Narrative Review Article

Vitamin D in the Prevention and Management of Type 2 Diabetes: Mechanistic Insights and Therapeutic Potential

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ABSTRACT

Type 2 diabetes (T2D) is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion, resulting in elevated blood glucose levels. Recent studies have highlighted vitamin D as a potential modulator of glucose metabolism and insulin sensitivity. Vitamin D appears to improve insulin action by enhancing pancreatic β-cell function and reducing systemic inflammation factors crucial for effective glycemic control. Epidemiological evidence indicates that individuals with low vitamin D levels are at higher risk for developing T2D, whereas supplementation offers benefits, particularly among those who are deficient or in the early stages of the disease. However, findings across clinical trials remain inconsistent, emphasizing the need for further research to clarify optimal dosing, duration, and target populations. This review examines current evidence on the role of vitamin D in the management of T2D and explores its potential implications for prevention and therapy.

Keywords: Type 2 diabetes; Vitamin D; Therapy; METABOLISM; β-CELLS; Insulin; Insulin Sensitivity; Immunity

INTRODUCTION

Diabetes is a chronic, progressive metabolic disorder that was estimated to affect 589 million adults aged 20-79 worldwide, and the number of people living with the disease is projected to rise to 853 million by 2050 (1). Among these cases, approximately 90% are classified as type 2 diabetes (T2D) (1). The disease is characterized by insulin resistance, impaired insulin secretion, and chronic hyperglycemia (2). Current therapies for T2D primarily focus on controlling blood glucose levels but do not reverse disease progression. Despite advances in pharmacologic and lifestyle interventions, many patients continue to face a high risk of cardiovascular, renal and neurological complications, highlighting the unmet need for novel therapeutic approaches to treat T2D (3).

In recent years, vitamin D has emerged as a promising therapy as accumulating evidence suggests it may influence glucose metabolism, enhance insulin action, and modulate inflammatory pathways involved in T2D (4, 5). Several studies have consistently shown that individuals in the lowest quartile of blood 25-hydroxyvitamin (a metabolite of vitamin D) have a 30–50 % higher risk of developing T2D compared with those in the highest quartile, and that low vitamin D status correlates with higher fasting glucose and hemoglobin A1C (HbA1C) levels among patients with established diabetes (6-8).

Given these findings, understanding the mechanistic and clinical links between vitamin D and T2D has

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become a topic of growing scientific interest. The purpose of this review is to examine current evidence linking vitamin D status with T2D, integrating insights from basic science, epidemiological studies, and clinical trials. Specifically, this paper explores the mechanistic pathways through which vitamin D influences glucose metabolism, assesses the outcomes of vitamin D supplementation in individuals with or at risk for T2D, and discusses the implications of these findings for disease prevention and clinical management.

VITAMIN D METABOLISM

Vitamin D metabolism involves a multi-step process that converts inactive precursors into the biologically active hormone responsible for a wide range of metabolic effects. The pathway begins in the skin, where exposure to ultraviolet B (UVB) radiation converts 7-dehydrocholesterol into previtamin D_3, which is then thermally isomerized to vitamin D_3 (cholecalciferol) (9) (Figure 1). Additional vitamin D may be obtained from dietary sources in the form of either vitamin D_2 or D_3, but endogenous synthesis remains the major contributor for most individuals. Vitamin D_3, once formed, is transported to the liver bound to vitamin D–binding protein (DBP), where it undergoes hydroxylation by 25-hydroxylase (CYP2R1) to form 25-hydroxyvitamin D [25(OH)D], the major circulating metabolite and the standard clinical biomarker of vitamin D status (9, 10) (Figure 1). This metabolite is subsequently delivered to the kidneys, where 1α-hydroxylase (CYP27B1) catalyzes its conversion to 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], the biologically active form, also known as calcitriol (11).

Calcitriol exerts its biological effects by binding to the vitamin D receptor (VDR), a ligand-activated nuclear receptor widely expressed not only in classical target organs such as the intestine, bone, and kidney, but also in numerous non-classical sites including pancreatic β-cells, skeletal muscle, adipose tissue, and immune cells (11). This widespread distribution highlights its far-reaching influence in metabolic homeostasis and immune modulation.

At the cellular level, 1, 25$(OH)_2$D binds to intracellular VDR, which forms a heterodimer with the retinoid-X receptor (RXR) and interacts with vitamin D response elements (VDREs) located in promoter regions of numerous target genes (10, 11). Through this genomic pathway, vitamin D regulates the expression of genes involved in calcium transport, insulin secretion, lipid metabolism, and immune signaling. VDR expression in both classical (intestine, bone, kidney) and non-classical tissues (pancreas, skeletal muscle, adipose tissue, and immune cells) underlie vitamin D's multifaceted physiological impact (11-13). In addition to these well-characterized genomic actions, vitamin D can also initiate rapid, non-genomic signaling events, such as modulation of intracellular calcium fluxes and activation of mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways, which may acutely influence insulin exocytosis and cellular insulin responsiveness (10). Collectively, these genomic and non-genomic mechanisms provide the foundation for understanding vitamin D's integrative role in β-cell function, insulin sensitivity, and inflammation in the context of T2D.

ROLE OF VITAMIN D IN PANCREATIC B-CELLS

Pancreatic β-cells are central to glucose regulation, and accumulating evidence indicates that vitamin D plays multiple direct and indirect roles in supporting function of β-cells. Several studies have demonstrated that activation of the VDR enhances intracellular calcium flux, an essential trigger for insulin granule

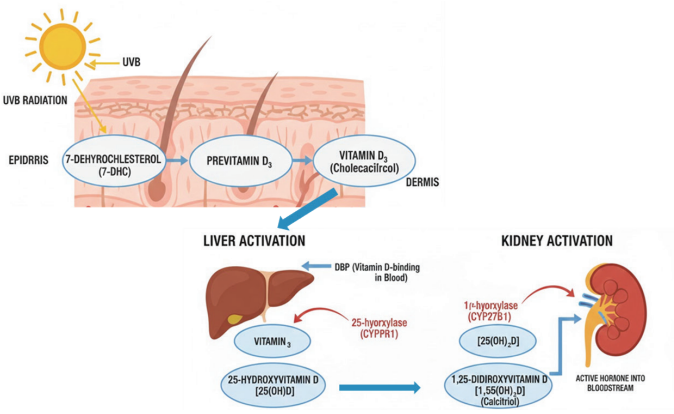

Figure 1. *Multi-step process of Vitamin D metabolism from 7-dehydrocholesterol to active 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] (also known as calcitriol). In skin, UVB converts 7-dehydrocholesterol to previtamin D_3 followed by isomerization to vitamin D_3 (cholecalciferol). Then vitamin D_3 is transported to the liver where it bound to vitamin D–binding protein (DBP). Subsequently, vitamin D_3 is hydroxylated by 25-hydroxylase (CYP2R1) to form 25-hydroxyvitamin D [25(OH)D], 25(OH)D is the major circulating metabolite in blood, is subsequently delivered to the kidneys, where 1α-hydroxylase (CYP27B1) catalyzes its conversion to active 1,25$(OH)_2$D.*

exocytosis. Taneera *et al* recently reported that vitamin D upregulated genes related to calcium channels and VDR expression is higher in human islets than in other metabolic tissues and is reduced in hyperglycemic donors (14). VDR levels positively correlated with genes regulating voltage-gated calcium channels(14). Overall, vitamin D enhances insulin secretion primarily through modulation of calcium dynamics, suggesting therapeutic relevance for T2D.

Furthermore, vitamin D provides cytoprotective benefits that help maintain β-cell viability. Vitamin D reduces β-cell exposure to inflammatory and oxidative stress by upregulating antioxidant enzymes and downregulating pro-inflammatory mediators. Giulietti examined showed that 1,25-dihydroxyvitamin D_3 was able to down-regulate the expression of inflammatory factors including TNF-alpha, IL-6, IL-1 and IL-8 in monocytes from T2D patients, confirming anti-inflammatory effects of vitamin D in T2D (15).

Additional studies have shown that vitamin D increases expression of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), thereby reducing reactive oxygen species generated under chronic hyperglycemia the diabetic rats (16). In consistency, Tao *et al* reported that vitamin D/VDR activation increases SOD and phospholipid hydroperoxide GPx activities and other antioxidant enzymes, thereby suppressing oxidative stress and improving insulin sensitivity(17). Together, these findings support a broader antioxidant role for vitamin D that may help protect β-cells from oxidative injury associated with diabetes progression.

Taken together, these findings suggest that vitamin D may support pancreatic β-cell function through multiple complementary mechanisms. By enhancing intracellular calcium dynamics, vitamin D promotes efficient insulin granule exocytosis and glucose-stimulated insulin secretion. Its anti-inflammatory and antioxidant actions further protect β-cells from cytokine-induced injury and oxidative stress, both of which are central drivers of β-cell dysfunction in diabetes. Vitamin D also reinforces cellular defense pathways by increasing expression of SOD, GPx, and other antioxidant enzymes, while simultaneously suppressing pro-inflammatory cytokines and limiting mitochondrial damage. Collectively, these genomic and non-genomic effects highlight the critical role of vitamin D in preserving β-cell integrity and sustaining insulin-secretory capacity, which may contribute to slowing T2D progression in vitamin D-deficient individuals.

ROLE OF VITAMIN D IN INSULIN SENSITIVITY

Additionally, Vitamin D contributes to improved insulin sensitivity in peripheral tissues. Insulin-responsive tissues, including skeletal muscle, liver, and adipose tissue, express both the vitamin D receptor (VDR) and the enzyme 1α-hydroxylase, enabling local conversion of 25(OH)D to its active form $1,25(OH)_2D$ and allowing direct modulation of metabolic processes (12, 18). In skeletal muscle and adipose cells, it enhances glucose uptake by increasing the expression of insulin receptors and glucose transporter type 4 (GLUT4)(15, 19). Additionally, vitamin D reduces the expression of pro-inflammatory cytokines that interfere with insulin signaling pathways (20). By mitigating these molecular barriers, vitamin D promotes more efficient insulin-mediated glucose utilization and helps maintain metabolic balance.

A key mechanism involves the regulation of intracellular calcium homeostasis. Proper calcium balance is required for optimal insulin signaling, GLUT4 vesicle translocation, and glucose uptake in skeletal muscle. Vitamin D helps maintain this balance by supporting calcium channel activity and preventing excessive cytosolic calcium accumulation, which is known to impair insulin receptor signaling (21-23). Vitamin D also improves insulin sensitivity by suppressing chronic low-grade inflammation, a major contributor to insulin resistance in obesity and T2D. Activation of VDR downregulates pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, while increasing expression of anti-inflammatory mediators such as IL-10 (20, 24). These changes reduce activation of NF-κB and JNK pathways, thereby decreasing inhibitory serine phosphorylation of IRS-1 and enhancing insulin signal transduction (25).

Another mechanism relates to vitamin D's role in lipid metabolism and adipocyte function. Vitamin D promotes differentiation of adipocytes toward a more insulin-responsive phenotype, reduces ectopic lipid accumulation in liver and skeletal muscle, and upregulates genes involved in mitochondrial fatty acid oxidation (26, 27). By reducing lipotoxicity, vitamin D helps preserve insulin sensitivity at the cellular and tissue levels. Vitamin D also modulates the renin–angiotensin–aldosterone system (RAAS), which is frequently overactivated in insulin-resistant states. Suppression of renin expression by vitamin D reduces RAAS-mediated oxidative stress and improves

endothelial function, both of which are linked to enhanced insulin sensitivity (28, 29). Finally, vitamin D may indirectly support insulin sensitivity by preserving pancreatic β-cell function. When vitamin D reduces β-cell stress and compensatory hyperinsulinemia, the insulin receptor is less prone to desensitization, helping maintain normal tissue responsiveness (30).Collectively, these effects, modulation of calcium signaling, reduction of inflammation, regulation of lipid metabolism, RAAS suppression, and preservation of β-cell function, highlight vitamin D as a significant regulator of insulin action across multiple tissues (13).

ROLE OF VITAMIN D IN IMMUNITY

Vitamin D is a key immunomodulatory hormone that influences both innate and adaptive immune responses. Immune cells, including monocytes, macrophages, dendritic cells and activated T and B lymphocytes, express VDR as well as the activating enzyme CYP27B1, enabling local conversion of 25(OH)D to its active form (1,25-dihydroxyvitamin D_3) and allowing these cells to respond directly to vitamin D signaling (31).

Innate Immunity

Vitamin D enhances innate immune defense through multiple mechanisms. One of its hallmark actions is the stimulation of antimicrobial peptide production, including cathelicidin (LL-37) and β-defensin, in monocytes and macrophages (32). These peptides disrupt microbial membranes, improve intracellular killing, and enhance chemotaxis, thereby strengthening pathogen clearance. By promoting these antimicrobial pathways, vitamin D helps maintain effective host defense while preventing excessive activation of innate immune sensors that can drive metabolic stress. In addition to its antimicrobial functions, vitamin D tempers the magnitude of innate immune responses as aforementioned. It suppresses the transcription of pro-inflammatory cytokines through VDR-mediated inhibition of NF-κB and MAPK signaling pathways. Supporting this, Giulietti *et al*. demonstrated that treatment with 1,25-dihydroxyvitamin D_3 significantly reduced the expression of TNF-α, IL-6, IL-1β, and IL-8 in monocytes isolated from individuals with T2D (15). This downregulation of cytokine production indicates that vitamin D not only controls pathogen-driven immune activation but also prevents the excessive innate immune signaling that contributes to metabolic dysfunction.

Adaptive Immunity

Vitamin D is a key modulator of adaptive immune responses, exerting broad effects on T-cell differentiation and function. Through the activation of the VDR on T lymphocytes, vitamin D shifts the immune system away from pro-inflammatory phenotypes toward more regulatory and tolerogenic pathways (31, 32). One of its primary actions is the suppression of Th1 and Th17 lineage development—two subsets associated with heightened immune reactivity, autoimmunity, and chronic metabolic stress. By inhibiting transcription factors, vitamin D reduces production of hallmark cytokines including IL-2, IFN-γ, and IL-17 (31), thereby dampening prolonged adaptive immune activation. Conversely, vitamin D promotes the expansion and functional activity of regulatory T cells (Tregs), which play a central role in maintaining immune tolerance and preventing inappropriate or excessive T-cell activation (32). Increased Treg activity contributes to reduced tissue inflammation, improved self-tolerance, and greater immune balance—factors that may indirectly protect metabolic organs from immune-derived stress.

Vitamin D further shapes adaptive immunity by modulating dendritic-cell behavior. It inhibits dendritic-cell maturation, decreases expression of MHC class II and costimulatory molecules such as CD80/CD86, and limits their capacity to prime naïve T cells (32). As a result, antigen presentation is dampened, and the adaptive immune response shifts toward a more controlled, less inflammatory state. This tolerogenic dendritic-cell phenotype is a key mechanism by which vitamin D prevents excessive T-cell proliferation and supports long-term immune homeostasis. Collectively, these actions demonstrate that vitamin D helps maintain adaptive immune balance by suppressing pro-inflammatory T-cell lineages, enhancing regulatory T-cell networks, and limiting dendritic-cell–driven immune activation. These immunoregulatory effects complement vitamin D's broader metabolic roles and may contribute to improved glycemic stability and reduced immune-mediated metabolic stress in individuals with impaired glucose homeostasis.

CLINICAL IMPLICATIONS OF VITAMIN D IN DIABETES

Accumulating clinical evidence suggests that vitamin D status has both preventive and therapeutic relevance for T2D. Observational studies indicate that maintaining serum 25-hydroxyvitamin D [25(OH)

D] concentrations above 30 ng/mL (75 nmol/L) is associated with improved glycemic control, lower insulin resistance, and reduced inflammatory markers (24, 30). However, randomized clinical trials (RCTs) have produced heterogeneous outcomes, reflecting variability in baseline vitamin D levels, supplementation doses, and study populations (33, 34).

Several interventional studies have demonstrated that vitamin D supplementation may modestly improve insulin sensitivity and β-cell function, particularly in individuals with prediabetes or baseline deficiency (13, 35, 36). For instance, Pittas *et al*. reported a significant reduction in diabetes incidence among participants receiving 4,000 IU/day of cholecalciferol who achieved serum levels ≥ 50 ng/mL. Similarly, interventions combining vitamin D with calcium improved insulin sensitivity indices and fasting glucose levels in vitamin D–deficient adults (37). Nonetheless, some large-scale RCTs have shown neutral results, emphasizing that supplementation is most beneficial in deficient or at-risk populations rather than the general population(38).

Vitamin D may also exert indirect benefits on diabetes complications. Adequate vitamin D levels have been linked to lower risk of diabetic nephropathy, retinopathy, and cardiovascular disease, likely due to its anti-inflammatory and endothelial-protective effects (39-41). In patients with established diabetes, supplementation has been shown to reduce C-reactive protein, IL-6, and TNF-α concentrations, suggesting attenuation of chronic low-grade inflammation (42). From a clinical management perspective, screening for vitamin D deficiency in individuals with diabetes or metabolic syndrome is increasingly recommended, particularly in high-risk groups such as older adults, those with obesity, or individuals with limited sun exposure (43). Correction of deficiency—through dietary supplementation, fortified foods, or sensible sunlight exposure—should be individualized based on serum 25(OH)D measurements, comorbidities, and potential contraindications (e.g., renal impairment or hypercalcemia).

Recent clinical research continues to clarify the role of vitamin D in the prevention and management of T2D, although findings remain heterogeneous and highly dependent on baseline vitamin D status, dose, and population characteristics.One of the most significant recent trials is the 2024 Finnish Vitamin D Trial (FIND), which evaluated whether long-term supplementation with 1,600 IU or 3,200 IU of vitamin D_3 could prevent progression to diabetes in older adults without T2D at baseline (44). Over nearly five years of follow-up, the study found no significant reduction in diabetes incidence compared with placebo. However, exploratory subgroup analyses suggested a possible benefit among individuals with lower BMI or lower baseline 25(OH)D levels, highlighting that vitamin D supplementation may have greater preventive potential in metabolically vulnerable or deficient groups rather than the general population.

Complementing these findings, a 2024 meta-analysis pooling multiple randomized controlled trials reported modest improvements in fasting blood glucose, fasting insulin, and HbA1c among individuals with prediabetes or insulin resistance who received vitamin D supplementation(45). The benefits were most pronounced in trials using higher doses and in participants with baseline 25(OH)D concentrations below sufficiency, reinforcing the importance of achieving adequate serum levels for metabolic benefit. Nevertheless, variability across studies, particularly in dosing strategies, treatment duration, and participant characteristics, continues to limit the consistency of outcomes.

Another umbrella review published in 2025, analyzing over 30 randomized trials involving individuals with prediabetes, concluded that vitamin D supplementation improves glycemic markers but does not consistently prevent the onset of T2D (46). These results suggest that vitamin D may be metabolically supportive but is unlikely to replace established preventive strategies such as weight reduction and physical activity. Recent smaller interventional studies in 2023–2024 have further refined this perspective. In adults with established T2D and vitamin D deficiency, high-dose vitamin D supplementation produced significant reductions in fasting insulin, HOMA-IR, and HbA1c, along with improvements in inflammatory markers such as CRP and IL-6 (47). These improvements were particularly notable in individuals with obesity, elevated baseline HbA1c, or marked deficiency, populations in whom insulin resistance and chronic inflammation are more severe.

Collectively, these contemporary findings indicate that vitamin D supplementation is unlikely to provide broad, population-level diabetes prevention, but may offer meaningful metabolic benefits for people with prediabetes or T2D who are vitamin D–deficient or at high risk for insulin resistance. As a result, current clinical thinking continues to support targeted supplementation rather than universal screening or universal supplementation. Future studies should continue to evaluate personalized dosing strategies, interactions with obesity and ethnicity, and clinically meaningful long-term outcomes.

CONCLUSION

Vitamin D exerts diverse actions across endocrine, metabolic, and immune pathways that collectively influence glucose homeostasis and the pathophysiology of T2D. It supports pancreatic β-cell function by enhancing calcium-dependent insulin secretion and by reducing inflammatory and oxidative stress, thereby helping to preserve endogenous insulin production. In peripheral tissues, vitamin D improves insulin sensitivity by promoting GLUT4-mediated glucose uptake, maintaining intracellular calcium homeostasis, reducing lipotoxicity, and mitigating chronic low-grade inflammation. In addition, vitamin D's broad immunomodulatory actions attenuate both innate and adaptive immune activation, lowering metabolic stress that contributes to insulin resistance.

These mechanistic insights provide a compelling biological rationale for considering vitamin D as a complementary component of T2D treatment. While vitamin D alone is unlikely to replace established pharmacologic therapies, maintaining adequate vitamin D status may enhance β-cell resilience, improve tissue responsiveness to insulin, and strengthen the overall metabolic environment in which conventional treatments operate. However, clinical trials examining vitamin D supplementation have shown mixed outcomes, likely due to differences in baseline deficiency, dosing regimens, population heterogeneity, and study duration.

Taken together, the available evidence suggests that vitamin D may offer therapeutic benefit as an adjunct to existing T2D treatments, particularly in individuals with documented deficiency or high inflammatory burden. Future research should prioritize well-designed randomized clinical trials that account for baseline vitamin D status, explore optimal dosing strategies, and evaluate whether targeted supplementation can meaningfully enhance clinical outcomes when integrated into comprehensive diabetes management.

CONFLICT OF INTEREST

The author declares no conflicts of interest related to this work

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