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Vitamin D and Exercise in Diabetes Management: Potential Benefits for Insulin Sensitivity and Prevention

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A B S T R A C T

There is increasing evidence supporting the synergistic role of vitamin D supplementation and regular exercise in the prevention and management of type 2 diabetes mellitus (T2DM). Vitamin D is not only essential for bone health but also plays a significant role in glucose metabolism, insulin secretion, inflammation modulation, and gut microbiota balance. Similarly, exercise enhances insulin sensitivity, glucose uptake, and reduces adiposity while improving overall metabolic function. This review explores the mechanisms by which both interventions independently and jointly affect insulin signaling, beta-cell function, lipid metabolism, and inflammatory pathways. Combined, vitamin D and exercise may offer greater improvements in glycemic control and reduction of diabetes-related risk factors than either intervention alone. However, factors such as vitamin D toxicity and inappropriate exercise intensity must be considered. Personalized approaches, guided by clinical evaluation, are essential to optimize outcomes in individuals with or at risk of T2DM

Keywords: Vitamin D, Exercise, Diabetes Mellitus type 2

1. Introduction

Type 2 diabetes mellitus (T2DM) is an increasingly prevalent global health issue, marked by the body's resistance to insulin, impaired glucose metabolism, and chronic inflammation (1,2). With the growing prevalence of type 2 diabetes mellitus (T2DM), there is a rising interest in lifestyle interventions that can support or enhance conventional medical therapies. Vitamin D supplementation and regular exercise have gained attention as effective, non-pharmacological strategies. Each has demonstrated the ability to improve insulin sensitivity and overall metabolic function through unique yet potentially synergistic biological pathways.

Vitamin D, long recognized for its role in bone metabolism, is now being explored for its regulatory effects on pancreatic β-cell function, insulin secretion, and systemic inflammation (3). At the same time, exercise remains a cornerstone in diabetes management, promoting glucose uptake in skeletal muscle and improving overall metabolic flexibility (4). Recent evidence indicates that the co-administration of vitamin D supplementation with regular exercise may produce synergistic effects, offering enhanced benefits in glycemic control and the prevention of diabetes-related complications. This review aims to explore the individual and combined roles of vitamin D and exercise in managing and preventing T2DM, with a focus on their impact on insulin sensitivity, inflammatory markers, and metabolic health.

2. Vitamin D and Diabetes

Vitamin D is well-known for its role in bone health, but recent research has highlighted its involvement in glucose metabolism and insulin sensitivity. In individuals with diabetes, vitamin D deficiency is often observed and may contribute to insulin resistance, a key characteristic of Type 2 diabetes.

Mechanism of Action:

Vitamin D may directly influence insulin synthesis and secretion by binding to the vitamin D receptor (VDR) in pancreatic beta cells, with supporting evidence from the presence of a vitamin D response element within the human insulin gene promoter. Additionally, vitamin D activation in beta cells can occur through the enzyme 25(OH)D-1α-hydroxylase (CYP27B1), which plays a crucial role in calcium regulation, a vital factor for insulin secretion. In peripheral insulin-target tissues, active vitamin D metabolites are believed to enhance insulin sensitivity by upregulating insulin receptor expression, activating transcription factors involved in glucose metabolism, and modulating calcium levels, which are essential for insulin-mediated intracellular processes (5). One study demonstrated that preincubation of INS1E cells with 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) markedly enhanced glucose-stimulated insulin secretion at elevated glucose concentrations (22 mM), while 25-hydroxyvitamin D (25(OH)D) did not show a similar effect (6).

Vitamin D may also modulate insulin metabolism by activating a second messenger system, which subsequently enhances insulin secretion and sensitivity. This effect could be mediated through an increased influx of calcium and intracellular glucose within beta cells, in addition to suppressing pro-inflammatory cytokine release (7). In one study, vitamin D supplementation significantly reduced HbA1c levels in patients with Type 2 Diabetes Mellitus (T2DM) who were concurrently receiving metformin treatment. However, the effects on insulin resistance and other metabolic parameters, such as fasting insulin levels, were not sustained, which may be attributed to the administration of insufficient vitamin D doses to achieve optimal serum levels (8).

After absorption in the small intestine, vitamin D may influence gut microbial communities through indirect systemic pathways. The vitamin D receptor (VDR), which is abundantly expressed in the proximal colon, functions as a transcription factor regulating the expression of over 1,000 host genes involved in processes such as intestinal homeostasis, inflammation regulation, tight junction integrity, pathogen defense, commensal bacterial colonization, and mucosal immunity. Among the VDR-regulated targets are defensins, cathelicidin, claudins, Toll-like receptor 2 (TLR2), zonulin occludens, and nucleotide-binding oligomerization domain-containing protein 2 (NOD2) (9). A study involving patients with T2DM revealed a reduced abundance of butyrate-producing bacteria, such as *Eubacterium spp*. In contrast, there was an observed increase in lipopolysaccharide (LPS)-producing bacteria, including *Escherichia coli* and *Pseudomonas spp.,* as well as sulfate-reducing bacteria like *Bilophila wadsworthia*. This microbial composition indicates a dysbiotic state characterized by chronic inflammation and compromised intestinal barrier function, which are common in T2DM. Notably, higher circulating levels of vitamin D were associated with an increase in beneficial butyrate-producing bacteria and a reduction in pathogenic LPS-producing bacteria. These findings suggest that vitamin D may play a modulatory role in restoring microbial balance and mitigating gut-associated inflammation in individuals with T2DM (10).

1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$], the active form of vitamin D, also exerts significant effects within adipose tissue by regulating inflammation, adipogenesis, and adipocyte secretory functions. Several studies have shown that 1,25$(OH)_2D_3$, through its interaction with VDRs in adipose tissue, modulates key physiological processes. Specifically, 1,25$(OH)_2D_3$ suppresses the secretion of chemokines and pro-inflammatory cytokines in human adipocytes. Moreover, it suppresses the activation of nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling cascades, leading to a downregulation of gene expression involved in inflammatory processes (11).

Deficiency and Diabetes Risk:

Vitamin D deficiency has been linked to elevated levels of parathyroid hormone (PTH), which can promote lipogenesis, obesity, and insulin resistance. A reduction in circulating vitamin D leads to an increase in PTH secretion, which subsequently raises intracellular calcium (Ca^{2+}) concentrations. Elevated intracellular Ca^{2+} may impair insulin receptor function in peripheral tissues and inhibit the activity of the GLUT4 glucose transporter, disrupting normal glucose uptake and contributing to metabolic dysregulation (12). Serum total 25-hydroxyvitamin D [25(OH)D], includes both 25$(OH)D_3$ and 25$(OH)D_2$, serves as the primary biomarker for evaluating vitamin D status. Serum 25(OH)D concentrations in the general population can vary widely due to multiple factors, including seasonal variations, geographic latitude, cultural practices that limit UVB exposure, skin pigmentation, body mass index (BMI), sex, age, physical activity levels, dietary vitamin D intake through fortification or supplementation, and underlying genetic predispositions (13).

Individuals with insufficient vitamin D levels are at an increased risk of developing type 2 diabetes mellitus (T2DM). Several studies have found that patients with T2DM are more likely to suffer from vitamin D deficiency compared to healthy controls. Moreover, vitamin D deficiency is more prevalent among individuals with T2DM than those with type 1 diabetes mellitus, indicating a stronger association with the pathogenesis of T2DM (14). Higher vitamin D levels are also associated with lower levels of inflammatory biomarkers, improved HOMA-IR (a measure of insulin resistance), and a more favorable lipid profile. These benefits may be attributed to vitamin D's role in suppressing the renin-angiotensin-aldosterone system, improving pancreatic β-cell function, enhancing endothelial health, and exerting immunomodulatory effects (15).

3. Exercise and Diabetes

Exercise is a cornerstone in the management of Type 2 diabetes. It improves insulin sensitivity, enhances glucose uptake by muscles, and helps reduce overall blood glucose levels.

Mechanism of Action:

Exercise training is an effective therapeutic intervention for individuals with insulin resistance, primarily by enhancing glucose uptake in skeletal muscle through insulin-independent mechanisms. This mechanism is facilitated by enhanced translocation of glucose transporter-4 (GLUT-4) to the plasma membrane and increased phosphorylation of AMP-activated protein kinase (AMPK) in response to physical activity. Since skeletal muscle is responsible for approximately 80% of peripheral glucose uptake, these adaptations significantly improve glycemic control (16). Additionally, exercise-induced changes in the gut microbiota have been closely linked to improvements in glucose homeostasis and insulin sensitivity. In individuals who respond positively to exercise, the gut microbiome shows an increased capacity for short-chain fatty acid (SCFA) biosynthesis and enhanced catabolism of branched-chain amino acids. In contrast, non-responders exhibit microbial profiles marked by elevated production of metabolites associated with adverse metabolic outcomes (17).

A 12-week structured exercise program has been shown to significantly enhance insulin resistance, glycemic control, and overall quality of life in individuals with type 2 diabetes mellitus (T2DM). Participants demonstrated substantial reductions in HOMA-IR, fasting insulin, fasting and postprandial blood glucose, and HbA1c levels. In addition, improvements were noted across various quality of life domains, including physical and psychological well-being, social interactions, and environmental satisfaction. The intervention also resulted in improved functional capacity, as evidenced by increased distance in the six-minute walk test, and higher physical activity levels, which were positively correlated with enhanced insulin sensitivity (18). Physical activity exerts insulin-like effects by reducing intracellular fat stores, enhancing lipid oxidation, and upregulating key signaling proteins such as AKT, which collectively improve muscle function and regulate circulating glucose levels. Furthermore, exercise-induced adaptations—including increased nitric oxide (NO) production, reduced oxidative stress, lower pro-inflammatory cytokine levels, and elevated antioxidant enzyme activity—play a crucial role in improving insulin sensitivity in individuals with type 2 diabetes mellitus (12).

Types of Exercise:

- **Aerobic Exercise (e.g., walking, cycling):** Aerobic exercise involves continuous, rhythmic movements of large muscle groups, as seen in activities like walking, jogging, and cycling. According to the latest American Diabetes Association (ADA) guidelines, aerobic sessions should ideally last a minimum of 30 minutes per day, performed on 3 to 7 days per week. Engaging in moderate to vigorous aerobic exercise (65%–90% of maximum heart rate) has been shown to enhance VO_2max and cardiac output, which are strongly linked to reductions in both cardiovascular and all-cause mortality in individuals with type 2 diabetes mellitus (19). Aerobic training induces key physiological adaptations, such as increased mitochondrial density, improved insulin sensitivity, enhanced oxidative enzyme activity, greater vascular compliance and reactivity, improved pulmonary and immune function, and elevated cardiac output. Moderate to high volumes of aerobic exercise are consistently linked to significant reductions in cardiovascular and all-cause mortality among individuals with both type 1 and type 2 diabetes mellitus. In type 1 diabetes, aerobic exercise enhances cardiorespiratory fitness, reduces insulin resistance, and improves lipid profiles and endothelial function. For individuals with type 2 diabetes, consistent aerobic training effectively lowers HbA1c, triglyceride levels, blood pressure, and insulin resistance. Furthermore, high-intensity interval training (HIIT) has emerged as an efficient approach for enhancing skeletal muscle oxidative capacity, insulin sensitivity, and glycemic control in type 2 diabetes, and is considered safe for individuals with type 1 diabetes without adversely affecting glycemic stability (20).
- **Resistance Training (e.g., weight lifting):** Resistance exercise, which includes movements using free weights, weight machines, body weight exercises, or elastic resistance bands, has been shown to have a variety of beneficial effects in individuals with type 2 diabetes. Studies suggest that resistance training can lead to improvements ranging from 10% to 15% in key areas such as strength, bone mineral density, blood pressure, lipid profiles, cardiovascular health, insulin sensitivity, and muscle mass. These benefits contribute to overall metabolic health and enhance the management of type 2 diabetes by improving both muscular and cardiovascular functions (19). Resistance training provides numerous health benefits for adults, such as enhanced muscle mass, body composition, strength, physical function, mental health, bone mineral density, insulin sensitivity, blood pressure, lipid profiles, and cardiovascular health. For those with type 2 diabetes, resistance training has been shown to improve glycemic control, reduce insulin resistance, decrease fat mass, lower blood pressure, and increase both strength and lean body mass, contributing to better overall metabolic health (20)

4. Combining Vitamin D and Exercise for Diabetes Management :

Recent studies suggest that combining vitamin D supplementation with regular exercise may have additive or synergistic effects on insulin sensitivity and glucose control. Three mechanisms have been proposed for how exercise-induced activation of the vitamin D–VDR axis may improve lipid profiles. First, vitamin D may promote lipolysis by suppressing parathyroid hormone (PTH) secretion. Second, it could reduce serum triglycerides by decreasing hepatic triglyceride synthesis and release, while also enhancing insulin secretion and sensitivity, which may improve lipid metabolism and overall metabolic health (11). An animal study found that the combination of vitamin D supplementation and exercise successfully improved liver function and reduced insulin resistance. This combination also led to significant reductions in body weight, BMI, visceral fat, insulin levels, glucose levels, and HOMA-IR. These effects were associated with the upregulation of Akt and the downregulation of PEPCK and G6Pase expressions. Additionally, the combined effects of vitamin D and exercise more significantly upregulated AMPK, PGC-1α, and UCP1, further improving metabolic health (21,22).

Exercise also led to a significant increase in the expression of vitamin D receptors in both muscle and adipose tissue, which are key determinants of peripheral insulin sensitivity. This enhancement in receptor expression may play a crucial role in improving insulin action and overall glucose metabolism in peripheral tissues (11). In middle-aged patients with type 2 diabetes mellitus (T2DM), 12 weeks of vitamin D supplementation resulted in a significant increase in 25(OH)D levels and improvements in bone health. In contrast, endurance exercise primarily led to a reduction in body fat percentage. Interestingly, while exercise alone could potentially negatively affect bone health, this effect was mitigated when combined with vitamin D supplementation (23). An 8-week aerobic exercise program increased GLP-1 levels and decreased DPP-4 levels. When combined with $25(OH)D_3$ supplementation, this program also resulted in higher serum $25(OH)D_3$ levels. These changes may help manage and reduce risk factors associated with type 2 diabetes (12).

Potential Risks and Considerations:

While both vitamin D and exercise have significant benefits, there are some considerations:

- **Vitamin D Toxicity:** Very high doses of vitamin D can saturate the vitamin D binding protein (VDBP), leading to elevated levels of free 25(OH)D and $1,25(OH)_2D$. These elevated levels may enter cells, bind to vitamin D receptors (VDR), and alter gene expression. While studies show small improvements in muscle strength and physical performance with high doses (e.g., 600,000 IU), the clinical significance remains unclear. Excessive vitamin D (up to 500,000 IU) can also transiently increase bone turnover markers, potentially raising fracture risk. Further investigation is needed to assess the long-term impact of these changes on bone health and muscle function (24).

- **Exercise Intensity and Safety:** Moderate-intensity training encourages β-cell growth and proliferation, likely through the Akt and IRS2 signalling pathways. On the other hand, high-intensity exercise may induce β-cell hypertrophy as an adaptive response to reduced insulin content and increased levels of stress hormones such as glucocorticoids and epinephrine. These findings imply that varying exercise intensities activate different molecular mechanisms that affect β-cell function and survival under healthy conditions (25). Overexercising or following incorrect exercise routines can lead to injury, particularly for individuals who are new to exercise or have underlying health conditions. Therefore, a balanced exercise approach, coupled with consultation from a healthcare provider, is essential. Based on these findings, the American Diabetes Association (ADA) advises individuals with type 2 diabetes to participate in either 150 minutes of moderate-intensity aerobic activity, such as walking, or 75 minutes of vigorous-intensity aerobic exercise per week (11).

Conclusion

The combination of maintaining adequate vitamin D levels and engaging in regular physical activity presents a powerful strategy for managing type 2 diabetes and improving insulin sensitivity. While both factors offer independent benefits, their synergistic effect may lead to better blood sugar control and enhanced diabetes prevention. However, vitamin D supplementation should be used cautiously, as excessive amounts can lead to toxicity. Similarly, exercise routines should be personalized based on individual fitness levels and consistently followed to achieve long-term benefits. Before starting any new regimen, especially for those with diabetes or other underlying health conditions, it's essential to consult with a healthcare professional. This dual approach of adequate vitamin D levels combined with regular exercise offers a comprehensive method for enhancing insulin sensitivity and managing type 2 diabetes. Vitamin D supplementation supports insulin function and reduces inflammation, while exercise promotes muscle glucose uptake and weight management. Together, they form a holistic approach to improving metabolic health and reducing the risk of chronic complications. If considering supplementation or beginning a new exercise routine, discussing these strategies with your healthcare provider is crucial to ensure the best fit for your individual health needs.

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