

Effect of Vitamin D₃ Supplementation on Improving Glucose Homeostasis and Preventing Diabetes: A Systematic Review and Meta-Analysis

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Context: Observational studies report consistent associations between low vitamin D concentration and increased glycemia and risk of type 2 diabetes, but results of randomized controlled trials (RCTs) are mixed.

Objective: To systematically review RCTs that report on the effects of vitamin D supplementation on glucose homeostasis or diabetes prevention.

Data Sources: MEDLINE, EMBASE, SCOPUS, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment, and Science Citation Index from inception to June 2013.

Study Selection: Trials that compared vitamin D₃ supplementation with placebo or a non-vitamin D supplement in adults with normal glucose tolerance, prediabetes, or type 2 diabetes.

Data Extraction and Synthesis: Two reviewers collected data and assessed trial quality using the Cochrane Risk of Bias tool. Random effects models were used to estimate mean differences (MD) and odds ratios (OR). The main outcomes of interest were HOMA-IR, HOMA-B, hemoglobin A1c levels, fasting blood glucose, incident diabetes, and adverse events.

Data Synthesis: Thirty-five trials (43,407 patients) with variable risk of bias were included. Vitamin D had no significant effects on insulin resistance (HOMA-IR: MD, -0.04; 95%CI, -0.30 to 0.22, I²=45%), insulin secretion (HOMA-B: MD, 1.64; 95%CI, -25.94 to 29.22, I²=40%), or A1c (MD, -0.05%; 95%CI, -0.12 to 0.03, I²=55%) compared with controls. Four RCTs reported on progression to new diabetes and found no effect of vitamin D (OR, 1.02; 95%CI, 0.94 to 1.10, I²=0%). Adverse events were rare, and there was no evidence of publication bias.

Conclusions: Evidence from available trials shows no effect of vitamin D₃ supplementation on glucose homeostasis or diabetes prevention. Definitive conclusions may be limited in the context of the moderate degree of heterogeneity, variable risk of bias, and short-term follow-up duration of the available evidence to date.

Vitamin D plays a key role in calcium metabolism and bone health. Low levels of blood 25-hydroxyvitamin D (25[OH]D) are associated with osteomalacia, rick-

ets, reduced bone mineral density (BMD), and increased risk of fractures. Supplementation of vitamin D is known to reduce the risk of major osteoporotic fracture in older

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Abbreviations:

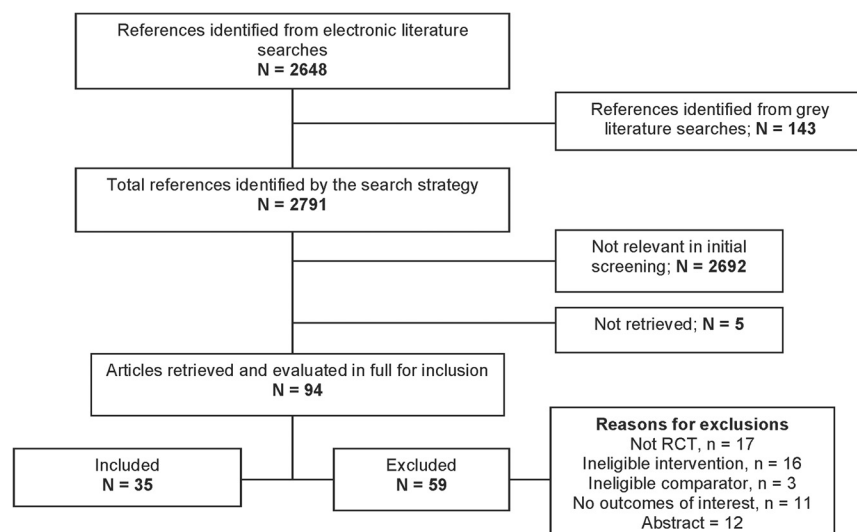


Figure 1. Flow Diagram of Study Retrieval and Selection

adults, (1) although the target blood 25OHD level remains controversial.

Beyond skeletal health, vitamin D has also been associated with several common diseases, including type 2 diabetes. It has been observed that people with prediabetes and established diabetes have lower blood 25[OH]D concentrations than patients with normal glucose tolerance (2, 3). Furthermore, in longitudinal observational studies, higher levels of 25[OH]D are associated with lower rates of incident diabetes (4, 5). In contrast to the generally accepted benefits of vitamin D on bone health, the evidence for claims related to glycemic control and diabetes prevention is largely based on observational studies. Such studies may be limited by selection bias and potential confounding that cannot be adequately accounted for by non-randomized study designs.

Numerous randomized controlled trials (RCTs) have been conducted to investigate whether vitamin D supplementation has a causal effect on glucose homeostasis and incident diabetes. Recent systematic reviews of RCTs concluded that there was insufficient evidence to recommend the use of vitamin D for improving glycemic control and preventing diabetes (2, 6, 7). Several RCTs have been published since those reviews were conducted. Therefore, we undertook a systematic review to provide an updated analysis of the evidence from RCTs on the effects of vitamin D supplementation on glucose homeostasis for patients with normal glucose tolerance, prediabetes, and established type 2 diabetes. Furthermore, we set out to examine whether vitamin D supplementation is effective in preventing progression to diabetes in those with and without prediabetes.

Materials and Methods

We conducted a systematic review of the literature using a prespecified research protocol. Our methods for identifying, selecting, evaluating, and synthesizing the evidence are described below.

Literature Search

A research librarian conducted a systematic search of the literature using the following electronic databases from inception to June 2013: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment, Cochrane Central Register of Controlled Trials, Science Citation Index Expanded, Conference Proceedings Citation Index–Science, and Scopus. We

searched “Epub ahead of print” and “in process” records in PubMed, ClinicalTrials.gov, and the International Clinical Trials Registry Platform to identify studies in progress. The searches were restricted to English language articles due to lack of translation resources. We used a combination of controlled vocabulary and key words related to vitamin D and diabetes. **Supplement 1** provides the MEDLINE search terms, which were adapted for the remaining databases.

In addition, we searched conference abstracts from the Canadian Diabetes Association, American Diabetes Association, European Association of the Study of Diabetes, and the International Diabetes Federation back to 2010. We identified abstracts through BIOSIS Previews, scanned the reference lists of systematic reviews and included studies, and contacted experts in the field who had conducted trials in this area to identify any additional trials.

Study Selection

Randomized controlled trials examining the effects of vitamin D₃ (cholecalciferol) supplementation with or without calcium compared with placebo or other nonvitamin D supplementation in adults without known diabetes, with prediabetes, or with established type 2 diabetes were considered eligible for inclusion in the review. Trials examining active or synthetic vitamin D formulations or enrolling patients with type 1 or gestational diabetes were excluded. We excluded trials with ergocalciferol (D₂) to increase the external validity of results, as vitamin D₃ is the most commonly consumed vitamin D form. Eligible studies must have reported at least one of the following coprimary outcomes of interest as defined by the investigators: insulin sensitivity and insulin secretion by homeostasis model assessment (HOMA-IR or -B, respectively), hemoglobin A1c, fasting blood glucose, or incident diabetes. We did not include trials that report on complicated measures of glucose homeostasis (eg, clamp) because the heterogeneity of these methods does not permit meta-analyses and to maximize the clinical relevance of the findings.

Initially, one reviewer screened titles, keywords, and abstracts to exclude studies that did not meet broad relevance cri-

teria. Two independent reviewers assessed the full publications of studies that were identified as potentially relevant or unclear using a standardized assessment form. Reviewers resolved disagreements by consensus and third-party adjudication.

Quality Assessment

Two reviewers independently assessed the methodological quality of the RCTs using the Cochrane Collaboration Risk of Bias tool, (8) which consists of seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other sources of bias. Discrepancies were resolved through consensus and third party adjudication.

Data Extraction and Analysis

We extracted study and patient characteristics, inclusion and exclusion criteria, interventions, and the following outcomes: insulin sensitivity, insulin secretion, hemoglobin A1c, fasting blood glucose, incident diabetes, blood 25[OH]D, parathyroid hormone, and adverse events (hypercalcemia, nephrolithiasis, hypercalciuria, fracture, death, and “other” serious adverse events). One reviewer extracted data using a standardized form, and a second reviewer verified the data for accuracy and completeness.

We summarized study findings qualitatively and pooled study results in a meta-analysis using random effects models when the populations, interventions, and outcomes were comparable. For dichotomous outcomes, we calculated odds ratios (OR) using the Mantel-Haenszel method, and for continuous variables, we calculated weighted mean differences (MD) using the inverse variance method.

We based the meta-analysis on changes from baseline when the mean and standard deviations of the change scores were reported; otherwise, we compared final values. Whenever provided, we used intention-to-treat data in the analyses. When two or more doses of vitamin D were examined in the same study, we compared data from the highest dose with no vitamin D. We pooled studies that used placebo, calcium, or vitamin C as “no vitamin D” controls; vitamin C is known to have no effect on our outcomes of interest (9). We included outcomes only if quantitative data were reported or could be derived from graphs. Means and standard deviations of change or final scores were required for data to be included in meta-analysis; we contacted the corresponding authors to request these data when not reported in the article.

For all outcomes, we analyzed the data based on baseline glucose tolerance classified as: normal glucose tolerance, prediabetes, and type 2 diabetes. We considered impaired fasting glucose, impaired glucose tolerance, and early diabetes all to be “prediabetes.” To explore subgroup-treatment interactions, we planned a priori subgroup analyses for HOMA–insulin resistance (HOMA–IR), A1c, and progression to diabetes based on baseline 25[OH]D levels (<20 ng/mL vs. ≥20 ng/mL, or as defined by author), dose of vitamin D (<2000 IU/d vs. ≥2000 IU/d), body mass index (BMI) (<25 vs. 25 to < 30 vs. >30), calcium supplementation (yes vs. no), and risk of bias (low vs. unclear vs. high).

For all estimates, we computed the 95% confidence intervals (CIs). We quantified statistical heterogeneity using the I-squared (I^2) statistic, and considered heterogeneity as low ($\leq 25\%$), moderate ($>25\%$ – 50%), or high ($>50\%$), although we did not pre-

specify any degree of heterogeneity that would preclude meta-analytic pooling. Publication bias was assessed through visual inspection of funnel plots. RevMan software version 5.2 was used to perform meta-analyses (10).

Results

We identified a total of 2791 studies, of which 35 RCTs (11–45) met our eligibility criteria and were included in the systematic review (Figure 1). A list of the excluded studies and the reasons for their exclusion is available from the authors by request. A summary of the characteristics of the included studies is provided in Table 1. Briefly, the RCTs were published between 1984 and 2013, with the majority published within the last three years (median, 2011; interquartile range (IQR), 2010 to 2012). Patients with normal glucose tolerance, prediabetes, and type 2 diabetes were included in 18, 4, and 11 RCTs, respectively. Two RCTs included a mixed population of patients with normal and impaired glucose tolerance. The median dose of vitamin D supplementation was 3332 IU/d (IQR, 1000 to 5536). Follow-up duration ranged from 4 weeks to 7 years (median, 16 weeks; IQR: 12 weeks to 52 weeks).

Methodological quality

The methodological quality of the RCTs was variable. Overall, 11 RCTs were rated as having “low” risk of bias, 13 as having “unclear” risk of bias, and 11 as having “high” risk of bias. Although trials were required to be described as randomized to meet our eligibility criteria, 16 studies did not provide a clear description of the method used to generate random allocation. In 19 studies it was unclear whether allocation was sufficiently concealed. Incomplete outcome data was a concern in nearly half of the studies ($n = 17$) due to significant loss to follow-up or lack of clear reporting of attrition rates. Generally, the RCTs used adequate measures to ensure blinding to treatment assignment and reported all prespecified outcomes. An overview of the risk of bias assessment and funding source for each study is provided in Table 1.

Vitamin D and parathyroid hormone levels

Twenty-two studies reported 25[OH]D levels at end-point or change from baseline. Across the 14 studies that reported change from baseline scores, 25[OH]D levels increased by an average of 18.7 ng/mL (95% CI, 16.0 to 21.4) in patients treated with vitamin D compared with no vitamin D. Heterogeneity for this pooled estimate was high ($I^2=97\%$), likely due to large variability in the doses of vitamin D, baseline 25[OH]D levels, and population characteristics. Parathyroid hormone significantly decreased in patients receiving vitamin D compared with the

Table 1. Characteristics of Included Studies

First author, Year, Country	ROB	Patient population, number enrolled	Mean age	Female (%)	Vitamin D ₃ dose +/- calcium	Control	Follow-up duration
Ardabili HR, 2012 Iran	Low	Women with polycystic ovarian syndrome and vitamin D deficiency, <i>n</i> = 60	27	100	50,000 IU/20 days	Placebo	2 months
Avenell A, 2009 UK	Low	Recent osteoporotic fracture and vitamin D deficiency D, <i>n</i> = 5292	77	85	800 IU/day +/- calcium (1,000 mg/day)	Placebo +/- calcium (1000 mg/day)	62 months
Ayesha I, 1998 India	High	Type 2 diabetes, <i>n</i> = 32	57	NR	450,000, 300,000, or 150,000 IU once	Placebo	12 weeks
Beilfuss J, 2012 Norway	Unclear	Overweight or obese, <i>n</i> = 445	50	61	40,000 or 20,000 IU/week + calcium (500 mg/day)	Calcium (500 mg/day)	12 months
Bock G, 2011 Austria	Unclear	Healthy, <i>n</i> = 59	34	49	140,000 IU/month	Placebo	12 weeks
Breslavs ky A, 2013 Israel	High	Type 2 diabetes, <i>n</i> = 47	66	53	1,000 IU/day	Placebo	12 months
Carrillo AE, 2013 USA	High	Overweight or obese, <i>n</i> = 23	26	52	4,000 IU/day + calcium (500 mg/day)	Calcium (500 mg/day)	12 weeks
Davidson MB, 2013 USA	Low	Prediabetes, <i>n</i> = 117	52	67	Based on patient weight (mean: ~89,000 IU/week)	Placebo	12 months
de Boer IH, 2008 USA	High	Women with normal or impaired glucose tolerance, <i>n</i> = 33951	63	100	400 IU/day + calcium (1,000 mg/day)	Calcium (1000 mg/day)	7 yr (median)
Gepner AD, 2012 Low	Low	Healthy, postmenopausal women, <i>n</i> = 114	64	100	2,500 IU/day	Placebo	4 months
Grimnes G, 2011 Norway	Low	Healthy with vitamin D deficiency, <i>n</i> = 104	52	48	20,000 IU/twice per week	Placebo	6 months
Harris SS, 2012 USA	Unclear	Overweight or obese with early or prediabetes, <i>n</i> = 100	57	51	4,000 IU/day + calcium (600 mg/day)	Calcium (600 mg/day)	12 weeks
Heshmat R, 2012 Iran	Unclear	Type 2 diabetes, <i>n</i> = 42	56	64	300,000 IU once	Placebo	3 months
Jorde R, 2009 Norway	High	Type 2 diabetes, <i>n</i> = 36	56	44	40,000 IU/week	Placebo	6 months
Jorde R, 2010 Norway	High	Overweight or obese, <i>n</i> = 438	48	64	40,000 IU/week + calcium (500 mg/day)	Placebo + calcium (500 mg)	12 months
Kota SK, 2011 India	High	Type 2 diabetes, <i>n</i> = 30	40	33	60,000 IU/week + calcium (1 g/day) + anti-tubercular treatment	Anti-tubercular treatment	12 weeks
Longenecker CT, 2012 USA	Low	Human immunodeficiency virus and vitamin D deficiency, <i>n</i> = 45	45	22	4,000 IU/day	Placebo	12 weeks
Major GC, 2007 Canada	High	Overweight or obese women, <i>n</i> = 84	43	100	400 IU/day + calcium (1,200 mg/day)	Placebo	15 weeks
Mitri J, 2011 USA	Low	Early diabetes or impaired fasting glucose, <i>n</i> = 92	57	51	2,000 IU/day + calcium (800 mg/day) vs. vitamin D ₃ (2,000 IU/day) vs. calcium (800 mg/day)	Placebo	16 weeks
Muldowney S, 2012 Ireland	Unclear	Healthy, <i>n</i> = 442	30 / 71	54	600, 400, or 200 IU/day	Placebo	22 weeks
Nagpal J, 2009 India	High	Healthy, centrally-obese men, <i>n</i> = 100	44	0	120,000 IU/2 week	Placebo	6 weeks
Nikooyeh B, 2011 Iran	Unclear	Type 2 diabetes, <i>n</i> = 90	51	61	1,000 IU/day + calcium (500 or 300 mg/day)	Calcium (300 mg/day)	12 weeks
Nilas L, 1984 Denmark	Unclear	Healthy, postmenopausal women, <i>n</i> = 149	50	100	2,000 IU/day + calcium (500 mg/day)	Placebo + calcium (500 mg/day)	2 yr
Parekh D, 2010 India	Unclear	Type 2 diabetes, <i>n</i> = 28	44	57	300,000 IU once	Placebo	4 weeks
Petchey WG, 2013 Australia	Low	Chronic kidney disease, <i>n</i> = 28	66	29	2,000 IU/day	Placebo	6 months

(Continued)

Table 1. Continued

First author, Year, Country	ROB	Patient population, number enrolled	Mean age	Female (%)	Vitamin D ₃ dose +/- calcium	Control	Follow-up duration
Pittas AG, 2007 USA	Unclear	Normal or impaired glucose tolerance, <i>n</i> = 445	71	58	700 IU/day + calcium (500 mg/day)	Placebo	3 yr
Shab-Bidar S, 2011 Iran	Unclear	Type 2 diabetes, <i>n</i> = 100	53	57	1,000 IU/day + calcium (340 mg/day)	Calcium (340 mg/day)	12 weeks
Soric MM, 2012 USA	High	Type 2 diabetes, <i>n</i> = 37	55	59	2,000 IU/day	Vitamin C (500 mg/day)	12 weeks
von Hurst PR, 2010 NZ	Unclear	Women with insulin resistance and vitamin D deficiency, <i>n</i> = 106	42	100	4,000 IU/day	Placebo	6 months
Wamberg L, 2013 Denmark	Unclear	Obese with vitamin D deficiency, <i>n</i> = 52	40	71	7,000 IU/day	Placebo	26 weeks
Witham MD, 2010 Scotland	Low	Type 2 diabetes, <i>n</i> = 61	65	33	200,000 or 100,000 IU once	Placebo	16 weeks
Wood AD, 2012 Scotland	Low	Healthy, <i>n</i> = 305	64	100	1,000 or 400 IU/day	Placebo	12 months
Yiu YF, 2013 Hong Kong	Low	Type 2 diabetes and vitamin D deficiency, <i>n</i> = 100	65	51	5,000 IU/day	Placebo	12 weeks
Zhu W, 2013 China	High	Obesity, <i>n</i> = 53	27	91	125 IU/day + calcium (600 mg/day) + energy restriction	Energy restriction	12 weeks
Zittermann A, 2009 Germany	Unclear	Overweight or obese, <i>n</i> = 200	48	67	3,332 IU/day	Placebo	12 months

IU = international units; mg = milligram; N = number; ROB = risk of bias

control group in a meta-analysis of 10 studies (MD, -9.8 pg/mL; 95% CI, -11.4 to -8.2; $I^2=72\%$).

Insulin sensitivity and secretion

The most commonly reported measure of insulin sensitivity was HOMA-IR. A total of 17 studies were included in a meta-analysis comparing HOMA-IR change from baseline or final scores between vitamin D and no vitamin D groups (Figure 2). Eight RCTs examining 884 patients with normal glucose tolerance showed no effect of vitamin D on insulin sensitivity (MD, 0.02; 95% CI, -0.14 to 0.18), with no evidence of heterogeneity ($I^2=0\%$). Four studies on patients with prediabetes similarly found no effect of vitamin D (MD, -0.17; 95% CI, -0.69 to 0.35), though heterogeneity was moderate ($I^2=47\%$). A pooled estimate of six studies that examined patients with type 2 diabetes also showed no significant difference between vitamin D and no vitamin D (MD, -1.46; 95% CI, -4.27 to 1.34). Heterogeneity was high ($I^2=77\%$) however, and was attributable to two RCTs, one favoring the control group (no vitamin D) (23) and the other favoring vitamin D (32). These trials were similar in terms of their population and duration of follow-up, but differed in the vitamin D regimen (300,000 IU once by intramuscular (IM) injection vs. 1000 IU daily oral dose). When these two trials were excluded, no evidence of heterogeneity was found. Because very high infrequent doses of vitamin D are thought to be associated with an unfavorable benefit/risk ratio (46, 47) we repeated the analysis of studies in patients

with type 2 diabetes after excluding studies that administered vitamin D in a single large dose, (23, 34, 41) and vitamin D was significantly favored (MD, -2.51; 95% CI, -3.92 to -1.10; $I^2=0\%$).

Five RCTs examining HOMA-B across patients with varying levels of baseline glucose tolerance found no significant effect of vitamin D, with only moderate ($I^2=40\%$) heterogeneity across studies.

Glycemia status

The effect of vitamin D on A1c was examined in 15 RCTs. No significant differences were found between the treatment groups for individuals with normal glucose tolerance (MD, 0.01%; 95% CI, -0.03 to 0.05; $I^2=0\%$) or type 2 diabetes (MD, -0.20%; 95% CI, -0.52 to 0.11; $I^2=60\%$) (Figure 3). The high heterogeneity for the pooled estimate of A1c in patients with type 2 diabetes was attributable to a single RCT that found a significant effect favoring vitamin D (32). When removed from the pooled estimate, there was no evidence of heterogeneity (I^2 decreased from 60% to 0%). A pooled estimate of three studies in patients with prediabetes showed a trend toward significance ($P = .07$; MD, -0.08%; 95% CI, -0.18 to 0.01; $I^2=40\%$), however the mean difference in A1c was small.

The effect of vitamin D on fasting blood glucose was reported in 25 RCTs. Overall, no significant effect was found for vitamin D supplementation (MD, -0.18 mg/dL; 95% CI, -1.26 to 0.90; $I^2=21\%$) (Supplement 2). For

patients with prediabetes, a trend towards statistical significance ($P = .06$) favoring vitamin D was observed (MD,

-2.16 mg/dL; 95% CI, -4.32 to 0.00 ; $I^2 = 0\%$), though the effect was small.

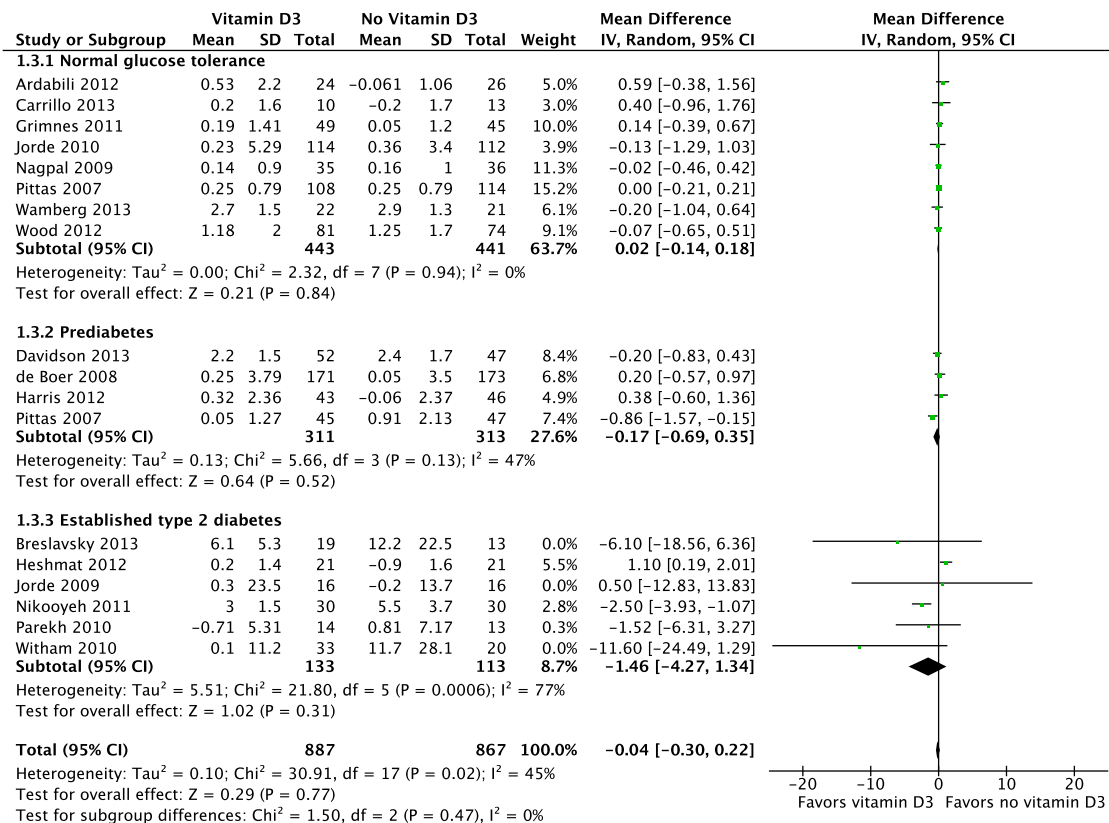


Figure 2. Forest Plot for Vitamin D₃ vs. no vitamin D₃ for insulin sensitivity (HOMA-IR)

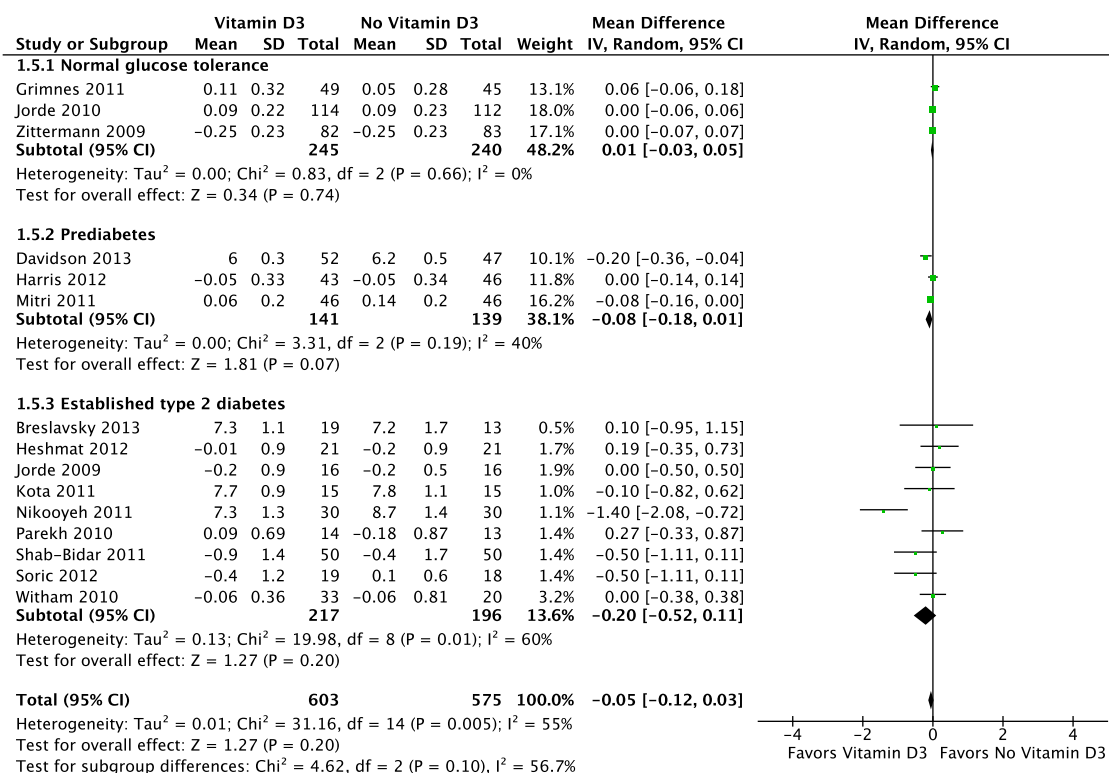


Figure 3. Forest Plot for Vitamin D₃ vs. no vitamin D₃ for A1c levels (%)

Progression to diabetes

Three studies reported progression to impaired glucose tolerance or diabetes in patients with normal glucose levels at baseline. There was no statistically significant difference in progression towards diabetes with vitamin D vs. no vitamin D (OR, 1.02; 95% CI, 0.94 to 1.10; $I^2=0\%$). One study in patients with impaired glucose tolerance similarly found no difference between treatment groups in the proportion of patients that progressed to overt type 2 diabetes (OR, 1.37; 95% CI, 0.41 to 4.62) (Figure 4).

Safety

Few adverse events were reported across the 35 included studies. There were no significant differences in the rates of hypercalcemia, nephrolithiasis, hypercalciuria, fracture, death, or other serious adverse events for patients receiving vitamin D compared with controls.

Subgroup analyses

The planned subgroup analyses for HOMA—IR and A1c did not show any statistically significant subgroup-effect interactions ($P > .05$ for all comparisons). The small number of studies reporting progression to diabetes precluded subgroup analysis for this outcome.

Publication bias

Funnels plots for each of the meta-analyses appeared to be symmetrical with one exception: HOMA—IR appeared to be missing smaller studies showing no effect of vitamin D. This may have led to an overestimation of the mean treatment effect; however, as no significant difference was found between vitamin D and no vitamin D for this outcome, any publication bias would have little impact on the interpretation of the findings.

Discussion

Overall, our systematic review and meta-analysis of 35 RCTs with a total of 43,407 patients found no evidence for the use of vitamin D₃ supplementation to prevent diabetes in individuals without diabetes, or to reduce insulin resistance and hyperglycemia in those with prediabetes or established type 2 diabetes. The lack of benefit was consistent across study populations, vitamin D dose, and trial quality. Improvement in A1c and fasting blood glucose for the vitamin D group bordered on statistical significance in studies examining prediabetes; however, the magnitude of the effect was small and would not be considered clinically important in patients with established type 2 diabetes.

The results of the present review are qualitatively similar to those in a recent systematic review and meta-analysis of vitamin D supplementation that reported on glycemic control and insulin resistance, (6) but quantitatively more precise given that our review includes 20 more trials and nearly 3000 more patients.

The lack of evidence of a beneficial effect of vitamin D has often been attributed to suboptimal dosing. Two-thirds of the included trials used vitamin D doses of at least 2000 IU/d. Despite the relatively short treatment period of most trials, blood 25[OH]D levels showed a marked increase over the course of the trials with commensurate decreases in parathyroid hormone. Given the median patient baseline 25[OH]D levels of 17.8 ng/mL across the studies and an average increase of 18.7 ng/mL with supplementation, many of the treated patients would have met or exceeded blood levels of 30 ng/mL (75 nmol/l) recommended by some as optimal for health (48, 49). Overall, this suggests to us that suboptimal dosing is unlikely to be responsible for the lack of effects observed in the RCTs to date.

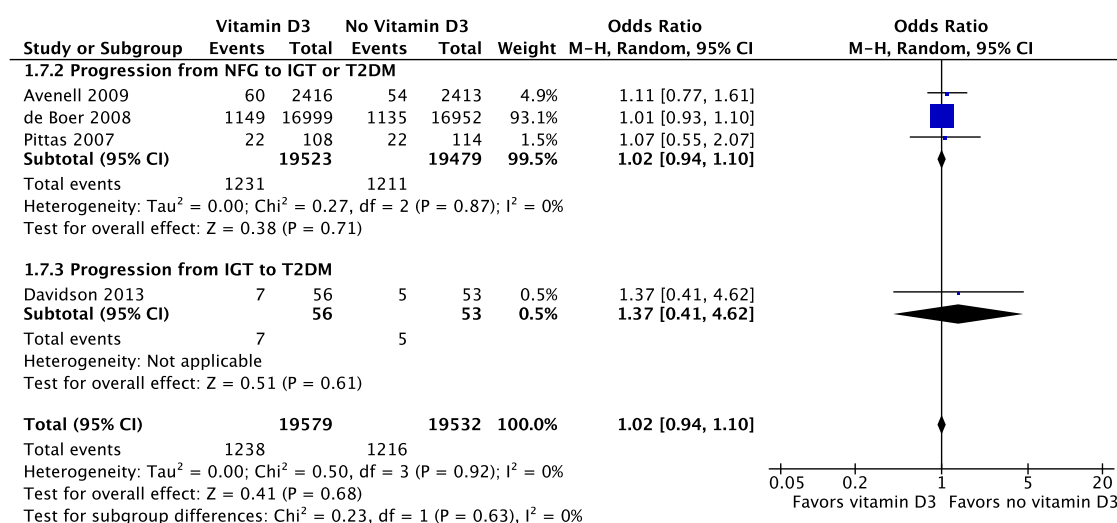


Figure 4. Forest Plot for Vitamin D₃ vs. no vitamin D₃ for progression to diabetes

Another potential reason for lack of benefit in the observed trials is short duration of follow-up. With the exception of four long-term trials that were designed for nondiabetes outcomes, (12, 19, 33, 36) three of which used relatively low vitamin D (400 to 800 U/d), all trials had durations of 12 months or less. For slowly progressive conditions such as prediabetes or type 2 diabetes, long-term studies are required to fully assess the benefit of an intervention.

Despite an increasing number of trials, the body of evidence is further limited by predominantly small sample sizes and variable study quality. Moreover, most trials focused on short-term or intermediate outcomes, such as glycemia status and insulin resistance. While such surrogate measures may be important for clinical decision-making, patient-important outcomes requiring long-term follow-up, such as progression to diabetes and development of microand macrovascular complications, were rarely investigated. Ongoing trials with longer follow-up may address these limitations in the evidence (50, 51).

Our English-language only systematic review and meta-analysis of RCTs has limitations. Despite efforts to comprehensively search electronic and gray literature sources, some trials may exist that have not been included. However, visual inspection of funnel plots raise little concern of publication bias, and due to the negative findings across outcomes, it is unlikely that unpublished negative studies would significantly alter the results or conclusions of this review. Although we examined 35 trials, we could not always analyze the reported outcomes of interest as information regarding variance was not always reported nor provided by authors after attempts at contact. In addition, we did not have access to individual patient level data, and this might have permitted us to undertake more detailed subgroup analyses than we could using aggregate trial data. Finally, given that vitamin D₃ is the more common form of supplementation, we focused our review on trials with vitamin D₃, and excluded trials of vitamin D₂. Recognizing there is disagreement on whether the two forms are equivalent or vitamin D₃ is more potent, (52, 53) we believe the results would be applicable as vitamin D₂, as it is unlikely to be more potent than vitamin D₃.

Conclusion

Although most observational studies have shown an association between low blood 25[OH]D concentration and increased glycemia and risk of diabetes, the RCTs we examined collectively show no evidence that raising 25[OH]D levels through supplementation modifies diabetes-related outcomes. The current evidence does not

support the use of vitamin D supplementation to improve glucose homeostasis or insulin resistance in the short term. Definitive conclusions from the available evidence to-date may be limited in the context of a moderate degree of heterogeneity introduced by a small number of studies and variable risk of bias. However, in the absence of evidence supporting an effect of vitamin D on short-term outcomes, the likelihood of benefit for patient-important outcomes such as progression to diabetes or microand macrovascular outcomes is debatable, but will remain to be seen in larger and longer-term trials currently underway.

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