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ORIGINAL ARTICLE

Prevalence of Vitamin D Insufficiency in Patients with Dry Eye Disease

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ABSTRACT

Background: Dry Eye Disease (DED) is a complex ocular condition which, due to its various factors, is capable of causing visual impairment and diminish an individual's quality of life. Among the many potential factors included, DED is vitamin D deficiency. The following investigation focused on the extent of vit D_3 deficiency, its prevalence, severity in association with DED.

Methods: This prospective cross-sectional hospital-based study was conducted at Tertiary care hospital, Murree, from June 2022 to June 2023. I enrolled 375 participants through non-probability consecutive sampling (200 with DED, 175 controls). All participants filled the Ocular Surface Disease Index (OSDI), and underwent Schirmer's I Test and Tear Break-Up Time (TBUT). For Serum 25-hydroxyvitamin D [25(OH)D] levels, measurements were done using ELISA. For analysis, I used SPSS v25.0. You used independent t-tests for comparing continuous variables, while chi-square tests with Cramer's V were used for analyzing categorical data. I considered a $p < 0.05$ as statistically significant.

Results: Mean serum vitamin D_3 concentrations were considerably lower in DED patients compared to the control group (21.5 ± 7.6 ng/ml vs. 34.4 ± 7.8 ng/ml; $t(373) = -16.20$, $p < 0.001$). DED patients also had a increased prevalence of deficiency of vitamin D (69.0%) compared to the controls (36.6%) which was statistically significant. Higher OSDI severity was linked to a greater prevalence of vitamin D deficiency, $\chi^2(6) = 113.7$, $p < 0.001$, Cramer's V = 0.389.

Conclusion: Patients with dry eye should examine their vitamin D levels since low vitamin D_3 may be linked to the development and severity of eye issues.

Keywords: Dry eye disease, Vitamin D_3 deficiency, Schirmer's test, TBUT

INTRODUCTION

Dry eye disease (DED) results from a deficiency in either the quality or quantity of tears, leading to discomfort, fluctuating vision, and/or exposure of the corneal surface[1]. Globally, DED is becoming more of a public health concern; its prevalence is estimated to differ by 5 to 50% depending on the population studied and the criteria used for diagnosis[2]. Specifically, the prevalence reported in hospital studies in South Asian countries is in the range of 25 to 30%[3]. DED has the ability to greatly hinder a person's ability to perform everyday activities, and in combination with the aforementioned risk factors of older age, female sex, comorbid conditions of the body, and environmental factors[4,5], the ramifications on quality of life become even more severe[4,5]

DED can significantly limit a person's capacity to execute daily tasks, and when coupled with the additional risk factors of advanced age, female gender, bodily comorbidity, and environmental factors[6]. the consequences on the DED individual's quality of life grow disproportionally worse[7,8]

Numerous clinically oriented researches observed that individuals suffering from DED had considerably lower serum of it. A study reported that 64% of DED patients were vitamin D deficient in comparison to only 38% of the control group[1]. Likewise, McCann et al. (2022) illustrated an important negative relationship between vitamin D levels and the OSDI symptom scores[9]. A systematic review conducted by Chan et al. (2022) also, hypovitaminosis D and its associated risk and severity of DED has proven true across varied populations[10].

Apart from observational studies, the interventional data also attests to the importance of vitamin D. a study illustrate that supplementation of vitamin D in deficient patients leads to improvements in Schirmer's test, TBUT, and OSDI scores[11]. Notwithstanding this mounting evidence, methodological inconsistencies, variations in sample size, and differences in diagnostic criteria have led to inconsistencies across different populations. Studies have shown that patients with DED have lower serum vitamin D levels but this does not seem to correlate strongly with all the tear constituent parameters[12].

There is increasing attention on the growing prevalence of DED and the ambiguous contribution of vitamin D deficiency in its pathogenesis. Therefore, the objective of the study was to determine the prevalence of vitamin D insufficiency in patients diagnosed with DED and to assess its correlation with the severity of DED. As the first study to approach this imbalance in the Pakistani DED population, the study focuses on exposing risk factors which may be modified.

METHODOLOGY

A prospective cross-sectional hospital-based study was conducted at the Tertiary care hospital, Murree, from June 2022 to June 2023. Ethical approval was obtained from the institution's review committee, and study participants provided informed written consent.

WHO sample size calculator to define the sample size for the study based on the previously studied prevalence of vitamin D deficiency in patients with DED which is 60%. At a 95% confidence level, 5% margin of error, and 0.60 population proportion, the required sample size was 369. To account for anticipated data attrition, 375 participants were enrolled. I employed a non-probability consecutive sampling technique, including all consenting eligible patients who presented during the study period until the sample size for the study was reached.

All participants, regardless of sex, fell within the 16- to 55-year age range. Exclusion criteria included patients with active infectious conditions of the eye, chemically burned dry eyes with associated eye disease, contagious eye diseases, vitamin A deficiency, a history of eye surgery, eye surface reconstruction, autoimmune disease, pregnancy, lactation, or being postmenopausal. Also, to prevent confounding effects, contact lens wearers were excluded from the study.

All participants filled out the OSDI, a validated 12-item questionnaire designed to measure the symptoms frequency, visual disturbances, and situational triggers. We obtained a full medical and ocular history, then conducted a thorough ophthalmological examination. For the participants, we conducted an unanaesthetized Schirmer's I Test and Tear Break-Up Time teste with fluorescein dye. A Schirmer's I reading of less than 10 mm in 5 min and/or TBUT of

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less than 10 sec was considered abnormal.

To determine serum 25-hydroxyvitamin D [25(OH)D] levels, venous blood was collected and processed at the diagnostic laboratory of CMH Murree for the newly developed enzyme-linked immunosorbent assay (ELISA) test. The results obtained were categorized into deficient (<20 ng/ml), insufficient (20–29.9 ng/ml), and sufficient (≥30 ng/ml) for the purpose of analysis. Participants with a DED group assignment were OSDI clinically symptomatic (OSDI score ≥13) and who possessed test results satisfying the Schirmer's I or TBUT abnormality criterion, while those lacking DED evidence were placed in the control category.

Statistical Package for the Social Sciences (SPSS) software version 25.0 was utilized for data analysis. Age, OSDI score, TBUT, Schirmer's test, and serum vitamin D concentration as continuous variables were reported with mean and standard deviation. For categorical variables (sex, comorbidities, vitamin D categories, OSDI severity) frequencies and percentages were used. Before carrying out parametric tests, the normality of continuous data was evaluated. Homogeneity of variance assumption was used with Levene's test. Independent samples t-tests were used to determine differences between the means of the examined groups since normality and variance tests reported no significant differences. Group comparisons of categorical variables were conducted using the chi-square (χ^2) test, with Cramer's V employed for effect size estimation. A 0.05 level was used for the determination of statistical significance.

RESULTS

A total of 375 participants were enrolled in the study, with 200 in the DED group and 175 in the control group. Between-group mean ages did not differ significantly (37.6 ± 9.3 vs. 38.9 ± 9.6 years; t(373) = -1.35, p = 0.178). The proportion of the sexes was also comparable; in the DED group, 54.5% were female, and in the control group, 58.3% were female ($\chi^2(1) = 0.54$, p = 0.461).

In the DED cohort, systemic comorbidities were more common. For diabetes mellitus, 14.5% of the cases were DED as opposed to 9.7% of the controls ($\chi^2(1) = 2.02$, p = 0.155) and for hypertension, 11.5% of the DED cases compared to 5.1% of the controls ($\chi^2(1) = 4.73$, p = 0.030.

Table 1: Demographic and Clinical Characteristics of Participants (n = 375)

Variable	DED Group (n=200)	Control Group (n=175)	Test (df)	p-value	Cramer's V
Age (years, mean ± SD)	37.6 ± 9.3	38.9 ± 9.6	t(373) = -1.35	0.178	–
Male, n (%)	91 (45.5)	73 (41.7)	$\chi^2(1) = 0.54$	0.461	–
Female, n (%)	109 (54.5)	102 (58.3)	–	–	–
Diabetes Mellitus (DM), n (%)	29 (14.5)	17 (9.7)	$\chi^2(1) = 2.02$	0.155	–
Hypertension (HTN), n (%)	23 (11.5)	9 (5.1)	$\chi^2(1) = 4.73$	0.030	0.112
'Serum Vitamin D_3 (ng/ml)'	21.5 ± 7.6	34.4 ± 7.8	t(373) = -16.20	<0.001	–
Vitamin D Deficient (<30 ng/ml)	138 (69.0)	64 (36.6)	$\chi^2(1) = 41.8$	<0.001	0.331

Abbreviations: DED = Dry Eye Disease; DM = Diabetes Mellitus; HTN = Hypertension.

Table 2: Vitamin D_3 Categories in Participants With and Without DED (n = 375)

Vitamin D_3 Category	DED Group (n=200)	Control Group (n=175)	Total n (%)	χ^2 (df=1)	p-value	Cramer's V
Deficient (<30 ng/ml)	170 (85.0)	51 (29.1)	221 (58.9)	120.3	<0.001	0.566
Normal (≥30 ng/ml)	30 (15.0)	124 (70.9)	154 (41.1)	–	–	–

Table 3: Comparison of Dry Eye Parameters Between Groups (n = 375)

Parameter	DED Group (n=200)	Control Group (n=175)	t(df=373)	p-value
OSDI Score	34.7 ± 9.4	10.4 ± 3.6	32.26	<0.001
TBUT (s)	8.15 ± 1.7	15.7 ± 2.5	-34.19	<0.001
Schirmer's Test (mm)	9.3 ± 2.3	18.6 ± 1.9	-42.74	<0.001
'Serum Vitamin D_3 (ng/ml)'	21.5 ± 7.6	34.4 ± 7.8	-16.20	<0.001

Independent samples t-test applied. df = 373

Table 4: Association Between OSDI Severity and Vitamin D_3 Status (n = 375)

OSDI Severity	Deficient n (%)	Insufficient n (%)	Sufficient n (%)	Total	χ^2 (df=6)	p-value	Cramer's V
None	8 (5.9)	33 (24.4)	94 (69.6)	135			
Mild	13 (21.3)	15 (24.6)	33 (54.1)	61			
Moderate	33 (50.0)	27 (40.9)	6 (9.1)	66	113.7	<0.001	0.389
Severe	52 (46.0)	40 (35.4)	21 (18.6)	113			
Total	106 (28.3)	115 (30.7)	154 (41.1)	375			

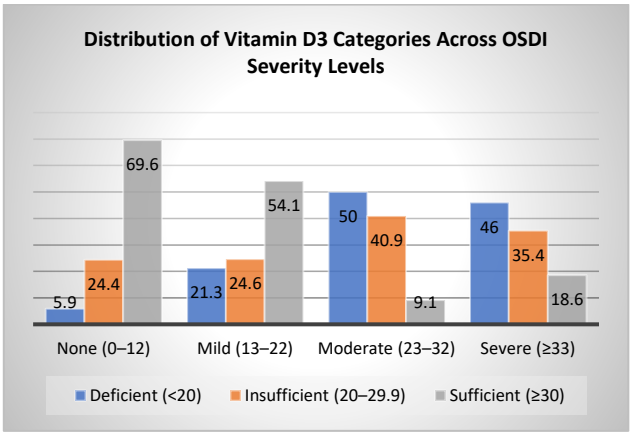

Figure 1: Distribution of serum vitamin D_3 status (<20 ng/ml deficient, 20–29.9 ng/ml insufficient, ≥30 ng/ml sufficient) across OSDI-defined dry eye severity groups.

Serum vitamin D_3 concentrations were markedly reduced in the DED group compared with controls (21.5 ± 7.6 ng/ml vs. 34.4 ± 7.8 ng/ml; t(373) = -16.20, p < 0.001). Vitamin D_3 deficiency (<30 ng/ml) was significantly more common in the DED group (69.0%) than among controls.

Dry eye parameters also differed significantly between groups. The DED group reported higher OSDI symptom scores (34.7 ± 9.4 vs. 10.4 ± 3.6; t(373) = 32.26, p < 0.001), shorter tear break-up time (8.2 ± 1.7 vs. 15.7 ± 2.5 seconds; t(373) = -34.19, p < 0.001), and reduced Schirmer's test values (9.3 ± 2.3 vs. 18.6 ± 1.9 mm; t(373) = -42.74, p < 0.001).

There was a noteworthy inverse relationship when examining various OSDI-defined severity categories in relation to vitamin D_3 status. In participants who reported no dry eye symptoms, 69.6% had sufficient levels of vitamin D_3 and only 5.9% had a deficiency. On the other end of the spectrum, in the most severe DED classification, 46.0% of participants had a deficiency of vitamin D_3 and only 18.6% had sufficient levels. This was significant in a statistical sense ($\chi^2(6) = 113.7$, p < 0.001, Cramer's V = 0.389).

DISCUSSION

In the present study, involving 375 participants (200 with DED and 175 controls), vitamin D_3 levels were significantly lower among patients those with DED as opposed to participants without the condition (21.5 ± 7.6 ng/ml vs. 34.4 ± 7.8 ng/ml, $p < 0.001$). Vitamin D_3 deficiency was observed in a substantially larger proportion of individuals with DED (69.0%) compared to those without the condition (36.6%), and this difference was statistically significant ($p < 0.001$). Tear film stability and production were reduced, with mean TBUT of 8.1 ± 1.7 seconds and Schirmer's test of 9.3 ± 2.3 mm in cases, compared to 15.7 ± 2.5 seconds and 18.6 ± 1.9 mm in controls. Symptom severity was likewise greater, reflected in OSDI scores (34.7 ± 9.4 vs. 10.4 ± 3.6, $p < 0.001$). Comorbidities such as diabetes and hypertension were more frequent in those suffering from DED (26.0%) than in those who did not (14.9%, $p = 0.008$). DED's severity and presence are greatly attributable to vitamin D deficiency.

Our observations were in concordance with those by who showed that oral vitamin D supplementation substantially improved Schirmer's test, TBUT, and OSDI scores in deficient DED patients, emphasizing the positive impact that correcting deficiency vitamin D has on DED patients[13,14]. Similarly, another study in a placebo-controlled trial reported that topical vitamin D drops improved tear stability and symptom relief in meibomian gland dysfunction associated DED, directly supporting the positive influence vitamin D has on ocular surface stability. These results affirm the findings that patients with lower vitamin D levels experienced greater symptom severity and had dysfunctional tear production[15].

Observational studies have returned similar findings. More than 60% of DED patients had vitamin D deficiency and significantly lower serum levels than controls[16], as reported by Khadilkar e in his Indian hospital-based study. This reflects our own prevalence data (69% deficiency in DED). Studies demonstrated a correlation between vitamin D deficiency and higher OSDI scores as well as a reduction in TBUT, further supporting our finding[17].

Conversely, some studies documented lower serum vitamin D levels for DED patients and did not find strong correlation for TBUT values, indicating not all parameters for assessing tear function are affected to the same extent[18]. This discrepancy could be due to small sample size relative to the scope of our study and methodological differences. In the same vein, a study evaluating a nutritional supplement blend containing vitamin D3, lutein and curcumin, reported improved OSDI and Schirmer scores but the improvement could not be attributed solely to vitamin D[19].

Our results align with findings from larger reviews. For example, in a review of nutritional supplements for DED, Dikci, et al. (2020) highlighted that vitamin D supplementation especially improved signs and symptoms in patients that were deficient[20]. In a similar manner, some studies summarized mechanisms through which vitamin D affects the immune system, diminishes pro-inflammatory cytokines, and reinforces barriers of the ocular surface, all of which can help explain the biological rationale for the association we observed[21,22]

In general, our findings align with the latest interventional studies and the body of observational research which indicate vitamin D deficiency increases both the risk and the severity of DED. Some contradictions, such as those reported by Daldal et al. (2021), suggest the degree of impact of vitamin D deficiency on DED may depend on various factors, including the population in question, vitamin D levels at baseline, and the diagnostic criteria used (23). The absence of contradictions in this research field only adds strength to the assertion of vitamin D deficiency as a modifiable risk on DED.

Participants diagnosed with dry eye disease (DED) not only exhibited a cumulative lower status of vitamin D_3 with higher frequency of 'deficiency' status than those without DED, but also had worse clinical and symptomatic manifestations as compared to controls with no DED. While some parameter-specific association studies report discrepancies, most of the reviewed and trial studies align with our findings.

Since the research involved only one tertiary care facility, the results may not be generalizable to broader populations. "Due to the cross-sectional design, the study is unable to demonstrate causality and the relationship of vit D_3 insufficiency to dry eye pathology." Other considerations including seasonal variation, diet, time spent outdoors, and the genetic control of vitamin D metabolism were not factored in. More sophisticated technologies, such as tear osmolarity, imaging of the meibomian glands, and inflammatory biomarker assays, could have advanced understanding of the various disease mechanisms and the research would have benefited from their inclusion.

To ascertain whether vitamin D_3 has a causal role in DED, future studies must consist of larger, multi-center cohorts according to a longitudinal or interventional study framework. Also, to establish the most effective supplementation regimen for deficient patients, that is, through which route (oral or topical) and providing for which length of time, supplementation through a randomized controlled study design is vital. Mechanistic pathways might be clarified through studies that include the analysis of tear fluid for vitamin D, the imaging of the ocular surface, and the profiling of cytokines. Understanding how vitamin D deficiency affects DED severity will be improved by analyzing population-specific risk factors, such as lifestyle, comorbid conditions, and genetic factors.

CONCLUSION

Our analysis has shown that 'there is a widespread vitamin D_3 deficiency within DED' afflicted individuals which correlates with the presence and severity. Lower levels of vitamin D_3 correlated with unstable tear film, lower tear production, and higher symptom severity. These results suggest that vitamin D_3 deficiency should be considered a key modifiable factor in the progression of DED, and management of these patients speaks to the importance of assessing their vitamin D status.

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