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REVIEW

Immune Function of Vitamin D in Type 1 Diabetes Mellitus

Jingbo Li[1,2*], Bing Xiao[1], Yufei Xiang[1]

[1]*Diabetes Center, Institute of Metabolism and Endocrinology, The Second Xiangya Hospital and Key laboratory of Diabetes Immunology Central South University, Ministry of Education, Changsha, China*
[2]*Children's Hospital Los Angeles, Los Angeles, USA*

Abstract

Vitamin D is a well-known fat-soluble vitamin which is essential in the homeostasis of calcium and phosphorus. Vitamin D deficiency causes skeletal disorders, including rickets, osteomalacia, and osteoporosis. However, recent studies revealing the immunomodulatory effects of vitamin D have opened up a new understanding and possibility in this field. It has been proved that vitamin D is related to a variety of autoimmune diseases. Type 1 diabetes mellitus (T1DM), being generally accepted as autoimmune mediated, is also proposed to be associated with the vitamin D status of the human body. Here, we reviewed briefly the epidemiological correlation between the vitamin D status and prevalence of T1DM, the possible mechanisms underlying this correlation, and clinical trials focusing on the therapeutic prospects of vitamin D in the treatment of T1DM.

Keywords: *vitamin D; type 1 diabetes mellitus (T1DM); immunomodulation.*

1. Vitamin D: source, metabolism, and function

The D vitamins are a group of sterols that have a hormone-like function. The two main forms of vitamin D are: vitamin D2 or ergocalciferol, and vitamin D3 or cholecalciferol (Figure 1). The human body obtains vitamin D2 from diet (mainly plants) and obtains vitamin D3 from both diet (mainly animal tissues, especially fatty fish) and endogenous synthesis in the skin under exposure to UVB. Furthermore, vitamin D3 needs to be hydroxylated twice to the active form of the D vitamin. The first hydroxylation occurs in the liver catalyzed by the 25-hydroxylase, which converts vitamin D3 into 25-hydroxyvitamin D3 [25(OH)D3. 25(OH)D3,which is the major form of storage and detection of vitamin D3, binds to vitamin D binding protein (VDBP) in the plasma and is transported throughout the body [1]. The second hydroxylation takes place in the kidney catalyzed by 1-α-hydroxylase, generating the bioactive 1α,25-dihydroxyvitamin D3 (1α,25-(OH)2D3) [2]. On arrival at its target organs or cells, 1,25-(OH)2D3 binds to vitamin D receptor (VDR), then the complex heterodimerizes with the retinoid X receptor (RXR). The heterodimer subsequently binds to the specific DNA sequence, called vitamin D responsive elements (VDREs) to exert its biological effects at the transcriptional level [3]. Additionally, VDR and 1,25-(OH)2D3 complex also intervene in the function of nuclear transcriptional factors, including NF-κB and active-protein-1 in a dose-dependent manner. All the genes with VDREs in the promoter regions play a crucial role in immunoregulation, and abnormal expression may lead to autoimmune diseases [4,5].

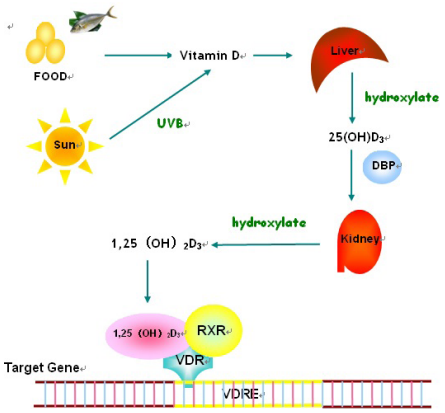

Figure 1. *Metabolism and bioactive mechanism of vitamin D. The human body obtains vitamin D from both diet and endogenous synthesis; vitamin D is not biologically active, but are converted in vivo to the active form, 1α,25-(OH)2D3, by two sequential hydroxylation reactions; 1α,25-(OH)2D3 is a fat-soluble particle, which exerts its transcription-modulating effects via binding to specific DNA sequence.*

[*] ***Corresponding author:*** *Jingbo Li. Diabetes Center, Institute of Metabolism and Endocrinology, The Second Xiangya Hospital and Key laboratory of Diabetes Immunology Central South University, Ministry of Education, Changsha, China. E-mail: lijingbo2277@126.com*

2. Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease induced by several immune cells and cytokines that lead to destruction of the β cells within the islets of the pancreas, resulting in dysfunction of glucose homeostasis. The disturbance of immune tolerance leads to nonspecific insulitis, the exact mechanism of which still remains unknown. The disease process is thought to begin months to years before the onset of hyperglycemia, and clinical symptoms become apparent when approximately ≥90% of pancreatic β cells are destroyed [6].

Specific antibodies or molecules can be detected in the T1DM patients, including glutamate decarboxylase 2 (GAD2; also known as GAD65), receptor-type tyrosine-protein phosphatase-like N (also known as islet cell antigen 512; ICA512), and insulin. Existence of these antibodies can help clinicians make the diagnosis of T1DM. In addition, it is well known that T1DM has strong association with genetic susceptibility and different environmental factors. These factors include short-term exclusive breast-feeding and early introduction of cows' milk [7] or cereals [8], enterovirus infections [9], and vitamin D deficiency [10].

3. Evidences linking vitamin D with T1DM

3.1. Observational Study

Epidemiological studies

Several cross-sectional studies have reported associations between low vitamin D status and prevalence of T1DM [11-15]. It has been known that more UV helps the human body to obtain more vitamin D. An observational study of a large, population-based sample of US youth confirmed that those born in wintertime had the lowest risk of developing T1DM [16], while those born around summertime experienced the highest risk of T1DM. This might explain why low maternal vitamin D status indicates a high risk of T1DM in the offspring. Contradictorily, a newly published paper denied this trend. Miettinen et al. concluded from a cross-sectional study, which recruited 343 T1DM patients and the same number of healthy controls, that there was no difference in the serum 25(OH)D3 concentration between the mothers whose children later developed T1DM and those of non-diabetic healthy children [17].

Recent studies have revealed that a higher predicted 25(OH)D3 score was associated with glucose homeostasis and a small increment in fasting plasma glucose concentrations among participants free of diabetes [18,19] and that there was an inverse correlation between concentrations of vitamin D and insulin primarily in adolescent male subjects [20]. At the same time, a Swiss study showed a similar trend, with 60.5% vitamin D deficient cases among 129 individuals with T1DM. In the research of Gupta et al., they found the low serum vitamin D levels elevated the risk for early-stage diabetes [19]. Other studies noted lower 25(OH)D3 levels in T1DM patients compared with healthy controls [22-25] and found that 25(OH)D3 levels were much lower in individuals with poorly controlled T1DM, ketoacidosis, and other complications [26]. In a cross-sectional study of 517 adolescent patients, it was confirmed that retinopathy was associated with vitamin D deficiency as an independent risk factor [27]. Also, a prospective observational follow-up study found that in patients with T1DM, severe vitamin D deficiency independently predicted all-cause mortality but did not develop microvascular complications in the eye and kidney [11]. On the other hand, Thrailkill [1] discovered the phenomena that more VDBP was excreted in T1DM patients compared with healthy controls, which could lead to the vitamin D deficiency of T1DM patients.

Although studies mentioned above indicated the effect of vitamin D on the prevalence of T1DM, a large prospective birth cohort in Finland reported no association between vitamin D intake and the risk [28] of T1DM or islet cell antoantibodies in their offspring at high genetic risk. Supporters argued that the low level of sunlight in Finland attributed to the negative outcome, but a study in Florida, a solar-rich region of the US, also failed to find significant differences in vitamin D levels between healthy control subjects and type 1 diabetic patients; both groups had a high level, about 70%, of vitamin D insufficiency [29].

Genetics studies

Because epidemiological studies have already thrown light on the association between vitamin D status and prevalence of T1DM, it was reasonable to deduce that there should be evidence on the genetic level of this association should it really exist. Genetic studies have been carried out worldwide to elucidate the genetic basis of vitamin D and T1DM. Results are conflicting and fail to provide a simple answer to this question [30-40]. Four well-known polymorphisms in the VDR genes have been implicated in susceptibility to T1DM. They were FokI , ApaI, TaqI, and BsmI. Different results have been reported from varied ethnic backgrounds. A research by Panierakis et al. reported the association of all these four single nucleotide polymorphisms with T1DM prevalence in the Greek population [31], while others reported that just one or several of the polymorphisms might indicate susceptibility to T1DM. BsmI polymorphism was proved to be related to the prevalence of T1DM in Brazilian, Japanese, Polish and Chinese populations [30,32,34,36]; TT genotype and T allele of the TaqI polymorphism were reported to be more frequent in health controls than those in T1DM patients among people living in Iran and South Croatia [33,39], though this association was concluded to negative by Chang et al. in their research carried out in Taiwan [34]. In addition to these, the FF genotype was found to be a risk factor for T1DM [37,38]. On the contrary, Kahles et al. and Manuel reported no association between VDR gene polymorphisms and susceptibility to T1DM among German and Portuguese populations, respectively [35,40]. Recently, a systematic review was released that investigated the association between polymorphisms in the VDR gene and T1DM risk using meta-analysis; the researchers concluded that the BsmI polymorphism was associated with an increased

risk of T1DM, especially in Asians, while the FokI, ApaI and TaqI polymorphisms were not [41]. Although the authors declared modestly that more studies were required to confirm their results, it was clear that they have already provided a comprehensive understanding of the association between VDR gene polymorphisms and T1DM.

3.2. Experimental studies

As observational studies showed connections between vitamin D and the prevalence of T1DM, researchers worldwide endeavored to explore its possible mechanism. Wu et al. [42] discovered that VDR deletion affected IκBα through mRNA transcription, protein translation, protein-protein interaction, posttranslational modification, and protein degradation. Such deletion subsequently led to a decreasing level of IκBα protein, which in turn led to the activation of NF-κB and put the VDR-/- cell in a proinflammation state. Du et al. [43,44] found that vitamin D3 could restore the activated innate immunity destruction to a certain extent. They showed that 1,25-(OH)2D3 could inhibit the expression of CD14, Toll-like receptor (TLR4), IL-1, and TNF-α, as well as reducing the NF-kB-p65 phosphorylation levels of the monocytes in the patients with LADA and/or T1DM [43]. This result positively corresponded to Khoo's research [45]. These results proved that 1,25-(OH)2D3 had the ability to regulate the innate immune system associated with over-expression of TLRs and TLR signaling. Research has confirmed that 1,25-(OH)2D3 could suppress the production of pro-inflammatory cytokines such as IFN-γ, IL-17 and IL-2 [45,46], and up-regulate CTLA-4 and FoxP3 of T cells. Both might be important factors that suppress inflammatory outcomes of autoimmune diseases [46].

3.3. Interventional Studies

Several clinical trials have been carried out to detect the effect of vitamin D intervention on the prognosis of T1DM. It is likely that vitamin D supplementation did not exert a therapeutic effect on the residual β-cell function [44,45,47,48], though it was reported that intervention with vitamin D could reduce the insulin dose needed to control serum glucose levels temporarily [47]. So, to our disappointment, vitamin D supplementation failed to improve the prognosis of T1DM. Nevertheless, new data are needed before we shut the door completely. Encouraging results have been reported previously that intervention with an inactive form of VD, 1,α-(OH)D3, exerts a protective effect on the residual beta-cell function of LADA, another type of autoimmune diabetes [49]. Li et al. confirmed the fact that fasting C-peptide (FCP) and postprandial C-peptide (PCP) levels decreased significantly in the insulin-alone group while C-peptide levels remained stable in the vitamin D plus insulin group after 1 year's intervention. Additionally, an interesting correlation was proposed that the incidence rates of T1DM increased inversely to the reduced officially recommended daily intake of vitamin D by infants over the years from 1965 to 2005 in Finland, suggesting indirectly the effect of vitamin D supplementation on the pathogenesis of T1DM [50]. Moreover, it has been proposed that high dosage of vitamin D promises to generate positive outcomes from this area [48], while the research that has drawn the negative results mentioned previously used a low dose of vitamin D. Pilot studies have proved the safety of a high dosage of vitamin D [51]. The next step should be well-designed clinical trials to elucidate the protective role of this high dose of vitamin D on the prognosis of T1DM. Furthermore, trials mentioned above all recruited patients as candidates, so it's possible that vitamin D intervention does not have a therapeutic effect but can prevent the pathogenesis of the disease to some extent. After all, retrospective studies have already proved the possibility of this preventive effect of vitamin D supplementation [48]. Cohort studies are required to clarify the protective role on predisposed predisease populations; such research is ongoing worldwide, so it won't be long before we can finally discover an answer to this question.

Summary

In summary, studies reveal promising association between vitamin D and T1DM, but this association is not conclusive, with conflicting data existing. More well-designed studies are required to explain this conflict. Systemic review using meta-analysis is a promising method to solve the puzzle with already available data. And also, the exact mechanism of the effects of vitamin D on the T1DM pathogenesis remains unclear yet. Creative exploration are needed to lead us to a comprehensive understanding of the framework. Therapeutic trials are ongoing aiming to prove the interventional benefits of vitamin D on T1DM. In the future, multi-center, double-blinded RCTs are required to make the final answer.

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