Chapter

Vitamin D Deficiency and Diabetes Mellitus

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Abstract

Vitamin D (VD) is a molecule that can be synthesized directly in the humans' body or enter the organism with food in the form of inactive precursors. To exert its biological action, VD undergoes two-stage hydroxylation (at the 25th and 1st position) catalyzed by cytochromes P450, the presence of which has already been shown in almost all tissues of the human body. The product of hydroxylation is hormone-active form of vitamin D–1,25$(OH)_2$D. 1,25$(OH)_2$D binds to specific vitamin D receptor (VDR) and regulates the expression of genes involved in bone remodeling (classical function) and genes that control immune response, hormone secretion, cell proliferation, and differentiation (nonclassical functions). VD deficiency is prevalent around the globe and may be one of the key factors for diabetes development. The direct association between vitamin D deficiency and type 1 (T1D) and type 2 (T2D) diabetes has been proven. Detection of VDR in pancreas and adipose tissue, skeletal muscles, and immune cells allowed implying the antidiabetic role of vitamin D by enhancing insulin synthesis and exocytosis, increasing the expression of the insulin receptor, and modulating immune cells' functions. This chapter summarizes data about relationship between VD insufficiency/deficiency and development of T1D and T2D, and their complications.

Keywords: cholecalciferol, vitamin D deficiency, vitamin D receptor, CYP27B1 (1α-hydroxylase), type 1 diabetes mellitus, type 2 diabetes mellitus, immune response

1. Introduction

Vitamin D (VD) is a unique bioregulatory molecule as it can be synthesized in the skin in addition to its dietary sources. VD in its metabolically active form, 1,25$(OH)_2$D (calcitriol), is a secosteroid hormone produced after hepatic (at carbon atom 25) and, not exclusively, kidney (at carbon atom 1) hydroxylations. The well-studied function of VD is associated with its ability to regulate metabolic processes in skeletal tissue by affecting mineralization, maintaining a balance between the formation and resorption of bone tissue, and thereby contributing to the prevention of osteoporosis and the occurrence of fractures. In addition to being involved in calcium-phosphate metabolism, the variety of physiological effects of VD also extends to extra-skeletal tissues, since the vast majority of their species possesses vitamin D receptor (VDR). Furthermore, most of these tissues also express the cytochrome P450 enzyme, CYP27B1, responsible for converting 25-hydroxyvitamin D (25OHD), the main circulating metabolite of VD, to hormonally active

form–1,25$(OH)_2$D. 1,25$(OH)_2$D through VDR controls the expression of both those genes that participate in mineral homeostasis and bone remodeling, and genes (about 500) that participate in various cellular pathways that affect physiological and cellular mechanisms, such as immunomodulation, hormone secretion, inhibition of cell proliferation, and induction of cell differentiation.

Recent epidemiological studies have indicated the association between VD deficiency and both type 1 (T1D) and type 2 (T2D) diabetes mellitus. Moreover, impaired glucose tolerance and diabetes have been shown to ameliorate in VD-deficient individuals after VD supplementation. Vitamin D deficiency, which may be a key factor for diabetes development, is prevalent around the globe, with an estimated one billion people being vitamin D deficient. The role of VD in diabetes became clearer after the discovery of VDR in the pancreas, adipose tissue, skeletal muscle cells, and immune cells, which indicates a regulatory effect of VD on glucose homeostasis. Vitamin D can directly enhance insulin synthesis and its release from pancreatic β-cells as well as increase the expression of the insulin receptor in peripheral tissues. It can also indirectly exert an antidiabetic effect by acting on cells of the immune system that secrete pro-inflammatory cytokines as mediators affecting weight gain, systemic inflammation (contributes to insulin resistance), and autoimmune-mediated destruction of pancreatic β-cells. These findings suggested that VD deficiency probably has a causal relationship with diabetes mellitus. Some studies have also reported that VD deficiency was not the cause, but the result of diabetes. Regardless of whether this deficiency is one of the causes of diabetes or its consequence, it is obvious that low levels of VD are closely associated with poor regulation of diabetes and its complications; however, the extent of this relationship and its clinical relevance are not well established.

The aim of the present chapter is to summarize the latest evidence linking VD insufficiency/deficiency with the development of T1D and T2D and their complications. We also analyzed different intervention studies with VD supplements to determine their influence on glucose metabolism and delineated the underlying mechanisms. Previous reviews on the role of VD in diabetes mellitus have been published in recent years. Here, priority was given to the most recent and convincing available evidence.

2. Role of vitamin D in immune regulation and inflammatory responses

The first data concerning the potential role for VD and its active metabolite 1,25$(OH)_2$D in modulating the immune response were obtained as a result of the treatment of tuberculosis and leprosy caused by mycobacteria [1]. However, the mechanisms underlying these observations have been clarified more recently with several important discoveries: (1) the upregulation of CYP27B1 and VDR expression in activated human inflammatory cells, thus providing their ability both to produce 1,25$(OH)_2$D in the site of inflammation and to respond to this hormonally active metabolite; and (2) the participation of 1,25$(OH)_2$D in modulating the multiple pathways of the innate and adaptive immune system. The influence of 1,25$(OH)_2$D on the different cell types of these immune system segments is outlined in **Figure 1**.

Innate immune response involves the activation of Toll-like receptors in monocytes/macrophages as well as in a number of cells such as placenta trophoblasts, keratinocytes, and epithelial, intestinal, lung, and corneal cells, representing first-barrier defenses. VD affects innate immunity through its stimulatory action on the synthesis of defensin β2 and cathelicidin antimicrobial peptide (CAMP) upon Toll-like receptors' activation. These low molecular weight host defense

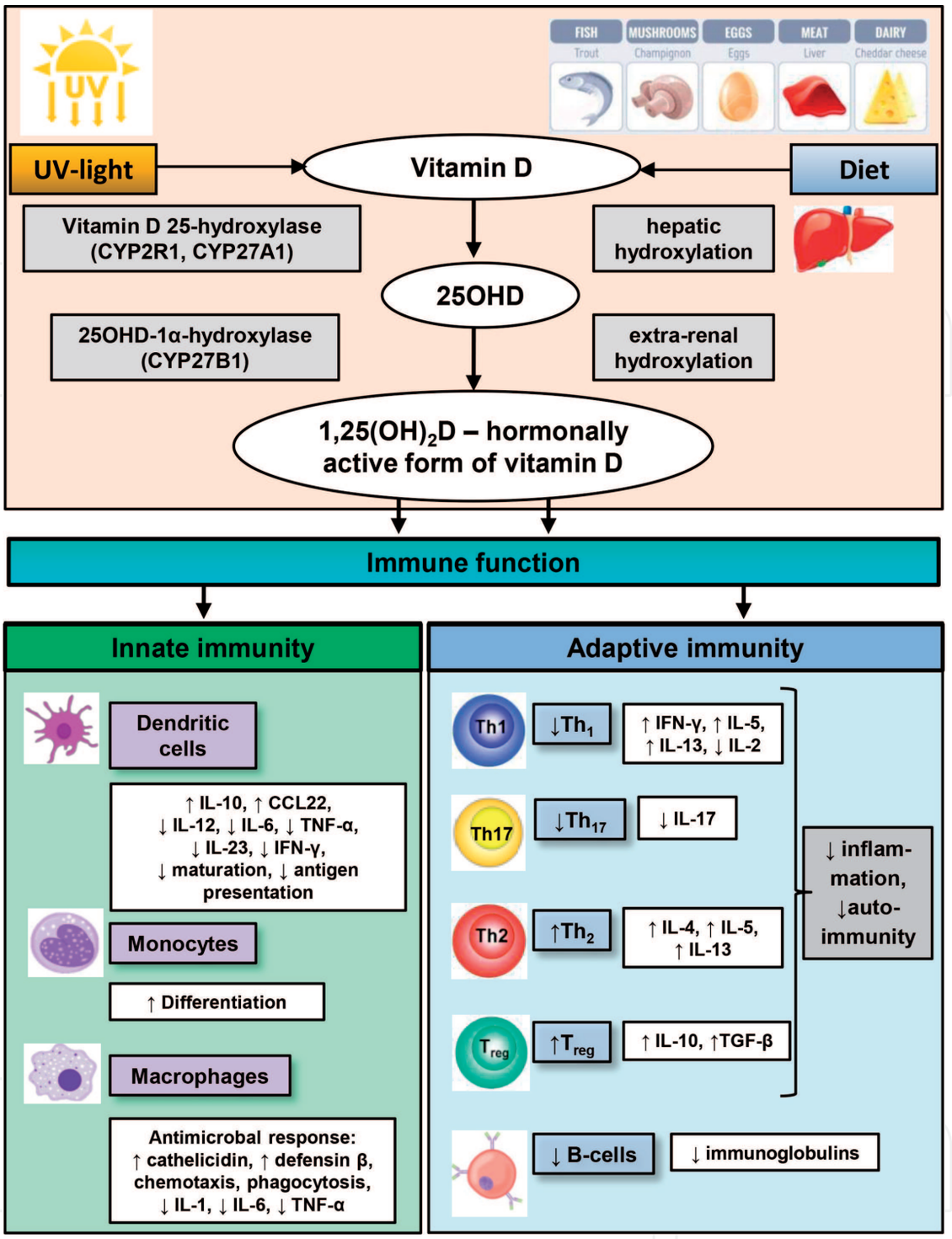

Figure 1.
Vitamin D in immune modulation. 1,25(OH)2D, 1,25-dihydroxyvitamin D; 25OHD, 25-hydroxyvitamin D; IFN-γ, interferon-γ; ILs, interleukins; TGF-β, transforming growth factor β; Th1, type 1 T helper; Th2, type 2 T helper; Th17, type 17 T helper; TNF-α, tumor necrosis factor-α; Treg, regulatory T cells.

antimicrobial peptides demonstrate a broad spectrum of activity against bacteria, viruses, and fungi in the immune cells and are also synthesized in a variety of other cell types [1]. CAMP is known to be a direct transcriptional target of VD, which is induced by binding of $1,25(OH)_2$D-VDR/retinoid X receptor (RXR) complex to the VD response elements (VDRE) in the gene promoter [2]. VD can also modulate innate immune system by increasing chemotaxis, autophagy, and phagolysosomal fusion of phagocytic cells. Notably, VD's action on macrophages was established to be modulated by interleukins. In particular, VD increases the antimicrobial activity of macrophages formed after the IL-15 stimulus, while phagocytic macrophages do

not respond to vitamin D after the IL-10 stimulus, regardless of their high phagocytic activity [1, 3].

Vitamin D shows an inhibitory action on the adaptive immune system, the responses of which include the ability of T and B lymphocytes to produce cytokines and immunoglobulins, respectively, to specifically combat antigens presented to them by macrophages and dendritic cells (DCs). Experimental studies have yielded encouraging results on the immunomodulatory effect of calcitriol on T helper (Th) cells. In particular, $1,25(OH)_2D$ was shown to suppress the immune responses mediated by Th1 cells capable of producing such pro-inflammatory cytokines as IL-2, IL-6, interferon γ (IFN-γ), and tumor necrosis factor-α (TNF-α) [4]. The lack of IFN-γ prevents further antigen presentation to T lymphocytes and their recruitment, while lower IL-2 production impedes T lymphocyte proliferation and differentiation. It has been recently demonstrated that calcitriol also increases formation and activity of CD4+/CD25+ regulatory T cells (Treg) as seen by elevated FoxP3 and IL-10 expression [5]. Increased levels of IL-10 as well as other cytokines with anti-inflammatory properties, induced by calcitriol, block Th1 differentiation, thus shifting the balance from Th1 to Th2 cell phenotype [6]. Many of the effects of VD on Th1 cells, which were previously considered to be implicated in the pathogenesis of several autoimmune diseases, can now be attributable, at least in part, to the inhibitory action of $1,25(OH)_2D$ on the formation and activity of Th17 cells, producing IL-17 [5]. The overall impact of VD on Th cells is related to the suppression of antigen-presenting cells (APCs) of the innate immune system, including the most potent dendritic cells. This modulatory effect of $1,25(OH)_2D$ induces a "tolerogenic state" associated with the differentiation of Treg cells, autoreactive T cell apoptosis, reduced production of inflammatory cytokines, and increased levels of the anti-inflammatory cytokines.

Chromatin immunoprecipitation assay revealed VDR binding to a VDRE in the proximal area of IL-10 promoter in antibody-producing cells of the immune system, or B-cells [7]. $1,25(OH)_2D$ blocked the proliferation of activated B-cells and stimulated their apoptosis. It also inhibited maturation of activated B-cells into plasma cells and memory cells that is consistent with the inhibitory action of VD on the secretion of IgM and IgG [8]. Several observational trials showed an inverse relationship between serum IgE and 25OHD levels, while others indicated a positive correlation [9].

Due to the ability of VD to suppress the adaptive immune system, the role of VD deficiency and supplementation in inflammatory and autoimmune diseases acquires more comprehensive support. In a number of animal models, including autoimmune diabetes, inflammatory arthritis, experimental allergic encephalitis, and different mouse models of enterocolitis, calcitriol prevented the initiation and reduced the disease progression. However, despite strong experimental evidence, human studies are less convincing to prove a role for VD in the modulation of adaptive immune system of individuals affected by autoimmune diseases. In this respect, some trials have confirmed beneficial effect of VD on different inflammatory disease progression, inflammatory markers, and T cell subsets, whereas others have not shown any promising result [10, 11].

3. Vitamin D in maintaining pancreatic β-cell function and regulating insulin sensitivity

As demonstrated in the previous section, VD is one of the key players in the control of immune homeostasis, and here, we will examine in more detail the molecular mechanisms, showing how inadequate VD status and inflammation can

contribute to pancreatic β-cell dysfunction and the formation of insulin resistance (IR). Comprehensive results of experimental and clinical studies have shown that vitamin D is a potential regulator of pancreatic β-cell survival, Ca^{2+} levels, insulin secretion, and insulin signaling (**Figure 2**).

Vitamin D plays an immunomodulatory role in preventing pancreatic β-cell dysfunction and death, via VDR, which is expressed along with Cyp27B1 in APCs, activated T cells, and islet pancreatic β-cells [12]. These effects have been demonstrated in many studies of nonobese diabetic mice using $1,25(OH)_2D$ or analogs. Conversely, $1,25(OH)_2D$-deficient mice showed a tendency to develop more aggressive form of T1D, if the deficiency is present at an early age. The bioactive form of VD protects against the development of insulitis in the pancreas or reduces their

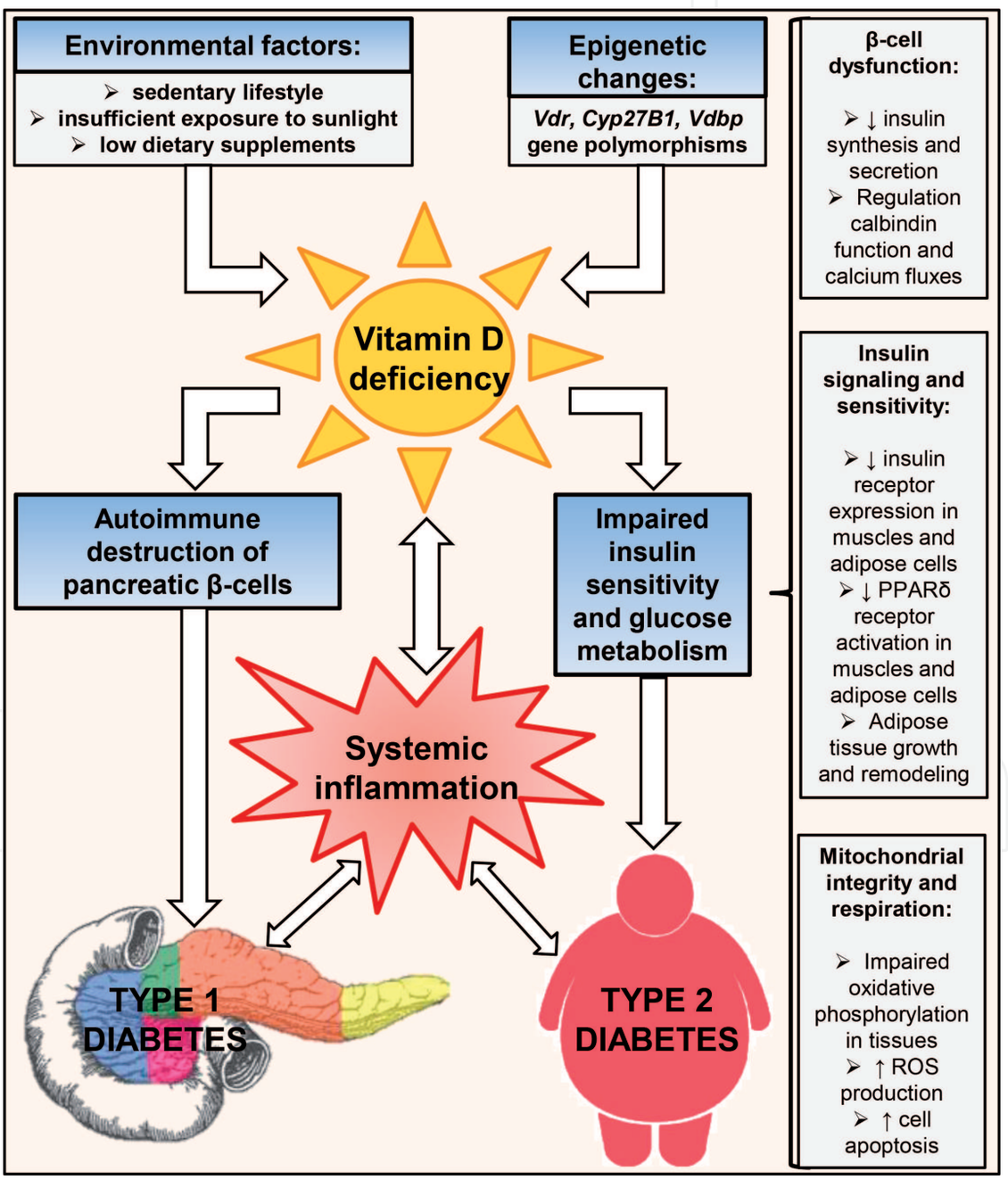

Figure 2.
Mechanisms of glucose homeostasis deregulation related to vitamin D deficiency status. Cyp27B1, 25-hydroxyvitamin D 1-alpha-hydroxylase gene; Vdr, vitamin D receptor gene; Vdbp, vitamin D-binding protein gene.

severity through a dual mechanism of action on both pancreatic β-cells and immune cells [13].

In pancreatic islets, $1,25(OH)_2D$ decreases, as was shown in *in vitro* and *in vivo* experiments, the expression of pro-inflammatory cytokines (e.g., IL-6), which are involved in the pathogenesis of T1D, making β-cells less chemoattractive and less prone to inflammation [14]. This leads to a decrease in T-cell recruitment and infiltration, an increase in regulatory cells, and a delay in the autoimmune process. In addition, $1,25(OH)_2D$ reduces the expression of MHC class I, leading to a decrease in the vulnerability of islet β-cells to the action of cytotoxic T lymphocytes [13, 14].

At the level of the immune system, $1,25(OH)_2D$ inhibits the differentiation and maturation of DCs and promotes their apoptosis, preventing them from becoming APCs, which is the first step in initiating an immune response. It has also been shown that $1,25(OH)_2D$ restores suppressor cells, reduces cytokine formation by Th1 cells responsible for β-cell death, and shifts the immune response toward Th2 cell activation, leading to more benign inflammatory response in pancreatic islets. $1,25(OH)_2D$ suppresses the formation of IL-6, a direct stimulator of Th17 cells involved in the pathogenesis of various autoimmune diseases, including T1D [15]. On the other hand, $1,25(OH)_2D$ exerts an antiapoptotic effect on cytokine-induced apoptosis of pancreatic β-cells. It induces and maintains high protein levels of the A20 (anti-inflammatory protein; inhibits NF-κB signaling), leading to a decrease in nitric monoxide (NO) levels. In fact, NO is able to directly induce β-cell dysfunction and death, or indirectly may affect β-cell function through the induction of Fas expression. Fas is a transmembrane cell surface receptor and a member of the TNF receptor superfamily. Activation of these receptors occurs under the influence of inflammatory cytokines secreted by mononuclear cells that infiltrate islet cells. Reduction of the NO level leads to inhibition of all the above mechanisms and allows realizing cytoprotective effect on islet β-cells. The ability of $1,25(OH)_2D$ to counteract the cytokine-induced expression of Fas in human pancreatic islets at both mRNA and protein levels, modulating the cell death signal cascades and preventing β-cell apoptosis, was established [16].

Several trials have reported that VD deficiency caused impairment of glucose-mediated secretion of insulin in rat pancreatic β-cells, which was restored after VD supplementation. However, the results of clinical studies are not unambiguous as VD adequacy was not always associated with the improvement of insulin secretion. This stimulatory effect of VD is important for the prevention of T2D and may have different explanations. The bioactive form of VD is able to induce insulin secretion through direct binding of VDR-RXR complex to VDRE previously identified in the promoter of insulin gene in pancreatic β-cells [17]. In accordance with this finding, mice with a lack of functional VDR showed impaired insulin secretion after stimulation with glucose [18]. It is noteworthy that VDRE can stimulate not only the transcription of the insulin gene but also many other genes involved in the organization of the cytoskeleton, cell growth, differentiation, and survival of pancreatic β-cells.

In addition to genomic effects, rapid nongenomic mechanism of VD action appears to be involved in depolarization-stimulated insulin exocytosis by regulating intracellular Ca^{2+}. This effect of calcitriol is realized through a membrane VDR-mediated increase in the synthesis of inositol trisphosphate and phospholipase C that promotes the release of Ca^{2+} from endoplasmic reticulum and diacylglycerol-mediated PKC activation. In turn, activated PKC phosphorylates the ATP-dependent K^+ channels and L-type voltage-dependent Ca^{2+} channels. Ultimately, these effects lead to depolarization of the cytoplasmic membrane and the opening of Ca^{2+} L-type and T-type channels that increase intracellular Ca^{2+} level and, accordingly, insulin secretion [19]. Activation of PKA signaling pathways by calcitriol, apparently, is also involved in the regulation of L-type voltage-dependent Ca^{2+} channels.

It has been suggested that increased intracellular Ca^{2+} induced by VD may enhance the expression of cAMP-responsive element-binding protein (CREB), responsible for maintaining efficient transcription of insulin gene and insulin exocytosis, as well as for the glucose sensing and pancreatic β-cell survival [20]. Increased expression of proteins involved in providing low resting Ca^{2+} level, such as calcium-binding proteins (parvalbumin, calbindin-D_{28k}, and calbindin-D_{9k}), plasma membrane Ca^{2+}-ATPase, and Na^{+}/Ca^{2+}-exchanger, can be another mechanism by which vitamin D affects insulin secretion [21]. Furthermore, preclinical studies have shown that VD improves β-cell function by reducing the excess activity of the renin-angiotensin-aldosterone system [22].

Optimal intracellular levels of Ca^{2+} are essential not only for the proper function of pancreatic β-cells but also for insulin-responsive tissues, including liver, adipose tissue, and skeletal muscles. Impaired regulation of extracellular and intracellular Ca^{2+} concentrations due to abnormal transduction of insulin signaling in target tissues may evoke dephosphorylation and decreased activity of glucose transporter-4 (GLUT-4), leading to a phenomenon known as peripheral insulin resistance. The results of several studies confirmed that VD deficiency is involved in the onset of IR. Moreover, an adequate VD level was shown to improve insulin resistance associated with T2D [23]. In addition to the effect of calcitriol on insulin sensitivity related to regulation of extracellular Ca^{2+} concentration and its influx into cells through cell membranes, the active metabolite of VD seems to be an inducer of insulin receptor expression, which in turn improves insulin sensitivity [23]. Another mechanism underlying the beneficial effects of calcitriol on insulin sensitivity is related to activation of the peroxisome proliferator-activated receptor delta (PPARδ) [22]. Activated PPARδ, as a transcription factor, reduces fatty acids-evoked IR in adipose tissue and skeletal muscles. A secondary elevation of parathyroid hormone (PTH) in response to VD deficiency can also increase the concentration of intracellular Ca^{2+} in insulin-sensitive tissues and exacerbate IR by decreasing the number of GLUT1 and GLUT4 in the cell membranes of adipose tissue, liver, and muscle, thereby reducing glucose uptake [24].

An important endocrine and metabolic organ, playing a crucial role in glucose homeostasis and energy balance, is adipose tissue. This tissue is also the major site of VD storage in an organism that can sequestrate a fat-soluble prehormone and significantly decrease its level in blood circulation. It was found that VD exerts an important effect on the expression of genes implicated in promoting adipogenesis and adipose tissue remodeling. VDR is expressed in adipocytes in early stages of adipogenesis and mediates inhibitory effect of calcitriol on adipocyte differentiation through Wnt/β-catenin and mitogen-activated protein kinase (MAPK) signaling pathways [25]. Suppressive action of $1,25(OH)_2D$ on transcription factors, such as PPARγ and CAAT/enhancer-binding protein α (C/EBPα), alters the expression of numerous genes involved in lipolysis, lipogenesis, secretion of adipokines, insulin sensitivity (via GLUT4 expression), and transfer of fatty acids across the membrane [26].

The association between obesity, IR, and VD deficiency is a subject of intense research. A characteristic feature of hypertrophic enlargement of adipose tissue is elevated release of pro-inflammatory cytokines (TNF-α, IL-6, IL-8, MCP1, and resistin) by adipose-resident macrophages and activated T lymphocytes, whereas secretion of adiponectin, an anti-inflammatory and insulin-sensitizing bioregulatory molecule, by adipocytes is reduced [27]. Thus, one of the harmful consequences of obesity is impaired secretion of adipokines and systemic inflammation, which coexists with IR and favors the development of T2D as a key contributing factor. VD is known to protect against IR associated with inflammation by modulating the function of immune cells and secretion of adipokines (adiponectin and

leptin). It has been reported in numerous trials using animal models and in several human observational studies that higher VD levels are accompanied by lower inflammatory markers including TNF-α, IL-6, and C-reactive protein in healthy persons, and in those with inflammation-associated diseases, such as arteriosclerosis, inflammatory polyarthritis, and diabetes [28]. As for adipokines, positive correlation was shown between VD and adiponectin, and inverse correlation between VD and leptin [29]. Finally, VD by targeting mitochondrial respiratory functions through multiple mechanisms also attenuates oxidative stress and exerts key beneficial effects on controlling inflammation, impaired energy metabolism, and cell apoptosis. However, this topic is beyond the scope of this chapter. Vitamin D functions associated with the regulation of β-cell function and insulin sensitivity are summarized in **Figure 2**.

4. Vitamin D deficiency and type 1 diabetes mellitus

Type 1 diabetes mellitus is an autoimmune disorder caused by the progressive T-cell-mediated destruction of insulin-producing β-cells in the pancreas. T1D is commonly diagnosed in childhood and young adults, who are ultimately at risk of the long-term complications of diabetes [30]. This autoimmune condition is characterized by a state of hypoinsulinaemia and insulin-like growth factor (IGF-1) deficiency. T1D is triggered by a combination of both genetic and environmental factors including viral infections, dietary antigens, disruption in the gut microbiota, and VD deficiency [31].

Data regarding the presence of VDR in immune cells (B- and T-lymphocytes) and their ability to produce hormonally active form of VD locally, which acts on immune cells in auto-/paracrine manner, give the evidence that VD is an important regulator of multiple pathways of innate and adaptive immunity. In addition to immune-modulating properties, VD seems to play a role in the regulation of insulin secretion from β-cells. Respectively, VD insufficiency/deficiency is frequently reported to be associated with immunological disorders such as T1D, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, inflammatory bowel disease, hepatitis, asthma, and respiratory infections [32]. The link between the state of VD deficiency and T1D is a latter-day considerable area of interest; however, the presence of the clear association and especially causal relationship between low VD status and the occurrence of T1D still remains disputable and controversial.

Most of the international epidemiological and clinical studies have provided evidence to this causal relationship primarily in children. It has been reported previously that low 25OHD concentrations are fairly prevalent in the UK children with T1D [33]. Moreover, it has been shown that genetic factors affecting the VD metabolic pathway during the pregnancy can be related to the development of T1D. Another study emphasized that the fetal environment, including maternal VD metabolism, may be one of those factors that can lead to the early onset of T1D in Finnish children [34]. The study of VD level and its associated factors in Korean youth with T1D showed that serum 25OHD and $1,25(OH)_2D$ levels were lower in T1D cases than in healthy controls [35]. Nevertheless, in other cross-sectional study of subjects in Seoul National University Children's Hospital, there was no significant difference in the frequency of VD deficiency or serum 25OHD level between healthy and pediatric T1D patients [36].

There is much less data available regarding adult patients with T1D. It has been observed that the serum concentration of VD is negatively associated with IR in adult diabetic patients recruited in Poland [37]. In Algerian population, the

link between VD deficiency and an increased risk of T1D was also found [38]. In contrast, there was no difference reported between Turkish adult T1D patients and healthy controls according to their vitamin D levels [39]. The exact reason for these conflicting results is unclear; thus, we can assume that the interplay of genetic, nutritional, and environmental factors seems to affect the circulating level of VD status marker (25OHD) in adult T1D patients.

The cellular and molecular mechanisms underlying the VD deficiency in patients with TID deserve further thorough and comprehensive study. More recently, in addition to measuring the level of 25OHD, increased attention has been paid to new experimental directions, in particular, the investigation of the state of the VD auto-/paracrine system, including the following key components: VDR, CYP27B1, and 24-hydroxylase (CYP24A1).

Different genetic factors including mutations are known to modify serum 25OHD concentration. Several single nucleotide polymorphisms (SNPs) in the metabolic pathway of VD contribute as the genetic component to VD status. There is a set of studies dedicated to the associations between T1D and mutations related to VD metabolism genes such as VD-binding protein (VDBP), VDR [34, 40, 41], and CYP24A1. Moreover, polymorphisms in CYP2R1 gene encoding the enzyme involved in 25-hydroxylation of VD were also shown to be associated with a higher risk of T1D. Thus, polymorphisms in VD metabolism genes may contribute to susceptibility to T1D in Korean children [35]. Another study linked T-cell proliferation with VDBP level and reported higher levels and frequencies of serum anti-DBP antibodies in patients with T1D vs. healthy controls. This study postulated that VDBP, which was shown to be expressed in cells of pancreatic islets, can act as an autoantigen in T1D [42]. Furthermore, it has been reported that lower maternal third trimester VDBP levels and cord blood VDBP levels have been associated with a higher risk of T1D in offspring [43, 44]. At the same time, there is a lack of studies related to the investigation of the role of CYP27B1 in immune cells, such as monocytes, macrophages, and T-cells, which could shed light on the involvement of impaired VD metabolism in the pathogenesis and/or prevention of T1D. Thus, as VD biosynthesis and its signaling are regulated by genes encoding the VDR and enzymes of VD activation/catabolism, their polymorphisms may significantly alter the bioavailability and specific effects of VD metabolites.

Taken together, these data point to a role of VD deficiency in increasing the risk of T1D progression that provides the basis for further prospective studies on developing guidelines for vitamin D intake to prevent VD deficiency in patients with T1D and to treat this disease.

Since VD is considered a potential diabetes risk modifier, more studies appear to evaluate the role of vitamin D as an adjunctive therapy in improving glycemic control. The recent international study revealed that the majority of participants in Finland, Germany, and Sweden (97–99%) and 50% in the US receiving VD supplements during infancy demonstrated a reduced risk of T1D [45]. In another clinical trial, patients with T1D and low 25OHD concentrations were treated with different doses of cholecalciferol once daily for 3 months depending on their VD status, and as a result, it has been established that cholecalciferol can potentially improve the glycemic control [33]. Recent studies have shown favorable changes in HbA1c, C-peptide, insulin dose, and insulin sensitivity in VD-supplemented patients; therefore, cholecalciferol is increasingly attracting attention as a potential additional therapy in patients with T1D. In a double-blinded randomized controlled trial, which included Indian children with T1D, oral VD supplementation was used for six months in addition to insulin therapy. It has been proven that VD treatment may serve as an adjuvant to insulin therapy for children with T1D due to its effect on augmenting residual β-cell function and improving insulin secretion [46]. Some

representative studies on mechanisms of VD action in T1D described a beneficial effect of its supplementation on regulatory T-cells, with an increase in their percentage [47], suppressive capacity [48], and reduced progression to undetectable C-peptide.

However, some other studies have not demonstrated a beneficial effect of VD supplementation in preventing/improving the course of T1D or its complications. The prospective Environmental Determinants of Diabetes in the Young (TEDDY) Study demonstrated no benefit of maternal VD supplementation during pregnancy on the risk of islet autoimmunity in the offspring [49]. According to the review [32], there was no beneficial impact of VD supplementation on β-cell function, HbA1c levels, or insulin requirement.

The reason for these conflicting results is unclear. Nevertheless, we can presume the presence of a plethora of factors that may affect the results. Differences in study design, seasonal differences, stages in the progression of diabetes, ethnic origin of the populations, age and gender of patients may contribute. Therefore, further randomized controlled trials with a larger sample of patients are needed to gain more insight into the relationship between VD and T1D and to investigate VD replacement in preventing T1D.

The life expectancy of T1D patients has increased substantially during the last decades due to the availability of exogenous insulin, though it is still shorter than that of healthy people and associated with the development of chronic complications. Traditionally, the diabetic complications have been classified as either microvascular (retinopathy, nephropathy, and neuropathy) or macrovascular (cardiovascular disease, cerebrovascular accidents, and peripheral vascular disease). Although intensive glycemic control significantly reduced the incidence of microvascular and macrovascular manifestations, the majority of patients with T1D are still developing these outcomes. Most clinical trials related to the influence of VD supplementation on diabetes-associated complications have been performed in patients with T2D. To date, a limited number of experimental and clinical trials are available regarding the effect of VD on complications associated with T1D.

Diabetic ketoacidosis, which is the most dangerous and life-threatening complication of mainly T1D that results from insulin deficiency or excess of adrenaline or cortisol, is found to be associated with low VD level. VD is known to protect against viral and bacterial infections, which were shown to be triggering factors for diabetic ketoacidosis [50]; as a result, VD supplementation can become an integral part of diabetic ketoacidosis prevention and management. Nephropathy is another well-characterized complication of T1D, resulting in proteinuria and urinary loss of micronutrients. It has been previously found that the dietary supplements may modulate VD balance, attenuate polyuria, proteinuria, and renal hypertrophy in experimental T1D [51]. In addition, it has been reported that VD may reduce diabetic nephropathy not only by improving blood glucose and insulin levels but also by modulating hexosamine pathways in kidneys [52]. More recently, it has been shown that $1,25(OH)_2D$ may improve diabetic cardiomyopathy in T1D rats by modulating autophagy through the β-catenin/TCF4/GSK-3β and mTOR pathway [53]. Several studies have also demonstrated an association between low VD levels and diabetic peripheral neuropathy. Since VD is a well-known neurosteroid, a possible beneficial effect of its supplementation on preventing diabetic peripheral neuropathy can be assumed; nevertheless, further studies are needed.

Type 1 diabetes mellitus is a secondary cause of osteoporosis, characterized by reduced bone mass and disturbed bone microarchitecture. Patients with T1D have increased fracture risk that may be determined by the low 25OHD levels. Diabetic retinopathy, advanced cortical cataracts, and diabetic neuropathy are the risk factors for increased number of falls and, as a result, fracture because of

visual impairment and alterations in balance [54]. Replacement of VD along with calcium has been found to improve the bone mineral density in children with T1D; therefore, an adequate calcium level and VD supplementation are important for the prevention of T1D-associated osteoporosis [55].

According to available experimental and clinical data, new recommendations for T1M patients have been developed including obligatory assessment of serum 25OHD level and prescription of personalized doses of vitamin D in order to avoid the development of T1M complications or at least detain its progression.

5. Vitamin D deficiency and type 2 diabetes mellitus

Type 2 diabetes mellitus, formerly known as adult-onset diabetes, is a complex chronic metabolic disorder that has become one of the most serious public health-care problems worldwide. According to the data of the World Health Organization, 2.2 million people died from diabetes in 2012 and 1.6 million people died in 2015, and diabetes is expected to be the 7th cause of death by 2030. The incidence of T2D is estimated to account for 90% of all diabetes cases. T2D is characterized by dysfunction of pancreatic β-cell, systemic inflammation, and hyperglycemia due to insufficient insulin production, insulin action, or both [56]. A high diabetes-associated concentration of glucose in the blood over an extended period can cause heart disease, diabetic retinopathy, renal failure, poor blood circulation in the limbs, and, as a consequence, amputations.

T2D mainly develops as a result of the summation of genetic, environmental, and other risk factors [57]. To date, an increased risk of developing T2D in monozygotic twins with a statistical reliability of about 96% has been convincingly shown. Moreover, the risk of developing this disease in children from diabetic parents is 40% higher than in the offspring of healthy parents. T2D is now regarded as an endocrine-metabolic disease of a polygenic nature. About 75 loci have already been identified, damage to the sequences of which can be directly associated with the risk of developing T2D. These genes encode proteins with very different functions, such as ion channels (KCNJ11; potassium inwardly rectifying channel, subfamily J, and member 11), various transcription factors (TCF7L2, transcription factor 7-like 2), receptors (IRS1, insulin receptor substrate 1; MTNR1B, melatonin-receptor gene; and PPARγ2), growth factors (IGF2BP2, insulin-like growth factor two binding protein 2), as well as CDKN2A (cyclin-dependent kinase inhibitor 2A), HHEX (hematopoietically expressed homeobox protein), and FTO (fat mass and obesity-associated protein) [58–60].

Despite the growing body of data on the relationship between the risk of developing T2D and certain genes, improper food behavior and the sedentary lifestyle are still considered the key reasons for the development of the disease. In a number of experimental and clinical studies, VD has been shown to exhibit various non-skeletal properties that significantly regulate glucose metabolism. Furthermore, human studies have clearly revealed an inverse association between vitamin D status and the prevalence of T2D. It was found in numerous observational studies that the concentration of 25OHD negatively correlates with deteriorated glucose homeostasis, IR, and impaired β-cell function [61]. Low blood serum 25OHD levels were associated with the negative changes in a number of metabolic parameters, indicative of IR, including BMI (body mass index), HOMA-IR (homeostatic model assessment for IR), TG (triglycerides), HDL (high-density lipoproteins), LDL (low-density lipoproteins), TC (total cholesterol), and HbA1c [62]. More recently, large-scale epidemiological studies have been carried out as for the dependence of the risk of T2D developing on the availability of VD. VD deficiency has been shown

to be widespread in both men and women in different age groups among Saudi citizens, and this was accompanied by hyperglycemia in 90 percent of patients [63]. T2D patients studied in India also showed VD deficiency of varying severity in 77% of subjects [64]. The association between a low serum of 25OHD concentration and an increased risk of developing T2D can be partially explained by an increase in fat mass. A study of serum 25OHD in patients with T2D from the urban area of Cairo with limited exposure to the sun and overdressing habit revealed a decrease of its level by 13% compared with the control. Depleted level of the prohormone has been found to be related to a higher risk of insulin resistance [65].

However, as it turned out, not all studies confirmed a decrease in VD contents in patients with T2D. Using the method of high-performance liquid chromatography in tandem with mass spectrometry, significantly higher levels of VD were demonstrated in patients with T1D and T2D in comparison with the control group [66].

Overall, most of the data presented here suggest a pivotal role of VD in the regulation of insulin secretion and confirm that the decreased insulin sensitivity at target organs may be attributable to VD inadequacy [67]. The relationship between VD deficiency and IR could be realized at the level of modulation of immune processes and inflammation, since VD deficiency is associated with an increase in inflammatory markers. In addition, genetic polymorphisms of VD-related genes such as VDR, CYP2R1, and CYP27B1 may predispose to impaired glycemic control and T2D [68].

As we mentioned earlier, VD mediates its biological activity through VDR, which belongs to the family of steroid hormone receptors. Many VDR gene SNPs have been identified to be related to T2D, in particular to insulin synthesis and release [69]. The most reported VDR SNPs associated with diabetes are Fok1, Bsm1, Taq1, and Apa1. Recently, the study of these polymorphisms is becoming increasingly popular because their detection can be a reliable diagnostic characteristic in determining the risk of T2D development. The association between VDR polymorphisms and abdominal obesity has shown that patients with Bsm1 and Apa1 polymorphisms have low vitamin D status, which is accompanied by an increase in the concentrations of TC, LDL, and TG [69]. The results of another study show that body weight and BMI were significantly associated with polymorphisms Bsm1 and Taq1, while Bsm1 strongly correlated with elevated HbA1c level. The frequency of the heterozygous genotype of the Bsm1 polymorphism was significantly greater in type 2 diabetics than in controls [70]. A study of this parameter in a group of patients with T2D from India revealed that it was Taq1 and Bsm1 polymorphisms that were closely associated with diabetes [71]. Thus, it can be concluded that the detection of different types of VDR gene polymorphisms is a reliable prognostic parameter for the risk of T2D. In addition, the type of polymorphism appears to be race-specific.

Despite a large amount of data on the association of CYP27B1 polymorphisms with the risk of T1D, the effect of different SNP variants of this gene in the development of T2D is unclear to this day [72, 73].

While the closest relationship between VDR polymorphism in T2D has long been established, the discovery of the effect of CYP2R1 gene polymorphisms on the risk of developing this disease was a real step forward. Among a large group of tested SNPs of CYP2R1 gene, only two of them showed reliable association with the incidence of T2D. However, none of the tested polymorphisms were independently associated with serum 25OHD levels [74].

The effect of VD supplementation on glucose metabolism in patients with T2D remains controversial. It was shown that replenishing VD deficiency with high doses of cholecalciferol helped to reduce non-HDL cholesterol and caused significant normalizing changes in metabolic parameters of glucose homeostasis

(fasting glucose and serum insulin) and a decrease in oxidative stress and DNA damage [75, 76]. VD supplementation also caused an increase in insulin secretion and insulin sensitivity in T2D patients [77]. Nevertheless, some research groups did not find any effect, or only a slight decrease in fasting plasma glucose and an improvement in IR were seen. Basically, patients with VD deficiency and impaired glucose tolerance at baseline demonstrated these latter effects [68].

In addition to the ability of VD to reduce the risk of T2D, an adequate level of this vitamin in the body is also important for correcting diabetes-related pathologies such as retinopathy, nephropathy, neuropathy, and secondary osteoporosis caused by diabetes. Moreover, patients with already diagnosed T2D also have a risk of developing VD deficiency, in particular, due to the progression of nephropathy caused by diabetes [78]. Serum 25OHD was shown to be significantly reduced in patients with diabetic nephropathy [79]. Thus, the relationship between VD deficiency and the incidence of type 2 diabetes and related complications is likely to be bilateral.

Continuing the discussion on diabetic complications, we may note that vitamin D deficiency correlates with the risk of diabetic retinopathy. However, the reliable establishment of this relationship is problematic due to a number of limiting factors: cross-sectional structure, small sample size, ethnic variation, and heterogeneity in criteria that do not contribute to the identification of VD deficiency. Nevertheless, at least two state-of-the-art meta-analyses of observational studies indicate that D hypovitaminosis among T2D patients is associated with a significantly increased risk of diabetic retinopathy [80, 81].

A meta-analysis of data on the relationship between VD deficiency and the development of diabetes-induced neuropathy also revealed a strong correlation. Recovery of insulin secretion, increasing insulin sensitivity of target tissues, and reducing the inflammatory response have been proposed as potential mechanisms for improving the clinical manifestations of diabetic neuropathy following VD supplementation [82]. Furthermore, several independent studies have established serum 25OHD levels to predict cardiovascular complications or to assess the possible protective role of VD intake in patients with T2D. Diabetic patients with 25OHD < 36 nmol/L manifested approximately 21% higher risk for developing macrovascular disease [83].

There is no doubt that achieving normal levels of 25OHD is an important factor in preventing the onset of T2D or for eliminating the complications associated with the disease. However, at the moment, the question of the VD dosage and duration of the complex therapy of patients with T2D remains unresolved. Based on interventional trials, it can be postulated that the VD dose needs to be more than 2000 IU per day to raise blood 25OHD levels above 80 nmol/L, which is considered to be sufficient to reduce the risk of T2D [84]. However, the results of a double-blinded, placebo-controlled, randomized trial with 4000 IU of VD did not improve HbA1c or OGTT (oral glucose tolerance test)-based indices of β-cell function or insulin secretion in patients with stable T2D. The ambiguity of the results may be due to the following factors: the baseline 25OHD concentration was too high (<27 ng/mL), whereas a significant reduction in HbA1c and fasting glucose after VD supplementation was reported only among patients with baseline 25OHD < 20 ng/mL; VD may have no detectable effect in persons with well-controlled diabetes (good glycemic control, HbA1c-6.6%); and/or metformin treatment, which may have masked a small effect of VD supplementation [85]. These data indicate the need for individual VD therapy for each patient with a risk of development or with an already established diagnosis of T2D. When choosing this type of therapy, it is necessary to take into account the initial level of 25OHD in the patient's blood, changes in this level during therapy, as well as the presence of other drugs in the treatment regimen that can affect the manifestation of the beneficial effects of VD.

6. Conclusion

A two-way relationship between VD status and T1D and T2D can be argued. At the moment, it seems undeniable that there is a causal association between the risk of diabetes mellitus development and numerous polymorphisms in genes responsible for metabolism (CYP2R1 and CYP27B1) and signaling (VDR) of VD. Despite the fact that diabetes mellitus is a multifactorial disease, and it is unlikely that VD deficiency is the main cause of this pathology, there is no doubt that it may be used in the complex treatment of diabetes mellitus and its complications. The importance of more comprehensive and randomized clinical trials to determine the therapeutic role of vitamin D in preventing the progression of glucose intolerance in groups at high risk of developing T2D should be noted.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

$1,25(OH)_2D$	1,25-dihydroxyvitamin D
25OHD	25-hydroxyvitamin D
APCs	antigen-presenting cells
BMI	body mass index
CYP	CYP2R1 vitamin D-25-hydroxylase
CYP24A1	25-hydroxyvitamin D-24-hydroxylase
CYP27B1	25-hydroxyvitamin D-1-alpha-hydroxylase
DCs	dendritic cells
IFN-γ	interferon-γ
IGs	immunoglobulins
ILs	interleukins
IR	insulin resistance
NF-κB	nuclear factor kappa B
PPARs	peroxisome proliferator-activated receptors
PTH	parathyroid hormone
RXR	retinoid X receptor
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
TGF-β	transforming growth factor β
Th1	type 1 T helper
Th17	Th17 type 17 T helper
Th2	type 2 T helper
TNF-α	tumor necrosis factor-α
Treg	regulatory T cells
VD	vitamin D
VDR	vitamin D receptor
VDRE	vitamin D response element

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