The role of vitamin D in glycaemic control: a review of randomised controlled trials

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Abstract

Vitamin D deficiency and diabetes mellitus are both global health concerns with increasing prevalence. Recent research suggests a potential link between vitamin D status and the development and progression of various types of diabetes. This review aims to analyse the clinical evidence on the relationship between vitamin D supplementation and glycaemic control across different populations: individuals with prediabetes, type 1 diabetes (T1D), type 2 diabetes (T2D), and gestational diabetes mellitus (GDM). A systematic search of randomised clinical trials (RCTs) published from 2014 to 2024 was conducted in PubMed, Scopus, and Web of Science. Sixteen studies met the inclusion criteria. The findings were mixed. In prediabetes, vitamin D improved serum 25(OH)D levels, but effects on glycaemic parameters were inconsistent. In T1D, supplementation was associated with reduced insulin requirements and improved C-peptide levels, especially in children with vitamin D deficiency. T2D results were variable: some trials reported improvements in HbA1c and HOMA-IR, while others found no significant changes. In GDM, supplementation improved fasting insulin response and reduced adverse pregnancy outcomes. Overall, vitamin D supplementation shows potential benefits in certain contexts, particularly in T1D and GDM. However, heterogeneity in dosage, duration, and baseline characteristics limits the generalisability of findings. Further high-quality RCTs are needed to define optimal regimens and identify subpopulations most likely to benefit.

Keywords: Vitamin D, supplementation, diabetes mellitus, glycaemic control, randomised clinical trials

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Introduction

Diabetes mellitus (DM) encompasses a group of endocrine-metabolic disorders characterised by chronic hyperglycaemia due to insulin deficiency, resistance, or both. It is a major public health concern, with an estimated global prevalence of 537 million adults in 2021, projected to rise to 783 million by 2045.[1] Among the different forms of DM, type 2 diabetes (T2D) accounts for over 95% of cases, largely driven by sedentary lifestyles and obesity.[2] Type 1 diabetes (T1D) and gestational diabetes mellitus (GDM) also represent significant challenges. Vitamin D, a fat-soluble secosteroid hormone obtained through sun exposure, diet, or supplementation, has classically been associated with calcium homeostasis and bone health. However, growing evidence suggests its involvement in glucose metabolism, particularly through its influence on insulin secretion, beta-cell function, and inflammatory processes.[3] Vitamin D receptors (VDRs) are expressed in pancreatic beta cells, and active vitamin D [1,25$(OH)_2$D] may enhance insulin synthesis and secretion by modulating intracellular calcium levels.[4] Observational studies have consistently demonstrated associations between vitamin D deficiency and an increased risk of developing T2D and GDM, as well as poorer glycaemic control in established diabetes.[5-7] However, findings from interventional studies remain inconsistent, possibly due to differences in study design, dosage, baseline vitamin D status, and population characteristics. For example, while some trials reported improvements in glycaemic outcomes after vitamin D supplementation, others—including large-scale randomised trials—failed to demonstrate significant effects.[8-11] These discrepancies highlight the importance of a comprehensive evaluation of randomised clinical trial (RCT) evidence. Accordingly, this review examines RCTs published over the past decade to assess the role of vitamin D supplementation in glyca emic control among populations with prediabetes, T1D, T2D and GDM.

Methods

A literature search was conducted in PubMed, Scopus, and Web of Science databases to identify RCTs published between January 2014 and January 2024. The search was limited to studies conducted in humans, written in English or Spanish. The following Medical Subject Headings (MeSH) terms and keywords were used in various combinations: cholecalciferol, calcitriol, vitamin D, 1 alpha, 25 dihydroxycholecalciferol, and diabetes mellitus. Boolean operators (AND, OR, NOT) were applied to optimise the search strategy. Inclusion criteria were: (i) original RCTs; (ii) studies assessing the effects of vitamin D supplementation in individuals with prediabetes, T1D, T2D, or GDM; and (iii) articles reporting metabolic outcomes such as glycaemic control, insulin secretion or sensitivity, HbA1c, or beta-cell function. Exclusion criteria included: (i) observational studies, reviews, or meta-analyses; (ii) studies conducted in animals; (iii) studies not reporting relevant glycaemic outcomes; and (iv) duplicate publications. Duplicates were removed using Zotero reference management software (Zotero [Computer software]. Corporation for Digital Scholarship,

Roy Rosenzweig Center for History and New Media, Fairfax, Virginia, USA. Available at: https://www.zotero.org). A total of 16 studies met the inclusion criteria and were included for data extraction and qualitative analysis.

The study selection process is summarised in a flow diagram (Figure 1), adapted from PRISMA guidelines.[12]

Data from the included RCTs were independently extracted by two reviewers using a standardised template. For each study, the following variables were collected: authors, year of publication, study population (diabetes status), intervention details (dosage of vitamin D and duration), and primary metabolic outcomes (glycaemic control, HbA1c, insulin secretion or sensitivity, and β-cell function). Any discrepancies between reviewers were resolved through discussion and consensus.

Given the heterogeneity across studies in terms of design, populations, and intervention protocols, a quantitative synthesis (meta-analysis) was not feasible. Instead, a qualitative synthesis was performed. The analysis focused on grouping and narratively describing the findings according to diabetes type (prediabetes, T1D, T2D, GDM), dose and duration of vitamin D supplementation, and reported outcomes. Patterns, consistencies, and divergences between studies were highlighted to provide an integrated overview of the current evidence.

Results

A total of 16 RCTs were included, evaluating the effects of vitamin D supplementation on glycaemic outcomes in populations with prediabetes, T1D, T2D, and GDM. The studies varied in design, vitamin D dosage, intervention duration, and outcome measures.

Vitamin D and prediabetes

Five RCTs investigated the effects of vitamin D supplementation in individuals with prediabetes. Most studies reported significant increases in serum 25(OH)D levels following supplementation, with doses ranging from 4 000 to 88 865 IU/week over 8 weeks to 1 year.[13-17] However, glycaemic outcomes were inconsistent, as shown in Table I. One large-scale study found a reduced risk of progression to diabetes in participants maintaining serum 25(OH) D levels above 100 nmol/L.[14] In contrast, other trials reported no significant improvements in insulin sensitivity, insulin secretion, or glycemic control despite increases in vitamin D status.[15-17]

Vitamin D and Type 1 Diabetes

The role of vitamin D in T1D was assessed in three studies, mainly involving paediatric populations. These trials indicated that supplementation with 3 000 to 6 000 IU/day of cholecalciferol or alfacalcidol for periods ranging from 3 to 12 months led to reductions in daily insulin requirements and increases in C-peptide levels (Table II), suggesting improved beta-cell function.[18-20] In particular, one study highlighted a significant decrease in HbA1c among children with baseline vitamin D deficiency.[19]

Vitamin D and Type 2 Diabetes

Six RCTs evaluated vitamin D supplementation in patients with T2D. Results were mixed, as shown in Table III. Some trials

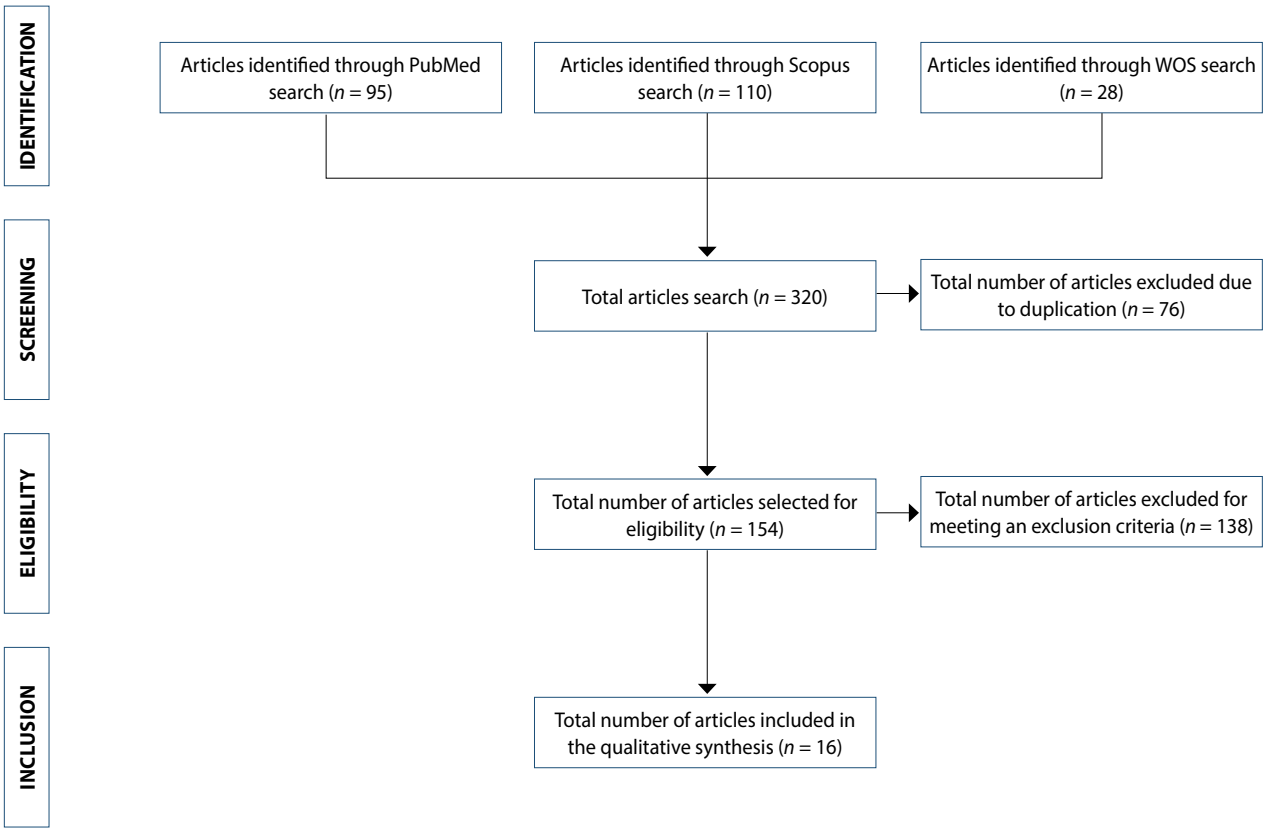

Figure 1: Flow diagram of study selection and inclusion in the qualitative synthesis (adapted from PRISMA 2020)

Table I: Summary of RCTs in prediabetes

Study	Population	Vitamin D Dose	Duration	Main Outcomes
Davidson et al. (2021)	58 prediabetics	35,714 IU/week	1 year	↑ 25(OH)D; no change in glycemic markers
Dawson-Hughes et al. (2020)	1 211 prediabetics	4,000 IU/day	6 months	↓ DM risk with high 25(OH)D
Gagnon et al. (2019)	46 prediabetics	2,000-6,000 IU/day	6 months	No sig. changes in insulin sensitivity
Mousa et al. (2020)	33 overweight adults	4,000 IU/day	16 weeks	No sig. changes in insulin/glucose
Wagner et al. (2018)	21 prediabetics	30,000 IU/week	8 weeks	↑ 25(OH)D; no glycemic benefit

Table II: Summary of RCTs in patients with type 1 diabetes

Study	Population	Vitamin D Dose	Duration	Main Outcomes
Ataie-Jafari et al. (2020)	31 adults	3,000 IU/day	12 months	↓ insulin dose; ↑ C-peptide
Giri et al. (2021)	43 children	6,000 IU/day	3 months	↓ HbA1c in vitamin D-deficient patients
Panjiyar et al. (2019)	42 children	3,000 IU/day	12 months	↓ fasting glucose and HbA1c

Table III: Summary of RCTs in patients with type 2 diabetes

Study	Population	Vitamin D Dose	Duration	Main Outcomes
Jehle et al. (2020)	29 adults	300,000 IU IM	1 dose	↓ HbA1c, HOMA-IR, albuminuria
Krul-Poel et al. (2021)	136 adults	50,000 IU/day	6 months	No sig. change in glycemic markers
Lemieux et al. (2018)	48 adults	5,000 IU/day	6 months	↑ M value and disposition index
Ryu et al. (2020)	79 adults	1,000 IU/day	24 weeks	No change in HbA1c or HOMA-IR
Strobel et al. (2019)	43 adults	1,904 IU/day	6 months	↑ 25OHD; insulin correlated with levels
Jorde et al. (2018)	256 adults	20,000 IU/week	5 years	No difference in DM incidence

Table IV: Summary of RCTs in patients with gestational diabetes

Study	Population	Vitamin D Dose	Duration	Main Outcomes
Asemi et al. (2020)	27 pregnant women	50,000 IU/week	6 months	↓ polyhydramnios and neonatal hyperbilirubinemia
Yeow et al. (2021)	13 pregnant women	4,000 IU/day	6 months	↑ insulin response; ↓ HbA1c

demonstrated improvements in insulin resistance (HOMA-IR), HbA1c, or beta-cell function following supplementation with 1 000–50 000 IU/day or 300 000 IU intramuscularly.[21,22] Other studies, however, did not find significant changes in glycaemic control, even in vitamin D-deficient individuals.[23-25] One large-scale, five-year study reported no effect on the incidence of T2D with 20 000 IU/week supplementation.[26]

Vitamin D and Gestational Diabetes Mellitus

Vitamin D supplementation in the context of GDM was investigated in two clinical trials, as shown in Table IV. Supplementation with 4 000–50 000 IU of vitamin D_3 led to improvements in fasting insulin response and modest reductions in HbA1c.[27,28] Additionally, one of the studies reported fewer adverse pregnancy outcomes, such as polyhydramnios and neonatal hyperbilirubinaemia, among those receiving vitamin D.[27]

Discussion

This review summarises the evidence from RCTs evaluating the effects of vitamin D supplementation in patients with prediabetes, T1D, T2D, and GDM. Overall, findings suggest that while vitamin D supplementation consistently raises serum 25(OH)D levels, its impact on glycaemic outcomes varies across populations and study designs.

In individuals with prediabetes, the majority of studies demonstrated a significant increase in vitamin D status without consistent improvements in insulin sensitivity, insulin secretion, or glycaemic control.[13-17] One large-scale RCT reported a reduced risk of developing diabetes in participants maintaining high serum 25(OH)D levels.[14] However, other trials with similar designs and dosages failed to replicate these effects.[15-17] Variability in baseline vitamin D status, intervention duration, and metabolic phenotype may explain the inconsistent results.

In T1D, particularly in paediatric populations, vitamin D supplementation appears more promising. Several studies observed reduced insulin requirements and preserved C-peptide levels following high-dose supplementation.[18-20] These findings align with mechanistic studies suggesting that vitamin D modulates beta-cell function and immune responses via VDR-mediated pathways.[4] Children with vitamin D deficiency seem to derive the greatest benefit,[19] indicating a potential role for targeted supplementation in this subgroup.

Evidence in T2D is more conflicting. Some studies reported improvements in HbA1c, HOMA-IR, and beta-cell function,[21,22] while others showed no significant changes in glycaemic parameters despite effective correction of vitamin D insufficiency.[23-25] A five-year trial failed to demonstrate any protective effect against

diabetes onset in high-risk individuals.[26] Differences in population characteristics, as well as variability in vitamin D dosage and duration, may contribute to these divergent results. The evidence suggests that while vitamin D may have modest metabolic effects in T2D, it is unlikely to serve as a standalone therapeutic strategy.

In GDM, supplementation was associated with improved insulin response and a modest reduction in HbA1c.[27,28] One study also reported lower rates of polyhydramnios and neonatal hyperbilirubinemia, suggesting broader maternal and neonatal benefits.[27] These findings support the role of vitamin D in pregnancy, where deficiency is prevalent and may contribute to insulin resistance and adverse outcomes.

Despite promising signals, the current body of evidence presents limitations. Heterogeneity across trials—regarding vitamin D formulations, dosing regimens, baseline vitamin D levels, duration, and outcome measures—hampers comparability and limits the ability to draw firm conclusions. Future research should focus on high-quality, well-powered RCTs that target specific subgroups, explore optimal dosing strategies, and include long-term metabolic and clinical outcomes.

Although our review focused exclusively on randomised controlled trials in humans, it is important to acknowledge evidence from animal models that supports the biological plausibility of vitamin D's role in glycaemic regulation. Preclinical studies in diabetic rat models have shown that vitamin D supplementation improves insulin secretion, reduces HbA1c levels, and ameliorates insulin resistance. For example, vitamin D treatment in diabetic rats increased serum insulin and reduced HbA1c, with even greater improvements when combined with glimepiride, nearly restoring insulin levels to those of non-diabetic controls.[29] Similarly, vitamin D supplementation significantly improved both hyperglycaemia and hypoinsulinaemia in streptozotocin-induced diabetic rats.[30] Other investigations demonstrated that vitamin D deficiency impairs pancreatic islet insulin secretion and β-cell function, while supplementation restores secretory capacity through vitamin D receptor (VDR)-mediated pathways.[31,32] These preclinical findings provide important mechanistic context and reinforce the notion that future integrative analyses—including both human and animal data—may enhance understanding of the causal pathways underlying the observed associations.

Since diabetes frequently occurs as part of the metabolic syndrome, future studies should also evaluate whether vitamin D deficiency influences the prevalence of comorbidities such as hypertension, dyslipidaemia, and central obesity. Addressing these broader cardiometabolic endpoints may clarify whether vitamin D supplementation exerts benefits beyond glycaemic control.[33,34]

Conclusions

Vitamin D supplementation effectively improves serum 25(OH) D levels across populations with prediabetes, T1D, T2D, and GDM. However, its impact on glycaemic control varies. The most consistent evidence of benefit is seen in T1D and GDM, where supplementation may improve beta-cell function, insulin response, and pregnancy outcomes. In prediabetes and T2D diabetes, findings are more heterogeneous, with some studies reporting modest metabolic improvements and others showing no significant effects.

Current evidence does not support universal vitamin D supplementation as a primary strategy for glycaemic control in diabetes. Nonetheless, it may serve as a valuable adjunct in individuals with documented deficiency or specific clinical contexts. Future high-quality randomised trials are needed to define optimal dosing, identify responsive subgroups, and establish long-term benefits.

Conflict of interest

The authors declare they have no conflicts of interest that are directly or indirectly related to the research.

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