# The Relationship Between Vitamin D Deficiency and Ocular Surface Clinical Parameters in Patients with Non-Sjögren Dry Eye

## Non-Sjögren Kuru Göz Hastalarında Vitamin D Eksikliği ile Oküler Yüzey Klinik Parametreleri Arasındaki İlişki

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**ABSTRACT Objective:** To investigate the effect of vitamin-D deficiency on ocular surface clinical parameters in Non-Sjögren dry eye patients. **Material and Methods:** Forty patients with serum vitamin D deficiency and 24 control subjects with normal vitamin D levels were included in this study. Ocular surface disease index (OSDI) questionnaire, tear break-up time (TBUT), corneal fluorescein staining and Schirmer 1 test without topical anesthesia were performed to all patients. **Results:** The median vitamin-D levels were 10.5 (9.5-12.5) ng/mL in study and 24.5 (17.6-35.2) ng/mL in the control group (p<0.001). The median OSDI scores were 27.77(18.75-37.50) in study, 8.33 (6.25-28.41) in control group (p =0.071). The mean TBUT were 5.18±2.15 and 7.36±3.10 seconds and Schirmer scores were 12.18±6.44 and 18.57±8.99 mm in the study and control groups. TBUT scores and Schirmer 1 results of the study group were significantly lower than the control group (p=0.01 and 0.007 respectively). There was also a significant difference in corneal fluorescein staining score between groups (p<0.001). **Conclusion:** Vitamin-D deficiency seems to have an effect on ocular surface parameters however does not influence OSDI scores in patients with Non-Sjögren dry eye syndrome.

**Key Words:** Dry eye syndromes; vitamin D

**ÖZET Amaç:** Non-Sjögren kuru göz hastalarında vitamin-D eksikliğinin oküler yüzey klinik parametrelere olan etkisini araştırmak. **Gereç ve Yöntemler:** Serum vitamin-D eksikliği olan 40 hasta ve normal vitamin-D değerleri olan 24 kontrol hastası çalışmaya dahil edildi. Oküler yüzey hastalık indeksi (OYHİ), göz yaşı kırılma zamanı (GYKZ), korneal floresein boyanma ve topikal anestezisiz Schirmer 1 test tüm hastalara uygulandı. **Bulgular:** Çalışma grubunda vitamin-D düzeyleri median değeri 10,5 (9,5-12,5) ng/mL, kontrol grubunda ise 24,5 (17,6-35,2) ng/mL idi (p<0,001). Çalışma grubunda OYHİ median değeri 27,77 (18,75-37,50), kontrol grubunda ise 8,33 (6,25-28,41) idi (p=0,071). Ortalama GYKZ, çalışma ve kontrol grubunda sırasıyla 5,18±2,15 ve 7,36±3,10 saniye, Schirmer değerleri 12,18±6,44 ve 18,57±8,99 mm idi. Çalışma grubunda GYKZ ve Schirmer 1 düzeyleri, kontrol grubundan anlamlı olarak daha düşüktü (p=0,01 and 0,007 sırasıyla). Korneal floresein boyanma değerlerinde gruplar arasında anlamlı fark vardı (p<0,001). **Sonuç:** Vitamin-D eksikliğinin; oküler yüzey parametrelerine etkisi olabilir ancak Non-Sjögren kuru göz sendromunda OYHİ düzeylerini etkilememiştir.

**Anahtar Kelimeler:** Kuru göz sendromları; vitamin D

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Vitamin-D is a fat-soluble pro-hormone and has immunomodulatory properties.[1-3] Vitamin-D deficiency plays an important role in development of cancer and several autoimmune diseases.[1,2] It has also been found that environmental and hormonal factors, the fat-soluble vita-

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mins such as vitamin-D may play a role in the pathogenic immunoregulatory process of Primary Sjögren's syndrome (Pss).[4-6] Low levels of vitamin-D may be related with low complements components and the presence of cryoglobulins in predicting eventual development of lymphoma in patients with Ss.[5]

Dry eye is an inflammatory, autoimmune, multifactorial disease of the tears and the ocular surface with various signs and symptoms.[5-9] It is observed in approximately 33% of the world population. Dry eye disease contains two etiopathogenic groups. These are aqueous tear-deficient dry eye and evaporative dry eye. Aqueous tear deficient group includes Ss and Non-Ss dry eye groups.[5] Non-Ss dry eye disease has several causes as lack of lacrimal gland, impairment or dysfunction of the lacrimal gland, reflex block and drug action.[8] Non-Ss dry eye is a form of aqueous tear-deficiency when the systemic autoimmune features have been excluded.[8]

Non-Ss dry eye can also be secondary to different conditions such as medications, hormonal changes, environment and neural alterations. Although the mechanism of Non-Ss dry eye pathogenesis is not clearly understood, hyperosmolarity and the inflammation are known to be responsible.[8]

Based on the role of anti-inflammatory and immunoregulatory properties of vitamin-D; the deficiency of vitamin-D may induce dry eye as an autoimmune and inflammatory disease. Because of close relationship between vitamin-D and inflammation, we aimed to investigate the effect of vitamin-D deficiency on tear break-up time (TBUT), corneal staining, Schirmer test and ocular surface disease index (OSDI) scores in Non-Ss patients.

## MATERIAL AND METHODS

The study was undertaken between March 2013 and July 2013, in Training and Research Hospital, Department of Ophthalmology and was designed as a prospective clinical study. This study was carried out with the Institutional Review Board/Ethics Committee approval. Informed consent was obtained from each patient. The research adhered to the tenets of the Declaration of Helsinki.

Forty patients with serum vitamin D deficiency and 24 control subjects without serum vitamin D deficiency were included in the study. The patients with vitamin-D deficiency were referred to our polyclinic randomly from the family medicine department. The patients with PSs or other systemic rheumatic diseases, vitamin B12 deficiency, ocular surface disorders, wearing contact lenses and a history of any ocular surgery were excluded from the study. Vitamin D status may be affected by factors such as food fortification and sun exposure.[3] We asked the patients with an interview about the daily intake of the fatty fish (salmon, tuna, mackerel, etc.), dairy products, egg yolks, and which contain vitamin D.[3] The nutritional status and eating habits of the patients were similar. Serum concentrations of vitamin D were measured by LC-MS/MS method (*Shimadzu API 3200, Applied biosystem,USA*).[10] All blood samples were only taken between March and July because of the possible variation throughout the year. The serum vitamin D levels was described as; severe deficiency <10 ug/L, moderate deficiency 10-24 ug/L, desired > 30 ug/L and toxic >150 ug/L)[10]. Dry eye symptoms as; irritation, a foreign body sensation, burning, presence of stringy mucus discharge and transient blurring of vision were assessed by the ocular surface disease index (OSDI; Allergan, Inc, Irvine, CA, USA) questionnaire. The OSDI consists of 12 questions on symptoms within the past week and yields scores ranging from 0 (least severe) to 100 (most severe). A score of 12 is typically used as a cutoff for normal, 13-22 for mild dry eye, 23-32 for moderate dry eye, and ≥ 33 for severe dry eye.[11-13] The total OSDI score was measured as; total OSDI score x 25/total number of questions answered.[11,12]

The TBUT and Schirmer 1 test were evaluated after a full ophthalmologic examination. TBUT and Schirmer 1 test without topical anesthesia were performed to all patients thirty minutes intervals after the ophthalmologic examination by the same examiner. Patients were avoided from ocular manipulations and any top-

ical drops prior to the tests since this may affect the results. The examiner was masked as to the vitamin D status of the subjects.

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 instillment of fluorescein and the appearance of the first randomly distributed dry spot was enrolled as the TBUT. This method was repeated three times for each eye, and the average of the results was registered as the mean TBUT.[11] TBUT of less than 10 seconds was accepted as abnormal. Corneal fluorescein staining was evaluated using cobalt blue illumination following the 15-point NEI/Industry scale (grades of 0-3 for five regions of the ocular surface), after TBUT measurements.[14]

The Schirmer 1 test was applied without anesthesia by placing a standardized strip of filter paper in the 1/3 lateral tarsal conjunctiva away from the cornea. Outcomes were expressed in millimeters after 5 minutes of wetting.[15]

### STATISTICAL ANALYSIS

Data were analyzed using SPSS 18.0 for Windows. All data were presented as mean ± standard deviation or median and interquartile range. The number of patients in the study and control group were determined according to the Post-hoc power analysis. Categorical variables were compared by the chi-square test. Comparison of parametric values between the two groups was performed by means of independent samples t test. Comparisons of nonparametric values between the 2 groups were performed by Mann-Whitney U test. A two-tailed p value < 0.05 was regarded as significant.

## RESULTS

The mean age of study group subjects and control subjects were 50±16 years (range 28-77 years) and 45±13 years (range 24-63 years), respectively (p=0.162). Thirty six of them were female and 4 of them were male in study group, 17 of them were female and 7 of them were male in control group. More female and older population in the study group was purely coincidental. The baseline characteristics of subjects were shown in Table 1. The median vitamin-D levels were 10.5 (9.5-12.5) ng/mL in the study group and 24.5 (17.6-35.2) ng/mL in control group (p<0.001). The OSDI scores were 27.77 (18.75-37.50) in study, 8.33 (6.25-28.41) in control group. The difference between groups was not significant (p =0.071). The mean TBUT, were 5.18±2.15 and 7.36±3.10 seconds and Schirmer 1 score of study group and control group were 12.18±6.44 and 18.57 ±8.99 mm respectively. The TBUT scores and Schirmer 1 test values of study group were significantly lower than the control group (p=0.01 and p=0.007 respectively). The mean corneal fluorescein staining score was 1.45±1.13 in study group and 0.17±0.38 in control group (p<0.001).

**TABLE 1:** The baseline characteristics and clinical parameters of subjects.

| Parameters | Study group (n=40) | Control group (n=24) | p |
|---|---|---|---|
| Mean age ± SD, years | 50±16 | 45±13 | 0.162 |
| Gender (Female/Male) | 36/4 | 17/7 | 0.08 |
| SerumVitamin-D levels, ng/mL median (interquartil range) | 10.5 (9.5-12.5) | 24.5 (17.6-35.2) | <0.001 |
| OSDI scores median (interquartil range) | 27.77 (18.75-37.50) | 8.33 (6.25-28.41) | 0.071 |
| TBUT, seconds (mean ± SD) | 5.18±2.15 | 7.36±3.10 | 0.01 |
| Corneal fluorescein staining score (mean ± SD) | 1.45±1.13 | 0.17±0.38 | <0.001 |
| Schirmer test scores, mm (mean ± SD) | 12.18±6.44 | 18.57±8.99 | 0.007 |

SD: Standard deviation; OSDI: Ocular surface disease index; TBUT: Tear break up time.

## DISCUSSION

Clinically, the reduced intake of vitamin-D is found to increase the prevalence of certain autoimmune diseases, such as type I diabetes mellitus, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus and inflammatory bowel diseases.[10] Vitamin-D binding protein (DBP) binds the vitamin-D metabolites with high affinity.[10] DBP may play a role as a neutral acute-phase reactant. The important immunoregulatory functions of the fat-soluble vitamins (vitamins A, D and E) and their role in the regulation of autoimmune diseases have been shown.[15,16] Especially the vitamin-D deficiency occurs at a higher rate in patients with autoimmune disorders.[15,17-19]

The effect of environmental and hormonal factors, such as vitamin D were mentioned in the pathogenic process of dry eye disease.[4,6] It is now accepted that dry eye is a localized autoimmune disease and irregular protective immunoregulation and proinflammatory pathways of the ocular surface cause this disorder.[20]

Recent studies have focused on the inflammatory biologic markers in establishing treatment strategies to cover the multifactorial nature of Non-Ss dry eye.[8] Increased levels of proinflammatory cytokines and markers have been observed in the tears and the ocular surface of Non-Ss dry eye patients. Upregulation of inflammatory cytokines, including interleukin-1α and IL1β has been observed in Non-Ss dry eye.[8]

Bang et al. emphasized the clinical and pathogenic significance of vitamin-D metabolites in Pss.[21] Müller et al. found severely diminished blood concentrations of vitamin-D levels in patients with Pss.[22] Galor et al. mentioned the small but favorable effect of higher vitamin D levels on dry eye symptoms.[23]

The relation between vitamin D deficiency and Ss was shown in previous studies.[1-4] Agmon-Levin et al. emphasized that low levels of vitamin-D correlated with the presence of peripheral neuropathy and lymphoma among PSs patients in their study.[4]

In our study none of the patients had autoimmune disease like Ss which could affect the ocular surface parameters. We researched the possible link between vitamin-D deficiency and ocular surface clinical findings in Non-Ss dry eye. TBUT scores and Schirmer 1 test values of the study group were significantly lower than the control group. In contrast, the difference in OSDI scores were not significant between groups. This may be due to the small size of the patients in our study. We demonstrated that vitamin-D deficiency may be associated with the dry eye symptoms according to decreasing TBUT and Schirmer values and increasing the corneal staining scores.

Kinds of systemic therapies are being used to induce tear components or mucin secretion and to reduce inflammation and dry eye symptoms. Some of them are; forms of steroidal and nonsteroidal antiinflammatory agents, oral cholinergic agonist, vitamin A and D, neurotransmitters and neuropeptides besides usual topical drops used for dry eye treatment.[14] The vitamin-D supplementation is suggested for chronic autoimmune diseases and recommended in the treatment of the many rheumatic conditions.[4,16] Tincani et al. referred that vitamin-D supplementation as an additional way for optimization of Ss treatment. Because of the associations between hypovitaminosis D and severe complications of Ss, it can be proposed that vitamin D supplementation should be given to patient with Ss.[5] Although it is difficult to suggest that oral vitamin D supplementation decreases the symptoms of dry eye; as we learned from phone visits; correction of decreased serum vitamin-D levels with oral supplementations may reduce some of the dry eye symptoms (irritation, a foreign body sensation, burning, presence of stringy mucus discharge and transient blurring of vision) of these patients. But there is no statistically proven data about this subject. There is a need to look at the changes of the parameters when the vitamin-D level would be normalized in vitamin-D deficient group, but we could not convince all the patients to come to the hospital again for a new examination after the oral supplementation. Other studies can be also made

to compare the changes in ocular surface clinical parameters after the oral supplementation of vitamin-D. This is the one of the limitation criterions of our study.

Vitamin A levels can also be evaluated based on the role of vitamin A on dry eye disease.[16] But we could not reach the datas of all patients. We could observe the nutritional status and eating habits of the patients and other nutrition status except vitamin-D by an interview. There is no statistically proven data about this subject. The results could have been affected because of the coincident higher female rate and older population in the study group in our study. These are the other limitation criterions of our study.

Bozkurt et al. mentioned serum 25-(OH)D levels were significantly lower in the winter compared with the summer season in local Turkish population.[24] They told about the prevalence of 25-(OH)D deficiency was 94% in the winter and 85% in the summer. They emphasized no differences in the 25-(OH)D levels according to age or sex. Although Turkey is a Mediterranean country, they suggest checking periodically the levels of 25-(OH)D of Turkish people and giving appropriate supplements. There are limited data on the prevalence of vitamin D deficiency among healthy people in the other Mediterranean countries. Vierucci et al. detected vitamin D deficiency in 49.9% of healthy adolescents in Italy.[25]

So evaluation of serum vitamin-D levels in patients with dry eye symptoms is important, the role of vitamin-D should not be disregarded in their clinical follow up. Further studies including large populations are needed to investigate the possible role of vitamin D levels in Non-Ss dry eye disease.

## REFERENCES


1. Smyk DS, Orfanidou T, Invernizzi P, Bogdanos DP, Lenzi M. Vitamin D in autoimmune liver disease. Clin Res Hepatol Gastroenterol 2013;37(5):535-45.
2. Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. Nutrients 2013;5(7):2502-21.
3. Health Quality Ontario. Clinical utility of vitamin d testing: an evidence-based analysis. Ont Health Technol Assess Ser 2010;10(2):1-93.
4. Agmon-Levin N, Kivity S, Tzioufas AG, López Hoyos M, Rozman B, Efes I, et al. Low levels of vitamin-D are associated with neuropathy and lymphoma among patients with Sjögren's syndrome. J Autoimmun 2012;39(3):234-9.
5. Tincani A, Andreoli L, Cavazzana I, Doria A, Favero M, Fenini MG, et al. Novel aspects of Sjögren's syndrome in 2012. BMC Med 2013;11:93. doi: 10.1186/1741-7015-11-93.
6. Stevenson W, Chauhan SK, Dana R. Dry eye disease: an immune-mediated ocular surface disorder. Arch Ophthalmol 2012;130(1):90-100.
7. Labbé A, Liang Q, Wang Z, Zhang Y, Xu L, Baudouin C, et al. Corneal nerve structure and function in patients with non-sjogren dry eye: clinical correlations. Invest Ophthalmol Vis Sci 2013;54(8):5144-50.
8. Na KS, Mok JW, Kim JY, Joo CK. Proinflammatory gene polymorphisms are potentially associated with Korean non-Sjogren dry eye patients. Mol Vis 2011;17:2818-23.
9. Peral A, Domínguez-Godínez CO, Carracedo G, Pintor J. Therapeutic targets in dry eye syndrome. Drug News Perspect 2008;21(3):166-76.
10. Sahillioğlu B, Serdar MA, Erkal N, Erdem G, Bakırı F, Yıldırımkaya MM, et al. [Method validation of tandem mass spectrometry for 25-Hydroxyvitamin D3 and comparison of this method with other methods]. Turk J Biochem 2011;36(1):73-9.
11. Miller KL, Walt JG, Mink DR, Satram-Hoang S, Wilson SE, Perry HD, et al. Minimal clinically important difference for the ocular surface disease index. Arch Ophthalmol 2010;128(1):94-101.
12. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol 2000;118(5):615-21.
13. Tung CI, Perin AF, Gumus K, Pflugfelder SC. Tear meniscus dimensions in tear dysfunction and their correlation with clinical parameters. Am J Ophthalmol 2014;157(2):301-310.e1.
14. Alves M, Reinach PS, Paula JS, Vellasco e Cruz AA, Bachette L, Faustino J, et al. Comparison of diagnostic tests in distinct well-defined conditions related to dry eye disease. PLoS One 2014;9(5):e97921.
15. Demir HD, Aydın E, Sezer E, Yardım H. Evaluation of plasma vitamin A and E levels and tear film changes in patients with psoriasis vulgaris. Korean J Ophthalmol 2013;27(3):158-61.
16. Szodoray P, Horvath IF, Papp G, Barath S, Gyimesi E, Csathy L, et al. The immunoregulatory role of vitamins A, D and E in patients with primary Sjogren's syndrome. Rheumatology (Oxford) 2010;49(2):211-7.
17. Abrahamsen B, Harvey NC. The role of vitamin D supplementation in patients with rheumatic diseases. Nat Rev Rheumatol 2013;9(7):411-22.
18. Pelajo CF, Lopez-Benitez JM, Miller LC. Vitamin D and autoimmune rheumatologic disorders. Autoimmun Rev 2010;9(7):507-10.
19. Golan S, Shalev V, Treister G, Chodick G, Loewenstein A. Reconsidering the connection between vitamin D levels and age-related macular degeneration. Eye (Lond) 2011;25(9):1122-9.
20. Stern ME, Schaumburg CS, Pflugfelder SC. Dry eye as a mucosal autoimmune disease. Int Rev Immunol 2013;32(1):19-41.

21. Bang B, Asmussen K, Sørensen OH, Oxholm P. Reduced 25-hydroxyvitamin D levels in primary Sjögren's syndrome. Correlations to disease manifestations. Scand J Rheumatol 1999;28(3):180-3.

22. Müller K, Oxholm P, Sørensen OH, Thymann M, Høier-Madsen M, Bendtzen K. Abnormal vitamin D3 metabolism in patients with primary Sjögren's syndrome. Ann Rheum Dis 1990; 49(9):682-4.

23. Galor A, Gardener 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):437-41.

24. Bozkurt S, Alkan BE, Yıldız F, Gümüş S, Sezer N, Ardıçoğlu Ö, et al. Age, sex, and seasonal variations in the serum vitamin D3 levels in a local Turkish population. Arch Rheumatol 2014;29(1):14-9.

25. Vierucci F, Del Pistoia M, Fanos M, Erba P, Saggese G. Prevalence of hypovitaminosis D and predictors of vitamin D status in Italian healthy adolescents. Ital J Pediatr 2014;40:54. doi: 10.1186/1824-7288-40-54.