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Serum Levels of 25-Hydroxyvitamin-D and C-Reactive Protein in Acne Vulgaris Patients

Akne Vulgaris Hastalarında 25-Hidroksivitamin D ve C-Reaktif Protein Düzeyleri

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ABSTRACT Objective: Acne vulgaris is a disease of pilosebaceous unit. Although multiple factors contribute to the development of acne, inflammation is the key component in the pathogenesis. C-reactive protein (CRP) is a well-known marker of inflammation and there are few reports studying the antioxidant, and anti-inflammatory effects of vitamin D in acne. In the present study, the aim was to compare serum vitamin D and CRP levels in acne patients with control subjects. **Material and Methods:** 65 patients with acne vulgaris, and 41 healthy subjects were enrolled in this cross-sectional study. Serum vitamin D and CRP levels of both groups were evaluated. **Results:** No significant association was found between the occurence of acne vulgaris and serum 25-hydroxy-vitamin D and CRP levels (p=0.692, p=0.300, respectively). **Conclusion:** Vitamin D deficiency was determined to be equivalent in both acne patients and healthy subjects. This result might be due to the affection of the whole Turkish population with the same problem. Larger size studies which investigate the status of vitamin D levels in patients with acne, could provide making more precise interpretations.

Keywords: Acne vulgaris; c-reactive protein; inflammation; vitamin D

ÖZET Amaç: Akne vulgaris pilosebase ünitenin bir hastalığıdır. Akne gelişimine pek çok faktör katkıda bulunsa da, inflamasyon patogenezdeki ana bileşendir. C-reaktif protein (CRP) iyi bilinen bir inflamatuar belirteçtir ve vitamin D'nin aknedeki antioksidan ve antiinflamatuar etkilerini inceleyen birkaç çalışma bulunmaktadır. Bu çalışmanın amacı akne hastaları ile kontrol grubu arasında serum vitamin D ve CRP düzeylerini karşılaştırmaktır. **Gereç ve Yöntemler:** 65 akne vulgaris ve 41 sağlıklı kontrol kişileri bu kesitsel çalışmaya dâhil edilmiştir. Her iki grupta da serum vitamin D ve CRP düzeyleri değerlendirilmiştir. **Bulgular:** Akne vulgaris varlığı ile serum 25-hidroksi-vitamin D ve CRP düzeyleri arasında bir ilişki gösterilememiştir (p=0,692, p=0,300, sırasıyla). **Sonuç:** Vitamin D eksikliğinin hem akne hem de kontrol grubunda eşit olarak bulunması, bu sorunun tüm Türkiye popülasyonunu ekileyen genel bir problem olmasına bağlanabilir. Akne hastalarında vitamin D düzeyinin araştırılması için daha geniş gruplarla yapılacak çalışmalar, daha net yorumların yapılabilmesini sağlayabilir.

Anahtar Kelimeler: Akne vulgaris; c-reaktif protein; inflamasyon; vitamin D

Acne vulgaris (AV), disease of the pilosebaceous unit, is characterized by inflammatory and non-inflammatory lesions, presented as comedones, papules, pustules, and nodules.[1] Many factors contribute to the development of AV, including hormones, follicular pluggings and hyperkeratinization of follicles, increase in the levels of sebum secretion, *Propionibacterium acnes (P. acnes)* colonization, and inflammation.[1-4]

In the acne follicle infiltration of CD4+ T cells and T helper (Th) 1 cytokine profile has been shown which is thought to be a cellular response

against the *P. acnes* antigens within the follicular lumen. *P. acnes* promotes the development of inflammation by inducing monocytes via toll like receptor (TLR) 2-dependent pathways to secrete proinflammatory cytokines such as interleukin (IL)-8, and IL-12.[2] Neutrophils, are attracted to pilosebaceous unit by IL-8 and other chemotactic factors, releasing lysosomal enzymes that lead the rupture of the follicular epithelium and inflammation. Meanwhile, IL-12 contributes the inflammatory process by Th1 mediated immune response. Furthermore, *P. acnes* releases lipases, proteases, and hyaluronidases that contribute to tissue injury and inflammation.[3] In addition, monocytes in acne lesions stimulate the expression of IL-1 and tumor necrosis factor-α (TNF-α).[4] Thus, acne is a local chronic inflammatory status.

C-reactive protein (CRP) is an acute-phase protein that appears after injury, infection, or inflammation and disappears when the injury heals, or when the infection or inflammation subsides. CRP is synthesized exclusively by the liver in response to inflammatory cytokines, particularly IL-1, IL-6 and TNF-α.[5] It may be assumed that if the inflammation in acne is high enough to be systemic, serum CRP levels may be elevated in AV patients.

25- hydroxyvitamin D (25(OH)D) plays role in the functioning of the immune system through its effects on T and B lymphocytes, dendritic cells and macrophages. Furthermore, it has antioxidant and anti-comedogenic properties.[6] It also affects the proliferation and differentiation of keratinocytes and sebocytes.[7] Based on these characteristics of vitamin D, it has been hypothesized that there may be a link between the pathophysiology of acne and vitamin D.

There are only few studies separately evaluating vitamin D and CRP levels in AV patients. To the best of our knowledge, this is the first study to have investigated the levels of vitamin D and CRP in AV patients. The aim of this study was to compare serum levels of 25 (OH)D and CRP in patients with AV and healthy controls and to evaluate the association between disease severity and levels of these parameters.

MATERIAL AND METHODS

The study was reviewed and approved by the local ethics committee (The protocol number: 957, Date of approval: 03/09/2016), and all individuals gave written informed consent. The study was carried out according to the principles expressed in the Declaration of Helsinki.

A cross-sectional study was planned to investigate the relationship between acne and CRP, vitamin D levels, and the association of these parameters with the disease activity of AV patients.

65 patients with AV and 41 healthy controls were enrolled in the study. Previously, vitamin D deficiency has been demonstrated to be related with obesity, thus subjects within the normal limits of body mass index (BMI; 18-25 kg m^2) were included. All subjects participated in the study during the same period (November 2017 to December 2017) to avoid seasonal variations in vitamin D levels. None of the subjects were applying daily sunscreen, and none had smoking or alcohol consumption habit.[8]

Exclusion criteria of the study were as follows; having a history of any systemic treatment, particularly vitamin D or calcium supplementation therapy or phototherapy within the last six months; diagnosis of a systemic disease, such as diabetes mellitus, parathyroid or thyroid disorders, autoimmune diseases, anemia, atopy, chronic renal or liver disease, malignancy; pregnancy or breastfeeding. Informed consent was obtained from each participant.

Complicated variants of acne that may affect the levels of CRP and vitamin D, such as acne fulminans, acne conglobate and hidradenitis suppurativa (acne inversa) were excluded from the present study.

ASSAY OF CRP AND 25-HYDROXY-VITAMIN D

Patients gave venous blood samples following a 12-hour fasting period. Measurements of the serum CRP levels were performed using a spectrophotometric system (Cobas c 501; Roche Diagnostics, Mannheim, Germany). The serum concentration of 25(OH)D was determined for each participant

on the day of enrollment using liquid chromatography/tandem mass spectrometry (Quattro Premier XE; Waters Corporation, Milford, MA, USA). Serum 25(OH)D concentrations ≤20 ng/mL were defined as deficient.[9]

EVALUATION OF DISEASE SEVERITY

Severity of acne vulgaris was assessed according to the International Consensus Conference on Acne classification system: mild (few to several comedones, papules, and pustules; no nodules); moderate (several comedones, papules, and pustules; few to several nodules); and severe (numerous comedones, papules, and pustules; many nodules). At the baseline, each patient's age, sex, weight, height, and disease duration were recorded. The BMI was calculated as weight (kg)/height (m^2).

STATISTICAL ANALYSIS

The Number Cruncher Statistical System 2007 (NCSS; Kaysville, Utah, USA) program was used for the statistical analysis. The descriptive data was expressed with mean±standard deviation, numeric variables and percentages. Mann-Whitney U-test was used for statistical analysis. Kruskal-Wallis test was used to determine whether there is difference between the groups. The correlations were assessed by Spearman correlation analysis. $p<0.05$ was considered statistically significant.

RESULTS

AV patients and controls were all age and gender-matched ($p>0.05$). The mean disease time of AV patients was 37.97±28.10 months. Eight patients (12.3%) had mild, 14 patients (21.5%) had moderate, and 43 patients (66.2%) had severe AV.

Serum CRP value of AV patients was 3.79±0.95, and CRP of controls was 3.54±0.45, and the difference was not statistically significant ($p=0.300$; $p>0.05$). The mean 25(OH)D value in AV patients was 10.22±6.11, while it was 10.37±7.41 in controls, and the difference was not statistically significant ($p=0.692$; $p>0.05$). However vitamin D deficiency was noted in both AV group and the controls (Table 1).

AV patients were also divided into two groups according to the severity of the disease as mild-moderate (n=21) and severe (n=43), there was no significant difference between mild-moderate acne, severe acne and control groups in terms of the CRP (3.85±1.02, 3.76±0.92, 3.54±0.45, respectively $p=0.321$; $p>0.05$) and 25(OH)D (11.00±8.04, 9.82±4.91, 10,37±2,41, respectively $p=0.917$; $p>0.05$) (Table 2).

Additionally, there was no correlation between these values, and disease severity or the duration of the disease ($p>0.05$).

TABLE 1: C-reactive protein (CRP), and 25-hydroxyvitamin D levels of acne vulgaris patients and healthy controls.

		Patients (n=65)	Controls (n=41)	[a]p
CRP	Min-max (med)	3.3-7.8 (3.5)	3-6.3 (3.5)	**0,300**
	Mean±SD	3.79±0.95	3.54±0.45	
25 (OH)D	Min-max (med)	3-37.6 (9.1)	3-35.5 (8.2)	**0,692**
	Mean±SD	10.22±6.11	10.37±7.41	

[a]Mann Whitney U Test..

TABLE 2: C-reactive protein (CRP), and 25-hydroxyvitamin D levels according to acne severity.

		Mild-moderate (n=22)	Severe (n=43)	Controls (n=41)	[a]p
CRP	Min-max (med)	3.3-7.4 (3.5)	3.3-7.8 (3.5)	3-6.3 (3.5)	**0.321**
	Mean±SD	3.85±1.02	3.76±0.93	3.54±0.45	
25 (OH)D	Min-max (med)	3-37.6 (8.7)	3-19.6 (9.8)	3-35.5 (8.2)	**0.917**
	Mean±SD	11.00±8.04	9.82±4.91	10.37±7.41	

[a]Kruskal Wallis Test.

DISCUSSION

AV, a chronic inflammatory disease, occurs due to multiple factors.[1] The abnormal desquamation of the follicular epithelium, insulin-like growth factor 1 (IGF-1) and androgen-stimulated increase in sebum production, *P. acnes* colonization within the follicles and inflammation triggers hyperkeratinization and the obstruction of the pilosebaceous follicles leading to the occurence of acne lesions.[10-12]

Inflammation is the key component in the pathogenesis of acne. IL-1, a proinflammatory cytokine, is thought to be the trigger of the activation of keratinocyte proliferation. In acne lesions increase of many proinflammatory cytokines including TNF-α, IL-1β, IL-8 and IL-10, matrix metalloproteinases, β-defensin 4, and granulysin has been reported. Increase in the production of the chemokine, IL-8 and the activator protein (AP)-1, provides migration of circulating inflammatory cells to the tissue.[13-15] Expression of proinflammatory cytokines; such as TNF-α, IL-1, IL-8, IL-12 and IL-23 increase through the reduction of intracytoplasmic levels of cyclic adenosine monophosphate (cAMP) by phosphodiesterases in acne involved skin.[15,16] Among these cytokines IL-1 is the trigger in the remodeling of the pilosebaceous unit and initiation of comedogenesis, while IL-8 is the molecule that attracks neutrophils to the pilosebaceous unit and IL-12 induces the expression of antimicrobial peptides.[3,16] Moreover, microbial ligands (such as P. acnes) can activate several pathways that may cause the release of inflammatory cytokines (IL-1, IL-6, IL-8, IL-10, IL-12 and TNF-α). TLR activation also leads to the release of antimicrobial peptides, (human β defensin 1 and human β defensin 2) that play an important role in innate immune responses.[17] The ligands of receptors expressed in sebocytes; such as androgens and estrogens, Peroxisome proliferator-activated receptor (PPAR) ligands, neuropeptides (NP), liver-X receptor ligands, histamines, retinoids, and vitamin D are some of the factors that affect the functioning of sebocytes.[16,18] Hormonal, microbiological, and immunological mechanisms contribute to the development of AV. In the present study, we investigated whether vitamin D and CRP levels was associated with acne vulgaris. We expected to find lower levels of vitamin D and higher levels of CRP in acne patients due to inflammation in the acne-involved skin. However present study failed to find any correlation between these parameters and AV.

Vitamin D plays role in the proliferation and differentiation of keratinocytes and sebocytes and there have been studies showing the effects of vitamin D in acne patients. In cultured sebocytes, vitamin D treatment is shown to reduce the expression of inflammatory biomarkers, such as IL-6, IL-8, and matrix metalloproteinase.[19] *P. acnes*-induced Th17, which stimulates the expression of IL-17, an inflammatory cytokine that is increased in acne patients, is also inhibited by vitamin D.[20] Furthermore, vitamin D shows antimicrobial effects by inducing antimicrobial peptides, such as LL-37, in human sebocytes.[21] Active vitamin D metabolites effect human sebocytes and keratinocytes via the nuclear vitamin D receptors (VDRs).[22] 1,25 dihydroxyvitamin-D3 (1,25 [OH] 2D3) was demonstrated to inhibit the proliferation and stimulate the differentiation of keratinocytes that may result in comedone formation, probably the first step of acne.[1,2,23]

There are also clinical studies showing vitamin D deficiency in acne patients. Lim et al. demonstrated that vitamin D deficiency is more common in acne patients as compared with controls.[7] Yıldızgören et al. demonstrated that serum levels of vitamin D was lower in patients with nodulocystic acne than that of the control group.[6] In the same study, it was hypothesized that vitamin D deficiency may contribute to development of comedones due to its role in the process of proliferation and differentiation of keratinocytes and sebocytes.[6] Tehrani et al. introduced the therapeutic effect of vitamin D in acne.[24] Moreover, oral vitamin D supplementation was found to be effective in the treatment of acne in the study involving 39 patients.[24]

With these reports supporting the immune regulatory function of vitamin D in sebocytes, it may be assumed that vitamin D may have antiin-

flammatory effects in acne patients. In the present study no significant differences in the mean vitamin D concentration between acne patients and healthy controls was found. However, participants of the study both in acne group and in control group, had low vitamin D levels, consistent with vitamin D deficiency of which is a common problem in Turkish population.

CRP, the most commonly used biomarker of inflammation, is an acute phase protein that is produced predominantly by hepatocytes under the influence of cytokines such as IL-6 and TNF-alpha which are shown to be elevated in AV patients.[25] Serum levels of CRP has been widely studied in several diseases, as it is a cheap and accessible marker of inflammation.

In this study, we found no significant difference in the serum levels of CRP between acne and control groups. Similarly to our findings, Namazi et al. showed no significant difference between CRP levels in acne and control groups.[5] Moreover; median levels of CRP were found to be higher in controls.[5] Vergou et al. found no statistical difference in the CRP levels between acne and control groups in the study evaluating the correlation of thyroid disorders with the presence of acne.[26] In other studies investigating the association of AV with polycystic ovary syndrome (PCOS) increased levels of CRP were reported.[27,28] In the present study, we excluded cases with thyroid disorders or PCOS, since these diseases might also induce inflammation. In the present study we aimed to investigate the acne induced inflammation upon serum levels of CRP. In the study mentioned afore, Namazi et al. showed higher mean CRP levels in the severe acne group than in the moderate acne group.[5] In our study, we found no significant difference in the CRP levels, regardless of the severity of acne.

CONCLUSION

The inflammatory process taking place in the acne follicle was shown to increase some inflammatory cytokines in the circulation. Due to this inflammation, we expected to find higher levels of CRP and lower levels of vitamin D in acne patients, but current work did not demonstrate any correlation between vitamin D or CRP levels and AV occurrence. Low serum vitamin D levels among Turkish population might be a general problem that can affect the comparison between the controls and the patients which may have limited the ability of this study to draw significant conclusions. The lack of not studying high sensitive CRP levels is another limitation of the study. Another limitation of the study could be small numbers of participants. New studies involving more patients would be appropriate to evaluate the realtionship of acne, CRP and vitamin D levels. Measuring other inflammatory cytokines would also be helpful in defining the severity of the inflammation in acne. Defining a serum marker for the severity of acne would provide scoring the disease severity in daily practice, and would also help the development of new treatment strategies by targeting the pathogenic factors in acne.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ezgi Aktaş Karabay, Aslı Aksu Çerman;* ***Design:*** *Ezgi Aktaş Karabay****; Control/Supervision:*** *Ezgi Aktaş Karabay;* ***Data Collection and/or Processing:*** *Ezgi Aktaş Karabay;* ***Analysis and/or Interpretation:*** *Ezgi Aktaş Karabay, Aslı Aksu Çerman;* ***Literature Review:*** *Ezgi Aktaş Karabay;* ***Writing the Article:*** *Ezgi Aktaş Karabay;* ***Critical Review:*** *Aslı Aksu Çerman;* ***References and Fundings: Materials:*** *Ezgi Aktaş Karabay.*

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