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Original Article

Impact of vitamin D supplementation on the ocular surface in patients with vitamin d deficiency

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Abstract

Aim: The aim of this study was to determine the effect of vitamin D (vit D) supplementation on the ocular surface parameters in patients with vit D deficiency.

Material and Methods: In total, 63 patients with serum vit D deficiency were included. Patients were treated with an oral dose of 300.000 IU cholecalciferol. The ocular surface disease index (OSDI) questionnaire, fluorescein tears breakup time (FBUT), Oxford score, and Schirmer's 1 test were performed for all patients. The data was obtained initially and at 4, 8, and 12 weeks after vit D supplementation.

Results: Forty-nine of the patients were female and 14 were male. The mean age was 30.8±9.7 (18–58) years. All 63 patients came to the first follow-up, 57 patients came to the second follow-up, and 48 patients came to the third follow-up. The OSDI and Oxford scores yielded statistically significant decreases, while Schirmer's 1 test and FBUT values showed a statistically significant increase after treatment with vit D. A positive correlation was observed between vit D values and FBUT and Schirmer's 1 values; there was a negative correlation between OSDI values ($r=0.286$ and $p<0.001$, $r=0.219$ and $p=0.032$, $r = -0.357$ and $p<0.001$, respectively). The dry eye findings improved significantly after vit D supplementation in all cases.

Conclusion: During clinical follow-up, it is important to evaluate serum vit D levels in patients with dry eye syndrome (DES). Increasing their vit D levels will help clinicians to treat DES quickly and effectively.

Keywords: Dry eye syndrome; schirmer's 1 test; vitamin D deficiency

INTRODUCTION

Dry eye syndrome (DES) is the most common chronic ocular surface disease worldwide. Epidemiologic studies have identified prevalence rates ranging from 7–33% (1). Genetic and environmental factors play an important role in DES (2). Patients with DES suffer from ocular inconveniences such as red eye, irritation, blurred and fluctuating vision, and foreign body sensation in the eyes (3). There are two main types of DES: aqueous tear deficiency and evaporative. In the first one, tear hyperosmolarity occurs when lacrimal secretion decreases under normal evaporation conditions. In the second type, tear hyperosmolarity is caused by excessive evaporation from the tear film exposed in the existence of an ordinarily functioning lacrimal gland (4). There are many risk factors for DES, such as age, certain medications, smoking, reproductive status, use of contact lenses, prolonged screen time, ophthalmic surgeries, environmental factors, and certain systemic diseases such as diabetes, rheumatoid arthritis, scleroderma, and Sjogren's syndrome (4). The inflammatory process has an increasingly recognized importance in DES; this is evidenced by increased levels of inflammatory cytokines such as tumor necrosis factor α (TNFα) and interleukin 1 (IL-1) in the corneal and conjunctival epithelia and tear fluid, and infiltration of CD4+ T-cells into the conjunctival tissue (5,6). In addition, inflammatory cytokines such as IL-2, IL-5, IL-6, IL-8, IL-10, and IFN-ɣ levels have been shown to be increased in DES patients (7). Therefore, anti-inflammatory drugs have an important role in DES treatment and target one or more of the inflammatory mediators/pathways (8).

Vitamin D (vit D) is a fat-soluble vitamin that has an important role in various physiological and immunomodulatory processes in all tissues; therefore, researchers have recently come to call vit D a "prohormone" (9,10). As the role of vit D in the human body has become more understood, vit D supplementation has become part of treatments for many chronic and systemic diseases

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and cancers (11,12). The relationship between vit D and some eye diseases such as uveitis, age-related macular degeneration, and DES, has been investigated in many studies (13-16). A recent study have shown a possible role that vit D could play in healing corneal wounds (17). Vit D also plays an important role in autoimmunity, which is closely related to DES (18,19). This study investigates a possible relationship between DES and vit D deficiency and to determine whether vit D supplementation is effective in relieving DES via ocular surface changes.

MATERIAL and METHODS

This clinical study was undertaken between September 2018 and December 2019 at the Department of Ophthalmology and Internal Medicine Clinic at the Diyarbakir Gazi Yasargil Training and Research Hospital. This study received ethics committee confirmation from the aforementioned hospital, and the study adhered to the principles of the Declaration of Helsinki. Informed consent received from all participants.

Based on the exclusion criteria, 63 of 159 patients who were admitted to the Internal Medicine Outpatient Clinic with weakness, fatigue, and body pain and whose vit D level was lower than 20 ng/ml were included. Patients with vit D deficiency were identified at Internal Medicine Outpatient Clinic by measuring serum 25-hydroxy D (25-OHD) level. Individuals with vit D level < 20 ng/ml were referred to the ophthalmology department for the evaluation of ocular surface diseases. Patients were excluded from the study if they had autoimmune diseases such as lupus, scleroderma, or Sjogren's syndrome; used contact lens; had any corneal diseases such as infections, opacity or epithelium defects; or had a history of corneal surgery, including penetrating keratoplasty or refractive surgery. Those using artificial eye drops or other ophthalmic drugs in the last 6 months for eyelid margin inflammation, DES, or other ophthalmic disorders were also excluded from this study. Patients with vit D deficiency were treated with an oral dose of 300.000 IU cholecalciferol (Devit-3 ampoule®, IM/Oral, Deva, Turkey) two times at two-week intervals. Serum vit D levels were measured at each visit. Oral maintenance dose (Devit-3®, 50.000 IU/15ml, Oral, Deva, Turkey) treatment was continued in patients with vit D levels above 20 ng/ml. Data were obtained at baseline and at 4, 8, and 12 weeks after vit D supplementation. Patients with vit D levels below 20 ng/ml during follow-up were excluded from the study. Patients did not use any other medicines (oral/topical) to treat DES during this time.

Only the right eyes of all of the patients were evaluated to determine the relationship between ocular surface changes and vit D deficiency. Schirmer's 1 tests and FBUT tests were carried out for all patients following a full ophthalmologic examination. Schirmer's 1 tests without topical anesthesia were performed to evaluate patients' tear secretion. For 5 minutes, filter papers (Color Bar, Eagle Vision Inc., Memphis, TN) were placed in the lateral canthus. Readings were reported as millimeters of wetting (<5 mm: severe DES, 5–10 mm: slightly DES, >10 mm: normal). Patients' tear breakup time was then measured after fluorescein staining. Fluorescein was located in the lower conjunctival sac using a fluorescein strip (Haag-Streit, Köniz, Switzerland). Patients were instructed to blink, and the tear film was then examined using the cobalt blue filter of a slit lamp biomicroscope. An average of three measurements was recorded. A tear breakup time of <10 seconds was considered as abnormal (19). Corneal staining was also carried out using the Oxford rating system (Grade 0 = no corneal staining, Grade 1 = minimal staining, Grade 2 = mild staining, Grade 3 = moderate staining, Grade 4 = marked staining, and Grade 5 = severe staining) (20). Symptoms were assessed using the ocular surface disease index (OSDI) questionnaire (Allergan, Irvine, CA, USA; 12). The OSDI is composed of 12 questions about symptoms experienced within the past week; it yields scores ranging from 0 (least severe) to 100 (most severe). Total OSDI score was assessed as a total score × 25/total number of questions answered. The overall OSDI score defined the ocular surface as normal (0-12 points) or as having mild (13-22 points), moderate (23-32 points), or severe (33-100 points) disease (21,22).

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 21.0 (SPSS Inc., USA). Normality was checked using the Shapiro–Wilk test. Numerical values were defined as mean ± standard deviation and categorical variables as a percentage. A paired sample test was used to compare data before and after treatment. The relationship between the variables was evaluated using Pearson's correlation test. Finally, $p < 0.05$ was considered to be statistically significant.

RESULTS

One hundred fifty-nine patients whose vit D level was lower than 20 ng/ml were evaluated for ophthalmic examination. DES were detected in 72 (45.3%) patients. Based on the inclusion criteria, 63 patients were included in the study: 49 were female, 14 were male. The mean age was 30.8 ± 9.7 (18–58) years. All 63 patients attended their first measurements, 57 patients came to the second follow-up, and 48 patients came to the third follow-up. At baseline, the mean vit D level was 11.3 ± 4.1 (3.0–19.3) ng/ml. OSDI score was 40.6 ± 8.0 at pre-treatment, 37.0 ± 7.7 after 4 weeks, 32.5 ± 8.8 after 8 weeks, and 28.3 ± 7.3 after 12 weeks ($p<0.001$, all visits). Tear secretion measured by Schirmer's 1 test was 16.6 ± 6.6 mm at pre-treatment, 17.3 ± 6.1 mm after 4 weeks, 18.2 ± 5.7 mm after 8 weeks, and 17.9 ± 4.9 mm after 12 weeks ($p = 0.125$, $p = 0.004$, and $p = 0.011$, respectively). FBUT was 5.1 ± 3.2 s at pre-treatment, 5.9 ± 3.0 s after 4 weeks, 7.5 ± 2.6 s after 8 weeks, and 8.1 ± 2.8 s after 12 weeks ($p = 0.009$, $p <0.001$, and $p <0.001$, respectively). All the measures showed a statistically significant improvement after treatment with vit D at each following visit, as shown in Table 1.

Table 1. The effect of vitamin D supplementation on ocular surface parameters

	Pre-treatment (n = 63)	Post-treatment 4 weeks (n = 63)	p*	Pre-treatment (n = 57)	Post-treatment 8 weeks (n = 57)	p*	Pre-treatment (n =48)	Post-treatment 12 weeks (n = 48)	p*
OSDI score	40.6 ± 8.0	37.0 ± 7.7	**<0.001**	40.7 ± 7.9	32.5 ± 8.8	**<0.001**	40.7±8.1	28.3 ± 7.3	**<0.001**
Schirmer's 1 test (mm)	16.6 ±6.6	17.3 ± 6.1	0.125	16.5 ± 6.8	18.2 ± 5.7	**0.004**	16.5±6.8	17.9 ± 4.9	**0.011**
FBUT (sec)	5.1 ± 3.2	5.9 ± 3.0	**0.009**	5.2 ± 3.2	7.5 ± 2.6	**<0.001**	5.2 ± 3.4	8.1 ± 2.8	**<0.001**

OSDI: Ocular surface disease index, FBUT: fluorescein tear breakup time * Paired sample test

Table 2. Oxford values before and after vitamin D supplementation

	Absent (0)	Minimal (1)	Mild (2)	Moderate (3)	Marked (4)	Severe (5)
Pre-treatment (n = 63)	14 (22%)	37 (59%)	12 (19%)	-	-	-
4 weeks (n = 63)	36 (57%)	26 (41%)	1 (2%)	-	-	-
8 weeks (n = 57)	45 (79%)	12 (21%)	-	-	-	-
12 weeks (n = 48)	45 (94%)	3 (6%)	-	-	-	-

Results are denoted as 'number (percent)' of subjects

There was a positive correlation between vit D values and FBUT and Schirmer's 1 values; there was a negative correlation between OSDI values ($r = 0.286$ and $p < 0.001$, $r = 0.219$ and $p = 0.032$, and $r = -0.357$ and $p < 0.001$, respectively). At baseline, corneal staining was absent in 14 (22%) patients, whereas 37 (59%) patients had minimal staining, and 12 (19%) patients had mild staining. None of the patients had moderate, marked, or severe corneal staining. There was a decrease in corneal staining after vit D supplementation (Table 2).

DISCUSSION

DES is among the most frequently established diagnoses in an ophthalmology practice. Despite the increasing understanding of the pathogenic factors involved in DES, the etiology remains unclear (2-4). Vit D deficiency is common in the world, especially among pregnant women. Low Ultraviolet B ambient level causes this risk to occur more frequently (23). Vit D plays an important role in various physiological and immunomodulatory processes in all tissues (9,10). The immunomodulatory effect of vit D has been shown in many studies (24-26). In addition, research suggests that vit D is a significant factor connecting natural and adaptive immunity—the two of these functions may be compromised under conditions of vit D deficiency (27).

Due to the role of vit D in inflammatory processes, which are also involved in DES, there has been expanding attention in the relationship between vit D deficiency and DES in recent years. This study investigated the effects of vit D supplementation on DES in patients with vit D deficiency experiencing DES via ocular surface changes.

The relationship between the deficiency of vit D level and DES has been reported in some studies, with lower vit D levels in DES patients. When the 25(OH)D levels were stratified in these studies, vit D deficiency was found to be more common in the DES cases (28,29). In contrast, Jee et al. reported no association between DES and vit D levels in their study, finding that vit D levels were similar in DES and non-DES groups (13).

Decreased tear secretion is an important agent in the improvement of DES, and Schirmer's 1 test is the most commonly used screening test to assess tear production (30). Vit D may regulate tear secretion in the lacrimal glands (31). Recent studies have shown that people with vit D deficiency had low Schirmer's 1 test scores, showing worse symptoms and indications of DES (32,33). Bae et al. reported that vit D supplement in patients with refractory to conventional treatment DES increased Schirmer's 1 test (34). This effect is attributed to the fact that supplementation increases tear secretion and reduces tear instability. The increase in Schirmer's 1 tests shows tear secretion increasing without the use of artificial eye drops, further showing an improvement in DES. Jin et al. reported that this may be related to decreased parasympathetic nerve function and inadequate functioning of lacrimal gland epithelial and myoepithelial cells as a result of vit D deficiency (31). In this study, after 4 weeks of vit D supplementation, the baseline means Schirmer's 1 test value increased, but this increase was not statistically significant. At 8 and 12 weeks, the Schirmer's 1 tests saw a statistically significant increase. In addition, a positive correlation has seen between vit D level and Schirmer's 1 values.

The OSDI score is a current and reliable questionnaire for determining ocular discomfort, vision-related dysfunction, and environmental triggers in DES and it can be easily used to diagnose DES in daily clinical practice (35). Yildirim et al. found low OSDI scores in the patients in their studies—further, vit D levels were negatively correlated with OSDI score (32). Yang et al. also found that there was a negative correlation between OSDI and vit D levels in older adults (36). In another study, no significant differences were found between patients in control and vit D deficiency groups in terms of changes in OSDI scores (33). However, vit D supplementation has been shown to decrease the severity of DES in patients complaining of moderate or severe ocular pain intensity (34). In the current study, OSDI scores were negatively correlated with vit D supplementation at each follow-up. The OSDI scores decreased from baseline levels to a degree that was statistically significant. In patients who received vit D supplementation, the decrease in the OSDI score indicated the amelioration of subjective complaints of DES.

The Oxford rating scheme was improved to measure the quantity of epithelial surface damage in DES patients. This is helpful both in the first diagnostic of DES, as well as in observing ocular surface disease over time (37). The decrease in the Oxford grading of corneal staining after vit D supplementation may refer that increased vit D levels resulted in an improvement in tear quality and/or the health of the epithelial cells (38). Improvement in corneal staining is an indicator of improved DES. In this study, the following treatment corneal staining was improved. There was no moderate, marked or severe staining during the study. Therefore, patients with low vit D levels who received supplementation healed (as measured by corneal staining). In addition, there was a negative correlation between Oxford scores and vit D level in this study after vit D supplementation; these changes were statistically significant.

The FBUT test is a useful screening test for DES. Measurement of tear film stability using fluorescein is useful for diagnosing DES and follow-up of its treatment (39). Research has shown that people with vit D deficiency have low FBUT scores (32,33). Kurtul et al. suggested that vit D deficiency may be related to DES because of its association with lower FBUT values and higher corneal staining scores (33). Yildirim et al. reported that vit D levels positively correlated with FBUT scores (32). Yang et al. reported no association between FBUT and vit D levels (36). In this study, FBUT scores were positively correlated with vit D supplementation at each follow-up.

This study had some limitations. The primary limitation is the relative lack of cases. In fact, a total of 159 patients were analyzed, but only 63 of these met the inclusion criteria. In addition, a 12-week follow-up was not performed for all patients because not all of the patients attended their outpatient clinic appointments. The patients did not report any adverse events as the reason for not being able to visit the outpatient clinic during phone calls. The second limitation is the short follow-up period. Longer treatment duration is needed in future studies. Third, only some DES parameters used in this study, and other parameters such as tear cytokine level and impression cytology should be analyzed after vit D supplementation. Knowing how cytological changes occur under the microscopic observation of the ocular surface after vit D supplementation will allow us to better understand the effects of vit D. Fourth, it is well known that seasonal changes affect the baseline levels of vit D (40). In winter and autumn, vit D levels are expected to be low, affecting DES. This research lasted for more than one year, and the season of the data collection period was also not taken into account in this study.

CONCLUSION

In conclusion, in patients with low vit D, vit D supplementation may improve ocular surface discomfort and reduce the use of topical medication, thus decreasing the cost of DES treatment. Both vit D deficiency and DES are common; therefore, clinicians should confirm if the DES patients have vit D deficiency in order to provide proper and cost-effective care. The evaluation of serum vit D levels in patients with DES is important in their clinical follow-up and will help practitioners to treat DES quickly and effectively. Researchers should be aware of refractory DES that persists despite the use of artificial eye drops, considering the possibility that these patients may have vit D deficiency. The lower cost of vit D supplementation, as opposed to artificial eye drops, is another important point. If patients with vit D deficiency report improvements in DES when treated with supplementation of vit D, this will ultimately decrease the cost of treating DES.

Competing interests: The authors declare that they have no competing interest.

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