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Assessment of the role of vitamin D and interleukin-17 in the pathogenesis of acne vulgaris

Akne vulgaris patogenezinde D vitamini ve interlökin-17'nin rolünün değerlendirilmesi

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Abstract

Background and Design: The helper 17 (Th17) cells and interleukin-17 (IL-17) are thought to play a role in the pathogenesis of acne vulgaris (AV). Vitamin D, involved in bone metabolism, has also been shown to decrease proinflammatory cytokines through inhibition of Th17 cells and toll-like receptor 2 expression on monocytes.. We aimed to evaluate the effect of IL-17 and vitamin D levels in the pathogenesis of AV in our study.
Materials and Methods: Between October 2015 and April 2017, 80 AV patients (49 women/31 men) and 80 healthy controls (40 women/40 men) were admitted to the study. Demographic and clinical features were recorded. Blood samples were collected from all participants. IL-17, was studied by sandwich ELISA method and vitamin D was studied by the chemiluminescence method.
Results: In the patient group vitamin 25-Hydroxyvitamin D3 [25(OH)D3] level was significantly higher than the control group (p=0.038). There was no statistically significant difference between the two groups at IL-17 level (p=0.959). According to the global acne grading system, vitamin D level in the mild group was 18.5 (12.8-23.1) ng/mL while the vitamin D level in the moderate-severe group was 18.0 (11.2-23.1) ng/mL. There was no significant relationship between the severity of AV lesions and the vitamin 25(OH)D3 levels (p=0.623). IL-17 levels in the mild group was 534.7 (207.4-640.0) pg/mL, In the moderate-severe group, the level of IL-17 was found to be 368.1 (137.6-640.0) pg/mL. There was no significant relationship between the severity of AV lesions and IL-17 level in the patients either (p=0.256).
Conclusion: In this study, which examined the role of vitamin D and IL-17 levels in the pathogenesis of AV disease, no significant relationship between AV disease and vitamin D and IL-17 levels was obversed.
Keywords: Acne vulgaris, vitamin D, IL-17

Öz

Amaç: Akne vulgaris (AV) patogenezinde T helper 17 (Th17) hücrelerinin ve interlökin-17'nin (IL-17) rolü olduğu düşünülmektedir. Kemik metabolizmasında rol aldığını bildiğimiz D vitaminin de monositler üzerinde Toll-like reseptörü 2 ekspresyonunu ve Th17 hücrelerini inhibe ederek proenflamatuvar sitokilerin üretimini azalttığı yolunda veriler bulunmaktadır. Çalışmamızda AV patogenezinde IL-17 ve D vitamini düzeylerinin etkisini değerlendirmek amaçlanmıştır.
Gereç ve Yöntem: Çalışmaya Ekim 2015 ve Nisan 2017 arasında AV tanısı alan 80 olgu (49 kadın/ 31 erkek) ve 80 sağlıklı kontrol (40 kadın/40 erkek) dahil edildi. Demografik ve klinik özellikler takip formuna kaydedildi. Tüm katılımcılardan kan örnekleri toplandı. IL-17, sandviç ELISA yöntemiyle, D vitamini ise kemilüminesans yöntemiyle çalışıldı.
Bulgular: Hasta grubunda 25 Hidroksivitamin D3 [25(OH)D3] vitamini düzeyi kontrol grubuna göre anlamlı olarak yüksekti (p=0,038). IL-17 düzeyinde ise iki grup arasında istatistiksel olarak anlamlı fark bulunmadı (p=0,959). Global akne derecelendirme sistemine göre hafif şiddetli olan AV olgularında D vitamini düzeyi 18,5 (12,8-23,1) ng/mL iken orta-şiddetli grupta D vitamini düzeyi 18,0 (11,2-23,1) ng/mL olarak saptandı. Lezyonların şiddetiyle 25(OH)D3 vitamini düzeyi arasında anlamlı ilişki olmadığı gözlendi (p=0,623). Hafif şiddetli grupta IL-17 düzeyi 534,7 (207,4-640,0) pg/mL iken orta-şiddetli grupta IL-17 düzeyi 368,1 (137,6-640,0) pg/mL olarak saptandı. Hastalarda AV lezyonlarının şiddetiyle IL-17 düzeyi arasında anlamlı ilişki olmadığı gözlendi (p=0,256).

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Sonuç: AV hastalığının patogenezinde D vitamini ve IL-17 düzeylerinin rolü olup olmadığı araştırılan bu çalışmada AV hastalığı ile D vitamini ve IL-17 düzeyleri arasında belirgin bir ilişki gözlenmemiştir.
Anahtar Kelimeler: Akne vulgaris, D vitamini, IL-17

Introduction

Follicular epithelial hyperproliferation and the resulting follicular clogging, hormonal effects, increased sebum release and the presence of *Propionibacterium acnes* play a role in the development of acne vulgaris (AV). The mechanism triggering and initiating the formation of microcomedones, the precursor to all AV lesions, and the factors influencing the subsequent emergence of inflammation have not been fully understood. The helper 17 (T_h17) cells have been shown recently to be the fundamental trigger for tissue inflammation and to play a role in the pathogenesis of many inflammatory and autoimmune diseases such as psoriasis, rheumatoid arthritis, multiple sclerosis and the Crohn's disease. Although it has been evidenced that the immune response playing a role in AV is stimulated both by the innate immune system through toll-like receptor 2 (TLR2) and by the acquired immunity through activated Th1 lymphocytes, the recent studies suggest that the T_h17 cells and interleukin-17 (IL-17) are also involved in the process. Known to play a role in bone metabolism, vitamin D has been shown today to take part also in immunoregulation. There is evidence that vitamin D inhibits the TLR2 expression on monocytes and the T_h17 cells, reducing the production of proinflammatory cytokines[1-4]. Our study aims to assess the effect of the IL-17 and vitamin D levels on the pathogenesis of AV.

Materials and Methods

Approval was obtained for this study on 23/10/2015 with decision 15 of the Adnan Menderes University Faculty of Medicine Scientific Research Ethics Committee (approval number: numbered 53043469-050.04.04). The study was supported by the Adnan Menderes University Faculty of Medicine Scientific Research Projects (approval number: TPF-15071).

The study included 80 patients (49 female/31 male) who were diagnosed with AV at the Adnan Menderes University Faculty of Medicine, Outpatient Clinic of the Department of Dermatology and Venereology between October 2015 and April 2017 and 80 healthy controls (40 female/40 male).

Those who were found to have a chronic disease in their anamnesis and physical examination, those who used a vitamin D preparation in the past one month, and those who were younger than 15 years and older than 45 years were excluded from the study. In addition, those who received a systemic or topical treatment for AV disease in the past month were excluded from the patient group.

All the patients and those in the control group were read the informed consent text and informed consent form and their signed consents were obtained on a voluntary basis before the study. The demographic data of all participants such as their age and gender were recorded. The severity of disease was measured using the global acne grading system in the AV group. All study subjects were informed about the study prior to their participation and signed the consent form.

Sample collection and measurements

Fasting blood samples were taken from all patients and controls and were stored at -70 Celsius degrees until the time they would be used to study the parameters to be assessed. IL-17 was measured with the sandwich ELISA method using an Elabscience Biotechnology, Co. Ltd. Kit. Vitamin D was studied with the chemiluminescence method using an Architect C8000 (Abbott, IL) kit on an immune analyzer.

Statistical Analysis

The chi-square test was used in intergroup comparisons of categorical data. The unpaired t-test was used in group comparisons of normally distributed variables and the descriptive statistics were shown as means ± standard deviations. The Mann-Whitney U test was used in group comparisons of not normally distributed variables and the descriptive statistics were shown as medians (25-75 percentile). All hypotheses were checked at α=0.05 significance level. The statistical significance was set at $p<0.05$. The results were analyzed with the SPSS Statistics 23 Program.

Results

The patient group consisted of 49 (61.2%) females and 31 (39.8%) males. There were 40 (50%) females and 40 (50%) males in the control group. There was no significant difference between the patient and control groups with respect to gender distribution.

The ages of the patient group ranged between 15 and 26 with a median value of 20 (19-22). The ages of the control group ranged between 15 and 28 with a median value of 21 (19-22). No significant difference was found between the median ages of the patient and control groups (p=0.162). The body mass index (BMI) of the patient group ranged between 15.7 kg/m^2 and 37.5 kg/m^2 with a mean value of 21.094±3.03 kg/m^2. The BMI of the control group ranged between 16.0 kg/m^2 and 32.4 kg/m^2 with a mean value of 22.509±2.99 kg/m^2. The BMI value of the patient group was significantly lower than that of the control group (p=0.003).

None of the subjects included in the study had skin type 1, 5 or 6. There were 31 (38.8%) subjects in the patient group who had skin type 2, 46 (57.5%) subjects with skin type 3 and 3 (3.7%) subjects with skin type 4. There were 42 (52.5%) subjects in the control group who had skin type 2, 29 (36.3%) subjects with skin type 3 and 9 (11.2%) subjects with skin type 4. There was a significant difference between the skin phototypes of the patient and control groups (p=0.014).

Table 1. Comparison of the vitamin 25-Hydroxyvitamin D3 levels in the patient and control groups

	Patient	Control	p
Vitamin 25(OH)D3 (ng/mL)	18.90 (11.50-22.95)	17.20 (10.40-19.30)	**0.038**

25(OH)D3: 25-Hydroxyvitamin D3

When the patients were assessed according to the global acne grading system, 34 patients had mild AV (42.5%), 45 patients moderate AV (56.25%) and 1 patient severe AV (1.25%).

Vitamin D results

The vitamin 25-Hydroxyvitamin D3 [25(OH)D3] level in the patient group had a median value of 18.90 (11.50-22.95) ng/mL. The vitamin 25(OH)D3 level in the control group had a median value of 17.20 (10.40-19.30) ng/mL. The vitamin 25(OH)D3 level in the patient group was significantly higher than in the control group (p=0.038) (Table 1).

In the patient group, 22 (27.5%) subjects were included in the study in the winter months and 58 (72.5%) in the spring months. In the control group, 46 (57.5%) subjects were included in the study in the winter months and 34 (42.5%) in the spring months. The distribution of the patient and control groups by the season of sampling was significantly different (p=0.001).

A significant difference was found between the vitamin 25(OH)D3 levels of male and female patients, the median vitamin 25(OH)D3 level of the male subjects was 21.5 (17.9-27.0) ng/mL and the median vitamin 25(OH)D3 level of female patients was 14.3 (10.1-20.4) ng/mL (p=0.001) (Table 2).

The median vitamin 25(OH)D3 level measured in the spring months was higher than the vitamin 25(OH)D3 level measured in the winter months in both groups (p=0.001) (Table 3).

Interleukin-17 results

The median IL-17 level of the patient group was 469.71 (157.26-640.00) (pg/mL) and the median IL-17 level of the control group was 468.40 (153.54-640.00) (pg/mL), there was no statistically significant difference between the two groups (p=0.959) (Table 4).

According to the global acne grading system, the patients' severity of AV was 10 as the lowest and 32 as the highest with a mean value of 20.2. When the AV patients were divided into two groups according to the global acne grading system as <18 (mild) and >18 (moderate to severe), the median vitamin D level was 18.45 (12.75-23.12) ng/mL in the mild group and 17.95 (11.18-23.13) ng/mL in the moderate-severe group. No significant correlation was found between the severity of AV lesions of the patients and their vitamin 25(OH)D3 levels (p=0.623). While the median IL-17 level was 534.70 (207.36- 640.00) pg/mL in the mild group, it was 368.05 (137.64-640.00) pg/mL in the moderate-severe group. No significant correlation was found between the severity of AV lesions of the patients and their IL-17 levels (p=0.256) (Table 5).

Discussion

The possible roles immune system components play in the pathogenesis of AV is being investigated from many perspectives[5,6]. This study aimed at evaluating the effect of IL-17 and vitamin D levels on AV.

A better understanding of non-osteogenetic effects of vitamin D such as its anti-proliferative, proapoptotic and immunomodulating effects has led to reassessment of this vitamin for its different properties. In the skin, vitamin D plays a major role in the normal keratinocyte development and functioning. Therefore, vitamin D is thought to have an effect in the comedogenesis stage of AV. There is evidence that vitamin D may play an important role in the functioning of the immune system with the mediation of vitamin D receptors that have been shown to be present in T cells, B cells, neutrophils, macrophages and dendritic cells[7,8]. Vitamin D stimulates the production of regulatory T cells, reduces the production of Th1 and Th17 cells and inhibits plasma cell generation and dendritic cell maturation. Eventually, it reduces the generation of proinflammatory cytokines [(e.g. IL-2, IL-3, tumor necrosis factor-alpha, interferon-gamma (IFN-γ)] and enhances the generation of anti-inflammatory cytokines (e.g. IL-4, IL-5, IL-10 and transforming growth factor- beta). The exact opposite holds true with vitamin D deficiency[9,10].

Studies have shown the active role of Th1 and Th17 lymphocytes in the inflammation stage of AV pathogenesis. A study has demonstrated that Th1 cells increase the AV lesions with the induction of *Propionibacterium acnes (P. acnes)* starting from the early periods of the disease. AV, with the influence of Th1 cells (high IFN-γ and low IL-4 producers), is usually associated with cellular immune response to both bacterial and T cell-mediated autoimmune tissue injury[11]. In another study, Th1-related IFN-γ and Th17-related IL-17 levels were found to be higher in AV lesions[1]. Kistowska et al.[12] have recently shown the presence of a different Th1/Th17 subgroup where IFN-γ and IL-17 were elevated concurrently. IL-17 shows its effect by stimulating keratinocytes and increasing the release of proinflammatory cytokines.

Table 4. Comparison of the interleukin-17 levels of the patient and control groups

	Patient	Control	p
IL-17 (pg/mL)	469.71 (157.26-640.00)	468.40 (153.54-640.00)	0.959

IL-17: Interleukin-17

Table 2. Comparison of the vitamin 25-Hydroxyvitamin D3 levels of the patient and control groups by gender

		Patient	p	Control	p	Total	p
Mean vitamin 25(OH)D3 (ng/mL)	Male	21.5 (17.9-27.0)	**0.001**	15.7 (12.4-18.8)	**0.285**	17.50 (13v.50-23.00)	**0.005**
	Female	14.3 (10.1-20.4)		13.7 (10.2-19.9)		14.30 (10.25-20.20)	

25(OH)D3: 25-Hydroxyvitamin D3

Table 3. Comparison of the vitamin 25-Hydroxyvitamin D3 levels of the patient and control groups by season

		Patient	p	Control	p	Total	p
Mean vitamin 25(OH)D3 (ng/mL)	Winter	13.5 (10.5-20.7)	**0.042**	11.5 (9.0-15.6)	**0.000**	12.55 (9.37-16.57)	**0.001**
	Spring	19.0 (13.5-25.0)		19.2 (15.9-25.6)		19.05 (14.50-25.22)	

25(OH)D3: 25-Hydroxyvitamin D3

Table 5. Comparison of the vitamin 25-Hydroxyvitamin D3 and interleukin-17 (pg/mL) levels of the subjects with respect to the severity of acne vulgaris

Severity of AV	Mild (AV score <18), (n=34)	Moderate-Severe (AV score >18), (n=46)	p
Vitamin 25(OH)D3 (ng/mL)	18.45 (12.75-23.12)	17.95 (11.18-23.13)	0.623
IL-17 (pg/mL)	534.70 (207.36-640.00)	368.05 (137.64-640.00)	0.256
AV: Acne vulgaris, 25(OH)D3: 25-Hydroxyvitamin D3, IL-17: Interleukin-17			

Studies have shown that vitamin D can suppress both the Th1 and Th17 lymphocytes. *P. acnes* stimulation has been shown to induce IL-17 mRNA and protein expression in the absence of vitamin D and to decrease the induction of both IL-17 mRNA and protein expression when vitamin D is supplied before activation with *P. acnes*.

In a 2014 study where vitamin D levels of 43 patients with nodulocystic AV and 46 healthy controls were investigated, the mean 25(OH)D3 level was observed to be significantly lower in the patients with AV than in the control group[13]. The mean 25(OH)D3 level was 11.2±5.9 ng/mL in those with nodulocystic AV and 19.7±8.1 ng/mL in the healthy group. This is different from the results of our study, but also to be noted are the fewer number of participants with a higher mean age comapared with our study population. Similar to our findings, no significant difference was found between the patient and control groups in terms of age, gender or BMI. Also, similarly, the patients in this study were included in the winter and autumn months and they were not questioned about their diets. Moreover, the subjects were selected only from those with severe AV and the relationship between AV severity and vitamin D level was not explored. In a study made by Toossi et al.[14] in 2015, the median 25(OH)D3 level was found to be 8.4 (1.4-99); (5-14.1) ng/mL in those with AV and 10.4 (3.1-56.7), (6.58-20.25) ng/mL in the healthy group and no significant difference was found between the median 25(OH)D3 serum concentrations of the two groups (p=0.14).That study included 39 AV patients, 28 females and 11 males, and 40 control subjects, 28 females and 12 males. The number of participants was smaller compared to our study, however similarly, the proportion of female participants was higher and there was a significant difference between the ages of the patient and control groups. The season in which the participants were included in the study was not mentioned and, as in our study, the diets of the participants were not questioned. Unlike our study, participants were questioned about polycystic ovary syndrome (PCOS). It was also mentioned in that study that the prevalence of PCOS was higher in patients with AV than in normal population[14]. Contrary to expectations, vitamin D was found significantly higher in the AV group in our study (p=0.038). There are not many studies investigating the relationship between vitamin D and AV and the number of subjects in such studies is usually small. Furthermore, the studies conducted so far do not cover the entire factors affecting the vitamin D level such as seasonal differences, diet, latitude, altitude, clothing, use of sunscreens and skin type. The reason for the high level of vitamin D found in the patient group in our study may be because the patient group was included more in the spring months and not all the above-mentioned parameters affecting the vitamin D level could be matched in the patient and control groups. In the study of Toossi et al.[14], no statistically significant difference was found between the median 25(OH)D3 concentrations of the patients with mild and moderate to severe/very severe AV (p=0.29). There was also no association in our study between the severity of AV lesions of the patients and their vitamin 25(OH)D3 levels (p=0.623).

IL-17 is a proinflammatory cytokine and its primary function is host defense against microbial infections. It also plays a role in inflammatory events such as autoimmune diseases, cancer and metabolic disorders. Having the capacity to stimulate the production of various antimicrobial peptides, IL-17 also induces production of neutrophil-stimulating chemokines such as IL-18 in the epithelial cells. It has been shown that there are ample neutrophils in late-stage AV lesions and there are increased IL-8 levels in AV biopsies. In addition to its property of inducing proinflammatory cytokine secretion in the perifollicular area, *P. acnes* is thought to produce low molecule weight chemotactic factors and cause accumulation of neutrophils in acne comedones[14-16]. Agak et al.[1] investigated in 2014 whether or not AV-causing pathogenic *P. acnes* would increase IL-17 production in human peripheral blood mononuclear cells. They found out that both living *P. acnes* and fragmented *P. acnes* (ATCC strain 6919) stimulated IL-17 production at the highest level seven days after the activation. Other cutaneous pathogens including *Mycobacterium tuberculosis* and *Mycobacterium leprae* are reported to cause considerably lower IL-17 induction than *P. acnes*. No significant difference was found between the median IL-17 levels of the patient and control groups in our study (p=0.959). There was also no significant correlation between the severity of AV lesions and the IL-17 level (p=0.256). The number of studies investigating the role of IL-17 in the pathogenesis of AV is very limited and such studies are based on tissue measurements. In our study, the IL-17 levels were studied in the blood. No difference was found in the AV patients compared to the control group. The results can be interpreted as IL-17 having not much role in the pathogenesis of AV. More accurate results can be obtained in future studies where the amount of *P. acnes*, the amount of IL-17 in the tissue and the amount of IL-17 in the blood are measured simultaneously in the same patient.

Study Limitation

The primary limitation of our study was not being able to eliminate the role of seasonal differences as the samples were collected during a long period of time. Moreover, the patient and control group equivalence was not observed with respect to a number of factors affecting the vitamin D level (e.g. hour of the day, diet, clothing and use of sunscreens). For more accurate results, the IL-17 and vitamin D levels before and after treatment can be studied in AV patients. The measurements can be performed in a patient group of a narrower age interval and of the same gender. Although no remarkable relationship was observed between the AV disease and the vitamin D and IL-17 levels, the negative results of our study do not suggest that this issue should not be explored in further studies.

Conclusion

In our study, the IL-17 levels were studied in the blood. No difference was found in the AV patients compared to the control group. The results can be interpreted as IL-17 having not much role in the pathogenesis of AV. More accurate results can be obtained in future studies where the amount of P. acnes, the amount of IL-17 in the tissue and the amount of IL-17 in the blood are measured simultaneously in the same patient.

Ethics

Ethics Committee Approval: Approval was obtained for this study on 23/10/2015 with decision 15 of the Adnan Menderes University Faculty of Medicine Scientific Research Ethics Committee (approval number: numbered 53043469-050.04.04).

Informed Consent: All the patients and those in the control group were read the informed consent text and informed consent form and their signed consents were obtained on a voluntary basis before the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.E.T., E.Ş., Concept: A.E.T., E.Ş., Design: A.E.T., E.Ş., Data Collection or Processing: A.E.T., E.Ş., A.K., Analysis or Interpretation: A.E.T., E.Ş., Literature Search: A.E.T., E.Ş., Writing: A.E.T., E.Ş., G.K., N.Ş., M.U., A.K.

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