Vitamin D Deficiency Effect on Retina in Children: Review Article

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Abstract

A number of ophthalmological conditions that significantly impact the structure and function of the retina have been associated with vitamin D deficiency. These conditions include glaucoma, diabetic retinopathy, age-related macular degeneration (AMD), and optic neuritis. Each of these disorders can lead to varying degrees of visual impairment or even blindness if not properly managed. Recent studies have highlighted the potential role of vitamin D not only in maintaining general ocular health but also in modulating inflammatory and immune responses within retinal tissues. Vitamin D is believed to influence both the functional and anatomical integrity of the retina through its effects on cellular processes such as apoptosis, oxidative stress reduction, and neuroprotection. Additionally, evidence suggests that vitamin D may play a part in the pathological mechanisms underlying certain retinal diseases, possibly by regulating angiogenesis and reducing retinal vascular abnormalities. These findings underscore the importance of maintaining adequate vitamin D levels for retinal health and disease prevention.

Key words: ***Retina, Vitamin D, Nerve layer*.**

Introduction

It is increasingly acknowledged that vitamin D insufficiency is a pandemic. Lack of understanding that moderate sun exposure is the main source of vitamin D for the majority of people is the main cause of vitamin D insufficiency. Foods fortified with vitamin D are often insufficient to meet an adult's or child's vitamin D needs, since very few foods naturally contain the vitamin. The most accurate biomarker to assess a person's vitamin D level is [25(OH) D] form (calcidiol), which is the inactive form of vitamin D. The active form of vitamin D, [1.25(OH)2D3] (cholecalciferol), modulates inflammation, angiogenesis, oxidative stress, and fibrosis by controlling gene expression in specific cells and tissues via both genomic and non-genomic pathways **(1)**.

Although the bioavailable fractions may theoretically be more clinically informative, serum [25(OH)D] is thought to be the best marker for determining vitamin D status and accurately reflects the free fractions of the vitamin D metabolites. This is what vitamin D deficiency means. Most publications define vitamin D inadequacy as a range of serum/plasma [25(OH)D] concentrations below 75 nmol/L (or 30 ng/ml). A threshold of <25 or <30 nmol/L (10/12 ng/ml) is thought to indicate severe vitamin D insufficiency since it significantly raises the risk of osteomalacia and nutritional rickets **(2)**.

Epidemiology of Vitamin D deficiency

Deficiency in vitamin D is a worldwide public health concern. Worldwide, 50% of individuals suffer from vitamin D insufficiency, and around 1 billion people are vitamin D deficient. The aged, obese, inhabitants of nursing homes, and hospitalized patients are the groups most likely to suffer from vitamin

D insufficiency. Regardless of age or latitude, the incidence of vitamin D insufficiency was 35% greater in obese people [(3)].

Between 50% and 60% of hospitalized patients and inhabitants of nursing homes in the US were vitamin D deficient. People who utilize a lot of skin protection and have greater skin melanin content, especially in Middle Eastern nations, may be at risk for vitamin D insufficiency. Over 90% of newborns in Iran, Turkey, and India are vitamin D deficient, compared to 47% of African American infants and 56% of Caucasian infants in the United States. In the adult population, nearly 80% of individuals in Bangladesh, India, and Pakistan are vitamin D deficient, compared to 35% of adults in the United States. In contrast to 90% in Turkey, 96% in India, 72% in Pakistan, and 67% in Iran, 61% of the older population in the United States is vitamin D deficient [(4)].

Risk factors

For infants, adolescents, and adults up to age 50, the recommended daily intake of vitamin D is 200 IU (international units; 200 IU is equal to 5 micrograms [μg]). People between the ages of 51 and 70 should consume 400 IU (10 μg) of vitamin D per day, while those beyond 70 should get 600 IU (15 μg). Vitamin D insufficiency risk factors include [(5)]:

- Factors associated with exposure to sunlight.
- Darker pigmentation of the skin.
- The winter season.
- Greater latitude.
- Skin protection, such as wearing a veil.
- The amount of clouds.
- Applying sunscreen.
- Elements associated with food consumption.
- Exclusive nursing, which puts the baby at danger.
- Age-related and disease-related factors.
- Obesity.
- Aging kidneys and immobility exacerbate older age.
- Crohn's disease, cystic fibrosis, severe liver disease, and kidney disease malabsorption syndromes.
- Drug interactions: corticosteroids, thiazides, cimetidine, and anticonvulsants.
- Drugs that reduce absorption include cholestiramine, mineral oil, laxatives like orlistat, and others.

A lack of vitamin D may be caused by a number of factors [(6)]:

1. reduced consumption and/or absorption of food. Vitamin D deficiency may result from a number of malabsorption diseases, including cysticfibrosis, inflammatory bowel disease, gastric bypass, celiac disease, short bowel syndrome, and chronic pancreatic insufficiency. Elderly people are more likely to consume less vitamin D orally.
2. less exposure to the sun. The skin absorbs between 50% and 90% of vitamin D from sunshine, with the remainder coming from food. To avoid vitamin D insufficiency, one must spend twenty minutes a day in the sun with more than forty percent of the skin exposed. As people age, their skin produces less vitamin D. Vitamin D synthesis on the skin is lower in those with darker skin. Vitamin D insufficiency may also result from less sun exposure, as shown in patients who are

institutionalized or who stay in hospitals for an extended period of time. People who regularly use sunscreen have less effective UV exposure.

3. reduced synthesis inside the body. Defective 25-hydroxylation may result in a lack of active vitamin D in those with chronic liver diseases like cirrhosis. Hyperparathyroidism, renal failure, and 1-alpha hydroxylase deficiency are all associated with defects in 1-alpha 25-hydroxylation.
4. elevated catabolism in the liver. Pharmaceuticals like carbamazepine, phenobarbital, Clotrimazole, rifampin, dexamethasone, nifedipine, and spironolactone all contribute to the breakdown of vitamin D by 450 e n z y m e s w h i c h a c t i v.
5. resistance of the end organ. Hereditary vitamin D resistant rickets is characterized by end organ resistance to vitamin D. Determining the length of vitamin D insufficiency via a subgroup analysis may have yielded crucial details on the likelihood of retinal structural damage. A more precise evaluation may eventually be possible by using tripton 3D OCT technology to measure the choroidal thickness.

Retina and Vitamin D

The retina and choroid contain vitamin D receptors and some enzymes related to vitamin D metabolism and pathways. According to some research, vitamin D may play a part in the retina's morphological and functional characteristics as well as the pathophysiology of certain retinal diseases. Diabetes, retinopathy, and age-related macular degeneration, and certain ophthalmological conditions include optic neuritis conditions that have been linked to vitamin D insufficiency and impact the formation of the retina. The study of the connection between vitamin D levels and retinal illness is a novel idea, and there is a significant void in the literature about studies that have concentrated on children [(7)].

Vitamin D and Eye Conditions

One major worry is the possible impact of vitamin D deficiency on human health. More and more research has been published recently, particularly in the last few years, since the last review articles on vitamin D and ocular diseases were published. Some of these studies are prospective and look at the relationship between serum vitamin D levels and ocular diseases as well as the potential therapeutic benefits of vitamin D. There are now review papers accessible on vitamin D and eye disorders [(8)].

Apart from the skin, the eye is the only primary organ that receives direct sunlight exposure. Sunlight-mediated ultraviolet B (UV-B) conversion of 7-dehydrocholestrol to vitamin D3 is the main way that humans get vitamin D3. Enzymes containing cytochrome P-450 hydroxylate vitamin D3 at position 25, producing 25(OH) vitamin D3 (25(OH)D3). 1 α-hydroxylase then transforms 25(OH)D3 into the active 1α,25-dihydroxyvitamin D 3 (1,25(OH)2D3). The enzyme z y m e 2 4-hydroxylase may also convert 25(OH)D3 to 24R,25 dihydroxyvitamin D3 (24,25(OH)2D3). The main sources of vitamin D in those who are not often exposed to sunlight are dietary and/or supplementary vitamin D3. Vitamin D is significant in terms of comorbidities even if it does not directly cause eye illness. The focus of research has switched to the effects of vitamin D on eye health due to the availability and effectiveness of regulatory enzymes and vitamin D receptors in ocular tissues. The retinal pigment epithelium (RPE), the ganglion cell layer, and the retinal photoreceptor layer are among the layers that have been found to contain enzymes and hydroxylases (CYP27B1, CYP27A1, CYP2R1, and CYP24A1) that activate and regulate vitamin D metabolism in addition to vitamin D receptors [(9)].

Research indicates that vitamin D has an impact on the cells in the eyes. First discovered in the human retina, vitamin D-dependent calcium-binding protein. Subsequently, vitamin D receptors (VDR) were identified using immunohistochemical staining in the cornea, lens, ciliary body epithelia, retinal pigment epithelia, corneal endothelium, ganglion cell layer, and photoreceptors. Vascular endothelial cells express VDRs in the retina and choroid. More recently, vitamin D hydroxylase was found in the corneal epithelium, endothelium, sclera, non-pigmented ciliary epithelium, and retinal pigment epithelium; these cells are believed to be involved in the metabolism of vitamin D [(10)].

Numerous eye conditions, such as diabetic retinopathy, dry eye, glaucoma, uveitis, and age-related macular degeneration, may be at risk for vitamin D deficiency. Tears, aqueous humor, and vitreous humor have been found to contain vitamin D metabolites. Additionally, it has been demonstrated that choroidal endothelial cells and retinal vascular cells express vitamin D receptors. Vitamin D has been shown to be an independent risk factor for glaucoma in several studies; nevertheless, the connection between vitamin D and Glaucoma is yet unknown. Because of its anti-oxidant and anti-inflammatory properties, vitamin D may be involved in the oxidative stress route in addition to the increased IOP pathway. Through antioxidant signaling pathways, 1,25(OH)2D3 reduced the effects of oxidative stress from hydrogen peroxide-induced toxicity in human RPE cells in an in vivo research. This resulted in decreased levels of cytokines, vascular endothelial growth factor (VEGF), and reactive oxygen species (ROS) [(11)].

Numerous research have recently asserted an inverse relationship between IOP and glaucoma and vitamin D3 levels in its hydroxylated form (25hydroxyvitamin D3 or calcifediol, abbreviated 25(OH)D3). According to a different study, vitamin D dramatically changed the genes linked to inflammation in glaucoma. It suppressed the expression of carbonic anhydrase (CA), angiotensin I–converting enzyme (ACE), and Ras homologue gene family member A (RhoA) while significantly increasing the expression of the cytokine A20 precursor (CCL20) in the rats' small intestines. While CA inhibitors may decrease IOP and enhance blood flow in the retinal vasculature and optic nerve, ACE inhibitors are neuroprotective for cultured retinal neurons and can lower IOP in people. By suppressing RhoA with a subsequent vitamin D therapy, fluid outflow may be improved and aqueous outflow resistance decreased. Finally, a cytokine that responds to intraocular pressure, CCL2, may play a role in controlling intraocular pressure. discovered that patients' vitamin D levels were noticeably greater, while the other investigations came to the exact opposite result [(12)].

Vitamin D has been linked in several studies to uncommon or treatable eye conditions. In case-control studies conducted in Turkey, Italy, and Iran, it was shown that individuals with vernal keratoconjunctivitis had considerably lower blood vitamin D levels. Patients with keratoconus, retinal venous occlusions, and optic neuritis are also more likely to have vitamin D deficiencies. However, two trials found conflicting outcomes in children with allergic conjunctivitis [(13)].

Inflammation and oxidative stress cause photoreceptor degradation and seem to have a role in the pathogenesis of AMD. Vitamin D may lessen oxidative damage that causes photoreceptor degradation because it seems to boost the production of antioxidant genes. Actually, retinal pigment epithelium and retinal photoreceptor cells include the vitamin D receptor (VDR). Vitamin D may help lower long-term oxidative stress, prevent amyloid protein buildup, stop long-term inflammation, and therefore lower angiogenesis [(14)].

Additionally, research has shown that vitamin D has immunoregulatory properties and influences the development and function of the immunological and central neurological systems. According to some animal and in vitro research, vitamin D administration decreased inflammatory infiltration in the central nervous system by inhibiting the activity of antigen-presenting cells. There is growing evidence that vitamin D may have a preventive effect on the onset and progression of multiple sclerosis (MS). Whether vitamin D may help those with ocular neuritis as well (ON) is unknown. Our hypothesis is that vitamin D therapy decreases axonal loss in ON patients mainly because of its ability to control inflammation and maybe because of its neuroprotective qualities [(15,16)].

Numerous investigations have shown the non-skeletal consequences of low serum 25-hydroxyvitamin D (25(OH)D) concentrations; for instance, low 25(OH)D concentrations are linked to impaired visual acuity in elderly persons. Age-related macular degeneration (AMD) in older persons is the most frequent cause of impaired visual acuity associated with low serum 25(OH)D concentrations [(17)].

Vitamin D deficiency (VDD) has been linked in a number of studies to the pathophysiology of AMD. Low 25(OH)D concentrations have also been proposed to cause optic neuropathy by reducing the neuroprotective effect, which would impair older persons' visual acuity. Furthermore, via enhancing endothelial cell-dependent vascular vasodilatation, vitamin D has been shown to control the renin-angiotensin system and retinal micro vessel circulation [(18)].

According to certain research, vitamin D and the direct observation of microvascular damage are related. This was shown by both qualitative and quantitative retinal metrics. The link between vitamin D and microvascular damage may be explained in a number of ways. First, by endothelium activation, vitamin D may change the microvasculature's shape and organization. Endothelium is the primary factor that triggers pathological vascular disease in both large-vessel and microvascular disorders procedures. Therefore, via binding to vitamin D receptors (also known as DNA-binding transcription factors) expressed on endothelial cells, endothelial cells' activity is modulated. By increasing the generation of nitric oxide and decreasing the formation of reactive oxygen species, the activated endothelium subsequently encourages the migration and proliferation of endothelial cells [(19)].

Additionally, it lowers vascular tone by producing endothelium-derived constricting factors and suppresses the innate inflammatory process by altering certain signaling pathways. In light of this, it is possible that low vitamin D levels might prevent the initiation of these antioxidative and vasodilatory activities, which could lead to blood vessel damage. The retina may undergo structural and functional alterations as a result of changes in choroidal blood flow. The choroid contains a dense circulatory network and may be impacted by a number of systemic and local causes, such as vitamin D deficiency. Researchers found that those with vitamin D insufficiency had substantially lower subfoveal CT and inferior and nasal peripapillary CT values than people in normal health. Additionally, they discovered a favorable relationship between CT results and vitamin D levels [(20)].

Axial length, anterior segment structures, and posterior segment components have all been measured using the ultrasonic biometer for many years. Nonetheless, the preferred tool for study is optical coherence tomography (OCT), a cutting-edge technique that produces far better pictures and more precise measurements. An 870 nm super luminescent diode (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) in a spectral-domain OCT offers cross-sectional pictures with axial and lateral alignment, and 40,000 A-scans per second 3.9 and 11 μm lateral resolutions, respectively [(21)].

With the advancement of technology, optical coherence tomography may be used to measure every layer of the ocular anatomy. This research aims to assess the retinal nerve fiber layer (RNFL) and choroidal thickness in individuals with low vitamin D levels who do not have any other systemic or ocular diseases.

The DRI Triton SS-OCT device (Topcon, Tokyo, Japan) is a multi-modal sweeping source OCT with a non-mydriatic color fundus camera that was used to get structural data of the retina. With an axial resolution of 8 μm and a transverse resolution of 20 μm in tissue, this device uses a wavelength of 1,050 nm and can scan 100,000 A-scans per second. The retinal nerve fiber layer (RNFL) (between the inner limiting membrane (ILM) and the ganglion cell layer boundaries), ganglion cell layer (GCL) + (between RNFL and the inner nuclear layer boundaries), and GCL++ (between ILM and the inner nuclear layer boundaries) are the various retinal layers whose thicknesses are measured separately by the scan.as well as retinal thickness (from the ILM to the limits of the retinal pigment epithelium). The three primary protocols of the DRI OCT Triton device—Wide protocol 3D(H) + 5 LineCross 12x9mm Overlap 8; Macular protocol 3D Macula(H) 7x7mm; and Peripapilar protocol 3D Disc 6x6mm—were used in this OCT scan to measure the macular, peripapilar, and macular-peripapilar RNFL and GCL+ thicknesses. The same skilled operator conducted all the scans, blinded to whether or not each individual had a vitamin D deficit [(22)].

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