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Association Between Clinical Severity of Dry Eye Disease and Serum 25-Hydroxyvitamin D Levels,

Dr. Guru Prasad N S[1], Dr. Priyanka Sankaran[2], Dr. Anjali[3].

[1]Senior Resident, Department of Ophthalmology, KVG Medical College & Hospital, Sullia, Karnataka, India

[2]Senior Resident, Department of Ophthalmology, Andaman and Nicobar Islands Institute of Medical Sciences, Sri Vijaya Puram

[3]Assistant Professor, Department of Ophthalmology, Andaman and Nicobar Islands Institute of Medical Sciences, Sri Vijaya Puram

Correspondence:
Anjali.
Assistant Professor, Department of Ophthalmology, Andaman and Nicobar Islands Institute of Medical Sciences, Sri Vijaya Puram.

Email:
anjalikoteshwar@gmail.com

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Abstract

Background: Dry eye disease is a multifactorial ocular surface disorder in which inflammation plays an important role. Vitamin D has immunomodulatory and anti-inflammatory properties, and its deficiency has increasingly been associated with ocular surface abnormalities. Objective: To evaluate the association between clinical severity of dry eye disease and serum 25-hydroxyvitamin D levels. ***Materials and Methods***: This cross-sectional analytical study included 100 patients with dry eye disease. Clinical severity was assessed using the Ocular Surface Disease Index (OSDI), tear-film breakup time (TBUT), Schirmer I test, and ocular surface staining. Serum 25(OH)D levels were measured and categorized as deficient (<20 ng/mL), insufficient (20–29 ng/mL), or sufficient (≥30 ng/mL). Patients were classified as having mild, moderate, or severe DED. Correlations between serum vitamin D and dry-eye parameters were analyzed, with $p<0.05$ considered statistically significant. ***Results***: Of the 100 patients, 32% had mild, 40% moderate, and 28% severe DED. Mean serum 25(OH)D levels decreased significantly with increasing severity, from 30.6 ± 8.0 ng/mL in mild DED to 22.1 ± 6.7 ng/mL in moderate and 14.9 ± 5.2 ng/mL in severe DED ($p<0.001$). Vitamin D deficiency was present in 75.0% of severe cases compared with 15.6% of mild cases. Serum 25(OH)D correlated negatively with OSDI ($r=-0.58$) and positively with TBUT ($r=0.52$) and Schirmer I test ($r=0.49$), all $p<0.001$. ***Conclusion***: Lower serum 25-hydroxyvitamin D levels were significantly associated with increasing clinical severity of dry eye disease. Vitamin D deficiency may represent an important systemic factor associated with greater symptom burden and impaired tear-film function.

Keywords: Dry eye disease; vitamin D deficiency; 25-hydroxyvitamin D; OSDI; tear-film breakup time; Schirmer test.

INTRODUCTION

Dry eye disease (DED) is a multifactorial disorder of the ocular surface characterized by disruption of tear-film homeostasis and accompanied by ocular discomfort, visual disturbance, and varying degrees of ocular surface inflammation. Recent evidence has highlighted the potential role of systemic nutritional and inflammatory factors, particularly vitamin D, in the development and severity of DED. Singh et al. demonstrated a significant relationship between serum 25-hydroxyvitamin D [25(OH)D] levels and tear-film stability, suggesting that vitamin D status may influence both symptoms and objective parameters of dry eye disease.[1]

Vitamin D has important immunomodulatory and anti-inflammatory functions in addition to its established role in calcium and bone metabolism. Vitamin D receptors are expressed in several ocular tissues, and deficiency may contribute to ocular surface inflammation and impaired tear-film function. A recent retrospective cohort study further demonstrated an association between vitamin D deficiency and dry eye disease.[2] Systemic vitamin D supplementation has also been reported to improve clinical and immunological parameters among vitamin D-deficient patients with DED, supporting a possible biological relationship between vitamin D status and ocular surface health.[3]

A systematic review and meta-analysis evaluating vitamin D supplementation in DED reported improvement in several dry-eye-related outcomes, although differences among studies indicate that the relationship remains complex.[4] Clinical trials of topical vitamin D have similarly demonstrated potential benefits in patients with dry eye associated with meibomian gland dysfunction.[5] Oral vitamin D supplementation has also been investigated in vitamin D-deficient patients, with improvement reported in dry eye parameters following correction of deficiency.[6] Current evidence therefore suggests that vitamin D may influence tear production, tear-film stability, ocular surface inflammation, and symptom severity.[7]

However, the relationship between serum 25(OH)D concentration and the clinical severity of dry eye disease remains insufficiently characterized, particularly in the local population. Hence, the present study was undertaken to determine serum 25-hydroxyvitamin D levels in patients with DED and assess their association with clinical severity.

MATERIALS AND METHODS

Study Design and Setting

This hospital-based cross-sectional analytical study was conducted in the Department of Ophthalmology of a tertiary care teaching hospital. Patients presenting to the ophthalmology outpatient department with symptoms suggestive of dry eye disease were evaluated for eligibility.

Study Population

The study included adult patients diagnosed with dry eye disease on the basis of clinical symptoms and ocular surface assessment during the study period.

Sample Size

A total of 100 patients with dry eye disease were included. The sample size was estimated considering an expected correlation coefficient of approximately 0.30 between serum vitamin D levels and dry eye parameters, with a 95% confidence level and 80% statistical power. After allowing for incomplete observations, the final sample size was rounded to 100 participants.

Inclusion Criteria

- Patients aged 18 years or above.
- Patients with symptoms and clinical findings consistent with dry eye disease.
- Patients willing to undergo ocular examination and serum 25(OH)D estimation.

Exclusion Criteria

Patients with active ocular infection or inflammation unrelated to DED, recent ocular surgery or trauma, significant corneal disorders, contact lens use, systemic autoimmune disorders known to markedly affect the ocular surface, or current vitamin D supplementation were excluded. Patients receiving medications known to substantially interfere with tear production were also excluded.

Clinical Assessment

A detailed history was obtained regarding age, sex, occupation, duration of symptoms, systemic illnesses, medications, screen exposure, and other potential risk factors for dry eye disease.

Dry eye symptoms were evaluated using the Ocular Surface Disease Index (OSDI) questionnaire. All participants subsequently underwent a comprehensive ophthalmological examination, including visual acuity assessment, slit-lamp examination, and ocular surface evaluation.

The following dry eye parameters were assessed:

- Tear-film breakup time (TBUT): The interval between the last blink and appearance of the first dry spot after fluorescein instillation was recorded in seconds.
- Schirmer I test: Tear secretion was measured using standardized Schirmer strips over 5 minutes without topical anesthesia.
- Corneal/conjunctival staining: Ocular surface staining following fluorescein instillation was assessed and graded using a standardized clinical grading system.
- OSDI score: Symptom severity was quantified using the validated OSDI questionnaire.

Based on the combined clinical assessment, patients were categorized into mild, moderate, and severe dry eye disease groups.

Serum 25-Hydroxyvitamin D Estimation

A venous blood sample was collected from each participant under aseptic precautions. Serum was separated and 25-hydroxyvitamin D [25(OH)D] concentration was measured using the laboratory assay available at the study centre.
Vitamin D status was categorized as:

- Deficient: <20 ng/mL
- Insufficient: 20–29 ng/mL
- Sufficient: ≥30 ng/mL

Serum 25(OH)D concentrations were subsequently compared among the different clinical severity categories of dry eye disease.

Outcome Measures

The primary outcome was the association between serum 25(OH)D levels and clinical severity of dry eye disease. Secondary outcomes included the relationship of serum 25(OH)D levels with OSDI score, TBUT, Schirmer I test values, and ocular surface staining.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using SPSS software. Continuous variables were expressed as mean ± standard deviation or median and interquartile range, as appropriate, while categorical variables were presented as frequencies and percentages. Mean serum 25(OH)D levels among mild, moderate, and severe DED groups were compared using one-way ANOVA or the Kruskal-Wallis test, as appropriate. Categorical variables were compared using the chi-square or Fisher's exact test.

The association between serum 25(OH)D levels and OSDI, TBUT, Schirmer I test, and other quantitative dry eye parameters was assessed using Pearson's or Spearman's correlation coefficient according to data distribution. Multivariable regression analysis could be performed to identify whether serum vitamin D level was independently associated with DED severity after adjustment for relevant confounding variables. A p-value <0.05 was considered statistically significant.

RESULTS

A total of **100 patients with dry eye disease (DED)** were included in the study. The mean age of the participants was **45.8 ± 12.6 years**, and 58 (58.0%) were females. According to clinical severity, 32% had mild DED, 40% had moderate DED, and 28% had severe DED. Serum 25-hydroxyvitamin D [25(OH)D] levels progressively decreased with increasing severity of dry eye disease.

Table 1. Demographic and Clinical Characteristics of the Study Participants

Characteristic	Value (n=100)
Age (years), mean ± SD	45.8 ± 12.6
Age group	
18–30 years	14 (14.0%)
31–40 years	22 (22.0%)
41–50 years	27 (27.0%)
51–60 years	23 (23.0%)
>60 years	14 (14.0%)
Sex	
Male	42 (42.0%)
Female	58 (58.0%)
Duration of dry-eye symptoms (months), mean ± SD	13.7 ± 8.4
DED severity	
Mild	32 (32.0%)
Moderate	40 (40.0%)
Severe	28 (28.0%)
OSDI score, mean ± SD	36.9 ± 15.2
TBUT (seconds), mean ± SD	7.4 ± 2.8
Schirmer I test (mm/5 min), mean ± SD	10.6 ± 4.8
Serum 25(OH)D (ng/mL), mean ± SD	22.8 ± 9.3

The largest proportion of patients belonged to the 41–50-year age group (27.0%), and females constituted 58.0% of the study population. Moderate DED was the most common severity category, observed in 40% of patients.

Table 2. Clinical Parameters and Serum 25(OH)D Levels According to Dry Eye Severity

Parameter	Mild (n=32)	Moderate (n=40)	Severe (n=28)	p-value
OSDI score	19.8 ± 5.4	36.7 ± 6.8	56.8 ± 8.2	<0.001*
TBUT (seconds)	10.3 ± 1.8	7.1 ± 1.7	4.6 ± 1.5	<0.001*
Schirmer I (mm/5 min)	15.1 ± 3.3	10.2 ± 3.1	6.0 ± 2.5	<0.001*
Serum 25(OH)D (ng/mL)	30.6 ± 8.0	22.1 ± 6.7	14.9 ± 5.2	<0.001*

*Statistically significant at p<0.05.

There was a progressive deterioration in objective and subjective dry-eye parameters with increasing disease severity. Mean serum 25(OH)D decreased from **30.6 ± 8.0 ng/mL in mild DED to 14.9 ± 5.2 ng/mL in severe DED (p<0.001)**. Similarly, TBUT and Schirmer I values decreased significantly, whereas OSDI scores increased with increasing severity.

Table 3. Association Between Vitamin D Status and Severity of Dry Eye Disease

Vitamin D status	Mild (n=32)	Moderate (n=40)	Severe (n=28)	Total	p-value
Deficient (<20 ng/mL)	5 (15.6%)	17 (42.5%)	21 (75.0%)	43 (43.0%)	<0.001*
Insufficient (20–29 ng/mL)	11 (34.4%)	17 (42.5%)	6 (21.4%)	34 (34.0%)	
Sufficient (≥30 ng/mL)	16 (50.0%)	6 (15.0%)	1 (3.6%)	23 (23.0%)	
Total	**32 (100%)**	**40 (100%)**	**28 (100%)**	**100 (100%)**	

*Chi-square test; statistically significant at p<0.05.

Overall, **43% of patients were vitamin D deficient**, while 34% had insufficient and only 23% had sufficient serum vitamin D levels. Vitamin D deficiency was observed in **75.0% of patients with severe DED**, compared with 42.5% of those with moderate and 15.6% of those with mild disease. The association between vitamin D status and DED severity was statistically significant (p<0.001).

Table 4. Correlation of Serum 25(OH)D Levels with Dry Eye Parameters

Dry-eye parameter	Correlation coefficient (r)	p-value
OSDI score	**−0.58**	<0.001*
TBUT (seconds)	**+0.52**	<0.001*
Schirmer I test (mm/5 min)	**+0.49**	<0.001*
Ocular surface staining score	**−0.43**	<0.001*

*Pearson/Spearman correlation as appropriate; statistically significant at p<0.05.

Serum 25(OH)D showed a **moderate negative correlation with OSDI score (r=−0.58, p<0.001)**, indicating greater symptom severity at lower vitamin D concentrations. Significant positive correlations were observed with TBUT (r=0.52) and Schirmer I values (r=0.49), while ocular surface staining showed a significant negative correlation (r=−0.43).

DISCUSSION

The present study demonstrated a significant association between serum 25-hydroxyvitamin D [25(OH)D] levels and the clinical severity of dry eye disease (DED). Serum vitamin D concentrations decreased progressively from 30.6 ± 8.0 ng/mL in mild DED to 22.1 ± 6.7 ng/mL in moderate DED and 14.9 ± 5.2 ng/mL in severe DED (p<0.001). Furthermore, 75% of patients with severe DED were vitamin D deficient compared with only 15.6% of patients with mild disease.

These observations are consistent with Jain et al., who demonstrated an association between vitamin D deficiency and dry eye syndrome and suggested that vitamin D status may have an important influence on ocular surface health.[8] The potential relationship is biologically plausible because vitamin D receptors are present in ocular tissues, while the immunomodulatory and anti-inflammatory properties of vitamin D may contribute to the maintenance of tear-film and ocular surface homeostasis. A broader systematic review by Chan et al. also highlighted the potential involvement of vitamin D in several ocular disorders and emphasized its regulatory effects on inflammatory and immune pathways.[9]

In the present study, serum 25(OH)D showed a significant negative correlation with OSDI score (r=−0.58, p<0.001), indicating that patients with lower vitamin D levels experienced greater dry-eye symptom severity. Conversely, vitamin D levels showed significant positive correlations with TBUT (r=0.52) and Schirmer I test values (r=0.49). These results agree with the meta-analysis by Liu et al., which demonstrated an association between vitamin D deficiency and dry eye syndrome.[10] Similarly, Kuo et al. reported an association between vitamin D deficiency and the severity of dry-eye symptoms, further supporting a relationship between systemic vitamin D status and DED.[11]

Genetic mechanisms may also contribute to this association. Meng et al. investigated vitamin D receptor polymorphisms and reported that variations in the vitamin D pathway may influence susceptibility to DED.[12] Furthermore, Hwang et al. demonstrated that vitamin D supplementation enhanced the efficacy of topical artificial tears, suggesting that correction of vitamin D deficiency may potentially improve the response to conventional dry-eye therapy.[13]

The significant relationship between serum vitamin D and ocular surface parameters in the present study is also supported by Khamar et al., who identified associations between vitamin D levels, ocular surface inflammatory factors, and corneal dendritic cell characteristics in evaporative dry eye.[14] Earlier, Meng et al. reported that lower serum vitamin D concentrations were associated with an increased risk of dry eye syndrome, providing additional support for the present findings.[15]

The study has certain limitations. Its cross-sectional design does not establish a causal relationship between vitamin D deficiency and DED. The study was conducted at a single centre with a relatively modest sample size, and environmental, dietary, sunlight-exposure, and seasonal factors that can influence serum vitamin D concentrations were not fully assessed. Nevertheless, the consistent association of serum 25(OH)D with both subjective and objective DED parameters suggests that vitamin D status deserves consideration in patients with clinically significant dry eye disease.

CONCLUSION

Lower serum 25-hydroxyvitamin D levels were significantly associated with greater clinical severity of dry eye disease. Patients with severe DED had substantially lower serum vitamin D concentrations and a higher prevalence of vitamin D deficiency. Serum 25(OH)D was negatively correlated with OSDI and ocular surface staining scores and positively correlated with TBUT and Schirmer I test values. These findings suggest that vitamin D deficiency may be an important systemic factor associated with DED severity. Larger prospective studies are required to determine whether correction of vitamin D deficiency can improve clinical outcomes in dry eye disease.

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