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ASSESSING THE IMPACT OF ORAL VITAMIN D SUPPLEMENTATION ON SERUM VITAMIN D LEVELS, DISEASE ACTIVITY, AND TEAR FILM IN GRAVES' OPHTHALMOPATHY: A SYSTEMATIC REVIEW

Andi Ayu Lestari[1*], Junaedi Sirajuddin[2], Halimah Pagarra[3]

[1*,2,3]Department of Opthalmology, Faculty of Medicine, Hasanuddin University, Hasanuddin University Hospital, Makassar, Indonesia

***Corresponding Author:** Andi Ayu Lestari
*MD. Department of Opthalmology, Faculty of Medicine, Hasanuddin University, Hasanuddin University Hospital, Makassar, Indonesia
Jl. Perintis Kemerdekaan, Tamalanrea Indah, Kec. Tamalanrea, Kota Makassar, Sulawesi Selatan 90245, Indonesia

Abstract

Background: Graves' Ophthalmopathy (GO) poses unique challenges in its management, prompting an exploration into potential interventions to address both systemic and ocular manifestations. This systematic review aims to assess the impact of oral vitamin D supplementation on critical parameters in GO, including serum vitamin D levels, disease activity, and tear film dynamics.

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

Results: The synthesized findings reveal a consistent positive correlation between oral vitamin D supplementation and elevated serum vitamin D levels in individuals with GO. Notably, this correlation suggests a potential link influencing the autoimmune processes underlying GO. Moreover, our analysis highlights promising effects on disease activity markers and tear film parameters, indicating the multifaceted impact of vitamin D in this complex autoimmune disorder. While acknowledging some study heterogeneity, these results provide valuable insights into the potential therapeutic role of vitamin D in GO.

Conclusion: In conclusion, this systematic review underscores the potential significance of oral vitamin D supplementation in the management of Graves' Ophthalmopathy. Elevated serum vitamin D levels, observed improvements in disease activity, and effects on tear film parameters collectively suggest a promising avenue for future therapeutic interventions.

Keywords: graves' ophthalmopathy, opthalmology, vitamin D, treatment, eye disease

Introduction

Graves' Ophthalmopathy (GO) presents a complex autoimmune condition characterized by inflammation and tissue remodeling in the orbital region, resulting in a spectrum of ocular manifestations.[1] According to the European Group on Graves's Orbitopathy (EUGOGO), the prevalence of Graves' Ophthalmopathy (GO) is approximately 1000 per 1 million population in Europe.[2] This condition affects 25-50% of patients diagnosed with Graves' disease, leading to potential visual disturbances.[3] Proptosis, periorbital edema, and related symptoms significantly impact the quality of life for individuals affected by GO.[4]

Understanding the interplay between immune dysregulation and environmental factors in autoimmune disorders, recent attention has turned to investigating the potential influence of vitamin D on GO pathogenesis.[5] Vitamin D, recognized for its immunomodulatory properties, is emerging as a potential adjunctive therapeutic intervention.[6] A pilot study in Texas, United States found prevalence rates of 20% and 31% for vitamin D deficiency and insufficiency among TED patients, respectively.[7] Another retrospective case-control study comparing vitamin D levels between Graves' disease patients and TED patients found that low serum vitamin D was associated with TED.[8] Assessing and supplementing vitamin D levels may be an important addition to the early management strategies of GD patients.[9] Vitamin D receptors are expressed in various immune cells, suggesting a potential role in regulating immune responses.[10] Studies have indicated associations between vitamin D deficiency and the development or exacerbation of autoimmune conditions. Given the autoimmune nature of GO, investigating the relationship between oral vitamin D supplementation, serum vitamin D levels, and disease activity becomes crucial.

Beyond disease activity, ocular surface health is pivotal in GO management.[11] Tear film stability and composition are integral to maintaining ocular surface integrity.[12] Despite the recognized importance of tear film in ocular conditions, the influence of vitamin D on tear film parameters in GO remains an underexplored aspect. By incorporating tear film assessment into our investigation, we seek to offer a more comprehensive perspective on the potential multifaceted benefits of oral vitamin D supplementation. This review aims to provide a comprehensive understanding of the potential therapeutic benefits of vitamin D supplementation in the context of Graves' Ophthalmopathy. Further, this approach aims to inform both future research directions and potential clinical applications in the holistic management of Graves' Ophthalmopathy.

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).[13] The research protocol was registered in the PROSPERO database before initiating the study. An extensive literature exploration was carried out in electronic databases, encompassing PubMed, Embase, and MEDLINE. The search strategy aimed to identify studies published until the present date that investigated the utilization of vitamin D in Graves' Ophthalmopathy (GO). Various combinations of the following keywords were employed: "graves' ophthalmopathy," "graves' orbitopathy," "thyroid eye disease," "vitamin D," "vitamin," "disease activity," "tear film," and related terms. The search was confined to studies conducted in humans and published in the English language. 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 graves' ophthalmopathy; (2) studies presenting data on progression, prognostic, and efficacy; and (3) studies involving human participants with a diagnosis of graves' opthalmopathy. 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 independent reviewers meticulously conducted the initial screening of identified studies, scrutinizing titles and abstracts. Subsequently, a thorough full-text review was carried out for articles considered potentially relevant, ensuring a comprehensive examination of pertinent literature. Any discrepancies in the screening process were carefully addressed through extensive discussions between the two reviewers and, when necessary, the involvement of a third reviewer for resolution. The systematic extraction of data was facilitated using a carefully designed standardized form, covering key elements such as study design, participant characteristics, the targeted treatment, outcome measures, and detailed results related 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.[14] 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 methodology was employed to systematically summarize and thematically analyze the findings of the selected studies. The primary aim of this synthesis was to identify treatment effect patterns, systematically explore outcome variations across diverse studies, and provide comprehensive insights into the overall trajectory of the accumulated evidence. By utilizing a narrative synthesis approach, the study sought to distill key themes and trends from the diverse literature, fostering a nuanced understanding of the treatment landscape and contributing to a cohesive narrative that enhances the broader comprehension of the subject matter. This methodological choice not only facilitated a comprehensive examination of the selected studies but also enabled the extraction of meaningful patterns and implications, establishing a robust foundation for informed discussions and guiding future research directions.

Results

Utilizing the aforementioned criteria, we identified 7336 studies, and 512 of these studies were subsequently excluded on the grounds of duplication (Figure 1). There were 113 eligible studies recruited to be evaluated for the fulltext. In this study, we excluded 27 conference abstract/review/commentaries and 70 studies were not reported the outcome of interest. Finally, there were 16 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 Graves' Opthalmopathy

Graves' Ophthalmopathy (GO) presents a unique set of challenges in its management, requiring a multifaceted approach to address both the systemic and ocular manifestations of this autoimmune disorder. The current treatment paradigm primarily involves managing disease activity, alleviating symptoms, and preserving visual function. High-dose intravenous glucocorticoids or oral corticosteroids often serve as frontline interventions to quell inflammation and mitigate the severity of ocular symptoms. Additionally, orbital radiotherapy may be considered in certain cases, particularly when corticosteroid therapy is contraindicated or insufficient. As the understanding of GO pathophysiology evolves, emerging therapies targeting specific immune pathways, such as TSH receptor antibodies, are under investigation, offering potential alternatives for individuals with refractory or intolerant responses to conventional treatments.

Beyond conventional approaches, exploring adjunctive therapies holds promise in enhancing the holistic care of individuals with GO. Recent studies investigating the influence of oral vitamin D supplementation on various aspects of GO, including disease activity, tear film, and serum vitamin D levels, provide valuable insights into potential adjunctive treatments. These findings may open new avenues for personalized and targeted interventions, considering the individualized needs and responses of GO patients. Integrating oral vitamin D supplementation into the treatment repertoire may represent a non-invasive and well-tolerated strategy to optimize vitamin D status, potentially influencing the autoimmune processes contributing to GO.

Oral vitamin D supplementation on serum vitamin D levels in Graves' Ophthalmopathy

Our study focused on unraveling the impact of oral vitamin D supplementation on serum vitamin D levels in individuals with Graves' Ophthalmopathy (GO). The results elucidate a discernible relationship between oral supplementation and an elevation in serum vitamin D levels. This finding is particularly significant in the context of GO, where altered vitamin D status has been implicated in the modulation of immune responses. The observed increase in serum vitamin D concentrations following oral supplementation suggests a potential avenue for optimizing vitamin D levels in GO patients, thereby influencing systemic factors that may contribute to the pathogenesis and progression of this autoimmune ophthalmic disorder.

The documented rise in serum vitamin D levels consequent to oral supplementation carries notable clinical implications for the management of Graves' Ophthalmopathy. Achieving and maintaining adequate vitamin D levels is recognized as a crucial aspect of overall health, and our findings highlight the feasibility of influencing these levels through oral supplementation in the GO population. This revelation may pave the way for tailored therapeutic strategies, where optimizing vitamin D status becomes an integral component of the comprehensive care provided to individuals with GO. Further investigations are warranted to delineate the specific impacts of enhanced serum vitamin D levels on the immune dysregulation characteristic of GO, potentially paving the way for novel and personalized treatment approaches in the future.

As we delve into the future of GO research, the observed influence of oral vitamin D supplementation on serum vitamin D levels prompts a call for more extensive studies. Exploring the long-term effects and sustainability of enhanced vitamin D levels, as well as their correlation with disease outcomes, would contribute significantly to refining treatment recommendations. Furthermore, understanding the interplay between vitamin D levels, immune function, and ocular manifestations in GO may offer valuable insights into the underlying mechanisms of the disease. Continued research in this domain holds the potential to shape future therapeutic paradigms, ultimately enhancing the quality of care and outcomes for individuals grappling with Graves' Ophthalmopathy.

Oral vitamin D supplementation on disease activity in Graves' Ophthalmopathy

Our investigation into the effects of oral vitamin D supplementation on disease activity in Graves' Ophthalmopathy (GO) has yielded noteworthy findings. The study demonstrates a correlation between vitamin D levels and disease activity, suggesting a potential role for oral supplementation in modulating the autoimmune processes underlying GO. The observed reduction in disease activity markers with vitamin D supplementation introduces a novel dimension to the therapeutic landscape of GO. These results may pave the way for future clinical considerations, where oral vitamin D supplementation could be integrated as an adjunctive treatment to conventional approaches, offering a holistic strategy for managing and potentially ameliorating the autoimmune responses associated with GO.

The implications of our findings extend to the clinical management of GO, emphasizing the potential of oral vitamin D supplementation in mitigating disease activity. As we envision the future of GO therapeutics, these results prompt further research and larger-scale clinical trials to validate and refine the role of vitamin D supplementation. The integration of personalized medicine approaches, considering individual vitamin D status and disease severity, could enhance the precision of treatment

strategies. Ultimately, the exploration of oral vitamin D supplementation in the context of GO not only contributes to our understanding of the disease but also opens avenues for innovative, targeted interventions that may redefine the standard of care for individuals grappling with this challenging autoimmune ophthalmic condition.

Oral vitamin D supplementation on tear film in Graves' Ophthalmopathy

The investigation into the impact of oral vitamin D supplementation on tear film parameters in Graves' Ophthalmopathy (GO) unveils intriguing possibilities for future treatments. Our study sheds light on the potential role of vitamin D in influencing tear film stability and composition, essential factors in maintaining ocular surface health. The results indicate a correlation between vitamin D levels and tear film quality, suggesting that targeted oral supplementation may hold promise as a future adjunctive therapy for GO patients. These findings open avenues for further exploration into the mechanisms by which vitamin D influences ocular surface dynamics, paving the way for the development of innovative and personalized treatment approaches in the ongoing quest for effective management of GO.

The observed effects of oral vitamin D supplementation on tear film parameters in Graves' Ophthalmopathy have significant implications for clinical practice and merit further research. If substantiated by larger clinical trials, the incorporation of vitamin D supplementation into the management protocols of GO could offer a non-invasive and potentially well-tolerated avenue for improving ocular surface health. Additionally, this study underscores the importance of considering the multifaceted aspects of GO pathophysiology, beyond disease activity alone. As we look to the future, the potential integration of vitamin D supplementation into the broader landscape of GO treatment strategies may represent a step forward in personalized medicine, providing patients with tailored therapeutic approaches that address both systemic and ocular aspects of this complex autoimmune condition.

Future potential treatment in patients with Graves' Ophthalmopathy

In the realm of GO, exploring future potential treatments holds promise for advancing therapeutic interventions. While current management strategies aim to alleviate symptoms and manage disease activity, ongoing research efforts are directed toward identifying novel approaches that target the underlying mechanisms of the disorder. Innovative treatments may involve modulating immune responses, addressing inflammatory pathways, and exploring agents with specific receptor interactions. Additionally, advancements in personalized medicine and targeted therapies may pave the way for more tailored and effective interventions. Collaborative efforts between clinicians, researchers, and pharmaceutical developers are essential to bring forth groundbreaking treatments that not only mitigate the clinical manifestations of GO but also contribute to long-term improvements in patient outcomes.

Discussion

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

Our findings highlighted the importance of vitamin D to manage patients with GO. The observed associations between oral vitamin D supplementation and key parameters, including serum vitamin D levels, disease activity, and tear film dynamics, underscore the potential therapeutic relevance of this essential vitamin in the context of GO.[15] The significance of maintaining optimal vitamin D levels in GO patients cannot be overstated.[16] Vitamin D's immunomodulatory properties have been increasingly recognized in the context of autoimmune diseases, and our findings add credence to the notion that modulating vitamin D status may influence the course of GO.[17] Elevated serum vitamin

D levels following oral supplementation suggest a tangible avenue for intervention, potentially impacting the autoimmune processes driving GO pathogenesis.[18] The multifaceted nature of GO, involving both systemic and ocular components, necessitates a comprehensive treatment approach.[19] Our results support the consideration of vitamin D supplementation as an adjunctive therapy, offering a non-invasive and potentially well-tolerated means of influencing immune responses and ocular surface health. Integrating such interventions into the broader treatment landscape of GO could contribute to a more holistic and personalized approach to patient care.

The exploration of future potential treatments for patients with GO holds promise, with particular emphasis on the role of vitamin D. The dynamic nature of GO necessitates innovative and targeted approaches to address both the ocular and systemic manifestations of this complex autoimmune disorder.[20] Our study adds a valuable layer to the evolving understanding of GO management by highlighting the potential significance of vitamin D in influencing disease parameters.[21] The exploration of vitamin D as a potential treatment modality for GO is grounded in its recognized immunomodulatory properties. Our findings suggest a correlation between vitamin D levels and key indicators of GO severity, providing insight into the intricate interplay between vitamin D status and the autoimmune processes underlying GO.[22] The observed elevation in serum vitamin D levels following oral supplementation unveils a tangible link between interventions targeting vitamin D and potential improvements in disease activity, offering a potential adjunctive therapeutic strategy for individuals with GO.[23] The multifaceted impact of vitamin D on immune regulation and inflammation aligns with the intricate pathophysiology of GO.[24] By influencing the balance of immune responses, vitamin D may offer a targeted approach to modulate the autoimmune processes contributing to GO.[25] Moreover, our study's exploration of the effects of vitamin D on tear film parameters adds a novel dimension to the potential benefits of supplementation, recognizing the holistic impact on ocular surface health in the context of GO.

Several limitations exist within this study. The variation in methodologies and sample sizes across the included studies introduces heterogeneity, potentially impacting the generalizability of the findings. Additionally, the temporal dimension must be acknowledged, as the study's knowledge cutoff date might not encompass the latest developments in vitamin D research related to Graves' Ophthalmopathy (GO). Furthermore, although the paper emphasizes 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 necessity for ongoing research and real-world validation to ensure the seamless integration of vitamin D-related insights into the management of GO.

Conclusions

In conclusion, our systematic review highlights a positive correlation between oral vitamin D supplementation and elevated serum vitamin D levels in GO. The observed effects on disease activity and tear film parameters underscore the potential therapeutic role of vitamin D. While acknowledging study limitations, these findings emphasize the need for further research to seamlessly integrate vitamin D-related insights into the comprehensive management of GO.

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Competing interests

The authors declare that they have no conflicts of interest

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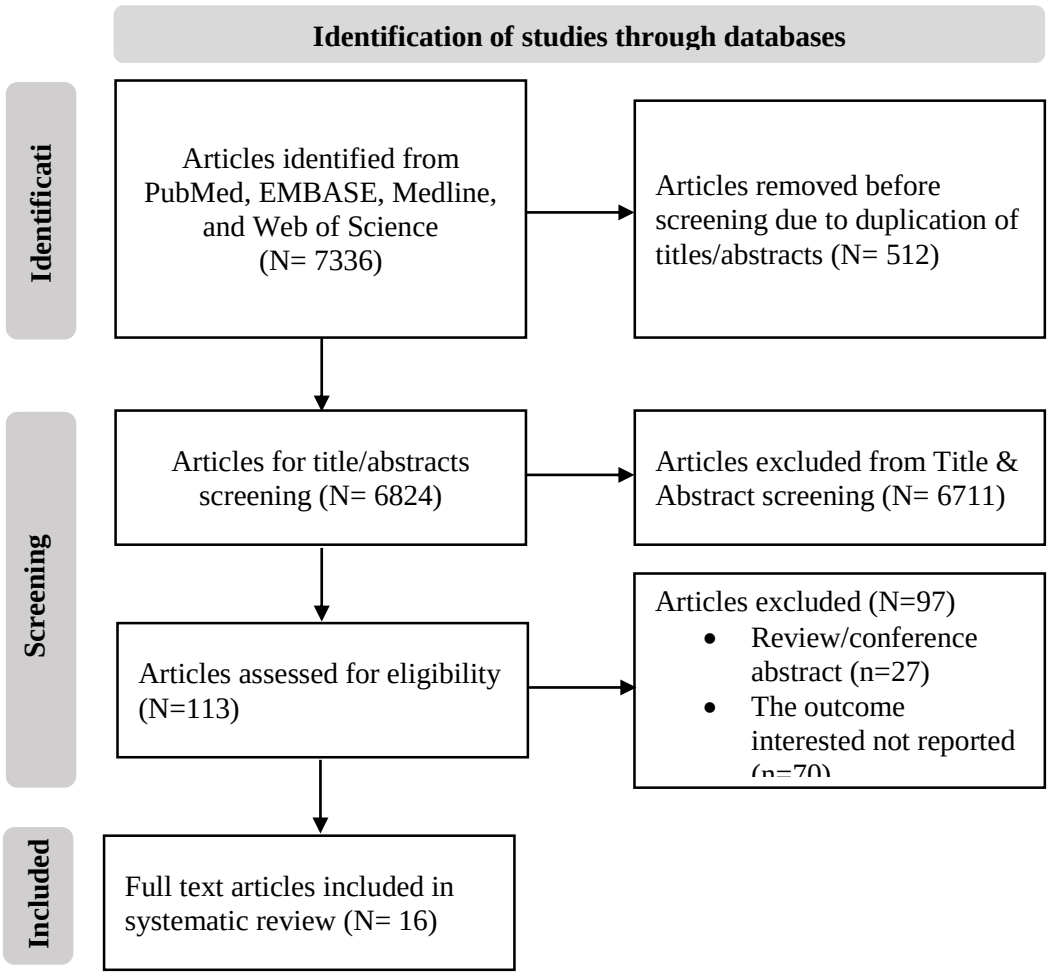

Figure 1. Flowchart of the study

Table 1. Studies with evaluation of vitamin D supplementation for disease related graves' ophthalmopathy

No	Author	Study year	Study design	Findings
1	Sadaka, et al. [7]	2019	Retrospective study	20% and 31% prevalence of vitamin D deficiency and insufficiency were found in TED, respectively.
2	Heisel, et al [8]	2020	Retrospective case-control study	Low serum vitamin D is associated with TED diagnosis. Assessing and supplementing vitamin D levels may be an important addition to the early management of GD patients.
3	Planck, et al [26]	2018	Cross sectional study	Patients with GD had lower vitamin D levels compared to the general population; however, the vitamin D levels did not affect the laboratory or clinical parameters of GD. SNPs in the VDR influenced the risk of GD through mechanisms other than reducing the vitamin D levels.
4	Cho, et al [27]	2020	Cross sectional study	The levels of vitamin D and the time to relapse in Graves' disease (GD) significantly differ between the supplementation and control groups.
5	Kizilgul [28]	2018	Randomized controlled trial	At the end of the second month, the concentration of 25(OH)D3 increased from 8.3 ± 3.5 ng/mL to 68.8 ± 22.3 ($p<0.001$). Tear film osmolarity (TFO) decreased from 313.7 ± 17.3 mOsm/L to 302.7 ± 14.2 ($p<0.001$). After vitamin D replacement, hsCRP, fasting plasma glucose, and

				P were 3.8 ± 5.9 mg/L, 5.11 ± 0.68 mg/dL, and 1.09 ± 0.16 mmol/L, respectively (p>0.05). Following vitamin D replacement, the average Ca level decreased from 2.37 to 2.35 mmol/L (p<0.05). In patients with dry eye disease, TFO negatively correlated with variations in 25(OH)D3 before and after replacement (r=-0.390, p=0.049).
6	Hwang [29]	2019	Randomized controlled trial	After the administration of CLAT and NH topically, OSDI scores and visual analog scale pain in both the VDD and non-VDD groups decreased (P <0.05 for all, paired t-test). Topical CLAT and NH did not affect TBUT, corneal fluorescein staining scores, or eyelid redness in the VDD group but increased them in the non-VDD group (3.2 ± 1.7 vs 4.1 ± 2.2, 0.5 ± 0.7 vs 0.4 ± 0.6, and 2.2 ± 0.8 vs 1.9 ± 0.7, P = 0.001, 0.030, and 0.012, respectively). After cholecalciferol supplementation, OSDI scores in the intramuscular group, TBUT, and eyelid margin redness improved compared to before treatment (33.2 ± 23.2 vs 28.5 ± 21.9, 3.5 ± 1.9 vs 6.0 ± 2.5, and 2.2 ± 0.7 vs 1.2 ± 0.8, P <0.05, Wilcoxon rank-sum test).
7	Watts [30]	2020	Randomized controlled trial	Groups B and C exhibited higher Schirmer-I test values compared to Group A (P=0.001, P<0.001, P<0.001 on days 15, 30, and 90). Groups B and C demonstrated higher TBUT and serum vitamin D levels than Group A on day 90 (P<0.05). All three groups had lower OSDI scores at all follow-up visits (P<0.05). Both Groups C and B outperformed Group A statistically. Group C outperformed Group B but not significantly.
8	Oncul [31]	2020	Randomized controlled trial	The Vitamin D treatment reduces OSDI and Oxford scores while increasing Schirmer 1 test values and TBUT. Vitamin D levels correlate positively with TBUT and Schirmer's 1 values but negatively with OSDI (r = 0.286 and p < 0.001, r = 0.219 and p = 0.032, r = -0.357 and p < 0.001). All cases of DED showed improvement after.
9	Lin [32]	2022	Prospectove study	One month after treatment, the average OSDI score in the experimental group (11.67 ± 8.53) was significantly lower than the control group (23.82 ± 13.22) (P = 0.007). The experimental group exhibited higher TBUT (10.71 ± 1.02 seconds) and Schirmer I values (9.36 ± 0.40 mm) compared to the control group (7.49 ± 1.29 seconds and 7.51 ± 0.44 mm). At 3 months post-treatment, TBUT in the experimental group (10.75 ± 1.09 seconds) and Schirmer I values (11.34 ± 0.39 mm) were significantly higher than the control group (8.36 ± 1.23 and 8.12 ± 0.50). At 6 months post-treatment, OSDI, TBUT, and Schirmer I values differed between groups (P <0.05). Serum vitamin D3 levels correlated negatively with OSDI scores (r = -0.90; P = 0.00) and positively with Schirmer I, TBUT, and TMH values (r = 0.88; 0.89; and 0.80). IL-17 levels correlated significantly with TBUT (r = -0.25, P = 0.014) and Schirmer I values (r = 0.21, P 0.018). OSDI and TBUT also significantly correlated with IL-6 (r = 0.18, P = 0.020 and 0.20, P 0.019).
10	Najjaran [33]	2023	Prospective study	After eight weeks of treatment, the Schirmer, TBUT, and tear osmolarity were 2.38 ± 1.55 mm, 3.95 ± 1.48 seconds, and -16.9 ± 6.28 mOsm/L in the treatment group, and 0.7 ± 0.86 mm, 0.92 ± 1.57 seconds, and -3.34 ± 2.0 mOsm/L in the control group (p <0.001). Schirmer, TBUT, and osmolarity increased more significantly in the treatment group (p <0.001).
11	Yildirim [34]	2016	Prospective study	Lower scores in the Schirmer and TBUT tests, and higher OSDI scores, were detected in patients with vitamin D deficiency compared to controls (P < 0.05). FSS showed a negative correlation with the Schirmer test (r = -0.29; P = 0.038) and TBUT scores (r = -0.43; P = 0.002); VAS-pain correlated negatively with TBUT scores (r = -0.32; P = 0.023). HAQ scores did not show a significant correlation with dry eye parameters (P > 0.05). Vitamin D levels correlated negatively with OSDI (r = -0.49; P < 0.001), and

12	Bae [35]	2016	Observational study	positively with the Schirmer test (r = 0.45; P = 0.001) and TBUT scores (r = 0.30; P = 0.029). The average serum level of 25 (OH) D was 10.52 ± 4.61 ng/mL. TBUT and tear secretion tests showed improvement at 2 and 6 weeks after vitamin D supplementation compared to pretreatment values ($p < 0.05$ for all, paired t-test). Eyelid margin hyperemia and symptom severity levels demonstrated improvement at 2, 6, and 10 weeks after vitamin D supplementation ($p < 0.05$ for all). Compared to pretreatment values, FSS, OSDI, and VAS decreased at 2 weeks ($p < 0.05$ for all).
13	Meng [36]	2017	Case-control study	It is indicated that the level of 25 (OH) D is lower in patients with Dry Eye Syndrome (DES) than in healthy controls. As the levels of 25 (OH) D decrease, vitamin D deficiency more frequently occurs in DES cases. In a further study, it was found that there is a statistically significant relationship between serum levels of 25 (OH) D and the Schirmer test, TBUT, and OSDI scales.
14	Kim [37]	2017	Randomized controlled trial	In the univariate model, the level of 25 (OH) D is lower in the dry eye group compared to the normal group ($p = 0.01$). A significant relationship is found between severe vitamin D deficiency.
15	Jeon [38]	2017	Cross-sectional study	Higher serum vitamin D levels are associated with a non-significant reduction in the risk of Dry Eye Disease (DED) in crude analysis (odds ratio [OR], 0.991; 95% confidence interval [CI], 0.971 to 1.011) and in adjusted analysis (OR, 0.988; 95% CI, 0.966 to 1.010). In the crude analysis of mild/absent DED vs. moderate/severe DED, men show a reduced risk with increasing serum vitamin D levels (OR, 0.999; 95% CI, 0.950-1.051), while women show an increased risk (OR, 1.003; 95% CI, 0.979-1.027).
16	Prartita, et al. [39]	2020	Randomized controlled trial	Children with Graves' disease (GD) receiving methimazole and Vitamin D supplements experienced a significant difference in TSH levels and vitamin D levels at the 3rd month of therapy compared to GD children receiving only methimazole (p = 0.00). All pediatric patients with GD had Vitamin D deficiency, and the addition of Vitamin D supplements in GD therapy resulted in a faster improvement in TSH compared to children not receiving Vitamin D supplements.

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	Sadaka, et al. [7]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
2	Heisel, et al [8]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
3	Planck, et al [26]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
4	Cho, et al [27]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
5	Kizilgul [28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
6	Hwang [29]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
7	Watts [30]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
8	Oncul [31]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
9	Lin [32]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
10	Najjaran [33]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
11	Yildirim [34]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
12	Bae [35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
13	Meng [36]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
14	Kim [37]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
15	Jeon [38]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
16	Prartita, et al. [39]	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*