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A study of the association between Vitamin D deficiency and Dry Eye Syndrome (DES) in the Indian population

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Purpose: A study of the association between vitamin D deficiency and dry eye syndrome (DES) in the Indian population. **Methods:** This was a cross-sectional, hospital-based observational study. Sixty patients diagnosed with vitamin D deficiency (<20 ng/dl) who met the inclusion criteria were sent to the Eye OPD from the Endocrinology OPD (case) were compared to 60 subjects with normal vitamin D levels (≥20 ng/dl) who attended the Eye OPD (controls). The examination of the tear film was done using Whatman filter paper in Schirmer test I and Schirmer test I (with anesthesia). The tear film break-up time (TFBUT) was determined by slit-lamp examination using the fluorescein stain, and scoring using the ocular surface disease index (OSDI) was done. **Results:** A significant difference in the mean values of Schirmer I and Schirmer I test (with anesthesia) ($P < 0.001$) was seen between the case and control groups. A significant difference in the mean values of TFBUT ($P < 0.001$) and OSDI scores ($P < 0.01$) was also seen between the two groups. **Conclusion:** A positive association was found between vitamin D deficiency and dry eye on comparing the above parameters.

Key words: Dry eye syndrome, OSDI, Schirmer test, TFBUT, vitamin D deficiency

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DES is a multifactorial disease of the tear film and the ocular surfaces that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface.[1] It is a chronic inflammatory condition of the ocular surface that is a result of tear hyperosmolarity and is accompanied by ocular surface symptoms, which can affect the quality of life of the patient. DES can arise due to environmental and behavioral conditions and is commonly found in the young population because of prolonged visual attention during computer use, playing video games, and reading and can also be an occupational hazard. The prevalence of dry eye in India based on the OSDI[2] questionnaire is 32%. The prevalence of DED in India is higher than the global prevalence and ranges from 18.4% to 54.3%.[3]

Vitamin D acts as an immunomodulatory agent; it plays an important role in immune regulation, enhances corneal epithelial barrier function, and because of its anti-inflammatory properties, it also plays a protective role in dry eye.[4]

The prevalence of vitamin D deficiency is reported worldwide, both in sunshine deficient and sunshine sufficient countries. Still, it is the most underdiagnosed and under-treated nutritional deficiency in the world.[5] The vast majority of these studies used serum 25 (OH) D level of <20 ng/ml as vitamin D deficiency.[6] The community-based Indian studies of the past decade done on apparently healthy controls reported a prevalence ranging from 50% to 94%.[7] Hospital-based studies showed a prevalence of vitamin D deficiency ranging from 37% to 99%.[8] A school-based study on premenarchal girls showed a prevalence of 34.2% of vitamin D.[9] Another school-based study done on schoolchildren aged 6–18 years showed a prevalence of 81% and 80%.[10]

There are many reasons for vitamin D deficiency being so common in India, which include increased indoor lifestyle preventing adequate exposure to sunlight mainly in the urban population due to modernization, pollution that hampers the synthesis of Vitamin D in the skin by UV rays, and changing food habits contributing to the low dietary calcium and Vitamin D intake.

Very few studies worldwide are available on the association of vitamin D deficiency with dry eye syndrome. DES is a fairly common problem that is multifactorial and affects the quality of life of the patient and vitamin D deficiency is also known to cause DES.

Methods

This was a cross-sectional; hospital-based observational study, which was conducted in a tertiary care government hospital in North India from March 2019 to December 2020. The study was conducted by good clinical practice and the declaration of Helsinki and prospectively approved by the institutional review board responsible for each participating institution.

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Participants

Inclusion criteria

The subjects with vitamin D levels of >20 ng/dl were taken as controls. The patients who were diagnosed with vitamin D deficiency (<20 ng/dl) were sent to the Eye OPD from the Endocrinology OPD and were taken as cases.

Exclusion criteria

The patients who had Sjogren disease or non-Sjogren syndrome dry eye (NSDE) such as primary lacrimal deficiencies, congenital alacrimia, Allgrove syndrome, lacrimal gland ablation, age-related lacrimal gland deficiency, or lacrimal gland infiltration like in Sarcoidosis were excluded. In addition, patients with AIDS or lymphoma, graft versus host disease, lacrimal gland duct obstruction, Meibomian gland dysfunction (MGD), non-cicatricial MGD, low blink rate, contact lens wear, and allergic conjunctivitis were not included in the study.

Technique

The patients who met the inclusion criteria were subjected to four tests. TFBUT was done first and then the conjunctival sac was washed with normal saline and after 30 min, Schirmer I test was done; 15 min later, Schirmer I test (with anesthesia) was done. After performing the above tests, the questions from the OSDI questionnaire were asked. All the above tests were conducted by the same person to rule out observer bias.

Schirmer I test was carried out using Whatman filter paper to measure both basal and reflex secretion, where the Whatmann strip was placed between the junction of the middle and the outer third of the lower lid. The time was noted and the strip was removed after 5 min or until the strips were completely saturated with tears and the reading was noted.

Schirmer I test (with anesthesia) was done to measure the baseline secretion. Topical anesthesia, proparacaine 0.5% eye drop, was instilled in the lower fornix of both the lower lid; the strip was removed after 5 min or until the strips were completely saturated with tears, the reading was noted.

Tear film break-up time, which is the number of seconds between the patient's last blink and the first appearance of a random dry spot on the cornea on slit lamp, was noted after one drop of 0.5% of fluorescein dye was applied to the conjunctival fornix of each eye.

OSDI score was calculated after asking the questionnaire to the patients.[2]

Statistical analysis

The sample size was calculated at 80% study power and alpha error of 0.05 assuming a standard deviation of 3.7 mm, mean tear film as measured by Schirmer test in vitamin D deficiency patients, to evaluate dry eye as found in the reference article. For a minimum detectable mean difference of tear film of 2 mm as measured by Schirmer test, 55 patients were required in each group as the sample size, which was further enhanced and rounded off to 60 patients in each group. The statistical analysis was performed using Statistical Package for Social Sciences software version 23 (SPSS Inc., Chicago, Illinois, USA). Analysis of variance (ANOVA) was used to analyze intragroup changes in continuous variables pre and postoperatively. In cases of normal distribution of data, mean and SD were used, while in cases where variables were not normally distributed, median was used. The Mann–Whitney U test was used to compare mean values of intergroup continuous variables. Categorical data were evaluated using the Chi-square test. Wilcoxon one sample nonparametric test was used to compare the means of intragroup continuous variables. For all measurements, a two-tailed test was used, and $P < 0.05$ was considered as significant for measured variables.

Results

The mean age was 65.55 ± 6.080 years in group 1 (cases) and 67 ± 5.523 years in group 2 (controls) ($P = 0.290$). There were no significant differences in terms of mean age. No significant difference was observed according to gender; both the groups were comparable according to gender. There was a significant difference in the mean values of the Schirmer I test 9.35 ± 4.422 in the right eye and 9.53 ± 5.013 in the left eye in the case group as compared to 14.97 ± 8.485 in the right eye and 14.53 ± 8.033 in the left eye in the control group with $P < 0.001$ [Table 1]. A significant difference was also found in the mean values of the Schirmer I test (with anesthesia) 4.65 ± 2.069 in the right eye and 4.83 ± 2.188 in the left eye in the case group as compared to 9.34 ± 5.522 in the right eye and 9.24 ± 5.418 in the left eye in the control group with $P < 0.001$ [Table 2]. There was a significant difference in the mean values of TFBUT 6.20 ± 3.030 in the right eye and 6.47 ± 2.914 in the left eye in the case group as compared to 10.45 ± 3.868 in the right eye and 10.42 ± 3.879 in the left eye in the control group with $P < 0.001$ [Table 3]. A significant difference was found in the mean values of OSDI 17.1822 ± 12.813 in the case group as compared to 24.0992 ± 15.975 in the control group with $P < 0.01$ [Table 4].

Discussion

Vitamin D deficiency causes symptoms associated with dry eyes and its supplementation decreases ocular surface inflammation

Table 1: Comparison of Schirmer 1 test among the groups

Group	Right Eye (mm)	Left Eye (mm)
Case		
n	60	60
Mean	9.35	9.53
Std. Deviation	4.422	5.013
Minimum	3	5
Maximum	18	20
Controls		
n	60	60
Mean	14.97	14.53
Std. Deviation	8.485	8.033
Minimum	2	2
Maximum	25	26
Total		
n	120	120
Mean	12.16	12.03
Std. Deviation	7.304	7.124
Minimum	2	2
Maximum	25	26
P	<0.001	<0.001

Table 2: Comparison of Schirmer I (with anesthesia) among the groups

Group	Right Eye (mm)	Left Eye (mm)
Case		
n	60	60
Mean	4.65	4.80
Std. Deviation	2.069	2.188
Minimum	2	2
Maximum	13	12
Controls		
n	60	60
Mean	9.34	9.24
Std. Deviation	5.522	5.418
Minimum	2	2
Maximum	18	18
Total		
n	120	120
Mean	7.50	7.52
Std. Deviation	4.819	4.752
Minimum	2	2
Maximum	18	18
P	<0.001	<0.001

Table 3: Comparison of TFBUT among the groups

Group	TFBUT (RE)	TFBUT (LE)
Case		
n	60	60
Mean	6.20	6.47
Std. Deviation	3.030	2.914
Minimum	2	2
Maximum	11	10
Controls		
n	60	60
Mean	10.45	10.42
Std. Deviation	3.868	3.879
Minimum	2	2
Maximum	13	14
Total		
n	120	120
Mean	7.33	7.44
Std. Deviation	3.640	3.553
Minimum	2	2
Maximum	13	14
P	0.001	0.001

and improves several tear film parameters such as tear film break up time (TBUT), eyelid margin hyperemia, and tear secretion.[11] Vitamin D makes the corneal epithelial cell barrier function better by regulating gap and tight junctions.[12] Vitamin D induces the production of IL10 and decreases inflammatory cytokines/factors such as IL1, IL6, TNF alpha, and C-reactive protein.[6] Vitamin D also reduces inflammation by increasing antioxidant cytokines in tears and suppressing both Th1 and Th2 cells.[13] By inducing the production of cathelicidin, vitamin D promotes the wound healing of the conjunctiva and cornea.[14] Vitamin D reduces tear osmolarity and improves the stability of tear film.[13]

In our study, 60 cases and 60 controls were evaluated and the association of vitamin D deficiency with dry eye syndrome was assessed by comparing the following parameters- Schirmer I test with and without anesthesia, TFBUT, and ocular surface disease index (OSDI). The first parameter, Schirmer I test, tends to be more useful if positive, that is, less than 10 mm of strip wetting. Scores of above 10 show less repeatability. Therefore, it is more useful in advanced disease. This test can determine the severity of dry eye and whether aqueous dysfunction exists but is an unreliable method for monitoring treatment success. It measures both the reflex and the basal secretion, that is, the secretion of the main lacrimal gland.

Demerci *et al.*[15] also conducted a study in Turkey, where they included 60 eyes of 30 patients with vitamin D deficiency (group 1) and 60 eyes of 30 healthy individuals (group 2) and evaluated them using the Schirmer I test. Schirmer I results in group 1 (8.5 ± 3.7 mm) were significantly lower compared with group 2 (16.6 ± 2.4) ($P < 0.001$ for all). The study demonstrated that vitamin D deficiency is associated with tear film dysfunction. Patients with vitamin D deficiency may be prone to dry eye.

Yildirim *et al.*[16] also demonstrated that patients with vitamin D deficiency developed dry eye and impaired tear function. Fifty premenopausal women with vitamin D deficiency (serum vitamin D levels <20 ng/mL) and 48 controls were included. Participants were assessed by Schirmer test. Lower scores in Schirmer test were detected in patients with vitamin D deficiency than in controls ($P < 0.05$).

Kurtul *et al.*[17] conducted a study in which 34 patients with serum vitamin D deficiency and 21 control subjects with normal vitamin D levels were included. The Schirmer I test was performed in all patients. The mean scores of the Schirmer tests were 12.18 ± 6.44 and 18.57 ± 8.99 mm in the study and control groups, respectively. The results of the study group were significantly lower than the control group ($P = 0.007$). The mean vitamin D levels were 11.50 ± 1.8 ng/ml in the study group and 32.8 ± 8.72 ng/ml in the control group ($P = 0.001$).

Our study also demonstrated a decrease in Schirmer I test values in patients with vitamin D deficiency.

In Schirmer I test (with anesthesia), a topical anesthetic agent is used, most commonly proparacaine 0.5% eye drop. It measures only the basal secretion, which is mainly the function of the accessory lacrimal gland. A value of < 10 mm for Schirmer I and <5 mm for Schirmer I (with anesthesia) is abnormal.[18]

There has been no other study that has taken Schirmer I test (with anesthesia) as a separate parameter to assess the tear film quality in a patient with vitamin D deficiency. Our study demonstrates that both reflex and basal aqueous component of tear secretion is reduced in patients with vitamin D deficiency.

The third parameter that was taken was TFBUT. It is the time taken for the first random spot to appear on the cornea after complete blinking. TFBUT measurement is an easy and fast method to assess the stability of tear film. It is a standard

Table 4: Comparison of OSDI among the groups

	OSDI
Case	
n	60
Mean	17.1822
Std. Deviation	12.81340
Minimum	5.00
Maximum	66.60
Controls	
n	60
Mean	24.0992
Std. Deviation	15.97568
Minimum	11.11
Maximum	66.60
Total	
n	120
Mean	20.6407
Std. Deviation	14.83247
Minimum	Group
Maximum	66.60
P	0.010

diagnostic procedure in dry eye clinics. Generally, a TBUT value of 10–35 s is considered normal. A value of <10 s is usually suspicious of tear film instability.

Demerci *et al*.[15] conducted a study where 60 eyes of 30 patients with vitamin D deficiency (group 1) and 60 eyes of 30 healthy individuals (group 2) were evaluated using the tear breakup time. The TBUT in group 1 (8.7 ± 0.6 s) was significantly lower compared with group 2 (18.1 ± 0.5).

Yildirim *et al*.[16] demonstrated that patients with vitamin D deficiency developed dry eye and impaired tear function. Fifty premenopausal women with vitamin D deficiency (serum vitamin D levels <20 ng/mL) and 48 controls were included. Participants were assessed by the TBUT. Lower scores of TBUT were detected in patients with vitamin D deficiency than in the control group ($P < 0.05$).

Jin *et al*.[19] conducted a retrospective observational study in 92 patients. TBUT was measured. The mean age was 53.38 ± 13.69 years. Mean serum 25 (OH) D level was 14.41 ± 5.98 ng/ml. TBUT positively correlated with serum 25 (OH) D levels (r = 0.389, $P = 0.001$; and r = 0.428, $P < 0.001$, Pearson correlation test). TBUT was shorter in the vitamin D-deficient group compared to the sufficient group ($P = 0.022$).[19]

In our study also, a significant decrease was noted in TFBUT in patients with vitamin D deficiency.

The last parameter taken in our study was OSDI. The index demonstrates sensitivity and specificity in distinguishing between the normal subjects and the patients with dry eye. The OSDI is a valid and reliable instrument for measuring DES (normal, mild to moderate, and severe) and its effect on vision-related function.[20] OSDI is very subjective and thus can vary from person to person. It was assessed on a scale of 0–100, with higher scores representing greater disability.

Jin *et al*. concluded that OSDI scores were not different between the groups.[19]

Demerci *et al*.[15] conducted a study in which the mean OSDI scores were significantly higher in group 1 (35.78 ± 21.44) as compared to group 2 (18.69 ± 17.21) ($P < 0.001$ for all). Patients with vitamin D deficiency developed dry eye and impaired tear function. Higher OSDI scores were reported in patients with vitamin D deficiency than in controls.

Our study also demonstrated a higher OSDI score in the patients who had vitamin D deficiency.

There is no pathognomonic sign by which we can distinguish dry eye with vitamin D deficiency only by a slit lamp. Patients with vitamin D deficiency should be further evaluated if they have syndromes causing dry eye and also dry eye patients be tested for vitamin D deficiency.

Considering the results of this study and the various other studies, we should consider evaluating vitamin D levels as a part of the basic workup of a patient with dry eye syndrome. If the levels are low, one of the additional therapeutic modalities could be the supplementation of vitamin D as it is a multifunctional hormone, which plays an important role in ocular health.

Some studies have studied the effect of vitamin D supplementation to improve the symptoms of DES. For example, Bae *et al*.[11] used 2,00,000 IU cholecalciferol intramuscular (i.m.) injection single stat dose. They observed that the OSDI scores decreased significantly at 2 weeks and 10 weeks ($P = 0.046$ and $P = 0.004$, respectively). TBUT increased significantly at 2 weeks and 6 weeks and then returned to pretreatment values at 10 weeks ($P < 0.001$, $P < 0.001$, and $P = 0.066$, respectively). Schirmer test values increased at 2 and 6 weeks significantly but at 10 weeks there was no significant increase ($P = 0.006$, $P = 0.015$, and $P = 0.140$, respectively).

Kizilgul *et al*.[21] investigated the effect of vitamin D replacement on tear osmolarity in patients with vitamin D deficiency in 44 patients. Patients were given 50,000 units of Vitamin D3 i.m. once weekly over 8 weeks. They observed that vitamin D replacement improved tear hyperosmolarity, which is considered to be induced by ocular surface inflammation. Improvement in tear osmolarity which is one of the main causes of discomfort in dry eye patients can lead to improvement of dry eye parameters.

An important limitation of this study is the lack of a control group consisting of patients with dry eye without vitamin D deficiency. Comparing tear film parameters between dry eye patients with or without vitamin D deficiency could be more helpful to clarify the pathogenesis of dry eye syndrome.

Conclusion

A significant difference in the mean values of Schirmer I and Schirmer I test (with anesthesia) (P value < 0.001) was seen between the case and control groups. A significant difference in the mean values of TFBUT (P value of < 0.001) and OSDI scores (P value of < 0.01) were also seen between the two groups. Therefore, there is a positive association between Vitamin D deficiency and dry eye syndrome.

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Conflicts of interest

There are no conflicts of interest.

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