Impact of Vitamin D Supplement on Dry Eye

Mautazbellah M. T. Mohammmed, Mariam M.B. Gebril

Ophthalmology Department, Faculty of medicine, University of Benghazi, Libya

Corresponding author: Mautazbellah M. T. Mohammmed

Email: muatazbellah.sanfaz@uob.edu.ly, **Mobile:** +218925337398

Article History: Received: 29.05.2023 **Revised:** 23.06.2023 **Accepted:** 28.06.2023

Abstract

Purpose: to demonstrate the connection between a lack of vitamin D and dry eyes and to assess how vitamin D supplements affect both dry eyes and tear production.

Methods: A total of 60 patients (120 eyes) attending Benghazi Teaching Ophthalmology Hospital were enrolled in the study, during the period from February 2021 to October 2021. The ocular surface disease index, the time test, and the schirmer test were used to evaluate each participant. For the examination of the serum vitamin D, blood samples were taken.

Results: There was significant increase in Tear Film Break-Up Time (TFBUT) and Schirmer test after follow up while there was significant decrease in Ocular Surface Disease Index (OSDI) after follow up.

Conclusions: Each patient's serum vitamin D levels must be checked when treating dry eye, and if they are low, a supplement may be helpful.

Keywords: Supplement, Dry Eye, Vitamin D.

Introduction

The term "dry eye disease" refers to a “multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film with potential damage to the

ocular surface. It is accompanied by increased osmolarity of the tear film and subacute inflammation of the ocular surface". It is an extremely common condition, particularly in postmenopausal women and elderly **(1).**

25-hydroxyvitamin D is another name for vitamin D. [25(OH)D], has long been acknowledged as one of the basic nutrients needed each day. The two main forms of vitamin D are ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Following exposure to ultraviolet radiation in the morning, cholecalciferol is mostly produced in the skin. Ergocalciferol can be gotten by eating specific foods or by subjecting plants to radiation. It is debated if there is a link between inflammation and vitamin D. Higher vitamin D levels have been connected to lower levels of inflammation, according to some studies, although the opposite has also been suggested. The Animal studies have demonstrated that the metabolites of The effects of vitamin D and its analogs are anti-inflammatory. **(2).**

In addition to influencing calcium homeostasis, vitamin D is a versatile hormone that also influences immune system control, cell development, and survival. Vitamin D can activate and affect numerous ocular tissues, indicating that it is a physiologically significant molecule with a typical level between 20 and 40 ng/mL. Epidemiological studies have demonstrated that Vitamin D levels and genetic variations affect a variety of visual conditions, including myopia, age-related macular degeneration, diabetic retinopathy, and uveitis. Moreover, vitamin D works at the cellular level to improve barrier function, lessen inflammatory mediators, and cause malignant cells to die. **(3).**

Due to its secretory and anti-inflammatory qualities, Dry eyes may be impacted by vitamin D. Lack of vitamin D may impair dopamine function, which regulates parasympathetic tone and lowers tear production. **(4).**

The anti-inflammatory and secretory properties of vitamin D may affect wet eye. Lack of vitamin D may compromise dopamine's ability to control parasympathetic tone and reduce tear production. **(5).**

Inflammatory mediators (cytokines) linked to the etiology of dry eye are protected from by it. By stimulating cathelicidin, an anti-microbial protein generated by corneal and conjunctival epithelial cells, it may help prevent dry eyes. It also facilitates corneal and conjunctival wound healing. **(6).**

Vitamin D concentrations in plasma have recently been revealed to be lower than those in tear fluid that is directly extracted from the accessory and lacrimal glands. Lacrimal and auxiliary glands, which produce tear fluid, express the putative vitamin D transporters megalin and cubilin. **(7).**

The retinal pigmentary Vitamin D receptors are present in the epithelium, endothelium, and corneal epithelium. **(8).**

Additionally, it has been revealed that vitamin D targets in salivary gland epithelium and myoepithelial cells are significant, and that the rat parotid glands' production of saliva is correlated with vitamin D levels. **(9).**

Ion and fluid transport in the salivary glands are regulated by is vitamin D. Consequently, vitamin D may control lacrimal glands' ability to produce tears by comparable methods. We still don't fully comprehend how vitamin D and dry eyes are related. Either vitamin D is created in the skin by exposure to sunlight or it is absorbed through the dietPrevitamin D3 is transformed first into The kidney converts 25-hydroxyvitamin D3 [25(OH)D] into its active form, 1a,25-dihydroxyvitamin D3 [1a,25(OH)D]. Assessment of a person's vitamin D status is done using serum 25(OH)D concentrations. **(10).**

One disorder where Sjögren's syndrome and severe forms of dry eye have both been linked to low vitamin D levels. which frequently includes severe aqueous deficient dry eye.

The results of According to the Dry Eye Questionnaire 5, for every 10 unit drop in vitamin D levels, the severity of dry eye symptoms rose by 1.24 units (normal values are between 20 and 40 ng/mL). It is less certain, though, if vitamin D helps with less severe cases of dry eyes. Even though Despite the fact that there was no relationship between vitamin D levels and the severity of dry eye (based on objective markers), people with higher vitamin D levels were found to have fewer symptoms related to the condition. **(11).**

Therefore, our goals were to show relationship between a vitamin D shortage and dry eyes as well as to assess how vitamin D supplements affected both conditions.

Patient and methods

▪ Following approval by the Ophthalmology Department (Faculty of Medicine / University of Benghazi) ethics committee, a total of 60 patients (120 eyes) receiving care at the Benghazi Teaching Ophthalmology Hospital were included in the study from February 2021 to October 2021. The Benghazi Teaching Ophthalmology Hospital conducts all examinations. The patients who were included matched the following inclusion and exclusion requirements.

Inclusion Criteria:

- Any patient with vitamin D deficiency and dry eye.
- Adult age above 45 years old.
- Both male and female.

- Patients with dry eye.
- Serum 25 hydroxycholecalciferol below 20 ng/ml.

Exclusion Criteria:

- Ophthalmological disease that defect tear film as Sjegren syndrome, systemic rheumatic diseases, vitamin B12 deficiency, ect.
- Ophthalmic surgery or corneal scar.
- Allergy to fluorescein or local anesthesia.
- History of smocking.
- Recent drugs use interfere with lacrimal function.
- Active ocular infection or allergi.
- Use of contact lenses.

All patients were subjected to the following:

▪ Written informed consent.

▪ History taking including:

- ✓ Name, gender, age, occupation.
- ✓ All participants were questioned Considering the symptoms and indicators of dry eye, including redness, burning, dryness, a feeling of something alien in the eye, temporary blurred vision, and photophobia.
- ✓ Diurnal variation of symptoms (if these symptoms were worse toward the end of the day or in the morning) and workplace stress (air conditioning) were asked to the patients.
- ✓ Also, history taking included smoking history, medical and surgical history, and topical and systemic drug intake.

▪ Slit lamp examination especially for conjunctival Time for tear film breakup and hyperemia. Slit lamp analysis included ocular signs of dry eye e.g. superficial punctate keratitis, mucous plaques and filaments on the cornea, lower tear meniscus, temporal conjunctival folds, thickened eyelid margins and telangiectasia of their blood vessels, and Meibomian gland orifices and their secretions.

▪ The lacrimal function assessment was performed in specific order by:

1- Tear breakup time (TBUT) can be measured using the Oxford Schema with 2% fluorescein corneal staining.
2- 2. A 0.4% Benox eye drop modification to the Schirmer's test.

3- 3- The 12-item OSDI (Ocular Surface Disease Index), a survey on the symptoms and telltale indicators of dry eyes. In the wake of the administration of vitamin D supplements for three months, these measurements were again performed.

▪ Blood test for serum 25 (OH) vitamin D by enzyme-linked immunoabsorbed assay at 1st day, and after 3 months (done in same laboratory) and supplement vitamin D (1,25 dihydroxy cholecalciferol) IM 200,000IU once monthly for three consecutive months for all participants.

The assessments of all subjects were done at same room in same stabile conditions. The interval time between The examinations/tests of the ocular surfaces lasted for at least five minutes.

Instrumentation:

❖ **Tear Film Break-up Time Test (TFBUT):**

In order to assess the tear film's stability, this technique was described. After being injected into the patient's tear film, fluorescein was instructed to distribute uniformly across the cornea by encouraging the patient to blink repeatedly. With the help of a slit lamp and a wide cobalt blue light beam, the tear film was inspected.The period between the last blink and the first dry patch appearing in the tear film is referred to as the TFBUT. **(Fig. 1)**. To a tear break-up time to identify dry eyes of less than 10 seconds will be considered the cut-off value.

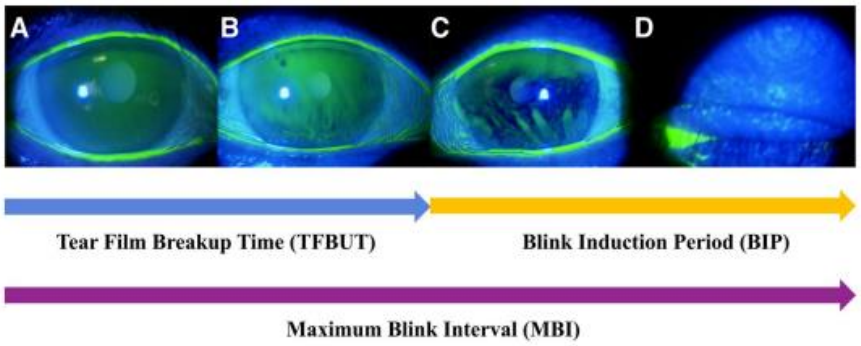

Figure (1): Tear film break up time test [12]

❖ **Schirmer Test:**

The test was carried out to determine how many tears were present (Fig. 2). Without using topical anesthesia, a In order to avoid touching the cornea or eyelashes, a I gently inserted a 35 X 5 mm Schirmer filter paper strip between each eye's bottom eyelid. The patient was told to gradually close their eyes. After five minutes, the strip was removed, and the amount of moisture

on the filter paper was calculated. A tear film thickness of less than 10 mm was considered dry. We noted the typical Schirmer test results for the left and right eyes.

Figure (2): Schirmer strips. [12]

❖ Ocular Surface Disease Index (OSDI)

Ocular Surface Disease Index© (OSDI©)[2]

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

Have you experienced any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

Have problems with your eyes limited you in performing any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

Add subtotals A, B, and C to obtain D (D = sum of scores for all questions answered) (D)

Total number of questions answered (do not include questions answered N/A) (E)

Please turn over the questionnaire to calculate the patient's final OSDI© score.

Figure (3): Ocular Surface Disease Index.

Ethical approval:

The research and data gathering complied with all applicable laws and the Helsinki Declaration's tenets. Approval by the ophthalmology department (faculty of medicine /University of Benghazi) and ethics committee.

Statistical analysis

IBM SPSS Statistics for Windows, version 23 (Armonk, New York: IBM Crop USA) was used to analyze the data. While non-parametric data is presented as median (percentile range), parametric data is expressed as mean SD. Paired student t-tests were used for the statistical comparisons the Wilcoxon signed rank tests on non-parametric data and the tests on parametric data. Categorical data were represented by frequency and percentage. The Spearman correlation coefficient test was used to assess the relationship between the variables (2-tailed). The level of relevance will be displayed at P0.05.

Results

Table (1): Demographic and clinical data of the studied group

		Patients (N=60)	
Age		55.2 ± 7	Median 54.5 (Range 46-72)
Gender	**M**	15	25%
	F	45	75%

Data are represented using mean ± SD or number (%) when appropriate

Patients' The median age was 55.2 years, with ranges ranging from 46 to 72. 75% of them were women. (Table 1).

Table (2): The lacrimal function assessment of the studied group before and after vitamin D supplement

	Basal (N=60)	**Follow up (N=60)**	**Z**	**P**
TFBUT	9 (7-10)	13 (11-15)	6.75	<0.001
Schirmer test	9 (8-11.7)	22 (19-25)	6.74	<0.001
OSDI	34 (31-37)	30 (28-32)	6.78	<0.001

The median of the data is shown (25th-75th Quartiles). Data analyzed using Wilcoxon signed rank test.

There was significant increase in TFBUT and Schirmer test after follow up while there was significant decrease in OSDI after follow up (Table 2).

Table (3): Vitamin D of the studied group before and after vitamin D supplement

	Basal (N=60)	**Follow up (N=60)**	**t**	**P**
Vitamin D	11 ± 3.8	31.3 ± 4.3	62.1	<0.001

The data are shown as mean SD. utilizing a paired t test to examine the data

There was significant increase in vitamin D after follow up (Table 3).

Table (4): Spearman correlation between vitamin D and lacrimal function assessment before vitamin D supplement

	r	**P**	**Correlation**
TFBUT basal	0.69	<0.001*	Direct
Schirmer test basal	0.87	<0.001*	Direct
OSDI basal	-0.89	<0.001*	Indirect

While there was a negative link between vitamin D and basal OSDI, there was a positive correlation between vitamin D and basal TFBUT and basal Schirmer test. (Table 4).

Table (5): Spearman correlation between vitamin D and lacrimal function assessment after vitamin D supplement.

	r	**P**	**Correlation**
TFBUT follow up	0.29	0.02	Direct
Schirmer test follow up	0.42	0.001	Direct
OSDI follow up	-0.69	<0.001	Indirect

While there was a negative link between vitamin D and follow-up OSDI, there was a positive correlation between vitamin D and follow-up TFBUT and Schirmer tests. (Table 5).

Discussion

About 60% of adults have dry eye disease, a prevalent, multifactorial, chronic ocular illness (13). The reported increased prevalence of dry eyes may be a result of racial differences or

environmental factors. The condition results in visual disruption, ocular discomfort (such as irritation and a feeling of a foreign body), and abnormalities of the cornea and conjunctiva (14). Current therapies for this persistent condition (such ocular lubricants) are not very successful. **(15).**

25-hydroxyvitamin D is another name for vitamin D [25(OH)D], has long been acknowledged as one of the basic nutrients needed each day. The two main forms of vitamin D are ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). While cholecalciferol is mostly formed in the skin as a result of exposure to UV radiation, ergocalciferol can be acquired by consuming specific foods. If a connection exists between vitamin D and inflammation, it is up for debate. Despite the fact that some studies (16) indicated that increased vitamin D levels reduced inflammation, some researchers contend that inflammation is the cause of decreased vitamin D. **(17, 18).** Animal tests have shown that the metabolites of vitamin D and its analogs have anti-inflammatory effects. **(17, 18).**

The few investigations into vitamin D's effects impact on dry eyes show conflicting outcomes. One disorder where Sjögren's syndrome, which commonly includes severe aqueous keratitis, has been associated with low vitamin D levels and severe forms of dry eye deficient dry eye. **(2).**

It was shown that the severity of For every 10 units lower vitamin D levels, dry eye symptoms as measured by the Dry Eye Questionnaire rose by 1.24 units. It is less certain, though, if vitamin D helps with less severe cases of dry eyes. Even though there was no correlation between vitamin D levels and the severity of dry eye (based on objective markers), People with higher vitamin D levels were found to have fewer symptoms related to the condition. **(11).**

Additionally, studies show that those with vitamin D deficiencies fared worse on tests that gauge tear production and quality, such as the TBUT and the Schirmer's test. **(19).**

Despite a non-significant correlation between blood vitamin D levels and the severity of dry eye disease, Jee et al. discovered that higher blood vitamin D levels decreased the chance of developing dry eye illness. **(20, 21).**

By establishing Our investigation into the effects of vitamin D supplementation on dry eyes is motivated by the link between a vitamin D deficiency and dry eyes eye and tear function.

This prospective cross-sectional study on 60 dry eye patients was undertaken by the ophthalmology division of the faculty of medicine at Benghazi University.

Our research showed that 75% of the patients were female, with a mean age of 55.2 7 years and a range of 46 to 72 years. The mean values before were TFBUT (9 sec), Schirmer test (9mm), and OSDI (34 point), and after were TFBUT (13sec), Schirmer test (22mm), and OSDI (30 point). The lacrimal function evaluation of the study group prior to and during vitamin D supplemental

usage identified a substantial increase in TFBUT and Schirmer test after follow up while a significant decrease in OSDI after follow up (p 0.001).

This was in line with the results of an El Said research et al. (3) that examined how the Individuals with vitamin D insufficiency can benefit from tear film. The patients in their study had a median age of 51.60 11.921 years and ranged in age from 20 to 67.

With a mean before of 11 ng/ml and an after of 31.3 ng/ml, the current study's comparison of the studied group's vitamin D levels before and after demonstrated a statistically significant increase in vitamin D after follow-up.

El Said et al. [3] revealed that the mean 25-hydroxy vitamin D level for the group under study was 8.22 4.814 ng/ml, with a range of 6 to 18.50 ng/ml. Following treatment, Increased vitamin D levels.

Yang et al. [2] found that, overall, the sample's At baseline, serum vitamin D levels increased by 36%, from 80.8 to 109.9 nmol/l. (p 0.001).

This is in agree with a study done by **Meng et al.** [22] Patients with DED had reduced serum 25(OH) vitamin D levels, according to a study. Furthermore, they discovered that the results of the TFBUT and Schirmer tests are affected by low vitamin D levels.

Another study done by **Yildirim et al.** [19] indicated that decreased TFBUT and Schirmer test outcomes were seen in patients with vitamin D deficiency.

In disagreement with our study **Jeon et al.** [23] demonstrated that there is no connection between DED and serum vitamin D levels. According to early studies, higher serum vitamin D levels were linked to a non-significantly lower incidence of DED. According to their findings, serum vitamin D levels climbed, men's risks decreased while women's risks rose.

Our research revealed a negative correlation between vitamin D and the baseline OSDI in the evaluation and a positive correlation between vitamin D and the baseline TFBUT and Schirmer test of lacrimal function prior to vitamin D supplementation. The Spearman connection link the evaluation and vitamin D of lacrimal function following vitamin D administration revealed a positive Schirmer and TFBUT follow-up tests and vitamin D, although there is a negative correlation between the OSDI and vitamin D.

In agreement with our study, **El Said et al.** [3] reported that the range of 1.0 to 12.5 mm and the mean value for the Schirmer test was 6.48 mm. TFBUT ranges from 0 to 8 seconds, with a mean value of 3.62 to 2.04 seconds. With a mean of 32.58 to 9.607 points, the OSDI had a range of 13 to 48 points. Schirmer's test and TFBUT scores were found to be significantly higher following therapy as compared to baseline levels (P 0.001). When compared to baseline levels, OSDI values were significantly reduced following therapy; they were 16.42 9.254 (P 0.001) after 10 weeks.

Yang et al. [2] The average OSDI score was found to be considerably lower after vitamin D treatment overall; at baseline, it was 21.0 14.1 and after vitamin D treatment, it was 10.5 10.4 (p = 0.02), demonstrating a decrease in the symptoms of dry eye. seven patients who have low vitamin D levels showed no discernible difference in tear quality according to Schirmer's test, which contrasts tear quality before and after treatment (22 10.79 vs. 21 12.49; p > 0.05).

Jin et al. [10] Schirmer's test revealed that the average TBUT was 3.34 1.61 seconds, the average OSDI was 33.92 23.28, and the average tear secretion was 6.52 4.63 mm. There was a positive connection between tear break-up time (TBUT) and serum 25 (OH) D levels (r = 0.389, p 0.001). Serum 25(OH)D levels and tear production had a positive correlation (r = 0.428, p 0.001). Ocular symptoms as evaluated by the OSDI and serum 25(OH)D levels did not correlate (r = 0.070, p = 0.549).

Liu et al. [24] found that there was a positive association between TBUT and serum 25 (OH) D levels (Pearson correlation test: r = 0.389, P = 0.001; and r = 0.428, P 0.001). The TBUT was shorter in the vitamin D-deficient group than the vitamin D-sufficient group in the vitamin D group (P = 0.022).

Jain et al. [25] TFBUT was discovered to have significantly reduced in vitamin D patients insufficiency. They also demonstrated that those with vitamin D deficiency had higher OSDI ratings.

Demerci et al. [26] conducted a study in which the average age of the vitamin D-deficient group OSDI scores were considerably higher (35.78 21.44). Patients with low vitamin D levels experienced dry eyes and insufficient tear production. Patients with vitamin D deficiencies reportedly had higher OSDI scores.

A significant difference in TBUT was discovered by one-way ANOVA (p = 0.005). In contrast to the sufficient group (4.09 1.81 seconds; p = 0.022) and the insufficient group (3.71 1.61 seconds), the inadequate group's tear break-up time (2.63 1.27 seconds) was shorter. Significant variations in tear secretion One-way ANOVA was used to compare the three groups (p = 0.005). The findings of Schirmer's test revealed that the inadequate group's tear secretion was lower (4.83 2.27 mm) than the sufficient group's (9.91 7.85 mm; p = 0.004).

Galor et al. [11] discovered revealed lower levels of DES symptoms were substantially correlated with higher vitamin D levels (1.24% decline for every 10% increase in vitamin D, p=0.01).

Conclusion:

Dry eye is a common problem. Insufficient tear volume or function is the cause of the shaky tear film and surface characteristics of the eye. tracking vitamin D levels in the blood is crucial while treating dry eye; if necessary, a supplement may be beneficial.

References:

1. **Rolando, M, Zierhut, M, & Barabino, S.** Should We reconsider the Classification of Patients with Dry Eye Disease?. *Ocul Immunol Inflamm*. 2021;29(3):521-523.
2. **Yang CH, Albietz J, Harkin DG.** Kimlin MG Schmid KL. Impact of oral vitamin D supplementation on the ocular surface in people with dry eye and/or low serum vitamin D. *Cont Lens and Anterior Eye*. 2018;41(1):69-76.
3. **El Said S, Basiony A, Amin M, El-deen S.** Impact of Vitamin D Supplementation on Dry Eye in People with Low Serum Vitamin D. *The Egyptian Journal of Hospital Medicine* 2021;84(1):2008-2013.
4. **Dartt DA, Willcox MD.** Complexity of the tear film: importance in homeostasis and dysfunction during disease. *Exp Eye Res.* 2013, 117:1-3. nmm.
5. **Holick MF, Chen TC**. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr. 2008;87(4):1080S-1086S
6. **Reins RY, McDermott AM.** Vitamin D: Implications for ocular disease and therapeutic potential. *Exp Eye Res*. 2015;134:101-110.
7. **Lu X, Elizondo RA, Nielsen R, Christensen EI, Yang J, Hammock BD, et al.** Vitamin D in tear fluid. Invest Ophthalmol Vis Sci 2015; 56(10): 5880–5887.
8. **Alsalem JA, Patel D, Susarla R., Coca-Prados M, Bland R, Walker EA, et al.** Characterization of vitamin D production by human ocular barrier cells. Invest Ophthalmol Vis Sci, 2014;55(4): 2140–2147.
9. **Stumpf WE & Hayakawa N.** Salivary glands epithelial and myoepithelial cells are major vitamin D targets. Eur J Drug Metab Pharmacokinet, 2007;32(3): 123–129.
10. **Jin KW, Ro JW, Shin YJ, Hyon JY, Wee WR, Park SG.** Correlation of vitamin D levels with tear film stability and secretion in patients with dry eye syndrome. *Acta ophthalmol*. 2007;95(3):e230-e235.
11. **Galor, A., Gardner, H., Pouyeh, B., Feuer W, Florez H.** Effect of a Mediterranean dietary pattern and vitamin D levels on Dry Eye syndrome. *Cornea*. 2014;33(5):437-441.
12. **Inomata T, Iwagami M, Hiratsuka Y, Fujimoto K, Okumura Y, Shiang T, et al**. Maximum blink interval is associated with tear film breakup time: A new simple, screening test for dry eye disease. Sci Rep. 2018;8(1):13443

13. **Viso E, Rodríguez-Ares MT, Abelenda D, Oubiña B, Gude F.** Prevalence of asymptomatic and symptomatic meibomian gland dysfunction in the general population of Spain. *Invest Ophthalmol Vis Sci*. 2012; 53(6): 2601-2606.
14. **Tavares Fde P, Fernandes RS, Bernardes TF, Bonfioli AA, Soares EJ.** Dry eye disease. *Semin Ophthalmol*. 2010; 25(3):84-93
15. **McGinnigle S, Eperjesi F, Naroo SA.** A preliminary investigation into the effects of ocular lubricants on higher order aberrations in normal and dry eye subjects. *Cont Lens Anterior Eye*. 2014; 37(2), 106-110.
16. **Marcotorchino J, Gouranton E, Romier B, Tourniaire F, Astier J, Malezet C, et al. (2012).** Vitamin D reduces the inflammatory response and restores glucose uptake in adipocytes. *Mol Nutr Food Res*. 2012;56(12):1771-1782.
17. **Autier P, Boniol M, Pizot C, Mullie P.** Vitamin D status and ill health: a systematic review. *Lancet Diabetes Endocrinol*. 2014;2(1):76-89.
18. **Henriksen VT, Rogers VE, Rasmussen GL. Trawick RH, Momberger NG D, et al.** Pro-inflammatory cytokines mediate the decrease in serum 25 (OH) D concentrations after total knee arthroplasty?. Medical hypotheses, 2014; 82(2): 134-137.
19. **Yildirim P, Garip Y, Karci AA, Guler T.** Dry eye in vitamin D deficiency: more than an incidental association. Int J Rheum Dis. 2016; 19(1): 49-54.
20. **Jee D, Kang S, Yuan C, Cho E, Arroyo JG;** Epidemiologic Survey Committee of the Korean Ophthalmologic Society. Serum 25- Hydroxyvitamin D levels and dry eye syndrome: differential effects of vitamin D on ocular diseases. PLoS ONE. 2016; 11(2): e0149294.
21. **Kurtul BE, Özer PA, Aydinli MS.** The association of vitamin D deficiency with tear break-up time and Schirmer testing in non-Sjögren dry eye. Eye. 2015; 29(8): 1081-1084.
22. **Meng YF, Lu J, Xing Q, Tao JJ, Xiao P.** Lower serum Vitamin D level was associated with risk of dry eye syndrome. *Med Sci Monit*. 2017;23:2211-2216.
23. **Jeon DH, Yeom H, Yang J, Song JS, Lee HK, Kim HC.** Are serum vitamin D levels associated with dry eye disease? Results from the study group for environmental eye disease. *J Prev Med Public Health*. 2017;50(6):369-376

24. Liu J, Dong Y, Wang Y. Vitamin D deficiency is associated with dry eye syndrome: A systematic review and meta-analysis. Acta Ophthalmol 2020;98(8):749-754.

25. Jain N, Sharma P, Chouhan JK. A study of the association between Vitamin D deficiency and Dry Eye Syndrome (DES) in the Indian population. *Indian J Ophthalmol*. 2022;70(2):500-504.

26. Demirci G, Karaman Erdur S, Ozsutcu M, Eliacik M, Olmuscelik O, Aydin R, et al. Dry Eye Assessment in Patients With Vitamin D Deficiency. Eye Contact Lens. 2018;44 Suppl 1:S62-S65.