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Understanding the Connection between Vitamin D and Diabetes: A Narrative Review

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ABSTRACT: Diabetes is a persistent medical condition distinguished by elevated concentrations of glucose in the bloodstream. This condition has a global impact, impacting millions of individuals, and inadequate management can result in a range of complications. Despite the absence of a cure for diabetes, exercise and diet, among other lifestyle components, can significantly impact its management. Interest in the potential function of vitamin D in the prevention and management of diabetes has increased in recent years. This article aims to investigate the correlation between vitamin D and diabetes, elucidate the possible mechanisms underlying its impacts, and survey the existing scientific literature that substantiates its efficacy.

KEYWORD: Diabetes, Vitamin D, Correlation, Review

INTRODUCTION

The relationship between vitamin D and diabetes has been extensively studied, with research indicating that vitamin D plays a significant role in both the pathogenesis and management of type 1 and type 2 diabetes. Vitamin D deficiency has been shown to predispose individuals to both types of diabetes, with its receptors found in beta cells and immune cells. Deficiency impairs insulin synthesis and secretion and may contribute to the onset of type 2 diabetes[1]. Epidemiological studies have also suggested a link between early-life vitamin D deficiency and the later development of type 1 diabetes [1]. Vitamin D supplementation has been observed to improve serum 25(OH) D levels and reduce insulin resistance, particularly in non-obese individuals, those with a vitamin D deficiency, and Middle Eastern populations. The benefits were more pronounced with high doses of vitamin D administered over a short term[2]. However, a large prospective study found no association between total vitamin D intake and type 2 diabetes, although there was a reduced risk associated with vitamin D intake from supplements and a combined intake of calcium and vitamin D[3]. A systematic review and meta-analysis highlighted that low vitamin D status, calcium, or dairy intake is consistently associated with prevalent type 2 diabetes or metabolic syndrome. Intervention studies suggest that vitamin D and calcium supplementation may prevent type 2 diabetes in high-risk populations, such as those with glucose intolerance[4]. Another study found a positive correlation between 25(OH)D concentration and insulin sensitivity, with hypovitaminosis D associated with insulin resistance and beta cell dysfunction[5]. Cross-sectional analyses have also shown independent associations of serum 25(OH)D concentration with insulin sensitivity and beta cell function among individuals at risk for type 2 diabetes[6]. Furthermore, vitamin D deficiency has been linked to an increased risk of gestational diabetes mellitus (GDM), with meta-analysis indicating a consistent association [7]. Vitamin D's role extends to its indirect influence on carbohydrate and lipid metabolism, potentially decreasing insulin resistance, severity of type 2 diabetes, and metabolic syndrome. However, the evidence from randomized control clinical trials is not conclusive, and further studies are needed to confirm these findings[8].Vitamin D deficiency contributes to insulin resistance and the onset of diabetes by affecting inflammation, cellular calcium and ROS signaling, and epigenetic alterations of diabetes-related genes[9]. Lastly, a systematic review found that higher vitamin D intake and status were associated with a lower risk of developing type 2 diabetes, and vitamin D supplementation improved insulin resistance in patients with glucose intolerance[10]. In summary, the evidence suggests a multifaceted role of vitamin D in diabetes pathogenesis and management, with potential benefits of supplementation in improving insulin sensitivity and reducing the risk of diabetes in certain populations. However, more high-quality research is needed to fully understand the mechanisms and to establish clear guidelines for vitamin D supplementation in the prevention and management of diabetes.

The Role of Vitamin D in Glucose Metabolism

Vitamin D is increasingly recognized for its roles beyond bone health, with growing evidence suggesting its involvement in glucose metabolism and potential implications for cardiovascular risk and diabetes management. Vitamin D status is modestly associated with lower glycemia and insulin resistance, with a slight decrease in these markers for each increase in plasma 25(OH)D levels in children and adolescents[1]. Vitamin D supplementation in healthy men with low vitamin D levels maintained insulin levels and HOMA-IR values, suggesting a role in preventing an increase in insulin resistance[11].Observational studies and meta-analyses indicate an inverse association between vitamin D and calcium intake and the prevalence and incidence of type 2 diabetes, with supplementation potentially beneficial in high-risk populations[12]. Vitamin D may influence insulin sensitivity and secretion, with low levels associated with increased inflammation and insulin resistance, although supplementation results are mixed[13]. The vitamin D endocrine system is involved in glucose homeostasis and insulin release, with genetic variations in the vitamin D receptor (VDR) gene potentially affecting susceptibility to diabetes and its complications [14].

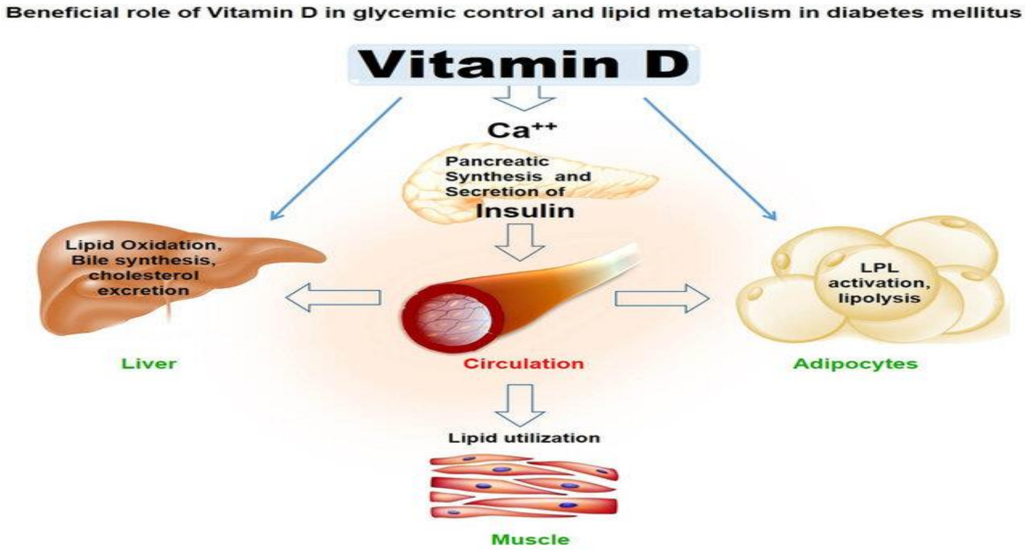

Figure 1:- Schematic role of vitamin D in insulin synthesis and secretion, and lipid metabolism in diabetic patients. Vitamin D directly or indirectly i.e. via calcium signaling enhances insulin synthesis and secretion which has impact on glycemic control in circulation enhance lipoprotein lipase activation that inhibit lipogenesis or increase lipolysis in adipose tissue; lipid utilization in muscles; and enhance lipid oxidation, bile synthesis, and cholesterol excretion by liver.

Vitamin D Deficiency and Its Impact on Diabetes Risk

Vitamin D deficiency has been extensively studied for its potential role in the development and progression of diabetes. The research indicates a complex relationship between vitamin D levels and the risk of both type 1 and type 2 diabetes, as well as the impact of vitamin D supplementation on glycemic control. Vitamin D deficiency is associated with an increased risk of type 2 diabetes, with lower plasma 25-hydroxyvitamin D [25(OH)D] concentrations linked to a higher cumulative incidence of the disease[4]. Deficiency in vitamin D may impair insulin synthesis and secretion, contributing to the development of type 2 diabetes, and vitamin D receptors have been identified in pancreatic beta cells and immune cells[8,15]. Vitamin D supplementation in individuals with prediabetes has been associated with a reduced progression to diabetes and improved insulin resistance and systemic inflammation[16]. In contrast, vitamin D supplementation did not prevent progression from prediabetes to diabetes in subjects without vitamin D deficiency, suggesting that supplementation may be more beneficial in deficient individuals[17]. Epidemiological studies suggest that vitamin D deficiency in early life could be linked to the later onset of type 1 diabetes, and certain polymorphisms within the vitamin D receptor gene are associated with type 1 diabetes in some populations[18]. Vitamin D supplementation in infancy is associated with a reduced risk of type 1 diabetes, indicating a potential preventive role[18].. Randomized controlled trials (RCTs) have shown mixed results, with some reporting moderate effects of vitamin D on glycemic control and insulin resistance in type 2 diabetes patients, while others have failed to demonstrate significant effects on insulin resistance or diabetes incidence [19].

Figure 2: Associations of vitamin D with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome

Therapeutic Potential of Vitamin D in Diabetes Management

Vitamin D has garnered attention for its potential role in the management and prevention of diabetes through its immunomodulatory and anti-inflammatory properties. Research has explored its effects on both type 1 and type 2 diabetes, as well as its influence on various metabolic and immune system functions.Vitamin D supplementation prevents the development of autoimmune diabetes in animal models and may correct defective suppressor function[1]. High doses of vitamin D can improve arterial properties in type 2 diabetic patients without significantly affecting glucose homeostasis parameters[20]. Vitamin D supplementation has been shown to decrease fasting plasma glucose, ketoacidosis, pro-inflammatory cytokines, and HbA1c, while increasing insulin secretion and sensitivity in diabetic rats[21]. Vitamin D's role extends beyond calcium metabolism, potentially serving as a biological inhibitor of inflammatory hyperactivity and offering therapeutic benefits for Th1-mediated autoimmune disorders, including type 1 diabetes[22]. Systematic reviews and meta-analyses indicate that vitamin D supplementation may reduce chronic low-grade inflammation in patients with type 2 diabetes[23]. Dietary vitamin D supplementation is associated with a reduced risk of type 1 diabetes in humans, suggesting a preventive role[16]. Observational studies and clinical trials suggest that vitamin D and calcium supplementation may improve glucose metabolism and have a role in preventing type 2 diabetes, especially in high-risk populations[24]. Clinical trials and molecular studies highlight vitamin D's potential in treating autoimmune diseases due to its immunomodulatory effects[25-26]. The therapeutic potential of vitamin D in diabetes management is supported by evidence of its immunomodulatory effects, ability to improve arterial properties, and potential to reduce inflammation and enhance glucose metabolism. While the benefits of vitamin D supplementation in preventing type 1 diabetes and managing type 2 diabetes are promising, further research is needed to fully understand its role and optimize its use in clinical settings.

Vitamin D Supplementation as a Preventative Strategy for Diabetes

Vitamin D supplementation reduced the incidence of diabetes in NOD mice, an animal model for human autoimmune diabetes, suggesting a potential for preventing type 1 diabetes[1]. Dietary vitamin D supplementation in infancy is associated with a reduced risk of type 1 diabetes, indicating a possible preventive effect[24]. Observational studies suggest that higher vitamin D intake and status are associated with a lower risk of developing type 2 diabetes[15-16].Vitamin D and calcium supplementation may benefit glucose metabolism and could be preventive in populations at high risk for type 2 diabetes, such as those with glucose intolerance8. Vitamin D supplementation improved insulin resistance in patients with baseline glucose intolerance and may lower the risk of type 2 diabetes in prediabetic individuals or those with a certain body mass index (BMI)[27]. Supplementation significantly reduced levels of glycosylated hemoglobin (HbA1c), fasting plasma glucose, and insulin resistance in prediabetics, with the effects influenced by various factors such as age, calcium coadministration, and baseline vitamin D status[18].The effectiveness of vitamin D supplementation may not be universal and could depend on individual baseline characteristics and the supplementation strategy[27].

Outcomes of Vitamin D Intervention in Diabetic Populations

Vitamin D supplementation has been associated with various beneficial outcomes in diabetic and prediabetic populations. These include improvements in arterial stiffness, pregnancy outcomes, insulin resistance, glycemic measures, antioxidant enzyme levels, and wound healing in diabetic foot ulcers. However, the impact on glucose homeostasis parameters is not consistently observed across all studies. Overall, vitamin D appears to play a supportive role in managing diabetes-related health issues, with certain factors influencing the degree of benefit. High doses of vitamin D supplementation were associated with significant decreases in arterial stiffness, as measured by the central aortic augmentation index, in type 2 diabetic patients, although no improvement in glucose homeostasis parameters was observed[20]. Calcium plus vitamin D supplementation in women with gestational diabetes mellitus resulted in decreased rates of caesarean section, maternal hospitalization, and improved newborn outcomes such as reduced cases of macrosomia and hyperbilirubinemia[28]. Observational studies suggest that higher vitamin D intake and status are associated with a reduced risk of developing type 2 diabetes, while vitamin D supplementation may improve insulin resistance in those with glucose intolerance[2]. Vitamin D supplementation in prediabetic overweight/obese women led to significant reductions in fasting blood glucose, post-oral glucose tolerance test glucose levels, hemoglobin A1c, and truncal subcutaneous fat, with some participants reverting to normoglycemia[29]. In Arab adults with prediabetes, vitamin D supplementation increased glutathione peroxidase-1 levels, an antioxidant enzyme, with the effect being more pronounced in males[27].Vitamin D supplementation may improve endothelial dysfunction in type 2 diabetic patients on metformin therapy by reducing inflammation and reactive oxygen species production[30].Diabetic foot ulcer patients receiving vitamin D supplementation showed improved wound healing and metabolic status, including reductions in ulcer dimensions, serum insulin, insulin resistance, and inflammatory markers[31]. Meta-analyses indicate that vitamin D supplementation does not significantly change HbA1c levels in a heterogeneous diabetic population but may reduce fasting glucose in those with poorly controlled diabetes[32]. A meta-analysis of prediabetics showed that vitamin D supplementation significantly reduced levels of HbA1c, fasting plasma glucose, and insulin resistance, with the effects influenced by factors such as age, calcium coadministration, and baseline vitamin D status[1].

Table 1. Clinical trials investigating the association between vitamin D supplementation and risk of diabetes.

Authors, year	Study types	country	Main results	N	Outcomes
Alloubani, et al , 2019[33]	A descriptive, cross-sectional, and correlational design	Saudi Arabia	The likelihood of having a deficiency in vitamin D was greater among the following groups: females (OR″= 2.06, p > .05); those with higher incomes (OR″=‴1.44, p .05); smokers (OR″=‴0.08, p >‴.05); and those who did not have sun exposure (OR″=‴8.50; p > .05). Moreover, physical activity serves as a prognostic indicator for Vitamin D deficiency (OR = 3.8; p > 0.05). Additionally, a reduced consumption of Vitamin D (OR 9.7; p > .05) and Calcium (OR″= 12.2; p > .05) was associated with a greater likelihood of having a Vitamin D deficiency liability by 3.2, 1.9, 1.8, 1.0, and 2.4, respectively, when the BMI, cholesterol, LDL, HDL, and FBS were increased by one unit.	350	Vitamin D Deficiency was widespread among Saudi citizens of all ages, including both males and females. Due to the correlation between vitamin D deficiency and major chronic diseases, it is critical to emphasize the importance of identifying risk factors for vitamin D deficiency screening.
Barbarawi et al ,2020[34]	a meta-analysis of RCTs	USA	The average age (6.7 years) was 63.5 years (SD = 6.7). In comparison to placebo, the RR for vitamin D was 0.96 (95% CI: 0.90-1.03); P = 0.30. The risk ratio for vitamin D supplementation (≥1000 IU/day) in clinical trials involving participants with prediabetes was 0.88 (95% CI: 0.79-0.99) when compared to placebo. On the contrary, the trials that examined lower concentrations using samples from the general population failed to demonstrate any reduction in	46,559	In comparison to a placebo, moderate to high concentrations (1000 IU/day) of vitamin D supplementation significantly decreased the incidence risk of T2DM.

			risk (RR, 1.02; 95% CI, 0.94-1.10; P, interaction by dose = 0.04).		
Yammine et al ,2020[35]	Meta analysis	Lebanon	The average differences after weighting were -9.93 (95% CI = -1.684 to -0.174, I2 = 97.8%, p = 0.01). The foot group had a significantly higher likelihood of having severe vitamin D insufficiency (3.6, 95% CI = 2.940 to 4.415, I2 = 40.9%, p < 0.0001). All of the studies that were considered were high quality. Significantly reduced vitamin D levels are linked to diabetic foot problems	1,644	. Severe vitamin D insufficiency is more common in patients who have diabetes infections or ulcers.
Lu et al, 2018[36]	Observational & meta analysis	China	61% were female, the average (SD) age was 51.4 (10.6) years, and the average (SD) body mass index (BMI) was 23.7 (3.4) kg/m2. With the exception of a previous CVD history, which was a criterion for exclusion in the biochemistry investigation, the initial characteristics of the genotyped participants were comparable to those of the subset with plasma 25(OH)D concentrations. The average plasma concentration of 25(OH)D was found to be 62.1 (20.2) nmol/l, which is in line with previously documented values in populations from China and Europe. Recruited participants had a mean plasma concentration of 25(OH)D that was 57.4 versus 68.4 nmol/l lower in the winter than in the summer; this difference was independent of age, sex, physical activity, and percent body fat.	512,891	The congruent risks of diabetes associated with genetically instrumented and biochemically measured differences in 25(OH)D via synthesis single nucleotide polymorphisms provide evidence that increased 25(OH)D has a preventative effect on diabetes.
Amraei et al , 2018[37]	Meta analysis	Iran	The results of eighteen studies, each examining 26 cases, were presented as means and averages. Among these studies, vitamin D deficiency was linked in twelve of the eighteen cases that examined GDM. The purpose of the present meta-analysis was to ascertain whether a significant disparity exists in the mean vitamin D levels between women who have gestational diabetes and those who do not. The average standard equation difference (SMD) was -2.26 (CI at 95% = -0.39 to -0.14), as predicted by the random effects model. This value suggests that heterogeneity was substantial, as evidenced by the I2 value of 68.8% (p < 0.001).	268	Low levels of 25(OH)D may be regarded as a risk factor during pregnancy, according to this finding. In addition, the results indicated a weak positive correlation between maternal vitamin D deficiency and GDM and suggested that the conclusion reached in a previous meta-analysis be tempered. Our findings indicate that a deficiency in vitamin D may ultimately elevate the risk of developing gestational diabetes. In

					light of the diversity of studies and the heterogeneity of numerous research initiatives.
Ehrampoush et al ,2021 [38]	cross-sectional study	Iran	The participants' mean age was 39.8 ± 10.8, while their mean vitamin D level was 23.1 ± 9.1. 1103 (51.1%) of the participants were male, while 1057 (48.9%) were female. As a collective, each subject exhibited insufficient levels of vitamin D. In contrast, 260 participants had severe vitamin D deficiency, while 845 participants had mild deficiency and 1055 participants had moderate deficiency. Out of all the variables that were examined, only a lack of correlation was observed between smoking and vitamin D deficiency (P ± 0.34). To illustrate, the mean body mass index (BMI) for mild, moderate, and severe deficiencies was a respective 23.77 ± 3.41, 28.98 ± 3.77, and 32.22 ± 3.42 (P < 0.001).	2160	As glycemic indices and insulin resistance, vitamin D level was significantly inversely related to fasting blood glucose, fasting insulin, 2-hour postprandial sugar level, 2-hour postprandial insulin, and HOMA2-IR. Furthermore, it was determined that the examined community exhibits a significant prevalence of vitamin D deficiency, with an outbreak rate of 100%.
Kaya et al ,2018[39]	Cross sectional study	Turkey	It was discovered that patients with vitamin D deficiency had a higher erythrocyte sedimentation rate than those with vitamin D sufficiency (P < 0.001). Furthermore, there was a negative correlation between erythrocyte sedimentation rate and 25-hydroxyvitamin D level (r =?0.265, P < 0.001). Patients who were deficient in vitamin D had higher levels of HbA1c and postprandial glucose than those who were adequate in vitamin D (P = 0.005 and P = 0.019, respectively). An erythrocyte sedimentation rate of 14.5 mm/h had a sensitivity of 70.1% and a specificity of 50.3% in receiver operating curve analysis when used to predict vitamin D deficiency.	294	Vitamin D deficient T2DM patients have a greater erythrocyte sedimentation rate than those with adequate vitamin D. An inverse correlation was observed between the rate of erythrocyte sedimentation and levels of vitamin D.
Bhatt et al, 2018[40]	Cross-sectional population-based study	India	the prevalence of vitamin D deficiency, insufficiency, and sufficiency was 68.6%, 25.9%, and 5.5. Subjects with vitamin D deficiency had substantially higher mean ages (p=0.004), systolic (p=0.05), diastolic (p=0.04) blood pressure, weight (p=0.03), BMI (p=0.04), and FBG (p=0.02) in comparison to those with vitamin D sufficiency or insufficiency. In	797	Asian Indian women who have pre-diabetes exhibit elevated blood glucose levels in correlation with reduced vitamin D levels.

			comparison to the second quintile, the unadjusted mean values of FBG were considerably lower in the fourth (p=0.02) and fifth (p=0.030) quintiles of 25(OH)D levels. In addition, after controlling for age and family income, FBG levels in the first quintile (p=0.012) and second quintile (p=0.003) of 25(OH)D levels, respectively, were significantly higher than in the fourth (p=0.012) and fifth (p=0.018) quintiles.		
Mahmood et al,2018[41]	Comparison	Pakistan	While the majority of participants exhibited decreased VD levels, a mere 9.8% of diabetic patients maintained normal VD levels. Significant differences (p<0.05) were observed in blood glucose and HbA1c levels between groups deficient and adequate in vitamin D, as well as between VD deficient and normal VD. However, no such difference was observed between VD insufficient and normal VD. VD, Ca, and Ph levels did not differ markedly between the good glycemic control group (n=46) and the poor glycemic control group (n=146), as determined by a comparison of biochemical parameters. VD was significantly (p0.05) associated with RBS and HbA1c levels in the group of diabetic patients with good glycemic control and VD deficiency, but not in the group of diabetic patients with poor glycemic control and VD insufficiency.	192	The majority of diabetic patients exhibited inadequate glycemic control. A significant correlation was observed between hypovitamin D and blood glucose and HbA1c levels in patients with glycemic control issues and VD deficiency. Consequently, it might be correlated with the advancement of additional complications.

Challenges and Considerations in Treating Diabetes with Vitamin D

Effectively treating diabetes with vitamin D requires careful attention to dosage, monitoring vitamin D levels, understanding potential interactions, accounting for individual variations, and promoting adherence to the treatment plan. By addressing these challenges and considerations, healthcare professionals can optimize the use of vitamin D in the management of diabetes.

Future Directions in Research on Vitamin D and Diabetes Management

Future research on vitamin D and diabetes management should focus on understanding the underlying mechanisms, establishing optimal dosage and duration, evaluating long-term outcomes, exploring personalized approaches, and investigating combination therapies. By addressing these areas of research, we can advance our knowledge and ultimately improve the effectiveness of vitamin D in the management of diabetes.

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