Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v30i19.3817

VITAMIN D SUPPLEMENTATION IN DRY EYE DISEASE: A SYSTEMATIC REVIEW

Muhammad Nur Agung Mappatanga[1], Junaedi Sirajuddin[1], Hasnah Eka[1]

[1]Department of Opthalmology, Faculty of Medicine, Hasanuddin University, Hasanuddin University Hospital, Makassar, Indonesia

***Corresponding authors:-** Muhammad Nur Agung Mappatanga, MD.
*Department of Opthalmology, Faculty of Medicine, Hasanuddin University, Hasanuddin University Hospital, Makassar, Indonesia
E-mail: dr.muhammadnuragungm@gmail.com

Abstract

Background: Dry eye disease (DED) is a multifactorial ocular condition characterized by a disruption in the tear film. This review aims to elucidate the potential mechanisms underlying the relationship between Vitamin D and DED, evaluate the consistency of findings across diverse studies, and identify areas for future research and clinical applications.

Methods: A systematic review was performed by searching relevant studies until November 2023 using the PubMed, MEDLINE, and EMBASE databases. Studies involving individuals with DED and has vitamin D supplementation were included in this review.

Results: The systematic literature search identified 12 studies meeting the inclusion criteria, covering various aspects of vitamin D and DED. The results of this systematic review shed light on the diverse aspects of vitamin D supplementation in the context of DED. By synthesizing findings from selected studies, the review examines the influence of vitamin D on DED symptomatology, clinical outcomes, and relevant biochemical markers. The results contribute to a nuanced understanding of the potential benefits or limitations of vitamin D supplementation in the management of DED. Detailed analysis of the selected studies offers valuable insights into the current state of knowledge and highlights areas that warrant further investigation.

Conclusion: In conclusion, this systematic review provides a comprehensive overview of the existing literature on vitamin D supplementation and its relevance to dry eye disease. The findings collectively suggest that vitamin D supplementation holds potential as a therapeutic intervention for DED, impacting symptoms, clinical outcomes, and associated biochemical markers. However, further research is warranted to elucidate optimal dosage, duration, and specific patient populations that may benefit most from this intervention.

Keywords: dry eye disease, opthalmology, vitamin D, treatment, eye disease

Introduction

Dry eye disease (DED) is a multifactorial ocular condition characterized by a disruption in the tear film, leading to symptoms of discomfort, visual disturbances, and potential damage to the ocular surface [1]. This instability can result in inflammation and damage to the eye's surface, as well as abnormal pain perception [2]. It is a prevalent and clinically significant disorder affecting millions of individuals globally, with a considerable impact on the quality of life and daily functioning of affected individuals [3]. The prevalence across the globe varies from 5% to 50%, contingent on the geographical

location [4]. While various etiological factors contribute to the development and progression of DED, emerging evidence suggests a potential role of systemic factors, including nutritional status.

Vitamin D, a fat-soluble secosteroid hormone, is traditionally recognized for its essential role in calcium metabolism and bone health [5]. However, recent research has expanded our understanding of its pleiotropic effects, encompassing immune modulation, anti-inflammatory properties, and potential contributions to ocular health [6]. Vitamin D's ability to modulate immune and inflammatory responses suggests that systemic supplementation may be an effective therapeutic approach [2]. The presence of Vitamin D receptors in ocular tissues, including the cornea and conjunctiva, raises intriguing questions about its influence on the homeostasis of the ocular surface.

Despite the growing interest in the relationship between Vitamin D and ocular health, the precise impact of Vitamin D supplementation on dry eye disease remains a subject of ongoing investigation [7]. In recent times, the insufficiency of vitamin D has been associated not solely with its acknowledged involvement in musculoskeletal disorders such as rickets or osteomalacia and mental health but also with various other conditions [8]. These encompass malignancies, type 2 diabetes mellitus, metabolic syndrome, hypertension, cardiovascular diseases, immune disorders, autoimmune disorders, and eye-related conditions. While individual studies have explored this association, a comprehensive synthesis of existing evidence through a systematic review is essential for a nuanced understanding of the potential benefits or limitations of Vitamin D supplementation in managing dry eye disease.

The rationale for this systematic review stems from the need to address existing gaps in the literature, assess the methodological quality of available studies, and provide clinicians and researchers with a consolidated and evidence-based perspective on the role of Vitamin D supplementation in dry eye disease. By systematically evaluating the existing body of literature, this review aims to elucidate the potential mechanisms underlying the relationship between Vitamin D and DED, evaluate the consistency of findings across diverse studies, and identify areas for future research and clinical applications.

Methods

Data sources, search strategy, and study selection

This systematic investigation adhered to the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [9]. The research plan was recorded in the PROSPERO database prior to the commencement of the study. A comprehensive literature search was conducted in electronic databases including PubMed, Embase, and MEDLINE. The search strategy was designed to identify studies published up to the present date that investigated the use of vitamin D in DED. The following keywords and their combinations were used: "dry eye disease", "keratokonjungtivitis sica", "vitamin D", "vitamin", "treatment" and related terms. The search was restricted to studies conducted in humans and published in English.

The outcomes of the electronic searches were brought into the EndNote bibliographic software. Studies were included if they met the following criteria: (1) original research articles reporting on the examination of vitamin D for dry eye disease; (2) studies presenting data on progression, prognostic, and efficacy; and (3) studies involving human participants with a diagnosis of DED. We did not include research that: (1) were not complete scientific articles; (2) were reviews, letters, or commentaries; (3) were written in languages other than English; and (4) were reevaluations of prior or initial studies.

Data extraction and quality assessment

Two autonomous reviewers meticulously conducted the initial screening of the identified studies by scrutinizing titles and abstracts. Subsequently, a comprehensive full-text review was undertaken for articles deemed potentially relevant, ensuring a thorough examination of pertinent literature. Any disparities in the screening process were judiciously addressed through extensive discussions between the two reviewers and, when necessary, the involvement of a third reviewer for resolution. The systematic data extraction process was facilitated using a meticulously crafted standardized form, encompassing key elements such as study design, participant characteristics, the targeted treatment,

outcome measures, and detailed results pertaining to the potential treatment and outcomes under investigation.

To gauge the quality and potential risk of bias within the included studies, the evaluation was conducted utilizing the established tools provided by the Joanna Briggs Institute [10]. The assessment encompassed a comprehensive analysis of potential biases related to study design, participant selection criteria, comparability of participant groups, the methodology employed for outcome assessment, and the reporting standards. This rigorous evaluation aimed to provide a robust foundation for the overall reliability and validity of the synthesized evidence, ensuring a comprehensive understanding of the methodological strengths and limitations inherent in the selected studies.

Data synthesis and analysis

A narrative synthesis approach was employed, wherein findings from the selected studies were systematically summarized and analyzed thematically. The primary objective of this synthesis was to discern patterns of treatment effects, systematically investigate variations in outcomes observed across diverse studies, and offer comprehensive insights into the overarching trajectory of the accumulated evidence. By adopting a narrative synthesis methodology, the study aimed to distill key themes and trends from the diverse literature, facilitating a nuanced understanding of the treatment landscape and contributing to a cohesive narrative that enriches the broader comprehension of the subject matter. This methodological choice not only allowed for a holistic examination of the selected studies but also facilitated the extraction of meaningful patterns and implications, offering a robust foundation for informed discussions and future research directions.

Results

Utilizing the aforementioned criteria, we identified 3627 studies, and 417 of these studies were subsequently excluded on the grounds of duplication (Figure 1). There were 164 eligible studies recruited to be evaluated for the fulltext. In this study, we excluded 21 conference abstract/review/commentaries, 44 studied other exposure, 57 studies were not reported the outcome of interest, and 13 studies were non-English study. Finally, there were 12 studies included in this study. The characteristics of the included studies are presented in Table 1. The risk of bias assessment using Joanna Briggs Institute's critical appraisal checklist is discussed in more detail in Table 2.

Treatment for patient with DED

Given that the disruption of tear film homeostasis is a pivotal event in the pathogenesis of Dry Eye Disease (DED), initiating a cycle of hyperosmolarity within the tear film and inflammation on the ocular surface, the primary objective of DED treatment is to restore this homeostatic equilibrium and break the associated vicious cycle. This can be accomplished through two distinct approaches: the prevention of corneal surface desiccation and the suppression of ocular inflammatory responses. Historically, tear substitutes, including lubricants, drops, ointments, and gels, have been pivotal in preventing corneal surface desiccation. These substitutes aim to address inadequate tear production by providing essential ocular lubrication, thereby reducing tear evaporation and stabilizing the tear film. Hyaluronic acid, a hydrophilic glycosaminoglycan naturally occurring in the human body, is frequently employed in tear substitutes due to its capacity to enhance tear film stability by increasing viscosity, improving retention time, and optimizing hydration and lubrication of the ocular surface.

For the management of ocular surface inflammation, topical corticosteroids serve as potent inhibitors of inflammatory mediators, effectively interrupting the sustained inflammatory cycle. They suppress matrix metalloproteinases (MMPs), acute phase cytokines IL-1 and TNF-α, chemokines, ICAM-1, and reduce leukocyte infiltration in inflamed ocular tissue. However, the limitations of these approaches become evident in the palliative nature of tear substitutes and the potential adverse events associated with prolonged use of topical corticosteroids, such as cataracts and ocular hypertension. Consequently, when existing treatments fail to achieve a safe and complete restoration of the physiological ocular status, alternative strategies are imperative.

Recent attention has turned to vitamin D as a potential alternative for preventing and treating DED, primarily due to its regulatory role in various immune-inflammatory processes. The active form of vitamin D, 1,25(OH)2D, exhibits the capability to inhibit cell proliferation, stimulate differentiation, and modulate inflammatory cytokines dependent on NF-κB activity across diverse cell types. Robust scientific evidence underscores 1,25(OH)2D as a potent immune system and inflammation modulator, enhancing innate immunity and inhibiting autoimmunity. Given its profound effects on immune regulation, vitamin D may influence the development of DED, a disorder intricately linked to dysfunctional immune regulation and inflammation. Consequently, systemic administration of vitamin D emerges as a potential adjuvant therapy for DED, offering a novel avenue for the management of this condition.

Evidence lingking DED with vitamin D

Various ocular pathologies, including uveitis, retinoblastoma, diabetic retinopathy, age-related macular degeneration, myopia, and dry eye, have been linked to vitamin D deficiency and genetic variations in its metabolic regulation. Initial insights into the pivotal role of vitamin D in ocular health emerged from preclinical investigations, revealing the presence of vitamin D receptors (VDR) and enzymes involved in vitamin D metabolism in numerous ocular cell types. This suggests that vitamin D functions as a paracrine/autocrine regulator within the eye. Experimental evidence supports this hypothesis, indicating that retinal and corneal cells can convert vitamin D to its active form, and under UV irradiation, they can synthesize vitamin D from exogenous 7-dehydrocholesterol.

Further substantiating the eye-specific role of vitamin D, its metabolites have been detected in tear fluid, aqueous humor, and vitreous humor, implying local production. Notably, 25(OH)D levels in human tears surpass corresponding serum concentrations. Mouse studies have underscored the critical role of vitamin D in corneal integrity, demonstrating impaired corneal epithelium healing with VDR gene inactivation and a beneficial effect on corneal epithelium barrier function.

In vivo studies have highlighted the potent modulatory role of vitamin D in the innate and adaptive immune system within the eye. Vitamin D inhibits corneal inflammation by suppressing Langerhans cell migration, reducing proinflammatory mediators, and mitigating inflammation in dry eye models. Vitamin D deficiency has been associated with reduced tear break-up time, lower Schirmer test values, tear hyperosmolarity, and tear film dysfunction, suggesting a correlation with dry eye symptoms. This association is supported by genetic evidence, with single-nucleotide polymorphisms in VDR genes linked to dry eye occurrence.

Several studies, including case–control and population-based studies, have established a significant association between low serum vitamin D concentrations and the occurrence of dry eye. While some studies found no direct correlation, a recent meta-analysis, encompassing a wide range of data, affirmed lower serum vitamin D levels in dry eye patients compared to healthy subjects, indicating a statistically significant association between vitamin D deficiency and dry eye symptoms. Collectively, these findings suggest that adequate sunlight exposure or vitamin D supplementation may be beneficial for individuals suffering from dry eye.

Vitamin D supplementation to manage DED

Vitamin D supplementation has demonstrated clinical improvement in Dry Eye Disease (DED) both in clinical settings and experimental models. Its anti-inflammatory properties are particularly significant in the context of treating ocular surface conditions such as DED and keratoconus (KC). Vitamin D plays a multifaceted role in corneal wound healing, leveraging its anti-inflammatory and extracellular matrix remodeling properties.

Following oral intake, both ergocalciferol and cholecalciferol forms of vitamin D are efficiently absorbed in the small intestine, peaking in plasma levels around 24 hours post-administration. Cholecalciferol appears to sustain more stable concentrations of serum 25(OH)D compared to ergocalciferol. Recent in vivo and in vitro studies propose that vitamin D absorption might involve mechanisms mediated by membrane carrier proteins, potentially including cholesterol transporters.

Furthermore, the concurrent ingestion of fat-containing food has been observed to enhance the absorption of vitamin D.

Despite the widespread recommendation of vitamin D supplementation for DED treatment, the number of clinical studies examining its impact remains limited. Notably, a study demonstrated a statistically significant improvement in average scores of Ocular Surface Disease Index (OSDI) and Dry Eye Questionnaire 5 (DEQ5) in the vitamin D group compared to the control after 8 weeks. Observational studies have reported positive effects of intramuscular vitamin D administration in patients with vitamin D deficiency and refractory DED, including enhanced tear secretion, reduced tear instability and inflammation at the ocular surface, and improved DED symptoms. Additionally, systemic vitamin D replacement therapy has shown promise in improving tear hyperosmolarity, ocular surface health, and dry eye symptoms. The association between low vitamin D concentrations and dry eye symptoms was suggested in a study, and systemic vitamin D supplementation demonstrated efficacy in enhancing the effects of topical lubricants in DED patients.

Potential side effects of management DED and vitamin D supplementation

Managing DED and incorporating vitamin D supplementation into the treatment regimen can offer promising outcomes, but it is essential to be aware of potential side effects associated with these approaches. In the case of DED management, commonly prescribed treatments such as artificial tears, anti-inflammatory medications, and punctal plugs may come with certain side effects. Artificial tears, while generally well-tolerated, can sometimes cause temporary blurred vision or discomfort upon application. Anti-inflammatory medications, such as corticosteroid eye drops, may lead to elevated intraocular pressure or an increased risk of infection with prolonged use. Punctal plugs, designed to prevent tear drainage and maintain moisture on the ocular surface, can occasionally cause irritation, tearing, or the formation of plugs visible at the tear duct openings.

On the other hand, vitamin D supplementation, often recommended for its potential immune system benefits and anti-inflammatory properties, may also have side effects. Excessive vitamin D intake can result in hypercalcemia, leading to symptoms such as nausea, vomiting, weakness, and, in severe cases, kidney damage. It is crucial to monitor vitamin D levels regularly and adjust supplementation accordingly to prevent toxicity. Additionally, individuals with certain medical conditions or those taking specific medications should consult their healthcare providers before initiating vitamin D supplementation to avoid potential interactions and adverse effects. Balancing the benefits and risks of both DED management and vitamin D supplementation is key to optimizing patient outcomes and ensuring their overall well-being. Regular monitoring and open communication with healthcare providers can help address any emerging side effects promptly and tailor treatment plans for individual needs.

Future potential treatment in patients with DED

In the realm of potential treatments for DED, the exploration of vitamin D supplementation has emerged as a noteworthy consideration. Research suggests that vitamin D, known for its immunomodulatory and anti-inflammatory properties, could play a role in managing the inflammatory aspects of DED. While vitamin D supplementation is not a standalone cure, it may be beneficial as an adjunctive measure, particularly for individuals with vitamin D deficiency or insufficiency.

Incorporating vitamin D into the overall treatment plan may involve optimizing levels through dietary adjustments, exposure to sunlight, and, when necessary, supplementation. Collaborative efforts between eye care professionals and healthcare providers could help tailor vitamin D interventions based on individual patient needs. Regular monitoring of vitamin D levels and adjusting supplementation accordingly could be part of a personalized approach to enhance the effectiveness of DED management.

Discussion

The novelty of our study is rooted in the exploration of vitamin D supplementation among individuals diagnosed with DED. Additionally, our investigation has unveiled vitamin D supplementation as a proposed therapeutic modality for patients afflicted with DED. The findings from our study indicate that vitamin D supplementation holds promise as a potential treatment option for individuals experiencing DED.

Our findings highlighted the importance of vitamin D to manage patients with DED. Our findings illuminate the potential therapeutic significance of vitamin D supplementation as an adjunctive approach for DED management. Vitamin D's anti-inflammatory properties, as evidenced in both experimental models and clinical observations, suggest its capacity to mitigate the inflammatory responses characteristic of DED [11]. Moreover, the involvement of vitamin D in corneal wound healing, coupled with its modulation of the innate and adaptive immune system within the ocular environment, positions it as a key player in maintaining ocular surface homeostasis [12]. The observed correlations between vitamin D deficiency and various DED parameters, including tear stability, hyperosmolarity, and inflammation, highlight the clinical relevance of adequate vitamin D levels [13]. Recognizing vitamin D as a potential treatment option adds a new dimension to the therapeutic landscape for DED, providing insights into a systemic approach that extends beyond traditional topical interventions.

The exploration of future potential treatments for patients with DED holds promise, with particular emphasis on the role of vitamin D. As discussed in our study, vitamin D supplementation emerges as a compelling avenue for consideration in the management of DED. The demonstrated anti-inflammatory properties of vitamin D, coupled with its involvement in immune system modulation, suggest its potential efficacy in addressing the underlying inflammatory processes associated with DED [14]. The findings underscore the need for further research to elucidate the specific mechanisms through which vitamin D influences ocular health and to establish optimal dosage regimens. Additionally, investigating the interplay between vitamin D and other treatment modalities could unveil synergistic effects for more comprehensive DED management strategies [15]. While our study contributes to the growing body of evidence supporting the potential benefits of vitamin D supplementation, future clinical trials and in-depth mechanistic studies are imperative to solidify its place as a viable and effective treatment option for DED patients.

There are some limitations of this study. The diversity in methodologies and sample sizes across studies can introduce heterogeneity, impacting the generalizability of the findings. Furthermore, the temporal dimension is a factor to consider, as the paper's knowledge cutoff date may not include the most recent developments in vitamin D research in dry eye disease. Finally, while the paper highlights the diagnostic, prognostic, and therapeutic potential of vitamin D, the translation of research findings into clinical practice may be influenced by external factors, such as healthcare infrastructure and patient heterogeneity. These limitations underscore the need for ongoing research and real-world validation to ensure the effective integration of vitamin D-related insights into DED management.

Conclusions

In conclusion, this comprehensive review underscores the multifaceted relevance of vitamin D supplementation in DED. The significance of vitamin D supplementation as a potential treatment in the context of DED patients is highlighted. As research and clinical applications continue to evolve, integrating vitamin D supplementation into clinical practice may enhance the precision of DED management and treatment, ultimately benefiting patients.

Acknowledgements

The authors would like to thank all the contributors in this study

Funding

There was no funding for this study

Competing interests
The authors declare that they have no conflicts of interest

References

1. Buckley RJ. Assessment and management of dry eye disease. Eye (London, England). 2018;32(2):200-3.
2. Rolando M, Barabino S. Dry Eye Disease: What Is the Role of Vitamin D? International journal of molecular sciences. 2023;24(2).
3. Uchino M, Schaumberg DA. Dry Eye Disease: Impact on Quality of Life and Vision. Current ophthalmology reports. 2013;1(2):51-7.
4. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. TFOS DEWS II Epidemiology Report. The ocular surface. 2017;15(3):334-65.
5. Dominguez LJ, Farruggia M, Veronese N, Barbagallo M. Vitamin D Sources, Metabolism, and Deficiency: Available Compounds and Guidelines for Its Treatment. Metabolites. 2021;11(4).
6. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. Microbiology and molecular biology reviews : MMBR. 2012;76(1):16-32.
7. Chan HN, Zhang XJ, Ling XT, Bui CH, Wang YM, Ip P, et al. Vitamin D and Ocular Diseases: A Systematic Review. International journal of molecular sciences. 2022;23(8).
8. Wintermeyer E, Ihle C, Ehnert S, Stöckle U, Ochs G, de Zwart P, et al. Crucial Role of Vitamin D in the Musculoskeletal System. Nutrients. 2016;8(6).
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical research ed). 2021;372:n71.
10. 2020 [Internet]. JBI Manual for Evidence Synthesis. Chapter 7: Systematic reviews of etiology and risk.
11. Yin K, Agrawal DK. Vitamin D and inflammatory diseases. Journal of inflammation research. 2014;7:69-87.
12. Reins RY, Hanlon SD, Magadi S, McDermott AM. Effects of Topically Applied Vitamin D during Corneal Wound Healing. PloS one. 2016;11(4):e0152889.
13. Malik D, Garg R, Sethi S, Mahendru R, Singh S. Serum Vitamin D Levels and Dry Eye Disease in Postmenopausal Women: A Case-Control Study at a Tertiary Care Center in Rural Haryana. International journal of applied & basic medical research. 2023;13(2):83-8.
14. Ao T, Kikuta J, Ishii M. The Effects of Vitamin D on Immune System and Inflammatory Diseases. Biomolecules. 2021;11(11).
15. Wei Y, Asbell PA. The core mechanism of dry eye disease is inflammation. Eye & contact lens. 2014;40(4):248-56.
16. Hassanpour K, Langari F, Akbarzadeh AR, Kanavi MR, Barani M, Kheiri B, et al. Safety and Efficacy of Topical Vitamin D in the Management of Dry Eye Disease Associated With Meibomian Gland Dysfunction: A Placebo-Controlled Double-Blind Randomized Controlled Trial. Cornea. 2023.
17. Gorimanipalli B, Shetty R, Sethu S, Khamar P. Vitamin D and eye: Current evidence and practice guidelines. Indian journal of ophthalmology. 2023;71(4):1127-34.
18. Kizilgul M, Kan S, Ozcelik O, Beysel S, Apaydin M, Ucan B, et al. Vitamin D Replacement Improves Tear Osmolarity in Patients with Vitamin D Deficiency. Seminars in ophthalmology. 2018;33(5):589-94.
19. Lin Y, Su H, Wu J, Yuan M, Zhang Y. Oral vitamin D(3) supplementation for femtosecond LASIK-associated dry eye vitamin D for LASIK dry eye syndrome. International ophthalmology. 2022;42(10):3145-52.
20. McCusker MM, Durrani K, Payette MJ, Suchecki J. An eye on nutrition: The role of vitamins, essential fatty acids, and antioxidants in age-related macular degeneration, dry eye syndrome, and cataract. Clinics in dermatology. 2016;34(2):276-85.

21. Najjaran M, Zarei-Ghanavati S, Arjmand Askari E, Eslampoor A, Ziaei M. Effect of oral vitamin D supplementation on dry eye disease patients with vitamin D deficiency. Clinical & experimental optometry. 2023;106(3):257-62.
22. Park SH, Hwang JS, Shin YJ. Effect of multivitamin drug on intractable dry eye symptoms. Frontiers in medicine. 2022;9:978107.
23. 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. Contact lens & anterior eye : the journal of the British Contact Lens Association. 2018;41(1):69-76.
24. Watts P, Sahai A, Kumar PR, Shamshad MA, Trivedi GK, Tyagi L. A prospective study to assess the role of vitamin D individually and in combination with cyclosporine in the treatment of dry eye in patients with deficient serum 25(OH)D levels. Indian journal of ophthalmology. 2020;68(6):1020-6.
25. Hwang JS, Lee YP, Shin YJ. Vitamin D Enhances the Efficacy of Topical Artificial Tears in Patients With Dry Eye Disease. Cornea. 2019;38(3):304-10.
26. Karaca EE, Kemer Ö E, Özek D, Berker D, Imga NN. Clinical outcomes of ocular surface in patients treated with vitamin D oral replacement. Arquivos brasileiros de oftalmologia. 2020;83(4):312-7.

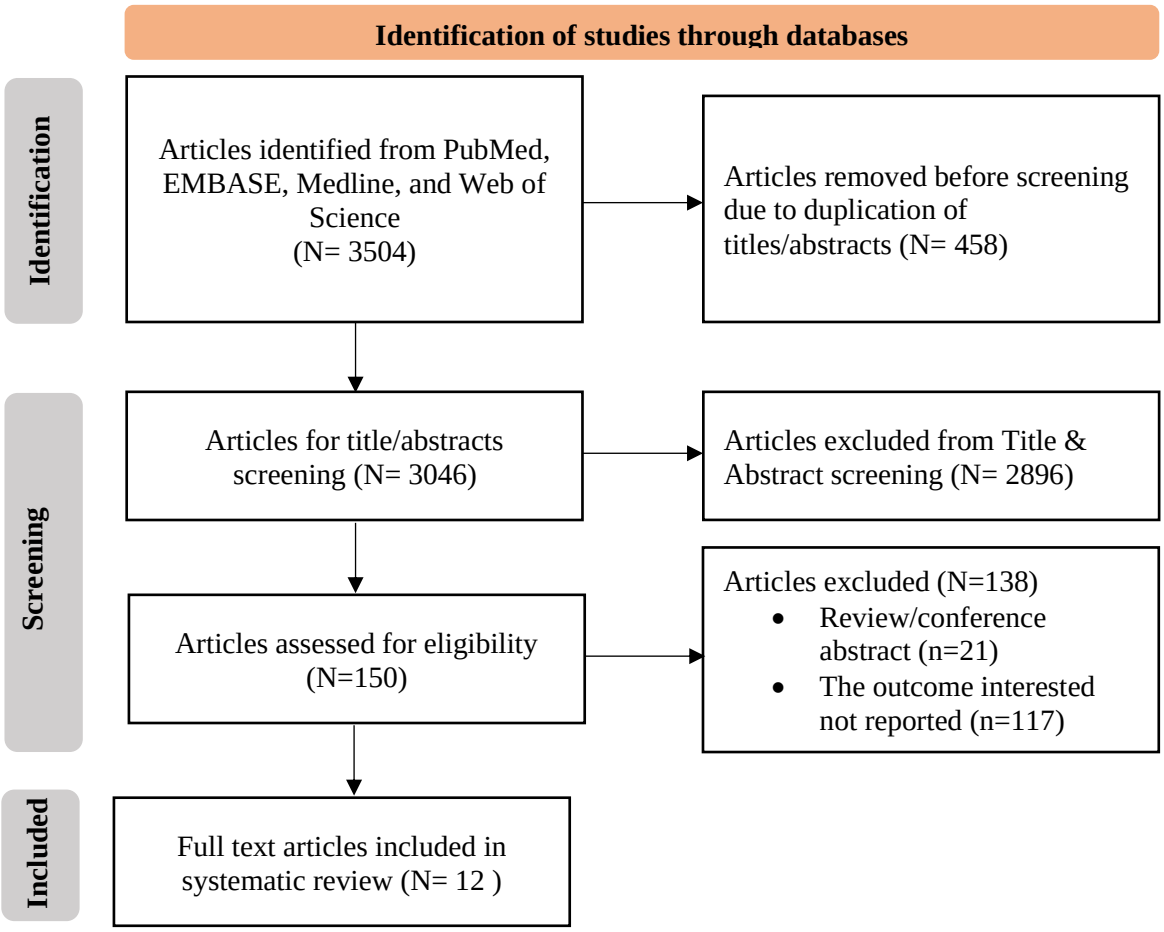

Figure 1. Flowchart of the study

Table 1. Studies with evaluation of vitamin D supplementation for dry eye disease

No	Author	Study year	Study design	Findings
1	Hassanpour, et al [16]	2023	Randomized control design	There was a significant difference between the treatment and control groups after 8 weeks for OSDI, DEQ5, Schirmer, TBUT, corneal fluorescein staining, and MG expressibility score
2	Gorimanipalli, et al [17]	2023	Retrospective observational study	Vitamin D plays a multifaceted role in corneal wound healing with its anti-inflammatory and extracellular matrix remodeling properties
3	Kizilgul, et al [18]	2018	Prospective clinical study	Tear film osmolarity, an important indicator of dry eye disease, decreased after successful vitamin D replacement
4	Lin, et al [19]	2022	Randomized control design	Vitamin D improved the outcome of DED patients
5	McCusker, et al [20]	2022	Randomized control design	Vitamin D level play an important role in patients with DED
6	Najjaran, et al [21]	2023	Randomized control design	Vitamin D supplementation as an adjuvant to routine dry eye treatment improves ocular surface hemostasis parameters, results in better tear stability and a more improved tear osmolarity in patients with vitamin D deficiency.
7	Park, et al [22]	2022	Prospective intervemtional randomized study	Oral administration of vitamin D was effective in stabilizing tear stability and alleviating symptoms in patients with intractable dry eye
8	Yang, et al [23]	2018	Prospective intervemtional randomized study	Low vitamin D levels (<50nmol/l) were associated with dry eye symptoms in older individuals but not those diagnosed with dry eye. Vitamin D supplement increased the vitamin D levels, and improved dry eye symptoms.
9	Malik, et al [13]	2023	Retrospective observational study	Vitamin D was significantly lower in DED. Vitamin D level play an important role in patients with DED
10	Watts, et al [24]	2020	Prospective intervemtional randomized study	Vitamin D levels play an important role in patients with dry eye and supplementation of vitamin D patients can lead to earlier and significant improvement in dry eye parameters
11	Hwang, et al [25]	2019	Retrospective observational study	Vitamin D supplementation enhanced the efficacy of topical treatment and can be used as potential adjuvant therapy for patients with DED
12	Karaca, et al [26]	2020	Prospective clinical study	Vitamin D replacement appeared to improve ocular surface health in patients with vitamin D deficiency

Table 2. Quality assessment and risk of bias of included studies for systematic review

ID	Study (Publication year)	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured in a valid and reliable way?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way?	Was appropriate statistical analysis used?	Total
1	Agrawal, et al. (2011)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
2	Aldebasi, et al. (2013)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
3	Cheng, et al (2012)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
4	Chow, et al. (1999)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
5	Crew, et al. (1997)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
6	Eissa, et al. (2007)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
7	El Azzouzi, et al. (2023)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
8	Fauconnet, et al.(2002)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
9	Hai-Rong, et al. (2019)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
10	Jaiswal, et al. (2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
11	Jeon, et al. (2001)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
12	Kopparapu, et al. (2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8

Note: * Risk of bias assessment was accessed by the Joanna Briggs Institute (JBI);
Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk . In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis. JBI, 2020. Available from https://synthesismanual.jbi.global