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CORRELATION OF INTERLEUKIN-23 SERUM LEVELS IN MEN WITH ACNE VULGARIS: A PRELIMINARY STUDY

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ABSTRACT

Background: Acne vulgaris (AV) is an inflammatory condition of pilosebaceous unit that is common in adolescents and young adults. The pathogenesis of AV is multifactorial, one of which is inflammation. Interleukin-23 (IL-23) has an important role in the activity of T helper 17 (Th17) cells that produce IL-17 in chronic inflammation. **Objective:** To determine the correlation between IL-23 serum levels and AV severity in men. **Methods:** This is an analytical observational preliminary study with a cross-sectional design involving 15 male subjects with AV who were divided into groups of AV severity based on Lehmann's criteria. The subjects were examined for IL-23 serum levels. Data were analyzed using Spearman's Rho non-parametric correlation test to determine the correlation between variables. **Results:** Mean IL-23 serum levels in men with AV was 111,05 ± 115,27 pg/ml, with mild AV was 210,57 ± 122,038 pg/ml, moderate AV was 103,65 ± 91,15 pg/ml and severe AV was 18,94 ± 15,76 pg/ml. There is a significant correlation between IL-23 serum levels and AV severity in men. (p = 0,001). IL-23 serum levels decreased with increasing AV severity (r = -0,756). **Conclusion:** There is a strong negative correlation between IL-23 serum levels and AV severity in men.

Keywords: Acne Vulgaris, Lehmann's Criteria of Acne Vulgaris Severity, Interleukin-23

INTRODUCTION

Acne vulgaris (AV) is a chronic inflammation of pilosebaceous follicles generally found in teenagers and early adulthood.[1,2] AV is marked by the appearance of comedones, papules, cysts, and pustules with a predilection on the face, neck, chest, and back.[3,4]

As much as 85% of the population had AV, most commonly found on the age of 15-25 years. Prevalence of AV on age 15-44 years is 34% of males and 27% of females, respectively. AV usually resolve quicker in males compared to females. However, males tend to have a worse presentation.[5,6] AV severity can be assesed by their clinical presentation using a consensus made by the Indonesian Society of Dermatology and Venereology according to Lehmann's gradation system which groups AV into three grades: mild, moderate and severe.[7]

The exact mechanisms for AV pathogenesis is
still unknown, but there are four main contributing factors: follicular hyperproliferation, increased sebum production, bacterial colonization, and inflammatory process.[8] The process of inflammation leading to AV is related to host immune response which targets *Propionibacterium acnes*, a commensal bacteria in human skin found in pilosebaceous follicles.[9]

Propionibacterium acnes can induce IL-17 secretion by Th17 lymphocytes, which is a subset of T cell that produces IL-17. IL-17 is a proinflammatory cytokine that has a prominent role in the pathogenesis of several skin diseases including AV. This cytokine is also increased along with AV severity. This indicates that AV can be mediated by Th17 lymphocytes.[10-12]

IL-23 have a role in the differentiation and expansion of Th17 cells from naive $CD4^+$ T cells.[13] IL-23 is also produced by the innate immune system such as dendritic cells and macrophages. This cytokine can facilitate the development of Th17 cells that produces IL-17 and other mediators which stimulates epidermal cells to produce cytokines and chemokines that attract and activate the innate immune system. A vicious cycle of inflammation involving IL-23/1L-17 axis causing a recurrent inflammation.[14]

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Based on the effects of IL-23 on the immune system, this cytokine has a dominant role in the pathogenesis of AV through the IL-23/IL-17 axis. The purpose of this preliminary study is to identify a correlation between IL-23 serum levels and AV severity in men.

METHOD

This is an analytical observational preliminary study with a cross-sectional design conducted in September 2020. Consecutive sampling was done involving 15 males subjects with AV in Semarang. The inclusion criteria for the subjects are as follows: men aged 15-25 years old, suffers from AV which is classified into mild, moderate, and severe grade based on Lehmann's criteria, and willing to be a research subject by signing an informed consent papers. The subjects were divided into three groups based on the grade of AV severity of mild, moderate and severe with a sample size of 5 subjects per group.

Physical examination of the subjects face was done by a dermatologist to determine the grade of AV severity based on Lehmann's criteria. Three milliliters of venous blood was sampled from the subjects, which were then centrifuged to obtain the serum components for examination of IL-23 serum levels using the ELISA method at GAKI Laboratory, Semarang.

The data were analyzed with a computer statistical analysis program. Correlation between IL-23 serum levels and grade of AV severity was analyzed with Spearman's Rho correlation test and a significant difference is determine if $p < 0,05$.

RESULTS

This research involves 15 subjects, with 5 subjects in each category (mild, moderate, severe) (33,3%) as described in Table 1.

Table 1. Research subjects characteristics

Variable	F	%	Mean ± SD	Median (min – max)
Age			20,27 ± 1,75	20 (17 – 23)
IL-23 (pg/ml)			111,05 ± 115,27	60,47 (7,31 – 377,5)
Grade of severity				
Mild	5	33,3		
Moderate	5	33,3		
Severe	5	33,3		

The subject's mean age was 20,27 ± 1,75 years old with the minimal age was 17 years old and the maximum age was 23 years old. Mean of IL-23 serum levels for all subjects was 111,05 ± 115,27 pg/ml, with the mininum level was 7,31 pg/ml and the maximum level was 377,5 pg/ml.

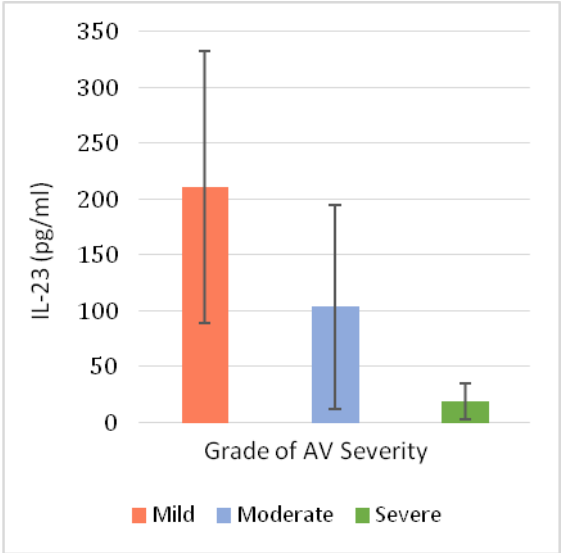

Figure 1. IL-23 serum levels based on grade of AV severity

IL-23 serum levels in subjects with mild grade of AV severity was 210,57 ± 122,038 pg/ml, with the minimum level was 60,47 pg/ml and the maximum level was 377,5 pg/ml. IL-23 serum levels in subjects with moderate grade of AV severity was 103,65 ± 91,15 pg/ml, with the minimum level was 10,36 pg/ml and the maximum level was 236,40 pg/ml. IL-23 serum levels in subjects with severe grade of AV severity was 18,94 ± 15,76 pg/ml, with the minimum level was 7,31 pg/ml and the maximum level was 45,88 pg/ml.

Table 2. Correlation test of IL-23 serum levels and AV severity

Variable	*P*	r
Grade of AV Severity IL-23	0,001	-0,756

Spearman's Rho correlation test showed that there was a significant correlation between IL-23 serum levels and grade of AV severity in males ($p = 0,001$). A correlation coefficient of more than 0,5 indicates a strong negative correlation between

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IL-23 serum levels and grade of AV severity (r = -0,756).

There was an inverse correlation between the two variables, such that a decrease in IL-23 serum levels correlates with an increase in grade of AV severity.

DISCUSSION

This preliminary study was conducted on 15 male research subjects in Semarang who were grouped based on the grade of AV severity into mild, moderate and severe AV severity groups based on Lehmann's criteria. Blood sample was taken from the subjects to examine the IL-23 serum levels. IL-23 levels have been extensively studied in relation to autoimmune conditions and chronic inflammation, but no previous studies have examined the association between IL-23 serum levels and AV conditions and severity.

Based on the research done by Purwaningdyah and Tjekyan, it was found that the occurrence of AV was higher in males than females.[5,15] This can be caused by the role of androgen hormones in men which can increase sebum production, leading to a more severe AV in males. In addition, women tend to have a higher awareness to seek medical attention in dealing with AV conditions.[15]

The age range of subjects in this study was 17-23 years. A study by Ayudianti et al showed that most AV patients were in the 15-24 year age group.[3] The incidence of AV is closely related to hormonal activity, where there is an increase in androgen hormones at puberty and then decreases after reaching its peak between the ages of 18-20 years.[16] Androgen hormones can stimulate sebaceous glands to produce more sebum thus propagate the occurrence of AV.[17]

The results of the study showed that the mean IL-23 serum levels in men suffering from AV was 111,05 ± 115,27 pg/ml, with the IL-23 serum levels at mild AV severity was 210,57 ± 122,038 pg/ml, moderate AV was 103,65 ± 91,15 pg/ml and the severe AV was 18,94 ± 15,76 pg/ml. Data analysis showed a *p* value of *p* = 0,001, which indicates that there is a significant correlation between IL-23 serum levels and AV severity in men. The correlation coefficient value obtained r = -0,756 which indicates a strong negative correlation, that is, if there is an increase in the grade of AV severity, there is a decrease in IL-23 serum levels in men. These results differ from the research hypothesis, namely that there is a positive correlation between IL-23 serum levels and AV severity in men.

IL-23 cytokine is known to have a major role in inducing differentiation of $CD4^+$ T cells into Th17 cells which produces IL-17, so that IL-17 levels are comparable to IL-23 which affects their production.[13] Based on a study by Murlistyarini et al and Ebrahim et al, it was found that there was a significant correlation between IL-17 levels and AV severity, where an increase in serum IL-17 correlates with an increase in AV severity.[10,12] This is in contrast with the results of this study which showed that a decrease in IL-23 serum levels is followed by an increase in AV severity in the subjects.

IL-17 is not only produced by Th17 cells, but also by the cells of the innate immune system such as mast cells and neutrophils granulocytes.[14] A research by Kelhala et al showed that Th17 pathways also contributes to an inflammatory response in AV.[18] Inflammation mediated by Th17 can be caused by a number of exogenous factors such as vitamin D3, UV radiation, or other cytokines like IL-9. So that apart from the role of IL-23, innate immune cells and the factors mentioned above also influence the production of IL-17.[14,18]

A study by Ibrahim et al showed a significant increase in serum IL-12 in subjects with AV when compared with healthy control.[19] During chronic inflammation, dendritic cells and macrophages produced IL-23 which drives Th17 differentiation. Dendritic cells and macrophages also produces IL-12 that stimulates Th1 cells to produce IFN-γ. Th17 differentiation is suppressed by IFN-γ by reducing IL-23 receptors, thus disrupting the 1L-23/IL-17 axis. This may cause a decrease in IL-23 levels.[13]

Various factors of the research subjects can also influence the results of this study. These include psychological stress conditions, obesity, and excessive fat and carbohydrates intake that can increase the release of proinflammatory cytokines.[20,21] However, this conditions was not explored further in this study. In addition, the assessment of AV severity in the subjects was carried out by physical examination to calculate the number and type of facial lesions. This could also

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bias the study because AV lesions in other locations such as back and chest in the subjects were not taken into account.

The calculating method of AV lesions by Lehmann's criteria describes the grade of AV severity by the number and type of AV lesions, so the grade of inflammation in the lesions is difficult to determine. According to a study by Maulinda et al, it was shown that there was no significant difference between IL-17 serum levels in the papulopustular and comedonal AV type. Comedones which are clinically non-inflammatory lesions have also undergone an inflammatory process with the discovery of proinflammatory cytokines such as IL-1α, TNF-α and $CD4^+$ T cells in comedone lesions.[22] So that the grade of AV severity assessed based on the type of AV lesion cannot reflect the grade of inflammation that occurs.

As it is a preliminary study, references regarding the correlation between IL-23 serum levels and AV severity are limited. Due to COVID-19 pandemic, physical examination of the subjects was done using photographs which could affect the assessment of the AV severity. In addition, the limited sample size of this study cannot fully represent the male population. This study did not examine IL-17 serum levels, the onset of AV in subjects and other confounding factors that could affect IL-23 serum levels AV and inflammatory conditions in the subjects.

CONCLUSION

In conclusion, there was a strong negative correlation between IL-23 serum levels and AV severity in men. In this study, it is necessary to further investigate the relationship between IL-23 serum levels and the grade of AV severity in men by using a larger number of samples and a wider population scope. In addition, it is necessary to investigate the involvement of other factors that can influence AV inflammatory conditions in men.

Ethical Approval

This study received Ethical Clearance from the Health Research Ethics Commission, Faculty of Medicine, Diponegoro University with ethical clearance number No. 217/EC/KEPK/FK-UNDIP/2020.

Conflicts of Interest

There are no conflict of interest in this study.

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