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The relationship between dry eye syndrome and serum fat-soluble vitamin levels

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ABSTRACT

Introduction and aim. Dry eye syndrome (DES) is a multifactorial ocular surface disease in which nutritional deficiencies, including fat-soluble vitamins, may play a role. This study aimed to investigate the relationship between serum levels of vitamins A, D, E, and K and DES.

Material and methods. A total of 70 eyes from 35 patients with DES and 70 eyes from 35 healthy controls were examined. Dry eye evaluation included tear osmolarity (TO), tear break-up time (TBUT), Schirmer I test, and the Ocular Surface Disease Index (OSDI). Serum vitamin levels (A, D, E, K) were measured using HPLC, LC-MS/MS, and chemiluminescence immunoassay.

Results. Patients with DES had significantly higher TO (312.7±4.9 vs. 295.2±6.5 mOsm/L, $p<0.001$) and OSDI scores (39.8±19.4 vs. 17.2±11.0, $p<0.001$), and significantly lower Schirmer I (7.0±1.8 vs. 17.3±1.3 mm, $p<0.001$) and TBUT values (7.3±0.8 vs. 16.1±0.7 s, $p<0.001$) compared with controls. Serum vitamin A (331.8±87.2 vs. 523.6±109.1 ng/mL, $p<0.001$) and vitamin D (14.8±6.9 vs. 34.6±14.9 ng/mL, $p<0.001$) levels were significantly lower in DES patients, whereas vitamin E and K did not differ between groups.

Conclusion. Deficiencies in vitamins A and D are associated with impaired tear film parameters and symptoms of DES. These findings suggest that assessing and correcting vitamin A and D deficiency may have clinical relevance in managing DES.

Keywords. dry eye, tear osmolarity, fat-soluble vitamin

Introduction

Hyperosmolarity, resulting from an increase in the concentration of particles in tears, contributes to the development of dry eye disease by causing tissue damage and inflammation of the ocular surface. Dry eye syndrome (DES) is a common and complex multifactorial condition that can lead to irritation, damage to the ocular surface, vision loss, and a decline in overall quality of life.[1,2]

The global prevalence of DES ranges from 5% to 87.5%.[3] Reduced tear production and volume, increased tear evaporation, and significant changes in the lacrimal glands, including histological, functional, and structural changes, define this condition. Atrophy of the meibomian glands and metaplasia of the ocular surface are observed. These factors contribute to local ocular changes that precede the onset of DES.[3]

Numerous studies have indicated that vitamin D plays a crucial role in tear production and cell differentiation, and that DES can develop as a result of vitamin D deficiency.[4-6] A recent study has shown that megalin and cubilin, components of tear fluid that transport vitamin D, are produced by the lacrimal and accessory glands.[7] Several other eye disorders, including age-related macular degeneration, diabetic retinopathy, myopia, and uveitis, as well as systemic conditions such as cardiovascular diseases and connective tissue disorders, are influenced by vitamin D levels.[8-13] Other fat-soluble vitamins, such as vitamins A, E, and K, also have various effects on human metabolism.[14] For example, vitamin A is essential for growth, reproduction, gene transcription, bone metabolism, and immune health, and it is important for both photopic and scotopic vision. Its deficiency, particularly in malnourished children, is associated with eye diseases such as corneal ulceration and keratomalacia.[15,16] Alpha-tocopherol, one of the eight isoforms of vitamin E, is among nature's most potent fat-soluble antioxidants, and its deficiency may contribute to the development of several autoimmune diseases.[17,18]

Additionally, vitamin K plays a crucial role in regulating bone and cartilage mineralization.[19,20]

While several studies have linked vitamin D deficiency with DES, only a few have simultaneously investigated other fat-soluble vitamins. Our study, therefore, provides a broader perspective by assessing vitamins A, D, E, and K together in relation to DES.

Aim

This study aims to determine the relationship between fat-soluble vitamin levels and dry eye syndrome and, in the presence of a relationship, to support the development of new treatment methods for DES with vitamin replacement.

Material and methods

Seventy eyes of 35 patients with DES (group 1) and 70 eyes of 35 healthy volunteers without symptoms of DES and without ocular or systemic conditions that could affect the tear film (group 2) were included in this study. The study was approved to the Institutional Ethics Committee (approval no: 2016-493), by the principles of the Declaration of Helsinki, and written informed consent was obtained from all patients.

Patients with a history of primary Sjögren's syndrome (pSS) or another systemic rheumatic disease, previous ocular surgery, current or recent systemic or topical drug use that may affect the lacrimal functional unit, active ocular infection, ocular allergy, current contact lens wear, and chronic tobacco or alcohol use were excluded. Visual acuity, slit-lamp, and fundus examinations were all performed on each patient. Tear osmolarity, Schirmer test, and tear break-up time (TBUT) were performed in sequence. Each subject was tested by the same ophthalmologist at the same time of day under the same fixed conditions, including the temperature and humidity. Five-minute (min) interval was determined between each measurement of the ocular surface. Three consecutive measurements were obtained for each test, and the mean values were used in the analysis. The mean data of both eyes for each patient were evaluated separately, and because the results between the two eyes were very similar, the results of the right eye were used for evaluation. Initially, all participants completed the ocular surface disease index (OSDI) survey. [21] Tear osmolarity measurements were evaluated using a TearLab osmometer (TearLab Corp., San Diego, CA). Tears were collected from the inferior lateral tear meniscus; 3 sequential measurements were made, and their average was used in the evaluation.[22] Tear osmolarity values ≤308 mOsm/L are within the expected physiological range, whereas values >308 mOsm/L indicate tear film instability.

As previously mentioned, the Schirmer I test was performed without topical anesthesia using a 5×35 mm filter strip (Schirmer Plus; GECIS, Czech Republic). The paper was removed from the eye after a 5-minute interval, and the length of the wet portion was measured using the millimeter lines on the paper as reference points. A Schirmer test value of less than 10 mm per 5 minutes was regarded as abnormal.

As previously mentioned, tear breakup time was assessed by examining the fluorescein-stained tear film (Pricon, Iscon, India) using cobalt blue light under a slit lamp and measuring the time between blinking and the appearance of the first dry spot. TBUT values less than 10 seconds were considered abnormal. Fluorescein was used only for the TBUT test.

The OSDI is a 12-item disease-specific questionnaire developed by Schiffmann et al. that allows the evaluation of symptoms related to ocular irritation as well as quality of life (QoL).[21] There are three subgroups in the scale: five items assess ocular discomfort, four assess visual functions, and three assess environmental triggers. Each item was scored 0 to 4. OSDI scores ranged from 0 to 100, with lower scores indicating a lower quality of life in terms of vision. A dry eye score greater than 15 was used to define dry eye.

After the eye examinations were completed, all participants were directed to the laboratory for plasma vitamin level assessment. Blood samples were collected from the antecubital vein between 08:00 and 11:30 in the morning after fasting overnight in Becton Dickinson's biochemistry tube with a gel separator. Serum was obtained by centrifuging the blood sample at 4000 g for 10 minutes after coagulation, as it was taken into the biochemistry tube. The serum was portioned into sample separation tubes and stored at –80°C until the study was conducted. The pre-study portioned serum sample was analyzed on the same day after

complete defrosting.

Vitamin K1 by LC-MS/MS method in Waters Corp. MS (USA), Vitamin A and Vitamin E by HPLC method in Shimadzu, SPD-M20A by HPLC analyzer (Japan), 25 dihydroxy vitamin D in Coulter UniCel DxI 800 (Germany) immunoassay analyzer using chemiluminescence method were analyzed.[23]

The deficiency was determined as <300 nanograms per milliliter(ng/mL) for vitamin A, <20 ng/mL for vitamin D, <5.5 micrograms per milliliter(μg/mL) for vitamin E, and, <1.1 ng/mL for vitamin K.[14]

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) software (version 20; SPSS Inc., Chicago, IL). The normality of the distribution of each parameter was checked using the non-parametric two-tailed Mann-Whitney U test. An independent study t-test was used to compare tear osmolarity, Schirmer I test, TBUT values, and OSDI scores between the groups. Statistical significance was set at $p<0.05$. This statistic was obtained using the sample size estimation software package, G*Power. Based on this calculation, the required sample size was 65 patients, considering tear osmolarity (TO), tear break-up time (TBUT), and Schirmer's test as the primary outcomes. The results obtained according to the statistical program were as follows: effect size d=0.60, α=0.05, power=0.80. The sample size was increased by 10% to account for potential dropouts. Consequently, 35 patients were required for each group.

Results

The mean age of the participants was 52.84±10.36 years (range: 38–70 years) in group 1 (19 women, 16 men) and 54.76±13.04 years (range: 33–67 years) in group 2 (17 women, 18 men). There were no significant differences in age or sex between the groups ($p_1=0.553$ and $p_2>0.999$, respectively). No differences were observed between the eyes for any of the parameters in the patients. All tear film parameters for the two groups are listed in Table 1. The mean tear osmolarity was 312.68±4.91 mOsm/L in group 1 and 295.2±6.51 mOsm/L in group 2. The OSDI scores were 39.82±19.36 and 17.19±10.97 in groups 1 and 2, respectively. The mean tear osmolarity and OSDI scores were significantly higher in group 1 than in group 2, while the Schirmer I test and TBUT measurements were substantially lower (p=0.001 for all). Vitamin A and D levels were significantly lower in group 1 than in group 2 (p=0.001), while vitamin E and K levels were similar in both groups (p>0.05) (Table 2). The vitamin A level was 331.84±87.22 ng/mL in group 1 and 523.6±109.08 ng/mL in group 2. The vitamin D level was 14.79±6.86 ng/mL in group 1 and 34.56±14.87 ng/mL in group 2. Group 1 patients exhibited statistically significant dry eye test results and significantly lower levels of vitamin A and D.

Table 1. The comparisons of the tear film parameters and OSDI scores between two groups (right eyes)

Parameter	*Group 1*	*Group 2*	*p*
Tear osmolarity (mOsm/L)	312.68±4.91 (290–320)	295.2±6.5 (272–306)	0.001
TBUT (sec)	7.3±0.8 (4–13)	16.1±0.7 (12–21)	0.001
Schirmer test (mm)	7.0±1.82 (4–14)	17.28±1.3 (13–22)	0.001
OSDI	34.82±19.36 (22–81)	17.19±14.97 (4–65)	0.001

Table 2. The comparison of the vitamin levels between two groups

Vitamin	*Group 1*	*Group 2*	*p*
A (ng/mL)	331.84±42.9 (208–733)	523.6±60.9 (309–701)	0.001
D (ng/mL)	14.79±6.86 (3–33.45)	34.56±14.87 (13.37–62.92)	0.001
E (µg/mL)	14.06±4.35 (7–24)	14.55±5.5 (6.7–34.2)	0.733
K (ng/mL)	1.32±0.51 (0.87–3.13)	1.40±0.46 (0.86–2.33)	0.584

Discussion

In this study, we investigated the relationship between the serum levels of fat-soluble vitamins and dry eye syndrome, which has not been previously studied.

There are human and animal studies in the literature showing the relationship between systemic diseases and vitamins A, D, and E.[12,23,24] In recent years, many studies have been conducted showing the factors associated with dry eye syndrome, and studies showing the connection between vitamin D deficiency and DES have also been intensively studied in the literature.[2-5,8,25-29] Some studies have shown that vitamin A deficiency can also cause DES and that DES is improved with oral omega-3 treatment.[30-32]

Numerous studies have discussed the role of vitamin D in tear secretion and the corneal epithelium. Lu et al. reported that the lacrimal and accessory glands are responsible for producing tear fluid, which contains megalin and cubilin proteins, that facilitate the transport of vitamin D.[6] Yin et al. found that corneal epithelial cells possess vitamin D receptors and 1-hydroxylase mRNA, as well as high concentrations of

vitamin D metabolites in both the aqueous and vitreous humor.[33] A meta-analysis conducted by Liu et al. revealed that patients with DES had lower serum vitamin D levels compared to healthy controls, suggesting that vitamin D deficiency may be a potential risk factor for DES.[25] According to this meta-analysis, vitamin D-deficient patients exhibited lower Schirmer test scores, which indicates reduced baseline and reflex tear production. This decrease in tear production may be attributed to vitamin D deficiency, which correlates with higher OSDI scores and reflects greater discomfort in affected individuals. However, TBUT scores, which assess the stability of the tear film, were similar between patients with vitamin D deficiency and the control groups. This indicates that vitamin D influences Schirmer test results and TBUT scores differently; vitamin D deficiency appears to be associated with significantly reduced tear production (as evidenced by lower Schirmer test scores) but does not seem to affect tear film stability (as indicated by comparable TBUT scores).

The novelty of our study lies in the simultaneous evaluation of all major fat-soluble vitamins in patients with DES, which extends beyond previous research primarily focused on vitamin D. In particular, our findings highlight that vitamin A deficiency, although less frequently studied, may also contribute to ocular surface impairment.

In the present study, the Schirmer test and TBUT values were significantly lower, TO was significantly higher, and serum vitamin D was significantly lower in the DES group. The fact that we only evaluated dry eye tests and did not perform an analysis at the receptor level may be considered a limitation of our study.

The role of vitamin D supplementation in treating patients with DES has been investigated since vitamin D deficiency has been shown to be a risk factor. One study demonstrated that vitamin D supplementation resulted in a significant decrease in TO,[2] while another study revealed a notable increase in TBUT and a reduction in OSDI scores.[28] Karaca et al. reported that Schirmer 1, TBUT, TO, and OSDI scores significantly improved at the end of an 8-week oral vitamin D supplementation treatment in patients with DES who had vitamin D deficiency.[34]

Szodoray et al. found that plasma levels of vitamin A and D in patients with primary Sjögren's syndrome (pSS) were comparable to those in the control group; however, vitamin E levels were significantly elevated. They observed that vitamin A levels were notably reduced in patients with pSS exhibiting extraglandular manifestations, suggesting a more systemic and severe disease course. This observation led them to hypothesize that decreased vitamin A levels, along with immunomodulatory activity, may play a critical role in the progression of the disease, particularly in cases with a generalized and more pronounced course of the disease.[24]

Alanazi et al. reported that in their study, they administered 1500 mg of oral vitamin A for three consecutive days to male patients in both the DES and control groups. The results showed a significant increase in TO after treatment in the DES group, while there was no change in TBUT and no significant changes in any

parameters in the control group. Consequently, the authors concluded that vitamin A enhances the quality of tears rather than their quantity.[30]

In this study, we measured the plasma concentrations of only the biologically active forms of vitamins A, E, 25(OH)2D3, and K. Our findings indicated that the DES group had significantly lower plasma vitamin D levels and lower, although not statistically significant, vitamin A levels. Furthermore, the DES group demonstrated significantly lower Schirmer test scores and TBUT than the control group. No vitamin treatment was evaluated in this study. Further research is needed on this topic.

Study limitations

This study has several limitations. First, the sample size was small, which makes it challenging to generalize the findings. Second, only the vitamin levels in the blood were examined, while the vitamin levels in the tears were not assessed. Future studies involving larger patient groups that examine vitamin levels in both tear secretion and serum will be essential for advancing the literature.

Conclusion

In conclusion, this study demonstrates that deficiencies in vitamins A and D – two vitamins essential for corneal epithelial function – may be associated with dry eye syndrome and vision-related quality of life. Furthermore, tear osmolarity may serve as a potential marker for vitamin deficiencies linked to DES. Additional research is needed to elucidate the pathophysiological mechanisms underlying the relationship between low vitamin levels and DES, as well as to investigate whether replenishing these deficient vitamins can result in improvements in the condition.

Declarations

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Author contributions

Conceptualization, C.G. and S.H.K.; Methodology, C.G. and S.H.K.; Software, C.G.; Validation, C.G. and S.H.K.; Formal Analysis, C.G.; Investigation, C.G. and S.H.K.; Resources, C.G.; Data Curation, C.G. and S.H.K.; Writing – Original Draft Preparation, C.G.; Writing – Review & Editing, C.G. and S.H.K.; Visualization, S.H.K.; Supervision, C.G. and S.H.K.; Project Administration, C.G.; Funding Acquisition, S.H.K.

Conflicts of interest

The authors have no conflict of interest to declare.

Data availability

The study data are held by the authors and can be made available upon request.

Ethics approval

The study was reviewed and approved by the Bagcilar Training and Research Hospital Ethics Committee with the 2016-493 registration number.

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