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Vit D and Interleukin-17 Levels in Patients with Acne Vulgaris Severity in Anbar Governorate.

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Abstract

Acne vulgaris is a common inflammatory skin disorder influenced by immune responses, particularly involving interleukin-17 (IL-17) and vitamin D (Vit.D). This study aimed to evaluate the relationship between serum IL-17 and Vit.D levels with acne severity. Blood samples were collected from 96 patients with acne vulgaris and 84 healthy controls in Haditha District, Anbar Governorate. Participants were matched by age and gender. Serum IL-17 and Vit.D levels were measured using Sandwich-ELISA. Results showed significantly higher IL-17 levels and lower Vit.D levels in acne patients compared to controls ($P < 0.0001$). Acne severity was positively correlated with IL-17 and inversely with Vit.D levels ($P < 0.001$). Female patients had higher IL-17 levels and more pronounced Vit.D deficiency than males. Although no direct correlation was found between IL-17 and Vit.D levels, both markers were significantly associated with disease severity and gender. ROC analysis demonstrated their diagnostic potential. In conclusion, elevated IL-17 and Vit.D deficiency are strongly linked to acne pathogenesis and may serve as biomarkers or therapeutic targets in acne management.

مستويات فيتامين د و الانترلوكين 17 لدى المرضى حب الشباب الشديد في محافظة الانبار

عبد الله زيد خلف، وجيه يونس العاني , عبد الله صالح حسن

خلاصة

يعد الجهاز المناعي أحد العوامل التي يمكن أن تؤثر على شدة حب الشباب الشائع، وهو حالة جلدية التهابية شائعة. يعد Interleukin-17 (IL-17) وفيتامين د (Vit.D) مكونين أساسيين يساهمان في تطور الالتهاب في حب الشباب. إن فهم العلاقة بين IL-17 ومستويات فيتامين د وشدة حب الشباب قد يوفر رؤى مهمة حول الأهداف المحتملة للعلاج وطرق علاج حب الشباب لدى الأفراد. تضمنت الدراسة 96 مريضا مصابا بحب الشباب و 84 مجموعة ضابطة في عينات الدم المستخدمة في هذه الدراسة. قسم المرضى والضوابط بالتساوي على أساس العمر والجنس وشدة الحالة. جمعت العينات في قضاء حديثة بمحافظة الأنبار. في هذه الدراسة استخدمت تقنية ELISA. لوحظ نقص فيتامين د. مصحوبًا بزيادة في IL-17 في المرضى الذين يعانون من حب الشباب الشائع مقارنةً بالأشخاص الأصحاء (قيمة P <0.0001). وارتبطت مستويات فيتامين د عكسيا مع شدة حب الشباب (P <0.001). وارتبطت مستويات IL-17 طرديا مع شدة المرض (P <0.001)، وشوهدت مستويات أعلى من IL-17 في الإناث مقارنة بالذكور (P <0.001). وكان الانخفاض في فيتامين د أكثر وضوحا بين الإناث منه بين الذكور. علاوة على ذلك، لم يلاحظ أي ارتباط بين مستويات مصل IL-17 وفيتامين د. ومع ذلك، كان هناك ارتباط سلبي قوي بين مستويات مصل IL-17 وفيتامين. د مقارنة بالجنس وأيضا على مستوى شدة المرض. وقد لوحظ وجود ارتباط سلبي ضعيف بين IL-17 وفيتامين د- مستويات المصل مقارنة بخطورة المرض. كما لوحظ وجود علاقة سلبية قوية بين مستويات IL-17 وفيتامين د في مصل الدم مقارنة بخطورة المرض والجنس. استخدم منحنى ROC لتقييم أداء IL-17 وفيتامين د. خاتمة. أظهرت هذه الدراسة أن IL-17، وهو السيتوكين الالتهابي، يؤدي إلى تفاقم حب الشباب. ومن ناحية أخرى، فقد تبين أيضًا أن نقص فيتامين د يزيد من شدة حب الشباب. هناك علاقة سلبية بين انخفاض فيتامين د ومستويات عالية من IL-17. يكون نقص أكثر انتشارًا في مرضى حب الشباب مقارنة بالأشخاص الأصحاء.

1. Introduction

The common dermatological condition known as acne vulgaris is characterized by inflammation and blockage of sebaceous glands and hair follicles (Alajeel & Hasan, 2021). is a chronic inflammatory disorder of pilosebaceous units with polymorphic nodules, including closed and open comedones, pimples, pustules, and nodules. It is detected in 85% of teenagers worldwide (Kutlu et al., 2023).The pathogenesis extrinsic to P. acnes colonization and infection is well known, and includes hormones, hyper keratinization and plugging of sebaceous ducts, sebum production, and the ensuing colonization insecurity and irritation of certain facts. In contrast, the formations and their interactions are not well understood in sequence (Alajeel & Hasan, 2021; Kang et al., 2005; Kutlu et al., 2023). The severity of AV is influenced by the immune system, particularly by T helper (Th) 1, Th2, and Th17 cells. Interleukin-17 (IL-17), which is produced by Th17 cells, has a part in acne, according to a study conducted by Kim's group. Another study highlighted how crucial Th1 and Th17 cytokines are to acne vulgaris. Both protein levels and the mRNA of IL-17A, a crucial Th17 signaling pathway effector cytokine, were significantly elevated in acne lesions. Moreover, they discovered an increase in Th17-related cytokines at the mRNA level, including IL-6, TGF-β, IL-1β, and IL-23 (Agak et al., 2014; Kelhälä et al., 2014). Vitamin D (Vit D) plays a crucial role in immune regulation, keratinocyte and sebocyte proliferation, and differentiation. Moreover, it functions as an antioxidant by inducing critical enzymes such as glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD), thereby helping to prevent comedone formation. Inflammatory papulopustular acne patients often exhibit reduced levels of these antioxidant enzymes. Deficiency of these antioxidants is frequently observed in papulopustular acne. Additionally, Vit D enhances the production of antimicrobial peptides like cathelicidin, highlighting its importance in acne pathogenesis (Alhetheli et al., 2020; Chang & Lee, 2019; Iqbal et al., 2023; Spiro & Buttriss, 2014). Importantly, the active form, 1,25-dihydroxyvitamin D, directly suppresses IL-17 gene transcription and impairs IL-17 production by Th17 cells in response to *P. acnes*, highlighting a potential therapeutic mechanism in acne. Although Vit D and IL-17 each have documented roles in acne vulgaris pathophysiology, few studies have simultaneously evaluated their relationship (A. Singh et al., 2021). Our study addresses this gap by comparing serum IL-17 and Vit.D levels between acne patients a know if you'd like this formatted in Harvard style or need full reference details.

2. Patients and Methods

This study involved a total of 96 patients diagnosed with acne vulgaris, comprising 48 males and 48 females. Each group was further categorized by a specialist physician into three subgroups based on disease severity: mild, moderate, and severe. Participants were matched for age, ranging from 13 to 20 years. An additional 84 healthy individuals served as the control group, equally divided into 42 males and 42 females, and matched by age with the patient cohort. Participants were recruited from intermediate and preparatory schools in Haditha City, as well as from the College of Basic Education/Haditha. The study procedures were conducted in the laboratories of the College of Basic Education/Haditha and Haditha General Hospital. Venous blood samples (5 mL) were collected using sterile, disposable gel tubes. Samples were allowed to clot at 37°C for 10–15 minutes, followed by centrifugation at 3000 rpm for 10–15 minutes to separate the serum, which was then stored at −20°C. Serum levels of interleukin-17 (IL-17) and vitamin D were measured using a sandwich ELISA kit (SunLong Biotech Co., Ltd., China) on a Human Reader Hs ELISA system (Germany).

2.1. Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics version 26. One-way and two-way ANOVA with Tukey's post hoc test, along with the Student's t-test, were used to assess group differences. Pearson's correlation coefficient (r) was applied to determine associations between variables. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values and assess the predictive performance (AUC) of serum biomarkers. The Shapiro–Wilk test confirmed the normal distribution of quantitative data, which were expressed as mean ± standard deviation (SD).

3. Results

Patient and control groups were similar in age and gender Table1. However, the patients' mean BMI ± SD was higher than the AV patients. For the IL-17 relationship between control groups and acne patients, the mean ± SD for the control group was (404.07±71.125) (pg/ml) with a percentage of (46.67%). For acne patients, it was (708.28±165.114) (pg/ml) and by a rate of (53.33%), which gave a p-value higher than (0.0001), which indicates that there are statistically significant differences in IL-17 between the control group and the patient group. The relationship between gender and IL-17, as the mean ± SD for the control group for males, was (344.95±49.419) (pg/ml) (N=42), while its value for females was (463.18± 25.284) (pg/ml) (N=42). Its value for acne vulgaris patients was (835.73± 95.976) (pg/ml) (N=48) for males and (580.83±112.756) (pg/ml) (N=48) for females, where the P value for males was higher than (0.0001) While the P value for females was higher than (0.0001), Table1. This suggests a significance between the IL-17 variant and acne vulgaris in males and females for both the patient and the control groups.

Table1: Clinical and Demographic Characteristics of Acne Patients and Control Subjects

Parameter	Mean Parameter ± SD		*p*-Value
	Controls	patients	
Age (year)	16.64±2.342	16.50±2.303	0.681
BMI (kg/m2)	18.994±2.378	24.086±4.576	< 0.0001
IL-17 (pg/mL)	404.07±71.125	708.28±165.114	<0.0001
Male	344.95±49.419	835.73±95.976	< 0.0001
Female	463.18±25.284	580.83±112.756	< 0.0001
Vit. D (ng/ml)	8.13±1.746	20.08±0.537	<0.0001
Male	19.60±0.218	9.21±1.544	< 0.0001
Female	20.55±0.256	7.05±1.181	< 0.0001
SD= Std. Deviation.			

The results showed the IL-17 for AV severity Table2 as the mean ±SD of mild, moderate, and severe stimulation (607.38±134.428, 695.24±166.814, and 822.22±116.456), respectively. The P value was higher than 0.001 between mild and severe, the P value = 0.0014 between moderate and severe, and the P value = 0.0 377between mild and moderate, all significant. The results of the study showed two-way ANOVA of variance (Tukey's test for comparative analysis) that the P values were statistically significant for the average acne severity of males as shown in Table2 where it is mean ± SD was mild (728.81±58.852), moderate (855.23±35.356) and severe (923.16±58.270) for males P values mild vs. moderate was higher than (0.001), mild vs. severe was higher than (0.001) and moderate vs. severe (0.007) were significant for all comparisons. The relationship between acne

severity and gender with IL-17 Results for females were mean ± SD (485.94±49.244), (535.26 ±40.658), (721.28±53.830) mild, moderate, and severe, respectively, P values mild vs. moderate (0.0179) mild vs. severe was higher than (0.001) moderate vs. severe was higher than (0.001) were significant for all comparisons.

Table2: Relationship Between Acne Severity with IL-17 And Vit.D and Genders

Parameter	Mean Parameter ± SD			Tukey's multiple comparisons test	P Value
	Mild	Moderate	Severe		
IL-17 (pg/ml)	607.38±134.428	695.24±166.814	822.22±116.456	mild vs. moderate	0.0377
				Mild vs. Severe	<0.001
				Moderate vs. Severe	0.0014
Male	728.81±58.852	855.23±35.356	923.16±58.270	Mild vs. Moderate	<0.001
				Mild vs. Severe	<0.001
				Moderate vs. Severe	0.007
Female	485.94±49.244	535.26 ±40.658	721.28±53.830	Mild vs. Moderate	0.0179
				Mild vs. Severe	<0.001
				Moderate vs. Severe	<0.001
Vit. D (ng/ml)	9.21±1.714	8.12±1.429	7.07±1.411	Mild vs. Moderate	0.0141
				Mild vs. Severe	<0.001
				Moderate vs. Severe	0.0188
Male	10.42±1.385	9.16 ±1.166	8.07±1.115	Mild vs. Moderate	0.0036
				Mild vs. Severe	<0.001
				Moderate vs. Severe	0.0137
Female	8.01±1.031	7.08 ±0.742	6.07±0.862	Mild vs. Moderate	0.0418
				Mild vs. Severe	<0.001
				Moderate vs. Severe	0.0243

The association between control groups and acne patients regarding Vit. D. Table1 for the control group, the mean ± SD was (8.13±1.746) (ng/ml) with a percentage of 46.67%, and for the acne patients, it was (20.08±0.537) (ng/ml) with a rate of 53.33%. This resulted in a p-value greater than (0.0001), indicating statistically significant differences in Vit. D between the patient group and the control group. The relationship between gender and Vit.D, as the mean ± SD for the control group for males, was (19.60±0.218) (ng/ml) (N=42), while its value for females was (20.55±0.256) (ng/ml) (N=42). Its value for acne vulgaris patients was (9.21±1.544) (ng/ml) (N=48) for males and (7.05±1.181) (ng/ml) (N=48) for females, where the P value for males was higher than (0.0001) While the P value for females was higher than (0.0001). This indicates a significance between the control group and acne vulgaris for males and females. The results showed the Vit.D for acne severity [Table 2] according to the mean ±SD of mild, moderate, and severe stimulation (9.21±1.714, 8.12±1.429 and 7.07±1.411) respectively. The P value was <0.001 between mild and severe, the P value 0.0188 between moderate and severe, and the P value 0.0141 between mild and moderate, all significant. The study's results showed that a two-way ANOVA of variance (Tukey's test for comparative analysis) showed that the P values were statistically significant for the average acne severity of males, where its mean ± SD was mild (10.42±1.385), moderate (9.16 ±1.166), and severe (8.07±1.115) for males. The p-value for Mild vs. Severe was greater than (0.001), Mild vs. Moderate (0.0036), and Moderate vs. Severe (0.0137). The relationship between acne severity and gender with VitD results for females were mean ± SD (8.01±1.031), (7.08±0.742), and (6.07±0.862) for mild, moderate, and severe, respectively. P values for Mild vs. Moderate (0.0418) and Mild vs. Severe greater than (0.001) and Moderate vs. Severe (0.0243) were significant for all comparisons. The results of linear regression analysis showed a non-significant correlation between IL-17 and (Vit. D) blood serum AV patient $p = 0.512$, $p = (0.068)$. Still, when compared with gender, it gave a strong negative correlation $p < 0.01$, $r = (-0.894)$ of IL-17 with male blood serum Vit.D concentration and a strong negative correlation $p < 0.01$, $r = (-0.843)$ of IL-17 with female blood serum Vit.D concentration. Also, when

studying the linear correlation between IL-17 and Vit. D in the AV patients' severity showed a weak positive correlation $p < 0.05$, $r = (0.415)$ of IL-17 with acne patients' mild blood serum (Vit. D) concentration, a medium positive correlation $p < 0.01$, $r = (0.587)$ of IL-17 with acne patients moderate blood serum (Vit. D) concentration and a weak positive correlation $p < 0.05$, $r = (0.377)$ of IL-17 with acne patients sever blood serum (Vit. D) concentration. So was the linear correlation between IL-17 and (Vit. D) AV patient's severity and gender. A strong negative correlation $p < 0.01$, $r = (-0.895)$ of IL-17 with AV patients' mild male blood serum (Vit. D) concentration, strong negative correlation $p < 0.01$, $r = (-0.922)$ of IL-17 with AV patients moderate male blood serum (Vit. D) concentration and There was a strong negative correlation $p < 0.01$, $r = (-0.782)$ of IL-17 with AV patients sever blood serum (Vit. D) concentration. There was a strong negative correlation $p < 0.01$, $r = (-0.813)$ of IL-17 with AV patients' mild female blood serum (Vit. D) concentration, a strong negative correlation $p < 0.01$, $r = (-0.932)$ of IL-17 with Av patients moderate female blood serum (Vit. D) concentration and a strong negative correlation $p < 0.01$, $r = (-0.785)$ of IL-17 with acne patients sever blood serum (Vit. D) concentration. We used a receiver operating characteristic curve (ROC) analysis to get the diagnostic values for IL-17 and Vit. D about patient and control differentiation. With an area under the curve (AUC) of 0.960 and a 95% confidence interval ranging from 0.921 to 0.984, $p = < 0.0001$, IL-17 demonstrated an excellent ability to differentiate between the control and acne vulgaris patient groups. At cutoff values of >512.94, the test's sensitivity and specificity were 83.33% and 100.00%, respectively Fig.1. With an area under the curve (AUC) of 0.970 and a 95% confidence interval ranging from 0.933 to 0.990, $p = < 0.0001$, vitamin D demonstrated an excellent ability to distinguish between the control and acne vulgaris patient groups. The test's sensitivity and specificity were 100.00% and 94.05%, respectively, at cutoff values of ≤11.975 Fig.2. The ROC curve showed good diagnostic accuracy for the area under the curve (AUC) for IL-17 and Vit D in the control and AV patient groups, which may help diagnose some conditions. It can also be used to distinguish people with acne from healthy people.

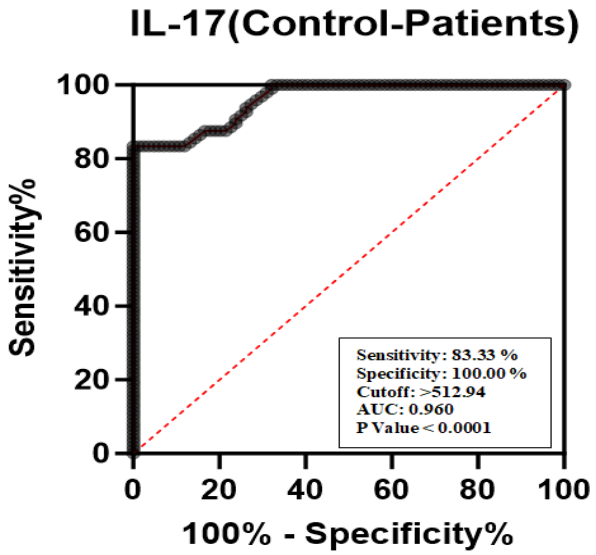

Figure1: ROC Curve Analysis of Serum IL-17 Levels Distinguishing AV Patients from Healthy Controls The ROC curve shows an area under the curve (AUC) of 0.960, indicating excellent diagnostic accuracy. At a cutoff value of >512.94 pg/ml, IL-17 demonstrates a sensitivity of 83.33% and a specificity of 100%. The analysis was statistically significant ($P < 0.0001$).

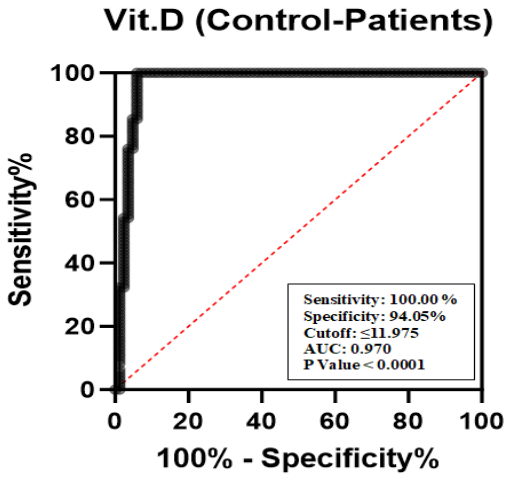

Figure2: Receiver Operating Characteristic (ROC) Curve Analysis of Serum Vitamin D Levels Differentiating AV Patients from Healthy Controls

The area under the curve (AUC) was 0.970, with a cutoff value of ≤11.975 ng/mL, yielding a sensitivity of 100.00% and a specificity of 94.05% (P < 0.0001).

4. Discussion

The pathogenesis of acne has lately been connected to several cytokines, including IL-17. Vitamin A (ATRA) and Vit.D inhibit P. acnes-driven Th17 differentiation and downregulate IL-17 synthesis at the mRNA and protein levels because they share a signaling pathway with the retinoid X receptor. Interestingly, greater suppression of retinoid orphan receptors α (RORα) and RORγ expression was found to indicate the synergistic activity of ATRA and Vit.D on retinoid receptors. The relationship between IL-17 and the development of acne in patients has been the subject of much research in the last several years. Proinflammatory cytokine IL-17 is involved in the etiology of numerous inflammatory disorders, including acne (A. Singh et al., 2021). A substantial relationship between IL-17 and acne was identified in their cross-sectional observational study on the link between interleukins and acne. In a survey by Egyptians to evaluate the level of interleukin 17 (IL-17) in the blood of patients suffering from acne vulgaris, they concluded that IL-17 is significantly higher in acne patients compared to the control group. Moreover, it increases considerably with Increased disease severity and in patients with scarring lesions. In a study that did not agree with our results they conducted on 80 acne patients, there was no statistically significant relationship between the severity of AV lesions and the level of IL-17. He conducted a study that agreed with our results on a group of acne patients (Akdeniz et al., 2018; El Husseiny et al., 2012; Maalmi et al., 2012). The results showed significant differences in levels between cases and controls for interleukin 17 levels. In another study that agreed with our results on a group of acne patients, the results were that the average levels of IL-17 in serum were significantly higher (P < 0.001) in acne sufferers in contrast to the group under control. There was a noteworthy relationship (P < 0.001) between the severity of acne and the levels of IL-17. His findings corroborated the association between IL-17 and the severity of acne in another study (Agak et al., 2014; Ebrahim et al., 2019; S. Singh et al., 2023). According to their findings, the severity of acne vulgaris was correlated with higher levels of IL-17. Furthermore, contrary to our findings, studies revealed that girls with acne vulgaris had higher levels of IL-17 than males with the same condition. This suggests that IL-17 may have a greater effect on women's acne severity. Our results showed a lower mean Vit.D for patients compared to control groups, a lower mean for females compared to males, and a correlation of Vit.D level with disease severity, as it was an inverse relationship with disease severity. In addition to providing the body with

Vit.D, the skin can respond to 1,25(OH) 2D, which is the active metabolite of Vit. D. Sebocytes exhibit robust expression of the critical components of the Vit.D system, including the 25-hydroxylase, 1α-hydroxylase, 24-hydroxylase, and Vit.D receptor. The interaction between 1,25(OH) 2D and calcium regulates skin differentiation. Vit.D is critical for the immune system and skin health. Vitamin D, in its active form, calcitriol, has anti-inflammatory (Akdeniz et al., 2018; Ebrahim et al., 2019; El Husseiny et al., 2012; S. Singh et al., 2023). Properties and may help regulate the skin's immune response. Moreover, Vit.D has been linked to the regulation of keratinocyte proliferation and differentiation, which is essential for maintaining skin health. Depending on the concentration, Vit.D can either promote or inhibit the growth of keratinocytes (≥10-8 M). According to Krämer et al., 1,25(OH) D has a biphasic effect on sebocytes, boosting Z95 sebocytes that proliferate slowly while repressing those that do so rapidly. Moreover, it has been demonstrated that in situations of low vitamin D, cultured sebocytes release higher levels of inflammatory cytokines (IL6, IL8, and MMP9) (Krämer et al., 2009; Lee et al., 2013; S. Singh et al., 2023). It has been demonstrated that Vit.D increases the skin's innate immune response and modulates the responses of T and B lymphocytes, dendritic cells, Toll-like receptor 2 (TLR2), and its co-receptor CD. Furthermore, Vit.D deacetylates and dephosphorylates the protein known as Forkhead box O (FoxO), activating it and further preventing the liver's synthesis of IGF-1. Furthermore, Vit.D triggers the FoxO signaling pathway, which successfully inhibits the mTORC1 (mammalian target of rapamycin complex 1) and prevents IGF-1 signaling, an important route in the development of acne. The emergence or worsening of acne symptoms may be linked to a deficiency of Vit.D. Maranda et al. conducted a thorough study and meta-analysis (Ahmed Mohamed et al., 2021; Lee et al., 2013; Lim et al., 2016; Rasti et al., 2022). In cases of Vit.D deficiency accompanied by acne vulgaris, the research showed that Vit.D supplements were linked to a decrease in the severity of acne, indicating a possible therapeutic role. Vit.D in acne therapy. The effect of vit was investigated by Chun et al. in a different investigation. Vit.D levels in relation to acne vulgaris severity. The researchers enrolled individuals with mild to moderate acne vulgaris and divided them into two groups. “One group received a placebo, while the other was administered Vitamin D tablets. After 12 weeks, the group receiving Vitamin D medication and the group receiving a placebo exhibited notably distinct levels of acne vulgaris”.

Conclusion

The current study recorded that there is no correlation between serum IL-17 levels and Vit.D levels. However, it showed that there are correlations between IL-17 Vit.D levels in terms of gender and in terms of disease severity, in addition to the existence of a direct relationship between IL-17 levels and AV severity. This study also revealed that There is an inverse relationship between the severity of AV and Vit.D. Therefore, it is worth studying the modification of Vit.D and IL-17 levels and their effect on the severity of AV, especially in patients with severe degrees of acne. Our results, along with previous studies, suggest that acne severity can be predicted by measuring IL-17 and Vit.D levels.

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