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Original Research Paper

Association between Vitamin D and Diabetic Retinopathy: The Clinical and Pathophysiological Perspective

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ABSTRACT:

Various emerging evidences show that the prevalence of diabetes and its most common complication i.e., diabetic retinopathy (DR) is increasing at a very rapid pace. Effective tools for its prevention and treatment are still a matter of ongoing researches. Since decrease level of vitamin D is very commonly associated with patients of diabetes and vitamin D has vascular protective properties, anti-inflammatory properties, and antioxidant actions. Multiple studies have reported the association of VD deficiency (VDD) with DR and its severity and progression, whereas the effects of vitamin D supplementation on the disease process are still not very clear. In this study we review the available evidences that supports the possible association of Vitamin D with DR and the protective role it could provide to the patients of diabetic retinopathy, so that we can conduct studies to see the beneficial effect of supplementation of vitamin D in diabetic retinopathy.

Keywords: Diabetes, Diabetic retinopathy, Vitamin D, Vitamin D deficiency, Anti-oxoidants

INTRODUCTION:

Vitamin D (VD) is a steroid hormone produced in the skin after exposure to sun irradiation in the form of cholecalciferol. Only 20% of total daily VD requirement is fulfilled by dietary sources [1]. Active VD is produced after hydroxylation in liver and kidney [1]. Activated vitamin D, acts through its cognate vitamin D receptor (VDR). There are two subtypes of VDR one is the membrane-located mVDR, and other is the nuclear-located nVDR. The non-genomic effects of VD, which are exerted within seconds to minutes after its activation and secondary signaling mechanisms implicated in channel responses, adipocyte metabolism, insulinotropic effects, and antiapoptotic pathways are regulated by mVDR. However, the genomic effects of VD is regulated by nVDR [1]. Vitamin D has both skeletal and non-skeletal effects. Among the various extra skeletal actions VD has been find to be involved in the regulation of fundamental processes involved in cardiovascular homeostasis [2], as well as in the inflammation modulation and tuning of the innate and adaptive immunity systems, which appear to be relevant in the response to respiratory viral infections [3, 4]. Moreover, different studies have shown the prevalence and role of hypovitaminosis D in diabetes, as well as the role of VD supplementation on the natural history of diabetes, its progression, and the complications [5, 6]. To define correctly the optimum level of vitamin D, there is quite strong consensus among experts that 25OHVD levels below 12 ng/mL (30 nmol/L) represent deficiency and levels above 30 ng/mL (75 nmol/L) are clearly sufficient. Conversely, it is still grey area about the clinical meaning of levels between 12 and 30 ng/mL with thresholds of sufficiency at 20 ng/mL, [7] or ≥ 30 ng/mL [8] according to different guidelines. Implementing the <20 ng/ml threshold [7], approximatively thirty three percent of the world population is vitamin D deficient [9]. Severe VD deficiency, defined as < 12 ng/ml, can be found in about seven percent of the global population [8].In a large cross-sectional study conducted in America on over 8000 subjects, 42% of the US population display insufficient VD levels in which the highest prevalence was among African-Americans (82%) [10]. The widespread deficiency of circulating VD [11] along with its detrimental skeletal effects [12] has been associated with development and progression of several diseases

such as aging [13], cancer, obesity [14].

A. Role of Vitamin D in Diabetes:

Reduced 25OHVD levels have been reported to be involved in the pathophysiology of skeletal fragility of patients with diabetes and in patients of endocrine diseases [15, 16]. In vivo studies have shown that T2DM rats display lower levels of 1,25OHVD as compared to controls [17], probably due to impaired renal and hepatic metabolism of VD [18]. Various studies has been reported that patients with T2DM had decreased levels of 25OHVD [19]. In a recent study, an inverse association has been reported between VD levels and poor glycemic control in patients with T2DM [20]. Low levels of 25OHVD are commonly found in obese non diabetic subjects, and are inversely correlated with BMI and adiposity [21].In a very long prospective cohort study (The Copenhagen City Heart Study) involving about 10,000 patients, reported an association between low VD levels and increased risk of T2DM; in fact, the cumulative incidence of T2DM increased with decreasing VD concentrations at baseline, and when categorized by VD concentrations patients in the lowest quartile had an hazard ratio of 1.35 (95% CI 1.0.9–1.66) of developing T2DM [22].

B. Diabetic Retinopathy: An Overview:

Diabetes is the leading cause of blindness in individuals between age 20 to 65y and diabetic retinopathy is the commonest complication of DM. According to a population-based study in Iran, the prevalence of diabetic retinopathy was 37% among type 2 diabetic patients [23]. A latest meta-analysis including 35 prevalence and four incidence studies of diabetic eye disease (DED) among individuals with diabetes in Europe has recently been published [24]. Any diabetic retinopathy (DR) was prevalent in 25.7% (95% CI 22.8–28.8%). The prevalence was significantly higher in persons with T1DM as compared to persons with T2DM (54.4% vs. 25.0%). The pooled mean annual incidence of any DR in patients with T2DM was 4.6% (95% CI 2.3–8.8%). It is very important to note that currently there are no widely effective interventions that can be used to prevent and/or to treat DR except for control glucose and blood pressure. Large epidemiological studies have shown that the threshold for the appearance of DR is at HbA1c levels of 6.5% [25].

C. Role of Vitamin D in Diabetic Retinopathy:

Aksoy et al, 2000 conducted a study and found an inverse relationship between presence and severity of DR, and VD concentrations, being the lowest in proliferative DR and the highest in diabetic patients without DR [26]. Yuan et al, 2019 in a hospital-based cross-sectional study consisting of 889 diabetic retinopathy (DR) and non-DR (NDR) patients showed that vitamin D deficiency is significantly associated with risk of proliferative diabetic retinopathy. They showed that an association between vitamin D deficiency and risk of PDR exists (OR=1.69, 95% CI 1.40-2.05; I2=0%, p=0.61). They also noted that an association between a nonlinear trend for vitamin D decrease with risk of DR was significant (chi2=16.53, p=0.0003) [27]. In another study conducted by Nadri et al, 2019 which included seventy-two consecutive cases of type 2 diabetes mellitus it was concluded that the serum vitamin D levels of $\leq$ 18.6 ng/mL serve as sensitive and specific indicator for proliferative disease, among patients of DR [28]. Ashinne et al, 2018 conducted a study and reported that in Asian Indians with type 2 diabetes, lower serum 25(OH)D was associated with increased severity of DR and the presence of VDD was associated with a two-fold increased risk for proliferative DR [29]. In a cross-sectional study conducted on patients aged from 20 and 60 years, to find out the impact of Vitamin D deficiency on retinopathy and hearing loss among type 2 diabetes patients, Bener et al, 2018 reported a strong positive association between vitamin D, retinopathy and hearing loss among T2DM patients [30]. In 2011, a cross-sectional study on over 500 patients showed that VD deficiency was associated with increased prevalence of DR in T1DM patients; in this study, the prevalence of DR was double in VD deficient as compare with VD sufficient patients (18% vs 9%, respectively; p = 0.02); and in logistic regression, DR was associated with VD deficiency (OR 2.12 [95% CI 1.03–4.33]) [31]. In a sub-analysis of the Field Study, a placebo-controlled trial on nearly 10,000 T2DM patients, showed that subjects with hypovitaminosis D had a higher cumulative incidence of microvascular events; in fact, a 50 nmol/L difference in VD levels was associated with a 18% (p = 0.007) increase in risk of microvascular complications [32]. In other sub-analysis of the Rotterdam Study, a prospective cohort study on over 5500 patients, showed that patients with hypovitaminosis D were at increased risk for DR, independently of the presence of cardiovascular risk factors [33]

D. Effect of vitamin D Supplementation:

The active form of VD calcitriol supplementation has been shown to reduce the choroidal vasculature angiogenesis [34]. However, despite the reasonable rationale discussed in the various above studies, the research on the effect of VD supplementation on DR in humans are still not in satisfactory numbers. In fact, although treatment of DR is often associated with the administration of dietary supplements [35] only small number of studies specifically supplementing VD in

patients with DR have been published so far [36]. These were short term studies mainly focusing on biochemical, immunological, and inflammatory markers of vascular damage in patients with DR showing marginal effects of the VD supplementation on these parameters [36].

E. Vascular Protection by Vitamin D in Diabetes: Mechanisms:

VD protects vessels against the harmful effect of diabetes by several interconnected mechanisms. An association between VD and vascular function has been described in patients with diabetes [37]. A report described improvement in vascular function parameters in diabetic patients, after oral supplementation of vitamin D [38]. Furthermore, in patients with diabetes and VD deficiency reduced endothelium-dependent microvascular function, assessed by iontophoresis of acetylcholine, when compared to patients with diabetes and non-deficient VD levels [39]. Experimental studies have shown that VD improves endothelial dysfunction and promotes vascular regeneration through the activation of VDR which further regulates the expression of numerous genes involved in basic processes of potential link to cardiovascular function [40]. It is noteworthy that VDR is expressed in EC, pericytes, and vascular smooth muscle cells (VSMC).

F. Proposed Mechanisms of VD Protection in DR:

F.1. Modulation of Nitric Oxide:

VD reduces oxidative stress In diabetic mice VD mitigates oxidative stress through a multitude of intertwined mechanisms, such as enhancing the antioxidant defence systems [41], preserving mitochondrial function restoring eNOS function, and reducing the activation of monoamine oxidases (MAO) [42].VD increases eNOS-dependent NO production VD promoted NO production in EC [37]. In the presence of oxygen, NADPH and other co-factors, eNOS catalyzes the oxidation of L-arginine to form L-citrulline and NO. Nitric oxide diffuses easily across the cell membrane to the adjacent VSMC where it leads to a cascade of events, resulting in VSMC relaxation and thereby dilation of the vessel. In addition, NO is known to exert vasculo-protective activities, such as enhancement of endothelial cell survival [43] and inhibition of platelet aggregation. Therefore, NO has key role in the pathogenesis of DR [44] and its modulation by VD may have protective effects in DR. A recent study showed that exposure to a high level of glucose caused upregulation of pro-inflammatory cytokines and a decrease in anti-oxidant enzyme expression both in vitro and in vivo. VD supplementation increased cell viability, reduced reactive oxygen species production and caspase-3/7 activities in high glucose-treated retinal pigmented epithelial cells suggesting that VD can protect the retina from high-glucose-induced oxidative damage and inflammation [45]. VD enhances vascular endothelial growth factor (VEGF) synthesis and release VEGF has a key pathogenetic role in proliferative DR [46]. VD induces up-regulation of VEGF and of its receptors, by direct binding of VDR to two areas of the VEGF promoter [47]. VEGF primarily exerts its effect in DR through the production of vasodilatory mediators. In addition, VEGF signalling through its cognate receptor, increases eNOS – indirectly via calmodulin, directly via phosphorylation of eNOS, and via increase of eNOS levels – and thereby increases NO.

F.2. Role of Vitamin D in Modulation of Inflammation and the Immune System:

Immune and inflammatory mechanisms also associated with development of diabetic retinopathy. Vitamin D reduces chronic inflammation [48] by inhibiting the activation of the ROS/ TXNIP/NLRP3 inflammasome pathway [49], and by suppressing the nuclear factor-κappaB (NF-κB) signaling pathway [50]. Apart from this, VD plays major role in the immune-system vascular activities like it increases the activity of myeloid angiogenic cells, by restoring their function and by enhancing their recruitment [51], it modulates the immune system [52], by promoting the innate immune response and inhibiting the adaptive immune response [53], and by regulating regulatory T cells and immature dendritic cells, and thereby halting the progression of angiopathy [54] and it also decreases the number and activation of macrophages and dendritic cells in the retina [55].Vitamin D decreased diabetes-induced ROS and exerted protective effects against retinal vascular damage and cell apoptosis in association with inhibition of the ROS/ TXNIP/NLRP3 inflammasome pathway in diabetic rat and in human retinal cells [55]. Moreover , patients with proliferative DR were reported to have decreased serum level of 1,25OHVD and increased production of IFN-γ, TNF-α, IL-6, and IL-17A, by anti-CD3 and anti-CD28 antibodies activated PBMCs whereas 1,25OHVD significantly inhibited the proliferation of PBMCs, as well as the secretion of IFN-γ, TNF-α, IL-6, and IL-17A [56].

F.3. Vitamin D and Advanced Glycation end Products (AGEs):

Advanced glycation end products (AGEs) are destructive molecules in the body that, at high levels, contribute to the progression of various chronic diseases. Numerous studies have suggested a modifying effect of vitamin D

on AGEs and their receptors. Kheirouri et al, 2020 did a study to summarize the effects of vitamin D on AGEs and their receptors They investigated the effect of vitamin D treatment on AGEs. Sixty percent of the interventional and experimental studies indicated that vitamin D treatment reduced AGE levels. They also found that no significant changes in the serum levels of AGEs after vitamin D treatment. They also reported a protective effect of vitamin D on RAGE protein or mRNA expression. Vitamin D treatment may possibly be beneficial to reduce AGE levels and to augment sRAGE levels, particularly in vitamin D-deficient situations. Treatment with this vitamin may be effective in reducing RAGE expression in some disease conditions, but might be even harmful under normal conditions. The inhibitory or stimulatory effects of vitamin D on AGE receptors are mediated by various signaling pathways, MAPK/NF-κB, ADAM10/MMP9 and AT1R. In populations with chronic diseases and concomitant hypovitaminosis D, vitamin D supplementation can be used as a strategy to ameliorate AGE-mediated complications by modifying the AGE-RAGE and sRAGE systems [57]. Low vitamin D status is correlated with increased insulin resistance, glycated hemoglobin and AGE formation [58]. In the diabetic retina, advanced AGEs, accumulated under hyperglycemic conditions, modify proteins promoting oxidative stress, increase inflammatory cytokines and induce anomalous crosslinking of ECM proteins that alter vascular structure and function [59]. AGEs could lead to the disorder of calcium signaling involving ROS generation, which, together with calcium mobilization, causes an inflammatory response through the activation of NLRP3 inflammasome [60]. So far very little evidence on the effects of 1,25(OH)2D3 supplementation on AGE formation in DR, has been reported. It has been described that hypovitaminosis D is of limited importance for the development of micro inflammation and accumulation of AGEs [61]. Other investigators demonstrated that 1,25 (OH)2D3 influences AGE–Receptor for the Advanced Glycation End product (RAGE) system significantly reducing RAGE gene expression in peripheral blood mononuclear cells of diabetic patients and, therefore, preventing vascular oxidative stress [62]. RAGE is significantly higher in the diabetic retina, particularly in Muller glia. RAGE signaling stimulates an inflammatory response. In fact, its inhibition decreases diabetes-induced capillary degeneration, blocks cytokine responses induced by high glucose in vitro and diabetes-induced upregulation of the retinal intercellular adhesion molecule (ICAM) in vivo [63, 64]. VD supplementation in T2DM patients down-regulates the levels of AGEs and the gene expression of its cognate receptor (RAGE); these mechanisms appear to be at least in part mediated by glyoxalase I enzyme (GLO1) – an enzyme involved in the degradation and removal of AGEs – as VD supplementation tends to increase its expression [65]. In addition, VD modulates the vascular effects of AGEs by reducing the diabetes-induced increase of IL-6 and of NFκB-p65 DNA binding activity, both key mediators of AGEs signalling [66]. AGEs and RAGE are among the major pathways involved in the pathophysiology of diabetic complications and of DR [67], as their interaction induces the translocation of NF-κB, and the subsequent transcription of endothelial dysfunction biomarkers, such as intercellular adhesion molecule-1 (ICAM-1), endothelin-1, and E-selectin [68].

CONCLUSIONS:

The above reviewed clinical and pathophysiological aspects suggest that VD deficiency has important role in the development and progression of DR. As discussed above that vitamin D deficiency is very common and it detrimental effects have a global impact [69], and related with the development and progression of T2DM, it can be suggested to determine the levels of VD in DR patients. Moreover, it can be suggested to integrate VD with cholecalciferol in patients with DR and severe VD deficiency, as well as in the general population [70]. We also seen that VD has a multidirectional protection to vascular cells enhancing vascular repair, reversing endothelial dysfunction, decreasing inflammation, and/or oxidative stress. Comprising all the above discussions we reach a conclusion that there is a strong rationale for a well-organized, randomized clinical trial to find the effect of VD supplementation on diabetic retinopathy in terms of its onset and progression as well as its complications.

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