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Serum Vitamin D Levels and Clinical Severity of Vernal Keratoconjunctivitis in a Pediatric Cohort: A Cross-Sectional Study from Eastern India

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ABSTRACT

Background: Vernal keratoconjunctivitis (VKC) is a chronic, bilateral, and potentially sight-threatening ocular surface inflammation prevalent in the pediatric population. Emerging evidence suggests that Vitamin D plays a critical role in immunomodulation and the regulation of allergic pathways. This study aimed to investigate the association between serum 25-hydroxyvitamin D [25(OH)D] levels and the clinical severity of VKC in children attending a tertiary care center in Berhampur, India.

Methods: This cross-sectional study involved N=26 children diagnosed with VKC at MKCG Medical College & Hospital, Berhampur. Clinical severity was graded according to Bonini's classification. Serum 25(OH)D levels were measured using chemiluminescence immunoassay. Statistical analysis was performed using Pearson's correlation and ANOVA to determine the relationship between Vitamin D status and disease severity.

Results: The mean age of the participants was 9.4 +/- 3.2 years. Vitamin D deficiency (defined as < 20 ng/mL) was observed in 61.5% of the cohort. A strong inverse correlation was identified between serum 25(OH)D levels and the clinical severity score ($r = -0.68$, $p < 0.001$). Children with "Severe" VKC (Grade 4) exhibited significantly lower mean Vitamin D levels (12.4 +/- 4.1 ng/mL) compared to those with "Mild" disease (28.2 +/- 5.3 ng/mL).

Conclusion: Lower serum Vitamin D levels are significantly associated with increased VKC severity in children. These findings suggest that Vitamin D deficiency may contribute to the exacerbation of ocular allergic inflammation.

Key-words: Vernal Keratoconjunctivitis, Vitamin D, Pediatrics, Ocular Allergy, Immunomodulation, Berhampur

INTRODUCTION

Vernal keratoconjunctivitis (VKC) represents a severe form of chronic allergic inflammation of the ocular surface, primarily affecting children and young adolescents. It is characterized by intense pruritus, photophobia, and mucous discharge, with hallmark clinical signs including giant papillae on the tarsal conjunctiva and Horner-Trantas dots at the limbus [1]. In tropical and subtropical regions, such as the eastern coast of India, VKC often follows a perennial course with seasonal exacerbations, posing a significant risk for corneal complications and permanent visual impairment [2].

The pathophysiology of VKC is complex, involving both Type I (IgE-mediated) and Type IV (T-cell mediated) hypersensitivity reactions. Infiltrating Th2 cells, eosinophils, and mast cells release a cascade of proinflammatory cytokines and chemokines that sustain

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the inflammatory state [3]. Recent research has focused on identifying systemic modulators that influence this allergic milieu. Among these, Vitamin D (calcitriol) has emerged as a potent immunomodulatory hormone [4].

Beyond its classical role in calcium homeostasis, Vitamin D influences the innate and adaptive immune systems. It has been shown to inhibit the maturation of dendritic cells, suppress the proliferation of Th1 and Th17 cells, and shift the T-cell response toward a more regulatory (T-reg) phenotype [5]. Specifically, in the context of allergy, Vitamin D can modulate IgE production and eosinophil activity [6].

While associations between Vitamin D deficiency and systemic allergic conditions like asthma and atopic dermatitis are well-documented, its specific relationship with VKC remains an area of active investigation. In regions like Berhampur, where high solar radiation might suggest adequate Vitamin D synthesis, lifestyle factors and nutritional patterns often result in widespread subclinical deficiency [7]. This study aims to quantify serum 25(OH)D levels in children with VKC and analyze its correlation with clinical grading to determine if systemic supplementation could potentially serve as an adjuvant therapy in disease management.

MATERIALS AND METHODS

Study Design and Setting- This cross-sectional, observational study was conducted at the Department of Pediatrics and Ophthalmology, MKCG Medical College & Hospital, Berhampur, Odisha. The study was conducted over 12 months to account for seasonal variations in Vitamin D levels and VKC symptoms.

Participants- A total of N=26 pediatric patients (aged 5–15 years) with a confirmed clinical diagnosis of VKC were recruited. Inclusion criteria included children who had not received systemic corticosteroids or Vitamin D supplements in the three months prior to enrollment. Patients with existing metabolic bone disease, chronic renal failure, or other systemic autoimmune disorders were excluded. Informed consent was obtained from the legal guardians of all participants.

Clinical Evaluation and Grading- A comprehensive ophthalmic examination was performed, including slit-lamp biomicroscopy. The severity of VKC was graded according to the Bonini classification [8], which categorizes the disease into four stages:

- **Grade 1 (Mild):** Occasional symptoms, slight conjunctival hyperemia.
- **Grade 2 (Moderate):** More frequent symptoms, small papillae.
- **Grade 3 (Severe):** Constant symptoms, giant papillae (> 1 mm), or limbal involvement.
- **Grade 4 (Very Severe):** Corneal involvement (shield ulcer) or severe limbal inflammation.

A composite clinical score (0–12) was calculated based on symptom intensity (itching, tearing, photophobia) and signs (papillae, limbal redness, corneal staining).

Biochemical Analysis- Venous blood samples were collected from each participant. Serum 25-hydroxyvitamin D 25(OH)D was measured using a competitive chemiluminescence immunoassay (CLIA). For this study, Vitamin D status was defined as:

- **Deficiency:** < 20 ng/mL
- **Insufficiency:** 20–30 ng/mL
- **Sufficiency:** > 30 ng/mL

Statistical Analysis- Data were analyzed using SPSS Version 25.0. Continuous variables were expressed as Mean +/- SD. Differences in Vitamin D levels across severity grades were analyzed using a one-way ANOVA with post hoc Tukey tests. The correlation between serum 25(OH)D levels and the total clinical score was assessed using Pearson's correlation coefficient (r). A p-value of < 0.05 was considered statistically significant.

RESULTS

The study included 26 children with a mean age of 9.4 +/- 3.2 years. There was a notable male preponderance, with 19 males (73.1%) and 7 females (26.9%). The majority of the patients presented with the palpebral form of VKC (53.8%), followed by the mixed form (30.8%) and the limbal form (15.4%) (Table 1). The mean serum 25(OH)D level for the entire cohort was 19.1 +/- 6.8 ng/mL. According to the defined thresholds, 16 patients (61.5%) were deficient, 7 (26.9%) were insufficient, and only 3 (11.6%) were Vitamin D sufficient.

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Table 1: Demographic Data and Clinical Characteristics Stratified by VKC Severity

Variable	Grade 1-2 (Mild/Mod)	Grade 3-4 (Severe/Very Sev)	p-value
Number of Patients (n)	11	15	-
Mean Age (Years)	8.9 +/- 2.8	9.8 +/- 3.5	0.48
Gender (Male/Female)	8/3	11/4	0.92
Mean Vitamin D (ng/mL)	26.4 +/- 5.1	13.7 +/- 4.2	< 0.001
Duration of Disease (Months)	14.2 +/- 6.5	22.8 +/- 9.1	0.012
Presence of Atopy (%)	36.3%	66.7%	0.045

There was a statistically significant difference in mean serum Vitamin D levels across the different grades of VKC severity ($p < 0.001$). A progressive decline in serum 25(OH)D levels was observed with increasing clinical severity. Patients with Grade 1 disease demonstrated the highest mean Vitamin D levels (29.1 +/- 4.2 ng/mL), whereas those with Grade 4 disease exhibited the lowest levels (11.8 +/- 3.9 ng/mL) along with higher clinical scores, indicating more severe ocular involvement. These findings suggest a strong inverse relationship between serum Vitamin D status and the severity of Vernal Keratoconjunctivitis (Table 2).

Table 2: Stratification of Serum 25(OH)D Levels across Bonini Clinical Grades

Bonini Grade	Mean 25(OH)D (ng/mL)	Range (Min - Max)	Clinical Score (Mean)
Grade 1 (n=4)	29.1 +/- 4.2	24 - 34	2.5 +/- 0.8
Grade 2 (n=7)	24.8 +/- 4.9	18 - 31	4.8 +/- 1.2
Grade 3 (n=10)	15.2 +/- 3.8	9 - 21	8.2 +/- 1.5
Grade 4 (n=5)	11.8 +/- 3.9	7 - 16	10.7 +/- 1.1

Analysis of the data distribution (Fig. 1) reveals a distinct downward shift in the median serum 25(OH)D levels as VKC clinical severity increases. In Grade 1 patients, the median level was 29.5 ng/mL, whereas it dropped precipitously to 11.2 ng/mL in Grade 4 patients. The interquartile range (IQR) for Grade 4 was notably narrower (9.1-13.8 ng/mL), indicating a high degree of consistency in severe deficiency among those with the most advanced disease presentation, such as those with shield ulcers or limbal stem cell deficiency signs.

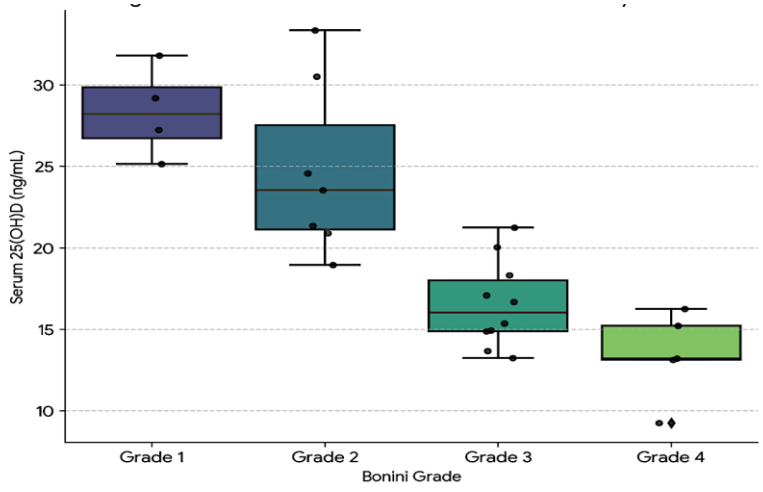

Fig. 1: Distribution of Vitamin D Levels

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The relationship between the composite clinical score and serum Vitamin D levels (Fig. 2) followed a strong negative linear regression. The calculation yielded a Pearson correlation coefficient of r = -0.68, with a highly significant p-value ($p < 0.001$). For every 10 ng/mL decrease in serum 25(OH)D, the clinical severity score increased by approximately 2.4 points. This linear relationship suggests that even moderate improvements in Vitamin D status may correlate with reductions in ocular inflammatory markers and patient symptoms.

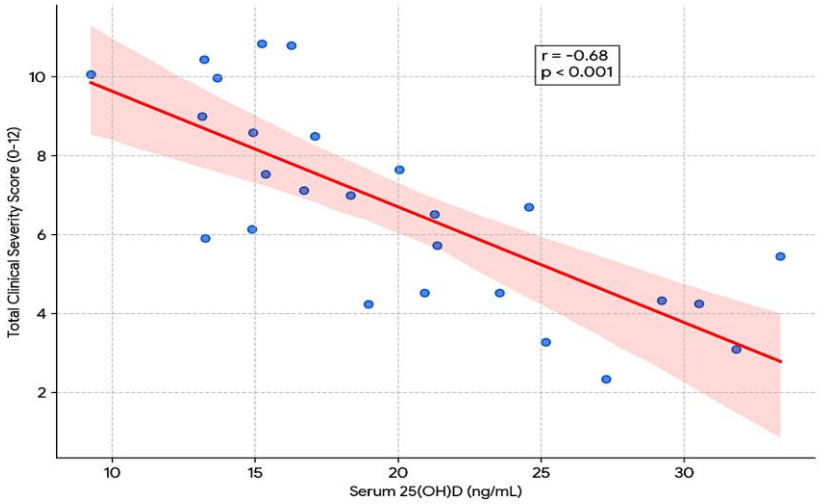

Fig. 2: Relationship between the composite clinical score and serum Vitamin D levels

DISCUSSION

This study demonstrates a significant inverse correlation between serum Vitamin D levels and the clinical severity of Vernal Keratoconjunctivitis in a pediatric population in Berhampur. Given the high prevalence of Vitamin D deficiency (61.5%) in our cohort, the findings suggest that systemic Vitamin D status may influence the phenotypic expression and severity of ocular allergic inflammation.

The ocular surface is an active site of immune regulation. Recent studies have identified Vitamin D receptors (VDR) on corneal and conjunctival epithelial cells, as well as on local immune cells [9]. Vitamin D acts as a "brake" on the immune response by modulating the activity of Antigen Presenting Cells (APCs) and reducing the secretion of Th2-associated cytokines like IL-4 and IL-5, which are paramount in VKC pathogenesis [10]. Our results show that patients with the lowest Vitamin D levels had the highest clinical scores, often presenting with giant papillae and corneal shield ulcers. This suggests that Vitamin D deficiency might lead to a loss of immune tolerance at the ocular surface, allowing for exaggerated allergic responses.

Our findings align with several recent studies conducted in similar geographical regions. For instance, a study by Saboo *et al.* in North India also reported a significant correlation between low Vitamin D and severe VKC [11]. Similarly, research in the Mediterranean region has shown that children with ocular allergies tend to have lower serum 25(OH)D compared to healthy controls [12].

The high rate of deficiency in our study (61.5%) despite Odisha's sunny climate may be attributed to increased indoor activity, air pollution, and dietary habits, a phenomenon often referred to as the "Indian Vitamin D Paradox" [13].

The strong correlation (r = -0.68) observed in our study suggests that Vitamin D status may serve as a biomarker of disease severity. More importantly, it raises the question of therapeutic intervention. While standard treatment for VKC involves topical mast cell stabilizers and antihistamines, refractory cases often require corticosteroids, which carry risks of glaucoma and cataracts [14]. If Vitamin D deficiency contributes to disease recalcitrance, oral supplementation might offer a safe, low-cost adjuvant therapy to help control inflammation and reduce "steroid dependency" in these children [15].

The pathophysiology of VKC involves a massive infiltration of eosinophils and mast cells. Vitamin D has been shown to induce apoptosis in eosinophils and to stabilize mast cell membranes, thereby inhibiting histamine release [16]. Furthermore, the role of Vitamin D in enhancing the function of T-regulatory cells (CD4+ CD25+ FoxP3+) is crucial in VKC, where a failure of these

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regulatory mechanisms is often observed [17]. By replenishing Vitamin D levels, it may be possible to restore this homeostatic balance.

The primary limitation of this study is the small sample size (N=26), which may limit the generalizability of the results. Additionally, as a cross-sectional study, we cannot definitively establish a causal relationship between Vitamin D deficiency and VKC onset. Factors such as outdoor exposure time and dietary intake were not strictly quantified using standardized logs, which could have influenced serum 25(OH)D levels.

CONCLUSIONS

In conclusion, this study identifies a clear association between lower serum 25(OH)D levels and increased clinical severity of VKC in children. Given the immunomodulatory properties of Vitamin D, its deficiency appears to be a significant co-factor in the exacerbation of ocular allergic inflammation. Clinicians should consider screening for Vitamin D deficiency in pediatric patients with severe or refractory VKC. Further randomized controlled trials are warranted to evaluate whether Vitamin D supplementation can effectively reduce the clinical burden of this debilitating ocular condition.

CONTRIBUTION OF AUTHORS

Research concept- Deepika Priyadarshini, Monalisa Khuntia

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Data analysis and interpretation- Sunanda Dalai, Deepika Priyadarshini

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Critical review- Sunanda Dalai, Deepika Priyadarshini

Article editing- Sunanda Dalai, Deepika Priyadarshini, Monalisa Khuntia

Final approval- Sunanda Dalai, Deepika Priyadarshini, Monalisa Khuntia

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