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Role of serum 25-hydroxyvitamin D levels and vitamin D receptor gene polymorphisms in patients with rosacea: a case–control study

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Summary

Background. Vitamin D has significant effects on the immune system and thereby on the pathogenesis of rosacea. However, there is a lack of information on the vitamin D status and vitamin D receptors (VDRs) of patients with rosacea.

Aim. To evaluate the role of vitamin D in rosacea susceptibility.

Methods. A case–control study was conducted, enrolling patients with rosacea and healthy controls (HCs). Five *VDR* gene single nucleotide polymorphisms (SNPs) (*Cdx*2, *Fok*I, *Apa*I, *Bsm*I and *Taq*I) and serum 25-hydroxyvitamin D_3 [25(OH)D_3] levels were compared between patients and HCs.

Results. The study enrolled 60 patients (M/F: 14/46) and 60 age- and sex-matched HCs (M/F: 14/46). Age (mean ± SD) was 48 ± 11 years for both groups. The serum 25(OH)D_3 levels (median ± interquartile range) were higher in patients with rosacea (12.9 ± 6.8 ng/mL) than in HCs (10.5 ± 3.7 ng/mL) ($P < 0.001$). Subjects with high serum 25(OH)D_3 levels had a 1.36-fold increased risk of rosacea (95% CI 1.17–1.58). Heterozygous and mutant *Apa*I polymorphisms increased rosacea risk by 5.26-fold (95% CI 1.51–18.35) and 3.69-fold (95% CI 1.19–11.48), respectively, whereas mutant *Taq*I polymorphisms decreased the risk by 4.69 times (95% CI 1.37–16.67). Heterozygosity for *Cdx*2 alleles increased rosacea risk, whereas wildtype *Apa*I and mutant *Taq*I alleles decreased it.

Conclusions. The present study suggests that an increase in vitamin D levels may contribute to the development of rosacea. *Apa*I and *Taq*I polymorphisms, and heterozygous *Cdx*2, wildtype *Apa*I and mutant *Taq*I alleles were significantly associated with rosacea. These results indicate a possible role of vitamin D and VDR pathways in the pathogenesis of rosacea, although causality could not be assessed.

Introduction

Rosacea is a chronic, inflammatory skin disease characterized by flushing, facial erythema, telangiectasia, and inflammatory papules and pustules.[1] Although clinical subtypes and variants are clearly described,[2,3] the pathogenesis of rosacea has not been precisely elucidated. Genetic predisposition, immune system dysregulation, microorganisms, epidermal barrier dysfunction, neurogenic inflammation, abnormal vascular reactivity and ultraviolet (UV) radiation may contribute to the pathogenesis of the disease.[4]

Vitamin D is a pro-hormone produced by keratinocytes using UV irradiation from 7-dehydrocholesterol to produce pre-vitamin D, which is then converted to vitamin D_3.[5] Subsequently, vitamin D_3 is turned into an active form identified as 25-hydroxyvitamin D_3 [25(OH)D_3], the serum form that is monitored to determine the vitamin D status of patients. However, the final and biologically active form, 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$], exerts its actions

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through nuclear vitamin D receptors (VDR) and Retinoid X receptors (RXRs) on target cells.[5,6]

Serum $1,25(OH)_2D_3$ has significant effects on the innate and adaptive immune systems by regulating expression of antimicrobial peptides (AMPs); in keratinocytes, the main one is cathelicidin.[5] The effects of $1,25(OH)_2D_3$ on cathelicidin expression in human keratinocytes is based on RXR but is not related to the upregulation of VDR expression.[6] Cathelicidin expression and function is changed in some inflammatory skin disorders and in rosacea.[7] In patients with rosacea, the facial skin contains high levels of cathelicidin.[8] The role of mast cells in rosacea is also mediated by their effects on increasing activation of cathelicidin proteins.[9]

The human *VDR* gene has been mapped to chromosome 12 (12q13.1), and has several polymorphic variants, including the single nucleotide polymorphisms (SNPs) *Apa*I, *Eco*RV, *Bsm*I, *Taq*I, Tru9I and *Fok*I.[10] In addition to being the most frequently studied SNPs in the *VDR* gene, all five are involved with coding and promoter regions of the *VDR* gene. The *Fok*I polymorphism, also referred to as the start codon polymorphism, is located in the exon 2 region, whereas the remaining polymorphisms are located between exons 8 and 9 in the *VDR* gene. *Cdx*2 is a polymorphism consisting of a G>A change in the promoter region of the *VDR* gene. Although several polymorphisms in the *VDR* gene have been described, the impact of these polymorphisms on VDR protein function is not clear.[10]

Although numerous papers have been published on vitamin D_3 and skin diseases such as vitiligo, psoriasis, atopic dermatitis and chronic urticaria, knowledge on the vitamin D status and VDRs in patients with rosacea is inadequate.[11–14] The aim of the present study was to assess the association between rosacea and serum $25(OH)D_3$ levels and the *VDR* SNPs *Cdx*2, *Fok*I, *Apa*I, *Bsm*I and *Taq*I.

Methods

The study was approved by Ankara Numune Training and Research Hospital Ethics Committee of Clinical Studies (code E-16-1120) and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Participants and study protocol

This case–control study recruited patients from the Dermatology Outpatient Clinic of Ankara Numune Training and Research Hospital between October 2016 and February 2017. Inclusion criteria included age ≥ 18 years and agreement to participate. Exclusion criteria were pregnancy/lactation, use of medications known to affect serum vitamin D_3 levels and any history of inflammatory skin disease.

In total, 120 participants (60 patients with rosacea and 60 age- and sex-matched HCs) were enrolled. Demographic data including age, sex, and personal and family medical history were recorded for all participants. Molecular analyses were performed at the Biochemistry and Genetics laboratories of Ufuk University Medical Faculty. All patients with rosacea had their diagnosis confirmed in accordance with the guidelines of the National Rosacea Society Expert Committee, and the disease subtype, duration, onset and localization, along with previous and current therapies and precipitating factors, were evaluated.

Preparation of serum and analyses

A venous blood sample (10 mL) was taken from each participant, using four different anticoagulant tubes (13×75 mm $\times$ 3.0 mL each; BD Vacutainer® K^2-EDTA 5.4 mg, BD, Plymouth, Cornwall UK) to investigate serum $25(OH)D_3$ levels and VDR polymorphisms after 8 h of fasting. All the participants were tested during the winter period (November, December and January) because of the potential seasonal variation in vitamin D status.

A competitive electrochemiluminescence protein assay (Roche Diagnostics, Mannheim, Germany) was the method used to measure serum $25(OH)D_3$ levels. Vitamin D insufficiency was defined as serum $25(OH)D_3$ values < 30 ng/mL, while deficiency was defined as values < 20 ng/mL. Participants who were vitamin D-insufficient or -deficient at baseline were allowed to take supplements containing vitamin D.

Molecular analysis of vitamin D receptor polymorphisms

After extraction of DNA from peripheral blood leucocytes, the five *VDR* SNPs (*Cdx*2, *Fok*I, *Bsm*I, *Apa*I and *Taq*I variants) were analysed. A primer extension-based method (SNaPshot® Multiplex System; Applied Biosystems Inc./Life Technologies, Foster City, CA, USA), was used to detect the respective polymorphisms, using in-house designed primers. Fragment analysis was performed on a genetic analyser (ABI 3130; Applied Biosystems Inc./Life Technologies) and the accompanying software (GeneMapper® Software

v4.0; Applied Biosystems Inc./Life Technologies) was used for data analysis.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows (v21.0; IBM Corp., Armonk, NY, USA). Genome-wide association studies were conducted with the SNP association package in the R software program. A Shapiro–Wilk test was used to test numerical variables for normal distribution. Data were expressed as mean ± SD or median ± interquartile range (IQR) as appropriate. Demographic and clinical characteristics of the study population were analysed using descriptive statistics. Categorical variables were described with frequencies and percentages. The Mann–Whitney *U*-test was used to compare serum 25 $(OH)D_3$ levels, and the χ^2 test was used to compare genotype and allele frequencies between groups. Binary logistic regression analysis was used to determine whether the variables vitamin D_3 and *VDR* SNPs were a risk factor for rosacea. Multiple logistic regression analysis was used to investigate the relationship between rosacea and the alleles. The strength of the association between rosacea risk and the *VDR* gene polymorphisms was assessed by OR with corresponding 95% CI. Hardy–Weinberg equilibrium was used to compare allele frequencies. The differences between recessive and dominant models were described. The Kruskal–Wallis test was used to assess the relationship between disease duration and *VDR* SNPs. $P < 0.05$ was considered statistically significant.

Results

Participants

The study enrolled 60 patients (M/F: 14/46) and 60 age- and sex-matched HCs (M/F: 14/46). Age (mean ± SD) was 48 ± 11 years for both groups, and disease duration (median ± IQR) was 36 ± 72 months. The distribution of patients according to demographic and clinical characteristics is shown in Table 1.

Vitamin D deficiency

Of the 60 patients, 52 (87%) exhibited vitamin D_3 deficiency and 59 (98%) exhibited vitamin D_3 insufficiency. The entire control group were both vitamin D-deficient and -insufficient. Serum $25(OH)D_3$ levels (median ± IQR) were higher in patients with rosacea (12.9 ± 6.8 ng/mL) compared with HCs (10.5 ± 3.7

Table 1 Demographic and clinical details of patients with rosacea (n = 60).

Parameter	Result
Age, years	
Mean ± SD	48 ± 11
Range	17–71
Disease duration (months)	
Median ± IQR	36 ± 72
Range	0.5–480
Systemic diseases, *n* (%)	
Hypertension	16 (27)
Diabetes mellitus	14 (23)
Thyroid gland disease	8 (13)
Asthma or chronic obstructive lung disease	7 (12)
Major depression	6 (10)
Coronary artery disease	4 (7)
Arrhythmia	1 (2)
Migraine	1 (2)
Medication due to systemic disease, *n* (%)	
Positive	30 (50)
Negative	30 (50)
Family history of rosacea, *n* (%)	
Positive	6 (10)
Negative	54 (90)
Triggering factors, *n* (%)	
UV light exposure	41 (68)
Heat	48 (80)
Emotional stress	42 (70)
Spicy food	22 (37)
No triggering factor	5 (8)
Type of rosacea, *n* (%)	
Erythematotelangiectatic	33 (55)
Papulopustular	18 (30)
Erythematotelangiectatic and papulopustular	4 (7)
Phymatous	1 (2)
Granulomatous	1 (2)
Steroid-induced	1 (2)
Erythematotelangiectatic and phymatous	1 (2)
Erythematotelangiectatic and ocular	1 (2)
Localization of rosacea, *n* (%)	
Cheeks	42 (70)
Chin	9 (15)
Nose	6 (10)
Forehead	13 (22)
Central face	9 (15)
Entire face	15 (25)
Previous treatment options, *n* (%)*	
Topical metronidazole	18 (30)
Topical antibiotics (tetracycline, erythromycin)	7 (12)
Oral isotretinoin	6 (10)
Oral tetracycline	5 (8)
Oral antibiotics other than tetracycline	1 (2)
Vascular laser	1 (2)
No treatment	33 (45)
Current treatment options, *n* (%)*	
Topical metronidazole	6 (10)
Oral isotretinoin	5 (8)
Topical antibiotics (tetracycline, erythromycin)	4 (7)
Oral tetracycline	1 (2)
No treatment	45 (75)

IQR, interquartile range; UV, ultraviolet. *Some patients received > 1 treatment agent.

ng/mL) ($P < 0.001$). Subjects with high serum $25(OH)D_3$ levels had a 1.36-fold increased rosacea risk (95% CI 1.17–1.58).

Nucleotide polymorphisms

There were no significant differences in *Cdx*2, *Fok*I or *Bsm*I nucleotide polymorphisms between patients and HCs, whereas *Apa*I and *Taq*I polymorphisms were significantly different between the two groups (Table 3). Compared with the wildtype *Apa*I polymorphisms, heterozygous and mutant *Apa*I polymorphisms increased rosacea risk by 5.26-fold ($P < 0.01$, 95% CI 1.51–18.35) and 3.69-fold ($P = 0.02$, 95% CI 1.19–11.48), respectively. Mutant *Taq*I polymorphisms decreased rosacea risk nu 4.69 times compared with wildtype *Taq*I polymorphisms ($P = 0.01$, 95% CI 1.37–16.67). These results revealed that heterozygous and mutant type *Apa*I polymorphisms increased rosacea risk, whereas mutant *Taq*I polymorphisms were protective against rosacea (Table 2).

The mutant allele frequencies of the five *VDR* SNPs in the Turkish population are presented in Table 3. No significant risk or protective effect on rosacea as observed for either *Fok*I or *Bsm*I alleles in any model comparison. However, some alleles of *Cdx*2, *Apa*I and *Taq*I nucleotides were shown to be significantly associated with rosacea in some models. The results showed that heterozygosity for *Cdx*2 alleles increased rosacea risk, whereas wildtype *Apa*I and mutant *Taq*I alleles decreased it (Table 4).

Clinical subtypes

There were no significant differences between the clinical subtypes of rosacea in terms of *VDR* SNPs, disease duration or serum $25(OH)D_3$ levels in the patient group.

Table 3 Single nucleotide polymorphisms of the *VDR* gene, nucleotide changes and allele frequencies of the Turkish population.

SNP	RFLP	dbSNP	AA change	WT	Mutant	MAF, %
1	*Cdx2*	rs11568820	–	G	A	42
2	*Fok*I	rs2228570	M1T	C	T	35
3	*Bsm*I	rs1544410	–	G	A	27
4	*Apa*I	rs11168271	–	G	T	50
5	*Taq*I	rs731236	–	T	C	26

AA, amino acid; dbSNP, Database of Single Nucleotide Polymorphisms; MAF, mutant allele frequency; RFLP, restriction fragment length polymorphism; SNP, single nucleotide polymorphism.

Table 2 Comparison of the genotype distribution and allele frequencies of single nucleotide polymorphisms between patients and healthy controls and their associations with rosacea.

Genotypes*	Patients ($n = 60$), *n* (%)	HCs ($n = 60$), *n* (%)	OR (95% CI)	*P*
Cdx2 G/A polymorphism				0.24
Wildtype	60 (36)	67 (40)	1 (ref)	
Heterozygous	37 (22)	25 (15)	2.19 (0.79–6.08)	0.14
Mutant	3 (2)	8 (5)	0.64 (0.10–4.02)	0.64
*Fok*I C/T polymorphism				0.92
Wildtype	52 (31)	48 (29)	1 (ref)	
Heterozygous	40 (24)	42 (25)	1.42 (0.54–3.70)	0.48
Mutant	8 (5)	10 (6)	0.99 (0.20–4.94)	0.99
*Bsm*I G/A polymorphism				0.73
Wildtype	33 (20)	40 (24)	1 (ref)	
Heterozygous	48 (29)	45 (27)	1.71 (0.22–13.26)	0.61
Mutant	18 (11)	15 (9)	0.46 (0.08–2.71)	0.39
*Apa*I G/T polymorphism				< 0.05†
Wildtype	20 (12)	40 (24)	1 (ref)	
Heterozygous	43 (26)	28 (17)	5.26 (1.51–18.35)	< 0.01†
Mutant	37 (22)	32 (19)	3.69 (1.19–11.48)	0.02†
*Taq*I C/T polymorphism				0.01†
Wildtype	37 (22)	17 (10)	1 (ref)	
Heterozygous	47 (28)	47 (28)	0.43 (0.14–1.30)	0.14
Mutant	17 (10)	37 (22)	−4.69 (1.37–16.67)	0.01†

HC, healthy control. *Mutant and heterozygous polymorphisms were compared with wildtype; †$P < 0.05$ was considered statistically significant.

Table 4 Significant associations of the *Cdx2*, *Apa*I and *Taq*I alleles and rosacea in various models.

Nucleotides	Patients (n = 60)	HCs (n = 60)	OR (95% CI)	P
Cdx2, *n* (%)				
WT/M (overdominant model)	38 (63%)	45 (75%)	1 (ref)	
Heterozygous	22 (37%)	15 (25%)	2.51 (1.03–6.12)	0.04
*Apa*I, *n* (%)				
Mutant	22 (37%)	19 (32%)	1 (ref)	0.01
WT (codominant model)	12 (20%)	24 (40%)	0.29 (0.10–0.84)	< 0.01
WT (recessive model)	12 (20%)	24 (40%)	0.25 (0.10–0.67)	
*Taq*I, *n* (%)				
WT	22 (37%)	10 (17%)	1 (ref)	0.03
Mutant (codominant model)	10 (17%)	22 (37%)	0.23 (0.07–0.74)	0.01
Mutant (recessive model)	10 (17%)	22 (37%)	0.30 (0.12–0.79)	

WT, wildtype.

Discussion

Although rosacea is a widespread dermatological disease that compromises quality of life in both sexes, its aetiology and pathophysiology is not yet well defined. Recent studies have shown high levels of cathelicidin in patient lesions compared with normal skin.[8] Yamasaki *et al.*[15] showed that the skin of patients with rosacea expressed higher amounts of Toll-like receptor (TLR)-2, while Moura *et al.*[16] demonstrated higher levels of TLR2 and TLR4 and lower expression levels of Langerhans cells in the skin of patients with rosacea compared with that of HCs. Mast cells also play a central role in rosacea inflammation by amplifying cathelicidin activation.[9] These results indicate an altered innate immune response in patients with rosacea.

It can be speculated that UV radiation may contribute to the pathogenesis of rosacea by increasing the synthesis of vitamin D_3. Vitamin D_3 has significant effects on the immune system by regulating expression of AMPs, particularly cathelicidin.[17] As cathelicidin gene expression is regulated by VDR-dependent and -independent pathways,[18] it is not clear how vitamin D_3 status may affect patients with rosacea. Ekiz *et al.* showed that patients with rosacea have relatively high serum $25(OH)D_3$ levels compared with HCs, suggesting that increased vitamin D levels may lead to the development of rosacea.[19] The present study found similar results, indicating a possible mechanistic role of vitamin D in the pathogenesis of rosacea. The fact that the patients were vitamin D-depleted (even if less depleted than the HCs) argues against a causal role for this hormone. However, the causality could not be assessed because of the case–control design. In addition, the study was performed in winter, and thus it is possible that results would have been different in summer.

Several studies have pointed to an association between polymorphisms of the *VDR* gene and endocrine diseases,[20] cancers,[21,22] autoimmune diseases,[23] and skin diseases such as psoriasis, vitiligo, atopic dermatitis and urticaria.[11–14] However, there are no such large series in the literature on rosacea and *VDR* gene polymorphism from which to draw clear conclusions. A single study on this topic included 27 patients with rosacea fulminans, 110 patients with rosacea stage I–III and 61 healthy individuals. The authors found a predominance of the less active *Bsm*I *VDR* allele 1 in patients with rosacea fulminans, and they suggested involvement of the VDR pathway in rosacea.[24] In the present study, we found that heterozygous and mutant *Apa*I polymorphisms increased the risk of rosacea, whereas mutant *Taq*I polymorphisms decreased the risk. Similarly, heterozygous *Cdx2* alleles increased rosacea risk, whereas wildtype *Apa*I and mutant *Taq*I alleles decreased risk.

Limitations of the study include the small sample size and the high proportion of female patients. As the study was conducted at a single research centre, generalizability of the study findings may be limited. Causality could not be evaluated because of the study's case–control design.

Conclusion

To our knowledge, this is the first report on association of these five SNPs of the *VDR* gene with rosacea. This study found an association between rosacea risk and vitamin D and *VDR* SNPs, indicating a possible role of vitamin D and VDR pathways in rosacea. Although the relationship between vitamin D levels and rosacea may not be directly causal, it is possible that rosacea and elevated vitamin D levels are both induced by UV exposure, but by separate and unrelated mechanisms. Further prospective studies eliminating confounding factors and assessing more patients from different ethnic populations are required to determine whether *VDR* SNPs and vitamin D play a role in genetic susceptibility to rosacea. The association between RXR polymorphisms and rosacea should also be further assessed for its potential role in cathelicidin expression.

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What's already known about this topic?

- Vitamin D3 has an impact on the immune system by regulating expression of AMPs, particularly cathelicidin, in keratinocytes.
- Cathelicidin expression and function is changed in rosacea.

What does this study add?

- Vitamin D and VDR SNPs may be associated with rosacea.
- Increased vitamin D levels may contribute to the development of rosacea.
- Heterozygous and mutant type *Apa*I polymorphisms increased rosacea risk, whereas mutant *Taq*I polymorphisms were protective against rosacea.
- Similarly, heterozygous *Cdx*2 alleles increased rosacea risk, whereas wildtype *Apa*I and mutant *Taq*I alleles decreased it.

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