Molecular Mechanisms from Insulin-Mimetic Effect of Vitamin D: Treatment Alternative in Type 2 Diabetes Mellitus

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Abstract

Type 2 Diabetes Mellitus (T2DM) is a complex metabolic disorder characterized by insulin resistance and beta-cell dysfunction. Recent research highlights the role of vitamin D in glucose homeostasis and its potential insulin-mimetic effects. This review explores the molecular mechanisms by which vitamin D enhances insulin sensitivity, preserves beta-cell function, and modulates inflammatory and oxidative stress pathways. Vitamin D influences insulin receptor expression activates the PI3K/AKT pathway, and regulates PPAR-γ, thereby improving glucose uptake and metabolic control. Additionally, vitamin D exerts anti-inflammatory and antioxidant effects, reducing cytokine-induced insulin resistance. Clinical studies suggest that vitamin D supplementation may serve as an adjunctive therapy for T2DM, although further research is needed to determine optimal dosing and patient-specific responses. This review underscores the potential of vitamin D as a promising alternative or complementary approach in the management of T2DM.

Keywords: Vitamin D and insulin signaling, Bifidobacterium, Insulin-mimetic effect, Type 2 Diabetes Mellitus (T2DM), Glucose metabolism, Pancreatic β-cell function, Vitamin D receptor (VDR), Insulin resistance, Glucose homeostasis

Introduction

Type 2 Diabetes Mellitus (T2DM) is a growing global health concern, affecting millions of individuals and contributing to significant morbidity and mortality. The increasing incidence of T2DM is driven by a combination of genetic, environmental, and lifestyle factors, including poor dietary habits, sedentary behavior, and obesity. It is primarily characterized by insulin resistance, where peripheral tissues such as skeletal muscle, liver, and adipose tissue exhibit a diminished response to insulin signaling, leading to chronic hyperglycemia. Over time, pancreatic β-cells attempt to compensate by increasing insulin secretion; however, prolonged stress on these cells leads to dysfunction and eventual failure, exacerbating the progression of diabetes. Current therapeutic strategies for T2DM include lifestyle modifications, oral hypoglycemic agents, and insulin therapy. While these interventions can help regulate blood glucose levels, they often come with limitations such as side effects, patient compliance issues, and the progressive nature of β-cell deterioration (1). As a result, there is a continuous search for novel therapeutic agents that can improve glycemic control while addressing the underlying pathophysiology of T2DM. In recent years, vitamin D has emerged as a potential modulator of glucose homeostasis, sparking interest in its insulin-mimetic properties and its possible role in diabetes prevention and management.

Vitamin D, a fat-soluble secosteroid, is well known for its crucial role in calcium and bone metabolism. However, beyond its classical functions, vitamin D has been found to influence various metabolic and immune processes through its interaction with the vitamin D receptor (VDR), which is widely expressed in multiple tissues, including those involved in glucose metabolism. Epidemiological studies have consistently shown an association between vitamin D deficiency and an increased risk of developing T2DM (2). Individuals with lower serum levels of 25-hydroxyvitamin D [25(OH)D] often exhibit impaired insulin secretion, decreased insulin sensitivity, and a higher prevalence of metabolic syndrome. The presence of VDR in pancreatic β-cells and insulin-sensitive tissues suggests that vitamin D may play a direct role in modulating insulin action and glucose metabolism. Vitamin D is believed to exert its insulin-mimetic effects through several mechanisms, including enhancement of insulin receptor expression and signaling, upregulation of glucose transporter type 4 (GLUT4), reduction of inflammation, and protection of pancreatic β-cells from oxidative stress and apoptosis. Furthermore, vitamin D has been shown to influence hepatic gluconeogenesis, lipid metabolism, and immune regulation, all of which contribute to the overall metabolic profile in T2DM patients. Despite promising preclinical and epidemiological evidence, clinical trials investigating the role of vitamin D supplementation in improving glycemic control have yielded mixed results. Factors such as baseline vitamin D status, genetic variability, differences in supplementation regimens, and study design limitations may account for the inconsistencies observed in clinical outcomes. Therefore, further research is needed to elucidate the optimal dosage, duration, and patient populations that may benefit the most from vitamin D therapy. In this article, we aim to provide a comprehensive overview of the molecular mechanisms by which vitamin D exerts its insulin-mimetic effects. We will explore its impact on insulin receptor activation, glucose transport, pancreatic β-cell function, inflammatory pathways, hepatic gluconeogenesis, and lipid metabolism (2, 3). Additionally, we will discuss the potential therapeutic implications of vitamin D supplementation in the management of T2DM and the need for further research to establish evidence-based clinical recommendations. Understanding these molecular interactions will help determine whether vitamin D can serve as a viable adjunct therapy for improving insulin sensitivity and metabolic control in individuals with T2DM.

Vitamin D and Its Role in Metabolic Regulation

Vitamin D, traditionally recognized for its role in bone health and calcium homeostasis, has garnered increasing attention for its involvement in metabolic regulation, particularly in glucose and lipid metabolism. Beyond its classical functions, vitamin D exerts profound effects on various metabolic pathways by interacting with nuclear receptors, modulating gene expression, and influencing hormone secretion. The discovery of vitamin D receptors (VDRs) in pancreatic β-cells, skeletal muscle, adipose tissue, and the liver suggests a broader role in energy homeostasis and metabolic health (Fig.1). Emerging evidence indicates that vitamin D deficiency is linked to an increased risk of metabolic disorders, including insulin resistance, type 2 diabetes mellitus (T2DM), obesity, and dyslipidemia. The biological effects of vitamin D in metabolic regulation are primarily mediated through its active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2D_3$], which binds to the VDR and modulates key metabolic processes at the cellular level. One of the primary ways vitamin D regulates metabolism is through its influence on insulin secretion and sensitivity. Pancreatic β-cells, responsible for insulin production, express VDRs and enzymes required for vitamin D activation, indicating a direct role in insulin regulation (3). Experimental studies have demonstrated that vitamin D enhances insulin gene transcription by upregulating pancreatic and duodenal homeobox 1 (PDX-1), a key transcription factor involved in β-cell function. Furthermore, vitamin D plays a crucial role in maintaining β-cell viability by reducing oxidative stress and apoptosis, both of which are implicated in β-cell dysfunction in T2DM. Additionally, vitamin D regulates intracellular calcium homeostasis in β-cells, which is essential for insulin granule exocytosis and secretion. Studies in vitamin D-deficient animals have shown impaired insulin release, while supplementation improves insulin secretion and glucose tolerance, reinforcing the importance of vitamin D in pancreatic function.

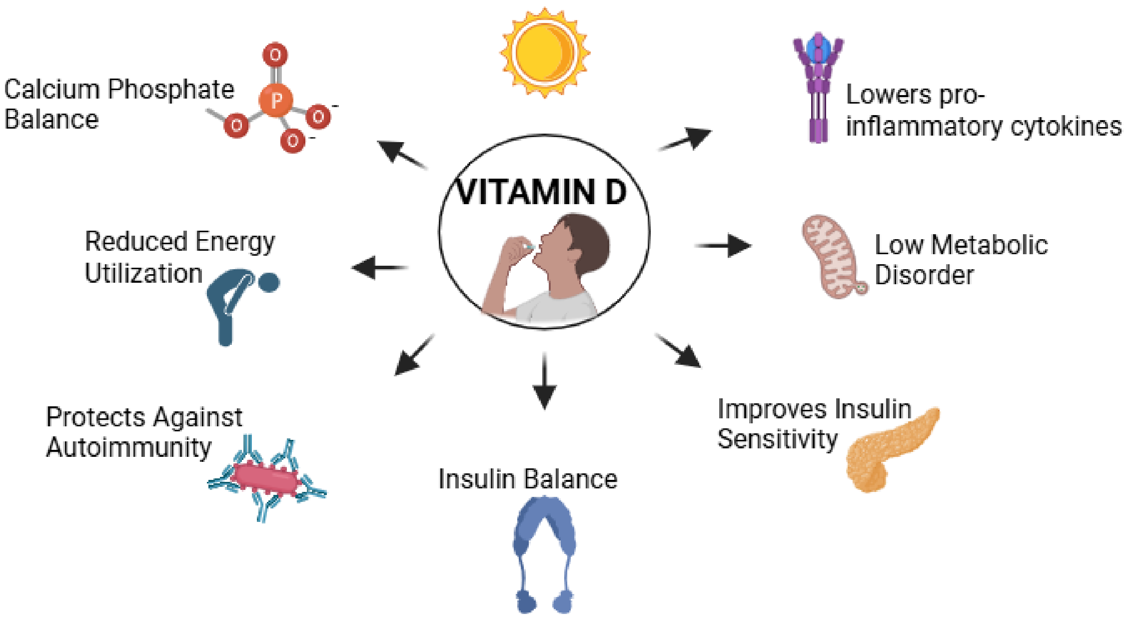

Fig.1 Viamin D role in Diabetic Patient

Beyond the pancreas, vitamin D has a significant impact on insulin sensitivity in peripheral tissues, including skeletal muscle, liver, and adipose tissue. Insulin resistance, a hallmark of metabolic disorders, occurs when these tissues fail to respond effectively to insulin, leading to elevated blood glucose levels. Vitamin D enhances insulin signaling by upregulating insulin receptor expression and activating key components of the insulin signaling pathway, such as phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt). In skeletal muscle, vitamin D promotes glucose uptake by increasing the translocation of glucose transporter type 4 (GLUT4) to the cell membrane, thereby improving insulin sensitivity. Similarly, in the liver, vitamin D suppresses hepatic gluconeogenesis by downregulating glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK), enzymes involved in glucose production (4). Moreover, vitamin D modulates adipose tissue function by reducing inflammation and improving lipid metabolism, which are key factors contributing to insulin resistance and metabolic dysfunction. Inflammation is a critical factor linking vitamin D to metabolic disorders. Chronic low-grade inflammation is a common feature of obesity and insulin resistance, with pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) playing a major role in disrupting insulin signaling. Vitamin D exerts potent anti-inflammatory effects by inhibiting nuclear factor-kappa B (NF-κB), a key transcription factor that regulates the expression of inflammatory cytokines. In macrophage studies, vitamin D has been shown to suppress NF-κB activation, leading to decreased production of pro-inflammatory mediators. Additionally, in adipose tissue, vitamin D reduces macrophage infiltration and promotes the polarization of macrophages toward an anti-inflammatory phenotype. These effects collectively contribute to improved insulin sensitivity and metabolic health, highlighting the immunomodulatory role of vitamin D in metabolic regulation.

Oxidative stress is another important factor in the pathophysiology of metabolic disorders, and vitamin D has been implicated in reducing oxidative damage. Reactive oxygen species (ROS) are known to impair insulin signaling, promote β-cell apoptosis, and contribute to the progression of T2DM. Studies have demonstrated that vitamin D enhances the expression of antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, thereby reducing oxidative stress in metabolic tissues. In pancreatic β-cells, vitamin D upregulates nuclear factor erythroid 2-related factor 2 (Nrf2), a master regulator of antioxidant defense, protecting β-cells from oxidative damage and preserving their function. Similarly, in skeletal muscle and adipose tissue, vitamin D mitigates oxidative stress-induced insulin resistance, further supporting its role in metabolic regulation. Recent research has also explored the relationship between vitamin D and gut microbiota, which plays a crucial role in metabolic health (4, 5). The gut microbiome influences energy homeostasis, glucose metabolism, and inflammation, and dysbiosis has been linked to metabolic disorders such as obesity and T2DM. Emerging evidence suggests that vitamin D modulates gut microbiota composition by increasing the abundance of beneficial bacterial species such as Lactobacillus and Bifidobacterium while reducing the levels of pro-inflammatory bacteria. Additionally, vitamin D enhances intestinal barrier integrity by upregulating tight junction proteins, reducing endotoxemia and systemic inflammation. These effects highlight a potential indirect mechanism through which vitamin D influences metabolic regulation by modulating gut microbiota and intestinal permeability.

Insulin Signalling Pathway and Glucose Homeostasis

The insulin signalling pathway is a complex and highly regulated biological system that ensures the maintenance of glucose homeostasis, the balance of blood glucose levels within a narrow physiological range. Insulin, a peptide hormone secreted by the β-cells of the pancreas, plays a pivotal role in orchestrating glucose metabolism by facilitating cellular glucose uptake, promoting glycogen synthesis, regulating lipid metabolism, and inhibiting gluconeogenesis. The release of insulin is primarily triggered by an increase in blood glucose levels following carbohydrate intake. Once secreted, insulin binds to its specific receptor on the plasma membrane of insulin-sensitive tissues such as skeletal muscle, liver, and adipose tissue, initiating a cascade of intracellular signaling events that regulate multiple metabolic processes. The failure of insulin signaling, often seen in insulin resistance and type 2 diabetes mellitus (T2DM), leads to metabolic dysregulation, chronic hyperglycemia, and a cascade of associated complications, including cardiovascular diseases, neuropathy, nephropathy, and retinopathy. Understanding the molecular mechanisms of insulin action and glucose regulation is therefore essential for developing therapeutic strategies aimed at restoring insulin sensitivity and preventing metabolic disorders. The insulin signaling cascade begins when insulin binds to the insulin receptor (IR), a transmembrane tyrosine kinase receptor composed of two extracellular α-subunits and two intracellular β-subunits. This interaction leads to receptor autophosphorylation on specific tyrosine residues, which serves as a docking site for insulin receptor substrate (IRS) proteins. The IRS proteins act as adaptors, transmitting the insulin signal by activating multiple downstream pathways, the most significant being the phosphoinositide 3-kinase (PI3K)/Akt pathway (5). Upon activation, PI3K catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3), a secondary messenger that recruits Akt (also known as protein kinase B, PKB) to the plasma membrane. The phosphorylation of Akt is a crucial event in insulin action, as it directly promotes the translocation of glucose transporter type 4 (GLUT4) vesicles to the plasma membrane in skeletal muscle and adipose tissue. GLUT4 is responsible for facilitating the entry of glucose into cells, thereby reducing blood glucose levels. This mechanism is particularly significant in skeletal muscle, which accounts for the majority of insulin-stimulated glucose disposal. When insulin signaling is impaired due to insulin resistance, GLUT4 translocation is diminished, leading to reduced glucose uptake and persistent hyperglycemia, a hallmark of diabetes.

Beyond glucose transport, insulin plays a critical role in hepatic glucose metabolism, ensuring that the liver appropriately regulates glucose production and storage. Under normal conditions, insulin suppresses hepatic gluconeogenesis, the process by which glucose is synthesized from non-carbohydrate precursors, by inhibiting key gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase). Simultaneously, insulin promotes glycogenesis, the conversion of glucose into glycogen, by activating glycogen synthase (GS) while inhibiting glycogen synthase kinase-3 (GSK-3). These processes ensure that excess glucose is stored rather than being released into circulation. However, in insulin resistance and T2DM, hepatic insulin signaling is impaired, leading to uncontrolled hepatic glucose production and exacerbating hyperglycemia. This phenomenon, often referred to as "hepatic insulin resistance," is a major contributor to fasting hyperglycemia in diabetic patients. The liver thus becomes a key target for therapeutic interventions, with drugs such as metformin acting to reduce hepatic glucose output and improve insulin sensitivity. In addition to its effects on glucose metabolism, insulin exerts profound regulatory control over lipid metabolism, ensuring that energy storage and utilization are appropriately balanced. Under normal physiological conditions, insulin promotes lipogenesis, the synthesis of fatty acids and triglycerides, while inhibiting lipolysis, the breakdown of stored fat into free fatty acids. This is primarily mediated through the activation of sterol regulatory element-binding protein-1c (SREBP-1c), a transcription factor that enhances the expression of lipogenic enzymes such as acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) (6). At the same time, insulin suppresses hormone-sensitive lipase (HSL), an enzyme responsible for breaking down stored triglycerides into free fatty acids. This dual effect ensures that fat is stored when energy supply is abundant and mobilized only when needed. However, in the context of insulin resistance, these regulatory mechanisms become disrupted, leading to increased lipolysis, elevated free fatty acid levels, and ectopic fat deposition in non-adipose tissues, such as the liver, pancreas, and skeletal muscle. This contributes to the development of non-alcoholic fatty liver disease (NAFLD), lipotoxicity, and pancreatic β-cell dysfunction, further exacerbating metabolic dysregulation and increasing the risk of T2DM. Maintaining glucose homeostasis requires a delicate interplay between insulin and its counter-regulatory hormones, including glucagon, epinephrine, cortisol, and growth hormone. During fasting or energy-demanding states, glucagon, secreted by α-cells of the pancreas, plays an opposing role to insulin by stimulating hepatic glycogenolysis (the breakdown of glycogen to glucose) and gluconeogenesis, ensuring that glucose is available for essential tissues, particularly the brain. The balance between insulin and glucagon secretion is fundamental in maintaining euglycemia (normal blood glucose levels). In insulin resistance, however, this balance is disrupted, leading to excessive hepatic glucose output and chronic hyperglycemia. Additionally, stress hormones such as epinephrine and cortisol further modulate glucose metabolism by promoting gluconeogenesis and inhibiting insulin action during stress or prolonged fasting. The dysregulation of these counter-regulatory mechanisms is a major contributor to the progression of prediabetes to overt diabetes, underscoring the importance of maintaining insulin sensitivity. Given the complexity of insulin signaling and its critical role in metabolic health, various therapeutic strategies have been developed to restore insulin function and improve glucose homeostasis. Pharmacological approaches, including biguanides (e.g., metformin), thiazolidinediones (e.g., pioglitazone), GLP-1 receptor agonists, and SGLT2 inhibitors, target different aspects of insulin resistance and glucose metabolism. Additionally, lifestyle modifications, such as dietary interventions, regular exercise, and weight management, have been shown to significantly improve insulin sensitivity and reduce the risk of T2DM. Emerging research is also exploring novel insulin-mimetic compounds, gene therapy, and molecular modulators of insulin signaling pathways as potential therapeutic options. Moreover, the role of micronutrients such as vitamin D, magnesium, and omega-3 fatty acids in enhancing insulin action is being actively investigated, offering new avenues for adjunctive therapy in diabetes management.

Molecular Mechanisms of the Insulin-Mimetic Effect of Vitamin D

Vitamin D, traditionally known for its role in calcium and bone metabolism, has gained significant attention for its potential involvement in glucose homeostasis and insulin sensitivity. Emerging evidence suggests that vitamin D exhibits insulin-mimetic properties by enhancing insulin secretion, improving insulin receptor signaling, reducing inflammation, and mitigating oxidative stress (7). These multifaceted effects make vitamin D a promising therapeutic candidate for managing insulin resistance and type 2 diabetes mellitus (T2DM). The molecular mechanisms underlying these effects involve direct interactions with pancreatic β-cells, insulin-sensitive tissues, and systemic inflammatory pathways.

- **Enhancement of Insulin Secretion in Pancreatic β-Cells**

A key mechanism through which vitamin D exerts its insulin-mimetic effect is by stimulating insulin secretion from pancreatic β-cells. The biologically active form of vitamin D, 1,25-dihydroxyvitamin D (1,25$(OH)_2$D), binds to the vitamin D receptor (VDR) expressed in β-cells, leading to the modulation of genes involved in insulin synthesis and release. One of the primary ways vitamin D enhances insulin secretion is through its regulation of calcium homeostasis.

Calcium influx is a crucial step in insulin exocytosis, and vitamin D facilitates this process by increasing the expression and activity of voltage-gated calcium channels in β-cells. Additionally, vitamin D enhances intracellular calcium signaling, ensuring that β-cells respond effectively to glucose stimulation. Furthermore, vitamin D is involved in the maintenance of β-cell mass and function (7). It protects β-cells from apoptosis by upregulating anti-apoptotic proteins such as Bcl-2 and downregulating pro-apoptotic proteins like Bax. This protective effect is particularly relevant in T2DM, where chronic hyperglycemia and lipotoxicity contribute to β-cell dysfunction. By preserving β-cell viability and insulin-secreting capacity, vitamin D helps maintain glucose homeostasis and prevents the progression of diabetes.

- **Improvement of Insulin Receptor Signaling and Glucose Uptake**

Beyond insulin secretion, vitamin D plays a crucial role in enhancing insulin receptor signaling in peripheral tissues such as skeletal muscle, adipose tissue, and the liver. Insulin signaling is mediated by the activation of the insulin receptor (IR) and subsequent phosphorylation of insulin receptor substrate-1 (IRS-1), which triggers downstream signaling cascades. Vitamin D has been shown to upregulate the expression of IR and IRS-1, leading to improved activation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway. This pathway is essential for the translocation of glucose transporter 4 (GLUT4) to the cell membrane, enabling efficient glucose uptake by insulin-responsive tissues (Fig.2). Additionally, vitamin D influences lipid metabolism by reducing lipotoxicity-induced insulin resistance (7, 8). It modulates the expression of genes involved in fatty acid oxidation and lipid storage, thereby preventing excessive accumulation of triglycerides in muscle and liver tissues. This effect is particularly important because lipid accumulation is a major contributor to insulin resistance, as it interferes with insulin signaling and promotes inflammation. By enhancing insulin sensitivity at the molecular level, vitamin D supports efficient glucose utilization and metabolic balance.

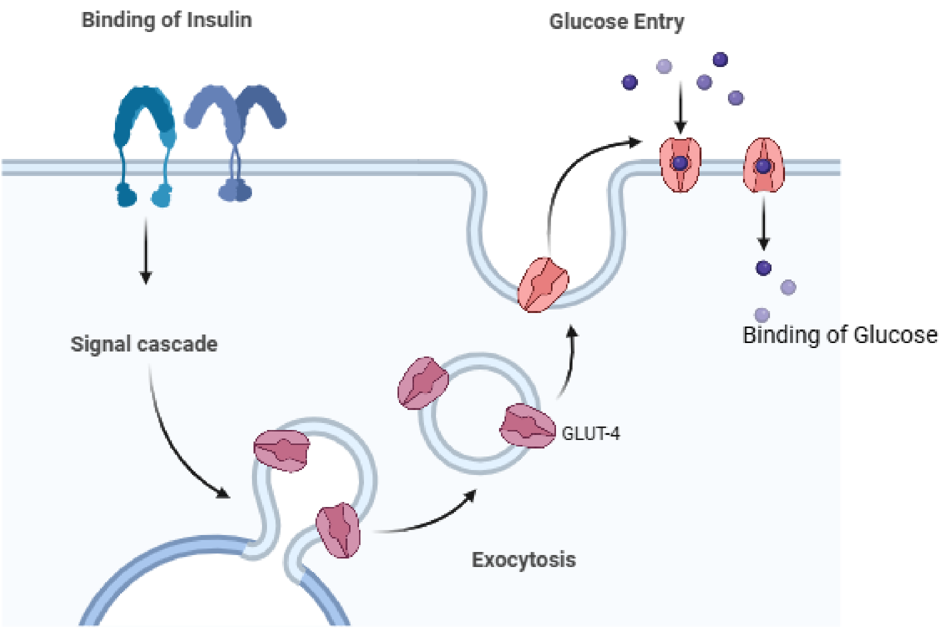

Fig.2 Binding of Glucose to Insulin

- **Anti-Inflammatory Effects and Reduction of Insulin Resistance**

Chronic low-grade inflammation is a major factor contributing to insulin resistance and the development of T2DM. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) disrupt insulin signaling by inducing serine phosphorylation of IRS-1, which impairs its ability to activate downstream pathways. Vitamin D exerts potent anti-inflammatory effects by inhibiting nuclear factor-kappa B (NF-κB), a key transcription factor involved in cytokine production (8). This inhibition results in a decrease in pro-inflammatory mediators, thereby improving insulin sensitivity. Moreover, vitamin D modulates immune cell activity in adipose tissue, shifting the balance from pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages. This shift reduces adipose tissue inflammation, which is a significant contributor to systemic insulin resistance. The reduction of inflammatory mediators in the circulation not only improves insulin signaling but also protects pancreatic β-cells from inflammatory damage, further supporting their insulin-secreting function.

- **Mitigation of Oxidative Stress and β-Cell Protection**

Oxidative stress is a key player in the pathophysiology of T2DM, contributing to β-cell dysfunction, insulin resistance, and chronic inflammation. Reactive oxygen species (ROS) generated by mitochondrial dysfunction impair insulin signaling and promote apoptosis of β-cells. Vitamin D has been shown to possess antioxidant properties by upregulating the expression of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx). These enzymes neutralize ROS and reduce oxidative damage in insulin-responsive tissues. Additionally, vitamin D enhances mitochondrial function and biogenesis, which are crucial for maintaining energy homeostasis and efficient glucose metabolism. By improving mitochondrial activity, vitamin D supports optimal insulin action and prevents metabolic dysfunction associated with diabetes (9). The reduction in oxidative stress also plays a role in preserving β-cell function, ensuring sustained insulin secretion and glucose regulation.

Clinical trials Supporting the Role of Vitamin D in T2DM

Several clinical trials have investigated the role of vitamin D supplementation in the prevention and management of type 2 diabetes mellitus (T2DM). Below is an overview of notable studies:

1. Diabetes Prevention with Active Vitamin D (DPVD) Study

- **Objective:** To assess whether eldecalcitol, an active vitamin D analogue, can reduce the development of T2DM among adults with impaired glucose tolerance.
- **Design:** Double-blind, multicenter, randomized, placebo-controlled trial.
- **Participants:** 1,256 Japanese adults aged 30 years and older with impaired glucose tolerance.
- **Intervention:** Participants were randomized to receive either 0.75 µg of eldecalcitol daily or a placebo.
- **Duration:** Median follow-up of 2.9 years.
- **Results:** The cumulative incidence of diabetes was 12.5 per 1,000 person-years in the eldecalcitol group and 14.2 per 1,000 person-years in the placebo group, a difference that was not statistically significant.
- **Conclusion:** Eldecalcitol did not significantly reduce the incidence of T2DM in individuals with impaired glucose tolerance.

2. Meta-Analysis of Vitamin D Supplementation on Glycemic Control

- **Objective:** To evaluate the impact of vitamin D supplementation on glycemic control in patients with T2DM.
- **Design:** Systematic review and meta-analysis of randomized controlled trials.
- **Participants:** Data from multiple clinical trials involving T2DM patients receiving various dosages of vitamin D supplementation.
- **Results:** The analysis indicated that vitamin D supplementation had a modest but significant effect on improving glycemic control, as evidenced by reductions in fasting plasma glucose and HbA1c levels.
- **Conclusion:** Vitamin D supplementation could be beneficial for glycemic control in T2DM patients.

3. Effect of Vitamin D on Regression to Normal Glucose Regulation and Progression to Diabetes in a Randomized Controlled Trial

- **Objective:** To determine the effect of vitamin D supplementation on regression to normal glucose regulation and progression to diabetes among adults with prediabetes.
- **Design:** Randomized, double-blind, placebo-controlled trial.
- **Participants:** Adults with prediabetes.
- **Intervention:** Participants received vitamin D supplementation or placebo.
- **Results:** Vitamin D supplementation was associated with a higher likelihood of regression to normal glucose regulation and a lower risk of progression to diabetes.
- **Conclusion:** Vitamin D supplementation may promote regression to normal glucose regulation and reduce the risk of progression to diabetes in adults with prediabetes.

4. Effects of Vitamin D Supplementation on Prevention of Type 2 Diabetes in Patients with Prediabetes: A Systematic Review and Meta-Analysis

- **Objective:** To assess the effects of vitamin D supplementation on the prevention of T2DM in individuals with prediabetes.
- **Design:** Systematic review and meta-analysis of randomized controlled trials.
- **Participants:** Individuals with prediabetes.
- **Intervention:** Vitamin D supplementation compared to placebo.
- **Results:** The meta-analysis found that vitamin D supplementation was associated with a non-significant reduction in the risk of developing T2DM.
- **Conclusion:** Vitamin D supplementation may have a modest effect on reducing the risk of T2DM in individuals with prediabetes, but further research is needed.

5. Vitamin D Supplementation for Prevention of Type 2 Diabetes Mellitus: To D or Not to D?

- **Objective:** To review the evidence on vitamin D supplementation for the prevention of T2DM.
- **Design:** Comprehensive literature review.
- **Findings:** Observational studies suggest an association between low vitamin D levels and increased risk of T2DM, but randomized controlled trials have provided mixed results regarding the efficacy of vitamin D supplementation in preventing T2DM.
- **Conclusion:** While low vitamin D levels are associated with increased risk of T2DM, current evidence from randomized controlled trials does not conclusively support vitamin D supplementation for the prevention of T2DM.

6. Baseline Characteristics of the Vitamin D and Type 2 Diabetes (D2d) Study

- **Objective:** To describe the baseline characteristics of participants in the D2d study, which aims to determine if vitamin D supplementation can prevent T2DM.

- **Design:** Multicenter, randomized, double-blind, placebo-controlled trial.
- **Participants:** Adults at risk for diabetes, defined by meeting at least two of the 2010 ADA glycemic criteria for prediabetes.
- **Intervention:** Participants were randomized to receive either 4,000 IU of vitamin D3 daily or a placebo.
- **Conclusion:** The D2d study is designed to provide insights into the role of vitamin D supplementation in the prevention of T2DM.

7. A Randomized Controlled Trial of High-Dose Vitamin D in Recent-Onset Type 2 Diabetes

- **Objective:** To assess the effects of high-dose vitamin D supplementation on glycemic control in patients with recent-onset T2DM.
- **Design:** Randomized, double-blind, placebo-controlled trial.
- **Participants:** 50 Caucasian individuals recently diagnosed with T2DM.
- **Intervention:** Participants received either high-dose vitamin D3 supplementation or a placebo.

Table 1: Clinical Trials Investigating the Role of Vitamin D in T2DM

Study Design	Participants	Vitamin D Dose & Duration	Primary Outcome	Key Results	Reference
RCT	2,423 prediabetic adults	Vitamin D3 (4000 IU/day) for 2.5 years	T2DM Incidence	12% lower risk of T2DM in Vitamin D group compared to placebo.	(10)
Cohort Study	5,000 participants	Dietary & supplemental Vitamin D for 5 years	T2DM Risk	Higher baseline Vitamin D correlated with reduced diabetes risk.	(11)
RCT	92 prediabetic adults	Vitamin D3 (2000 IU/day) + Calcium for 4 months	Insulin Sensitivity	Improved insulin sensitivity and β-cell function.	(12)
Meta-analysis	15 RCTs (T2DM patients)	Various Vitamin D dosages	HbA1c & Fasting Glucose	Significant improvement in HbA1c and fasting glucose levels.	(13)

RCT	275 T2DM patients	Vitamin D3 (5000 IU/week) for 6 months	Insulin Sensitivity	Increased insulin sensitivity reduced fasting glucose.	(14)
Cross-sectional Study	681 T2DM patients	Baseline Vitamin D levels measured	Glycemic Control	Higher Vitamin D associated with better glycemic control.	(15)
RCT	96 T2DM patients	Vitamin D2 (50,000 IU/week) for 8 weeks	β-cell Function	No significant effect on insulin resistance but improved β-cell function.	(16)
RCT	61 T2DM patients	Vitamin D2 (100,000 IU single dose) for 8 weeks	Endothelial Function	Improved insulin resistance and endothelial function.	(17)
Cohort Study	3,000 individuals	Vitamin D status assessed over 10 years	T2DM Risk	Vitamin D deficiency linked to a 40% higher T2DM risk.	(18)
RCT	150 T2DM patients	Vitamin D3 (50,000 IU/week) for 12 weeks	Insulin Sensitivity & HbA1c	Improved insulin sensitivity and lower HbA1c levels.	(19)
RCT	511 prediabetic individuals	Vitamin D3 (4000 IU/day) for 6 months	Insulin Sensitivity	No major effects on insulin resistance.	(20)
RCT	96 T2DM patients	Vitamin D3 (10,000 IU/day) for 1 year	HbA1c & β-cell Function	No significant changes in HbA1c, but improved β-cell function.	(21)
Cross-sectional Study	126 healthy adults	Baseline Vitamin D levels measured	Insulin Sensitivity	Positive correlation between Vitamin D levels and insulin sensitivity.	(22)
RCT	81 T2DM patients	Vitamin D-fortified yogurt for 12 weeks	Fasting Glucose & HbA1c	Improved fasting glucose and reduced HbA1c.	(23)

Meta-analysis	27 RCTs (T2DM patients)	Various Vitamin D dosages	Glycemic Control	Vitamin D supplementation improved insulin resistance and glucose metabolism.	(24)

Preclinical Evidence Supporting the Role of Vitamin D in Type 2 Diabetes Mellitus (T2DM)

Preclinical studies, including in vitro and in vivo animal models, have provided substantial evidence supporting the role of vitamin D in regulating glucose homeostasis and mitigating the pathophysiological mechanisms underlying Type 2 Diabetes Mellitus (T2DM). These studies demonstrate that vitamin D influences pancreatic β-cell function, insulin secretion, insulin sensitivity, inflammation, oxidative stress, and lipid metabolism, all of which contribute to the progression of T2DM. The presence of vitamin D receptors (VDRs) and vitamin D-metabolizing enzymes in metabolic tissues such as the pancreas, liver, muscle, and adipose tissue further supports its crucial role in glucose regulation.

1. Impact of Vitamin D on Pancreatic β-Cell Function and Insulin Secretion

Vitamin D plays a significant role in pancreatic β-cell function by regulating insulin synthesis, secretion, and survival. Pancreatic β-cells express VDRs and enzymes responsible for vitamin D activation, suggesting a direct role in insulin regulation. In animal studies, vitamin D deficiency has been associated with impaired insulin secretion and β-cell dysfunction. For instance, studies in vitamin D receptor knockout (VDR-KO) mice have shown reduced insulin secretion and glucose intolerance, which were reversed by vitamin D supplementation (25). Another study demonstrated that 1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$] increases insulin gene transcription by upregulating pancreatic and duodenal homeobox 1 (PDX-1), a key transcription factor involved in β-cell maturation and insulin production. Furthermore, vitamin D has been found to protect β-cells from apoptosis induced by hyperglycemia and oxidative stress, thereby preserving β-cell mass and function.

2. Vitamin D and Insulin Sensitivity in Peripheral Tissues

In addition to its effects on β-cells, vitamin D enhances insulin sensitivity in peripheral tissues, including skeletal muscle, liver, and adipose tissue. Animal models of T2DM have demonstrated that vitamin D supplementation improves insulin sensitivity by upregulating insulin receptor expression and enhancing glucose uptake. In skeletal muscle, vitamin D promotes glucose transporter type 4 (GLUT4) translocation to the cell membrane, facilitating glucose uptake and utilization. In the liver, vitamin D reduces hepatic gluconeogenesis by downregulating glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK), two key enzymes involved in glucose production. Additionally, in adipose tissue, vitamin D has been shown to modulate adipokine secretion, reducing pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) while increasing adiponectin, an insulin-sensitizing hormone.

3. Anti-Inflammatory Effects of Vitamin D in T2DM

Chronic low-grade inflammation is a key contributor to insulin resistance and β-cell dysfunction in T2DM. Vitamin D exhibits potent anti-inflammatory properties by inhibiting the activation of nuclear factor-kappa B (NF-κB), a transcription factor that regulates pro-inflammatory cytokine production (26). Studies in diabetic animal models have shown that vitamin D supplementation reduces the expression of inflammatory markers such as TNF-α, IL-6, and interleukin-1β (IL-1β), leading to improved insulin signaling and glucose metabolism. Moreover, vitamin D has been found to reduce macrophage infiltration in adipose tissue, shifting the balance from pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages, thereby improving metabolic function and reducing insulin resistance.

4. Role of Vitamin D in Reducing Oxidative Stress in T2DM

Oxidative stress plays a crucial role in the pathogenesis of T2DM by impairing insulin signaling, promoting β-cell apoptosis, and increasing insulin resistance. Vitamin D has been shown to enhance the expression of antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, thereby reducing oxidative damage in metabolic tissues. In a study using diabetic rats, vitamin D supplementation significantly decreased markers of oxidative stress, including malondialdehyde (MDA) and reactive oxygen species (ROS), while increasing antioxidant enzyme activity. Furthermore, vitamin D activates nuclear factor erythroid 2-related factor 2 (Nrf2), a key regulator of cellular antioxidant defense, providing additional protection against oxidative damage in β-cells and insulin-sensitive tissues.

5. Vitamin D and Gut Microbiota in Metabolic Regulation

Emerging evidence suggests that vitamin D may influence metabolic health through its effects on gut microbiota. The gut microbiome plays a critical role in energy metabolism, glucose homeostasis, and inflammation. Studies in diabetic animal models have demonstrated that vitamin D supplementation alters gut microbiota composition by increasing the abundance of beneficial bacterial species such as Lactobacillus and Bifidobacterium while reducing harmful bacteria associated with metabolic dysregulation (27). Additionally, vitamin D has been shown to enhance intestinal barrier function by upregulating tight junction proteins, reducing systemic inflammation, and improving insulin sensitivity. These findings highlight a novel mechanism through which vitamin D may modulate metabolic health and reduce the risk of T2DM.

6. Vitamin D in Lipid Metabolism and Obesity-Associated Insulin Resistance

Obesity is a major risk factor for T2DM, and vitamin D has been implicated in modulating lipid metabolism and body fat distribution. Animal studies have shown that vitamin D supplementation reduces lipogenesis and promotes lipolysis by modulating key enzymes involved in lipid metabolism. In high-fat diet-induced obese mice, vitamin D treatment significantly reduced visceral adiposity, improved lipid profiles, and enhanced insulin sensitivity. Furthermore, vitamin D has been shown to regulate the expression of peroxisome proliferator-activated receptor gamma (PPAR-γ), a transcription factor involved in adipocyte differentiation and lipid storage (28). By modulating PPAR-γ activity, vitamin D promotes healthier fat distribution and reduces obesity-associated insulin resistance.

7. Effects of Vitamin D Deficiency on T2DM Development

Preclinical models have also provided evidence that vitamin D deficiency contributes to the development and progression of T2DM. Studies in vitamin D-deficient mice have shown increased insulin resistance, β-cell dysfunction, and impaired glucose tolerance. Additionally, vitamin D-deficient animals exhibit higher levels of inflammation, oxidative stress, and dyslipidemia, all of which are associated with T2DM. These findings suggest that maintaining adequate vitamin D levels is essential for metabolic health and may serve as a preventive strategy against T2DM.

Potential Therapeutic Implications and Challenges of the Insulin-Mimetic Effect of Vitamin D in Type 2 Diabetes Mellitus

Vitamin D has gained significant attention as a potential therapeutic agent in Type 2 Diabetes Mellitus (T2DM) due to its insulin-mimetic effects, which influence various aspects of glucose metabolism and insulin signaling. Numerous preclinical and clinical studies have suggested that vitamin D can enhance pancreatic β-cell function, improve insulin sensitivity in peripheral tissues, and mitigate systemic inflammation—three key factors in the pathogenesis of T2DM. The presence of vitamin D receptors (VDRs) and vitamin D–dependent enzymes in pancreatic β-cells, adipose tissue, liver, and skeletal muscle indicates its direct regulatory role in glucose metabolism. Vitamin D enhances insulin secretion by upregulating the expression of the pancreatic and duodenal homeobox 1 (PDX-1) gene, which is crucial for β-cell survival and function. Additionally, vitamin D modulates the expression of insulin receptors and glucose transporter 4 (GLUT4), thereby improving insulin sensitivity and facilitating glucose uptake in muscle and adipose tissues. Its anti-inflammatory properties further contribute to metabolic regulation by inhibiting the nuclear factor-kappa B (NF-κB) pathway, reducing the secretion of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which are known to impair insulin signaling. These molecular mechanisms highlight the potential of vitamin D as an adjunct therapy for managing T2DM, particularly in individuals with vitamin D deficiency or insulin resistance (28, 29).

Despite these promising therapeutic implications, several challenges must be addressed before vitamin D can be widely adopted as a treatment for T2DM. One of the primary concerns is the inconsistency in clinical trial results investigating the effects of vitamin D supplementation on glycemic control. While some studies have reported significant improvements in fasting blood glucose, HbA1c levels, and insulin sensitivity, others have shown minimal or no beneficial effects. These discrepancies may be attributed to variations in study design, baseline vitamin D status of participants, duration of supplementation, and dosage differences. Furthermore, the optimal dosage of vitamin D required to exert significant metabolic effects remains unclear. Excessive vitamin D intake can lead to hypercalcemia, nephrocalcinosis, and cardiovascular complications, emphasizing the need for carefully designed dosing strategies. Another major challenge is the individual variability in response to vitamin D supplementation, which is influenced by genetic polymorphisms, obesity, ethnicity, and underlying metabolic conditions. For instance, individuals with obesity often exhibit vitamin D sequestration in adipose tissue, leading to lower bioavailability and reduced efficacy of supplementation (29). Additionally, the interaction of vitamin D with commonly prescribed antidiabetic medications, such as metformin and sulfonylureas, raises concerns regarding its clinical applicability and safety profile.

Moreover, large-scale, long-term clinical trials are required to establish the efficacy, safety, and sustainability of vitamin D supplementation in T2DM management. Current research is also exploring potential combination therapies that include vitamin D alongside other agents such as omega-3 fatty acids, magnesium, and probiotics to enhance its metabolic benefits. Personalized medicine approaches, which consider genetic and metabolic variability among patients, could further improve the effectiveness of vitamin D therapy. Future research should focus on identifying specific patient subgroups that are most likely to benefit from vitamin D supplementation and refining dosing guidelines to minimize risks. Additionally, regulatory agencies and healthcare policymakers need to establish standardized recommendations for vitamin D supplementation in diabetes care. Addressing these challenges through robust clinical research, improved patient stratification, and combination treatment strategies will be crucial in unlocking the full therapeutic potential of vitamin D as an insulin-mimetic agent for T2DM. If successfully integrated into clinical practice, vitamin D could offer a cost-effective, widely accessible, and relatively safe intervention for improving glycemic control and reducing diabetes-related complications, especially in populations with a high prevalence of vitamin D deficiency (30).

Conclusion

The molecular mechanisms underlying the insulin-mimetic effect of vitamin D suggest that it could be a valuable adjunct in the management of Type 2 Diabetes Mellitus (T2DM). Vitamin D's role in regulating insulin secretion, enhancing insulin sensitivity, and modulating inflammatory pathways highlights its potential to address key pathophysiological aspects of diabetes. The presence of vitamin D receptors (VDRs) in pancreatic β-cells, skeletal muscle, and adipose tissue, along with its ability to influence glucose transporter activity and intracellular signaling pathways, further supports its significance in metabolic regulation. Preclinical and clinical studies have provided promising evidence of vitamin D's beneficial effects on glucose homeostasis, insulin resistance, and β-cell function. However, variations in study outcomes emphasize the need for further investigation to determine optimal supplementation strategies, patient-specific responses, and long-term safety. Factors such as genetic predisposition, baseline vitamin D levels, and individual metabolic profiles may influence treatment efficacy, necessitating personalized approaches in clinical applications. Despite these challenges, vitamin D remains an attractive, cost-effective, and widely accessible potential therapeutic agent for T2DM. Future large-scale, well-designed clinical trials are crucial to establishing definitive guidelines for its use in diabetes management. If validated, vitamin D supplementation could be integrated into standard therapeutic regimens, offering a complementary strategy to improve glycemic control, reduce complications, and enhance overall metabolic health in individuals with T2DM.

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