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# A case-control study on rosacea and vitamin D levels

## Rozasea ve D vitamini düzeyleri üzerinde bir vaka kontrol çalışması

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**Abstract**

Aim: Rosacea is a chronic inflammatory dermatosis characterized by several features such as temporary erythema (flushing), permanent erythema, papules, pustules and telangiectasia in the face. In this study, our aim is to investigate the role of serum vitamin D levels in the pathogenesis of rosacea.

Methods: 50 patients with rosacea and 50 age and gender matched healthy controls were included in this study. In patients with rosacea and control group, serum parathyroid hormone (PTH), vitamin D levels and serum calcium levels were measured and the results were compared statistically.

Results: Serum vitamin D levels in patients with rosacea were significantly higher than the control group (respectively 10,55 ng/ml and 8,50 ng/ml). The median of serum calcium level was found to be 8,20 mg/dl in the group of patients with rosacea and 8,55 mg/dl in the control group. Serum calcium levels of the control group were significantly higher than the group of patients with rosacea. There was no statistically significant difference in terms of serum parathormone levels between the group of patients with rosacea and control group. The increase in serum vitamin D levels may lead development of rosacea.

Conclusion: As a result, the increase in serum vitamin D levels is associated with rosacea.

**Keywords:** Rosacea, Vitamin D, Cathelicidin, Parathormone

**Öz**

Amaç: Rozasea yüz bölgesinde geçici eritem (flushing), kalıcı eritem, papül, püstül ve telenjiektazi gibi çeşitli özelliklerle karakterize olan kronik inflamatuvar bir dermatozdur Bu çalışmada amacımız rozasea patogenezine etki edebilecek serum vitamin D düzeylerinin rolünü araştırmaktır.

Yöntemler: Dermatoloji polikliniğine başvuran 50 rozasea hastası ile yaş ve cinsiyet açısından eşleştirilmiş 50 sağlıklı kontrol grubu alındı. Rozasealı hastalarda ve kontrol grubunda serum paratiroid hormonu (PTH), D vitamin seviyeleri, serum kalsiyum düzeyleri ölçüldü ve istatistiksel olarak karşılaştırıldı.

Bulgular: Rozasealı hasta grubunun serum 25-hidroksivitamin D düzeyi medianı 10,55 (6,30-38,60) ng/ml, kontrol grubunun ise 8,50 (4,50-25,60) ng/ml olarak saptandı. Rozasea'lı hasta grubunun serum vitamin D düzeyi kontrol grubundan anlamlı olarak yüksek bulundu (p=0,013). Rozasealı hasta grubunun serum kalsiyum düzeyi medianı 8,20 (7,20-9,20) mg/dl, kontrol grubunun ise 8,55(7,60-11,40) mg/dl olarak saptandı. Kontrol grubunun serum kalsiyum düzeyi rozasealı hasta grubundan anlamlı olarak yüksek bulundu (p=0,000). Rozasealı hasta grubu ve kontrol grubu arasında serum parathormon düzeyleri açısından istatistiksel olarak anlamlı farklılık saptanmadı (p=0,194).

Sonuç: Serum vitamin D düzeylerinin yükselmesi rozasea gelişimi ile ilişkili olabilir.

**Anahtar kelimeler:** Rozasea, Vitamin D, Katelisidin, Parathormon

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## Introduction

Rosacea is a chronic inflammatory dermatosis characterized by several features such as temporary erythema (flushing), permanent erythema, papules, pustules and telangiectasia in the face area [1]. Secondary features such as skin burning, tingle, dry appearance, edema, ocular involvement and phymatous changes may also be seen in patients [2]. There are four subtypes of Rosacea; erythematous-telangiectatic, papulopustular, ocular and phymatous type. The most common type is the erythematous-telangiectatic type [3]. The prevalence has a wide range, from 0.1% to 22% [2]. Although a relation has been determined between rosacea and various chronic systemic diseases (gastroesophageal reflux, hyperlipidemia, hypertension, cardiovascular diseases), the pathophysiology is not clear [4]. The pathogenesis of rosacea has not been clearly understood yet. The expression of various genes that play a role in the innate and acquired immune systems has been shown to increase in patients with rosacea. Microorganisms such as *Demodex folliculorum*, *Staphylococcus epidermidis*, ultraviolet (UV) rays, and transient receptor potential family are among the blamed factors for the etiology [1,2,5].

Vitamin D is a steroid hormone synthesized in epidermal keratinocytes by UV-B light (290-315 nm) or taken with diet. In order to be active hormone, vitamin D should be converted to 1,25-dihydroxy vitamin D by 25- and 1-alpha hydroxylation [6]. There is now evidence that vitamin D plays an important role in cutaneous immunity in addition to its effects on calcium homeostasis and bone metabolism [7]. Vitamin D affects the acquired immune system by the activation of T cell and maturation of dendritic cells. It is also argued that it increases innate immunity in the skin and increases the antimicrobial defense which is effective in epithelial surfaces [8]. In recent years, vitamin D has become increasingly important in the management of diseases such as skin cancers, psoriasis, acne, rosacea, hair loss and atopic dermatitis [6].

The aim of this study is to investigate the role of serum vitamin D levels in patients with rosacea.

## Materials and methods

Fifty patients with rosacea who admitted to dermatology outpatient clinic and 50 age and gender matched healthy controls were included in the study between November 2016 and February 2017. The study was approved by the ethics committee and all the patients participating in the study were signed a consent form. This is a case-control type study. Gender, age, body mass index, Fitzpatrick's skin type, smoking, sunscreen usage habit and daily sun exposure time (in minutes) of patients with rosacea and control group were recorded. According to dermatological examination findings, patients were grouped as erythematous-telangiectatic, papulopustular and phymatous type in addition to ocular involvement. All patients diagnosed with rosacea were referred to eye examination. The disease duration of patients with rosacea was recorded as 1-3 years, 3-5 years and >5 years.

The individuals under the age of 18, using any medication that could affect vitamin D levels, receiving calcium supplements and with chronic systemic disease were excluded from the study. The control group was matched with the patient group in terms of age, sex, and body mass index. People in the control group had no systemic disease, healthy subjects without vitamin D and calcium supplementation. The control group was preferred to those living in the same society and similar in lifestyle.

Serum parathyroid hormone (PTH) and vitamin D levels were measured by Abbott Architect ci8200 device using chemiluminescence method, serum calcium levels were measured by Abbott Architect ci8200 autoanalyzer.

Statistical analysis

The findings of this study were analyzed by SPSS-18.0 statistical program. Normal distribution fitting of continuous variables was tested by Kolmogorov-Smirnov test. The descriptive statistics of continuous variables with non-normal distribution were expressed as median (minimum-maximum). The presence of statistically significant difference for continuous variables between groups were examined by Student t test and Mann Whitney U test for nonparametric variables. Chi-square test was used for proportional correlations. $P<0.05$ was accepted as the threshold of statistical significance for all tests.

## Results

Twenty-five (50%) female and 25 (50%) male patients with rosacea were included in the study. Twenty-five (50%) female and 25 (50%) male healthy volunteers were included in the study as a control group. The mean age of the group of patients with rosacea was 50 (±11.44) and the mean age of the control group was 51,04 (±11,82). There was no statistically significant difference between the group of patients with rosacea and control group in terms of age and gender ($p>0.05$). The mean of body mass index (BMI) was 29.58 (±3.80) in the group of patients with rosacea and 29.33 (±3.53) in the control group. 17 individuals in the rosacea group and 24 individuals in the control group were smoking. There was no statistically significant difference between the group of patients with rosacea and control group in terms of BMI and smoking ($p>0.05$). 14 individuals in the group of patients with rosacea and 11 patients in the control group were using sunscreen. There was no statistically significant difference between the group of patients with rosacea and control group in terms of sunscreen use, daily sun exposure and Fitzpatrick's skin type ($p>0.05$). The comparative demographic characteristics of the group of patients with rosacea and the control group are shown in Table 1.

In the group of patients with rosacea, there were 26 (52%) patients with a disease duration of 1-3 years, 14 (28%) patients between 3-5 years and 10 (20%) patients with a disease duration of >5 years. Twenty-one (42%) of patients had erythematous-telangiectatic type, 11 (22%) of them had papulopustular type, 6 (12%) of them had erythematous-telangiectatic type with ocular involvement, 10 (20%) of them had papulopustular type with ocular involvement and 2 (4%) of them had phymatous type with ocular involvement.

The median of serum 25-hydroxyvitamin D level was found to be 10.55 (6.30-38.60) ng/ml in the group of patients with rosacea and 8.50 (4.50-25.60) ng/ml in the control group. Serum vitamin D levels of the group of patients with rosacea were significantly higher than the control group ($p=0.013$). The

median of serum calcium level was found to be 8.20 (7.20-9.20) mg/dl in the group of patients with rosacea and 8.55 (7.60-11.40) mg/dl in the control group. Serum calcium levels of the control group were significantly higher than the group of patients with rosacea (p=0.000). There was no statistically significant difference in terms of serum parathormone levels between the group of patients with rosacea and control group (p=0.194). The laboratory values of the patient group with rosacea and control group are comparatively shown in table 2.

Table 1: Demographic characteristics of patients with rosacea and control group

| | Patients with Rosacea N=50 | Control N=50 | p* |
|---|---|---|---|
| Age | 50±11.44 | 51.04±11.82 | 0.65 |
| Gender (F/M) | 25/25 | 25/25 | 1 |
| BMI (kg/m$^2$) | 29.58±3.80 | 29.33±3.53 | 0.74 |
| Smoking (Yes) | 17 | 24 | 1 |
| Sun Exposure | | | |
| <10 min | 3 (%75) | 1 (%25) | |
| 10-20 min | 9 (%47.4) | 10 (%52.6) | 0.124 |
| 20-30 min | 7 (%30.4) | 16 (69.6) | |
| >30 min | 31 (%57.4) | 23 (%42.6) | |
| Use of sunscreen (Yes) | 14 (%28) | 11 (%22) | 0.48 |
| Fitzpatrick's skin type | | | |
| Type 1 | 4 (%8) | 3 (%6) | |
| Type 2 | 22 (%22) | 24 (%48) | 0.905 |
| Type 3 | 22 (%22) | 22 (%44) | |
| Type 4 | 2 (%4) | 1 (%2) | |

* Chi-Square Test

Table 2: Laboratory parameters of patients with rosacea and control group

| | Patients with Rosacea N=50 | Control N=50 | P |
|---|---|---|---|
| 25-Hydroxy vitamin D (ng/ml) | 10.55(6.30-38.60) | 8.50(4.50-25.60) | 0.013 * |
| Calcium (mg/dl) | 8.20(7.20-9.20) | 8.55(7.60-11.40) | 0.000 * |
| Parathormone (pg/ml) | 47.30(13.60-120.60) | 47.60(17.70-187.10) | 0.194 |

***** p<0.05

## Discussion

Rosacea is a chronic inflammatory skin disease that mostly affects middle-aged blonde women with light skin and blue eye, although it can be seen in any person [5,9]. Rosacea has multi-factorial pathology including vasoactive and neurocutaneous components as well as innate and acquired immunity. Each of these factors contributes to the disease in different proportions [2]. Under normal physiological conditions, triggering of the innate immunity leads to a controlled increase in cytokines and antimicrobial peptides (AMP) in the skin. These normal signal pathways are disrupted in patients with rosacea. It has been shown that basal levels of cathelicidin, an AMP, and kallikrein 5 (KLK 5), a serine protease that breaks down cathelicidin into its active peptide form, LL-37 are increased in patients with rosacea [10,11]. KLK 5 and LL-37 are higher in the skin with rosacea as well as their structures are different. In the skin with rosacea, LL-37 is converted into shorter fragments that regulate processes such as leukocyte chemotaxis, angiogenesis and expression of extracellular matrix components [11-13].

The expression of cathelicidin in keratinocytes is strongly induced by vitamin D, which is activated in keratinocytes by UV light, which is a well-known trigger of rosacea [14]. In addition, toll-like receptor 2 (TLR 2) and matrix metalloproteinase levels, which activate KLK 5 have also increased in patients with rosacea [15,16].

Nowadays, the impairments in the expression, function, or processing of cathelicidin LL-37 are blamed in the etiology of diseases such as atopic dermatitis, psoriasis and rosacea [17]. Atopic dermatitis is a type of chronic inflammatory eczema. Some studies suggest that the underlying mechanism is initially epidermal dysfunction and subsequently immunological activation, but many animal studies, case reports, and randomized clinical trials have suggested that vitamin D may alleviate the symptoms of atopic dermatitis via various mechanisms including immunomodulation [6]. Mutgi et al. and Heimbeck et al. have shown in their studies that in patients with atopic dermatitis and vitamin D deficiency, the disease improved and the severity of the disease reduced as a result vitamin D replacement [18,19]. In the treatment of psoriasis, vitamin D analogs have been used for many years, but the molecular mechanisms behind the clinical effects are not clearly understood [6,17]. Topical vitamin D analogues, such as calcipotriol, reduce proinflammatory cytokines in the skin and strongly increase the expression of cathelicidin. Some studies have begun to investigate whether or not serum vitamin D levels correlate with cutaneous AMP expression in psoriatic patients [17]. Kim et al. have found in their study that cathelicidin expression in the lesional skin of patients with psoriasis was higher in the group with sufficient serum vitamin D level than in the group with serum vitamin D deficiency [20].

When we look at the studies in which serum vitamin D levels were investigated in patients with rosacea, the only one study has been conducted by Ekiz et al., from our country. In this study, serum vitamin D levels in patients with rosacea were found to be higher when compared to the control group, and it was argued that high serum vitamin D levels may lead development of rosacea [21]. Similarly, in our study, serum vitamin D levels were statistically significantly higher in the rosacea group than in the control group, whereas serum vitamin D levels in both groups were lower than those of in the study of Ekiz et al. This difference could be attributed to the fact that our study was performed in the Central Anatolian region, the blood samples were taken from the patients in the winter period (November-February) and the mean age and BMI was higher.

Conclusion

As a result, the increase in serum vitamin D levels is associated with rosacea. In the future, new therapeutic approaches that block the expression of cathelicidin via the vitamin D pathway may come into question. Prospective clinical trial or metaanalysis with larger series in different centers which will support these results are needed.

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