# Vitamin D and its Relationship to Ocular Diseases: A Systematic Review

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J Health Allied Sci[NU] 2024;14:54–65.

## Abstract

**Introduction** Vitamin D plays a vital role in the proper functioning of various systems of the human body. Conventionally, it is known that its deficiency can impair, among other factors, calcium homeostasis, bone metabolism, and immune system regulation. Besides having anti-inflammatory and antiangiogenic properties, 25(OH)D also acts in maintaining the integrity of the human retina, favoring the idea of it being a protective factor for certain ocular diseases.

**Objective** Therefore, the purpose of this review was to collect data from the literature which support the importance of vitamin D for ocular health.

**Methods** Through the Scientific Electronic Library Online and the National Library of Medicine databases, a compendium was created on the subject.

**Results** In total, 31 articles in English published between 2016 and 2020 were found. These articles were reviewed and categorized by diseases in order to study each disorder thoroughly. It is noticed that 25(OH) D is, in fact, a potential protective factor against such diseases, including diseases that affect both the surface of the cornea and the ocular tissues that have vitamin D receptors.

**Conclusion** Vitamin D is a protective hormone in the eye, and its deficiency is related to a variety of ocular diseases. Therefore, the supplementation of 25(OH)D can be considered as a complementary treatment for patients with these diseases, since it brings relevant benefits.

**Keywords**
- Vitamin D
- 25(OH)D
- ocular diseases
- serum levels
- systematic review

## Introduction

Vitamin D is one of the essential organic substances for the maintenance of various systems of the body. This hormone can be synthesized in the skin, with the action of ultraviolet rays or obtained through the intake of animal-origin foods, such as fish or egg yolk, for example. It plays a key role in calcium homeostasis, bone metabolism, and immune system regulation. Thus, it is essential that its levels are in the appropriate parameters.[1–3]

**article published online**
April 14, 2023

**DOI** https://doi.org/10.1055/s-0043-1762915.
**ISSN** 2582-4287.



Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

This vitamin is characterized by its fat-soluble compounds, which can be of two types: ergocalciferol (D2), synthesized in the skin over ergosterol, and cholecalciferol (D3), from cholesterol. Both types are transported to the liver where they are modified through hydroxylation and form calcidiol that travels to the kidney where, similarly, the metabolically active form of vitamin D (calcitriol) is formed. Before going through this activation process, vitamin D is absorbed by the small intestine through passive diffusion, then incorporated by lipid, and enters the lymphatic system and bloodstream, where it binds to a protein and is carried to the liver and kidney to be activated. Thus, the biological effect of vitamin D is triggered from its connection, in active form, with specific cell receptors.[2]

Vitamin D deficiency may occur in the serum level or in other fluids—such as tears—for reasons such as a diet-lacking vitamin D and, mainly, insufficient sun exposure. Individuals who have certain conditions—suffer recurrent falls and fractures, pregnant women, breastfeeding women, persons over 60 years old, with dark skin, osteoporosis or metabolic bone diseases, cancers, diabetics, and obesity, among others—are more prone to have the deficiency.[3]

Vitamin D, according to recent studies, in addition to having anti-inflammatory, antiangiogenic properties contributing to good blood circulation that carries oxygen to the retina, also has an effect of maintaining the integrity of the human retina. Such effects would probably explain the results obtained by researchers that have associated a higher concentration of 25 (OH)D with a lower incidence of ocular diseases such as retinoblastoma (RB), age-related macular degeneration, dry eye syndrome, myopia, vernal keratoconjunctivitis (VKC) in children, keratoconus, cataract, glaucoma, and uveitis.[4]

Based on the above, the aim of the study is to analyze the association between vitamin D deficiency and the incidence of ocular pathologies through a systematic review of conducted research and studies that have correlated 25(OH)D with such ocular diseases.

## Materials and Methods

Through a systematic review of scientific articles and methodical analysis of their content, we designed a review study that correlates with the most recent studies on the role of vitamin D in the incidence of ocular pathologies. Through the Scientific Electronic Library Online and the National Library of Medicine databases, a compendium of articles was created that associated the mentioned factors. These articles were reviewed and categorized by diseases in order to study each disorder thoroughly.

The ocular diseases analyzed were myopia, cataract, diabetic retinopathy, age-related macular degeneration (AMD), glaucoma, diabetic retinopathy, age-related cataract, uveitis, dry eye syndrome, and VKC, and RB.

The keywords used in the databases were the names of the main ocular diseases—mentioned above—(in English), "electrochemiluminescence" and "ocular diseases"; these were crossed with one of the following words: "Vitamin D" and "25-hydroxyvitamin D" (►**Fig. 1**).

In total, 31 articles written in English published between 2016 and 2020 and with human participants only were reviewed; analysis and report of such articles were performed between the dates 28 February, 2020 and 3 April, 2020 (►**Table 1**).

## Results and Discussion

From the analyzed studies, a correlation between serum or tear Vitamin D levels and ocular diseases is observed. 25(OH) D is a protective factor against such diseases, including diseases that affect both the corneal surface (such as dry eye syndrome) and the ocular tissues that have vitamin D receptors (VDRs; e.g., AMD, glaucoma, myopia, and uveitis).[15,16]

Specifically, in the cornea, the protective factors occur, after the interaction of the active form of vitamin D with its receptor, by the generation of a greater transepithelial resistance of human corneal epithelial cells, helping to maintain the shape and integrity of the cornea[24] since the vitamin deficiency is closely linked to tear hyperosmolarity and tear film dysfunction[19]; on the contrary, in different ocular tissues, there are protective factors associated with different effects, such as anti-inflammatory and antiangiogenic.

The anti-inflammatory effect happens because the immune system cells possess a large amount of VDR receptors and the active *CYP27B1* gene that produces 1-alpha-hydroxylase, an enzyme that acts in the synthesis of calcitriol (active form of vitamin D).[19] Calcitriol is responsible for modulating the expression of several inflammatory cytokines, fighting the inflammatory process and neurodegeneration—factors that cause intense pain in patients with glaucoma, for example. It was also observed that this effect can occur by inhibiting the Langerhans cells migration into the cornea.[32–34]

As for its anti-angiogenic action, the $1.25(OH)_2D_3$ form inhibits specific stages of the angiogenic process, and the probable causative mechanism is related to the induction of apoptosis in angiogenic epithelial cells. However, it is noteworthy that the effect of such a mechanism in ocular diseases still requires further studies.

Uveitis can affect the quality of life negatively, not only because of poor visual functioning but also because of associated systemic disorders treatments. Devilliers et al cite that the immunological privilege of certain ocular compartments explains the character of the very rapid evolution of certain infections, including in the immunocompetent (a thinking in particular of necrotizing retinitis); it is known that vitamin D strengthens the immune system ocular.[35]

Li et al conducted a systematic review seeking to relate the degree of glaucoma to serum concentrations of vitamin D. Although many publications have reported a difference in serum vitamin levels between patients with glaucoma and normal subjects, the association between serum vitamin levels and glaucoma in humans remains controversial.[36]

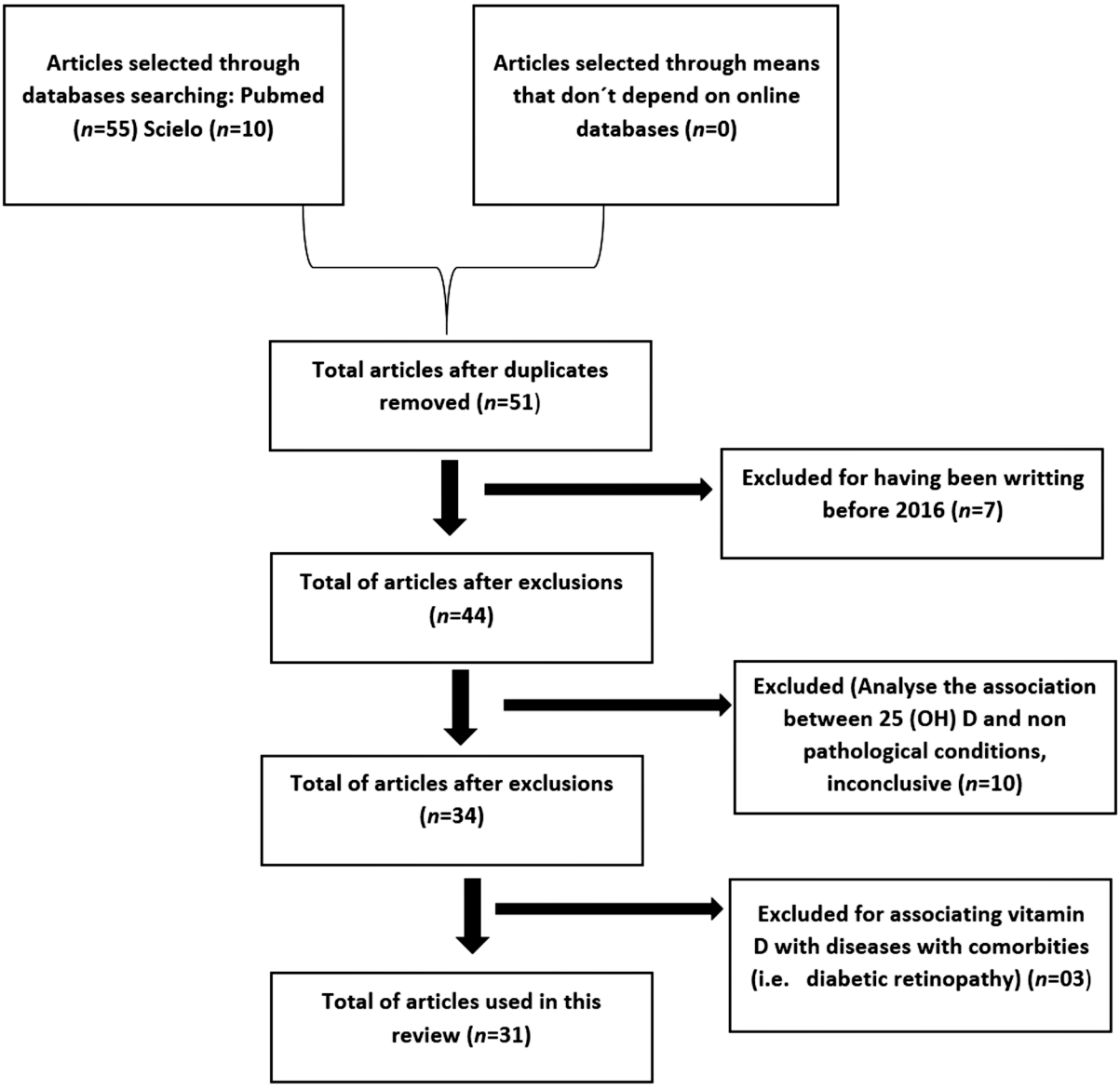


**Fig. 1** Flowchart of the choice of articles for review. Note: *n* refers to the number of articles.

In addition, searches report vitamin D exerts some inverse relation with some of the major ophthalmic diseases such as AMD and glaucoma.[37–39]

Vitamin D has antineoplastic through influencing cell differentiation, apoptosis regulation, anti-angiogenesis, and cell cycle arrest in various tumors. Animal studies suggested that vitamin D analogs inhibited RB tumor growth in athymic mice by increasing apoptosis, which is associated with the upregulation of both the p53 and p21 proteins.[40]

Regarding the cornea, it is important to highlight that low serum concentrations of vitamin D are a problem that affects the whole world. It is estimated that one billion people are deficient or insufficient serum concentrations of vitamin D. It is estimated that one billion people are deficient or insufficient serum concentrations of vitamin D. Studies reveal that at the same time, 10 million people around the world are blind due to severe corneal problems illness. Dealing with epithelial tissue, communication of the epithelial communicating junction. Patients with a low dosage of vitamin D may lead to increased gap junction communication and thus cause a mismatch in the epithelial health of the cornea, associated with epithelial regeneration. Other studies demonstrated that elevated epithelial calcium concentrations stimulate gap junction connectivity in corneal epithelial cells, and it depends on vitamin D to increase the absorption of calcium by the body.[41]

This study presents, as limiting factors, the short number of studies involving the relationship between the variables mentioned—which is why several ocular pathologies were included in this review; in addition, the studies under analysis are not standardized (they have, mainly, study design, method, ocular disease, biological matrix, and different population sample).

It is observed, therefore, through several studies, that vitamin D is a protective factor in the eye and its deficiency is related to ocular diseases such as dry eye syndrome,

**Table 1** Summary of articles used in the manuscript

| Authors and Year of Publication | Journals | Study Type and Sample | Intervention and Results | Outcome/ Conclusions |
|---|---|---|---|---|
| Jung and Jee 2020[16] | Indian Journal of Ophthalmology | Cross-sectional study. A sample of 25,199 individuals aged 20 years or older who underwent 25(OH)D serum level and ocular refraction examinations. | The relationship between the two variables was checked from a database. Linear regression analysis adjusted to confounders showed that the increase of 1 ng/mL of vitamin D significantly decreases the refractive error caused by myopia by 0.01 D. | Serum 25(OH)D levels were inversely associated with myopia in Korean adults; thus, acting as a protective factor. |
| Millen et al 2019[5] | Investigative Ophthalmology and Visual Science | Prospective longitudinal study. A sample 1, 225 individuals without late age-related macular degeneration (AMD) at visit the third and with serum 25 (OH)D examination at the second visit. | Serum 25(OH)D-levels examinations and, in two visits (third and fifth) with an 18-years difference between them, fundus examinations were performed. A lower incidence of early AMD was found than in those with higher serum vitamin D levels. | High vitamin D concentrations, approximately greater than 70 nM, may be associated with lower odds of incidence of early age-related macular degeneration cases. |
| Meng et al 2019[6] | Medical Science Monitor | Case-control study. 259 individuals have participated; of these, 124 had dry eye syndrome (DES) and 135 were healthy controls. | Clinical and demographic data were collected in addition to blood (for vitamin D) and single nucleotide polymorphisms (SNPs) of vitamin D receptors (VDR). In DES patients, higher frequencies of Apa-1 and lower frequencies of Taq-1 were found. There was no significant association between Bsm-1 and Fok-1 with DES. | SNPs of VDR genes (Apa-1 and Taq-1) have demonstrated to be associated with higher risks of DES. |
| Lai et al 2019[7] | Journal of Clinical Laboratory Analysis | Cross-sectional study. 21 individuals without ocular diseases were recruited for the study, | Blood and tear samples were collected from the 21 individuals. Through concordance coefficients, it was verified the possibility of using electrochemiluminescence (Electrogenerated Chemiluminescence - ECL) to detect blood and tear vitamin D levels. | Vitamin D levels can be measured through blood and tear fluid using ECL. Tear vitamin concentration does not correlate with the one found in blood. |
| Khamar et al 2019[8] | Investigative Ophthalmology and Visual Science | Cross-sectional study. A sample of 80 participants with 47 individuals with evaporative DES and 33 healthy controls. | DES was observed from the analysis of six nociceptive factors correlating them with 34 soluble factors (including vitamin D) in tears Several significant associations (direct and inverse relationships) of four of the six nociceptive factors with DES were obtained. The highest vitamin D concentration was effective against the factors. | Dysregulated soluble factors (such as vitamin D deficiency) affect nociceptive and inflammatory factors linked to DES and its symptoms. Thus, increased cellular response to vitamin D in tears improves symptoms of DES. |
| Hwang et al 2019[9] | Cornea | A retrospective cohort study. A sample of 116 individuals | All received artificial tears (CLAT), sodium hyaluronate (HU) and were able to choose | The effect of topical administration of CLAT and HU depended on serum 25(OH)D levels. |

(*Continued*)

**Table 1** (*Continued*)

| Authors and Year of Publication | Journals | Study Type and Sample | Intervention and Results | Outcome/ Conclusions |
|---|---|---|---|---|
| | | with DES, divided into groups with vitamin D deficiency (52) and without deficiency (64). Those with a history of autoimmune diseases, corneal surgery, corneal diseases and corneal opacity were excluded. | how or whether they would supplement vitamin D. DES was evaluated by several parameters.<br>After two weeks, it was indicated that only the group that received vitamin D via IM improved in terms of tear film breakup time (TBUT), ocular surface disease index (OSDI), and eyelid margin hyperemia. | Therefore, 25(OH)D can be used as complementary therapy for patients with DES.<br>In addition, cholecalciferol via IM was more effective compared to the oral route. |
| Ghiglioni et al 2019[10] | International Journal of Immunopathology and Pharmacology | Cohort study. A sample with 242 children with vernal keratoconjunctivitis (VKC). | Follow-up from March to November 2016. 60 (group 1) of the total had cyclosporine treatment and 11 (group 2) with tacrolimus, while the other 148 with mild VKC did not require treatment.<br>Vitamin D levels were measured in spring and autumn, with a difference of 170 days between the tests.<br>The treatment increased serum vitamin D levels, suggesting clinical improvement of VKC and its symptoms, in addition to a greater resistance to sunlight exposure. | The presence of hypovitaminosis D is confirmed in children with VKC; however, significant differences in the increase in vitamin D concentration between groups 1 and 2 were not noticed, thus requiring large-scale studies on the subject. |
| Ayyagari et al 2019[11] | Molecular Vision | A cohort study with African descent involving 357 patients with primary open-angle glaucoma (POAG), 178 of which had advanced disease-controlled levels. | Demographic, clinical and blood tests (for vitamin D) were collected. There was evaluation of the visual field based on the severity of the local damage. A significant difference (or almost) was detected between serum 25(OH)D levels: those with advanced glaucoma had lower levels than<br>the control group ($P \sim 0.01$) and with early glaucoma ($P = 0.0543$). | Patients with advanced glaucoma have lower levels of vitamin D compared to patients with early glaucoma and with the control group. |
| Abdellah et al 2019[12] | Journal of Ophthalmology | Case-control study. 710 individuals were selected; 325 of these were cataract patients and 385 were from control group. | All were examined for blood vitamin D.<br>There was a significant difference between the studied groups: the group with cataract presented lower serum 25(OH)D levels than the control group. The lowest levels were found in<br>nuclear cataracts. | Vitamin D levels were critically below normal in cataract patients and it may pave the way for studies with patients with age-related cataracts. |
| Kim and Park 2018[13] | Medicine (Baltimore). | Case-control study. 96 individuals were recruited (30 with late AMD, 32 with early AMD and 34 from control group). | Blood (for vitamin D) test and fundus examination were performed.<br>There was a significant difference in serum 25 (OH)D levels between control group (highest concentration) and the one with late AMD; | Vitamin D deficiency in Koreans may be associated with increased risk of (early and late) AMD and subretinal fibrosis. Studies with larger groups are necessary for confirmation. |

**Table 1** (*Continued*)

| Authors and Year of Publication | Journals | Study Type and Sample | Intervention and Results | Outcome/ Conclusions |
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| | | | between control group and the one with early AMD, control group had higher concentrations. Finally, in the late AMD group, those with subretinal fibrosis had the highest 25(OH)D deficiency. | |
| Yang et al 2018[14] | Contact Lens Anterior Eye | Cohort study Three linked studies were conducted: one (1) with 29 older adults (40-70 years); one (2) with 29 DES patients; and one (3) with a group of 32 individuals with DES or vitamin D insufficiency. | Serum vitamin D level and DES symptoms were evaluated according to several parameters. In group 3, vitamin D supplementation occurred. In (1) low levels of vitamin D (<50nmol/l) were associated with the OSDI scores - DES symptoms; in 3, by increasing serum 25(OH) D levels at 29 mol/l, the corneal staining was reduced ($P < 0.05$). | Low vitamin D levels were associated with symptoms of DED in older adults, but not in those with DES. Vitamin D supplementation improved symptoms of DES, tear quality and ocular surface conditions. |
| Skowron et al 2018[15] | FOLIA MEDICA CRACOVIENSIA | Systematic review. A selection of articles that studied the relationship between vitamin D and ocular diseases. | Focusing on treatment, the selected diseases were myopia, AMD, glaucoma, diabetic retinopathy, retinoblastoma and uveitis. Anti-inflammatory, anti-angiogenic and anti-neoplastic properties of calcitriol, a substance which amplifies the expression of VDR, were discovered. | Many studies indicate that vitamin D deficiency is correlated with the diseases mentioned, but the reasons for it are not fully explained. Vitamin D appears to act as a protective factor in the eye. |
| McMillan J. 2018[17] | Cureus | Cohort study. A sample of more than 2,000 individuals who visited a general ophthalmology service. | Pentacam test was performed in the participants who were divided into a group that received daily supplementation of 25 (OH)D and another who did not. Beneficial responses to diseases occur only when there are levels close to 50 ng/cc, while an optimal response occurred from the levels around 70-80 ng/cc. | Vitamin D supplementation in the evaluated patients demonstrated improvement in myopia and keratoconus; also, such application has benefits for DES, glaucoma, cataracts and other ocular diseases. |
| Kizilgul et al 2018[18] | Seminal of Ophthalmology | Cohort study. 44 patients with vitamin D deficiency who were followed-up by the Department of Endocrinology and Metabolism of a hospital in Turkey. | For an eight-week period, patients received a weekly dose of 50,000 IU of 25(OH) D intramuscularly. Demographic, clinical and biochemistry data (tear function osmolality—TFO—at the beginning and after the eight weeks) were recorded. A significant decrease of TFO after supplementation was found. | As a consequence of the presence of VDRs and 1α-hydroxylase in different parts of the eye, vitamin D replacement improves tear hyperosmolarity, which is considered to be induced by an inflammation of the ocular surface. |

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**Table 1** (*Continued*)

| Authors and Year of Publication | Journals | Study Type and Sample | Intervention and Results | Outcome/ Conclusions |
|---|---|---|---|---|
| Demirci et al 2018[19] | Eye Contact Lenses | Case-control study. 60 individuals were recruited, 30 with vitamin D deficiency and 30 healthy controls. | All were assessed by parameters of DES, and measurement of serum 25(OH)D levels. Patients with vitamin D deficiency showed significantly higher tear osmolality values, OSDI and fluorescein staining scores (FSS) modified with Oxford scale; they also presented significantly lower TBUT and Schirmer test (ST) values compared to controls ($P < 0,001$). | This study demonstrated that vitamin D deficiency is associated with tear hyperosmolarity and tear film dysfunction. Thus, it was considered that patients with vitamin D deficiency were more prone to develop DES. |
| Williams et al 2017[20] | JAMA Ophthalmology | Cross-sectional study. 3,168 individuals aged 65 years or older without aphakia, pseudophakia late AMD or vision impairment due to cataract were selected in 6 study centers. 371 individuals had myopia and 2797 did not have it. | The following parameters were analyzed: time of UVB exposure, eye refractive error, SNPs of genes of the vitamin D metabolism, serum vitamin D levels and years of education. In those aged 14 to 39 years, there was an inverse association with myopia; however, there was no independent relationship of myopia with 25(OH)D or with genes of its metabolism. | It was concluded that increased UVB exposure, particularly in adolescents and young adults, reduced myopia risks; however, no direct relationship between myopia and vitamin D or related genes was found. |
| Park and Choi 2017[21] | Ophthalmic Epidemiology | Cross-sectional study. Participants: 16,086 adults aged 40 years or older who had serum 25(OH)D levels test and who had never been diagnosed with or had never undergone to cataract surgery. | The study used a database, performing odds ratio (OR) and a 95% confidence interval. Serum 25(OH)D levels are inversely associated with the risk of incidence of nuclear cataract ($P < 0.001$). | There is an inverse relationship between nuclear cataract and vitamin D levels in serum; however, further studies relating such vitamin and the development of nuclear cataract are necessary. |
| Meng et al 2019[6] | Medical Science Monitor | Case-control study. There were 140 participants; 70 with DES and 70 healthy controls. | Blood samples (for vitamin D) and clinical data were collected. DES symptoms were analyzed using parameters. Serum 25(OH)D levels were significantly lower in cases than in controls. There were significant relationships: direct of 25(OH)D with ST and inverse with OSDI and TBUT. | Vitamin D deficiency was related to DES and its symptoms. It is indicated, therefore, that vitamin D can act favorably and adjunctively for the patient with DES. |
| McKay et al 2017[22] | Ophthalmology | Cross-sectional study. 4,496 participants over 65 years of age were randomly included in the study. Of these, 2,137 had no signs of AMD; 2,209 | Blood (for 25(OH)D), fundus examination and data such UV radiation exposure and diet were collected. Moreover, SNPs were analyzed for 7 genes. Serum 25(OH)D deficiency (<30nmol/L) was associated with | Serum 25(OH)D deficiency may affect neovascular AMD; however, because there is low OR, there may be confounders - they would make the data unreliable. There was no direct relationship between |

**Table 1** (*Continued*)

| Authors and Year of Publication | Journals | Study Type and Sample | Intervention and Results | Outcome/ Conclusions |
|---|---|---|---|---|
| | | had early AMD; and 150 had late AMD (of which 104 were in the neovascular stage of the disease). | neovascular AMD; however, the OR is low. Furthermore, after Bonferroni correction, there was no direct association between SNPs and AMD (at any stage). | SNPs and AMD and, therefore, there is no basis for the association between vitamin D and AMD. |
| Li et al 2017[23] | Nutrients | Systematic review with meta-analysis 19 case-control studies with humans which associated vitamins B6, B12 or D with glaucoma were selected. Of these, nine related to POAG; four on normal tension glaucoma (NTG) and six on exfoliative glaucoma (EXG). | Articles were selected from online databases. The keywords were: “glaucoma” (in the title) and “vitamin” (in the abstract). The difference in the levels of these vitamins between glaucoma patients and control ones was not significant after performing the meta-analysis, as there were contrasting results among studies; however, the sample size and study location may have influenced the outcome. | There is no association of vitamins (B6, B12 and D) in blood with the different types of glaucoma. However, more studies on the subject are necessary, particularly multicentered and with larger samples. |
| Jin et al 2017[24] | Acta Ophthalmology | Retrospective observational study. A total of 92 medical records (79 included) of patients from a South Korean hospital were analyzed. For exclusion criteria it was evaluated: autoimmune diseases, corneal surgery, corneal diseases or corneal opacity. | Subjects were divided into groups according to serum 25(OH)D levels (deficient, inadequate and sufficient). Parameters for DES evaluation was used. Positive and significant associations were found among serum vitamin D levels, TBUT and ST. OSDI and FSS showed no significant difference among the three groups. | Higher tear film stability and secretion correlated to higher serum vitamin D levels. Thus, it is suggested that vitamin D supplementation may be useful in the treatment of DES. |
| Cuellar- Partida et al 2017[25] | International Journal of Epidemiology | Mendelian randomization (MR) study of a previous meta-analysis study that included 32 studies with a total of 37,382 adults of European descent and 8,376 of Asian descent. | SNPs of genes related to blood 25(OH)D concentrations were analyzed as instrumental variables, using data (refractive error and serum vitamin D levels) based on the meta-analytic study. The estimated effect of a 10 nmol/L increase of 25(OH)D in myopia when analyzing refractive errors was -0.02 dioptres (D) in Caucasians and 0.01 D in Asians. | The contribution of vitamin D to myopia improvement is very small and indistinguishable from 0. Thus, it is suggested that the relationship of vitamin D with myopia was probably due to confounders such as the time spent outdoors. |
| Yildirim et al 2016[26] | International Journal of Rheumatic Diseases | Case-control study. 50 premenopausal women with serum vitamin D deficiency and 48 control women (normal vitamin D concentrations) were recruited. | Serum 25(OH)D levels and parameters related to hypovitaminosis D and DES were analyzed. In patients with vitamin D deficiency or fatigue, there were significantly lower ST and TBUT and higher OSDI. The visual analogue scale for pain (VAS) was related to lower TBUT values. | In vitamin D deficiency, there was lower tear stability and secretion and higher OSDI compared to the control group. Thus, it is indicated that vitamin D acts as a protective factor against the development of DES. |

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Journal of Health and Allied Sciences[NU] Vol. 14 No. 1/2024 © 2023. The Author(s).

**Table 1** (*Continued*)

| Authors and Year of Publication | Journals | Study Type and Sample | Intervention and Results | Outcome/ Conclusions |
|---|---|---|---|---|
| Tideman et al 2016[27] | European Journal of Epidemiology | Prospective cohort study with 2,666 six-year-old children in whom serum 25 (OH)D levels and myopia were evaluated. | Cycloplegic refraction, serum vitamin D levels; Vitamin D-related SNPs and the time spent outdoor were measured. An increase in the axial length (AL) has been demonstrated in children with a low 25 (OH) D level, even after adjustment for time spent outdoors; in these children, lower 25(OH)D levels were also associated with a higher risk of myopia. | It is implied that, regardless of time spent outdoors, vitamin D has an inverse effect on AL in addition to determining the development of myopia. Thus, future investigative and functional studies are essential. |
| Shetty and Nagaraja 2016[28] | Translational Vision Science and Technology | Cross-sectional study. 19 patients with mild signs but critical symptoms of DES and 19 healthy individuals (control group) were selected to participate the study. | Participants underwent an analysis of (among other) parameters for DES and serum 25(OH) D levels. Compared to the control group, patients with signs of DES (lower vitamin D levels) had higher OSDI; 25(OH)D was not significantly related to TBUT and ST. | Low vitamin D levels provoke severe DES symptoms in patients with mild signs of the disease. |
| Sethu et al 2016[29] | Eye and Vision (London) | Cohort study 48 healthy individuals without ocular or systemic diseases participated. | Blood and tear samples (for 25(OH)D in such) were collected. Significant data showed that 25(OH)D levels were, on average, twice as high in tears as in serum and that there is a positive correlation between serum and tear fluid 25(OH). | Higher 25(OH)D levels were observed in the tear fluid than in the serum. It is suggested to consider tear vitamin D levels to study its role with reference to ocular surface diseases. |
| Lv et al 2016[30] | BMC Ophthalmology | Case-control study. 71 POAG patients and 73 control group individuals from Han ethnic group participated the study. | 25(OH)D levels and SNPs of VDRs (Cdx-2, Fok I, Bsm I and Taq I) were measured by blood collection. The levels of 25(OH)D in patients with POAG were significantly lower than in the age- matched control group. Significant differences in the allelic frequency of Bsm I genotypes (higher frequencies of “B” Allele) and Taq I (higher frequency “t” allele) were detected between the groups. | Vitamin D deficiency and presence of BsmI ’B’ and Taq I ’t’ alleles are relevant risk factors for glaucoma. However, additional studies on the causes of these noted changes between groups and its possible association with vitamin D are essential. |
| Kwon et al 2016[31] | Medicine (Baltimore) | Cross-sectional study. A total of 15,126 individuals aged 20 years or older, who completed the ophthalmologic survey and had no history of ocular surgeries. | Through a database, the study used clinical information and serum 25(OH)D levels. Separating groups by time of sunlight exposure, it was observed that those with an exposure longer than 2 hours had a significantly lower risk of myopia. Those with higher 25(OH)D levels had lower prevalence of myopia. | Fewer hours of sun exposure and low 25(OH) D levels result in a higher incidence of myopia in Korean adults. |

**Table 1** (*Continued*)

| Authors and Year of Publication | Journals | Study Type and Sample | Intervention and Results | Outcome/ Conclusions |
|---|---|---|---|---|
| Kim et al 2016[32] | Korean Journal of Ophthalmology | Cross-sectional study. 123,331 patients over 20 years of age who attended a South Korean hospital were included. | Glaucoma was evaluated from fundus examinations. In addition to this test, participants underwent blood collection (for vitamin D) and answered questionnaires to sociodemographic data. When comparing patients by 25(OH)D levels, the OR of glaucoma in fourth-quintile women compared to the first was significantly lower after adjusting by sex. | Low vitamin D levels are independently related to higher risks of glaucoma in women. |
| Jee et al 2016[33] | PLoS One | Cross-sectional study. 16,396 over 19 years old individuals with DES were selected for the study. | All underwent interviews, blood tests for vitamin D and ocular examinations. The risk of DES decreased significantly after the increase of the quintile values for 25(OH) D; but, after adjustment for confounders, the relationship was no longer significant. For those with higher serum 25(OH)D levels, there was significant OR, in men only, for cataract, diabetic retinopathy and late AMD. | No vitamin D association with DES was demonstrated. The ORs indicated that vitamin D had greater effect for diabetic retinopathy and late AMD than in cataracts and DES. |
| Bae et al 2016[34] | Scientific Reports | A retrospective cohort study Participants were 105 individuals with DES refractory to conventional treatment. | Vitamin D levels and parameters for DES were measured before treatment. All have received cholecalciferol (200,000 IU via IM). After two weeks of treatment, a significant improvement was observed on the VAS, FSS and OSDI scores. TBUT, tear secretion and eyelid margin hyperemia have also indicated significant improvement after two and six weeks (for the first two) and after two, six and ten weeks for the third. | The IM administration of cholecalciferol promoted higher tear secretion and stability and lower chances of both ocular surface and eyelid margin inflammation. It is suggested its use for the treatment of patients with DES refractory to conventional treatment. |

 

myopia, VKC, AMD, uveitis, advanced glaucoma, and cataracts. Thus, the supplementation of 25(OH)D is indicated as a complementary treatment for patients with these diseases, since it can bring relevant benefits, assisting them in the control of several symptoms.

Conflict of Interest
None declared.

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