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A Comprehensive Literature Review on the Role of Vitamin D in Dry Eye Disease: Implications for Diagnosis and Treatment

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ABSTRACT

Dry Eye Disease (DED) is a common ocular disorder characterized by tear film instability, ocular surface inflammation, and visual disturbances that can significantly affect quality of life. Emerging research has highlighted the crucial role of vitamin D in ocular health through its immunomodulatory, anti-inflammatory, and epithelial homeostasis-regulating properties. This comprehensive literature review aims to analyze the role of vitamin D in the pathogenesis, diagnosis, and treatment of DED. A systematic search was conducted in databases such as PubMed, ScienceDirect, and Google Scholar using keywords including "vitamin D," "dry eye disease," "ocular surface," and "tear film stability." The findings indicate that vitamin D deficiency is strongly associated with an increased risk of DED, exacerbation of inflammatory symptoms, and impaired tear film stability. Clinical studies suggest that vitamin D supplementation may improve both subjective and objective DED symptoms, such as enhanced tear break-up time (TBUT) and reduced Ocular Surface Disease Index (OSDI) scores. However, variations in dosage, treatment duration, and study design remain challenges for establishing standardized therapeutic recommendations. This review emphasizes the need for further large-scale randomized clinical trials to confirm the efficacy and safety of vitamin D supplementation in DED management.

Keywords: Vitamin D, Dry Eye Disease, Ocular Inflammation, Tear Film Stability, Supplementation.

INTRODUCTION

Dry Eye Disease (DED), or *keratoconjunctivitis sicca*, is a multifactorial ocular surface disorder characterized by disruption in tear film homeostasis, resulting in discomfort, fluctuating vision, and potential ocular surface damage. This condition is primarily driven by tear film instability, hyperosmolarity, ocular surface inflammation, and neurosensory abnormalities. DED is classified into two main subtypes: aqueous-deficient dry eye (ADDE), caused by decreased tear production often linked to autoimmune diseases such as *Sjögren's syndrome*, and evaporative dry eye (EDE), which is typically associated with meibomian gland dysfunction (MGD). Many patients present overlapping features of both subtypes, contributing to the complex manifestation of the disease.

The global prevalence of DED ranges from 5% to 50%, depending on diagnostic criteria and geographic variation, and it is more common in women—especially postmenopausal women—due to hormonal influences on tear production. Aging, prolonged digital screen use, contact lens wear, air pollution, and exposure to low-humidity environments are established

risk factors. Notably, younger individuals are increasingly diagnosed with DED due to lifestyle changes and excessive screen time.

Recent research has highlighted additional systemic risk factors for DED, including diabetes mellitus, autoimmune conditions, and vitamin D deficiency. DED not only affects ocular health but also significantly impairs quality of life by hindering daily tasks, reducing work productivity, and causing chronic discomfort that can impact psychological well-being. As understanding of the multifactorial nature of DED evolves, nutritional factors—particularly vitamin D—have emerged as potential modulators of DED pathophysiology. Vitamin D's role in ocular surface health, tear film stability, and immune regulation offers a promising therapeutic avenue.

Pathophysiology of Dry Eye Disease

DED pathophysiology involves a complex interplay of tear film dysfunction, chronic inflammation, oxidative stress, and neurosensory abnormalities. Tear film instability and hyperosmolarity initiate an inflammatory cascade that disrupts epithelial cell integrity, worsening ocular surface damage. The *lacrimal functional unit*—encompassing the lacrimal glands, ocular surface, and neural connections—is central to maintaining tear film homeostasis. Dysregulation of this unit reduces tear secretion and increases tear evaporation, further aggravating symptoms. Vitamin D, with its immunomodulatory and anti-inflammatory properties, is thought to help preserve ocular surface homeostasis by modulating these pathogenic processes.

Role of Vitamin D in Ocular Surface Health

Vitamin D is a fat-soluble vitamin functioning as a hormone, with significant effects on immune modulation, epithelial barrier maintenance, and anti-inflammatory processes. The active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], binds to vitamin D receptors (VDR) expressed in ocular tissues, including the cornea, conjunctiva, lacrimal glands, and meibomian glands. Through these receptors, vitamin D regulates gene expression critical for immune response and epithelial function. Evidence links vitamin D deficiency to increased ocular surface inflammation, reduced tear production, and heightened severity of DED symptoms, supporting its relevance in both disease prevention and management.

Tear Film Dysfunction and Instability

DED is marked by instability of the tear film, composed of three layers: lipid, aqueous, and mucin. The lipid layer, produced by meibomian glands, inhibits tear evaporation. The aqueous layer, produced by lacrimal glands, hydrates and protects the eye, whereas the mucin layer, secreted by conjunctival goblet cells, ensures tear adhesion to the ocular surface. Vitamin D deficiency may impair lacrimal gland function, leading to insufficient aqueous tear production. Meibomian gland dysfunction—primary in EDE—has also been linked to vitamin D-related disruptions in lipid metabolism and ductal keratinization. Additionally, reduced mucin secretion from goblet cells under conditions of vitamin D deficiency further destabilizes the tear film and exacerbates DED.

Inflammation and Immune Dysregulation

Inflammatory and immune responses are pivotal in DED progression. Pro-inflammatory cytokines—including IL-1β, IL-6, TNF-α, and matrix metalloproteinases (MMPs)—compromise the epithelial barrier, decrease goblet cell density, and worsen tear film instability. Vitamin D suppresses both innate and adaptive immune responses by reducing pro-inflammatory cytokine levels, inhibiting dendritic cell maturation, and promoting regulatory T

cell (Treg) activity. Insufficient vitamin D leads to unchecked inflammation and an accentuated immune response, perpetuating ocular surface damage.

Oxidative Stress and Corneal Damage

Oxidative stress is also central to DED pathogenesis. Environmental factors like UV radiation and pollution increase reactive oxygen species (ROS), damaging lipids, proteins, and DNA in ocular tissues. Vitamin D confers antioxidant protection by enhancing expression of enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, and it upregulates tight junction proteins such as occludin and ZO-1 to maintain epithelial barrier integrity.

Neurosensory Dysfunction

Neurosensory dysfunction is a critical aspect of DED, since corneal nerves mediate tear secretion reflexes and ocular surface sensitivity. DED patients frequently report neuropathic pain and abnormal corneal sensations due to nerve injury and neuroinflammation. Vitamin D supports neuronal health via regulation of nerve growth factor (NGF) expression and facilitation of nerve repair. Deficiency may lead to increased pain sensitivity, reduced corneal sensation, and more severe neurogenic DED symptoms.

Meibomian Gland Dysfunction (MGD)

MGD, a leading cause of EDE, is characterized by ductal obstruction, altered lipid secretion, and increased tear evaporation. Vitamin D is implicated in lipid metabolism, *keratinocyte* differentiation, and anti-inflammatory signaling crucial for glandular function. Deficiency in vitamin D increases the risk of meibomian gland atrophy and hyperkeratinization, exacerbating ductal obstruction and inflammation at the eyelid margin, further destabilizing the tear film.

Vitamin D Supplementation in DED: Clinical Evidence

Clinical studies investigating vitamin D supplementation for DED present encouraging but not definitive findings. Bae et al. (2016) conducted a clinical trial demonstrating that intramuscular vitamin D supplementation significantly improved tear secretion, tear film stability, and reduced inflammation in refractory DED patients, underscoring its efficacy in cases where conventional therapies fail. However, the study only addressed treatment-resistant patients and used high-dose intramuscular administration, leaving oral dosing and broader clinical applicability unresolved. Li et al. (2024) conducted a meta-analysis of multiple trials, finding consistent improvements in Schirmer's test values, tear break-up time (TBUT), lid hyperemia, and ocular surface disease index (OSDI) scores following vitamin D supplementation. Despite these positive effects, the meta-analysis also identified considerable heterogeneity in dosing, administration route, and patient populations, highlighting the need for standardized therapeutic protocols.

This study aims to address these gaps by evaluating the safety, efficacy, and optimal dosing of oral vitamin D supplementation—administered in defined low-to-moderate dosages—on tear film homeostasis and inflammatory markers in a broader DED cohort, including cases of mild to moderate severity. The anticipated outcome is to provide robust, evidence-based recommendations for clinicians and patients, positioning vitamin D supplementation as an accessible, cost-effective adjunct therapy to enhance ocular surface health and quality of life in DED management.

METHOD RESEARCH

This study utilized a systematic literature review approach to analyze the role of vitamin D in the management of Dry Eye Disease (DED). A comprehensive search was conducted in multiple electronic databases, including PubMed, ScienceDirect, and Google Scholar, to identify relevant studies published between 2010 and 2024. The keywords used were: "vitamin D," "dry eye disease," "ocular surface," "tear film stability," "meibomian gland dysfunction," and "ocular inflammation." Boolean operators such as AND and OR were applied to combine search terms for more precise results.

Inclusion criteria were: (1) studies published in English, (2) clinical trials, observational studies, or systematic reviews examining the effects of vitamin D on DED or ocular surface health, and (3) studies reporting at least one clinical outcome (e.g., Schirmer's test, tear break-up time [TBUT], Ocular Surface Disease Index [OSDI]). Exclusion criteria included non-peer-reviewed articles, conference abstracts without full texts, animal studies, and studies lacking sufficient data on vitamin D dosage or outcomes.

The study selection process followed the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines. Titles and abstracts were screened by two independent reviewers, followed by a full-text review to assess eligibility. Data extraction was conducted using a standardized form capturing information such as author, year, study design, sample size, intervention details, and primary outcomes. The quality of the included studies was assessed using the Cochrane Risk of Bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies. Results were synthesized narratively due to heterogeneity in study designs and interventions.

RESULTH AND DISCUSSION

Biological Functions of Vitamin D

Vitamin D Metabolism and Signaling Pathway

Synthesis and Activation

Vitamin D exists in two primary forms: vitamin D_2 (ergocalciferol), derived from plant sources such as irradiated mushrooms and yeast, and vitamin D_3 (cholecalciferol), which is synthesized in the skin from 7-dehydrocholesterol (7-DHC) upon ultraviolet B (UVB) exposure or obtained from dietary sources like fatty fish, cod liver oil, and fortified dairy products 33,34. Both forms require enzymatic activation through a two-step hydroxylation process. First, in the liver, vitamin D undergoes hydroxylation by CYP2R1 (25-hydroxylase) to form 25-hydroxyvitamin D [25(OH)D or calcidiol], the primary circulating form used to assess vitamin D status. Second, in the kidney and other peripheral tissues, CYP27B1 (1α-hydroxylase) catalyzes an additional hydroxylation step, converting 25(OH)D into 1,25-dihydroxyvitamin D [$1,25(OH)_2D3$ or calcitriol], the biologically active form. The regulation of vitamin D levels is controlled by CYP24A1 (24-hydroxylase), an enzyme responsible for degrading excess $1,25(OH)_2D3$ into calcitroic acid, an inactive metabolite excreted in bile. This feedback mechanism ensures that vitamin D levels remain within a physiologically optimal range33.

Vitamin D Receptor (VDR) and Gene Regulation

Once activated, $1,25(OH)_2D3$ exerts its effects by binding to VDR, a nuclear receptor that functions as a ligand-activated transcription factor. Upon activation, VDR heterodimerizes with Retinoid X Receptor (RXR) and translocate into the nucleus, where it binds to specific DNA sequences known as Vitamin D Response Elements (VDREs) in the promoter regions of

target genes 35. This interaction modulates the transcription of over 900 genes, influencing key biological processes such as calcium homeostasis, immune regulation, oxidative stress response, and neuroprotection.

Vitamin D receptor (VDR) signaling orchestrates multiple critical physiological and cellular pathways, influencing calcium and phosphate homeostasis, immune regulation, vascular integrity, and neuroprotection at a molecular level. In calcium and phosphate metabolism, VDR activation upregulates the epithelial calcium channel TRPV6, facilitating intestinal calcium absorption, while enhancing the expression of calbindin-D9k, a cytosolic calcium-binding protein that buffers intracellular calcium and regulates its transport 35, 36. Additionally, VDR modulates NaPi-IIb, a sodium-phosphate cotransporter, to optimize phosphate uptake, crucial for skeletal mineralization and cellular energy metabolism. These processes are tightly regulated by 1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$], which binds VDR to form a heterodimeric complex with the retinoid X receptor (RXR), subsequently binding to vitamin D response elements (VDREs) on target gene promoters 35, 36.

Beyond mineral homeostasis, VDR signaling exerts potent immunomodulatory effects by influencing nuclear factor kappa B (NF-κB) signaling 37. The VDR-RXR complex interacts with IκBα, an inhibitor of NF-κB, thereby reducing nuclear translocation of NF-κB subunits (p65/p50) and suppressing the transcription of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α. Additionally, VDR enhances IL-10 expression via direct transcriptional activation, promoting an anti-inflammatory microenvironment and mitigating chronic inflammation 38. In monocytes and macrophages, $1,25(OH)_2D_3$ also upregulates cathelicidin antimicrobial peptide (CAMP), augmenting innate immune defenses against pathogens 36,37,38.

In vascular biology, VDR signaling is pivotal in angiogenesis regulation by downregulating VEGF expression through direct inhibition of hypoxia-inducible factor-1α (HIF-1α) transcriptional activity 39. This suppression is mediated via VDR-induced stabilization of von Hippel-Lindau (VHL) protein, which facilitates proteasomal degradation of HIF-1α under normoxic conditions. Furthermore, VDR represses MMP9, a key extracellular matrix metalloproteinase involved in endothelial remodeling and pathological neovascularization, through direct VDRE-mediated transcriptional control 37,38. These mechanisms collectively inhibit aberrant angiogenesis, particularly relevant in conditions like diabetic retinopathy and age-related macular degeneration 39,40.

In the central nervous system, VDR modulates neuroprotection and synaptic plasticity by regulating the expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) 41. VDR activation enhances BDNF transcription via epigenetic modulation, including histone acetylation of the BDNF promoter, fostering neuronal survival and synaptic plasticity. Additionally, $1,25(OH)_2D_3$ influences dopamine synthesis by upregulating tyrosine hydroxylase (TH), the rate-limiting enzyme in catecholamine biosynthesis, implicating VDR in neuropsychiatric and neurodegenerative disorders 42. Moreover, VDR signaling modulates glutamate excitotoxicity by enhancing glutamate transporter expression, preventing excessive synaptic glutamate accumulation and neuronal damage 42.

At a systems level, VDR-mediated signaling integrates metabolic, immune, and neurological processes, underscoring its role as a master regulator of cellular homeostasis. The complexity of VDR's interactions with chromatin remodeling proteins, co-activators (e.g., SRC-1, CBP/p300), and transcription factors (e.g., RUNX2, PPARγ) further expands its

regulatory potential, positioning vitamin D as a crucial modulator in health and disease 42,43. This broad spectrum of regulatory actions highlights the pleiotropic nature of vitamin D, making it essential for overall health and disease prevention.

Biological Functions of Vitamin D

Calcium Homeostasis and Bone Metabolism

Vitamin D is essential for maintaining calcium and phosphate homeostasis, which is critical for bone mineralization and skeletal integrity, acting through the vitamin D receptor (VDR) that, upon activation by 1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$], forms a heterodimer with the retinoid X receptor (RXR) and binds to vitamin D response elements (VDREs) to regulate gene transcription. In the small intestine, vitamin D increases calcium absorption by upregulating TRPV6 (epithelial calcium channel), calbindin-D9k (calcium-binding protein), and ATP2B1 (plasma membrane Ca^{2+}-ATPase), ensuring efficient calcium transport into the bloodstream. In the kidneys, it promotes calcium reabsorption via TRPV5, calbindin-D28k, and PMCA1b, reducing urinary calcium loss and maintaining systemic calcium balance. Within bone tissue, vitamin D supports osteoblast differentiation by inducing RUNX2 and osteocalcin expression for bone formation, while also regulating osteoclastogenesis through the RANKL/OPG pathway to maintain a dynamic balance between bone formation and resorption. Deficiency in vitamin D disrupts these processes, leading to skeletal disorders such as osteomalacia (defective bone mineralization), osteoporosis (reduced bone density and increased resorption), and rickets in children (impaired growth and deformities). These conditions underscore vitamin D's crucial role in bone health and the importance of maintaining adequate vitamin D levels for optimal musculoskeletal function.

Immune System Modulation

Vitamin D functions as a potent immunomodulator, regulating both innate and adaptive immune responses through vitamin D receptor (VDR)-mediated genomic and non-genomic mechanisms. In innate immunity, 1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$] enhances macrophage and monocyte antimicrobial activity by upregulating cathelicidin (LL-37) and β-defensins via VDRE activation on the CAMP gene, while also modulating toll-like receptors (TLR2, TLR4) and reactive oxygen species (ROS) production to strengthen immune defense. In adaptive immunity, vitamin D suppresses pro-inflammatory Th1 and Th17 responses by downregulating IFN-γ, IL-2, IL-17, and IL-23, while promoting regulatory T cell (Treg) expansion through FOXP3 upregulation, thereby enhancing immune tolerance and reducing autoimmunity. It also inhibits B-cell proliferation, differentiation, and antibody production by suppressing AID and Blimp-1, contributing to immune homeostasis. These mechanisms underlie vitamin D's protective effects in autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease, where it limits NF-κB-driven cytokine production, modulates microglial activation, and strengthens epithelial barriers. In ocular health, vitamin D mitigates inflammation in conditions like uveitis and dry eye disease (DED) by inhibiting NF-κB signaling, reducing IL-6 and TNF-α, and upregulating IL-10, while also modulating dendritic cell activity to suppress aberrant immune responses. Additionally, vitamin D provides protection in age-related macular degeneration (AMD) and diabetic

retinopathy (DR) by inhibiting VEGF-mediated angiogenesis and oxidative stress-induced retinal damage. Collectively, these immunoregulatory properties underscore vitamin D's critical role in maintaining immune balance and preventing inflammatory and degenerative eye diseases.

Anti-Inflammatory and Antioxidant Effects

Vitamin D exerts anti-inflammatory properties by downregulating NF-κB (nuclear factor kappa B) signaling, leading to decreased production of pro-inflammatory cytokines like TNF-α, IL-6, and IL-8. Simultaneously, it enhances antioxidant defense mechanisms by upregulating Nrf2 (Nuclear Factor Erythroid 2-related Factor 2), a master regulator of glutathione peroxidase and superoxide dismutase, which neutralize reactive oxygen species (ROS) 48,49.

Ocular Health and Dry Eye Disease

Vitamin D plays a crucial role in maintaining ocular surface homeostasis by regulating epithelial barrier integrity, tear film stability, and inflammatory responses through vitamin D receptor (VDR)-mediated genomic and non-genomic mechanisms48,49 .

Enhancement of Epithelial Barrier Integrity

Vitamin D strengthens the corneal and conjunctival epithelial barrier by upregulating the expression of tight junction proteins, including occludin, claudins, and zonula occludens-1 (ZO-1)50. The VDR-RXR complex binds to vitamin D response elements (VDREs) in the promoters of these genes, enhancing their transcription and promoting tight junction assembly. This fortification of intercellular adhesion prevents pathogen infiltration and reduces ocular surface permeability, essential for protecting against environmental stressors, allergens, and microbial infections. Additionally, vitamin D modulates cytoskeletal organization via RhoA/ROCK signaling, ensuring the maintenance of epithelial cell polarity and adhesion 28,50.

Regulation of Tear Film Stability

Vitamin D contributes to tear film homeostasis by modulating mucin and aquaporin production. It enhances the expression of MUC5AC, a gel-forming mucin secreted by conjunctival goblet cells, through the activation of SPDEF (SAM pointed domain-containing ETS transcription factor), which drives mucin gene transcription 51. This increase in mucin secretion improves tear film stability and reduces tear evaporation. Additionally, vitamin D upregulates AQP5, an aquaporin involved in water transport across the lacrimal and corneal epithelium, ensuring proper tear fluid balance and hydration of the ocular surface. Dysregulation of these pathways due to vitamin D deficiency contributes to tear film instability, a hallmark of dry eye disease (DED) 51,52.

Suppression of Corneal Inflammation

Vitamin D exerts potent anti-inflammatory effects on the ocular surface by inhibiting NF-κB signaling and reducing the expression of pro-inflammatory cytokines. In DED, vitamin D suppresses matrix metalloproteinase-9 (MMP9), a key enzyme involved in extracellular matrix degradation and corneal epithelial damage. The VDR-mediated inhibition of NF-κB prevents the transcription of MMP9, reducing corneal barrier disruption. Additionally, vitamin

D downregulates TNF-α, IL-6, and IL-1β while upregulating IL-10, shifting the ocular microenvironment toward an anti-inflammatory state 14,16,18, 53 .

Implications for Ocular Diseases

The immunomodulatory, anti-inflammatory, and epithelial-protective properties of vitamin D position it as a potential therapeutic target for various ocular diseases 50,51. In dry eye disease (DED), vitamin D supplementation may improve tear film stability, enhance goblet cell function, and reduce inflammatory damage. In age-related macular degeneration (AMD), vitamin D inhibits VEGF-driven angiogenesis by suppressing hypoxia-inducible factor-1α (HIF-1α) and matrix metalloproteinase activity, preventing choroidal neovascularization. In diabetic retinopathy (DR), vitamin D reduces oxidative stress-induced retinal damage by activating Nrf2 (nuclear factor erythroid 2-related factor 2), enhancing antioxidant defense mechanisms and preserving retinal vascular integrity50,51.

Angiogenesis and Cardiovascular Function

Vitamin D plays a crucial role in inhibiting pathological angiogenesis and maintaining vascular homeostasis, making it a key factor in preventing and managing retinal vascular diseases such as diabetic retinopathy (DR) and age-related macular degeneration (AMD). It suppresses vascular endothelial growth factor (VEGF), a primary driver of abnormal blood vessel formation, by downregulating hypoxia-inducible factor-1α (HIF-1α), which stabilizes under hypoxic conditions and induces VEGF expression. By inhibiting HIF-1α, vitamin D reduces VEGF-mediated neovascularization, thereby limiting uncontrolled angiogenesis commonly seen in DR and AMD. Additionally, vitamin D inhibits matrix metalloproteinase-9 (MMP9), an enzyme responsible for extracellular matrix degradation and endothelial cell migration, ensuring vascular stability and reducing vessel permeability. Its anti-inflammatory effects further protect vasculature by lowering the production of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) that upregulate VEGF and contribute to endothelial dysfunction. Beyond anti-angiogenic activity, vitamin D modulates the renin-angiotensin system (RAS) by suppressing renin gene expression and reducing angiotensin II (Ang II) levels, a potent vasoconstrictor linked to hypertension, oxidative stress, and vascular inflammation. By mitigating Ang II, vitamin D not only protects the retinal microvasculature but also lowers systemic vascular risks such as atherosclerosis and cardiovascular complications. Through these mechanisms—VEGF suppression, MMP9 inhibition, and RAS regulation—vitamin D serves as a critical factor for preserving retinal and systemic vascular integrity, highlighting its potential as an adjunct therapy for retinal diseases and cardiovascular health.

Sources and Metabolism of Vitamin D

Sources of Vitamin D

Vitamin D is essential for various physiological processes, and it is acquired through two primary pathways: dietary intake and endogenous cutaneous synthesis. Both pathways contribute to maintaining sufficient circulating levels of vitamin D, ensuring proper calcium and phosphate metabolism, immune regulation, and bone health 59.

Dietary Sources of Vitamin D

Dietary vitamin D is primarily obtained from natural and fortified food sources, with cholecalciferol (vitamin D_3) being the most bioavailable form, commonly found in fatty fish such as salmon, tuna, mackerel, and sardines, where it is synthesized in the fish's skin through

UVB exposure, similar to human vitamin D production. The vitamin D_3 content in fish varies based on species, diet, and sunlight exposure, with wild-caught fish typically containing higher levels than farmed fish. Other animal-derived foods like egg yolks and beef liver provide smaller amounts of vitamin D_3, which is biologically more active and effective at raising serum vitamin D levels compared to plant-based sources. Fortified foods, including milk, yogurt, breakfast cereals, orange juice, and margarine, are essential for individuals with limited sun exposure or dietary restrictions, with fortification typically using ergocalciferol (vitamin D_2) from yeast and fungi or cholecalciferol (vitamin D_3) from animal sources, the latter being more efficiently converted into its active form, 1,25-dihydroxyvitamin D (calcitriol). Both vitamin D_2 and D_3 undergo hepatic hydroxylation to form 25-hydroxyvitamin D [25(OH)D], the primary biomarker for vitamin D status, and subsequent renal hydroxylation by CYP27B1 to produce calcitriol, which binds to the vitamin D receptor (VDR) to regulate calcium-phosphate metabolism, immune function, and bone health. Given the limited natural dietary sources, food fortification remains critical for maintaining adequate vitamin D levels to support overall health and prevent deficiencies linked to conditions such as rickets, osteoporosis, and compromised immunity.

Endogenous Synthesis

The endogenous synthesis of vitamin D in the skin is a complex, finely regulated process that begins with ultraviolet B (UVB) radiation from sunlight. When UVB radiation, specifically in the 290-315 nm range, penetrates the epidermis, it interacts with 7-dehydrocholesterol (7-DHC), a sterol present in the skin. This photochemical reaction catalyzes the conversion of 7-DHC into previtamin D_3 via a photolysis process. The efficiency of this conversion is influenced by several factors, including UVB intensity, duration of exposure, geographical location, and skin pigmentation. The latter is due to the absorption properties of melanin, which reduces UVB penetration and, consequently, the synthesis of vitamin D in individuals with darker skin. Additionally, environmental factors such as age and the use of sunscreen can further modulate the synthesis process. As individuals age, the skin's capacity to produce 7-DHC diminishes, leading to a decreased ability to synthesize vitamin D. Sunscreen blocks UVB radiation, thus limiting vitamin D production, though it protects against the harmful effects of prolonged UV exposure 61,62,63.

Once formed, previtamin D_3 is unstable and undergoes a thermal isomerization process, where it spontaneously rearranges its molecular structure at body temperature, transforming into vitamin D_3 (cholecalciferol) over a period of several hours. This transformation is driven by the heat of the body and does not require enzymatic intervention. The newly synthesized vitamin D_3 is biologically inactive and needs to be activated before exerting its effects in the body. Vitamin D_3 enters the bloodstream, where it binds to vitamin D-binding protein (DBP), a glycoprotein synthesized by the liver. DBP facilitates the transport of vitamin D_3 to the liver, its primary site of initial hydroxylation, and prevents its rapid degradation in the bloodstream 61,62,63.

In the liver, vitamin D_3 undergoes the first hydroxylation step catalyzed by the enzyme CYP2R1 (25-hydroxylase), converting it into 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. This is the major circulating form of vitamin D and is used to assess the body's vitamin D status. In response to various physiological needs, CYP27B1 (1α-hydroxylase) in the kidneys and other tissues further hydroxylates 25(OH)D to produce the biologically active form, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] (calcitriol), which exerts its effects on target tissues by binding to the vitamin D receptor (VDR). Upon binding to the VDR, calcitriol

activates the transcription of genes involved in calcium and phosphate homeostasis, immune modulation, and bone health. The VDR forms a heterodimer with retinoid X receptor (RXR) and binds to vitamin D response elements (VDREs) in the promoter regions of target genes 64. The regulation of this synthesis and activation process is tightly controlled. For example, elevated levels of $1,25(OH)_2D$ trigger feedback inhibition on CYP27B1, preventing excessive activation of vitamin D, while CYP24A1 (24-hydroxylase) degrades $1,25(OH)_2D$ into an inactive metabolite, calcitroic acid, which is excreted in bile. This feedback mechanism ensures that the body maintains vitamin D levels within an optimal range, preventing both deficiency and toxicity 65.

The biosynthesis of vitamin D is a multi-step process influenced by various environmental and physiological factors. From the photoconversion of 7-DHC to the production of active $1,25(OH)_2D$, each step is crucial for maintaining adequate vitamin D levels in the body. The subsequent activation of the vitamin D receptor in target tissues regulates numerous biological functions, including calcium absorption, bone mineralization, immune modulation, and cellular differentiation. Thus, the endogenous synthesis of vitamin D is integral to homeostasis, and any disruption in this process can lead to disorders such as osteomalacia, osteoporosis, and impaired immune responses 66.

Metabolism of Vitamin D

Vitamin D metabolism is a tightly regulated process essential for calcium homeostasis, immune function, and cellular differentiation, beginning with the synthesis of Vitamin D3 (cholecalciferol) in the skin when 7-dehydrocholesterol is exposed to ultraviolet B (UVB) radiation, forming pre-vitamin D3, which is then converted to Vitamin D3. Once formed, Vitamin D3 is transported to the liver, where it undergoes hydroxylation by the enzyme CYP2R1 (25-hydroxylase) to produce 25-hydroxyvitamin D (25(OH)D or calcidiol), the primary circulating form used to assess vitamin D status. This metabolite is subsequently converted in the kidneys by CYP27B1 (1α-hydroxylase) into the biologically active form, 1,25-dihydroxyvitamin D (calcitriol), which binds to vitamin D receptors (VDR) in various tissues, forming a complex with the retinoid X receptor (RXR) to regulate gene transcription through Vitamin D response elements (VDREs). Beyond its classical roles in bone and calcium metabolism, calcitriol exerts significant extraskeletal effects, including modulation of immune responses and inhibition of abnormal angiogenesis in ocular conditions like age-related macular degeneration and diabetic retinopathy. Vitamin D levels are further regulated by CYP24A1 (24-hydroxylase), which degrades 25(OH)D and $1,25(OH)_2D$ into excretable metabolites, maintaining a critical balance between activation and catabolism. Disruptions in this balance can result in deficiency or toxicity, both of which have serious health implications. The presence of VDR in ocular tissues suggests a protective role of vitamin D in eye health, particularly through its anti-inflammatory and anti-angiogenic properties. Advances in understanding the genetic and enzymatic regulation of vitamin D metabolism, especially variations in CYP27B1 and CYP24A1 activity, offer potential for personalized therapeutic strategies and optimized supplementation to maintain optimal vitamin D levels and prevent related diseases.

Theoretical Frameworks Linking Vitamin D and Dry Eye Disease

Immune Modulation and Inflammation

Immune modulation and inflammation are central to the pathophysiology of various ocular diseases, particularly dry eye disease and age-related conditions. The interplay between

oxidative stress and inflammation exacerbates tissue damage and contributes to the progression of these diseases 75. Chronic inflammation, driven by immune cell infiltration and the release of pro-inflammatory cytokines, leads to further oxidative damage, creating a vicious cycle that can result in significant morbidity 76. Understanding these mechanisms is crucial for developing targeted therapeutic strategies aimed at reducing inflammation, restoring homeostasis on the ocular surface, and improving patient outcomes in ocular health. By addressing both immune modulation and oxidative stress, it may be possible to enhance the management of ocular surface diseases and protect against vision loss 77.

Immune Modulation and Inflammation in Ocular Health

Autoimmune Disease-Related Dry Eye Diseases

Autoimmune diseases, particularly Sjögren's syndrome, play a critical role in the pathogenesis of dry eye disease (DED) through immune-mediated destruction of the lacrimal glands, which are responsible for tear production. In Sjögren's syndrome, autoreactive T cells, B cells, and macrophages infiltrate the lacrimal glands, forming ectopic lymphoid structures that perpetuate chronic immune activation, resulting in glandular atrophy and reduced tear secretion. This immune response is driven by the release of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α, which not only induce epithelial cell apoptosis in the lacrimal glands but also promote ocular surface inflammation, leading to conjunctival hyperemia, keratitis, and goblet cell loss that reduces mucin production and destabilizes the tear film. Additionally, increased expression of matrix metalloproteinase-9 (MMP-9) and TNF-α further degrades the extracellular matrix, intensifying epithelial damage. This cascade establishes a vicious cycle of immune activation, inflammation, and ocular surface dysfunction, causing persistent and progressive dry eye symptoms. A thorough understanding of these immunopathological mechanisms is essential for developing targeted therapeutic strategies to modulate the immune response and alleviate DED associated with autoimmune conditions such as Sjögren's syndrome.

Oxidative Stress and Antioxidants in Age-Related Diseases

Oxidative stress plays a pivotal role in the pathogenesis and progression of age-related ocular diseases, particularly age-related macular degeneration (AMD) and dry eye disease (DED), by disrupting cellular homeostasis through excessive production of reactive oxygen species (ROS) generated from normal mitochondrial respiration and exacerbated by external factors such as UV radiation, pollution, smoking, and aging. In AMD, ROS-induced damage to the retinal pigment epithelium (RPE) and photoreceptor cells triggers cell death, nutrient transport impairment, and drusen formation between the RPE and Bruch’s membrane, leading to progressive retinal dysfunction. Although the eye is equipped with enzymatic antioxidants (e.g., superoxide dismutase, catalase, glutathione peroxidase) and non-enzymatic antioxidants (e.g., vitamins C and E) to neutralize ROS, chronic oxidative stress overwhelms these defenses, resulting in lipid peroxidation, DNA damage, and protein aggregation that accelerate retinal and ocular surface degeneration. In DED, oxidative stress destabilizes the tear film, impairs goblet cell function, and induces epithelial apoptosis, further deteriorating ocular surface integrity. Moreover, oxidative stress activates inflammatory pathways, particularly through nuclear factor kappa B (NF-κB), which upregulates pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and chemokines, perpetuating macrophage infiltration, neovascularization, corneal damage, and tear film breakdown. This creates a vicious cycle of oxidative damage and

inflammation, ultimately impairing visual function and exacerbating DED symptoms. Targeting oxidative stress and its downstream inflammatory cascade using antioxidant and anti-inflammatory therapies represents a promising strategy to slow the progression of AMD and DED, highlighting the importance of understanding these molecular mechanisms to develop effective treatments.

Dry Eye Disease and Tear Cytokines

In dry eye disease (DED), alterations in tear fluid composition result in elevated levels of pro-inflammatory cytokines, particularly IL-1, IL-6, and TNF-α, which create a chronic inflammatory milieu on the ocular surface and drive disease progression. These cytokines recruit and activate immune cells such as T lymphocytes, macrophages, and neutrophils, perpetuating inflammation and activating intracellular signaling pathways like NF-κB, MAPK, and JAK-STAT in corneal and conjunctival epithelial cells. This leads to the upregulation of adhesion molecules (ICAM-1, VCAM-1), increased chemokine release, and the activation of matrix metalloproteinases (MMPs) that degrade extracellular matrix components, induce epithelial cell apoptosis, and disrupt tear film stability. The altered cytokine profile in tears is not only a hallmark of DED pathogenesis but also serves as a biomarker for disease diagnosis and severity assessment. Targeted therapies aimed at inhibiting these cytokines or modulating their signaling pathways hold promise for reducing ocular inflammation, restoring tear film homeostasis, and improving clinical outcomes in DED patients.

Oxidative Stress in Retinal Pigment Epithelium

The retinal pigment epithelium (RPE) is essential for retinal health, supporting photoreceptors through nutrient exchange, visual pigment recycling, and maintaining the blood-retina barrier, but its high metabolic activity makes it highly vulnerable to oxidative stress. The retina's constant photoreceptor turnover, high oxygen consumption, and exposure to light lead to the generation of reactive oxygen species (ROS), which can overwhelm RPE antioxidant defenses and cause cellular damage. This oxidative damage activates pro-inflammatory pathways, resulting in the release of cytokines such as interleukin-8 (IL-8) and monocyte chemoattractant protein-1 (MCP-1), which recruit immune cells like macrophages and neutrophils to the site of injury, further exacerbating inflammation and tissue damage. Chronic oxidative stress and inflammation within the RPE are key drivers in the pathogenesis of age-related macular degeneration (AMD), accelerating retinal degeneration, impairing photoreceptor function, and ultimately causing irreversible vision loss. Therefore, targeting the oxidative and inflammatory processes in the RPE is crucial for developing therapeutic strategies to preserve retinal function and prevent disease progression.

Potential Role of Oxidative Stress in Ocular Surface Diseases

Oxidative stress is a key contributor to ocular surface inflammation in dry eye disease (DED), driven by environmental stressors such as air pollution, smoke, and UV radiation that generate reactive oxygen species (ROS). These ROS cause cellular damage to lipids, proteins, and DNA, compromising the integrity of the corneal and conjunctival epithelium while overwhelming the ocular surface's antioxidant defenses. The resulting oxidative damage triggers inflammatory cascades, activating pathways that release pro-inflammatory cytokines (IL-1, IL-6, TNF-α, MCP-1) and chemokines, which recruit immune cells like neutrophils, macrophages, and T-cells. This immune infiltration exacerbates inflammation by producing

additional cytokines and matrix metalloproteinases (MMPs), leading to epithelial apoptosis, tissue remodeling, and corneal damage, ultimately destabilizing the tear film and intensifying symptoms such as burning, itching, and visual disturbances. Therapeutically, enhancing ocular antioxidant defenses through topical or systemic antioxidant treatments presents a promising strategy to mitigate oxidative damage, reduce inflammation, and improve patient outcomes in chronic ocular surface diseases like DED. Moreover, vitamin D plays a vital role in tear production and ocular surface health, with its active form, calcitriol (1,25-dihydroxyvitamin D3), binding to vitamin D receptors (VDR) in corneal and conjunctival epithelial cells to regulate gene expression and maintain tear film stability.

Key Mechanisms of Vitamin D in Tear Production

Genomic Actions

The vitamin D receptor (VDR) is essential for mediating the biological effects of vitamin D, where its activation by calcitriol (the active form of vitamin D) triggers a conformational change, allowing the VDR to form a heterodimer with the retinoid X receptor (RXR). This VDR-RXR complex binds to vitamin D responsive elements (VDRE) in the promoter regions of target genes, initiating transcriptional regulation of genes involved in inflammation, immune response, and epithelial barrier function—processes vital for maintaining ocular surface homeostasis. Through VDR activation, vitamin D regulates the expression of mucin-related genes such as MUC5AC, a key component of the mucin layer of the tear film, which ensures lubrication and protection of the ocular surface. It also upregulates tight junction proteins like occludin and ZO-1 to preserve the structural integrity of corneal and conjunctival epithelia. These actions collectively stabilize the tear film, reduce inflammation, and maintain epithelial barrier function, making VDR activation by vitamin D a critical mechanism in preventing tear film instability and mitigating conditions like dry eye disease (DED), where inflammation and epithelial disruption are central pathological features.

Non-Genomic Actions

Vitamin D plays a vital role in maintaining tear film function by regulating calcium (Ca^{2+}) and chloride (Cl^{-}) ion channels through activation of the vitamin D receptor (VDR) on corneal and conjunctival epithelial cells, ensuring osmotic balance, fluid secretion, and hydration of the ocular surface. Calcium is essential for signal transduction, cell adhesion, and tight junction regulation, while chloride ions help maintain tear volume and buffering capacity; together, they support tear film stability and ocular surface protection. Beyond ion channel modulation, vitamin D activates intracellular signaling pathways, notably through phospholipase C (PLC), which generates second messengers like inositol trisphosphate (IP_3) and diacylglycerol (DAG) to activate protein kinase C (PKC). These pathways regulate cellular responses to stress, inflammation, and survival, which is particularly important under hyperosmolar conditions commonly observed in dry eye disease (DED). By modulating cytokine expression, promoting cellular hydration, and restoring epithelial integrity, vitamin D helps epithelial cells adapt to osmotic stress, thereby preventing tear film instability and inflammation. This dual action of ion channel regulation and intracellular signaling underscores vitamin D's crucial protective role in maintaining ocular surface health and mitigating the progression of DED.

Anti-Inflammatory Effects

Vitamin D exerts potent anti-inflammatory effects that are essential for maintaining ocular surface health, particularly in conditions like dry eye disease (DED). Through activation of the vitamin D receptor (VDR), vitamin D reduces the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which drive immune cell recruitment and exacerbate tissue damage, while simultaneously enhancing anti-inflammatory mediators like IL-10 and TGF-β to promote tissue repair and homeostasis. This balance of pro- and anti-inflammatory signals is critical in preventing chronic inflammation and epithelial dysfunction. Moreover, vitamin D plays a pivotal role in mitigating hyperosmotic stress-induced inflammation, a hallmark of DED caused by elevated tear film osmolarity. Hyperosmotic stress triggers inflammatory responses in corneal and conjunctival epithelia, but vitamin D, through VDR signaling, downregulates stress-induced cytokines such as IL-6 and MMP9 while boosting IL-10 production to resolve inflammation and protect the ocular surface. By reducing inflammatory damage, enhancing epithelial resilience, and preserving tear film integrity, vitamin D acts as a key modulator in preventing the progression and severity of DED.

Tear Fluid Compositionist

Tear fluid is a complex secretion composed of electrolytes, proteins, and lipids that collectively provide lubrication, nourishment, and protection for the ocular surface, ensuring comfort, preventing dryness, and maintaining clear vision by creating a smooth refractive surface on the cornea. Beyond lubrication, the tear film serves as a barrier against pathogens and supports immune defense, making its balanced composition vital for ocular health. Recent research indicates that tear fluid contains higher concentrations of vitamin D than serum, suggesting that local vitamin D metabolism occurs at the ocular surface. The active form of vitamin D, calcitriol, synthesized in the lacrimal glands and ocular tissues, is essential for tear production, epithelial cell regulation, and immune modulation, while also influencing the synthesis of mucins and lipids critical for tear film stability and protection against evaporative dry eye. By linking systemic nutrition to ocular surface integrity, vitamin D's presence in tear fluid underscores its key role in maintaining tear film homeostasis, enhancing immune defense, and preventing ocular surface diseases such as dry eye disease (DED).

Empirical Evidence on Vitamin D and Dry Eye Disease

Clinical Studies and Findings

Comparative Analysis of Vitamin D Levels in Dry Eye Patients vs. Controls

Vitamin D deficiency has been recognized as a potential risk factor for Dry Eye Syndrome (DES), as evidenced by studies showing its association with reduced tear production and worsened symptoms. Jain et al. reported that individuals with Vitamin D deficiency (<20 ng/ml) had significantly lower Schirmer test scores (9.35 ± 4.42 mm in the right eye and 9.53 ± 5.01 mm in the left eye) compared to controls (14.97 ± 8.49 mm and 14.53 ± 8.03 mm, respectively; $p < 0.001$), indicating reduced tear secretion. Basal tear secretion, measured using the Schirmer test with anesthesia, was also significantly lower in Vitamin D-deficient cases (4.65 ± 2.07 mm vs. 9.34 ± 5.52 mm; $p < 0.001$). Moreover, Tear Film Break-Up Time (TFBUT) was notably shorter in Vitamin D-deficient individuals (6.20 ± 3.03 s vs. 10.45 ± 3.87 s; $p < 0.001$), suggesting increased tear film instability. These findings were supported by a meta-analysis conducted by Liu et al., which reported that dry eye patients had mean Vitamin

D levels approximately 3.99 ng/ml lower than controls. Additionally, Ocular Surface Disease Index (OSDI) scores were significantly higher among Vitamin D-deficient individuals (mean difference: 10.70; p = 0.02), reflecting worse subjective symptoms, while Schirmer's test without anesthesia showed a significant reduction (mean difference: -6.38 mm/5 min; p = 0.002). Interestingly, the meta-analysis found no significant difference in TFBUT between groups (p = 0.15), indicating that Vitamin D deficiency may primarily affect tear production rather than tear film stability.

Table 1 : Comparative of analysis Vitamin D levels in DED Patient vs Control

Parameter	Dry Eye Patients (Vitamin D Deficiency)	Control Group (Normal Vitamin D)	p-value
Vitamin D Levels (ng/ml)	Lower by 3.99 ng/ml (meta-analysis)	Higher	0.002
Schirmer I Test (mm)	9.35 ± 4.42 (RE), 9.53 ± 5.01 (LE)	14.97 ± 8.49 (RE), 14.53 ± 8.03 (LE)	<0.001
Schirmer I with Anesthesia (mm)	4.65 ± 2.07 (RE), 4.80 ± 2.18 (LE)	9.34 ± 5.52 (RE), 9.24 ± 5.42 (LE)	<0.001
Tear Film Break-Up Time (s)	6.20 ± 3.03 (RE), 6.47 ± 2.91 (LE)	10.45 ± 3.87 (RE), 10.42 ± 3.88 (LE)	<0.001
OSDI Score	17.18 ± 12.81	24.10 ± 15.98	0.01

Vitamin D deficiency is strongly linked to reduced tear production and worsening dry eye symptoms, emphasizing the importance of Vitamin D assessment and supplementation in the management of Dry Eye Disease (DED). Vitamin D exhibits anti-inflammatory properties by downregulating pro-inflammatory cytokines, which can enhance tear secretion and promote ocular surface health. Supplementation, either alone or combined with anti-inflammatory nutrients such as omega-3 fatty acids, has demonstrated potential in improving clinical outcomes, including Schirmer's test scores and Tear Film Break-Up Time (TFBUT). However, current evidence is limited by heterogeneous study designs, inconsistent diagnostic criteria, variable Vitamin D measurement methods, and the absence of large-scale interventional trials. Confounding factors such as age, hormonal fluctuations, and systemic conditions further obscure causal relationships. Most studies are cross-sectional and fail to determine optimal dosage, duration, or form of Vitamin D therapy, while findings on tear film stability remain inconclusive, suggesting a greater impact on aqueous tear production. Future research should implement standardized diagnostic protocols, control for confounding variables, and include longitudinal randomized clinical trials to establish definitive therapeutic guidelines. Incorporating Vitamin D screening into DED management, especially for high-risk groups, could provide a comprehensive approach to alleviating symptoms and enhancing ocular surface health.

Consideration of Vitamin D Levels in Dry Eye Patients

Multiple studies, including those by Jain et al. and the meta-analysis by Liu et al., have shown that patients with Dry Eye Disease (DED) often have lower serum Vitamin D levels compared to healthy controls, suggesting the need for clinicians to consider Vitamin D screening in individuals with persistent or treatment-resistant dry eye symptoms. This is particularly important for patients with chronic or severe DED unresponsive to conventional treatments such as artificial tears and anti-inflammatory eye drops. High-risk groups, including

postmenopausal women, the elderly, individuals with autoimmune conditions like Sjögren's syndrome or rheumatoid arthritis, and those with limited sun exposure, should be prioritized for Vitamin D evaluation. Moreover, patients with systemic conditions such as diabetes, thyroid disorders, or metabolic syndrome—known to be associated with both Vitamin D deficiency and DED—also warrant screening. Additionally, individuals experiencing neuropathic ocular pain or symptoms disproportionate to clinical findings may benefit from Vitamin D assessment, given its role in nerve modulation and potential relevance to neurogenic dry eye symptoms.

Potential Role of Vitamin D Supplementation in Dry Eye Treatment

Vitamin D Supplementation Guidelines for Dry Eye Disease (DED)

Patients with chronic or severe Dry Eye Disease (DED) unresponsive to conventional therapies, such as artificial tears or anti-inflammatory drops, should undergo Vitamin D screening, particularly those in high-risk groups like postmenopausal women, elderly individuals, patients with autoimmune diseases (e.g., Sjögren's syndrome, rheumatoid arthritis), those with limited sun exposure, and individuals with metabolic conditions such as diabetes or thyroid disorders. Screening is recommended using serum 25-hydroxyvitamin D (25-OH-D) levels, with <20 ng/mL classified as deficient, 21–29 ng/mL as insufficient, and ≥30 ng/mL as sufficient. For patients with deficiency (<20 ng/mL), supplementation with 6,000 IU Vitamin D3 daily for 12 weeks or 60,000 IU weekly for 6–12 weeks is suggested, while severe deficiency (<10 ng/mL) may require intramuscular injections followed by maintenance oral therapy. Insufficient levels (21–29 ng/mL) can be treated with 2,000–6,000 IU daily or 50,000 IU weekly for 6 weeks, with a maintenance dose of 400–600 IU daily. Oral supplementation is preferred due to better absorption, though intramuscular routes are considered for severe cases or malabsorption syndromes. Serum levels should be rechecked after 8–12 weeks, with toxicity risks monitored by avoiding levels >50 ng/mL and adhering to upper safe limits (6,000 IU/day, 60,000 IU/week). Vitamin D supplementation has demonstrated benefits in reducing ocular surface inflammation, improving tear film osmolarity and corneal barrier function, increasing Schirmer's test scores, and alleviating neuropathic ocular pain, ultimately improving treatment outcomes and reducing the long-term severity of DED.

Multidisciplinary Collaboration for Comprehensive Management

DED is a multifactorial disease with systemic connections, and its management often requires collaboration with other specialties. Clinicians should coordinate with endocrinologists and primary care physicians to screen and manage Vitamin D deficiency, particularly in patients with comorbid conditions such as osteoporosis, diabetes, or autoimmune disorders. Educating patients on lifestyle modifications to maintain adequate Vitamin D levels is also crucial. This includes promoting safe sun exposure (15–30 minutes/day), dietary intake of Vitamin D-rich foods (such as fatty fish and fortified dairy products), and supplementation when necessary. Additionally, encouraging an anti-inflammatory diet rich in Omega-3 fatty acids is beneficial, as Vitamin D and Omega-3 have been shown to work synergistically to reduce inflammation in ocular surface diseases.

Future Directions for Clinical Practice

While existing studies provide promising insights, more robust randomized trials are needed to determine optimal dosing, treatment duration, and the efficacy of Vitamin D supplementation in different subtypes of dry eye (aqueous deficient vs. evaporative). Future clinical guidelines may establish threshold Vitamin D levels for increased DED risk and incorporate routine Vitamin D screening into dry eye evaluations, particularly in high-risk groups. Investigating topical Vitamin D formulations as a potential therapy for ocular surface inflammation and meibomian gland dysfunction could also be a valuable avenue for research. Furthermore, exploring personalized treatment approaches that consider genetic variations in Vitamin D metabolism and receptor expression may enhance individual responses to supplementation.

CONCLUSION

While vitamin D assessment and supplementation are not yet standardized in dry eye management, emerging evidence supports their potential role as part of a multidisciplinary approach to treating DED. Clinicians should remain aware of the link between vitamin D deficiency and ocular surface disease, particularly in high-risk patients, and consider vitamin D screening and supplementation as an adjunctive strategy when appropriate. Further research is needed to establish definitive treatment protocols and optimize patient outcomes, ensuring that the management of DED is *comprehensive* and effective. It is recommended that clinicians consider vitamin D screening and supplementation as an adjunctive strategy when conventional therapies alone are insufficient. Public health initiatives could also focus on increasing awareness of the role of nutrition, including vitamin D, in ocular health. Future research should aim to establish standardized treatment protocols, define optimal dosing and duration of vitamin D supplementation, and explore its synergistic effects with existing therapies to optimize patient outcomes and ensure a more *comprehensive* management of DED.

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