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Meta-Analysis

Effect of Vitamin D on Regression to Normal Glucose Regulation in Adults With Prediabetes

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Abstract

Meta-analyses of clinical trials have shown that vitamin D lowers the risk of progression from prediabetes to diabetes. Less is known about whether vitamin D promotes regression to normal glucose regulation (NGR). We conducted a systematic review and meta-analysis of clinical trials with vitamin D in adults with prediabetes that have reported on the outcome of regression to NGR.

We searched Medline (through PubMed), Embase, and the trial registry ClinicalTrials.gov from inception to July 3, 2024, for randomized, controlled trials of at least 6 months' duration that reported on the effects of oral vitamin D supplementation on NGR in adults with prediabetes.

The search identified 10 eligible trials, involving 4478 participants. The baseline characteristics of the study cohorts were: mean age range 20 to 74 years, mean body mass index range 24 to 38, mean blood 25-hydroxyvitamin D range 12 to 28 ng/mL. The median study duration range was 0.5 to 5 years. Across trials, 416 of 2253 (18.5%) participants randomly assigned to vitamin D reached NGR vs 312 of 2225 (14.0%) participants randomly assigned to placebo. In all trials, the relative risk of regression to NGR favored the vitamin D group, ranging from 1.09 to 12.6. After combining data, the summary relative risk of regression to NGR for vitamin D vs placebo was 1.27 (95% CI, 1.12-1.45), with no heterogeneity ($I^2 = 1\%$). Sensitivity analyses did not change the result. Participant-level variables were not available, limiting meaningful subgroup analyses.

In conclusion, vitamin D increases the likelihood of regression to normoglycemia in adults with prediabetes.

Key Words: vitamin D, normal glucose regulation, prediabetes, euglycemia

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; D_2, ergocalciferol; D2d, vitamin D and type 2 diabetes study; D_3, cholecalciferol; FG, serum or plasma fasting glucose; HbA_{1c}, glycated hemoglobin A_{1c}; HOMA, homeostatic model assessment; 2hG, serum or plasma glucose 2 hours after a 75-g oral glucose load; NGR, normal glucose regulation; OGTT, 75-g oral glucose tolerance test; RR, relative risk.

Prediabetes, a condition characterized by elevated glycemia that falls below the threshold for diabetes, affects a substantial portion of the world population. In the United States, an estimated 98 million adults aged 18 or older, constituting approximately 38% of the adult population, have prediabetes [1]. Worldwide, the prevalence of impaired glucose tolerance was 9.1% (464 million people) in 2021, with projections indicating an increase to 10% (638 million people) by 2045 [2]. The prediabetes state not only increases the risk of progressing to diabetes but is also linked to an elevated risk of cardiovascular diseases and other complications [3]. Although the most attention has been placed on preventing the progression from prediabetes to diabetes, there is a growing recognition of the benefit of achieving regression to normal glucose regulation (NGR) [4]. Regression to NGR is an important outcome because euglycemia is associated with a lower prevalence of microvascular disease compared to prediabetes, likely due to less long-term exposure to abnormal glucose levels, and because even transient regression to NGR confers a lower risk of developing diabetes [5-7]. These benefits underscore the importance of identifying and implementing effective strategies for achieving this metabolic reversal.

Vitamin D, traditionally known for its role in promoting skeletal health, reduces the risk of progression to diabetes in people with prediabetes based on meta-analyses of randomized controlled clinical trials [8-11]. Based on the evidence, the 2024 Endocrine Society Guideline on Vitamin D for the Prevention of Disease recommends empiric vitamin D in adults with high-risk prediabetes because of its potential to reduce progression to diabetes [12]. Although the effect of vitamin D in reducing the progression to diabetes in adults with prediabetes has been established, less is known about whether vitamin D promotes regression to NGR. To address this gap, we conducted a systematic review and meta-analysis of clinical trials that reported the effect of vitamin D on regression from prediabetes to NGR in adults with prediabetes.

Materials and Methods

The systematic review has been registered with the PROSPERO International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/PROSPERO; registration No. CRD420 20163522). The protocol follows the general guidelines

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provided in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [13].

Data Sources and Searches

We searched MEDLINE (via PubMed), Embase, and the trial registry ClinicalTrials.gov from inception through July 3, 2024, for English-language, randomized, placebo-controlled trials of oral vitamin D supplementation in nonpregnant adults with prediabetes that reported on NGR (Supplementary Appendix, eMethods-1) [14]. We searched for additional publications in personal reference lists and citation sections of recovered articles. We excluded letters, abstracts, and conference proceedings that were not published in full in peer-reviewed journals because discrepancies are common between abstract results and subsequent publication results [15].

Study Selection

Two reviewers (P.K. and A.G.P.) independently screened abstracts according to the inclusion criteria. An abstract was judged relevant if it reported original data from clinical trials in adults with prediabetes, with regression to NGR outcomes for an oral vitamin D intervention of any formulation vs a comparator group. Trials that included broader populations (eg, adults without prediabetes) but reported subgroup analysis specific to people with prediabetes were eligible. We excluded trials with children, pregnant or lactating women, hospitalized patients (including those in long-term care facilities), and patients with end-stage renal disease, diabetes (any type), or HIV at enrollment. We excluded trials using vitamin D–fortified food (eg, yogurt), or a combination of vitamin D and calcium to ensure the ability to isolate the specific effect of vitamin D on the outcome of interest. Trials that lasted less than 6 months were excluded to allow sufficient time for serum 25-hydroxyvitamin D (25[OH]D) levels to plateau and for the natural history of prediabetes to evolve [16-19]. Potentially relevant articles were screened in full text by P.K. and A.G.P., independently. Any discrepancies were resolved by consensus between the two independent reviewers, or in a group conference.

Data Extraction and Quality Assessment

Baseline characteristics and intervention and comparator were extracted at the study level, including whether participants received lifestyle advice. Glycemic eligibility criteria (eg, fasting glucose [FG], glycated hemoglobin A_{1c} [HbA_{1c}], and glucose 2 hours after a 75-g glucose load [2hG]), regression to NGR as defined by each trial, adverse events, and follow-up duration were extracted.

Authors of included manuscripts were not contacted for additional study details. For each trial, we assessed the risk of bias per the revised Cochrane risk of bias tool (RoB 2) [20].

Data Synthesis and Analysis

The primary outcome was regression to NGR as defined by each study (binary outcome), which we evaluated as a relative risk (RR). Data for the longest available follow-up time for each trial were used in the analysis. We used the I^2 statistic to quantify the degree of heterogeneity among trials in each meta-analysis [21]. We conducted sensitivity analyses that were not limited by ecological fallacy to explore heterogeneity between comparable trials [22, 23]. Two studies provided dual definitions of NGR, and a sensitivity analysis was performed using the alternate definitions for these two trials [24, 25]. Other sensitivity analyses included trials with an average follow-up duration of greater or equal to 1 year vs less than 1 year, after excluding trials with a moderate to high risk of bias, after excluding trials that did not provide a detailed definition of NGR, and after excluding the trial that used eldecalcitol as the intervention [26]. We did not perform sensitivity analyses by baseline blood 25(OH)D or vitamin D dose because there is no universally agreed-on definition of "high" vs "low" serum 25(OH)D level or vitamin D dose. We conducted meta-analyses for adverse events. We used the funnel plot approach to assess for publication bias [27] and the trim and fill method to impute missing studies [28]. We used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) methodology to assess the quality of evidence based on factors such as study design, risk of bias, inconsistency, indirectness, and imprecision [29].

Results

Search Results

The literature searches yielded 4590 unique citations between PubMed and Embase and 280 from ClinicalTrials.gov. Of these, 63 full-text articles were screened. The eFigure-1 in the Supplementary Appendix [14] summarizes the search results, and Table 1 summarizes the characteristics of the 10 trials that met the eligibility criteria [24-26, 30-36].

Participant Characteristics and Description of Interventions

The 10 trials involved 4478 participants (see Table 1). The baseline characteristics of the study populations were: 47% women, mean age range 20 to 74 years, mean body mass index (BMI) range 24 to 38, mean blood range 25(OH)D 12 to 28 ng/mL. The median study duration range was 0.5 to 5 years. Vitamin D (cholecalciferol or ergocalciferol) dosages ranged from 842 to 12 695 IU daily equivalent. The estimated weighted average for all trials combined was approximately 4300 IU daily equivalent.

Three trials were specifically designed and powered to reduce the incidence of diabetes as the primary outcome (see Table 1) [24, 26, 30]. In the vitamin D and type 2 diabetes (D2d) study, which tested 4000 IU of vitamin D_3 daily vs placebo in 2423 participants, 2 different definitions of NGR were used [24]. When NGR was defined as having both FG and 2hG load in the normal range (<100 mg/dL [5.6 mmol/L] and <140 mg/dL [7.8 mmol/L], respectively) regardless of HbA_{1c}, 8.7% of participants in the vitamin D vs 6.0% in the placebo group had regressed to NGR at the last visit (RR for vitamin D 1.45; 95% CI, 1.06-1.97) (see Fig. 1). When NGR was defined as 2 or 3 American Diabetes Association glycemic criteria in the normal range (FG <100 mg/dL [5.6 mmol/L], HbA_{1c} < 5.7% (39 mmol/mol) or 2hG <140 mg/dL) and none in the diabetes range, 12.4% of participants in the vitamin D vs 9.5% in the placebo group had regressed to NGR at the last visit over a median follow-up of 2.5 years (RR for vitamin D 1.31; 95% CI, 1.02-1.70). In the Trømso study, which tested 20 000 IU of vitamin D_3 weekly vs placebo in 511 participants, NGR was defined as having both FG and 2hG in the normal range (<108 mg/dL [6 mmol/L] and <140 mg/dL, respectively) regardless of

Table 1 . Characteristics of included trials, including participants characteristics at baseline

First author, publication y (country, sites)	Recruitment period	Prediabetes definition and key eligibility criteria	Mean age or range, y	Men, %	Race; ethnicity, %	Mean BMI	Mean 25(OH)D, ng/mL	Study duration	Intervention vs control (No. of participants)	Vitamin D use allowed outside trial	Primary outcome(s)	Normal glucose regulation definition
Davidson, 2013 (US, 1 site)	March 2009 to January 2012	FG 110-125 mg/dL or 2hG 140-199 mg/dL and 25(OH)D < 30 ng/mL	52	33	Hispanic, 87; Black, 13	38	22	Up to 1 y	Treat-to-target 25(OH)D 65-90 ng/mL, mean D_3 88 865 IU weekly (~12 695 IU daily) (n = 56) vs placebo (n = 53)	Allowed to continue and encouraged not to change	OGTT-based insulin sensitivity and secretion	Final 2hG <140 mg/dL
Dutta, 2014 (Eastern India, not reported)	August 2009 to January 2013	FG 100-125 mg/dL and/or 2hG 140-199 mg/dL and 25(OH)D < 30 ng/mL	47	41	Not reported	26	17	Mean 2.3 y	D_3 60 000 IU weekly (~8571 IU daily) for 8 wk, then 60 000 IU monthly (~2000 IU daily) (n = 68) vs no treatment (n = 57); all received calcium 500 mg daily	Not reported	New-onset diabetes, normal glucose regulation	Final FG <100 mg/dL and 2hG <140 mg/dL
Barengolts, 2015 (US, 1 site)	May 2011 to October 2013	FG 95-125 mg/dL and/or HbA_{1c} 5.7-6.9%), and 25(OH)D 5-29 ng/mL and prevalent medical problems	59	100	Black, 100	32	14	Up to 1 y	D_2 50 000 IU weekly (~7143 IU daily) adjusted to achieve 25(OH)D 40-100 ng/mL (n = 103) vs placebo (n = 102)	All received D_3 400 IU daily and advised to maintain usual diet	OGTT-based insulin sensitivity	Final FG <100 mg/dL or 2hG <140 mg/dL
Jorde, 2016 (Norway, 1 site)	March 2008 to March 2015	FG 108-124 mg/dL and/or 2hG 140-198 mg/dL	62	61	Not reported	30	24	Up to 5 y	D_3 20 000 IU weekly (~2857 IU daily) (n = 256) vs placebo (n = 255)	≤400 IU daily from nondietary sources	New-onset diabetes	Final FG FG <108 mg/dL and 2hG <140 mg/dL
Niroomand, 2019 (Iran, 3 sites)	July 2015 to November 2017	FG 100-125 mg/dL with/without 2hG 140-199 mg/dL and 25(OH)D < 30 ng/mL	47	23	Not reported	32	13	Up to 6 mo	D_3 50 000 IU weekly (~7143 IU daily) for 3 mo, then monthly (n = 81) vs placebo (n = 81)	Allowed to continue current supplements	HOMA-based insulin sensitivity	Final FG <100 mg/dL and 2-hG <140 mg/dL
Pittas, 2019 (USA, 22 sites)	October 2013 to December 2016	Two or 3 glycemic criteria (FG 100-125 mg/dL, 2hG 140-199 mg/dL, (HbA_{1c} 5.7-6.4%)	60	55	White, 67; Black,25; Asian, 5; Hispanic (any race), 9	31	28	Up to 5 y (event-driven)	D_3 4000 IU daily (n = 1211) vs placebo (n = 1212)	≤1000 IU daily from nondietary sources	New-onset diabetes	Definition 1: final FG <100 mg/dL and 2hG <140 mg/dL Definition 2: first occurrence of at least 2 criteria (FG, 2hG, HbA_{1c}) in normal range and none in diabetes range
Bhatt, 2020 (Northern India, 2 sites)	June 2015 to December 2018	FG 100-125 mg/dL or 2hG 140-199 mg/dL and 25(OH)D < 20 ng/mL	20-60	0	Asian Indian, 100	30	12	Up to 18 mo	D_3 60 000 IU weekly (~8571 IU daily) for 8 wk, repeated as needed to avoid "vitamin D deficiency," then 200 IU daily (n = 61)	No vitamin D allowed	New-onset diabetes	Definition 1: 2hG <140 mg/dL Definition 2: final FG <100 mg/dL

(*continued*)

Table 1 Continued

First author, publication y (country, sites)	Recruitment period	Prediabetes definition and key eligibility criteria	Mean age or range, y	Men, %	Race; ethnicity, %	Mean BMI	Mean 25(OH)D, ng/mL	Study duration	Intervention vs control (No. of participants)	Vitamin D use allowed outside trial	Primary outcome(s)	Normal glucose regulation definition
									vs placebo (n = 60); all received calcium carbonate daily			
Misra, 2021 (Northern India, NR)	February 2013 to December 2017	FG 100-125 mg/dL or 2hG 140-199 mg/dL and 25(OH)D < 30 ng/mL	47	0	Asian Indian, 100	Not reported	23	Up to 2 y	D_3 60 000 IU weekly (~8571 IU daily) for 8 wk, repeated as needed to avoid "vitamin D deficiency," (n = 67) then 200 IU daily vs placebo (n = 65)	No vitamin D allowed	New-onset diabetes	"Euglycemia" without specific criteria provided
Kawahara, 2022 (Japan, 3)	June 2013 to August 2019	2hG 140-199 mg/dL	61	56	Japanese, 100	24	21	Up to 3 y	Eldecalcitol 0.75 μg daily (n = 630) vs placebo (n = 626)	No vitamin D allowed	New-onset diabetes	Final FG <110 mg/dL and 2hG <140 mg/dL and HbA1c < 6.5%
Zaromytidou, 2022 (Greece, 1)	October 2017 to February 2019	FG 100-125 mg/dL, 2hG 140-199 mg/dL or HbA_{1c} 5.7-6.4%	74	NR	White, 100	30	20	Up to 1 y	D_3 25 000 IU weekly (~3571 IU daily) (n = 45) vs no treatment (n = 45)	Not reported	Change in glycemia (FG, 2hG, HbA_{1c})	"Normoglycemia" without specific criteria provided

All trials excluded participants with a history of preexisting diabetes; the study by Barengolts et al [33] allowed participants who were diagnosed with diabetes at screening to enter the study. Eldecalcitol is a synthetic analogue of calcitriol (1,25-dihydroxyvitamin D), the active form of vitamin D.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D_3; BMI, body mass index; D_2, ergocalciferol; D_3, cholecalciferol; FG, serum or plasma fasting glucose; HbA_{1c}, glycated hemoglobin A_{1c}; HOMA, homeostatic model assessment; 2hG, serum or plasma glucose 2 hours after a 75-g oral glucose load; OGTT, 75-g oral glucose tolerance test.

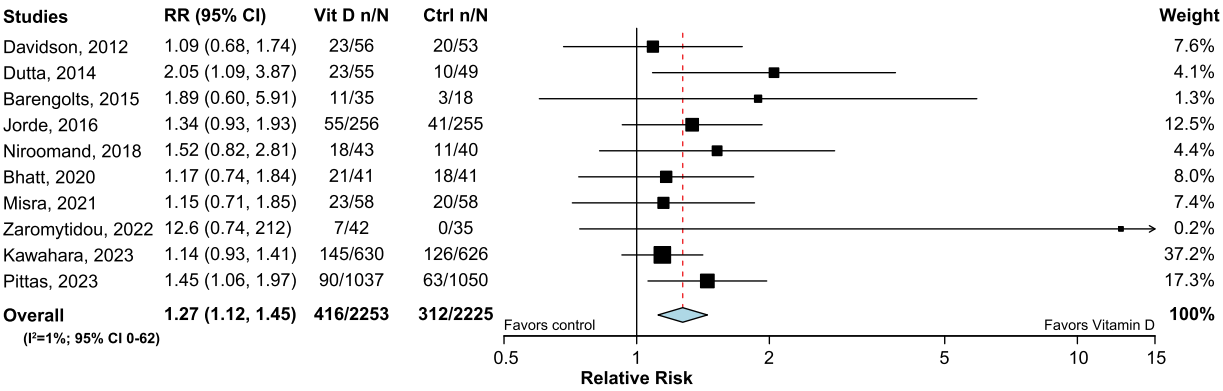

Figure 1. Regression from prediabetes to normal glucose regulation.

Abbreviations: CI, confidence interval; Ctrl, control; RR, relative risk; Vit D, vitamin D.

HbA_{1c} [30]. By the end of the study, 21.5% of participants in the vitamin D vs 16.1% in the placebo group had achieved NGR (RR 1.34; 95% CI, 0.93-1.93) (see Fig. 1). In the DPVD study, which tested 0.75 mcg of eldecalcitol vs placebo in 1256 participants, NGR was defined as meeting all 3 glycemic criteria (FG <110 mg/dL [6.1 mmol/L]), HbA_{1c} < 6.5% (48 mmol/mol), and 2hG <140 mg/dL) or both fasting glucose less than 100 mg/dL and HbA_{1c} less than 5.7%. By the end of the study, 23.0% of participants in the eldecalcitol and 20.1% in the placebo group had achieved NGR (hazard ratio 1.14; 95% CI, 0.93-1.41) (see Fig. 1) [26].

In addition to the 3 diabetes prevention trials, 7 other trials have reported on the effect of vitamin D on regression to NGR in people with prediabetes [25, 31-36] (see Fig. 1). In a 1-year trial in the United States among 109 adults with prediabetes and blood 25(OH)D levels below 30 ng/mL (mean 22 ng/mL), vitamin D_3 at a mean dose of 88 865 IU weekly in a treat-to-target approach resulted in 41% of participants in the vitamin D group vs 38% in the placebo group reaching NGR, defined as 2hG less than 140 mg/dL [31]. In an open-label trial in Eastern India among 125 adults with prediabetes and blood 25(OH)D levels below 30 ng/mL (mean 17 ng/mL), 60 000 IU weekly of vitamin D_3 for 8 weeks, then monthly for 2 years improved the likelihood of reaching NGR, defined as FG less than 100 mg/dL and 2hPG less than 140 mg/dL (42% of participants in the vitamin D group vs 20% in the placebo group) [32]. In a 1-year trial in the United States among 205 Black men with prediabetes or early diabetes on no medications and blood 25(OH)D levels below 30 ng/mL (mean 14 ng/mL), vitamin D_2 at 50 000 IU weekly resulted in 32% of participants in the vitamin D group vs 8% the placebo group reaching NGR, defined as FG less than 100 mg/dL and 2hPG less than 140 mg/dL [33]. In a 6-month trial in Iran among 162 adults with prediabetes and blood 25(OH)D levels below 30 ng/mL (mean 13 ng/mL), vitamin D_3 at 50 000 IU weekly resulted in 56% of participants in vitamin D vs 32% for placebo reaching NGR, defined as FG less than 100 mg/dL and 2hPG less than 140 mg/dL [34]. In an open-label 78-week trial among 121 overweight/obese Asian Indian women with prediabetes and blood 25(OH)D levels below 20 ng/mL (mean 12 ng/mL), vitamin D_3 at 60 000 IU weekly in a treat-to-target approach improved the likelihood of normoglycemia (51% for vitamin D vs 44% for placebo based on 2hG <140 mg/dL; 59% for vitamin D vs 29% for placebo based on FG <100 mg/dL) [25]. In a 2-year community-based trial in Northern India among 132 rural women with prediabetes and blood 25(OH)D levels below 30 ng/mL (mean 23 ng/mL), vitamin D_3 at 60 000 IU weekly in a treat-to-target approach resulted in more women reaching normoglycemia (40% for vitamin D vs 34% for placebo) [36]. In a 1-year trial in Greece among 90 adults with prediabetes and mean blood 25(OH)D levels of 20 ng/mL, vitamin D_3 at 25 000 IU weekly increased the likelihood of return to euglycemia (17% for vitamin D vs 0% for placebo) [35]. In the last two trials, the definitions of normoglycemia and euglycemia were not provided.

There was variability among trials in how participants were encouraged to follow the recommended lifestyle-based advice for diabetes prevention (Supplementary Appendix, eMethods-2) [14]. For example, the D2d study developed written Diabetes Prevention Program–based diabetes prevention material and held twice-a-year participant meetings focusing on traditional, lifestyle-based approaches to prevent diabetes [17]. In the study by Barengolts et al [33], participants were advised to maintain their diet and physical activity. The level of detail reported for recommended lifestyle interventions varied from study to study.

Methodological Quality

Six trials were assessed as being at low risk for bias [24-26, 30, 33, 35], 1 trial had some concerns in at least 1 domain [31], and 3 trials were at high risk for bias in at least 1 domain [32, 34, 36] (Supplementary Appendix, eFigure-2) [14].

Data Synthesis

After combining data from the 10 included trials, 416 out of 2253 (18.5%) participants in the vitamin D groups reached NGR, compared to 312 out of 2225 (14.0%) participants in the placebo group. In all trials, the RR of regression to NGR favored the vitamin D group, ranging from 1.09 to 12.6. Overall, participants in the vitamin D group were 27% more likely to regress to NGR than those in the placebo (summary RR of regression, 1.27 [95% CI, 1.12-1.45] for vitamin D vs placebo). The estimated absolute effect size was 44 more people per 1000 would regress to NGR (range, 23 more to 66 more) with vitamin D supplementation. There was no heterogeneity ($I^2 = 1\%$).

When using the GRADE methodology to assess the quality of evidence, there were no concerns in any category (study design, risk of bias, inconsistency, indirectness, and imprecision),

and the quality of the evidence for the summary result was rated as high, that is, ⊕⊕⊕⊕ (Supplemental Appendix, eMethods-4) [14].

When using the funnel plot to assess for publication bias, the *P* value for asymmetry was .025, per the Egger test for small-study effects [27]. The trim and fill method (ie, imputing missing studies on the "negative" side of the funnel) [28] did not change the result: The summary RR was 1.27 (1.12-1.45), and with imputed studies, the RR was 1.22 (1.08-1.38) (Supplementary Appendix, eFigure-3) [14].

Sensitivity Analyses

Two trials reported two different definitions of NGR [24, 25]. For the primary analysis, we used the data from the most common definitions of NGR (FG <100 mg/dL and 2hG <140 mg/dL in the D2d study [24], and 2hG <140 mg/dL in the study by Bhatt et al [25]). In sensitivity analyses using the other definitions, the result did not change (summary RR of regression, 1.26 [95% CI, 1.12-1.42] for vitamin D vs placebo).

Among the 6 trials with more than 1-year duration, the RR for regression to NGR was 1.22 (95% CI, 1.06-1.41) for vitamin D vs placebo. Among the remaining 4 trials with 1-year or less duration, the RR for regression to NGR was 1.26 (95% CI, 0.87-1.84) for vitamin D vs placebo. After removing 4 studies assessed at moderate or high risk for bias, the RR for regression to NGR was 1.22 (95% CI, 1.05-1.42) for vitamin D vs placebo. After removing 2 studies that did not provide a specific definition of NGR [35, 36], the RR for regression to NGR was 1.22 (95% CI, 1.06-1.40) for vitamin D vs placebo. Finally, after removing the DPVD study that tested eldecalcitol, the RR was 1.36 (95% CI, 1.15-1.60).

Adverse Events

Most trials did not provide details about adverse events. Six trials reported rates of hypercalcemia [25, 26, 30, 31, 33, 37] (Supplementary Appendix, eMethods-3) [14]. After combining data from these trials, the RR for incident hypercalcemia (restricted to trials with >0 events) was 2.05 [95% CI, 0.84-4.99]. Four trials reported serum calcium levels at the end of the trial [25, 30, 34, 36]. None of the trials reported statistically significant elevations in serum calcium with vitamin D vs placebo.

Discussion

Summary of Findings

This systematic review and meta-analysis found that vitamin D increases the likelihood of regression to NGR in adults with prediabetes by 27% compared to those in the control group, without heterogeneity among trials. The result was robust in sensitivity analyses accounting for variability in NGR definitions, study duration, risk of bias, and type of vitamin D formulation.

Comparison With Existing Literature

While it is well documented that vitamin D reduces the risk of progression to diabetes in adults with prediabetes [8-12], its effect on regression to euglycemia has been less extensively studied. Our findings align with other studies that have explored the effect of vitamin D on regression to NGR in adults with prediabetes. Zhang et al [11] conducted a meta-analysis of 5 trials involving 1080 participants with prediabetes [30-34] and reported a 48% increased likelihood of regression to NGR with vitamin D. Pittas et al combined individual participant data from the 3 vitamin D and diabetes prevention trials among adults with prediabetes [17, 26, 30]. During a median follow-up of 3.0 years, participants in the vitamin D group (cholecalciferol or eldecalcitol combined) were 30% more likely to have regressed to NGR at the last study visit than those in the placebo group [8]. Our meta-analysis focuses explicitly on the outcome of NGR. It includes a more extensive set of data, comprising 10 trials and 4478 participants, compared to previous analyses with fewer trials and participants, and provides robust evidence supporting the benefit of vitamin D on regression to NGR.

Safety

Although there was a trend toward a higher risk of hypercalcemia in the vitamin D group compared to the placebo, this result was not statistically significant, and the overall number of events was very low (0.7% vs 0.3% in the vitamin D vs control, respectively). No trials reported elevated serum calcium levels with vitamin D compared to control. In the D2d study —the largest vitamin D and type 2 diabetes prevention trial —adverse events were overall less frequent in participants randomly assigned to vitamin D [38]. These results suggest that vitamin D is a relatively safe intervention to improve glycemic outcomes in adults with prediabetes.

Clinical and Public Health Implications

The potential of vitamin D in promoting regression to NGR offers a valuable addition to current diabetes prevention strategies. Vitamin D is cost-effective, low-burden, and has a favorable safety profile. With the projected rise in cases of impaired glucose tolerance and impaired fasting glucose globally, particularly in low-income countries [2], vitamin D could serve as an accessible intervention to mitigate the global diabetes burden. The positive outcomes of regression to NGR with vitamin D in the included trials were observed alongside participants receiving more-than-average lifestyle-based interventions. Therefore, it is crucial to recognize that vitamin D should complement, not replace, lifestyle changes for diabetes prevention.

Limitations

A few limitations warrant consideration. The included trials were not specifically designed to assess NGR as a primary outcome since diabetes prevention trials typically focus on preventing progression to diabetes, a metabolic state with well-established adverse clinical consequences. However, emerging evidence suggests that reversal to NGR decreases the risk of developing diabetes, vascular complications, albuminuria, and microvascular integrity [5, 6], highlighting the importance of identifying and implementing effective strategies for achieving this metabolic reversal. The definitions of NGR varied across trials; however, the relative risk of regression to NGR favored the vitamin D group in all trials. Despite these limitations, the consistency of the findings (heterogeneity metric $I^2 = 1$) underscores the potential of vitamin D as an effective intervention for achieving NGR.

Conclusion

When evaluating the overall benefit of vitamin D in individuals with prediabetes, the advantage of regression to normoglycemia

should be considered alongside its well-established role in reducing the risk of progression to diabetes. Future research should explore higher doses of vitamin D and employ continuous glucose monitoring to capture time-in-normoglycemia, which provides a holistic measure of glycemic status, free from the typical fluctuations seen with conventional glycemic measures and less influenced by variables such as race or anemia.

Acknowledgments

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Author Contributions

P.M.K and A.G.P. researched data, wrote the first draft of the manuscript, and reviewed and edited the final draft. E.M.B. performed the data search and the statistical analysis and reviewed and edited the manuscript.

Disclosures

There are no conflicts of interest.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

Prior Presentation

This work was presented at ENDO 2024 on June 2, 2024.

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