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Assessment of Serum Interleukin-23 in Acne Vulgaris Patients and Its Correlation with Disease Severity

Mohammed S. Sultan[1], Magdy A. Elsohafy[1], Manal M. El-Dsouky[2], Osama G. Mansour*[1]
Departments of [1]Dermatology, Andrology & STDs and
[2]Medical Biochemistry, Faculty of Medicine, Mansoura University, Egypt
***Corresponding author**: Osama G. Mansour, **Mobile**: (+20)01060597017, **Email**: osamamans3@gmail.com

ABSTRACT

Background: Acne vulgaris (AV) is a chronic inflammatory disease of the pilosebaceous unit, which affects adolescents and young adults. Interleukin (IL)-23 and IL-17 have been found to significantly influence the chronic inflammatory response. Furthermore, the discovery of their pathways had contributed to a better understanding of the pathomechanism of inflammatory disorders.

Objective: This study aimed at measuring serum IL-23 concentrations among AV cases with different severities and to compare them with normal controls.

Patients and Methods: This case-control study included 80 subjects who were allocated into 2 groups: Group (A) included 40 cases with acne vulgaris, and group (B) included 40 healthy controls. In the patient group, the Global Acne Grading System Severity (GAGS) was utilized in evaluating the AV severity.

Results: The mean serum IL-23 level was statistically significantly greater in the AV group (48.57 ± 17.63 pg/mL) compared to the control group (11.81 ± 4.28 pg/mL). No significant differences were found regarding serum IL-23 concentrations between child versus adult, males versus females, as well as different nutritional status among AV group. There was significant increase in serum IL-23 concentrations with increased severity of AV group ($p < 0.001$).

Conclusion: Serum IL-23 is not only a marker of the pathogenetic process of AV but also it can serve as a prognostic predictor for AV severity.

Keywords: Serum interleukin-23, Acne Vulgaris, Global acne grading system, Pilosebaceous, Propionibacterium acnes.

INTRODUCTION

AV is a chronic inflammatory skin disorder. It causes significant limitations in social and psychological functions. Also, it usually causes cosmetic complaints. Although, AV commonly develops at puberty, it may also begin in the post-pubertal period [1].

AV presents as comedones (whiteheads and blackheads), papules, pustules, nodules, or cysts. Symptoms such as irritation, itching, and local pain can be associated with decreased quality of life (QOL). Scaring or facial deformities influence about 20% of teens with AV [2]. Acne affects up to 80% of the population and it is mostly found in those aged 15-25 years. Prevalence of acne on age 15-44 years is 34% of males and 27%of females, respectively. Acne lesions often resolve quicker in males in comparison with females. However, males often have a worse presentation [1].

Colonization of pilosebaceous units by Propionibacterium acnes (P. acnes) is a central factor contributing to AV by taking part in the skin inflammation as well as in cutaneous microbiota and innate immune response. Two other factors include an enhanced production and modified composition of the sebum, and hyper cornification of the pilosebaceous duct due to hyperproliferation and abnormal differentiation of keratinocytes in its upper part [3].

It has been recently shown that inflammatory response has a key role in inflammatory and noninflammatory lesions in AV. The inflammatory response in AV itself is related to Propionibacterium acnes that induce keratinocytes to release pro-inflammatory cytokines, mainly IL-1β [4]. Other cytokines associated with pathomechanism of AV include IL-6, IL-8, IL-10, and IL-12 [5].

Propionibacterium acnes induces the release of IL-17 cytokine by Th17 cells [6]. IL-17 has a key role in the pathomechanism of many skin conditions including AV. It is also increased with AV severity indicating that AV can be mediated by Th17 cells [7, 8].

Interleukin-23 has a role in the differentiation and expansion of Th17 lymphocytes from naive CD4+ T lymphocytes. It is also released from dendritic cells and macrophages. IL-23 can facilitate the development of Th17 lymphocytes, which release IL-17 and other cytokines that stimulate epidermal cells to secrete cytokines and chemokines with the subsequent activation of innate immune responses leading to a vicious cycle of inflammatory process involving IL-23/1L-17 axis causing a recurrent inflammation [9].

This study aimed at measuring the serum IL-23 concentrations in AV cases with different severities and comparing them with normal control individuals. It also aimed at further understanding the role of IL-23 in pathomechanism of AV and correlating it with its severity.

PATIENTS AND METHODS

This case-control study included 80 cases that were recruited from the Outpatient Clinic of Dermatology,

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Andrology and STDs of Mansoura University Hospitals. Participants were allocated into 2 equal groups: Group (A) included 40 cases with acne vulgaris, and Group (B) included 40 age- and gender-matched normal controls.

Inclusion criteria: Patients from both genders aged between 15 – 30 years diagnosed with acne vulgaris with different clinical variants, degrees and not receiving systemic treatment in the last 2 months.

Excluded criteria: Patients with history of topical or systemic treatment for AV in the last 60 days, and with a history or clinical evidence of other inflammatory skin diseases, acute or chronic infection, systemic diseases as diabetes mellitus, cardiovascular disease, chronic renal or liver diseases, endocrine pathies or auto immune diseases, and malignancy. Subjects on non-steroid anti-inflammatory drugs or hormonal medications e.g. corticosteroids.

Methods

Each participant was subjected to thorough history taking including age, gender, occupation, marital state, pregnancy and lactation, any special habit, any psychological disturbance, associated medical conditions, history of surgery, drug administration, any other autoimmune disease and duration of acne vulgaris. The participants were examined for weight, height, body mass index (BMI). Dermatologic examination included skin, hair, nails, oral and genital mucosa for exclusion of any associated disease. In the case group, AV severity was determined with GAGS [10]. GAGS considers 6 locations in the face, chest and upper back with a factor for each location according to its surface area (2 for forehead , 2 for each cheek, 1 for Nose, 1 for Chin , 3 for Chest/Upper back), distribution and density of pilosebaceous units. Each region is given a score according to the lesion (No lesion =0, One comedone = 1, Papule=2, One pustule = 3, One nodule = 4) and the sum of scores multiplied by the factors (Local score = Factor × Grade from 0 - 4), the sum of local scores represented the overall score (0–52). The severity is considered as mild with scores 1–18, moderate with scores 19–30, severe with scores 31–38, and as very severe with scores > 38 following the author's recommendation.

Laboratory workup

Using a disposable syringe, 3 ml blood was collected from each individual and then placed in a plain tube. The tubes were left for 30 min until coagulated and then underwent centrifugation for15 min. The resultant sera were collected and kept at−20°C till testing. Serum level of IL-23 was quantified utilizing a commercial kit (Human IL-23 ELISA Kit) using an antibody specific for humanIL-23 coated on wells. All standards and samples were placed into wells, any IL-23 present in a sample was bound to the wells by the immobilized antibody.

Assay Principles

The ELISA kit used the Sandwich-ELISA principle. The micro-ELISA plate was pre-coated with an antibody specific to Human IL-23. Standards or samples were added to plate wells to combine with the specific antibody. After that, a biotinylated detection antibody specific for Human IL-23 and Avid in-Horseradish Peroxidase (HRP) conjugate were added successively to each well and underwent incubation. Free components were washed. The substrate solution was added to each well. Only wells, which contain Human IL-23, biotinylated detection antibody and Avidin-HRP conjugate will appear bluish in colour. Stop solution was added for reaction termination and the colour changed into yellow. The optical density was measured spectrophotometrically at a wavelength of 450 ± 2 nm. The optical density value was proportional to Human IL-23 level.

Assay Procedure

We added 100 µL standard or sample to wells and incubated it over 90 minutes at 37°C. We discarded the liquid, then added 100 µL Biotinylated Detection Ab working solution to each well then incubated over 1 hour at 37°C. The plate underwent aspiration and washing three times then 100 µL HRP conjugate working solution was added with incubation for 30 minutes at 37°C. Then, the plate underwent aspiration and washing for five times then 90 µL substrate reagent was added and incubated for 15 minutes at 37°C. Finally, we added 50 µL stop solution and the plate was read at 450 nm and the results were calculated.

Ethical approval: Medical Ethics Committee of Mansoura Faculty of Medicine gave its approval to this study. All participants gave written consents after receiving all information. The Helsinki Declaration was followed throughout the study's conduct.

Statistical Analysis

Data were analysed by IBM-SPSS software (IBM. Corp. Released 2017. IBM SPSS Statistics for Windows, V 25.0. Armonk, NY: IBM Corp.). Qualitative data were described as numbers and percents. Quantitative data were first tested for normality by Shapiro Wilk's test. Presence of significant outliers (extreme values) will be tested for by inspecting boxplots. Quantitative data were described as means ± standard deviation (SD) if normally distributed or medians and interquartile ranges (IQR) if not. Quantitative data for two groups included independent-Samples t-test and for non-parametric equivalent, Mann-Whitney U test was used. The Pearson product-moment correlation was utilized to detect the strength and direction of a linear correlation among 2 continuous variables. The Spearman's correlation was utilized for measuring the strength and direction of the

relationship among 2 continuous or ordinal variables. A result was considered significant if p value ≤ 0.050.

RESULTS

Our study was conducted on AV 40 cases with a mean age of 21.5 ± 5.87 years, (ranged from 15 to 30). They were 52.5% children and 47.5% adults. They were 37.5% males and 62.5% females. A total of 40 age- and gender-matched normal subjects served as control group. Regarding AV group, mean BMI was 23.93 ± 2.75 kg/m^2. They were stratified according to BMI level into normal, overweight and obese, most of studied AV cases had normal BMI, whereas 25% were over weighted and only 7.5% were obese. No significant differences were found among cases and controls as regards anthropometric measures and nutritional status (p > 0.05 for each) as shown in table (1). The mean disease duration in AV cases was 23.32 ± 20.08 months, and it ranged from 1 to 84 months.

Table (1): Demographics and anthropometric data of the study groups

	AV (N = 40)		Control (N = 40)		*Test*	*p*
Age (years)						
Mean ± SD.	21.5 ± 5.87		22.43 ± 4.29		t=0.805	0.925
Median (Range)	18 (15 - 30)		22.5 (15 - 31)			
Age groups	**No**	**%**	**No**	**%**		
Child	21	52.5%	13	32.5%	X^2=3.274	0.070
Adult	19	47.5%	27	67.5%		
Sex						
Male	15	37.5%	15	37.5%	X^2=0	1
Female	25	62.5%	25	62.5%		
Weight (kg)						
Mean ± SD.	61.53±7.47		63.33±7.24		T=1.094	0.277
Median (Range)	60(42-85)		64(41-75)			
Height (m)						
Mean ± SD.	1.63±0.07		1.64±0.07		T=0.620	0.537
Median (Range)	1.61(1.5-1.8)		1.65(1.5-1.8)			
BMI (kg/m^2)						
Mean ± SD.	23.93±2.75		25.04±3.82		T=1.490	0.140
Median (Range)	23.3(18.7-30.1)		24.65(18.2-37.2)			
Nutritional status	**No**	**%**	**No**	**%**		
Normal BMI	27	67.5%	22	55.0%	X^2=1.692	0.425
Over weight	10	25.0%	12	30.0%		
Obese	3	7.5%	6	15.0%		

SD. Standard deviation, Range: Min. – Max. t: Student t-test; X^2, chi square test.

Mean acne score was 25.65 ± 9.46, it ranged from 9 to 43. All studied cases were stratified according to GAG score, 30% had mild, 42.5% had moderate, 10% had severe and 17.5% had very severe grades (Table 2).

Table (2): Acne score and severity among patients with acne vulgaris

	AV (N = 40)	
Acne score		
Mean ± SD.	25.65±9.46	
Median (Range)	24(9-43)	
Severity	**No**	**%**
Mild	12	30.0%
Moderate	17	42.5%
Severe	4	10.0%
Very severe	7	17.5%

In table (3), the mean serum IL-23 level was statistically significantly higher in the AV cases, than in controls ($p < 0.001$).

Table (3): Comparison of serum IL23 levels among patients with AV and controls.

	AV (N = 40)	**Control (N = 40)**	***Test***	***P***
Serum IL23 (pg/mL)				
Median (Range)	47.16(17.21-76.9)	10.34(5.45-20.94)	U=5	**<0.001***

Median, Range: non-parametric test U, Mann Whitney test

Table (4) showed the association between serum IL-23 concentrations with other studied parameters among AV group. No significant differences were detected regarding serum IL-23 concentrations between children versus adults, males versus females, as well as different nutritional status among AV group ($p > 0.05$ for each). Concerning the association between serum IL-23 level with other studied parameters among control group, no significant differences were revealed as regards serum IL23 level between children versus adults, males versus females, as well as different nutritional status among controls ($p > 0.05$ for each).

Table (4): Association between serum IL-23 with other studied parameters among acne vulgaris patients and control group.

	Serum IL-23 (pg/mL)					***Test***	***P***
	Mean	**±SD**	**Median**	**Range**			
Acne Vulgaris Patients							
Age groups							
Child	51.64	18.56	58.48	20.61	76.90	U=161	0.297
Adult	45.16	16.34	45.11	17.21	74.21		
Sex							
Male	48.09	21.07	42.35	17.21	76.90	U=183	0.900
Female	48.85	15.68	49.21	20.61	76.63		
Nutritional status							
Normal BMI	47.58	18.23	45.11	17.21	76.63	H=0.907	0.636
Over weight	48.71	13.74	46.71	32.25	76.21		
Obese	56.95	27.79	68.73	25.21	76.90		
Control Group							
Age groups							
Child	11.06	4.87	10.26	5.81	20.94	U=144.5	0.371
Adult	12.17	4.02	10.42	5.45	20.33		
Sex							
Male	11.35	3.56	10.34	5.45	17.07	U=182.5	0.889
Female	12.08	4.71	10.34	5.77	20.94		
Nutritional status							
Normal BMI	11.33	4.05	10.29	5.77	20.94	H=0.416	0.812
Over weight	11.88	4.23	10.38	5.45	20.21		
Obese	13.40	5.52	15.15	6.22	20.33		

t: Student t-test. U, Mann Whitney test. H, Kruskal Wallis test.

Table **(5)** demonstrated the relationship between serum IL-23 concentrations with severity among acne vulgaris patients. Serum concentrations of IL-23 showed significant increase with increased severity of AV group ($p < 0.001$).

Table (5): Association between serum IL-23 levels with severity among acne vulgaris patients.

	Serum IL-23 (pg/mL)		***Test***	***P***
	Mean ± SD.			
Severity				
Mild	28.56	7.13	H=32.461	<0.001*
Moderate	48.99	9.30		
Severe	64.19	2.79		
Very severe	72.92	4.66		

t: H, Kruskall Wallis test; *: Significant when $p<0.05$.

A receiver operating characteristic curve (ROC) of serum IL-23 was conducted to discriminate between AV cases and controls. A high accuracy AUC was found (AUC=0.997). At best cut-off value of 20.9 pg/mL, sensitivity was 95%, specificity was 100%, PPV was 100%, NPV was 95.2% and accuracy was 97.5% (Table 6). Grades of severity were merged into 2 categories (mild + moderate) and (severe + very severe). A ROC was conducted for prediction of severity. A high accuracy AUC was found (AUC=0.976). At best cut-off value of 61.3 pg/mL, sensitivity was 90.9%, specificity was 96.6%, PPV was 91%, NPV was 96.6% and accuracy was 95% (Table 6).

Table (6): Validity of serum IL-23 for discriminating AV cases from controls and for predication severity (severe + very severe) versus (mild+ moderate).

	IL-23 for discriminating AV cases from controls	**IL-23 for Predication severity (severe + very severe) versus (mild+ moderate)**
AUC	0.997	0.976
95% CI	0.990-1	0.935-1
P	<0.001	<0.001
Cut off (pg/mL)	>20.9	>61.3
Sensitivity (%)	95	90.9
Specificity (%)	100	96.6
PPV (%)	100	91.0
NPV (%)	95.2	96.6
Accuracy (%)	97.5	95.0

AUC, area under ROC curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Regression analysis was performed to predict susceptibility for AV, using age, sex, BMI and serum IL-23 level as confounders. Only serum IL-23 level was considered a predictor for AV susceptibility (Table 7).

Table (7): Logistic Regression analysis for prediction of AV susceptibility.

	P	**OR**	**95% C.I.**
Age	0.417	0.978	0.927-1.032
Sex	1.000	1.000	0.567-1.763
BMI	0.139	0.936	0.858-1.022
serum IL23	0.010	1.514	1.106-2.073

OR, odds ratio; CI, confidence interval. *: P value Significant <0.05

DISCUSSION

AV is a chronic inflammatory disease of pilosebaceous units, which affects adolescents and young adults [11]. The usual sites of AV lesions are face, chest, and upper back. Acne may present as comedones, papules, pustules, nodules, or cysts. Scars, sometimes keloids, can occur even after the resolution of inflammatory response [12].

AV is a multifactorial disorder, with genetic factors being the main factor for its pathomechanism [13]. It develops as a result of an interaction of increased sebum production, follicular epidermal hyper proliferation with subsequent plugging of the orifices, P. acnes activity, and inflammatory response [14]. It was proposed that the inflammatory response continues to occur in the early and late stages of the disease [15].

Interleukin-23 and IL-17 have been found to significantly influence chronic inflammatory response. Furthermore, the discovery of IL-23/IL-17 pathway has led to better understanding of the pathomechanism of inflammatory conditions [16]. Treatment of inflammatory disorders has advanced from general immunosuppression to biologic agents targeting the IL-23/IL-17 pathway e.g. IL-17, IL-12/23 and IL-23 inhibitors [17].

This study aimed at measuring serum IL-23 levels in cases with AV that have different severities and comparing them with normal control subjects, for better understanding of the role of interleukein-23 in pathomechanism of AV and correlating it with acne vulgaris severities. Our study included 80 subjects who were subdivided into 2 groups: Group A included 40 cases with AV, while group B included 40 age- and sex-matched normal controls.

The mean age in group A was 21.5 ± 5.87, while in group B was 22.43 ± 4.29 years. There were 37.5% males and 62.5% females in both groups. The present study demonstrated a non-significant difference among both groups as regards age and sex. Moreover, there was a female predominance among our cases. Our results coincide with **Albuquerque *et al*.** [18] study, where 452 adolescents are included in his study 62.4 % of them were females. Our results also agree with **AlKhabbaz *et al*.** [19] who revealed that differences in psychological triggers of acne can clarify its higher prevalence in females than in males. Polycystic ovary syndrome could also be a risk factor for some AV cases in females.

Our results revealed a non-significant difference among both groups as regards BMI. This agrees with **Szepietowski *et al*.** [20] study that did not find significant differences regarding BMI of AV cases and healthy control. But it is against **Lu *et al*.** [21] who reported that patients with AV had higher BMI. Also, **Al-Hussein *et al*.** [22] revealed that mean BMI in AV cases were significantly higher compared to controls.

The current study revealed that 30% of cases were mild, 42.5% were moderate, 10% were sever and 17.5%

were very sever and their score ranged from 9 to 43 with median of 24 (9 – 43). This is similar to **El-Tonsy *et al*.** [23] study, in which the disease was mild in 32%, moderate in 46%, and severe in 22% of studied patients.

To the best of our knowledge, our study is the first one to measure serum IL-23 concentrations in AV cases with different severities. The mean serum IL-23 level in our study was statistically significantly higher among the AV cases (48.57±17.63 pg/mL) compared to the control group (11.81±4.28 pg/mL) ($p<0.001$). Also, there was significant increase in IL-23 concentrations with increased severity of AV ($p<0.001$), it was higher among severe acne. Consistent with our findings, **Gerenova *et al.*** [24] reported an increase of serum IL-23 concentration with increasing AV severity. Also, consistent with our findings, **Schlapbach *et al*.** [25] showed that IL-23/Th17 axis is highly expressed in hidradenitis suppurativa (HS). Furthermore, targeting the IL-12/IL-23-common subunit p40 with monoclonal antibodies might serve as a novel therapeutic choice for HS. Also, **Matusiak *et al*.** [26], demonstrated that high expression of serum TNF-a, IL-1, IL-17, and IL-23 levels in HS. This agrees with **Wendling *et al*.** [27], who revealed that IL-23/Th17 pathway was involved in SAPHO syndrome. TH17 lymphocytes were increased in the peripheral blood of those with SAPHO syndrome. This also agrees with **Ebrahim *et al*.** [28] who assessed serum IL-17 concentrations among AV cases aiming at clearer understanding of its pathomechanism. They found that serum IL-17 levels were significantly greater among AV cases in comparison with control subjects and serum IL-17 concentrations increased significantly with increased disease severity and also in cases with scar lesions.

In this study, a non-significant association existed between serum IL-23 and age, weight¸ height, and BMI. Similarly, **Saleh *et al*.** [29], demonstrated that serum IL-19 concentration did not show significant correlation with age, sex, or duration of disease indicating that IL-19 level has a direct correlation with the inflammation in AV not with the demographics. ROC showed that the best cut-off point of serum IL-23 to discriminate between AV patients and control group was > 20.9 with sensitivity of 95.0%, specificity of 97.5%, PPV of 100%, NPV of 95.2% and total accuracy of 97.5%.

CONCLUSION

Serum IL-23 is not only a marker of pathogenetic process of AV but also it could be a prognostic predictor for severity in AV.

RECOMMENDATION

On the basis of our findings in this study, IL23 as a marker in AV and in conjunction with that from previous studies, we suggested that IL-23 was a significant biomarker that may have a key role in the pathogenetic process of AV and requires closer attention in the study dealing with management of acne vulgaris, more studies and wider sample groups are necessary to certificate our initial suggestions.

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