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VITAMIN D IN DIABETES MELLITUS: IMMUNOMODULATORY AND EPIGENETIC MECHANISMS BEYOND GLYCEMIC CONTROL

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ABSTRACT

Diabetes mellitus is a multifactorial metabolic disorder characterized not only by persistent hyperglycemia but also by immune dysregulation, chronic low-grade inflammation, oxidative stress, and progressive pancreatic β-cell dysfunction. In addition to disturbances in glucose metabolism, type 1 and type 2 diabetes involve complex interactions between genetic susceptibility, environmental triggers, and immunometabolic pathways. In recent years, vitamin D has emerged as a pleiotropic secosteroid hormone with biological functions extending far beyond its classical role in calcium and bone homeostasis. Accumulating experimental and epidemiological evidence indicates that vitamin D influences insulin secretion, insulin sensitivity, immune tolerance, inflammatory signaling, and cellular survival pathways. Vitamin D deficiency is highly prevalent worldwide and occurs disproportionately among individuals with diabetes. Suboptimal serum 25-hydroxyvitamin D levels have been associated with increased insulin resistance, impaired glucose-stimulated insulin secretion, heightened inflammatory cytokine production, and an increased risk of microvascular and macrovascular diabetic complications. Mechanistic

studies have demonstrated that vitamin D receptor activation modulates key pathways involved in β-cell preservation, adipokine regulation, oxidative stress reduction, and immune cell differentiation. Emerging research has further highlighted vitamin D's role in epigenetic regulation through effects on DNA methylation, histone modification, and microRNA expression, as well as its influence on gut microbiota composition and the gut–pancreas–immune axis. This review synthesizes current evidence regarding the immunometabolic, epigenetic, and gut-mediated actions of vitamin D in diabetes mellitus. It critically examines the inconsistencies observed in randomized supplementation trials and explores factors such as baseline deficiency, genetic variability, and disease stage. Finally, the review outlines future research priorities and precision-based strategies aimed at optimizing vitamin D interventions in comprehensive diabetic care.

KEYWORDS: Vitamin D, Diabetes Mellitus, Insulin Resistance, Epigenetics, Inflammation, Gut Microbiota, β-cell Dysfunction.

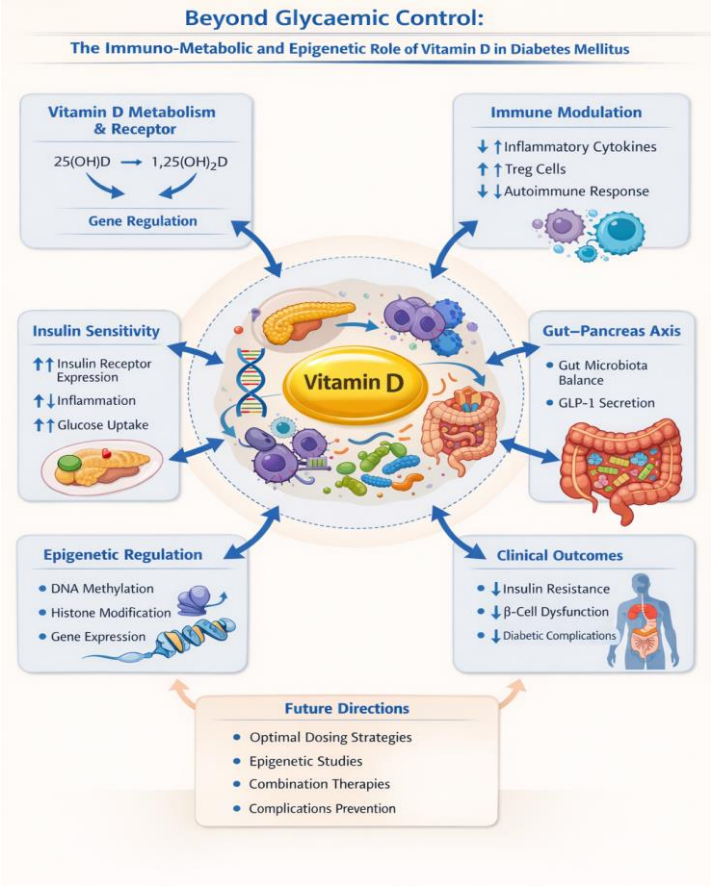

Fig. 1: Indicates schematic representation on The Immuno-Metabolic and Epigenetic Role of Vitamin D in Diabetes Mellitus.

1. INTRODUCTION

Diabetes mellitus (DM) is one of the major global health challenges, affecting more than 500 million individuals worldwide, and its prevalence is expected to increase substantially in the coming decades.[1,2] DM poses a serious health challenge in the 21st century. The disease encompasses a spectrum of metabolic abnormalities, primarily characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. However, the modern understanding extends beyond glycemic dysregulation to include chronic inflammation, immune imbalance, oxidative stress, endothelial dysfunction, and progressive β-cell exhaustion. Although chronic hyperglycemia remains the diagnostic hallmark, diabetes is now recognized as a systemic disorder characterized by chronic inflammation, immune dysregulation, oxidative stress, and progressive pancreatic β-cell failure.[3–5] Traditional management strategies primarily emphasize glucose-lowering pharmacotherapy. While these approaches reduce acute metabolic complications, they often fail to fully prevent long-term microvascular and macrovascular sequelae. This therapeutic gap has driven the investigation of adjunctive biological modulators capable of influencing underlying pathophysiological mechanisms.[2,5][2,5]

Vitamin D has emerged as an essential micronutrient with endocrine, paracrine, and autocrine functions. Beyond its classical role in calcium and bone metabolism, vitamin D significantly influences insulin sensitivity, β-cell survival, immune responses, and inflammatory pathways.[1,6,7] Initially recognized for its skeletal functions, vitamin D is now acknowledged as a systemic hormone exerting endocrine, paracrine, and autocrine effects. Its widespread receptor distribution across pancreatic islets, immune cells, adipose tissue, skeletal muscle, liver, and intestinal epithelium underscores its relevance in metabolic regulation. The widespread expression of the vitamin D receptor (VDR) in pancreatic islets, immune cells, adipose tissue, skeletal muscle, and the gastrointestinal tract highlights its critical role in metabolic homeostasis.[6,10] Accumulating evidence indicates that vitamin D deficiency is highly prevalent among individuals with type 1 and type 2 diabetes. This deficiency may not merely be a consequence of metabolic dysregulation but rather a contributing factor to disease progression. Therefore, exploring vitamin D's multifaceted role in diabetes may provide insights into integrative therapeutic strategies.[4,12]

2. OVERVIEW OF VITAMIN D METABOLISM AND RECEPTOR SIGNALING

2.1 Synthesis and Activation

Vitamin D is synthesized in the skin following exposure to ultraviolet B radiation or obtained from dietary sources. It is converted in the liver to 25-hydroxyvitamin D [25(OH)D], the major circulating form, and subsequently hydroxylated in the kidneys to its biologically active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D].[1,10]

Cutaneous synthesis begins when ultraviolet B (UVB) radiation (wavelength 290–315 nm) penetrates the epidermis and converts 7-dehydrocholesterol into previtamin D_3, which is then thermally isomerized into vitamin D_3 (cholecalciferol). Dietary intake provides either vitamin D_3 from animal sources, such as fatty fish, egg yolks, and fortified foods, or vitamin D_2 (ergocalciferol) from plant-based sources and supplements. Once formed or ingested, vitamin D enters the circulation bound to vitamin D-binding protein and is transported to the liver. Hepatic 25-hydroxylation, primarily mediated by the CYP2R1 enzyme, produces 25(OH)D, which has a relatively long half-life of approximately two to three weeks and is therefore considered the most reliable biomarker of overall vitamin D status. Serum 25(OH)D concentrations reflect the cumulative input from sunlight exposure, diet, and supplementation.

The second hydroxylation step occurs predominantly in the proximal renal tubules, where the enzyme 1α-hydroxylase (CYP27B1) converts 25(OH)D into 1,25$(OH)_2$D, the hormonally active form. This process is tightly regulated by parathyroid hormone, serum calcium and phosphate levels, and fibroblast growth factor-23, ensuring the maintenance of mineral homeostasis. Importantly, extra-renal expression of CYP27B1 has been identified in immune cells, pancreatic β-cells, adipose tissue, and intestinal epithelium, enabling local autocrine and paracrine production of active vitamin D. This tissue-specific activation supports immunomodulatory and metabolic functions independent of systemic calcium regulation, thereby extending the role of vitamin D beyond skeletal physiology into broader endocrine and immunometabolic regulation relevant to diabetes pathogenesis.

2.2 Signalling of Vitamin D Metabolism and Receptor

The biological actions of vitamin D are mediated by binding to the vitamin D receptor (VDR), a nuclear transcription factor that regulates the expression of more than 1,000 genes involved in glucose metabolism, immune regulation, and cellular differentiation (16,25).

VDR activation influences insulin gene transcription, calcium influx in pancreatic β-cells, and glucose uptake signalling pathways.[7,14] Polymorphisms in the VDR gene have been associated with altered insulin sensitivity and increased susceptibility to both type 1 and type 2 diabetes, suggesting a genetic component to vitamin D responsiveness.[14] Importantly, extra-renal activation occurs in immune cells, pancreatic β-cells, adipocytes, and intestinal epithelial cells, allowing localized autocrine and paracrine effects independent of systemic endocrine regulation. The biological actions of vitamin D are mediated through the vitamin D receptor (VDR), a ligand-activated nuclear transcription factor. Upon binding $1,25(OH)_2D$, VDR heterodimerizes with retinoid X receptor (RXR) and binds to vitamin D response elements (VDREs) within gene promoter regions.

Genomic signaling mediated by the vitamin D receptor (VDR) plays a central role in coordinating multiple metabolic and immunological processes relevant to diabetes. Upon binding of 1,25-dihydroxyvitamin D, the VDR–retinoid X receptor complex interacts with vitamin D response elements in target gene promoters, thereby modulating transcriptional activity in diverse cellular systems. This signaling cascade regulates insulin gene transcription within pancreatic β-cells and enhances the expression of calcium channel proteins necessary for glucose-stimulated insulin secretion. Simultaneously, it suppresses the production of pro-inflammatory cytokines while promoting anti-inflammatory mediators, thereby restoring immune balance. Vitamin D–dependent genomic activity also influences immune cell differentiation, shifting T-cell polarization toward regulatory phenotypes and modulating macrophage activation states. In addition, VDR signaling enhances cellular antioxidant defenses by regulating genes involved in oxidative stress responses. Emerging evidence further indicates that vitamin D facilitates the recruitment of epigenetic enzymes, including histone acetyltransferases and deacetylases, thereby influencing chromatin remodeling and long-term gene expression patterns. Through these integrated genomic mechanisms, vitamin D exerts broad immunometabolic control that extends beyond classical endocrine functions.

Non-genomic signaling via membrane-associated VDR activates rapid intracellular pathways, including MAPK, PI3K/Akt, and Ca2 + flux signaling. Genetic polymorphisms in VDR (FokI, TaqI, ApaI, and BsmI) influence receptor activity and may modify individual responsiveness to supplementation.

3. VITAMIN D AS AN IMMUNOMODULATOR OF DIABETES

3.1 Diabetes immune dysregulation

Pancreatic β-cells express both VDR and 1α-hydroxylase, allowing localized activation of vitamin D. Chronic low-grade inflammation is a defining feature of diabetes mellitus. Elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interferon-γ contribute to insulin resistance and pancreatic β-cell apoptosis.[5,19,20] In type 1 diabetes, autoimmune destruction of β-cells is mediated by dysregulated T-cell activation and loss of immune tolerance.[3,24]

Vitamin D supports glucose-stimulated insulin secretion (GSIS) through multiple coordinated molecular mechanisms within pancreatic β-cells. Activation of the vitamin D receptor enhances insulin gene transcription, thereby increasing the availability of preproinsulin for secretion in response to rising glucose levels. It also upregulates key pancreatic transcription factors, such as pancreatic duodenal homeobox-1 (PDX-1) and MafA, which are essential for β-cell maturation, maintenance of β-cell identity, and efficient insulin biosynthesis. In addition, vitamin D augments the activity of L-type voltage-dependent calcium channels, facilitating calcium influx following glucose-induced membrane depolarization. This calcium entry is crucial for triggering insulin granule exocytosis. Furthermore, vitamin D contributes to the stabilization of intracellular calcium oscillations, ensuring coordinated and sustained insulin release during hyperglycemic states. Through these integrated effects on gene transcription, calcium handling, and β-cell functional integrity, vitamin D plays a significant role in optimizing insulin secretory responses and maintaining glycemic homeostasis.

Vitamin D as an immunoregulator

Vitamin D modulates both innate and adaptive immune responses by suppressing T helper 1 (Th1) and Th17 cell activity while enhancing regulatory T-cell (Treg) differentiation (6,20,21). It inhibits antigen-presenting cell maturation and reduces cytokine-mediated β-cell damage, thereby protecting pancreatic islets from immune-mediated injury.[7,24] These immunosuppressive and anti-inflammatory effects are particularly relevant for preventing autoimmune β-cell destruction in type 1 diabetes and reducing inflammation-induced insulin resistance in type 2 diabetes.[3,7]

Vitamin D reduces pancreatic β-cell apoptosis through multiple protective mechanisms that counteract inflammatory and oxidative insults characteristic of diabetes. It suppresses the production and signaling of pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and

tumor necrosis factor-α (TNF-α), which trigger β-cell dysfunction and programmed cell death. By attenuating these inflammatory mediators, vitamin D prevents cytokine-induced nitric oxide production and mitochondrial damage within β-cells. Additionally, vitamin D decreases oxidative stress by enhancing antioxidant defenses, thereby limiting reactive oxygen species–mediated cellular injury. At the molecular level, it promotes the expression of anti-apoptotic proteins, such as Bcl-2, while simultaneously inhibiting pro-apoptotic pathways, including caspase activation cascades that execute programmed cell death. Through this integrated anti-inflammatory, antioxidant, and anti-apoptotic action, vitamin D contributes to the preservation of β-cell mass and functional integrity, which is crucial for maintaining long-term glycemic control.

These mechanisms are particularly relevant in type 1 diabetes, in which autoimmune destruction is predominant.

4. VITAMIN D AND INSULIN RESISTANCE

Vitamin D enhances insulin sensitivity through multiple mechanisms, including upregulation of insulin receptor expression, regulation of intracellular calcium homeostasis, and suppression of inflammatory signalling pathways, such as nuclear factor-κB (NF-κB) (5,15). Numerous observational studies demonstrate an inverse association between circulating 25(OH)D concentrations and insulin resistance indices, including fasting insulin levels and HOMA-IR.[4,12,19]

Additionally, vitamin D reduces adipose tissue inflammation by suppressing pro-inflammatory adipokine production and improving insulin signalling in adipocytes, thereby facilitating glucose uptake in peripheral tissues.[15]

4.1 Insulin resistance is central to the pathogenesis of type 2 diabetes

Vitamin D improves insulin sensitivity through coordinated molecular and metabolic mechanisms that influence peripheral tissues, including the skeletal muscle, adipose tissue, and liver. Activation of the vitamin D receptor enhances the expression of the insulin receptor, thereby improving insulin binding and receptor autophosphorylation. This effect strengthens downstream insulin signaling pathways, particularly the IRS-1/PI3K/Akt cascade, which plays a central role in mediating glucose uptake and glycogen synthesis. Enhanced Akt activation promotes the translocation of glucose transporter type 4 (GLUT4) to the plasma membrane in muscle and adipocytes, facilitating efficient cellular glucose uptake in response

to insulin. In the liver, vitamin D contributes to improved metabolic control by suppressing excessive hepatic gluconeogenesis through the modulation of key enzymes, such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, thereby reducing fasting hyperglycemia.

In addition to its direct effects on insulin signaling, vitamin D modulates adipokine secretion, increasing adiponectin levels while reducing leptin and pro-inflammatory cytokines derived from adipose tissue. Elevated adiponectin enhances insulin sensitivity and exerts anti-inflammatory and anti-atherogenic effects, whereas reduced leptin resistance and inflammatory signaling help mitigate adipose tissue–driven insulin resistance. Conversely, vitamin D deficiency has been consistently associated with an increased homeostatic model assessment of insulin resistance (HOMA-IR), elevated fasting plasma glucose, impaired glucose tolerance, and a higher risk of progression from prediabetes to overt type 2 diabetes. These associations suggest that inadequate vitamin D status may exacerbate insulin resistance and metabolic deterioration, reinforcing the importance of maintaining sufficient vitamin D levels as part of a comprehensive strategy for metabolic health and diabetes prevention.

5. IMMUNOMODULATORY ROLE AND EPIGENETIC REGULATION BY VITAMIN D IN DIABETES

5.1 Immune Dysregulation in Diabetes

Epigenetic mechanisms, including DNA methylation, histone modifications, and the regulation of noncoding RNAs, play a critical role in diabetes pathogenesis.[16,17] Vitamin D influences epigenetic programming by modulating chromatin accessibility and the transcription of genes involved in glucose metabolism, immune regulation, and inflammation.[16]

At the molecular level, activation of the vitamin D receptor (VDR) enables direct interaction with vitamin D response elements located in the promoter and enhancer regions of target genes. This interaction facilitates the recruitment of chromatin-modifying complexes, including histone acetyltransferases and histone deacetylases, which dynamically regulate histone acetylation and methylation states. Increased histone acetylation generally promotes an open chromatin configuration, enhancing the transcription of genes essential for insulin synthesis, β-cell survival, and anti-inflammatory signaling. Conversely, vitamin D suppresses the transcription of pro-inflammatory genes by promoting chromatin condensation at cytokine gene loci, thereby limiting NF-κB–mediated transcriptional activation. Through

these mechanisms, vitamin D serves as a bridge between environmental exposure (sunlight and dietary intake) and stable transcriptional reprogramming in metabolic tissues.

Furthermore, vitamin D-mediated epigenetic regulation extends to noncoding RNAs, particularly miRNAs that influence insulin secretion, endothelial integrity, and immune responses. For example, the modulation of miRNAs involved in β-cell differentiation and inflammatory pathways may help preserve pancreatic function and reduce autoimmune or metabolic stress-induced damage. Altered DNA methylation patterns in genes associated with insulin signaling and immune tolerance have been observed in individuals with vitamin D deficiency, suggesting that inadequate levels may predispose to persistent metabolic dysregulation. Importantly, epigenetic changes are potentially reversible, raising the possibility that early correction of vitamin D deficiency could restore favorable gene expression patterns and contribute to long-term metabolic resilience. These findings highlight the importance of vitamin D not only as a metabolic regulator but also as an epigenetic modifier influencing the trajectory of diabetes development and progression.

5.2 Vitamin D as an Immune Regulator

Activation of the VDR may alter methylation patterns of insulin-related genes and inflammatory mediators, thereby leading to long-term metabolic effects. These epigenetic modifications may partially explain the sustained metabolic benefits observed in individuals with adequate vitamin D status.[16,17]

Vitamin D plays a crucial role in maintaining immune homeostasis by modulating both innate and adaptive immune responses, mechanisms that are highly relevant in the pathogenesis of diabetes. Vitamin D suppresses the differentiation of proinflammatory T helper 1 (Th1) and T helper 17 (Th17) cells by activating the vitamin D receptor (VDR) in immune cells, thereby reducing the production of key cytokines, such as interferon-γ (IFN-γ) and interleukin-17 (IL-17). These cytokines are central mediators of autoimmune inflammation and β-cell cytotoxicity in type 1 diabetes and contributors to chronic, low-grade inflammation in type 2 diabetes. Concurrently, vitamin D promotes the expansion and functional activity of regulatory T cells (Tregs), which help maintain peripheral immune tolerance and suppress excessive immune activation. By enhancing Treg-mediated immune control, vitamin D contributes to limiting autoreactive T-cell responses directed against pancreatic β-cells.

In addition to its effects on T-cell polarization, vitamin D inhibits dendritic cell maturation,

leading to reduced expression of major histocompatibility complex (MHC) class II molecules and co-stimulatory markers required for T-cell activation. This promoted a more tolerogenic immune response. Furthermore, vitamin D influences the macrophage phenotype, shifting polarization from the pro-inflammatory M1 state—characterized by high production of TNF-α, IL-1β, and reactive oxygen species—toward the anti-inflammatory M2 phenotype, which supports tissue repair and resolution of inflammation. Through these integrated actions on immune cell differentiation and cytokine production, vitamin D mitigates autoimmune β-cell destruction in type 1 diabetes and reduces adipose tissue inflammation, which drives insulin resistance in type 2 diabetes. Collectively, these immunomodulatory properties indicate that vitamin D is a key regulator of the inflammatory milieu underlying both forms of diabetes.

5.3 Epigenetic Regulation by Vitamin D

Epigenetic modifications play a fundamental role in long-term metabolic programming by regulating gene expression without altering the underlying DNA sequence. These mechanisms—primarily DNA methylation, histone modification, and miRNA regulation—determine how genes involved in insulin secretion, inflammation, and glucose metabolism are expressed over time. Vitamin D has emerged as an important epigenetic modulator through activation of the vitamin D receptor (VDR), which interacts with chromatin-modifying enzymes and transcriptional co-regulators. Upon ligand binding, the VDR recruits histone acetyltransferases to specific gene promoters, promoting histone acetylation and transcriptional activation of genes involved in β-cell function, insulin signaling, and immune regulation. Simultaneously, vitamin D can influence the activity of DNA methyltransferases, thereby altering methylation patterns at promoter regions of metabolic and inflammatory genes.

In addition, vitamin D regulates the expression of key microRNAs, such as miR-375 and miR-126, which are critically involved in pancreatic β-cell proliferation, insulin secretion, endothelial integrity, and inflammatory signaling. Through coordinated chromatin remodeling at insulin-related gene loci—such as those governing insulin synthesis and β-cell transcription factors—vitamin D supports sustained metabolic stability. Conversely, vitamin D deficiency has been associated with hypermethylation of β-cell-specific genes and promoters of anti-inflammatory pathways, potentially leading to reduced insulin biosynthesis, impaired immune tolerance, and persistent inflammatory activation. Such epigenetic alterations may perpetuate metabolic dysfunction even before overt hyperglycemia becomes

evident. Therefore, maintaining adequate vitamin D status may not only provide immediate metabolic benefits but also contribute to long-term epigenetic resilience against diabetes progression and its complications.

6. Gut–Pancreas–Vitamin D Axis

Gut microbiota is increasingly recognized as a key regulator of metabolic and immune homeostasis. Vitamin D contributes to intestinal barrier integrity, thereby reducing endotoxemia-induced systemic inflammation.[22,23] It also influences gut microbial composition by promoting beneficial bacteria, such as *Akkermansia muciniphila*, which is associated with improved insulin sensitivity and metabolic outcomes.[22]

By modulating short-chain fatty acid production and enhancing incretin hormone secretion, particularly glucagon-like peptide-1 (GLP-1), vitamin D indirectly supports pancreatic β-cell function and glycemic control, establishing a functional gut–pancreas axis.[23] The gut microbiota is increasingly recognized as a metabolic regulator.

Vitamin D plays a pivotal role in maintaining intestinal barrier integrity and modulating gut microbiota, thereby establishing a functional gut–pancreas–immune axis that supports metabolic homeostasis. At the epithelial level, vitamin D enhances the expression of tight-junction proteins, such as claudin, occludin, and zonula occludens-1 (ZO-1), which strengthen intercellular junctions and reduce intestinal permeability. This barrier stabilization limits the translocation of lipopolysaccharide (LPS) and other endotoxins into the systemic circulation, thereby attenuating metabolic endotoxemia and chronic low-grade inflammation—key drivers of insulin resistance. In addition to preserving structural integrity, vitamin D influences microbial composition by promoting the growth of beneficial bacteria, particularly *Akkermansia muciniphila*, which has been consistently associated with improved insulin sensitivity, reduced adipose inflammation, and enhanced mucosal health. These microbial shifts are accompanied by increased production of short-chain fatty acids (SCFAs), such as butyrate and propionate, which serve as signaling molecules that improve insulin sensitivity, regulate immune responses, and support gut epithelial energy metabolism. Moreover, vitamin D-mediated enhancement of SCFA production contributes to increased secretion of glucagon-like peptide-1 (GLP-1), an incretin hormone that augments glucose-stimulated insulin secretion and promotes β-cell preservation. Through these coordinated mechanisms, vitamin D reinforces communication between the gut, immune system, and pancreas, thereby contributing to metabolic stability.

7. Vitamin D. and Oxidative Stress

Oxidative stress represents another critical pathway in the pathogenesis of diabetes and its vascular complications, as excessive reactive oxygen species (ROS) impair β-cell function, damage endothelial cells, and accelerate tissue injury. Pancreatic β-cells are particularly vulnerable to oxidative damage because of their relatively low intrinsic antioxidant capacity. Vitamin D exerts protective effects by activating the nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant signaling pathway, a master regulator of cellular redox balance. Activation of Nrf2 enhances the transcription of key antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase, and catalase, which collectively neutralize free radicals and limit lipid peroxidation. By reducing oxidative burden, vitamin D helps preserve insulin secretory function, prevent endothelial dysfunction, and inhibit the progression of microvascular damage. Furthermore, attenuation of oxidative stress reduces the activation of pro-inflammatory transcription factors, such as NF-κB, thereby linking antioxidant defense with anti-inflammatory signaling. Together, these actions position vitamin D as an important modulator of redox homeostasis in diabetes, potentially mitigating both metabolic dysfunction and long-term vascular complications.

8. Vitamin D. In diabetic complications

Emerging evidence suggests that vitamin D may exert protective effects against the development and progression of major diabetic complications, including nephropathy, retinopathy, neuropathy, and cardiovascular disease. In diabetic nephropathy, vitamin D has been shown to suppress renin–angiotensin–aldosterone system (RAAS) activation, reduce albuminuria, and attenuate glomerular inflammation and fibrosis through inhibition of pro-inflammatory cytokines and transforming growth factor-β (TGF-β). By stabilizing podocyte integrity and reducing oxidative stress within renal tissues, vitamin D may help slow the decline in the glomerular filtration rate. In diabetic retinopathy, its anti-inflammatory and anti-angiogenic properties may modulate vascular endothelial growth factor (VEGF) expression, decrease retinal capillary leakage, and reduce microvascular damage. Similarly, in diabetic neuropathy, vitamin D deficiency has been associated with increased nerve conduction abnormalities and neuropathic pain, whereas adequate levels may support neurotrophic signaling, reduce inflammatory mediators, and enhance neuronal repair mechanisms.

Cardiovascular disease, the leading cause of mortality in diabetes, may also be influenced by

vitamin D status. Vitamin D contributes to endothelial function by enhancing nitric oxide bioavailability, suppressing vascular smooth muscle proliferation, and mitigating oxidative stress-induced endothelial dysfunction. Its ability to downregulate systemic inflammation and reduce the formation of advanced glycation end-products (AGEs) further supports vascular protection. Moreover, vitamin D modulates lipid metabolism and may improve arterial stiffness and blood pressure regulation, thereby addressing multiple cardiovascular risk factors simultaneously. Collectively, through anti-inflammatory, antioxidant, antifibrotic, and endothelial-protective mechanisms, vitamin D appears to act on shared pathological pathways underlying diabetic microvascular and macrovascular complications. Although definitive interventional evidence remains limited, maintaining adequate vitamin D status may represent a supportive strategy to mitigate the long-term complication burden in individuals with diabetes.

9. Precision Medicine and its approaches

Future research should adopt a precision-oriented framework to better define the therapeutic role of vitamin D in DM. One promising direction involves genotype-guided supplementation, particularly considering polymorphisms in the vitamin D receptor (VDR) and genes involved in vitamin D metabolism (such as CYP2R1 and CYP27B1), which may influence individual responsiveness to supplementation. Stratifying participants based on baseline vitamin D deficiency is equally critical, as emerging evidence consistently suggests that metabolic benefits are more pronounced in individuals with serum 25(OH)D levels below sufficiency thresholds. Future trials should therefore prioritize enrolling deficient or insufficient populations rather than broadly supplementing heterogeneous cohorts. Additionally, combination therapy approaches integrating vitamin D with established antidiabetic agents—such as metformin, GLP-1 receptor agonists, SGLT2 inhibitors, or omega-3 fatty acids—may provide synergistic immunometabolic effects by targeting complementary pathways, including AMPK activation, incretin signaling, and inflammatory modulation. Longitudinal epigenetic studies are also warranted to explore how sustained vitamin D sufficiency influences DNA methylation patterns, histone modifications, and microRNA expression in genes regulating insulin secretion, immune tolerance, and oxidative stress, potentially clarifying long-term disease-modifying effects.

Determining the optimal serum 25(OH)D target range for metabolic health remains a key research priority. While traditional guidelines emphasize bone-related thresholds,

accumulating metabolic data suggest that maintaining levels between 40 and 60 ng/mL may be necessary to achieve maximal extraskeletal benefits without toxicity. Establishing evidence-based targets specific to diabetes prevention and management would refine clinical recommendations. Furthermore, the development of selective VDR agonists capable of dissociating metabolic and immunomodulatory effects from calcemic activity represents an innovative therapeutic avenue. Such agents, along with nanoformulated vitamin D delivery systems designed to enhance bioavailability and tissue-specific targeting, may optimize receptor activation while minimizing the risk of hypercalcemia and other adverse effects. Together, these strategies underscore the need to transition from generalized supplementation models to individualized, mechanism-driven interventions that fully harness the immunometabolic potential of vitamin D in diabetes care.

10. Clinical Evidence and Supplementation Trials

Despite strong mechanistic and observational evidence, randomized controlled trials evaluating vitamin D supplementation in diabetes have yielded inconsistent results.[11,18] Variations in baseline vitamin D status, supplementation dose, duration, genetic background, and disease stage may explain these discrepancies.[11,17]

In addition to these methodological variables, several other factors may have contributed to the heterogeneity observed across trials. Many studies enrolled participants with sufficient baseline 25(OH)D concentrations, thereby limiting the potential for measurable metabolic improvement following supplementation. In such populations, vitamin D repletion may not significantly influence glycemic indices because physiological pathways are already near optimal activation. Furthermore, differences in dosing regimens—including daily low-dose versus intermittent high-dose strategies—can affect steady-state serum levels and downstream receptor activation. Short intervention periods may also fail to capture long-term metabolic adaptations, particularly those mediated through epigenetic modifications or gradual improvements in insulin sensitivity. Variability in concomitant therapies, body mass index, adiposity-related vitamin D sequestration, and adherence rates further complicates the interpretation of outcomes.

The landmark D2d trial demonstrated a modest reduction in the progression to type 2 diabetes among individuals receiving vitamin D supplementation, particularly those with baseline vitamin D deficiency and high treatment adherence.[18] These findings underscore the importance of personalized supplementation strategies. Importantly, subgroup analyses

suggested that participants with lower baseline vitamin D levels experienced greater relative risk reduction, highlighting deficiency correction rather than universal supplementation as the key therapeutic principle. The trial also emphasized that adherence and sustained serum 25(OH)D elevation were critical determinants of benefit. Collectively, these insights support a precision medicine approach in which vitamin D supplementation is tailored according to baseline deficiency, metabolic risk profile, genetic susceptibility, and stage of dysglycemia. Such individualized strategies may enhance clinical efficacy and help reconcile inconsistencies observed in earlier trials.

11. Future Perspectives and Research Gaps

Future research should prioritize the identification of optimal vitamin D dosing strategies tailored to individual genetic and metabolic profiles to maximize therapeutic benefits. Longitudinal studies are needed to elucidate the epigenetic effects of vitamin D on genes involved in glucose metabolism, inflammation, and immune regulation. In addition, evaluating combination approaches that integrate vitamin D supplementation with lifestyle modification and standard pharmacological therapies may provide more effective and sustained metabolic control. Further investigation into the role of vitamin D in preventing or delaying the onset of diabetic microvascular and macrovascular complications is essential to establish its long-term clinical relevance in diabetes management.

12. CONCLUSION

Vitamin D plays a multifaceted role in diabetes mellitus, extending beyond glycemic regulation to immune modulation, epigenetic control, and gut microbiota interaction. Although vitamin D supplementation alone may not serve as a standalone therapy, maintaining adequate vitamin D levels represents a promising adjunctive strategy for comprehensive diabetes management. Precision-based approaches integrating vitamin D status, genetics, and disease stage may unlock its full therapeutic potential. Vitamin D exerts multifaceted effects in diabetes mellitus that extend far beyond glycemic control. By modulating pancreatic β-cell function, enhancing insulin sensitivity, suppressing inflammatory pathways, remodeling the epigenome, and maintaining gut microbial balance, vitamin D contributes to a comprehensive immunometabolic regulatory network. Although vitamin D supplementation alone cannot replace conventional therapy, maintaining adequate vitamin D status represents a promising adjunctive strategy for diabetes management. Precision-based approaches incorporating genetic background, baseline deficiency, and

disease stage may unlock the full therapeutic potential of vitamin D in preventing and mitigating diabetes progression and its complications.

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