The potential role of vitamin D supplementation in the treatment of Dry Eye Disease (DED): a systematic review

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ABSTRACT

Background: Dry Eye Disease (DED) is a prevalent condition that involves instability, increased osmolarity, and inflammation of the tear film and ocular surface. Vitamin D is known for its anti-inflammatory properties. Association between vitamin D deficiency and increased incidence of DED has been suggested. However, no study currently exists that systematically reviews the potential role of vitamin D as a treatment for DED.

Methods: The literature search was performed on December 2021 through PubMed, Scopus, ProQuest, EBSCOhost, ScienceDirect, and Cochrane Library using the relevant keywords. The risk of bias was assessed using the Cochrane Risk of Bias tool, ROBINS-I tools, and the Newcastle-Ottawa Scale.

Results: A total of 700 articles were found, 6 of which were considered relevant based on PRISMA protocol. The included articles consist of 2 case controls, a randomized interventional study, and 3 observational studies. Vitamin D supplementation improved tear stability, symptoms of dry eye disease, and serum vitamin D level affected the efficacy of topical therapy for DED.

Conclusion: Despite this beneficial finding, serum vitamin D level does not significantly correlate with DED symptoms which the multifactorial nature of the disease might cause.

Keywords: Dry Eye Disease, Vitamin D, Supplementation.


INTRODUCTION

The tear film is a thin fluid layer that provides a smooth surface over the cornea. It comprises 3 layers: the innermost mucin layer, aqueous layer, and outermost lipid layer. There is a complex mix of electrolytes, phospholipids, immunoglobulin, and surfactant proteins. Dry Eye Disease (DED) or Dry Eye Syndrome (DES) is characterized by the continuous sensation of eye dryness, discomfort, and pain. The International Dry Eye Workshop (DEWS) defined dry eye syndrome as a multifactorial disease of the tears and ocular surface that result in discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. The pathophysiology of this disease involves instability, increased osmolarity, and inflammation of the tear film and ocular surface. The prevalence of DES is estimated to be around 5% to 50% and can be as high as 75% among adults over 40 years old and women are more affected than men.

DED is usually treated using artificial tears such as sodium hyaluronate and Carbomer-Based Lipid-Containing Artificial Tears (CLAT), anti-inflammatory agents, autologous serum, and punctal occlusion procedure. The problem with these treatments is that the outcome is not always as predicted and the association between patients with treatment-refractory DES and its factors remain unclear. Vitamin D, well known for its role in bone metabolism and calcium absorption, affects the synthesis of surfactants and has anti-inflammatory properties. In neonates, vitamin D deficiency is associated with respiratory distress syndrome, and a study in the rat model showed that vitamin D supplementation improved lung functions. The association between vitamin D deficiency and increased incidence of DES has been suggested. A meta-analysis shows that vitamin D deficiency may be a risk factor for DES. To our knowledge, no study currently exists that systematically reviews the potential role of vitamin D in treating DES. Therefore, this study systematically assessed whether vitamin D supplementation could be beneficial as a treatment for DES in patients with or without vitamin D deficiency.

METHODS

The methodology of this review is based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol. The literature search was performed on December 2021 through the following scientific database: PubMed, Scopus, ProQuest, EBSCOhost, ScienceDirect, dan Cochrane Library. The literature search on PubMed was performed using Medical Subject Headings (MeSH) search with the
following keywords: (("Dry Eye Syndromes"[Mesh]) OR "dry eye") AND (("Vitamin D"[Mesh]). Manual hand-searching was also performed to identify relevant literature not found using the search engine. The inclusion criteria were: (1) Article published in English; (2) Full-text availability; (3) Study conducted on human subjects; (4) Original studies with the following randomized or non-randomized controlled trial, clinical trial, prospective or retrospective cohort, case-control, and case report. The exclusion criteria were: (1) Article published not in English; (2) Full-text article is unavailable or otherwise unable to be retrieved; (3) Studies conducted in vitro or in vivo, not on humans; and (4) Review studies or original articles.

Risk of bias assessment for randomized controlled trial was conducted using Cochrane Risk of Bias tools that analyzed seven aspects of bias. The risk of bias on non-randomized interventional studies was assessed using the ROBINS-I tool. The risk of bias in observational studies was assessed using the Newcastle-Ottawa Scale (NOS).

RESULTS

The search results and process in selecting the suitable articles to be included in this study can be viewed in Figure 1. Literature searching through 6 databases resulted in 700 titles, of which 456 are duplicates and thus removed. Screening through titles and abstracts resulted in 244 titles being removed; only 6 databases were selected. Full-text eligibility assessment was conducted and no further articles were excluded. Six literatures included in this study consist of 2 case-control studies, 1 randomized interventional study, and 3 observational studies.11-16 Risk of bias assessment of randomized study Cochrane using the risk of bias tool presented in Figure 2, a non-randomized interventional study using ROBINS-I in Figure 3 and observational study using NOS in Table 1. ROBINS-I risks of bias assessment of Yang et al. found low risk in all domains except measurement outcomes and selection of reported results, both of which were not explicitly stated. Hwang et al. have a considerable moderate risk compared to Yang et al. with data regarding 5 out of 8 domains were not explicitly stated. Cochrane Risk of bias assessment of Watts et al. found a generally low risk of bias. NOS consists of 8 items within 3 domains with a total maximum score of 9. Since the standard cutoff for high-quality study using NOS has not yet been established universally, we considered a study with ≥7 scores as a high-quality study. We found all 3 papers assessed by NOS had a score of 7, which we believe is a high-quality study. The detail of selected studies is summarized in Table 2.

Figure 1. Flowchart of the literature search strategy.

Figure 2. ROBINS-I risks of bias assessment in case-control studies.
DISCUSSION

In DED, inflammation plays an important role in the pathogenesis of this disease. Baudouin et al. proposed the concept of a “vicious cycle of inflammation,” which describes the positive feedback between inflammation, tear instability, and tear hyperosmolarity which then caused corneal and conjunctival cell apoptosis and thus increased inflammatory response. Vitamin D has anti-inflammatory properties to treat many other diseases. In the tumor microenvironment, vitamin D has been known to regulate the level of cytokine, inhibiting NF-kB signaling pathway, up-regulating MPK5, and inhibiting prostaglandin pathways and immune cells such as macrophage, B cells, and T cells. Considering the role of inflammation on DED pathogenesis, supplementation using anti-inflammation such as vitamin D, in theory, should be able to reduce the symptoms or enhance the efficacy of current treatment regimens with topical agents.

This study included articles that assessed the effect of vitamin D supplementation on DED symptom improvement. These studies used several clinical tests to quantify the improvement post-intervention, such as tear break-up time (TBUT), Ocular Surface Disease Index (OSDI), Fluorescence Staining Score (FSS), Schirmer test, Visual Analog Scale (VAS), etc. Two case-control studies are included by Yang et al. and Hwang et al. Yang et al. compare DED patients with vitamin D deficiency (VDD) on topical therapy and vitamin D supplementation leads to earlier improvement for patients with VDD. However, the difference between groups B and C was not statistically significant. Therefore, this study showed that topical cyclosporine gives no additional benefit in DED patients with VDD. However, vitamin D supplementation leads to earlier improvement and better response magnitude than group B.

They showed that CMC therapy with the addition of vitamin D and cyclosporine significantly improved TBUT and Schirmer better than the group treated with only CMC (group A). In this study, group C which was given both systemic and topical anti-inflammatory agents in vitamin D and topical anti-inflammatory drug—using cyclosporine, showed earlier improvement and better response magnitude than group B. However, the difference between groups B and C was not statistically significant.

In this study, the improvement of OSDI, TBUT, and lid hyperemia by topical treatment is significantly affected by supplementation of vitamin D through intramuscular injection (IM). This difference might be caused by different efficiency between oral and IM in increasing serum vitamin D. Some studies showed that high dose IM cholecalciferol is more effective in increasing serum vitamin D when compared to oral supplementation. One study also showed that supplementation of oral 2000 IU of cholecalciferol might be insufficient to elevate serum vitamin D.

Watts et al. is the only randomized intervention study found and included in this review. This study randomly divided 90 patients with DED and VDD into three groups; group A that receives CMC, group B that receives CMC and Vitamin D 2000 IU through the buccal spray, and group C that receive CMC, vitamin D, and 0.05% cyclosporine. Cyclosporine is a topical immunomodulatory agent with anti-inflammatory properties demonstrated to improve dry eye symptoms due to its effects on subconjunctival and lacrimal gland inflammation that caused increased tear production and goblet cell density.

Cochrane ROB risk of bias assessment in randomized studies.

OSDI score is higher in DED patients and supplementation of 1000 IU oral vitamin D for 8 weeks improved OSDI and FSS in vitamin D deficiency patients. Despite the improvement, regression analysis failed to show a significant correlation between vitamin D serum level and OSDI in the study group. Yang et al. argued that this result was because all participants in the dry eye group by nature of the inclusion criteria had high OSDI that did not vary in magnitude.

Hwang et al. study the effect of vitamin D supplementation and vitamin D deficiency (VDD) on topical therapy using CLAT and HU efficacy in DED patients. In this study, TBUT, FSS and severity of lid hyperemia only showed significant improvement in a non-VDD patient with normal vitamin D serum levels. In contrast, the Schirmer test only improved in VDD patients. FSS and lid hyperemia are related to inflammation of the ocular surface and eyelid. This study showed that the effect of topical therapy in improving clinical inflammation indicators is statistically proven, affected by the level of serum of vitamin D with its anti-inflammatory effect. Schirmer I tests was done without topical anesthesia to measure basal and reflexive tear secretion in this study. ANOVA analysis showed no significant difference in Schirmer test value in the two groups. Reduction of Schirmer test value in VDD group may be due to high variability of Schirmer test without anesthesia or decreased reflex tear flow in response to reduced ocular surface symptoms.

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study. However, after 10 weeks, only eyelid margin hyperemia, OSDI, and disease severity remain significantly better than pretreatment level.\textsuperscript{14} Eyelid margin hyperemia is related to meibomian gland dysfunction and eyelid inflammation that plays a major role in evaporative type DED.\textsuperscript{26} OSDI is a 12-item questionnaire developed to provide a rapid subjective assessment of ocular irritation consistent with DED.\textsuperscript{27} Disease severity in this study was assessed using a Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire.\textsuperscript{14} SPEED questionnaires, like OSDI, were developed to rapidly assessed symptoms of DED and its level of severity. This questionnaire showed a significant correlation with OSDI and was deemed suitable for detecting DED symptoms.\textsuperscript{28} They also found that objective tear stability was not sustained at 10 weeks after vitamin D injection but the subjective improvement and decreased inflammation persist.\textsuperscript{14}

Kizilgul et al. differ from other studies regarding the objective variable that indicates improvement after vitamin D supplementation. In this study, 44 patients with VDD are divided into DED and non-DED groups based on their Tear Film Osmolarity (TFO). Vitamin D is supplemented through intramuscular injection of 50,000 IU weekly for 8 weeks. After treatment, there is a significant increase of serum vitamin D. This study shows that supplementation for 8 weeks significantly improved TFO.\textsuperscript{15} In contrast to correlation data from Yang et al., this study indicates that TFO showed a negative correlation to the increase in serum vitamin D.\textsuperscript{14,15} This difference demonstrates that serum vitamin D level is correlated with objective measurement of tear instability, but this correlation is not reflected in OSDI.

Karaca et al. study the effect of vitamin D supplementation in VDD patients with meibomian gland disease with or without DED. Vitamin D supplementation in this study was given orally with a dose of 50,000 IU for 8 weeks and continued with 1,500–2,000 IU of oral vitamin D for up to 24 weeks. Like other studies, vitamin D supplementation significantly improved eyelid margin score, FSS, Schirmer I test, FSS, OSDI, TFO, and meibomian gland expressibility score. However, serum vitamin D does not correlate significantly with these variables.\textsuperscript{16} In contrast with Kizilgul et al’s findings, TFO does not correlate substantially with serum vitamin D levels.\textsuperscript{15} This shows that the correlation between serum vitamin D and TFO is inconclusive. The multifactorial nature of DED could cause this correlation. DEWS II described that DED is a multifactorial disease of the ocular surface which shows that vitamin D alone is not sufficient to correlate with the course of the disease despite the improvement of symptoms shown after supplementation.\textsuperscript{3}

Studies included in this systematic review all had similar limitations in which they are small sample sizes and, for the case of cohort studies, the lack of a control group. The only randomized study found during the literature search is Watts et al. which currently had the highest quality of evidence reviewed in this study. Therefore, there is a need for more research with better methodology and larger sample size to better understand the effect of vitamin D supplementation and DED, especially regarding its correlation.

**CONCLUSION**

Vitamin D supplementation improved tear stability and symptoms of dry eye disease and the level of serum vitamin D affected the efficacy of topical therapy for DED. Despite this beneficial finding, serum vitamin D level does not significantly correlate with DED symptoms which might be caused by the multifactorial nature of the disease. More research with a larger sample size and better methodology is needed to understand better the relationship between vitamin D supplementation and improvement of DED.

**COMPETING INTEREST**

The authors have declared that no competing interests exist.

**ETHICS CONSIDERATION**

This study has the following COPE and ICMJE protocols regarding the publication ethics guidelines for publication prior to the study being conducted.
FUNDING
The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

AUTHOR CONTRIBUTION
This work was carried out in collaboration between both authors. Author TA designed the study, collected the data and wrote the first draft of the manuscript. Author EC also managed the literature searches of the study. Both authors read and approved the final manuscript.

REFERENCE

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<th>Author (year)</th>
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<th>Intervention</th>
<th>Outcome</th>
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<tr>
<td>Yang et al. (2017)</td>
<td>Case-control</td>
<td>29 patients in the control group (54.2 ± 7.8 years old) and 29 patients in the dry eye group (56.1 ± 6.7 years)</td>
<td>Vitamin D supplementation of 1000 UI once per day for 8.6 weeks was given to patients selected for the supplement study</td>
<td>OSDI score is significantly higher in the dry eye group than in the control group (22.8 ± 16.0 vs. 11.4 ± 11.6; p = 0.0028)</td>
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<td>Outcome measurement</td>
<td>Vitamin D level is higher in dry eye group than in control group (87.7 ± 32.5 vs 61.1 ± 22.1 nmol/ml; p &lt; 0.001)</td>
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<td>OSDI did not significantly correlate with vitamin D level in the dry eye group (r = −0.23 p = 0.23)</td>
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<td>Supplement study</td>
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<td>The average OSDI score for the entire group was significantly lower after vitamin D treatment (baseline 21.0 ± 14.1 vs. after 10.5 ± 10.4)</td>
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<td>FSS significantly reduced after vitamin D treatment (before vs after, 0.53 ± 0.72 vs 0.31 ± 0.54; p = 0.03)</td>
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<td>No significant difference in tear meniscus, NITBUT, redness score for bulbar and limbal conjunctiva, Schirmer's test, and red phenol test</td>
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<td>Hwang et al. (2018)</td>
<td>Case-control</td>
<td>116 patients with DES were divided into two groups; vitamin D deficiency (VDD) group and non-VDD group with 12 ng/mL as a cutoff value</td>
<td>The patient then choose their source of vitamin D; none, injection of 200,000 IU once (IM group), and oral 2000 IU every day for 2 weeks</td>
<td>Response to topical CLAT and HU therapy is dependent on VDD</td>
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<td>Patients were treated using topical carbomer based lipid-containing artificial tear (CLAT) and 0.15% sodium hyaluronic acid (HU) for 2 weeks</td>
<td>Both OSDI and VAPS significantly decrease after topical treatment in both VDD and non-VDD group</td>
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<td>Topical therapy only improved TBUT, FSS, and severity of lid hyperemia significantly in the non-VDD group</td>
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<td>Schirmer's test only significantly decrease after topical therapy in the VDD group</td>
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<td>Response to topical CLAT and HU therapy is better after cholecalciferol supplementation</td>
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<td>OSDI score decreased in the IM group after supplementation when compared to pretreatment (p = 0.009) but not in none and oral group</td>
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<td>TBUT increases in the IM group after supplementation when compared to pretreatment (p &lt; 0.001) but not in none and oral group</td>
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<td>Lid margin hyperemia decreases in the IM group after supplementation when compared to pretreatment (p &lt; 0.001) but not in none and oral group</td>
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<td>Tear secretion and FSS were not different in all groups</td>
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| Watts et al. (2020) | RCT | 90 patients with DED and VDD were randomized into three groups | • Group A: treated with carboxymethylcellulose (CMC) 4 times per day  
• Group B: CMC + 2000 IU vitamin D through buccal spray once daily  
• Group C: CMC + 2000 IU vitamin D buccal spray + 0.05% cyclosporine 2 times per day | • Followed up on day-15, day-30, and day-90 for improvement  
• Outcome measurement: Schirmer test, TBUT, and OSDI | • Significantly higher TBUT score in day-90 at group B and C than group A (p < 0.05). There are no significant differences between groups B and C  
• TBUT group A only significantly increased at day-90 whereas, in group B and group C, significant increases are observed from day-15  
• Significantly higher Schimer's test I-value in day-90 at group B and C compared to group A (p < 0.05). There are no significant differences between groups B and C  
• Schirmer's test for group A only significantly increased at day-90 whereas in group B significant increases are observed from day-15 and group C from day-30  
• No significant response to mean OSDI score in all three groups in all follow-up time |
| Bae et al. (2016) | Cohort | 105 patients with DED | • Patients with vitamin D deficiency or insufficiency were treated with 200,000 IU intramuscular injection of cholecalciferol  
• Data were obtained at pretreatment, 2 weeks, 6 weeks, and 10 weeks after vitamin D supplementation  
• Outcome measurement: TBUT, FSS, Schirmer test. Hyperemia and telangiectasia of the eyelid margin, conjunctivochalasis (CCH), OSDI, and VAS | | • TBUT significantly increased in 2 weeks (p < 0.001), 6 weeks (p = 0.001) before returning to pre-treatment level at 10 weeks (p = 0.06)  
• FSS significantly decreases in 2 weeks (p = 0.013) but returned to pre-treatment level at 6 weeks (p = 0.083) and 10 weeks (p = 0.826)  
• Hyperemia significantly decreases after treatment and keep significantly improved until 10 weeks (p < 0.001, <0.001 and 0.006)  
• CCH is not significantly affected by treatment  
• Schirmer test significantly increases until 6 weeks but returned to pretreatment level at 10 weeks (p = 0.006, 0.015, 0.146)  
• OSDI score significantly decreases until 10 weeks post-treatment (p = 0.046 and 0.004)  
• VAS score significantly decreases until 2 weeks but returned to pretreatment level at 6 and 10 weeks (p = 0.005, 0.059 and 0.085)  
• Symptoms severity keep significantly decreases up to 10 weeks after treatment  
• Symptoms duration significantly decreases up to 6 weeks after treatment |
| Kizilgul et al. (2017) | Cohort | 44 patients with VDD were divided into DED and non-DED groups based on tear film osmolarity (TFO) with a cutoff of ≥309 mOsm/L | • Supplementation through injection of 50,000 IU of cholecalciferol once weekly for 8 weeks | | • TFO (313.7 ± 17.3 mOsm/L vs 302.7 ± 14.2 mOsm/L; p < 0.001) and serum parathyroid hormone (70.4 ± 21.9 pg/mL to 40.0 ± 14.5 pg/mL; p < 0.001) was significantly decreased after 8 weeks of treatment  
• Serum vitamin D level increased from 8.3 ± 3.5 ng/mL to 68.8 ± 22.3 ng/mL (p < 0.001) after treatment  
• The change of TFO is negatively correlated with the change of serum vitamin D before and after supplementation in DED patients (r = -0.390, p = 0.049) |
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<td>Karaca et al. (2020)</td>
<td>Cohort</td>
<td>40 patients with VDD with meibomian gland disease with or without DED were included</td>
<td>Patients received 50,000 IU of oral vitamin D over 8 weeks and then 1,500-2,000 IU per day for 24 weeks. Data were measured at baseline, 8, 12, and 24 weeks. Outcome measurement: eyelid margin score (LMS), meibomian gland expressibility score (MGS), FSS, Schirmer I test, TBUT, TFO, and OSDI</td>
<td>LMS significantly decreased after 12 weeks and 24 weeks. MGS significantly decreased after 8 weeks and kept decreasing up to 24 weeks. FSS significantly decrease after 12 and 24 weeks. Schirmer test value and TBUT increases at 8, 12, and 24 weeks. TFO and OSDI decrease at 8, 12, and 24 weeks. Serum level of vitamin D failed to show and correlation to all variables.</td>
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