



Serum Vitamin D Level and Body Mass Index in Children with Vernal Keratoconjunctivitis

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Abstract

Objectives: The purpose of this study was to evaluate the body mass index (BMI) value and serum 25-hydroxyvitamin D [25(OH)D3] level in children with vernal keratoconjunctivitis (VKC).

Methods: A total of 40 healthy, non-atopic children (control group) and 46 children with VKC (study group) were included in the study. The serum vitamin D [25(OH)D3] levels and BMI values were measured and compared between the 2 groups.

Results: The mean vitamin D level measured in the healthy children (mean: 19.01 ± 5.66 ng/mL, range: 9–33.09 ng/mL) was significantly different from the mean vitamin D level in the VKC-affected children (mean: 14.06 ± 5.02 ng/mL, range 4.37–31 ng/mL) ($p < 0.001$). The mean BMI in the VKC group (17.1 ± 2.5 kg/m²) was significantly higher than the mean BMI of the healthy children (mean: 16.5 ± 2.3 kg/m²; $p = 0.046$). A negative correlation (Spearman's $\rho = -0.275$; $p = 0.01$) was observed between the vitamin D level and the BMI value.

Conclusion: The results indicated that children with VKC had a lower serum vitamin D level and a higher BMI value compared with healthy, age- and sex-matched children.

Keywords: Body mass index, correlation, serum 25 (OH)D3, vernal keratoconjunctivitis, vitamin D deficiency.

Introduction

Vernal keratoconjunctivitis (VKC) is a chronic, allergic eye disease that is seasonally exacerbated and typically affects young children living in a hot and dry climate. The disease causes inflammation due to an allergic reaction of the entire ocular surface (1). It is characterized by a sticky, mucus-like discharge and the presence of large cobblestone papillae on the superior tarsal conjunctiva or at the limbus. Three forms of the disease have been described: (i) limbal VKC, where papillae are seen in the limbal conjunctiva; (ii) palpebral VKC, where papillae are observed in the tarsal part of the palpebral conjunctiva; and (iii) mixed VKC, where features of both

limbal and palpebral are found (2). The hypersensitive reaction on exposure to allergens can lead to exacerbations, as in other atopic reactions; asthma, allergic rhinitis, and eczema often coexist with VKC (1,29). Although the risk factors for VKC are thought to be environmental, genetic, endocrine, and neurogenic; the exact etiology still remains unclear (1,2).

Recently, an association between vitamin D deficiency [serum 25-hydroxyvitamin D; 25(OH)D3] and allergic disorders has been demonstrated (3–5). Patients with seasonal allergic conjunctivitis have been shown to have a lower level of vitamin D than normal individuals (6). Furthermore, vitamin D insufficiency and deficiency have been observed more commonly in VKC-affected children compared with healthy

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children, and it has been reported that the vitamin D level was lower in VKC patients (7,8).

An important factor to consider in VKC patients is the body mass index (BMI) value. Previously published studies have confirmed that patients with allergic conditions and atopy have high BMI values (9–11). A positive correlation was observed between the BMI values of Caucasian girls and the prevalence of atopy (11). In addition, numerous investigations have demonstrated that those who are overweight and obese were deficient in vitamin D and that a higher BMI value was associated with a lower vitamin D level (12–14). Since VKC is a type of allergic inflammatory disease, it is very likely that VKC patients possess higher BMI levels.

To the best of our knowledge, no study to date has evaluated the relationship between the vitamin D level and BMI values in VKC patients. A high BMI influences the vitamin D level, and alterations in the level of vitamin D modulate immunity, which could trigger allergic reactions, leading to VKC. The objective of this clinical study was to examine this relationship between the BMI value and vitamin D level in VKC patients as measured in the fall of 2019 during the months of September and October.

Methods

Study Design and Participants

This single-centered, observational, case-control study was conducted in a tertiary hospital in September–October, 2019. The study was approved by the Institutional Ethics Committee (Protocol no: 291) and conducted in accordance with the Declaration of Helsinki. Written, informed consent was obtained from the parents of all of the subjects enrolled. Children treated in the Department of Ophthalmology were examined. All of the patients participating in this study underwent a complete ophthalmologic examination that included assessment of refraction and visual acuity, slit lamp examination, IOP measurement with a Tono-Pen (Reichert Technologies, Depew, NY, USA), and fundoscopy.

The VKC diagnosis was based on patient history and the detection of cobblestone papillary hypertrophy in the superior tarsal conjunctiva and/or gelatinous yellow-grey infiltrates in the limbal area. The disease was classified as palpebral, limbal, or mixed phenotype. The patients were then referred to the Pediatric Allergy and Immunology Department of Dr. Ersin Aslan Research and Training Hospital for the evaluation of associated allergic diseases.

Control subjects were chosen from healthy, non-atopic children who had been previously admitted to the ophthalmology clinic for routine control examinations and had no eye disease other than refractive errors. The physical examination and blood test results, including biochemistry and complete blood cell count, were normal. None of the chil-

dren in the control group were affected by systemic disorders that could affect the vitamin D level, such as rheumatoid arthritis, cystic fibrosis, sarcoidosis, thyroid dysfunction, or obesity. Similarly, none used barbiturates, bisphosphonate, sulphasalazine, omega-3, calcium, or vitamin D. They had no prior indicators of vitamin D deficiency, such as diffuse joint or bone pain (especially of the spine, pelvis, and legs), muscle weakness, fatigue, difficulty walking, weak or soft bones (bending), or fractures.

Venous blood samples from the antecubital vein were collected from the study and control group patients in the morning after overnight fasting and transferred into tubes preloaded with the anticoagulant ethylenediaminetetraacetic acid. After centrifugation at 2000 g for 15 minutes, the samples were stored at -20°C until they were analyzed. High-performance liquid chromatography using a UV detector (Chromsystems, Munich, Germany) was used to measure the vitamin D level. A Chromsystems kit permitted simple and rapid determination of both serum 25-hydroxyvitamin D2 [25(OH)D2] and 25-hydroxyvitamin D3 [25(OH)D3]. Following protein precipitation, solid phase extraction was performed. It required only a small sample volume and had a stable internal standard, which ensured reliable quantification. In the current study, only the serum 25(OH)D3 level was measured. Estimation of the vitamin D level in circulation using 25(OH)D3 was more effective than the 25(OH)D2 level, possibly because it formed a more stable hormone-receptor complex. The detection limit for 25(OH)D3 was 5 ng/mL (15).

The participants were divided into 5 groups based on the serum vitamin D level (severe deficiency: <10 ng/mL, deficiency: 10–20 ng/mL, insufficiency: 20–30 ng/mL, normality: 30–100 ng/mL) (16). The height and weight of the individuals were recorded and the BMI values were calculated as weight (kg)/height (m) squared (9).

Statistical Analysis

The IBM SPSS Statistics for Windows, Version 26.0 package (IBM Corp., Armonk, NY, USA) was used to perform the requisite statistical analyses. The mean, SD, median, minimum, maximum, value frequency, and percentage were used to extract descriptive statistics. The distribution of the variables was ascertained using the Kolmogorov–Smirnov test. The independent samples t-test, the Mann–Whitney U test, and the Kruskal–Wallis test were used to compare quantitative data. A chi-square test was used to assess the qualitative data. The correlations were analyzed using the Spearman's correlation test.

Results

The study group consisted of 46 patients with VKC, of whom 37 (80.4%) were male and 9 (19.6%) were female.

The control group included 40 healthy individuals, of whom 30 (75%) were male and 10 (25%) were female. The descriptive statistics of the study participants from both groups are shown in Table 1. No statistically significant difference was found between the groups with respect to age or gender ($p=0.810$, $p=0.545$, respectively) (Table 2).

The mean overall 25(OH)D3 level in the males (17.022 ± 6.17 ng/mL) was greater than that of the females (14.7 ± 3.56 ng/mL), but this difference was not statistically significant ($p=0.158$). The mean 25(OH)D3 level in the study group was significantly lower than that of the control group ($p<0.001$) (Table 2).

Table 1 and Figure 1 show the distribution of the study participants with respect to the serum 25(OH)D3 level. Severe 25(OH)D3 deficiency was found in 10.9% of the VKC-affected children and in 5% of the healthy children. No significant relationship between 25(OH)D3 deficiency and gender was found in all of the participants from both groups ($p=0.789$); there was also no association between 25(OH)D3 deficiency and gender in either the control or the VKC group ($p=0.446$, $p=0.493$, respectively).

The mean BMI value in the healthy children was significantly different from the mean BMI value in the VKC-affected children ($p=0.046$) (Table 2).

A comparison of the 25(OH)D3 level and the BMI value in all participants demonstrated a negative correlation (Spearman's correlation $\rho=-0.275$, $p=0.01$). In the VKC

group, there was a strong statistically significant negative correlation between the BMI value and the 25(OH)D3 level (Spearman's correlation $\rho=-0.454$; $p=0.02$). The data of both groups, however, revealed a strong statistically significant positive correlation between age and BMI, (Spearman's correlation $\rho=0.4$; $p<0.001$).

Table 3 lists the 25(OH)D3 level according to VKC subtype. Note that there were no statistically significant differences in the mean 25(OH)D3 level among the different VKC sub-types ($p=0.266$).

Discussion

VKC is a severe eye disease that activates both immunoglobulin E (IgE)-mediated and non-IgE-mediated immune mechanisms. Elevated levels of allergy-specific antibodies and eosinophil counts are encountered in VKC patients, suggesting that VKC clinically resembles the pathophysiology of the allergic response (16). Along with its role in bone development, vitamin D is involved in various immune functions (17–20). Therefore, vitamin D deficiency is common among VKC patients (16).

BMI is an important factor that is currently taken into consideration in the case of allergic reactions. Several atopic patients have been shown to have an elevated BMI value (21). As VKC is an allergic disorder, an increased BMI value and a reduced vitamin D level is likely in VKC patients. We tested this hypothesis in our study and found that the mean vitamin

Table 1. Descriptive statistics of the control and study group variables

	Min-Max	Median	Mean \pm SD	n (%)
Age (Months)	60.0-204.0	103.5	104.8 \pm 33.4	
Sex				
Male				67 (77.9)
Female				19 (22.1)
Height (cm)	107.0-177.0	126.8	128.4 \pm 15.1	
Weight (kg)	18.0-76.0	26.0	28.8 \pm 11.5	
Body mass index (kg/m ²)	14.2-27.0	16.1	16.8 \pm 2.4	
Vitamin D (ng/mL)	4.4-33.1	15.0	16.5 \pm 5.8	
Vitamin D (ng/mL)				
Severe deficiency: <10				7 (8.1)
Deficiency: 10-20				57 (66.3)
Insufficiency: 20-30				19 (22.1)
Normality: 30-100				3 (3.5)
Vernal type				
Limbal				25 (54.3)
Palpebral				6 (13.0)
Mixed				15 (32.6)

Table 2. Comparison of parameters between the study and control groups

	Control group (n=40)			VKC group (n=46)			p
	Mean±SD	n (%)	Median	Mean±SD	n (%)	Median	
Age (Months)	103.9±24.9		103.5	105.7±39.6		101.5	0.810 ^t
Sex							
Male		30 (75.0)		37 (80.4)			0.545 ^{X²}
Female		10 (25.0)		9 (19.6)			
Height (cm)	127.8±11.0		127.0	128.9±18.0		126.5	0.637 ^m
Weight (kg)	27.4±7.2		26.0	30.0±14.2		24.5	0.290 ^t
Body mass index (kg/m ²)	16.5±2.3		15.6	17.1±2.5		16.4	0.046 ^m
Vitamin D (ng/mL)	19.0±5.7		17.5	14.3±5.0		13.0	0.000 ^m
Vitamin D (ng/mL)							
Severe deficiency: <10		2 (5.0)		5 (10.9)			0.105 ^{X²}
Deficiency: 10–20		24 (60.0)		33 (71.7)			
Insufficiency: 20–30		12 (30.0)		7 (15.2)			
Normality: 30–100		2 (5.0)		1 (2.2)			

t T-test; m Mann-Whitney U test; X² Chi-square test; VKC: Vernal keratoconjunctivitis.

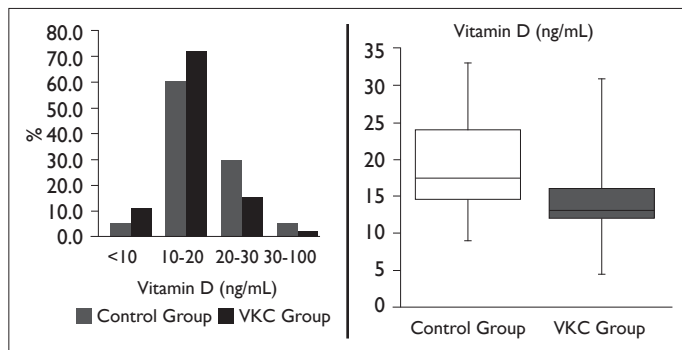


Figure 1. Percent distribution of vitamin D levels in the VKC and control groups and a comparison of vitamin D levels between groups.

D level in the VKC group was significantly lower than that of the healthy group. The BMI value was statistically significant higher in the VKC group. Other studies, which support our current findings, have also demonstrated that the vitamin D level is lower in allergic patients (3–6).

Vitamin D deficiency can alter the immune response. Vitamin D is shown to check the maturation and migration of dendritic cells and increase the production of interleukin 10 (IL-10), thereby suppressing allergic reactions. Vitamin D deficiency inhibits IL-10-producing cells and increases the number of pulmonary T helper type 2 (Th2) cells and eosinophils, as observed in VKC patients (22). It has been shown that vitamin D supplementation helps to suppress the damage caused by inflammation in allergic conjunctivitis by modulating the Th2 response, thus decreasing the infiltration of

Table 3. Vitamin D level in vernal sub-types

Vernal type	Vitamin D (ng/mL)			p
	Min-Max	Median	Mean±SD	
Limbal	4.4-31.0	13.0	13.6±5.2	0.266 ^K
Palpebral	8.0-25.0	11.1	13.9±6.2	
Mixed	12.0-22.0	14.0	15.8±4.0	

^KKruskal-Wallis test.

inflammatory cells into the conjunctiva (22). Vitamin D inhibits IgE production in B cells, and reduces eosinophilia and B cell-dependent allergic reactions (22). This clearly demonstrates that the immunomodulatory effects of vitamin D can lead to allergic conditions. The exact cause of the vitamin D deficiency in VKC is still unknown; however, the photophobia seen in VKC patients could be a contributing factor. As VKC patients are very sensitive to light and tearing worsens on exposure to light, these patients avoid sunlight exposure, leading to lower vitamin D production.

VKC is more common in boys, and approximately 80% of the VKC patients in the current study were male. Hence, the prevalence of VKC varies significantly between genders. Disease regression at puberty strongly supports the role of hormonal factors in the development of VKC (23). Although not statistically significant, the vitamin D level was higher

in the males of our study group. The precise reason is unknown. Several suggestions have been offered; one of which is that there is a decrease in the bioavailability of vitamin D as it is absorbed and stored by the adipose tissues because the amount of adipose tissue in boys is less than that of girls (24). However, the correlation between vitamin D deficiency and gender was not significant collectively when considering all of the participants in the present study. Furthermore, there was no correlation between vitamin D deficiency and gender in either the control group or the VKC group.

Vitamin D is a fat-soluble prohormone existing in 2 forms: D3 and D2. The vitamin synthesized in the skin on exposure to sunlight is vitamin D3 (cholecalciferol), while vitamin D2 (ergocalciferol) is mainly absorbed from the diet (25). Vitamin D3 is metabolized to 1,25-dihydroxyvitamin D3 (calcitriol) and forms a complex with the intracellular vitamin D receptor. This complex plays a major role in bone mineralization and the immune response. It primarily aids in bone mineralization by absorbing calcium and phosphorus from the intestines and kidneys (9). The absorption of calcium is increased by 50% and that of phosphorus by 75%. This highlights the importance of vitamin D in bone mineral density (15).

The findings presented in this study indicate a negative correlation between the vitamin D level and BMI. A study carried out with Hispanic-American adolescents revealed that a majority of the obese adolescents had a low vitamin D level (26). Another study, performed in children in Brooklyn, NY, USA, found an association between vitamin D insufficiency, age, and BMI in both genders (13). Several reasons have been proposed for hypovitaminosis D in obesity. Vitamin D is deposited in adipose tissue, which is present to a greater extent in individuals who are obese. The vitamin D is thus sequestered, which results in less bioavailability (27).

Interestingly, it was seen that in the VKC group, the level of vitamin D was negatively correlated with the BMI. The vitamin D level in the blood and the BMI value are influenced by a number of factors, including diet, exposure to sunlight, supplements, and systemic disorders. Although the study did not include children who suffered from any systemic disease or any vitamin D deficiency symptoms, limitations of the current study are the lack of participant values for bone mineral density, serum eosinophil level, length of daily sun exposure, or diet. In addition, this was a single-center study. Furthermore, it should be kept in mind that the level of vitamin D might be affected by geographic and climatic differences, as well as ethnic differences.

Conclusion

The current study analyzed the correlation between the vitamin D level and the BMI value in VKC patients. We found

that children with VKC had a lower serum vitamin D level and a higher BMI value compared with age- and sex-matched healthy children. This study provided a unique opportunity to evaluate the role of serum vitamin D and BMI in VKC patients. However, it is still unclear whether vitamin D deficiency develops because the VKC patients cannot tolerate sunlight, thereby leading to the deficiency, or if the vitamin D deficiency is the primary etiopathogenesis of VKC. It is also unknown whether the higher BMI level in VKC patients may be caused by staying inside for the most part.

Monitoring the serum vitamin D level in VKC patients might be beneficial, since if the vitamin D level is low, a supplement might help to minimize any negative effects caused by the vitamin deficiency, thereby providing a new therapeutic strategy. Further research is needed to evaluate the role of vitamin D deficiency in the pathophysiology of VKC. Our outcomes suggest a need to consider the clinical implications of vitamin D deficiency and an elevated BMI level in the VKC population.

Disclosures

Ethics Committee Approval: The study was approved by the ethics Committee of Dr Ersin Arslan Training and Research Hospital, Gaziantep, Turkey (Protocol no: 291).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Involved in design and conduct of the study (GKD, YK); preparation and review of the study (GKD, YK, BTA, BS); data collection (GKD); and statistical analysis (YK, BTA).

References

1. Singhal D, Sahay P, Maharana PK, Raj N, Sharma N, Titiyal JS. Vernal Keratoconjunctivitis. *Surv Ophthalmol* 2019;64:289–311.
2. Bonini S, Coassin M, Aronni S, Lambiase A. Vernal keratoconjunctivitis. *Eye (Lond)* 2004;18:345–51.
3. Reinholz M, Ruzicka T, Schaubert J. Vitamin D and its role in allergic disease. *Clin Exp Allergy* 2012;42:817–26.
4. Frieri M, Valluri A. Vitamin D deficiency as a risk factor for allergic disorders and immune mechanisms. *Allergy Asthma Proc* 2011;32:438–44.
5. Dogru M, Kirmizibekmez H, Yesiltepe Mutlu RG, Aktas A, Ozturkmen S. Clinical effects of vitamin D in children with asthma. *Int Arch Allergy Immunol* 2014;164:319–25.
6. Dadaci Z, Borazan M, Kiyici A, Oncel Acir N. Plasma vitamin D and serum total immunoglobulin E levels in patients with seasonal allergic conjunctivitis. *Acta Ophthalmol* 2014;92:e443–e6.
7. Bozkurt B, Artac H, Ozdemir H, Ünlü A, Bozkurt MK, Irkeç M. Serum Vitamin D Levels in Children with Vernal Keratoconjunctivitis. *Ocul Immunol Inflamm* 2018;26:435–9.
8. Zicari AM, Cafarotti A, Occasi F, Lollobrigida V, Nebbioso M,

- Pecorella I, et al. Vitamin D levels in children affected by vernal keratoconjunctivitis. *Curr Med Res Opin* 2017;33:269–74.
9. Reas DL, Nygård JF, Svensson E, Sørensen T, Sandanger I. Changes in body mass index by age, gender, and socio-economic status among a cohort of Norwegian men and women (1990-2001). *BMC Public Health* 2007;7:269.
 10. Bråbäck L, Hjern A, Rasmussen F. Body mass index, asthma and allergic rhinoconjunctivitis in Swedish conscripts - A national cohort study over three decades. *Respir Med* 2005;99:1010–4.
 11. Huang SL, Shiao GM, Chou P. Association between body mass index and allergy in teenage girls in Taiwan. *Clin Exp Allergy* 1999;29:323–9.
 12. Al-Horani H, Abu Dayyih W, Mallah E, Hamad M, Mima M, Awad R, et al. Nationality, Gender, Age, and Body Mass Index Influences on Vitamin D Concentration among Elderly Patients and Young Iraqi and Jordanian in Jordan. *Biochem Res Int* 2016;2016:8920503.
 13. Smotkin-Tangorra M, Purushothaman R, Gupta A, Nejati G, Anhalt H, Ten S. Prevalence of vitamin D insufficiency in obese children and adolescents. *J Pediatr Endocrinol Metab* 2007;20:817–23.
 14. Lagunova Z, Porojnicu AC, Lindberg F, Hexeberg S, Moan J. The dependency of vitamin D status on body mass index, gender, age and season. *Anticancer Res* 2009;29:3713–20.
 15. McKenna MJ, Murray B. Vitamin D deficiency. In: Bandeira, F, Hossein, G, Airton, G, editors. *Endocrinology and Diabetes: A Problem-Oriented Approach*. New York (NY): Springer; 2014. p. 293–304.
 16. Ghigliani DG, Bruschi G, Gandini S, Osnaghi S, Peroni D, Marchisio P. Vitamin D serum levels in children with vernal keratoconjunctivitis and disease control. *Int J Immunopathol Pharmacol* 2019;33:2058738419833468.
 17. Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. *J Immunol* 2007;179:1634–47.
 18. Smolders J, Damoiseaux J, Menheere P, Hupperts R. Vitamin D as an immune modulator in multiple sclerosis, a review. *J Neuroimmunol* 2008;194:7–17.
 19. Maynard CL and Weaver CT. Diversity in the contribution of interleukin-10 to T-cell-mediated immune regulation. *Immunol Rev* 2008;226:219–33.
 20. Penna G and Adorini L. 1 alpha,25-dihydroxyvitamin D-3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. *J Immunol* 2000;164:2405–11.
 21. Schachter LM, Peat JK, Salome CM. Asthma and atopy in overweight children. *Thorax* 2003;58:1031–5.
 22. Hartmann B, Heine G, Babina M, Steinmeyer A, Zügel U, Radbruch A, et al. Targeting the vitamin D receptor inhibits the B cell-dependent allergic immune response. *Allergy* 2011;66:540–8.
 23. Leonardi A, Secchi AG. Vernal keratoconjunctivitis. *Int Ophthalmol Clin* 2003;43:41–58.
 24. Wamberg L, Christiansen T, Paulsen SK, Fisker S, Rask P, Rejnmark L, et al. Expression of vitamin D-metabolizing enzymes in human adipose tissue -- the effect of obesity and diet-induced weight loss. *Int J Obes (Lond)* 2013;37:651–7.
 25. Yang CH, Albietz J, Harkin DG, Kimlin MG, Schmid KL. Impact of oral vitamin D supplementation on the ocular surface in people with dry eye and/or low serum vitamin D. *Cont Lens Anterior Eye* 2018;41:69–76.
 26. Kumaratne M, Early G, Cisneros J. Vitamin D deficiency and association with body mass index and lipid levels in Hispanic American adolescents. *Glob Pediatr Health* 2017;4:1–6.
 27. Migliaccio S, Di Nisio A, Mele C, Scappaticcio L, Savastano S, Colao A, et al. Obesity and hypovitaminosis D: causality or casualty? *Int J Obes Suppl* 2019;9:20–31.