Original Article

A prospective study to assess the role of vitamin D individually and in combination with cyclosporine in the treatment of dry eye in patients with deficient serum 25(OH)D levels

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Purpose: To study the efficiency of vitamin D3 (buccal spray) alone and combination of vitamin D3 with cyclosporine in the treatment of dry eye disease (DED) in patients with deficient serum 25(OH)D levels. **Methods:** Around 90 patients with DED with deficient serum 25(OH)D levels were included and randomized into three groups and were given treatment for dry eye (Group A- 0.5% carboxymethylcellulose (CMC), Group B- 0.5% CMC + 2000 IU vitamin D through buccal spray, Group C- 0.5% CMC + 2000 IU vitamin D through buccal spray + 0.05% cyclosporine). The patients were followed at day-15, day-30, and day-90 for improvement in tear breakup time (TBUT) and Schirmer's, and ocular surface disease index (OSDI) score. Improvement in serum vitamin D level was assessed at day-90. One way ANOVA test, paired *t*-test, and Chi-square test were used for analysis. **Results:** Group B and Group C had significantly higher in Schirmer's test-I values as compared to Group A ($P = 0.001$, $P < 0.001$, $P < 0.001$ at day-15, day-30, and day-90, respectively). Significantly higher values of TBUT and mean serum vitamin D levels were obtained in Group B and Group C as compared to Group A at day-90 ($P < 0.05$). OSDI scores of patients significantly decreased in all three groups at all follow-up visits ($P < 0.05$). Overall, Group C and Group B were found statistically better than Group A. Group C showed better results than Group B but they were nonsignificant. **Conclusion:** Vitamin D supplementation leads to earlier and significant improvement in TBUT, Schirmer's, and OSDI score in patients with vitamin D deficient DED.

Key words: Cyclosporine, dry eye, OSDI score, Schirmer's, TBUT, vitamin D

Dry eye disease (DED) is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.[1]

Recently, vitamin D deficiency has been suggested to be a contributory factor in DED.[2,3] Since inflammation is the core mechanism in DED, vitamin D acts by decreasing inflammatory cytokines and increasing antioxidant cytokines in tears and thus, improves the symptoms and signs of DED. The anti-inflammatory effect of activated vitamin D is achieved by blocking the activation of T-helper cells and cytotoxic T cells, and reducing the production of inflammatory mediators such as interleukin (IL)-2, IL-6, IL-8, and IL-12.[4-7] Furthermore, vitamin D inhibits inflammatory factors such as C-reactive protein (CRP), tumor necrosis factor (TNF)-α, IL-1, and IL-6, and induces IL-10 production.[8,9]

Cyclosporine-A (CsA) 0.05%, a topical immunomodulatory compound with anti-inflammatory properties have been demonstrated to be beneficial in the treatment of dry eye due to its effects on subconjunctival and lacrimal gland inflammation, resulting in an increase in tear production and conjunctival goblet cell density.[10,11]

Methods

This hospital-based, prospective interventional (randomized) study was carried out on 90 patients with dry eye symptoms with deficient serum 25(OH)D levels from January 2018 to October 2018 after obtaining approval from the institutional ethics committee.

Inclusion criteria were as follows:
- All patients who came to OPD with dry eye symptoms irrespective of their previous treatment status and with vitamin D deficiency were included in the study. We included a mixed type of dry eye patients in our study
- All cooperative patients
- A patient who gave informed consent for the study.

Exclusion criteria
- Preexisting ocular disease such as glaucoma or uveitis, ocular allergy, pterygium or blepharitis, ocular infections, corneal diseases were excluded

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- Patients who received concomitant medications that could cause dry eyes such as antihistamines, antidepressants, birth control pills, decongestants, gabapentin, sildenafil citrate, anticholinergic drugs, blood pressure medications, postmenopausal estrogen therapy, beta-blockers, antispasmodics, and diuretics were excluded
- Disorders of the lid or nasolacrimal pathway
- Contact lens users
- Secondary to ocular surgeries including refractive surgery
- Endocrine and metabolic disorders, pregnancy, vitamin-A deficiency and general malnutrition, and any other comorbid conditions (thyroid disease, chronic kidney disease, DM, or depression) that are associated with dry eye
- A patient who was allergic to medication (cyclosporine, vitamin D)
- An uncooperative or mentally challenged patient
- Patients who were unable to comprehend the questionnaire
- Patients who were refusing to give consent for the study.

Patients included in the study were divided into three groups: Group-A, Group-B, and Group-C and were given medical treatment for dry eye as described below:

Group A-
- 0.5% carboxymethylcellulose 4 times/day from 1st day to 90th day

Group B-
- 0.5% carboxymethylcellulose 4 times/day from 1st day to 90th day
- 2000 IU vitamin D through buccal spray once daily from 1st day to 90th day.

Group C-
- 0.5% carboxymethylcellulose 4 times/day from 1st day to 90th day
- 2000 IU vitamin D through buccal spray once daily from 1st day to 90th day
- 0.05% cyclosporine 2 times/day from 1st day to 90th day.

Patients were instructed to instil the artificial teardrop (CMC) at least 15 min after the cyclosporine drops.

A number of visits included in the study were four (first visit: day-0 [i.e., day of starting medical treatment], second visit: day-15, third visit: day-30, and fourth visit: day-90 of treatment). Serum 25(OH)D levels were assessed two times, once before starting treatment and once at 3 months of treatment.

The patients were subjected to the following examination; best-corrected visual acuity (by Snellen's chart), slit-lamp examination, non-contact tonometry to measure intraocular pressure, fundus examination with 90D as routine examination along with TBUT, Schirmer's test, and OSDI questionnaire on day-0, day-15, day-30, and day-90.

Method of measuring TBUT, Schirmer's test, and OSDI score:

TBUT was measured before Schirmer's test in all the cases following the standard guidelines of investigations in dry eye.

The TBUT and Schirmer-1 test were evaluated after a full ophthalmologic examination. TBUT and Schirmer-1 test without topical anesthesia were performed on all patients with a 30-min interval after the ophthalmologic examination by the same examiner. Patients were avoided from ocular manipulations before the tests since this may affect the results.

The TBUT was measured after fluorescein staining. Subjects were instructed to blink and the tear film was examined using the cobalt blue filter of a slit-lamp biomicroscope. The time interval in seconds between the instilment of fluorescein and the appearance of the first randomly distributed dry spot was considered as the TBUT. This method was repeated three times for each eye, and the average of the results was registered as the mean TBUT. TBUT of <10s was accepted as abnormal. The Schirmer-1 test was performed without anesthesia by placing a standardized strip of filter paper (Whatman filter paper no. 41) in the one-third lateral tarsal conjunctiva away from the cornea. Outcomes were expressed in millimetres after 5 min of wetting.

In Shimer's-I test wetting of 10–20 mm is normal, 5–10 mm is doubtful, less than 5 is diagnostic of poor lacrimal secretion. TBUT of 10 s is recommended as a cut-off point for normal individuals by both western and Indian authors.

OSDI score was recorded after asking the patients all the 12 questions as given in the OSDI questionnaire.

Ocular Surface Disease Index (OSDI):

The OSDI questionnaire is a 12-item questionnaire used worldwide to accurately assess the symptoms of ocular irritation related to dry eye and vision. The total OSDI score was calculated using the following formula:

OSDI score = (sum of scores/total number of answered questions) ×25.

The OSDI scores ranged from 0 to 100. Scores from 0 to 25 were considered normal, scores exceeding 25 indicate the presence of dry eye symptoms.

Improvement in dry eye symptoms following the administration of drugs was assessed in terms of improvement in TBUT, Shirmer's, and OSDI score of the patient at 2 weeks, 1 month, and 3 months.

Vitamin D levels [25(OH)D] were assessed by ROCHE COBAS 6000 instrument that works on COMPETITION PRINCIPLE. The optimal serum vitamin D[25(OH)D] level ranges between 30–80 ng/mL, and deficiency/insufficiency of vitamin D is considered when total 25(OH)D is <20 ng/mL.[12,13]

Statistical analysis

Linear variables were presented as mean, median, and standard deviation (SD). One way ANOVA test with *post hoc* Tukey HSD test was used to compare linear variables between the groups. For within-group pair-wise comparison, paired *t*-test was used for linear variables. Nominal/categorical variables were expressed as percentages and Chi-square test was used for their analysis. *P* value < 0.05 was taken as significant. Medcalc 16.4 version software was used for all statistical calculations.

Results

Out of a total of 90 patients, 52 were females and 38 were males with the mean age of 44.87 ± 14.77 (range = 20–80 years) [Table 1]. Maximum participants were in the age group 31–50 years i.e., 50% in Group A, 46.67% in Group B, and 46.66% in Group C. Mean age were 46.17 years, 44.97 years, and 43.47 years in Group A, Group B, and Group C, respectively. Around 63.33% of participants in Group A, 43.33% of participants in Group B, and 66.67% of participants in Group C were females.

Group-wise comparison of mean TBUT values: mean TBUT before treatment, at day-15 and at day-30 were not statistically significant between any pair of groups. However, at day-90, there were significantly higher values of mean TBUT were obtained in Group B and Group C (*P* < 0.05) as compared to Group A. However, Group B and Group C did not have significant difference (*P* > 0.05) [Table 2]. Comparison of mean TBUT values with respect to a different time interval in various groups showed that mean TBUT increased in Group A at day-15, day-30, and day-90 as compared to before treatment value but showed statistical significance at day-90 only. Moreover, in Group B, the increase in mean TBUT value was found statistically significant and higher than before treatment value from "day-15" and remained significant at day-30 and day-90 also. In Group C, mean TBUT followed the same pattern as Group B i.e. it increased from day-15 significantly and remained significantly higher till day-90.

Group-wise comparison of mean Schirmer's test-I values at various points of time during the study revealed that before treatment there was no significant difference in mean Schirmer's test-I values but at day-15, it was highest in Group C followed by Group B and Group A. Furthermore, on statistical analysis, Group A showed significantly low mean Schirmer's test-I values than Group B and Group C but there was no significant difference between Group B and Group C. Similar pattern was repeated at day-30 but at day-90, Group B had more mean Schirmer's Test-I values than Group C. However, it remained still nonsignificant in similar fashion as on day-15 and day-30 [Table 3]. Comparison in mean Schirmer's test-I values during the study with before treatment values revealed that in Group A, significantly higher mean Schirmer's test-I value was found at day-90 as compared to before treatment value but it remained nonsignificantly higher at day-15 and at day-30. In Group B, mean Schirmer's test-I value was significantly higher at day-15, day-30, and day-90 as compared to before treatment value. In Group C, significantly higher values of mean Schirmer's test-I were obtained at day-30 and day-90 but not at day-15 as compared to before treatment value.

All three groups were alike with respect to mean OSDI score at every point of time during the study (*P* > 0.05) [Table 4]. Mean OSDI score decreased significantly from day-15 and remained significantly lower at day-30 and day-90 also as compared to before treatment score in all three groups (Group A, Group B, and Group C).

Before treatment mean serum vitamin D level was statistically alike in all three groups (*P* = 0.258) but at 3 months in Group B and Group C, mean serum vitamin D level was significantly higher than Group A (*P* < 0.05) [Table 5]. No side effects were observed in any of the patient on vitamin D supplementation by buccal spray.

Table 1: Demographics of study population

Demographic characteristics	Value
Total no.* of patients	90
Total no.* of male	38
Total no.* of female	52
Mean±SD[†] age in years	44.87±14.77
The minimum age in years	20
Maximum age in years	80

no.*: Number, SD[†]: Standard deviation

Table 2: Comparison of groups w.r.t.* mean TBUT[†] (secs[‡]) at a different time interval

	Group	Mean±SD[§]	P[‡‡]	Significant from[#]
TBUT (seconds)				
Before t/t	A[¶]	4.52±2.61	0.494	
	B**	4.03±2.47		
	C[††]	4.10±2.22		
Day 15	A	4.57±2.37	0.819	
	B	4.85±2.75		
	C	4.75±2.23		
Day 30	A	4.65±2.57	0.090	
	B	5.62±3.13		
	C	5.60±2.51		
Day 90	A	4.95±2.75	<0.001	B.C
	B	7.22±3.71		A
	C	7.32±3.33		A

[‡‡]One way ANOVA[#] Tukey HSD test. w.r.t.*: with respect to. TBUT[†]: Tear breakup time. secs[‡]: seconds. SD[§]: standard deviation. t/t2: treatment. Group A[¶]: 0.5% carboxymethylcellulose. Group B**: 0.5% carboxymethylcellulose + 2000 IU vitamin D by buccal spray. Group C[††]: 0.5% carboxymethylcellulose + 2000 IU vitamin D by buccal spray +0.05% cyclosporine

Discussion

Dry eye is a multifactorial disease that has varied presentation and only clinical diagnosis is inadequate in most cases. A major difficulty in assessing DED is that there is no gold standard test.[14] Various questionnaires are often used in epidemiologic research studies to assess dry eye. In the current study, we used the OSDI questionnaire as it can reliably assess the severity, natural history, and effects of dry eye and has a sensitivity of 60% and specificity of 79%.[15] In addition to the OSDI questionnaire (for subjective assessment of symptoms), objective tests i.e. TBUT and Schirmer's-I test were also incorporated to evaluate and diagnose DED in the current study.

The present study was done on 90 patients, distributed in three groups, namely, Group A (30), Group B (30), and Group C (30). In our study, maximum participants i.e. 50% were in the age group 31–50 years in Group A, 46.67% in Group B, and 46.66% in Group C. Out of these participants, 26.67% in Group A, 20% in Group B, and 33.33% in Group C were in the age group of 31–40 years. These findings were consistent with the study of Banik *et al.*,[16] who reported an age group peak of 31–40 years (11%) after >70 years (11.4%) age group in the prevalence of dry eye. According to Sahai and Malik,[17] this peak reflects a

Table 3: Comparison of groups w.r.t.* mean Schirmer's-I value (mm[†]) at a different time interval

	Group	Mean±SD[‡]	P[††]	Significant from[‡‡]
SCHIRMER'S TEST -I (mm)				
Before t/t[§]	A2	5.88±3.97	0.054	
	B[¶]	7.62±4.65		
	C**	7.15±3.44		
Day 15	A	5.87±3.33	0.001	B, C
	B	7.83±3.92		A
	C	8.20±3.81		A
Day 30	A	6.17±3.61	<0.001	B.C
	B	8.85±4.17		A
	C	9.28±3.97		A
Day 90	A	6.63±4.00	<0.001	B.C
	B	11.07±4.70		A
	C	10.78±4.70		A

[††]One way ANOVA[‡‡] Tukey HSD test. w.r.t.*-with respect to. mm[†]-millimetre. SD[‡]-standard deviation. t/t[§]- treatment `. Group A2-0.5% carboxymethylcellulose. Group B[¶] - 0.5% carboxymethylcellulose + 2000 IU vitamin D by buccal spray. Group C**- 0.5% carboxymethylcellulose + 2000 IU vitamin D by buccal spray +0.05% cyclosporine

Table 4: Comparison of groups w.r.t.* mean OSDI[†] score at a different time interval

	Group	Mean±SD[‡]	P[††]
OSDI Score			
Before t/t[§]	A2	26.62±9.70	0.074
	B[¶]	31.39±8.31	
	C**	31.03±8.54	
Day 15	A	26.18±9.62	0.583
	B	28.31±7.81	
	C	28.04±8.31	
Day 30	A	25.75±9.76	0.997
	B	25.63±8.44	
	C	25.82±9.03	
Day 90	A	25.68±9.85	0.541
	B	23.41±9.46	
	C	23.10±10.09	

[††]One way ANOVA. w.r.t.* -with respect to. OSDI[†]-Ocular Surface Disease Index. SD[‡] -standard deviation. t/t[§]- treatment. Group A2-0.5% carboxymethylcellulose. Group B[¶] - 0.5% carboxymethylcellulose + 2000 IU vitamin D by buccal spray. Group C**- 0.5% carboxymethylcellulose + 2000 IU vitamin D by buccal spray +0.05% cyclosporine

dry eye state induced by environmental exposure to which this age group is being considered the most active occupationally and exceptionally prone. The age group 31–40 years showed a relative peak in dry eye prevalence (20%) in their study.

Moreover, it was found that dry eye was more common in females (63.33% participants in Group A, 43.33% in Group B, and 66.67% in Group C were females). This is in accordance with TFOS DEWS II report[18] which also states that dry eye is more common in females. As per the TFOS DEWS II report, female sex is a significant risk factor for the development of DED. Banik *et al.*[16] also reported a higher prevalence of dry eye in

Table 5: Comparison of groups w.r.t.* mean serum vitamin D levels (ng/mL†) at a different time interval

Vit.-D‡ (ng/mL)	Group	Mean±SD§	P‡‡	Significant from#
Before t/t2	A¶	14.84±3.50	0.258	
	B**	13.13±4.63		
	C††	14.57±4.64		
At 3 months	A	15.03±3.65	<0.001	B.C
	B	23.61±5.23		A
	C	26.06±5.93		A

‡‡One way ANOVA# Tukey HSD test. w.r.t.*-with respect to. ng/ml† -nanograms/milliliter. Vit.-D‡ -vitamin D. SD§-standard deviation. t/t2- treatment. Group A¶ -0.5% carboxymethylcellulose. Group B** -0.5% carboxymethylcellulose + 2000 IU vitamin D by buccal spray. Group C†† -0.5% carboxymethylcellulose + 2000 IU vitamin D by buccal spray +0.05% cyclosporine

females (31.2%) than in males (20.8%). Similar to these findings, females (22.8%) had a significantly higher prevalence than males (14.9%) as observed in the study of Sahai and Malik.[17] A study by Moss et al.[19] also revealed more prevalence of dry eye in females (16.7%) as compared to males (11.4%). Our study was no exception to this fact that dry eye is more prevalent in females as we had 52 females (57.8%) and 38 males (42.2%) in our study. These differences in sex distribution have been attributed to the effects of sex steroids (e.g., androgens and estrogens), hypothalamic-pituitary hormones, glucocorticoids, insulin, insulin-like growth factor-1, and thyroid hormones.

DED is a frequent pathology in daily clinical practice, and most therapeutic approaches essentially have in common the utilization of tear substitutes.[20-22] Bruix et al.[23] observed a significant ($P < 0.05$) decrease in the frequency of subjective symptoms and a significant ($P < 0.05$) improvement of tear film interface stability after CMC treatment in the mild and moderate dry eye at 3 months. Similarly, in our study, in Group A (0.5% CMC) statistically significant and higher Schirmer's test-I and TBUT values were found at day-90 as compared to before treatment value. OSDI score was also found to be significantly lower at day-90 as compared to before treatment score in Group A.

There are several studies showing an association between dry eye and vitamin-D deficiency. In this study, we examined the effect of vitamin-D supplementation on DED in patients with a vitamin-D deficiency in a total of 60 patients (30 in Group B and 30 in Group C). In addition, we studied the role of topical cyclosporine 0.05% drops in the improvement of symptoms and signs of dry eye in 30 vitamin D deficient patients (Group C). Role of topical cyclosporine in vitamin D deficient patients with the dry eye was evaluated by intergroup comparison of Group B and Group C. Vitamin-D status of patients was evaluated using serum 25(OH)D concentration. The concentration of 25(OH)D in the blood is regarded to be the best indicator of vitamin-D status and it reflects the supply of vitamin-D from both the diet and from cutaneous synthesis under the influence of solar ultraviolet light.[24]

In a cross-sectional data analysis done by Yoon et al.,[25] it was found that mean serum 25(OH)D levels of subjects with and without dry eye syndrome (DES) were 16.90 ± 6.0 ng/mL and 17.52 ± 6.07 ng/mL ($P < 0.001$). Inadequate sunlight exposure time and low serum 25(OH)D level were found to be the main risk factors for DES. These results suggest that sufficient sunlight exposure or vitamin-D supplementation may be useful in DES treatment. Similar results were obtained in our study. The patients with dry eye had a vitamin-D deficiency and they showed significant improvement in dry eye parameters after vitamin-D supplementation. Initially, the patients who had dry eye were screened for vitamin D deficiency. The patients who had dry eye and serologically confirmed vitamin D deficiency were included in the study and were supplemented with vitamin D. On follow-up, Schirmer's and TBUT significantly improved in both the groups in which vitamin D supplementation was done (Group B and Group C as compared to Group A). OSDI scores significantly decreased in all three groups from day-15 onwards. However, between-group comparison revealed a nonsignificant difference in the improvement of OSDI scores. Moreover, there was an early improvement in dry eye parameters (Schirmer's test I and TBUT) when vitamin D supplementation was done, thereby showing that vitamin D supplementation helps in improvement of dry eye symptoms and signs.

A similar study to ours was done by Bae et al.[26] using 2,00,000 IU cholecalciferol intramuscular (i.m.) injection single stat dose. OSDI 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 ($P < 0.001$, $P < 0.001$, $P = 0.066$). Schirmer's increased at 2 and 6 weeks significantly but at 10 weeks there was no significant increase ($P = 0.006$, $P = 0.015$, $P = 0.140$, respectively). In our study, after treatment of patients with vitamin-D buccal spray, there was significant improvement in Schirmer's test-I values at all follow-up visits as compared to patients not receiving any supplements i.e., Group B and Group C significantly higher as compared to Group A ($P = 0.001$, $P < 0.001$, $P < 0.001$ at day-15, day-30, and day-90, respectively). Significantly higher values of TBUT were obtained in Group B and Group C as compared to Group A at day-90 ($P < 0.001$) only. OSDI scores of patients significantly decreased, thereby showing the improvement of dry eye symptoms in all three groups at all follow-up visits. However, between-group comparison failed to show any significant difference in the improvement of OSDI scores.

Kizilgul et al.[27] investigated the effect of vitamin D replacement on tear osmolarity in patients with vitamin D deficiency on 44 patients. Patients were given 50,000 units of 25(OH)D3 i.m., once weekly, over a period of 8 weeks. The change of tear film osmolarity (TFO) was negatively correlated with the variation of 25(OH)D3 before and after replacement in patients with DED (r = -0.390, $P = 0.049$) and they concluded that as a consequence of the presence of vitamin D receptor (VDR) and 1α-hydroxylase in different parts of the eye, vitamin D replacement improves tear hyperosmolarity that is considered to be induced by ocular surface inflammation. Improvement in tear osmolarity which is the main cause of discomfort in dry eye patients can lead to improvement of dry eye parameters. These results are consistent with our study results, as on vitamin D supplementation the patients reported improvement of all dry eye parameters. The response obtained was early and the magnitude of the response was significantly higher when vitamin D supplementation was done (Group B and Group C significantly better than Group A).

Vitamin-D supplementation promoted tear secretion, reduced tear instability, and improved the symptoms of DED. Hence, evaluation of serum vitamin-D levels in patients with dry-eye symptoms is important and should not be disregarded in their clinical follow-up.

In our study, we also tried to evaluate the effect of additional cyclosporine topical eye drops in combination with vitamin D supplementation i.e. Group C, as various studies in the past have reported positive effects of cyclosporine drops in DED. Though till date no study has been done to see the effect of topical cyclosporine in vitamin D deficient DED but many studies have reported improvement of dry eye parameters on the use of cyclosporine drops.

Egorova *et al.*[28] concluded that topical use of cyclosporine emulsion 0.05% has a positive effect on morphofunctional parameters of the ocular surface and promotes basal tear secretion and precorneal tear film stability. The prognosis of dry eye in patients treated with cyclosporine 0.05% or artificial tears by using the ITF guidelines was assessed by Rao[29] who concluded that treatment with cyclosporine 0.05% may slow or prevent disease progression in patients with a dry eye at severity levels 2 or 3. Perry *et al.*[30] in their recently published study found that while topical cyclosporine is beneficial for all levels of dry eye, symptomatic improvement was greatest in patients with mild dry eye. It has been reported by Al-Nashar,[31] that topical cyclosporine 0.05% is effective in the treatment of DES which has an inflammatory cause.

In the present study, we tried to evaluate the role of topical cyclosporine drops in the management of dry eye in vitamin D deficient patients. We found that in Group C patients received both systemic and topical anti-inflammatory drugs in the form of vitamin D supplementation and topical cyclosporine drops respectively and they showed early improvement and magnitude of response was better as compared to patients who received vitamin D alone (Group B). However, the difference between the two was not statistically significant. Hence, in our study, we concluded that topical cyclosporine 0.05% drops had no added benefit in vitamin D deficient DED.

Since this is a pioneer study that evaluated the role of topical cyclosporine in vitamin D deficient dry eye, the results could not be compared and discussed with literature.

Conclusion

Vitamin D levels play an important role in patients with dry eye. We recommend that every dry eye patient should be screened for the vitamin-D deficiency by serological evaluation of 25(OH)D levels. Furthermore, supplementation of vitamin D in such patients can lead to earlier and significant improvement in dry eye parameters (Schirmer's Test-I, TBUT, and OSDI score). As popularly used, CMC drops can improve dry eye symptoms and signs after 3 months of use in vitamin D deficient dry eye patients but the effective improvement with CMC alone is significantly lesser when compared to a combination of vitamin D supplements + CMC in such patients. Topical cyclosporine drops are also indicated for treatment DED because of their anti-inflammatory effect. However, the addition of cyclosporine drops to vitamin D supplements + CMC regimen did not show any significant added effect in vitamin D deficient DED. Furthermore, this study proves that vitamin D supplementation by buccal spray is a safe and efficacious treatment modality of vitamin D deficiency-related dry eye conditions and it may be an alternate method of supplementation to the more invasive i.m. route.

Conflicts of interest

There are no conflicts of interest.

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