course and duration of the condition), and past history of medical treatment either topical or systemic.

General examination: Vital signs and the dermatological examination was done to assess the grade of acne as regards comedonal acne (comedones) papules or nodules, mild AV (comedones and a limited number of papulopustules), moderate AV (comedones, many inflammatory papules, and pustules), and

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nodulocystic acne (comedones, inflammatory lesions, and major nodules more than five mm in diameter and scarring is occasionally detected). Acne severity was assessed according to the GAGS [7] into mild (1-18), moderate (19-30), severe (31-38), and very severe (more than 39). Laboratory investigations included measurement of serum IL-17 concentration by using ELISA kits (INNOVA BIOTECH CO., LTD., No: In-Hu2141), based on the manufacturer's instructions. The assay range is 2.8 - 200 pg/ml. A volume of three ml venous blood was withdrawn from each subject, using EDTA-free sterile tube. The collected samples underwent centrifugation for 15 min at 3000 R/m within one hour of collection. The gathered serum was stored at -20 °C till analysis.

Ethical consideration: Study design was approved by The IRB of Faculty of Medicine, Mansoura University and based on the Helsinki Declaration. Informed consent was obtained from each included participant. Confidentiality was respected. Collected data were utilized for scientific purpose only.

Statistical analysis

SPSS software (PASW statistics for Windows, Chicago) version 25 was used to analyse the data. Numbers and percentages were used to define qualitative data. After determining normality using the Shapiro-Wilk and Kolmogorov-Smirnov tests, quantitative data were characterized using the mean ± SD for data with normal distribution and the median for data with non-normal distribution. The results were deemed significant at $P \leq 0.05$ level. To compare qualitative data between groups, Chi-square, Fisher exact test, and Monte Carlo tests were utilized. At least two groups under study were compared using the U and Kruskal Wallis tests respectively, for data that was not normally distributed. Two independent groups with properly distributed data were compared using the student t test. Three or more independent groups were compared using the One Way ANOVA test. The degree and direction of a linear association between two continuous variables that are not normally distributed and/or ordinal variables were assessed using Spearman's correlation. To assess the validity of continuous variables, the ROC curve was utilized.

RESULTS

Among acne vulgaris group mean age was 18.60 ± 2.85, most of them were females (55%), living in urban areas (60%), single (85%). Insignificant difference was found between acne vulgaris and control group regarding age, sex, residence, marital status, occupation and smoking (p >0.05) (Table 1).

Table (1): Sociodemographic characteristics of studied groups

		Acne group	**Control group**	**Test of significance**
		N=20(%)	**N=20(%)**	
Age/ years	Mean ± SD	18.60±2.85	20.15±3.18	t=1.62 p=0.113
Sex	Male Female	9(45) 11(55)	9(45) 11(55)	P=1.0
Residence	Rural Urban	8(40) 12(60)	11(55) 9(45)	χ^2=0.902 P=0.342
Occupation	Not working (student) Working	17(85) 3(15)	13(65) 7(35)	χ^2=2.13 P=0.144
Smoking		4(20)	4(20)	P=1.0
Marital status	Single Married	17(85) 3(15)	15(75) 5(25)	χ^2=0.625 P=0.429

χ^2=Chi-Square test, t: Student t test.

Table **(2)** showed lesion distribution among studied groups. Acne scars and seborrheic dermatitis showed significant increase in the acne vulgaris group compared to HC (P=0.017 and P=0.013 respectively). Acne scars occurred in 25% of cases and seborrheic dermatitis occurred in 45% of cases. IL-17 level displayed significant increase in acne group compared to HC and between scarring compared to no-scarring groups ($p < 0.001$).

Table (2): Lesion distribution and serum IL-17 level among studied groups and among scarring and non-scarring groups

	Acne group	**Control group**	**Test of significance**
	N=20(%)	**N=20(%)**	
Acne scars	5(25)	0	χ^2=5.71, P=0.017*
Seborrheic dermatitis	9(45.0)	2(10.0)	χ^2=6.14, P=0.013*
Serum IL-17 level (pg/ml)	85.52(47.6-851.88)	10.4(7-80.68)	Z=5.21, P=0.001*
	Scarring (n=20)	**Non scarring (n=20)**	
Serum IL-17 level (pg/ml)	85.52(47.6-851.88)	10.4(7-80.68)	Z=5.21, P=0.001*

Data expressed as median, z: U test, χ2: Chi-Square test, MC: Monte Carlo test, *statistically significant.

Table **(3)** showed that the mean disease duration was 5.10 ± 2.53. All patients had gradual onset and progressive course (100%). Most cases had moderate grade (50%) followed by mild and severe cases (25% each).

Table (3): Disease characters and grade among studied cases

	N=20	**%**
Disease duration (years), Mean ±SD	5.10±2.53	
Course (progressive)	20	100.0
Onset (gradual)	20	100.0
Grade		
Mild	5	25.0
Moderate	10	50.0
Severe	5	25.0

Table (4) showed that IL-17 revealed significant positive relationship with sex, smoking and family history. However, insignificant association was observed with age, residence, occupation, marital status, dietary habits and history of acne. IL-17 revealed significant correlation with acne scars. However, insignificant association was noticed between IL-17 and seborrheic dermatitis (P=0.569). IL-17 revealed a significant positive relationship with acne grade (P=0.003).

Table (4): Relationship between Serum IL-17 level (pg/ml) and sociodemographic, history among, grade and dermatological examination among studied cases

		Serum IL17 level (pg/ml)	**Test of significance**
Age/ years	<19	85.52(47.6-99.28)	Z=1.03
	≥19	90.32(68.4-851.88)	P=0.305
Sex	Male	88.96(75.6-851.88)	Z=2.05
	Female	75.2(47.6-99.28)	P=0.04*
Residence	Rural	87.24(68.4-156.4)	Z=0.424
	Urban	83.44(47.6-851.88)	P=0.671
Occupation	Not working (student)	85.52(47.6-795.2)	Z=1.22
	Working	98.62(75.6-851.88)	P=0.223
Smoking	-ve	81.02(47.6-99.28)	Z=2.41
	+ve	475.8(85.52-851.88)	P=0.016*
Marital status	Single	85.52(47.6-795.2)	Z=1.22
	Married	98.62(75.6-851.88)	P=0.223
Dietary habits	Healthy food	71.04(47.6-94.48)	
	Junk food	85.52(75.6-98.62)	Kw=0.413
	Spicy & junk food	85.52(68.28-851.88)	P=0.814
History of acne	-ve	86.2(86.2-86.2)	Z=0.260
	+ve	85.52(47.6-851.88)	P=0.795
Family history	-ve	75.4(47.6-86.2)	Z=2.28
	+ve	92.4(68.28-851.88)	P=0.02*
Grade	Mild	68.4(47.6-75.2)	
	Moderate	85.52(69.6-94.48)	Kw=8.66
	Severe	156.4(98.62-851.88)	P=0.003*
Acne scars	-ve	80.68(47.6-156.40	Z=2.40
	+ve	99.28(81.36-851.88)	P=0.016*
Seborrheic dermatitis	-ve	85.52(68.4-851.88)	Z=0.570
	+ve	75.6(47.6-156.4)	P=0.569

Z: U test, KW: Kruskal Wallis test, *statistically significant.

Table **(5)** showed that insignificant relationship was detected between IL-17 and disease duration and BMI but showed significant positive correlation with GAGS score.

Table (5): Relation between Serum IL-17 level (pg/ml) and diseases characters

	Serum IL17 level (pg/ml)	
	R	**P value**
Disease duration (years)	0.224	0.342
BMI (kg/m^2)	0.244	0.300
GAGS score	0.973	<0.001*

r: Spearman correlation coefficient

Table **(6)** showed that ROC curve was conducted to assess the validity of IL-17 level in differentiating between acne cases and control group. At cut off 57.94 (pg/ml) IL-17 displayed significant AUC that can distinguish between AV

cases and healthy controls with sensitivity 95% and specificity 95%. ROC curve was performed to evaluate validity of serum IL-17 level in differentiating mild from moderate to severe cases. At cut off 72.4 (pg/ml) IL-17 displayed significant AUC that could distinguish between mild and moderate to severe cases with sensitivity 93.3% and specificity 80%. ROC curve was performed to evaluate validity of serum IL-17 level in differentiating between scarring and non-scarring group. At cut off 92.4 (pg/ml), IL-17 displayed significant AUC that may distinguish between scarring and non-scarring with sensitivity 80% and specificity 80%.

Table (6): Validity of Serum IL-17 level

	AUC (95%CI)	P value	Cut off point	Sensitivity %	Specificity %
Differentiating between cases and control group					
Serum IL-17 level (pg/ml)	0.981 (0.943-1.0)	0.001*	57.94	95.0	95.0
Differentiating mild from moderate to severe cases					
Serum IL-17 level (pg/ml)	0.987 (0.946-1.05)	0.001*	72.4	93.3	80.0
Differentiating between scarring and non-scarring group					
Serum IL-17 level (pg/ml)	0.867 (0.683-1.05)	0.016*	92.4	80.0	80.0

AUC: Area under curve.

DISCUSSION

Acne vulgaris (AV) is a skin lesion that affects about 85% of subjects in adolescence and early adulthood. In general, AV often happens in areas with a great concentration of sebaceous glands, comprising the face and upper back areas. In typical PSUs, the formation of sebum is mainly performed by the sebaceous glands [8]. There are numerous subtypes of acne, comprising infantile acne, occupational acne, excoriated acne, chloracne, and acne induced by medications (such as steroids, isoniazid, lithium, and phenytoin). Such changes look like AV in terms of clinical and histological assessment, however the clinical condition and severity could discriminate them, and associated manifestations [9].

IL-17A increases CXC ligand 8 formation in epithelial cells and stimulates fibroblasts to recruit neutrophils, whereas neutrophils release free radicals that damage follicular integrity with subsequent aggravation of AV lesions. In addition, IL-17A synergises with different inflammatory cytokines, causing increased formation of both IL-6 and IL-8 [10].

This was a case-control study that was conducted on 20 cases with AV and 20 age- & sex-matched HC to assess serum IL-17 level in cases with AV to evaluate its role in AV pathogenesis, its correlation with disease severity and its clinical significance. All patients and controls were matched in residence, marital status, occupation, smoking, dietary habits, history of acne, history of topical or systemic treatment, BMI and family history. Therefore, no other factors can affect scope of our results.

Since sebum formation increases throughout puberty, older adolescents incline to have greater sebum formation compared to younger adolescents. Increased sebum concentrations encourage the growth of P. acnes, which are special bacteria involved in the inflammatory AV lesions and often are accompanied by extensive forms of AV [11, 12]. The average age of the cases in the present study was 18.60 ± 2.85 years. This is comparable with previous study as the majority of cases (68%) were found to be in the 18–35 age range [13]. It has been demonstrated that AV predominates among females [14], likewise the majority of AV cases in this study were females, which is comparable outcome with several studies [15, 16]. The higher incidence of female affection could be clarified by the fact that the higher concern of females towards this conditions compared to males. In addition, it could be linked to different factors such as using cosmetic products or elevated degree of stress factors in women.

The present study showed that the mean disease duration was 5.10 ± 2.53 years. All patients had gradual onset and progressive course. In a study by **George *et al***. [1] 46 patients (41.8%) had a duration of less than five years, while 14 patients (12.7%) had a total duration of >15 years.

Acne scars and seborrheic dermatitis revealed a significant elevation in the acne vulgaris group compared to the controls. Acne scars occurred in 25% of cases, and seborrheic dermatitis occurs in 45% of cases. The prevalence of acne scars in this study was lower than that in the previous study by **Liu *et al.*** [17] that included 37 studies comprising 24,649 AV cases. In addition, the pooled prevalence of acne scars in these cases was 47%. The lower percentage of scars in the present study may be explained as most cases in this study were moderate grade. Acne scars affected all degrees of AV, and the prevalence of acne scars increased with the severity of acne. Severe AV was frequently accompanied by extensive skin inflammation, which ultimately ends in acne scar formation.

In this study, the AV severity was assessed according to GAGS. Most cases had moderate grade (50%) followed by mild and severe cases (25% each). Similarly, **Khunger *et al***. [16] noticed that most of cases had acne grade II (55%) and grade III (28%) with 12% having grade IV and only 6% having grade I acne. **Raghavan *et al***. [18] observed that grade III acne was the most common (44%), followed by grade II (30%) and grade IV (18%).

The present study displayed that the IL-17 level revealed a significant increase in the acne group in comparison with healthy controls. Increased IL-17 in acne vulgaris may be explained by an immunogenic protein of P. acnes formed in the follicle. The production of cytokines may trigger differentiation of naive CD4+T cells to Th-17 cells that could release IL-17, inducing the inflammatory process [5]. In line with our findings, **Ebrahim *et al.*** [4] observed that serum IL-17 could be used as an indicator of disease pathogenesis as well as a possible prognostic predictor for severity and scarring in AV. In addition, **Agak *et al*.** [5] observed that P. acnes could trigger the discharge of IL-17 from CD4+T cells, and IL17+T cells were evident in perifollicular infiltrates of inflammatory lesions. On the other hand, this result is against the results of preceding studies who didn't detect significant difference in IL-17 values between cases of papulopustular and comedonal acne [19, 20]. Also, the level of IL-17 revealed a significant elevation in the scarring group compared to patients without scars. IL-17 showed significant correlation with acne scars. Studies on skin wound healing reported IL17 might be involved in the initial inflammatory stage of the wound, and it can suppress the wound healing process. The expression of IL-17 receptors on keratinocytes, and inflammatory cells proposes that IL-17 could interfere with different skin cells [21]. **Rodero *et al*.** [22] utilized IL-17 in mice and recorded that lack of IL-17 enhances skin tissue repair, explaining its action on wound healing. In addition, **Tan *et al.*** [23] recorded that hepatic fibrosis was accompanied by an increase in hepatic IL-17A expression. This could explain IL-17 role in the development of scarring lesions among AV cases.

IL-17 differed significantly compared to healthy controls and AV cases with different severities of AV. With increasing AV severity, mean serum IL-17 levels also rose. IL-17 showed significant positive correlation with acne grade and GAGS score. Increasing IL-17 serum level with elevated AV severity likely secondary to more prominent inflammatory response caused by Th17 cells and this came in agreement with the preceding results [24, 25]. Likewise, preceding researches noticed a significant increase in IL-17 values with the severity of AV [4, 26, 27].

At cutoff 57.94 pg/ml, IL-17 displayed a significant AUC that could distinguish between cases and controls with higher sensitivity and specificity. At cutoff 92.4 pg/ml, IL-17 revealed a significant AUC that could distinguish between scarring and non-scarring with 80% sensitivity and 80% specificity. At cutoff 72.4 pg/ml, IL-17 revealed a significant AUC, which could distinguish cases according to their severity with higher sensitivity and specificity. **Ebrahim *et al*.** [4] observed that IL-17 may be utilized in early diagnosis of AV when its level extend beyond the cutoff value with higher sensitivity, and specificity. In addition, it could be utilized as a prognostic indicator for AV (cutoff point ≥12.5pg/ml) especially in severe cases with higher sensitivity and specificity.

The present study displayed that IL-17 showed significant positive association with sex, smoking and family history. However, no significant correlation was observed with age, residence, occupation, marital status, dietary habit and history of acne, disease duration, BMI and seborrheic dermatitis. In line with our findings, **Elkamshoushi *et al*.** [28] observed that there were no statistically significant associations among the median IL-17 serum level with age, BMI, and smoking. However, **Bassiouny** & **Shaker** [29] and **Aly *et al*.** [30] reported that serum IL-17 levels showed a non-significant difference as regards gender.

Limitations: The relatively small sample size is considered the main limitation in our study, and it could be essential to conduct a larger scale study. Finally, this study didn't assess the IL-17-secreting cells, and so mush researches are suggested.

CONCLUSION

Serum IL-17 level can be utilized in diagnosis of patients with acne vulgaris. Moreover, it can be utilized as a predictor of disease severity and scarring.

RECOMMENDATIONS

Future studies with a large number of cases have to be conducted to confirm our results. Future studies assessing serum pre- and post-treatment are of great importance in the evaluation of the correlation between IL-17 and therapeutic efficiency.

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