Focus On Vitamin D In Diabetic Retinopathy

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Abstract:

The relationship between vitamin D and health has received increasing attention from the scientific and medical communities, in recent years. Vitamin D deficiencies have repetitively been associated with numerous acute and chronic diseases, including diabetic retinopathy. Its active metabolite, 1,25-dihydoxy vitamin D, acts as a modulator of cell proliferation, differentiation and apoptosis. Cumulative data from observational studies and various meta-analyses suggest that low serum vitamin D levels are associated with increasing severity diabetic retinopathy. Therefore, we made a descriptive review of the mechanisms linking a potential role of vitamin D with the current concepts of diabetic retinopathy pathophysiology.

Introduction

Diabetes mellitus continues to be a tremendous health burden in world. Diabetes mellitus (DM) is a large public health problem which affects more than 300 million individuals worldwide.[1] Diabetic retinopathy (DR) is among the most common diabetic complications, and is the leading cause of blindness among working-aged individuals all over the world.[2] The prevalence of DR varies from 20% to 80% in different studies. Recent estimates suggest that the number of people with diabetic retinopathy will increase to 191 million by 2030.[3]

Vitamin D is essential for a large number of physiologic processes. Vitamin D insufficiency has reached pandemic proportions, with more than half the world's population at risk.[4] Vitamin D insufficiency has been implicated in the pathophysiology of diabetes and also correlated with an elevated risk of cardiovascular disease, cancer, and mortality.[5, 6] Furthermore, vitamin D insufficiency has been associated with neurologic conditions, such as multiple sclerosis and Parkinson's disease.

Vitamin D Function and Health

Synthesis and its Actions

Vitamin D (ergocalciferol and/or cholecalciferol) is produced and excreted by basal skin keratinocytes exposed to ultraviolet radiation (UV-B), or directly provided by food. While skin vitamin D is transported into the liver bound to binding proteins (DBP), dietary vitamin D is absorbed by the gastro-intestinal tract and transported to the liver via the venous circulation and chylomicron remnants. Part of the vitamin D produced is stored in fat cells and may serve as an endogenous source of vitamin D. In the liver, vitamin D2 and vitamin D3 are hydroxylated in position 25 by several enzymes found in microsomal or mitochondrial fractions. Once produced in the liver, 25(OH)D is released into the bloodstream whilst bound to DBP. Alternatively, vitamin D can be metabolized in 25(OH)D in other tissues. In the kidney, 25(OH)D is converted to the active metabolite, 1,25(OH)2D, through the action of the enzyme 1-alpha-hydroxylase (CYP27B1), located in the proximal tubules. In excess, 1,25(OH)2D and 25(OH)D activate 24-hydroxylase (CYP24A1) and are degraded into 24-hydroxylated products, i.e., 24,25(OH)2D and 1,24,25(OH)3D, which have no biological activity. Once produced in the kidney, 1,25(OH)2D is released and transported into the bloodstream and is mainly bound to DBP until it reaches target tissues expressing vitamin D.

Modes of Action

Similar to other steroid hormones, vitamin D functions according to two modes of action: genomic action; a mechanism mediating gene transcription and non-genomic action; a rapid non-transcriptional action, mediated by the activation of secondary messengers and phosphokinase. [7, 8] The genomic pathway is mediated by the binding of 1,25(OH)2D with a high affinity vitamin D receptor (VDR). When activated, the VDR acts as a transcriptional factor and may directly or indirectly control 200 to 2000 genes in various tissues and cells.[9] This includes genes involved in mineral and bone homeostasis, but also genes controlling cell proliferation, differentiation, and apoptosis.[10] The VDR is ubiquitously expressed throughout the human body[11], including in immune cells, endothelial cells and vascular smooth muscle cells[12], but also in eye tissues, including the retina.

Role of Vitamin D in Diabetic Retinopathy

Animal studies have suggested that supplementation of

calcitriol [1,25(OH)2D], the hormonally active metabolite of vitamin D, is protective against retinal neovascularization and multiple other studies have revealed the anti-angiogenic effects of vitamin D.[13] Vitamin D deficiency (VDD),defined as a serum vitamin D concentration of 20 ng/mL, has also been associated with impairment of insulin secretion, metabolic syndrome, and systemic diabetic progression.[14-15] Since vitamin D metabolism is dependent on sunlight also, VDD follows a seasonal cycle, with vitamin D levels lower in the winter than in the summer.[14]

Payne et al assessed the relationship between vitamin D status and diabetic retinopathy and showed that the subjects with type 2 diabetes mellitus, especially those with PDR, had lower vitamin D levels. The use of multivitamins was also somewhat protective against vitamin D insufficiency. [16]

Long et al evaluated the relationship between vitamin D deficiency and retinopathy severity in diabetic patients with poorly or well controlled glycaemia , and suggested that vitamin D deficiency is associated with severe diabetic retinopathy in patients with well controlled diabetes. Risk factors found to be positively associated with increased severity of diabetic retinopathy were male, increased duration of diabetes and increased HbA1c levels. Correlation of vitamin D with diabetic retinopathy has been evaluated in a number of studies.[17]

Askoy et al. (2000) found that lower concentration of active vitamin D (1,25-dihyroxyvitamin D3) levels were associated with increased retinopathy.[18] In the same way, Gunger et al. (2015) compared 50 patients each of two groups: one with early-stage diabetic retinopathy with vitamin D deficiency and other with early stage diabetic retinopathy without vitamin D deficiency.[19] They found lower serum concentration of vitamin D was associated with early retinal nerve fiber layer thinning.[19] Also a study with sample size of 18 363 patients from NHANES (2008–2012) found vitamin D was associated with diabetic retinopathy.[20] Similarly, a study in a Chinese population of patients with type 2 diabetes used logistic regression analysis and found that vitamin D deficiency was an independent risk factor for diabetic retinopathy and that lower vitamin D levels were associated with increasing severity of diabetic retinopathy.[21] Likewise another study carried out in Japanese population of patients with type 1 diabetes also found that vitamin D deficiency is related to diabetic retinopathy.[22]

Vitamin D has been implicated in the pathogenesis of diabetic retinopathy through its effects on the immune system. Vitamin D has anti-inflammatory and anti-angiogenic role in diabetic retinopathy. Inflammatory cytokines, such as TNF-α, TNF-β, IL-6, and plasminogen activator inhibitor-1 are upregulated in patients with type 2 diabetes, and it has been shown that vitamin D decreases the production of several pro-inflammatory cytokines, such as IL-2, IL-6, IL-8, IL-12, and TNF-α.11 Vitamin D also exerts an anti-inflammatory effect by decreasing the proliferation of helper T-cells, cytotoxic T-cells and natural killer cells.[23]

Vitamin D may also contribute to diabetic retinopathy via angiogenesis mechanisms. Albert et al. have showed that the active metabolite of vitamin D, calcitriol, is a potent inhibitor of retinal neovascularization in vivo and also inhibits retinal endothelial cell capillary morphogenesis in vitro.[19] Additionally, calcitriol downregulates hypoxia-inducible factor-1 (HIF-1) transcriptional activity, as well as HIF-1 target genes, such as vascular endothelial growth factor (VEGF).[24] As several of the complications in diabetic retinopathy, such as macular edema and neovascularization, are driven by VEGF production[25, 26, 27] vitamin D could exert its positive effect via calcitriol mediated VEGF reduction.

Meta-analyses

Recent meta-analysis demonstrated the results of 15 observational studies and provided powerful evidence that serum 25(OH)D levels were related with an increased risk of DR in type 2 diabetes patients. This meta-analysis concluded that low 25(OH)D levels were associated with an elevated risk of DR.[28]

Another meta-analysis demonstrated a significant association between VDD and DR and a statistically significant difference in mean serum vitamin D levels between DR and non-DR patients.[29]

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Complete Resolution of Subretinal Fluid Unnecessary for Good Outcomes In Wet AMD

This phase 4 trial assessed the visual outcomes associated with subretinal fluid resolution in patients with active subfoveal choroidal neovascularization. Participants received monthly ranibizumab injections until complete intra- and subretinal fluid resolution (intensive arm) or until intraretinal fluid resolution with some remaining foveal subretinal fluid (<200 µm; relaxed arm). After 24 months, the groups showed similar BCVA improvements. The relaxed group required fewer injections and maintained more patients on 12-week dosing intervals. Visual outcomes are not significantly affected by lingering subretinal fluid, the study concludes. *Ophthalmology, May 2019*