Note

Vitamin D Deficiency Is Associated with Severity of Dry Eye Symptoms and Primary Sjögren's Syndrome: A Systematic Review and Meta-Analysis

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Summary

We aimed to examine the correlations between vitamin D deficiency, severity of dry eye symptoms and primary Sjögren’s syndrome (pSS) by performing a systematic review and meta-analysis. Online databases (PubMed, Cochrane Library, and Embase) were searched to identify controlled studies comparing (1) severity of dry eye symptoms between participants with and without vitamin D deficiency; and (2) serum vitamin D levels between patients with and without pSS. Eighteen studies were included. Overall, individuals with vitamin D deficiency had shorter tear breakup time (TBUT), lower Schirmer’s test scores and higher ocular surface disease index (OSDI) score than those without vitamin D deficiency. Additionally, serum vitamin D levels were found to be lower in pSS than controls. Our findings highlight the importance of vitamin D deficiency in the severity of dry eye symptoms and pSS.

Key Words interleukin 6, ocular surface disease index, Schirmer’s test, tear breakup time, Th1 cells, Th17 cells

Dry eye disease (DED) is a common cause of visual disturbance. The etiology of DED is multifactorial and it could be a manifestation of systemic diseases such as primary Sjögren’s syndrome (pSS). DED and pSS share some inflammatory responses at the lacrimal gland and ocular surface (1). Some studies have revealed that vitamin D facilitates inflammation regulation, ocular surface homeostasis and corneal epithelial barrier function (2, 3). However, the association between vitamin D deficiency, severity of dry eye symptoms and pSS remains controversial. We therefore conducted a systematic review and meta-analysis to address this issue.

Materials and Methods

Online databases (PubMed, Cochrane Library, and Embase) were searched on April 12, 2019 to identify controlled studies comparing (1) severity of dry eye symptoms between participants with and without vitamin D deficiency; and (2) serum vitamin D levels between patients with and without pSS. Eighteen studies were included. Overall, individuals with vitamin D deficiency had shorter tear breakup time (TBUT), lower Schirmer’s test scores and higher ocular surface disease index (OSDI) score than those without vitamin D deficiency. Additionally, serum vitamin D levels were found to be lower in pSS than controls. Our findings highlight the importance of vitamin D deficiency in the severity of dry eye symptoms and pSS.

Results

Eighteen studies that met the inclusion criteria were included (Supplemental Online Material, Fig. S1). The characteristics of included studies were summarized in Table S2. The pooled estimate of five studies involving 372 participants revealed that individuals with vitamin D deficiency had shorter TBUT than those without vitamin D deficiency (SMD = −2.63, 95% confidence interval [CI] = −4.116 to −1.141, I² = 96.9%) (Fig. 1A). The pooled analysis of six studies involving 401 participants revealed that individuals with vitamin D deficiency had a significantly lower Schirmer’s test score than those without vitamin D deficiency (SMD = −0.981, 95% CI = −1.843 to −0.119, I² = 93%) (Fig. 1B). The pooled analysis of six studies involving 430 participants re-
revealed that individuals with vitamin D deficiency had a significantly higher OSDI score than those without vitamin D deficiency (SMD = 0.573, 95% CI = 0.262 to 0.885, $I^2 = 53.7\%$) (Fig. 1C).

Twelve studies involving 2,135 individuals were included for the analysis of pSS. The pooled analysis showed that serum vitamin D level was significantly lower in patients with pSS than that in the control group (SMD = -0.297, 95% CI = -0.585 to -0.01, $I^2 = 86.9\%$) (Fig. 2). A sensitivity analysis excluding studies with non-healthy controls revealed a consistent result (9 studies; SMD = -0.44, 95% CI = -0.733 to -0.147).

**Discussion**

Inflammation is the key component involved in DED and ocular surface integrity. Several stress factors may disturb the ocular surface homeostasis and activate the inflammatory response, including environmental challenges, infection, inflammation, autoimmunity, and endogenic stress (4). Vitamin D has been shown to modulate inflammatory responses through several pathways, including inhibition of Th1 and Th17 cells by upregulating regulatory T cells; facilitation of T cell differentiation toward Th2 pathway; downregulation of interleukin 6 (IL-6) levels; and inhibition of adaptive immunity by regulating the interaction between antigen-presenting cells and lymphocytes (1, 2).

Li et al. revealed, in a previous meta-analysis, a non-significant association between vitamin D and pSS (5). However, the current analysis included more studies through a more comprehensive search of the existing literature, demonstrating a significantly lower serum vitamin D levels in patients with pSS.

The important role that vitamin D plays in DED and pSS was highlighted by recent studies demonstrating the efficacy of vitamin D supplementation in treating...
dry eye symptoms. Bae et al. reported that administration of vitamin D improved both subjective symptoms and objective scores in patients who were unresponsive to conventional medical treatment and surgical intervention for DED (6). Kizilgul et al. also revealed that vitamin D supplementation could improve tear quality in subjects with vitamin D deficiency by reducing tear osmolarity (7), which has been regarded as the hallmark of DED and will damage the ocular surface both directly and by initiating inflammation (8).

There were some limitations in our study. First, the number of studies eligible for analysis was limited. Second, the included studies were heterogeneous. There are several factors that can influence serum vitamin D levels, such as gender, age, sun exposure level, smoking status, and blood pressure. Moreover, we could only reveal correlations between vitamin D deficiency, dry eye symptoms and pSS but could not prove causality.

In conclusion, our study revealed that individuals with vitamin D deficiency are prone to more severe dry eye symptoms, and that pSS patients have lower serum vitamin D levels than controls. Further studies are required to clarify the underlying mechanisms and the therapeutic effects of vitamin D in alleviating dry eye symptoms.

Authorship
Che-Yuan Kuo and Tsung-Yu Tsai conceived and designed the study. Che-Yuan Kuo and Tsung-Yu Tsai contributed to the literature search and extracted data. Tsung-Yu Tsai and Yu-Chen Huang participated in statistical analysis. Che-Yuan Kuo, Yu-Chen Huang, Ko-Jo Lin and Tsung-Yu Tsai finished and reviewed the manuscript.

Tsung-Yu Tsai and Ko-Jo Lin contributed equally to this study as corresponding authors.

Disclosure state of COI
The authors declare that there are no conflicts of interest.

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Supporting information
Supplemental online material is available on J-STAGE.

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