Study of Association of Dry Eye Syndrome with Low Vitamin D Levels and Effect of Supplementation

Prasanta Kumar Nanda[1], Shradha Pattnaik[2], Bishnupriya Khuntia[3]

[1]Professor and HOD, Department of Ophthalmology, Regional Institute of Ophthalmology, SCB MCH, Cuttack, Odisha. [2]Postgraduate Resident, Department of Ophthalmology, Regional Institute of Ophthalmology, SCB MCH, Cuttack, Odisha. [3]Postgraduate Resident, Department of Ophthalmology, Regional Institute of Ophthalmology, SCB MCH, Cuttack, Odisha.

ABSTRACT

BACKGROUND

Dry eye disease, though common, is a frequently under-recognized clinical state whose aetiology and management are challenging. Many external and internal factors have been studied, which affects the stability of tear film. This study aims at determining the association between serum 25(OH) Vitamin D and Dry Eye Syndrome (DES) incidence and how treatment with supplementation affects the outcome.

METHODS

This is a case-control study with 75 DES cases and 75 healthy controls. The main parameter to detect the level of vitamin D was Serum 25(OH)D. The DES parameters included ocular surface disease index (OSDI) scales, tear film breakup time (TBUT), fluorescein staining score (FSS), eyelid margin hyperemia, tear secretion test and Schirmer test. The differences in each parameter between case and control groups were detected and the association of serum 25(OH) D and DES parameter were studied. Deficient patients were given vitamin D-supplementation. The DES parameters were followed up after 8 and 12 weeks. Comparison was done between pre-treatment and post-treatment values.

RESULTS

25(OH) D levels were lower in patients with DES than in healthy controls. Vitamin D deficiency was more common in the DES cases. Parameters were measured before treatment and after 8 and 12 weeks of vitamin D supplementation. Mean serum 25(OH)D level was 10.52 ± 4.61 ng/mL. TBUT, and tear secretion test showed an improvement at 8 and 12 weeks after vitamin D supplementation compared to pre-treatment values ($p < 0.05$ for all, paired t-test). Eyelid margin hyperemia and the severity of symptoms showed improvement at 8 and 12 weeks after vitamin D supplementation ($p < 0.05$).

CONCLUSIONS

A significant association between serum 25(OH)D level and DES incidence was detected in this study. It was found that vitamin D deficiency decreases the TBUT and Schirmer test values. Vitamin D supplementation promoted tear secretion, reduced tear instability, and reduced inflammation at the ocular surface and eyelid margin. Considering the effect of vitamin D on the immune system, it could be assumed that the immuno-regulatory effect of vitamin D might be influencing the development of DES.

KEYWORDS

Dry Eye, Vitamin D, Supplementation

Corresponding Author:
Dr. Shradha Pattnaik,
HIG-228, Sailashree Vihar,
Phase 7, Bhubaneswar- 751021,
Odisha.
E-mail: shradhapattnaik@gmail.com
DOI: 10.18410/jebmh/2019/672

Financial or Other Competing Interests: None.

How to Cite This Article:
Kumar Nanda P, Shradha P, Bishnupriya K. Study of association of dry eye syndrome with low vitamin d levels and effect of supplementation. J. Evid. Based Med. Healthc. 2019; 6(51), 3202-3207. DOI: 10.18410/jebmh/2019/672

Submission 03-12-2019,
Peer Review 05-12-2019,
Acceptance 19-12-2019,
Published 23-12-2019.

BACKGROUND

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.[1] Ocular surface inflammation is associated with excessive tear evaporation, which leads to tear film instability. The symptoms of dry eye include feeling of dryness, grittiness or foreign body sensation that gets worse throughout the day, burning sensation, red eyes, eyelids that stick together on waking up, and temporarily blurred vision which usually improves with blink. The causative mechanisms of dry eye include tear hyperosmolarity and tear film instability. **Intrinsic Factors:** Low blink rate behaviour, Wide lid aperture, gaze position, Aging, Low androgen pool, Systemic Drugs like antihistamines, beta-blockers, antispasmodics, diuretics, and some psychotropic drugs. **Extrinsic Factors:** Low humidity, High wind velocity, Occupational environment.

Pathophysiology

In intrinsic causes, the regulation of evaporative loss from the tear film is directly affected, e.g., by meibomian lipid deficiency, poor lid congruity and lid dynamics, low blink rate, and the drugs, like systemic retinoids. Vitamin A deficiency or the action of toxic topical preservatives, contact lens wear and ocular surface diseases, such as allergic eye disease increase evaporation by their pathological effects on the ocular surface. 25-hydroxyvitamin D (25(OH)D), known as vitamin D, has long been regarded as one of the indispensable daily nutrients. There are two main forms of vitamin D, ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). Ergocalciferol can be acquired via specific food intake or irradiation of plants, whereas cholecalciferol is mainly synthesized in the skin after exposure to ultraviolet light.[2] Vitamin D has been proven to be protective of myopia development, and has been linked with ocular conditions like ARMD, Diabetic Retinopathy and Uveitis. Levels of serum Vitamin D were inversely associated with early ARMD but not advanced disease.[3] The prevalence of Vitamin D deficiency ranged from 40% to 99%, with most of the studies reporting a prevalence of 80%-90%. According to the Research published in the International Journal of Rheumatic Diseases, vitamin D plays a role in dry eyes due to its anti-inflammatory properties. It may help prevent dry eyes by inducing cathelicidin, an anti-microbial protein that can helps in healing eye wounds. In the study by Galor et al in 2014, serum 25OHD levels were not found to be associated with severity of disease clinically but higher serum vitamin D levels were significantly correlated with a decrease in subjective dry eye symptoms, as determined by the Dry Eye Questionnaire.[4]

It has also been demonstrated that two commonly used tests for dry eye, Schirmer's test score (measure of tear production) and tear break up test (TBUT), appeared lower in people with vitamin D deficiency. Jee et al reported that increased serum vitamin D levels reduced the risk of having dry eye.[5] Vitamin D is known to affect cell differentiation. The rate of epithelial wound healing was decreased in Vitamin D Resistant (VDR) knockout animals (Elizondo et al., 2014)[6] In vivo studies have demonstrated that vitamin D can be anti-inflammatory at the ocular surface (Suzuki et al., 2000a).[7] In vitro, vitamin D appears to dampen the inflammatory response to infection (Xue et al., 2002).[8] Vitamin D augmented corneal epithelial barrier function through upregulation of the tight junction proteins Occludin and ZO-1 (Yin et al., 2011)[9] Ocular cells express vitamin D-related genes and can activate it. Vitamin D treatment is protective of ocular disease in animal models.[10] Effect of Vitamin D on dry eye has been studied with mixed opinions. In Sjogren's syndrome, which is accompanied by severe aqueous deficiency, an association with reduced vitamin D levels has been found.[11] Most of the Indian population live in areas with adequate sunlight throughout the year and are expected to have adequate Vitamin D. Contrary to this, the prevalence of Vitamin D deficiency is high in India. A 2019 pan-India study authored by diabetologist PG Talwalkar et al found that 70-90 per cent of Indians are deficient of vitamin D, and the deficiency can have adverse consequences.[12]

Biochemical studies have implicated vitamin D deficiency in many chronic diseases including infectious diseases, autoimmune diseases, cardiovascular diseases, diabetes and cancer. 25(OH)D is the most useful measure and reflects the Vitamin D status in the body because the level depends on the available and circulating Vitamin D.[13] According to the classification given by the US Endocrine Society, <20 ng/mL of serum 25(OH) D with consequent and consistent elevation of parathyroid hormone and a decrease in intestinal calcium absorption is considered to be Vitamin D deficiency.[14] The USDA Recommended Daily Allowance of vitamin D, regardless of race, season or geographic location, presently is:

Less than Age 50	200 IU
50	400 IU
50 – 70	600 IU
70+	800 IU

Supplements commonly available are D_3 (cholecalciferol), 1,25 $(OH)_2D_3$ and 1 alpha hydroxy vitamin D_3 (alfacalcidol). Intake of oral 60,000 IU of vitamin D_3 per week may be advisable for a short duration along with Calcium 1 gm/day for 8 weeks.

We wanted to determine the association between serum 25(OH)D and dry eye syndrome (DES) incidence and how treatment with supplementation affected the outcome.

METHODS

This is a case control study with 75 patients with dry eye syndrome taken as cases and 75 healthy age and sex matched controls conducted from February 2019 to October 2019 in the Department of Ophthalmology.

Parameters Included

Serum 25(OH) D, Tear break up time (TBUT), Schirmer's test, Fluorescein staining score (FSS), Ocular surface disease index (OSDI). Full information was given, and written consent was taken.

Inclusion Criteria

- Age group- 30-50 yrs.
- Schirmer's test <10 mm / 5 mins.
- or Tear Break Up Time <10 s

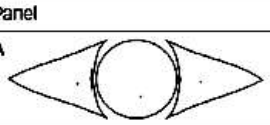
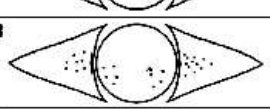
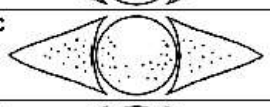
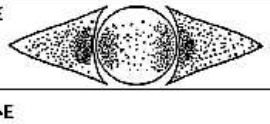
Exclusion Criteria

- Autoimmune diseases (such as Sjogren & Lupus syndrome)
- Intra-ocular surgery
- Corneal opacity
- Ocular Injuries
- Contact lens use
- Taking Vit D supplements

Serum 25(OH)D levels are classified as Adequate (≥20 ng/ml), Inadequate (12 to <20 ng/ml), and Deficient (<12 ng/ml). Hyperemia and telangiectasia of the eyelid margin was graded as 0= none, 1= mild, 2= moderate, 3= severe.

Fluorescein Staining Score (FSS)

Using Oxford grading system where surface damage to the exposed eye, is assessed by staining, and then graded against standard charts. 1 drop of 2% sterile fluorescein instilled into each conjunctival sac. The absorption peak of fluorescein sodium occurs between 465 - 490 nm and the emission peak between 520 - 530 nm. The 'cobalt' filter of slit-lamp is used.[15] Staining is represented by punctate dots on a series of panels (A-E). Staining ranges from 0-5 for each panel and 0-15 for the total exposed inter-palpebral conjunctiva and cornea. The dots are ordered on a log scale.

Panel	Grade	Verbal description
A 	0	Absent
B 	I	Minimal
C 	II	Mild
D 	III	Moderate
E 	IV	Marked
>E	V	Severe

Tear Break-Up Time

This test is performed to determine tear film stability. A fluorescein strip is moistened with saline and placed in the inferior fornix. This test should be done before any eye drops have been used or the lids manipulated. The patient is observed with a cobalt blue filter and diffuse illumination at the slit lamp. The time (in seconds) between a blink and the appearance of a dark spot in the fluorescein is the TBUT. The test is repeated 3 times and the average used to obtain the result. Ten seconds or greater is considered normal. The Ocular Surface Disease Index (OSDI) is commonly used and includes 12 questions related to experience during the previous week regarding ocular symptoms, the severity, how these affect visual function and the ocular response to environmental triggers. The score can range from 0–100 with a higher score being worse. The differences in each parameter between case and control groups were studied and the association of serum 25(OH)D and DES parameters were detected. The Vit D deficient dry eye patients were given supplements and the parameters were measured at the end of 8 weeks and 12 weeks. Parameters were then compared and any association/correlation was studied with paired t test.

RESULTS

Demographic Characteristics

Mean age of cases: 46.65 years., Mean age of controls: 45.8 years, Male to female ratio was kept 1:1, Mean S. 25 (OH)D level in cases: 14.14 ± 5.98 ng/ml in controls: 25.19 ± 2.79 ng/ml.

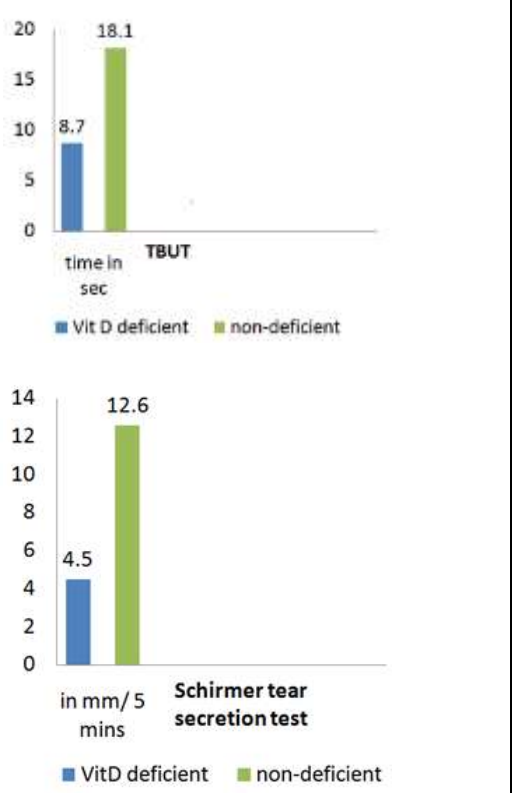


Chart 1. Dry Eye Parameters in Vit D. Deficient vs. Non-Deficient

TBUT was lower by 48% and Schirmer's test was lower by 35% for those who were Vit Deficient in comparison to controls

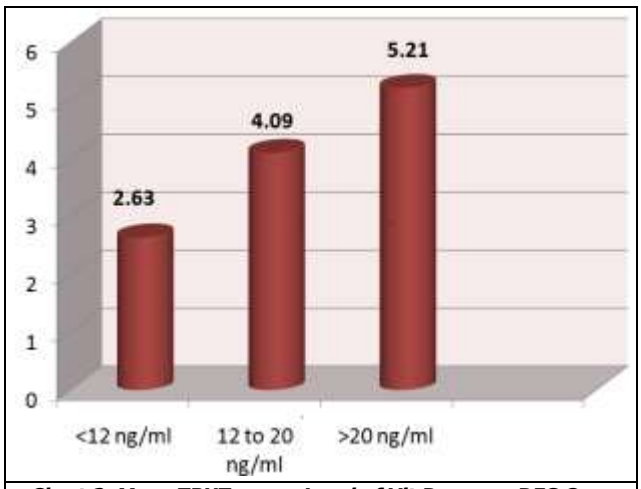


Chart 2. Mean TBUT as per Level of Vit D among DES Cases

Incidence of Vitamin D deficiency in cases and controls Incidence of vitamin D deficiency in DES patients: 40% (30 pts had low Vit D among 75 pts) Incidence of vitamin D deficiency in controls: 10.6% (8 pts among 75 controls). TBUT was lower by 48% and Schirmer's test was lower by 35% for those who were Vit D Deficient in comparison to controls. Mean TBUT in seconds- 8.7s; in controls: 18.1s Mean Schirmer's tear secretion in mm/5 mins: 4.5 mm/5 mins in cases 12.6 mm/5 mins in controls. Mean TBUT was grossly decreased in patients with Vit D deficiency.

FSS Grading among the Vit D deficient dry eye pts- 15 cases: mild/gr II, 9 cases: moderate/gr III, 5 cases: minimal/gr I, 1 case: marked/gr IV. Mean OSDI among the vit D deficient dry eye pts was found to be around 70.

Effects of Supplementation

Oral supplementation of vitamin D3, cholecalciferol 60,000 IU per week. 30 patients found deficient amongst DES cases, were studied. Assessment done at end of 8 weeks & 12 weeks.

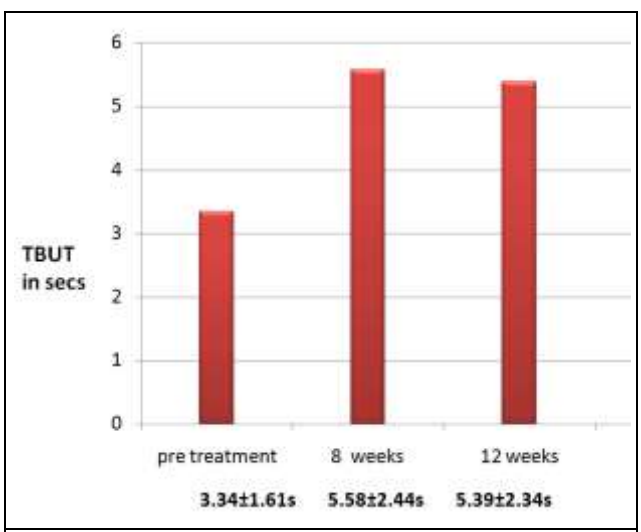


Chart 3. Effect on Supplementation on TBUT

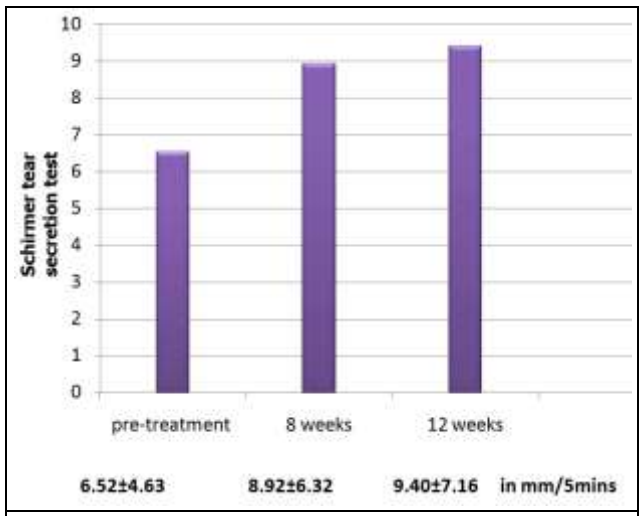


Chart 4. Effect on Supplementation on Schirmer's Test

FSS Grading among the Vit D deficient dry eye pts after supplementation- 20 cases: mild/gr II, 9 cases: minimal/gr I, 1 case: moderate/gr III. Mean OSDI among the vit D deficient dry eye patients after supplementation after 8 weeks was around 30.

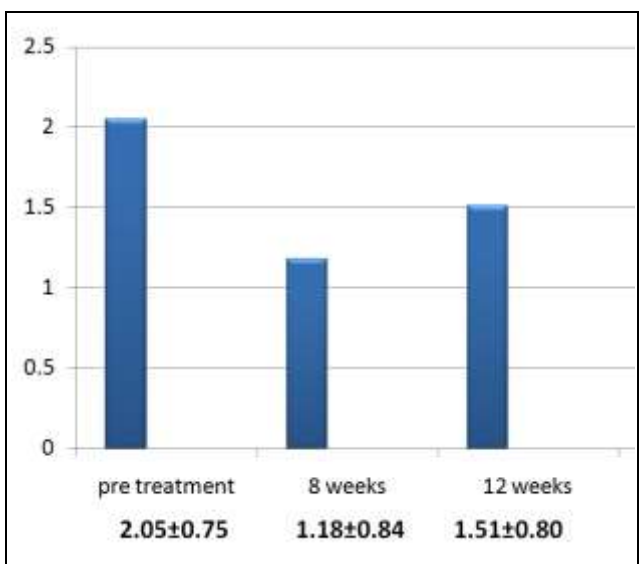


Chart 5. Effect of Supplementation on Eyelid Hyperemia

DISCUSSION

It was shown that 25(OH)D levels were lower in patients with DES than in healthy controls. Incidence of Vit D deficiency is 3.7 times more in DES pts than healthy controls. Galor et al, 2014 found Lower dry eye syndrome symptoms were significantly associated with higher vitamin D levels ($p = 0.01$)[4] TBUT, and tear secretion test showed an improvement at 8 and 12 weeks after vitamin D supplementation compared to pretreatment values ($p < 0.05$ for all, paired t-test). Eyelid margin hyperemia and the severity of symptoms showed improvement at 8 and 12 weeks after vitamin D supplementation ($p < 0.05$) Yildirim et al, 2016 also found Lower scores in Schirmer's test and TBUT, and higher OSDI scores in vitamin D deficient participants ($p < 0.05$)[16] Jin, Ro et al, 2017 stated

TBUT and secretion were correlated with serum vitamin D levels.[17] Kurtul et al, 2015[18] opined that TBUT and Schirmer-1 test lower in vitamin D deficient group (p = 0.01 and 0.007) but Jee et al,[5] didn't find an association between serum vitamin D levels and dry eye syndrome (p>0.05). This could be because Vitamin D levels differ according to the latitude, ethnicity, and culture of the study population.[19] Study by Chih-Huang Yang et al in 2018 also found Vitamin D supplement increased the vitamin D levels, and improved dry eye symptoms, the tear quality and ocular surface conditions.[20] Demirci, Goktug et al, 2018 concluded that vitamin D deficiency is associated with tear hyperosmolarity and tear film dysfunction.[21] Dry eye disease is a grossly under-diagnosed entity. Most of the times it is managed only symptomatically at most clinical set ups. Studies as this, will help in finding out the true cause and better management and patient satisfaction.

Limitation

Small sample size taken and similar studies with a bigger sample could yield more convincing results.

CONCLUSIONS

A significant association between serum 25(OH)D level and DES incidence was detected in this study. It was found that vitamin D deficiency affects the TBUT and Schirmer test values. It can be assumed that the immunoregulatory effect of vitamin D might influence the development of DES. Supplementation promoted tear secretion, reduced tear instability, and reduced inflammation at the ocular surface and eyelid margin. This indicates a protective role of vitamin D in the development of dry eye, probably by enhancing tear film parameters and reducing ocular surface inflammation. Vitamin D deficiency is easy to screen for and even easier to treat with sensible sunlight recommendations and Vitamin D supplementation. All it takes is a good 12 mins of mid-day sun exposure to get natural vitamin D3 or supplements which are easily available and safe. Therefore, patients with dry eye syndrome should be evaluated for vitamin D deficiency as it is a cause which can be easily tackled by the clinician.

ACKNOWLEDGEMENT

We thank Prof. Dr. Sumita Mohaptra for her insights and support. Special thanks to Dr. Jayaram Meher, Dr. Bishnu Prasad Rath and Dr. Ashutosh Pattanaik for helping with the data collection and patient management.

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