Original Article

# Serum vitamin D levels in children with vernal keratoconjunctivitis – A study from a tertiary care pediatric hospital of North India

*Meenakshi Wadhwani, Shikha Sharma[1], Rahul Singh[2]*

**Background:** To study the levels of vitamin D serum levels in children with vernal keratoconjuctivits (VKC) and comparing vitamin D levels in after giving vitamin D supplements between intervention and control group. **Methods:** The study was conducted in population between 1 to 12 years in tertiary care hospital in North India. Amongst children with VKC, full ocular examination along with Boninis clinical grading of VKC and serum vitamin D levels were assessed. Whole study group was randomly divided into two groups. Intervention group had received vitamin D powder while control group kept under observation. **Results:** A total of 88 children received vitamin D supplementation and 39 kept in control group. **Conclusion:** Our study suggests that children in intervention group showed improvement in serum vitamin D levels with the clinical improvement in VKC grading too.

**Key words:** Refractive error, vernal keratoconjunctivitis, vitamin D

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Vernal keratoconjunctivitis (VKC) is a recurrent and often severe form of bilateral chronic allergic disease of the ocular surface affecting mostly young males in the first decade of life, living in warm climates. Patients with VKC usually present with symptoms of itching, tearing, redness, photophobia, and mucoid sticky discharge. On ocular examination, the disease is characterized by giant papillae on the upper tarsal conjunctiva classically (cobblestone papillae) and Trantas dots at the limbus. In case of corneal involvement, superficial punctate epithelial keratopathy and shield ulcer are seen, which might lead to late corneal vascularization. The severity of symptoms rises during the hot season; however, the disease could be perennial.[1-10]

The precise etiology of VKC is still unclear; however, immunopathogenic mechanism has been suggested in previous studies stating the role of both IgE-dependent (type-I allergic) and IgE-independent (type-IV allergic) mechanisms.[1-6,11]

1,25-hydroxyvitamin D [1,25(OH)D3] or calcitriol, an active form of vitamin D, acts as a transcriptional factor after binding with the intracellular vitamin D receptor (VDR) in immune system cells.[2,12-15] Several studies have shown that 1,25-hydroxyvitamin D intensifies the expression of interleukin-10 (IL-10) and inhibits the maturation and migration of dendritic cells (DC), leading to decreased IL-12 and IL-23 cytokine formation. Moreover, it inhibits several inflammatory cytokines such as IL 17, IL 22, IL-2, IL-12, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α). Hence, vitamin D suppresses the allergic pathway and protects against atopic disorders. Vitamin D also inhibits Th1, Th2, and Th17 cells involved in the development of atopy and Th1-associated diseases.[2,14-20] Several studies revealed the existence of VDRs and vitamin D hydroxylases in many ocular cells which were capable to synthesize 1,25D3 from 25D3, suggesting possible in-situ vitamin D metabolism. *In vitro*, corneal limbal cells have been found to synthesize vitamin D on UVB exposure, like skin cells do.[20-22] VKC might be related to abnormal low 1,25-hydroxyvitamin D levels, like in other allergic disorders such as asthma and allergic rhinitis. VKC patients are more predisposed to develop vitamin D deficiency as they are bound to stay indoors due to intense photophobia associated with this disorder. This predisposes them to dry eye disease and hence VKC.[18,21] Our current study aims to find the possible relationship between children suffering from VKC and 25(OH) D3 levels in North India.

## Methods

The current study was conducted at a tertiary care hospital. In the current study, 88 children with vernal keratoconjunctivitis (VKC) and 39 healthy subjects were studied over the duration of 6 months as study and control arms, respectively. The study was

Assitant Professor, Guru Nanak Eye Centre, New Delhi, [1]Assistant Professor Biochemistry, Chacha Nehru Bal Chikitsalaya, [2]Assistant Professor, NIMS, Uttar Pradesh, Ophthalmology, India

Correspondence to: Dr. Meenakshi Wadhwani, Assistant Professor Ophthalmology, Guru Nanak Eye Centre, Maulana Azad Medical College, New Delhi, India. E-mail: mkgang08@gmail.com

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approved by the review board of the hospital. Written informed consent was acquired from all the parents.

Subjects with ocular comorbidities such as xerophthalmia, conjunctivitis, keratitis, or uveitis and children with systemic conditions that might alter 1,25-hydroxyvitamin D levels (including articular rheumatism, sarcoidosis, cystic fibrosis, and thyroid disorder), or subjects on medication (such as barbiturates, sulphasalazine, biphosphonate, vitamin D, and calcium) were excluded from the study.

Full ocular evaluation comprising unaided and best-corrected visual acuity, slit-lamp biomicroscopic evaluation, and posterior segment evaluation was done in all children. VKC was classified based on Bonini's clinical grading of VKC. The control arm included children with no ocular complaints except refractive error and without the abovementioned diseases. Otorhinological and pediatric referral was also done to rule out any co-associated allergic conditions.

Serum vitamin D levels and 1,25-hydroxyvitamin D levels were analyzed from fasting venous blood samples that were obtained in the morning after overnight fasting after recruiting the VKC children at the beginning of the study and at the follow-up visit at 3 months. Serum levels of vitamin D were analyzed using a chemoluminescent immunoassay on a Liaison automatic analyzer (Liason 25 OH Vitamin D, DiaSorin). Data were expressed as nanograms per milliliter. Pediatrician consultation was taken for all the children who were found to have deficient 1,25-hydroxyvitamin D levels. Only those children with deficient vitamin D levels children were administered oral vitamin D under the supervision of a pediatrician with a fixed dosage as per IAP.

Only serum 25(OH)D3 levels were determined as it has a more stable hormone-receptor complex and thus provides vitamin D levels more efficiently than 25(OH)D2. Following the Indian Academy of Pediatrics (IAP) guidelines for the prevention and treatment of vitamin D in children and adolescents, vitamin D concentrations of >20 ng/mL (50 nmol/L) were considered as sufficient, between 12 and 20 ng/mL (30–50 nmol/L) as insufficient, and <12 ng/mL (<30 nmol/L) as deficient.[2]

### Statistical analysis

The analysis was done after the entry of the data in a specifically designed database in Epi data. The entered data were exported, and the final data analysis was done using Stata 14. The distribution of participants with respect to age, gender, residence type, education status, income, etc., was tabulated. A *P* value of <0.05 was considered statistically significant. The association of vitamin D levels with the other variables was assessed using logistic regression models.

## Results

Out of 88 VKC children, 72.7% (n = 64) children were in the age group of 5–10 years (*P* = 0.014). The mean age of the VKC children was 6.73 ± 2.58 (1–16 years). Out of 88 VKC patients, only 67 patients completed the follow-up visit at the 3-month interval to reassess serum vitamin D levels. Out of 88 children, 73 (82.1%) were male and 15 (17.1%) were female (*P* = 0.754), while in the control arm, 22 (56.4%) were male and 17 (43.6%) were female. Grade-wise segregation of VKC patients demonstrated that maximum children (n = 42) presented with grade 2 of VKC (47.7%) with mild-to-moderate conjunctival involvement in the form of papillae, while the lowest percentage (3.4%) belonged to grade 4 of VKC, with corneal infiltrates and trantas dots (n = 3) (*P* = 0.014) [Table 1].

The mean serum 25(OH) D3 level was 15.67 ± 7.94 (range: 3.2–42.2 ng/mL). The mean serum 25(OH) D3 levels were 16.37 ± 8.10 (range: 5.2–28.6 ng/mL), 15.47 ± 8.03 (range: 3.2–42.2 ng/mL), 15.57 ± 7.67 (range: 6.5–21.57 ng/ml) in the age groups of <5 years, >5–10 years, and >10 years, respectively [Fig. 1]. At the 3-month follow-up visit after vitamin D supplementation, mean serum 25(OH) D3 levels were 31.60 ± 9.39 (range: 13.18–63.5 ng/mL). The mean serum 25(OH) D3 levels were 34.4 ± 7.07 (range: 24.2–44.4 ng/mL), 30.46 ± 9.86 (range: 13.18–63.5 ng/mL), and 39.5 ± 6.93 (range: 34.6–44.4 ng/mL) in the age groups of <5 years, >5–10 years, and >10 years, respectively, at the 3-month follow-up visit after vitamin D supplementation [Fig. 2]. The mean serum 25(OH) D3 level of children in the control arm was 20.53 ± 6.84 ng/mL.

**Table 1: Distribution of vernal keratoconjunctivitis (VKC) children according to the demographic parameters and serum vitamin D level**

| Patient characteristics | VKC Grade | | | | Total (*n*) |
|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | |
| Age Group | | | | | |
| <5 years | 8 | 8 | 1 | 2 | 19 |
| 5–10 years | 9 | 29 | 25 | 1 | 64 |
| >10 years | 2 | 1 | 2 | 0 | 5 |
| Gender | | | | | |
| Female | 4 | 5 | 5 | 1 | 15 |
| Male | 15 | 33 | 23 | 2 | 73 |
| Mean serum 25(OH)D3 level (ng/ml) | | | | | |
| <12 | 8 | 15 | 8 | 1 | 32 |
| 12–20 | 5 | 15 | 10 | 2 | 32 |
| >20 | 8 | 12 | 4 | 0 | 24 |
| Total | 21 | 42 | 22 | 3 | |

Severe vitamin D deficiency (<12 ng/mL) was found in 36.4% of VKC patients (n = 32). Sufficient vitamin D levels (>20 ng/mL) were found in 27.3% of VKC children (n = 24) ($P$ = 0.22). In this study, it was observed that the majority of VKC children with severe vitamin D deficiency (<12 ng/mL) belonged to grade 2 (17.1%) in the form of papillary reaction and grade 3 (9.1%) with superficial punctal keratitis of Bonini clinical grading of VKC,[3] respectively. Similarly, children with 12–20 ng/mL mostly presented with grades 2 and 3 (17.1% and 11.4%, respectively). The majority of VKC children with sufficient levels of vitamin D (>20 ng/mL) were observed to have grades 1 and 2 of VKC in the form of mild conjunctival involvement and papillary reaction, respectively (9.1% and 13.6%, respectively) ($P$ = 0.63) [Table 1]. Along with the selective administration of oral vitamin D in the vitamin D-deficient children, the VKC children with grades 2–4 were treated with conventional treatment in the form of topical lubricating and mast cell stabilizers. None of these children with VKC were treated with topical steroids.

On reassessing serum vitamin D levels at the 3-month follow-up visit, none of the children with VKC was found to have severe vitamin D deficiency (<12 ng/mL). Seven (10.5%) children still belonged to the insufficient category (12–20 ng/mL), and 60 (89.1%) patients rose to sufficient levels of vitamin D (>20 ng/mL) [Fig. 3]. Out of 67 VKC cases, the symptoms of VKC had improved from grades 2 and 3 to grade 1 in 50 out of 64 (78.1%) children, none of the children remained in grade 4, and 14 out of 21 children in grade 1 (66.6%) recovered from signs of VKC.

As shown in Table 2, we determined the odds ratio (95% confidence intervals) at the first visit of presentation and at the 3-month follow-up visit after vitamin D supplementation and did not find any correlation between the following variables: age, sex, and serum vitamin D levels.

## Discussion

In VKC, both IgE and non-IgE mechanisms appear to have a vital part in its etiopathogenesis.[1-6,11] Several studies have been conducted to find the relationship between 1,25-hydroxyvitamin D levels and allergy. In a meta-analysis conducted by Man *et al*.[20] assessing the risk of childhood asthma in vitamin D deficiency in 3424 subjects with vitamin D deficiency and 2756 subjects with vitamin D insufficiency, the relative risk was found to be 1.684 (1.321–2.148). VKC might be associated with atopy, asthma, atopic eczema, and allergic rhinitis in up to 50% of cases. Therefore, there might be a possibility of an association between VKC and vitamin D deficiency.[18,23]

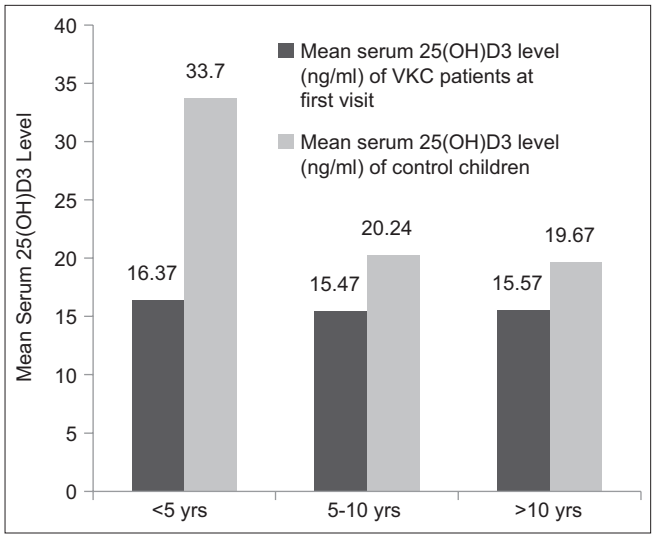


**Figure 1:** Mean serum 25(OH)D3 level in vernal keratoconjunctivitis (VKC) patients at the first visit and control arm children

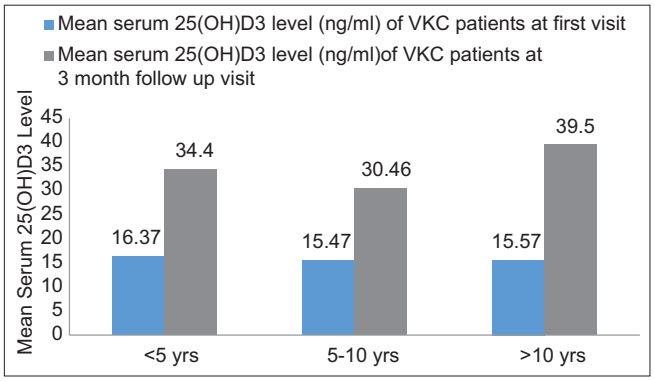


**Figure 2:** Mean serum 25(OH)D3 level in vernal keratoconjunctivitis (VKC) patients at the first visit and 3-month visit

**Table 2: Logistic regression analysis comparing vitamin D levels at baseline and three month follow-up in children with vernal keratoconjunctivitis (VKC)**

| Patient characteristics | First visit ($n$=88) | | | 3-month follow-up ($n$=67) | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% confidence intervals | $P$ | Odds ratio | 95% confidence intervals | $P$ |
| Age | | | | | | |
| <5 years | 1 | | | 1 | | |
| 5–10 years | 2.13 | 0.75:6.08 | 0.157 | 2.9 | 0.68:7.67 | 0.177 |
| >10 years | 1.35 | 0.18:10.01 | 0.769 | 1.34 | 0.06:26.75 | 0.845 |
| Sex | | | | | | |
| Male versus female | 0.66 | 0.19:2.27 | 0.507 | 0.75 | 0.16:3.41 | 0.715 |
| Serum vitamin D levels | | | | | | |
| <12 ng/mL vs. 12–20 ng/mL | 1.34 | 0.46:3.87 | 0.590 | 1.27 | 0.39:4.08 | 0.689 |
| <12 ng/mL vs. >20 ng/mL | 0.73 | 0.25:2.18 | 0.577 | 0.82 | 0.21:3.25 | 0.774 |
| 12–20 ng/mL vs. >20 ng/mL | 0.64 | 0.12:3.59 | 0.615 | 0.87 | 0.14:5.33 | 0.878 |

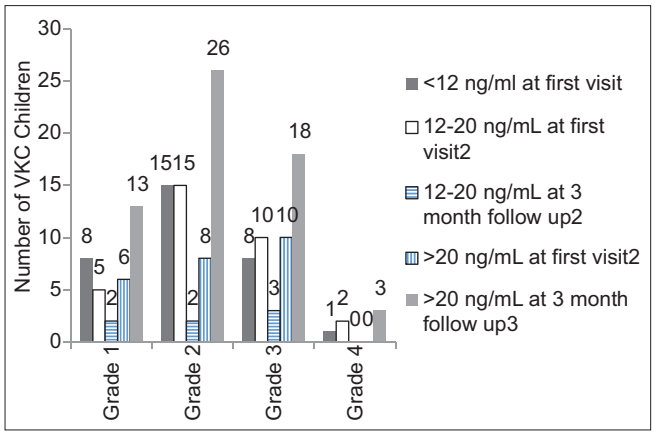


**Figure 3:** Segregation of vernal keratoconjunctivitis (VKC) children according to the Bonini clinical grading with respect to the vitamin D levels at the first visit and 3-month follow-up visit after vitamin D supplementation

As per Indian Academy of Pediatrics (IAP) guidelines for the prevention and treatment of vitamin D in children and adolescents, vitamin D concentrations of > 20 ng/mL (50 nmol/L) were considered as sufficient, between 12 and 20 ng/mL (30–50 nmol/L) as insufficient, and < 12 ng/mL (<30 nmol/L) as deficient.[2]

In the current study, we emphasized the low 1,25-hydroxyvitamin D levels in VKC patients. According to the IAP guidelines, we observed that the prevalence of vitamin D insufficiency (<20 ng/mL) and deficiency (<12 ng/mL) in VKC patients were 36.4% (n = 32) each. There was a significant association of deficiency of vitamin D levels with VKC. These children usually suffer from the characteristic photophobia and thus may prefer to stay indoors. Insufficient sunlight exposure in such cases could lead to the further lowering of 1,25-hydroxyvitamin D levels, not only in VKC but also in healthy children. In the present study, a higher prevalence of vitamin D deficiency was detected, which might be linked to the increased usage of TV and exposure to digital devices such as computers/internet, smartphones, and video games, ultimately leading to reduced outdoor activities, predisposing these children to dry eye disease, which is an important risk factor for developing VKC.

Factors such as skin pigmentation, sunscreen usage, extent of clothing, seasonal variation, and geographical latitude also affect vitamin D levels as its synthesis depends upon the amount of UVB reaching the skin.[21,22,24] Very few studies are available in the literature evaluating the importance of 1,25-hydroxyvitamin D in ophthalmic allergies. One such study conducted by Dadaci *et al*.,[17] reported lower serum 1,25-hydroxyvitamin D levels in patients with seasonal allergic conjunctivitis (SAC). The level of 1,25-hydroxyvitamin D was 8.19 ± 4.34 ng/mL (range: 3.0–17.97 ng/mL) and 11.66 ± 5.93 ng/mL (range: 3.30–25.92 ng/mL) ($P$ = 0.007) in SAC patients (n = 49) and in sex- and age-matched controls (n = 44), respectively. A recent study conducted by Zicari *et al*.[18] also revealed that serum vitamin D levels were low in 47 children with VKC as compared to 63 healthy controls. They also reported an increase in vitamin D on topical usage of cyclosporine 1% eye drops in VKC children. In addition, the attitude and compliance of parents and caretakers also get affected due to the recurrence of symptoms of this disease.[25]

In the current study, we have seen that on giving topical anti-allergic treatment along with oral vitamin D supplementation, both signs and symptoms improved along with the improvement in serum vitamin D levels. It is difficult to pinpoint the exact reason for the improvement in signs and symptoms – whether it was because of topical treatment or vitamin D supplementation or both – as we know that more than one mechanism has been speculated in the pathogenesis of VKC. This is the first study from North India where a correlation between serum vitamin D levels and children with VKC has been conducted.

### Limitation

Due to the recurrent course of this disease, the majority of patients were on topical medications, which made us incapable of assessing the 1,25-hydroxyvitamin D levels in VKC subjects with no previous management, and we were not able to assess the effect of topical management on 1,25-hydroxyvitamin D levels and vice versa.

## Conclusion

There was a significant association of deficiency of vitamin D levels with VKC. The evaluation of serum 1,25-hydroxyvitamin D levels in all VKC patients may not be prudent. Usually, children with vitamin D deficiency are predisposed to develop VKC. A larger cohort or case-control study would be able to provide more conclusive answers, which may help us formulate recommendations for clinical practice.

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**Conflicts of interest:** There are no conflicts of interest.

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