The Effect of Improved Serum 25-Hydroxyvitamin D Status on Glycemic Control in Diabetic Patients: A Meta-Analysis

Naghmeh Mirhosseini,[1] Hassanali Vatanparast,[2] Mohsen Mazidi,[3,4] and Samantha M. Kimball[1,5]

[1]Pure North S'Energy Foundation, Calgary, Alberta T2R 0C5, Canada; [2]College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Saskatchewan S7N 5A2, Canada; [3]Key State Laboratory of Molecular Developmental Biology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing 100101, China; [4]Institute of Genetics and Developmental Biology, International College, University of Chinese Academy of Sciences, Beijing 100101, China; and [5]St. Mary's University, Calgary, Alberta T2X 1Z4, Canada

Background: Type 2 diabetes is a global health concern, with an increased prevalence and high cost of treatment.

Objective: The aim of this systematic review and meta-analysis was to determine the effect of vitamin D supplementation and improved vitamin D status on glycemia and insulin resistance in type 2 diabetic patients.

Data Source: We searched PUBMED/Medline, Cumulative Index to Nursing and Allied Health, and Cochrane Library (until January 2017).

Study Selection: Prospective clinical trials were selected evaluating the impact of vitamin D supplementation on glycosylated hemoglobin (HbA1c), serum fasting plasma glucose (FPG), and homeostatic model assessment of insulin resistance (HOMA-IR) in diabetic patients.

Data Extraction and Synthesis: We used a random-effects model to synthesize quantitative data, followed by a leave-one-out method for sensitivity analysis. The systematic review registration was CRD42017059555. From a total of 844 entries identified via literature search, 24 controlled trials (1528 individuals diagnosed with type 2 diabetes) were included. The meta-analysis indicated a significant reduction in HbA1c [mean difference: -0.30%; 95% confidence interval (CI): -0.45 to -0.15, $P < 0.001$], FPG [mean difference: -4.9 mg/dL (-0.27 mmol/L); 95% CI: -8.1 to -1.6 (-0.45 to -0.09 mmol/L), $P = 0.003$], and HOMA-IR (mean difference: -0.66; 95% CI: -1.06 to -0.26, $P = 0.001$) following vitamin D supplementation and significant increase in serum 25-hydroxyvitamin D levels [overall increase of 17 ± 2.4 ng/mL (42 ± 6 nmol/L)].

Conclusions: Vitamin D supplementation, a minimum dose of 100 μg/d (4000 IU/d), may significantly reduce serum FPG, HbA1c, and HOMA-IR index, and helps to control glycemic response and improve insulin sensitivity in type 2 diabetic patients. (*J Clin Endocrinol Metab* 102: 3097–3110, 2017)

Type 2 diabetes has become a global health care problem. In North America, 57% of the total health care expenditure was spent on diabetes-related events in 2010, and it is estimated to grow by 34% between 2010 and 2030 (1). With its increasing prevalence and the high cost of treatment, diabetes places a remarkable economic burden on many countries (2). In Canada, diabetes prevalence rate was 9.2% in 2016, with the economic

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; RCT, randomized control trial; SD, standard deviation; SE, standard error.

burden of $3.4 billion, which is estimated to increase to 41% by 2026 (3). Diabetes contributes to 30% of stroke, 40% of heart attacks, 50% of kidney failure requiring dialysis, and 70% of nontraumatic lower limb amputations, and is a leading cause of blindness (4). A quarter of Canadians with diabetes indicate that cost of treatment influences their adherence (5). Low-cost treatments are needed to reduce morbidity, long-term medical costs, and mortality (6).

Emerging evidence demonstrates that vitamin D supplementation may play a role in the prevention of type 2 diabetes. Vitamin D deficiency is involved in abnormal glucose metabolism, altered insulin secretion, and type 2 diabetes (7–10). Vitamin D deficiency is common in type 2 diabetes (11). Mitri *et al.* (7) found that even a slight increase in vitamin D intake [from <5 μg/d (200 IU/d) to 12.5 μg/d (>500 IU/d)] decreased the risk of type 2 diabetes by 13%. Likewise, compared with patients with serum 25-hydroxyvitamin D [25(OH)D] levels <14 ng/mL (35 nmol/L), individuals with levels >25 ng/mL (62.5 nmol/L) had 43% lower risk of developing type 2 diabetes. Vitamin D deficiency might induce glucose resistance through impairing insulin secretion. Supplementation with vitamin D has been demonstrated to contribute to optimized glucose homeostasis in patients with type 2 diabetes (12–14).

Mechanistically, vitamin D provides protection from diabetes-related complications through its anti-inflammatory and immune-modulatory effects (15, 16), as well as attenuating the expression of proinflammatory cytokines involved in insulin resistance like interleukin-1 and interleukin-6 (17). At a cellular level, the active form of vitamin D, 1,25-dihydroxyvitamin D, regulates expression of the insulin receptor gene (18, 19), facilitates glucose transport into muscle cells (20), and suppresses renin gene expression following hyperglycemia by blocking renin–angiotensin activity (21, 22). In addition, elevation of parathyroid hormone in response to vitamin D deficiency may also reduce insulin release from pancreatic β cells (23).

Despite promising results in longitudinal observational studies, demonstrating the inverse association between serum 25(OH)D status and type 2 diabetes, results of clinical trials with vitamin D have been inconclusive. In the systematic reviews conducted by George *et al.* (24), Pittas *et al.* (14), and Mitri *et al.* (7), there was an improvement in fasting plasma glucose (FPG) and insulin resistance, when they investigated the patients with diabetes or impaired glucose tolerance, rather than the healthy population. Still, the potential benefits of vitamin D supplementation on glycemic control and insulin sensitivity are debated by others (25–27). The lack of appropriate evidence for the beneficial effects of vitamin D might be attributed to suboptimal dosing (28, 29), short duration of supplementation (30, 31), small sample size (28, 29, 32), and comorbid conditions like obesity (33). Obesity is associated with systemic low-grade inflammation leading to insulin resistance and metabolic disorders such as diabetes (34). Several studies have reported that vitamin D improves insulin sensitivity and decreases inflammation (14, 35). Obese individuals are more likely to be vitamin D deficient, and need two to three times higher doses of vitamin D supplementation for repletion (36). Each unit (kg/m^2) increase in body mass index (BMI) is associated with a 1.15% decrease in serum 25(OH)D concentrations (37).

Current evidence is inconclusive, and it remains unclear whether vitamin D supplementation through clinical trials has a favorable effect on glycemic control in patients with type 2 diabetes. The objective of the current review was to resolve the uncertainty by systematically reviewing the literature and performing a meta-analysis of randomized controlled trials investigating the effects of vitamin D supplementation in type 2 diabetic patients on glycemic parameters, including FPG, homeostatic model assessment of insulin resistance (HOMA-IR), and glycosylated hemoglobin (HbA1c).

Materials and Methods

Literature search strategy

We designed this study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines (38, 39). The protocol for our systematic review was registered with the International Prospective Register of Systematic Reviews, PROSPERO (registration CRD42017059555). The main exposure of interest was serum 25(OH)D concentration following vitamin D supplementation, and outcomes of interest were changes in HbA1c, FPG, and HOMA-IR levels subsequent to vitamin D administration and increased serum 25(OH)D levels in patients with type 2 diabetes. A comprehensive literature search [PubMed/Medline (Medical Literature Analyses and Retrieval System Online), Cochrane Central Register of Controlled Trials, and Cumulative Index to Nursing and Allied Health] was performed to identify articles from January 2000 until January 2017 that assessed the effect of vitamin D supplementation on glycemic measures in patients with type 2 diabetes.

Search terms included "type 2 diabetes mellitus" (or "HbA1c" or "hyperglycemia" or "insulin resistant" or "glucose") and "vitamin D" (or "vitamin D3" or "cholecalciferol" or "25 hydroxyvitamin D" or "vitamin D deficiency") in the title or abstract. The reference lists of the retrieved articles were scanned for additional eligible studies. An e-mail was sent to the correspondence author for additional data when relevant. Two authors (N.M. and M.M.) performed the initial screening of titles and abstracts.

Selection criteria

We reviewed all randomized control trials (RCTs) evaluating the effect of vitamin D administration on glycemic measures.

Eligible studies met the following criteria: (1) Study was placebo controlled; (2) study population was patients with type 2 diabetes; (3) participants were ≥18 years; (4) interventions were vitamin D supplementation with/without calcium supplementation vs placebo; (5) vitamin D supplementation dose was daily or weekly; (6) trial length was ≥2 months; (7) serum 25(OH)D levels and at least one of the glycemic measures (HbA1c, FPG, HOMA-IR) were reported at the beginning and at the end of the trial for both treated and control groups; and (8) study was published in English. Exclusion criteria were as follows: (1) nonclinical studies, observational studies, case-control or cross-sectional studies; (2) studies with insufficient information on outcomes, after the corresponding author was contacted; (3) narrative reviews, comments, opinion pieces, methodological reports, editorials, and letters; (4) study populations of healthy individuals, gestational diabetics, individuals with diabetic nephropathy, type 1 diabetics, and prediabetics; (5) intervention periods of <2 months; (6) vitamin D supplementation provided as a monthly or a single bolus dose; and (7) study performed in children (<18 years). Following the screening of titles and abstracts, duplicates were removed by two authors (N.M. and M.M.). Study selection, based on meeting the inclusion criteria, was approved by another author (S.M.K.). Any disagreements between the authors were resolved through discussion with the fourth author (H.V.) (Fig. 1).

Data extraction and management

Data were extracted by two authors (N.M., M.M.). Following assessment of methodological quality of the trials by the first and second reviewers (N.M. and M.M.), extracted data were approved by the other reviewers (S.M.K. and H.V.). Data extracted from each study included the following items: first author, reference, year of publication, country of study, study design, inclusion criteria, sample size, form of vitamin D, dose and frequency of vitamin D supplementation, method used for serum 25(OH)D measurement, any cosupplementation, calcium dose (if coadministered), control group, duration of supplementation, participants' characteristics [sex (n, % male), age, weight, BMI], comorbidities, baseline, and follow-up serum 25(OH)D levels and outcome measures (HbA1c, FPG, HOMA-IR).

Any further necessary calculation on study data, such as converting measuring units or calculating standard deviation (SD), was conducted by the first author (N.M.) and checked by another author (M.M.). Serum 25(OH)D levels were collated in nmol/L; a multiplication factor of 2.5 was used to convert 25(OH)D levels respectively from ng/mL to nmol/L (40). Plasma glucose levels were collated in mmol/L; we used a multiplication factor of 0.0555 to convert glucose levels respectively from mg/dL to mmol/L, as appropriate (41).

Quality assessment

The quality of selected RCTs was assessed by two authors (N.M., M.M.) using a checklist from the Cochrane Collaboration (42). The major criteria of the checklist were randomization, double blind (both patients and researcher/assessor), comparability of treatment groups, available follow-up information, if intent-to-treat analysis applied, and equal treatment used for treatment groups. The detailed checklist has been presented in the Cochrane Collaboration (42). Each criterion might be answered in three ways: yes (adequate information), no (inadequate information), or unclear information. Criteria answered with (1) yes, scored one point; (2) no, scored zero points; or (3) unclear information, scored as U and zero points. A total score was summed for each study. A study was considered good quality with a total score ≥9 points.

Data synthesis and statistical analysis

For each study, the effect size was calculated using the mean change from baseline in glycemic measures and SD for both treatment and control groups (42). The net change in each measurement was calculated by subtracting the mean measure at baseline from the mean measure at the end of the follow-up (43). SD was calculated using the standard error (SE) of the mean via the following formula: SD = SE of the mean × square root (n), where n is the number of the subjects (43). When SD of mean change for an outcome measure was not reported, we derived SD of mean change as the mean of the baseline and follow-up SDs for each group (24). If a study included more than two intervention groups, the highest dose of vitamin D supplementation was selected and its data presented in comparison with the placebo (control) group. If studies
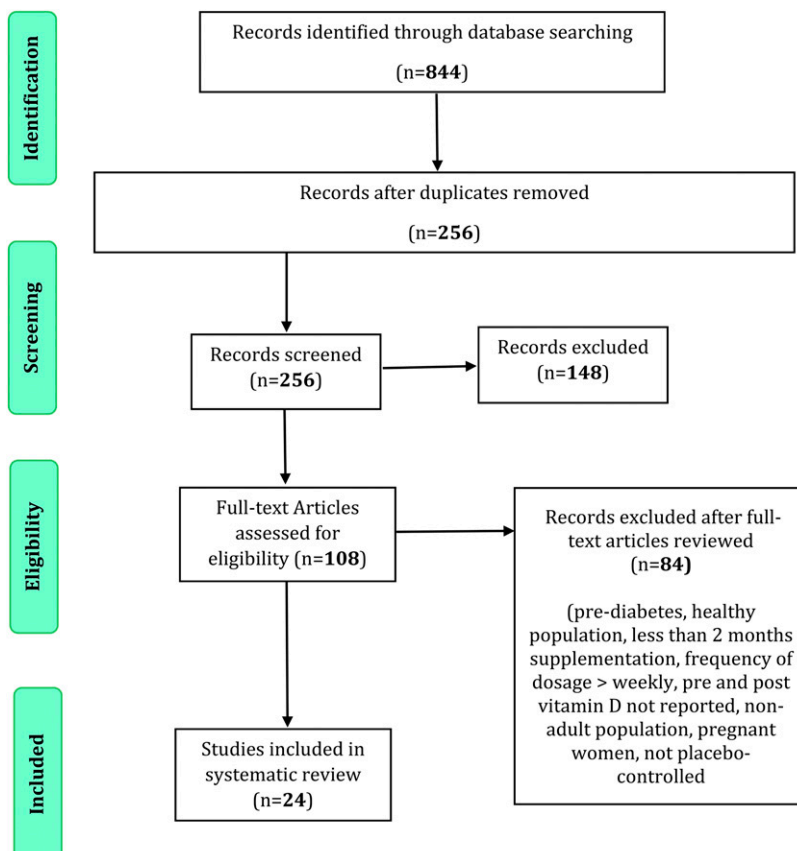

Figure 1. Study selection flow diagram (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).

compared both vitamin D and/or calcium supplementation vs placebo, they were treated as multiple studies (*i.e.*, vitamin D vs placebo and vitamin D plus calcium vs placebo).

Analyses were performed using Comprehensive Meta-Analysis V3 software (Biostat 2014, Englewood, NJ) (44). Random-effects models (DerSimonian-Laird method) were used to estimate expected heterogeneity of outcomes (45). Heterogeneity was assessed using I^2 index with I^2 values $\geq 50\%$ corresponded to the use of random-effects model, and the values $>60\%$ to 70% indicated substantial heterogeneity (46). The effect size was reported using standardized mean difference with a 95% confidence interval (CI). Significance was considered a *P* value <0.05. A sensitivity analysis was performed using the leave-one-out method (removing one study each time and repeating the analysis) (47). To address the impact of unique populations, we removed the nine clinical trials conducted in Iran and repeated the meta-analysis.

Publication bias

Potential publication bias was assessed using a visual inspection of Begg funnel plot asymmetry and Egger weighted regression tests (48). The Duval and Tweedie trim-and-fill method was used to adjust the analysis for the effects of publication bias (49).

Subgroup analysis

To address heterogeneity among study populations, subgroup analyses were performed as follows: coadministration of calcium vs vitamin D supplementation alone; vitamin D insufficiency vs sufficiency (50) at the beginning of the trial [serum 25(OH)D level <20 ng/mL (<50 nmol/L) vs ≥ 20 ng/mL (≥ 50 nmol/L)]; and normal vs high body weight status [normal (BMI <25 kg/m^2) vs overweight and obese (BMI ≥ 25 kg/m^2)]. Where applicable, we examined changes in weight and BMI over time, following vitamin D supplementation.

Results

Summary of searches and study selection process

A total of 844 unique citations was identified through searches, of which 256 records remained after removal of duplicates. After screening via titles and abstracts, 108 articles remained for further evaluation. Following further evaluation, 84 more articles were excluded for the following reasons: study design was not RCT (n = 13), conducted in healthy population or prediabetics (n = 28), duration of follow-up was too short (<2 months) (n = 6), monthly or single bolus dose of vitamin D supplementation (n = 6), studies conducted in children or pregnant women (n = 19), insufficient information of vitamin D status at the beginning of the intervention and/or at the end of the trial (n = 12). For three studies, an e-mail request for additional data was sent to corresponding author of each study, but with no response these studies were removed from further analysis. Therefore, a total of 24 clinical trials including 1528 participants with type 2 diabetes was included in the current meta-analysis (Fig. 1).

Characteristics of the included studies

Detailed information of the included studies is summarized in Table 1 (12, 28–33, 51–65). There were 24 studies published between 2009 and 2016 that met the inclusion criteria from different countries, including United States of America (n = 1), East Asia (n = 2), South East Asia (n = 1), South West Asia (n = 1), Australia and New Zealand (n = 2), Iran (n = 9), other Middle East countries (n = 3), Israel (n = 1), Europe (n = 3), and Nigeria (n = 1). All were randomized placebo-controlled trials, including three studies that compared vitamin D–fortified yogurt with plain yogurt (placebo) (52, 56, 65). One study used a combination of vitamin D and 200 mg/d calcium vs 200 mg/d calcium alone (58); and one study compared a higher dose of vitamin D [30 µg/d (1200 IU/d)] with a lower dose placebo [10 µg/d (400 IU/d)] (29). With the exception of two studies that included only women participants (12, 65), all studies included both men and women. Mean age varied from 40 to 67 years (28, 61). At the beginning of the trial, mean serum 25(OH)D levels varied from 7 ng/mL (17 nmol/L) (55) to 34 ng/mL (84 nmol/L) (51) in the intervention group. Serum 25(OH)D concentration was measured using radioimmunoassay (n = 6) (12, 32, 33, 57, 59), high-performance liquid chromatography (n = 4) (51, 52, 55), chemiluminescence immunoassay (n = 5) (54, 60, 62, 64), liquid chromatography mass spectrometry (n = 1) (53), and enzyme-linked immunosorbent assay (n = 6) (29–31, 51, 63, 65), and the method was not reported for two studies (28, 61).

Eleven studies included only type 2 diabetic patients who were vitamin D insufficient based on the Institute of Medicine [serum 25(OH)D <20 ng/mL (<50 nmol/L)] (51) at the beginning of the trial (12, 29, 31, 53, 55, 57, 58, 60–63). Five studies included overweight and obese (BMI ≥ 25 kg/m^2) diabetic patients (28, 33, 54, 59, 60). A range of vitamin D doses, from 10 µg/d (400 IU/d) to 212 µg/d (8500 IU/d), was administered in these trials (61, 64). Six studies included weekly doses of vitamin D rather than daily supplementation (32, 33, 51, 57, 61, 63).

Calcium was coadministered with vitamin D in five studies (33, 52, 56, 58, 61). Duration of vitamin D supplementation ranged from 2 months to 12 months (28, 33, 54, 57). As the main exposure of interest, we looked into serum 25(OH)D concentration following vitamin D supplementation. The mean change in serum 25(OH)D levels between the intervention and control groups is summarized for each study in Supplemental Fig. 1. Except for one study conducted by Anyanwu *et al.* (55), all studies reported a significant increase in serum 25(OH)D levels in the intervention group compared with the placebo group. Following the consumption of an average of 105 µg/d (4200 IU/d) vitamin D, compared

Table 1.   Characteristics of Included Studies

Reference	Location	N	Study Population	Mean Age	% Male	Duration of Trial	Vitamin D Dose	Control Group	Other Treatments	Treated Group 25(OH)D ng/mL (nmol/L) Baseline	End of Study	Outcomes Measured	25(OH)D Assay Method
von Hurst et al. (12)	New Zealand	81	Insulin resistant, vitamin D deficient <50	45	0	6 months	100 µg/d (4000 IU/d)	Placebo		8 (21)	32 (80)	FPG, HOMA-IR	RIA
Nasri et al. (51)	Iran	60	T2DM	55	28	12 weeks	50,000 IU/wk (~178 µg/d/ 7140 IU/d)	Placebo		34 (84)	66 (164)	HbA1c	ELISA
Shab-Bidar et al. (52)	Iran	100	T2DM	48	43	12 weeks	25 µg/d (1000 IU/d) (D3-fortified yogurt drink)	Placebo (yogurt drink)	Calcium (340 mg/d), oral hypoglycemic medication	15 (38)	29 (72)	HbA1c, FPG	HPLC
Breslavsky et al. (28)	Israel	47	T2DM, overweight & obese	67	23	12 months	25 µg/d (1000 IU/d)	Placebo		13 (32)	19 (47)	HbA1c, FPG	NA
Al-Sofiani et al. (53)	Saudi Arabia	20	Insulin resistant, vitamin D deficient (<50 nmol/L)	48	75	12 weeks	125 µg/d (5000 IU/d)	Placebo		10 (25)	36 (91)	HbA1c, FPG, HOMA-IR	LC-MS/MS
Yousefi Rad et al. (54)	Iran	58	T2DM, overweight	45	38	2 months	100 µg/d (4000 IU/d)	Placebo		16 (39)	28 (69)	HbA1c, FPG, HOMA-IR	CLIA
Anyanwu et al. (55)	Nigeria	42	T2DM, vitamin D deficient (<50 nmol/L)	50	43	12 weeks	75 µg/d (3000 IU/d)	Placebo		7 (17)	8 (19)	HbA1c, FPG	HPLC
Nikooyeh et al. (56)	Iran	60	T2DM	45	39	12 weeks	25 µg/d (1000 IU/d) (D3-fortified yogurt drink)	Placebo (yogurt drink)		17 (42)	31 (78)	HbA1c, FPG, HOMA-IR	HPLC
Nikooyeh et al. (56)	Iran	60	T2DM	45	39	12 weeks	25 µg/d (1000 IU/d) (D3-fortified yogurt drink)	Placebo (yogurt drink)	Calcium (500 mg/d)	17 (42)	30 (75)	HbA1c, FPG, HOMA-IR	HPLC
Patel et al. (29)	US	24	T2DM, vitamin D deficient (<62.5 nmol/L)	57	29	4 months	30 µg/d (1200 IU/d)	400 IU/d D3		17 (42)	28 (69)	HbA1c, FPG	ELISA
Tabesh et al. (57)	Iran	60	T2DM, nonsmoker, vitamin D deficient (<75 nmol/L)	50	48	2 months	50,000 IU/wk (~178 µg/d/ 7140 IU/d)	Placebo	Calcium placebo	11 (28)	32 (80)	HbA1c, FPG, HOMA-IR	RIA
Tabesh et al. (57)	Iran	60	T2DM, nonsmoker, vitamin D deficient (<5 nmol/L)	50	48	2 months	50,000 IU/wk (~178 µg/d/ 7140 IU/d)	Placebo (vitamin D & calcium)	Calcium (1000 mg/d)	12 (30)	30 (75)	HbA1c, FPG, HOMA-IR	RIA
Yiu et al. (30)	Hong Kong	100	T2DM	66	50	12 weeks	125 µg/d (5000 IU/d)	Placebo		8 (21)	58 (146)	HbA1c, FPG	ELISA
Jorde & Figenschau (32)	Norway	32	T2DM	48	56	6 months	40,000 IU/wk (~143 µg/d/ 5715 IU/d)	Placebo		24 (60)	47 (118)	HbA1c, FPG, HOMA-IR	RIA
Ryu et al. (58)	Korea	129	T2DM, vitamin D deficient (<50 nmol/L)	49	61	24 weeks	50 µg/d (2000 IU/d)	200 mg/d calcium	Calcium (200 mg/d)	11 (27)	30 (76)	HbA1c, FPG, HOMA-IR	CLIA
Kampmann et al. (31)	Denmark	16	T2DM, vitamin D deficient (<50 nmol/L)	Over 18	50	12 weeks	11,200 IU/d for 2 wk then 5600 IU/ d for 10 wk (~23 µg/d/ 933 IU/d)	Placebo		12 (31)	42 (105)	HbA1c, FPG	ELISA
Elkassaby et al. (59)	Australia	50	T2DM, obese	53	42	6 months	150 µg/d (6000 IU/d)	Placebo		24 (59)	51 (128)	HbA1c, FPG, HOMA-IR	RIA
Sadiya et al. (60)	Emirates	87	T2DM, vitamin D deficient (<50), obese	45	18	6 months	6000 IU/d for 3 mo then 3000 IU/ d for 3 mo (~112 µg/d/4500 IU/d)	Placebo		11 (28)	25 (62)	HbA1c, FPG	CLIA
Jorde et al. (33)	Norway	88	T2DM or impaired glucose tolerance, obese	45	43	1 year	40,000 IU/wk (~143 µg/d/ 5715 IU/d)	Placebo	Calcium (500 mg/d)	24 (60)	49 (123)	HbA1c, FPG, HOMA-IR	RIA
Kota et al. (61)	India	30	T2DM, TB, vitamin D deficient (<50 nmol/L)	40	66	12 weeks	60,000 IU/wk (~214 µg/d/ 8571 IU/d)	Placebo	Calcium (1000 mg/d), anti-TB medication	18 (45)	26 (64)	FPG, HbA1c	NA
Dalan et al. (62)	Singapore	61	T2DM, vitamin D deficient (<50 nmol/L)	53	54	16 weeks	4000 IU/d for 8 wk then 2000 IU/ d for 8 wk (~75 µg/d/3000 IU/d)	Placebo		18 (45)	32 (79)	HbA1c	CLIA
Al-Zahrani et al. (63)	Saudi Arabia	183	T2DM, vitamin D deficient (<50 nmol/L)	55	49	3 months	45,000 IU/wk for 2 mo then 1 bolus 45000 IU (~161 µg/d/6429 IU/d)	Placebo		10 (25)	33 (83)	FPG, HbA1c	ELISA
Ghavamzadeh et al. (64)	Iran	51	T2DM	51	41	14 weeks	10 µg/d (400 IU/d)	Placebo		8 (21)	18 (46)	HbA1c	CLIA
Jafari et al. (65)	Iran	59	T2DM, postmenopausal women	57	0	12 weeks	50 µg/d (2000 IU/d) (D3-fortified yogurt)	Placebo (plain yogurt)		25 (62)	35 (87)	HbA1c, FPG, HOMA-IR	ELISA

Abbreviations: CLIA, chemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; HPLC, high-performance liquid chromatography; LC-MS/MS, liquid chromatography mass spectrometry; RIA, radioimmunoassay; T2DM, type 2 diabetes mellitus; TB, tuberculosis.

with placebo, there was an overall increase of 17 ± 2.4 ng/mL (42 ± 6 nmol/L) in serum 25(OH)D levels. Because the mean of vitamin D supplementation dose across all included studies was 102 ± 61 µg/d (4074 ± 2450 IU/d) and the median 106 µg/d (4250 IU/d), a minimum dose of

100 µg/d (4000 IU/d) was recommended for vitamin D–lowering effect on glycemic measures (24).

BMI and its change over time were reported in 14 trials (28–33, 52, 53, 57, 58, 61–65). Following vitamin D supplementation, there was a slight decrease in BMI, compared

with the placebo (-0.19 kg/m^2; 95% CI: -0.34 to -0.04, $P = 0.01$) (Supplemental Fig. 2). Body weight information was available for five studies (52, 56, 60, 64, 65). Vitamin D–supplemented individuals did not show any significant change in body weight, relative to individuals in the placebo groups (-0.51 kg; 95% CI: -1.32 to 0.30, $P = 0.2$).

Risk of bias assessment

All included studies had a low risk of bias according to randomization, allocation concealment, and comparability of intervention groups at the beginning of the trial and equal treatment of intervention groups. However, there was a lack of information about intention-to-treat analysis. The quality assessment of the included trials resulted in 17 of 22 studies showing good quality, with the Cochrane score ≥ 9 (28, 30, 31, 33, 51–54, 56–60, 62–65) (Supplemental Table 1).

Pooled estimate of the effect of vitamin D on glycemic measures

Effect on HbA1c

There were 23 studies with sufficient data to be included in the meta-analysis to measure the overall effect of vitamin D supplementation and improved serum 25(OH)D status on HbA1c (28–33, 51–65). The total

number of included diabetic patients was 1477; of these, 746 received vitamin D supplementation with or without calcium, and 731 patients received placebo. Ten of 23 studies reported a significant reduction in HbA1c after vitamin D supplementation compared with placebo (51, 54, 55–57, 59, 61, 64, 65). Three additional studies showed a decreasing trend in the mean change of HbA1c in the vitamin D group compared with the placebo group; however, these differences were not statistically significant (52, 53, 60).

Based on a random-effect meta-analysis, comparing the mean change in HbA1c from baseline between vitamin D–supplemented and placebo groups, the overall effect was a significant reduction in HbA1c after vitamin D supplementation (standardized difference in mean: -0.30%; 95% CI: -0.45 to -0.15, $P < 0.001$) (Fig. 2).

In three studies, coadministration of vitamin D with calcium led to a significant decrease in HbA1c in the treated group vs placebo group (56, 57, 61). There was a significantly greater reduction in the mean change of HbA1c in the vitamin D with calcium of $-0.50\% \pm 0.2$ (95% CI: -0.89 to -0.09, $P = 0.01$) compared with vitamin D group of $-0.25\% \pm 0.08$ (95% CI: -0.41 to -0.09, $P = 0.003$; Table 2). In a subgroup analysis based on BMI at the beginning of the trial (<25 kg/m^2 as nonobese vs ≥ 25 kg/m^2 as obese), a significantly greater

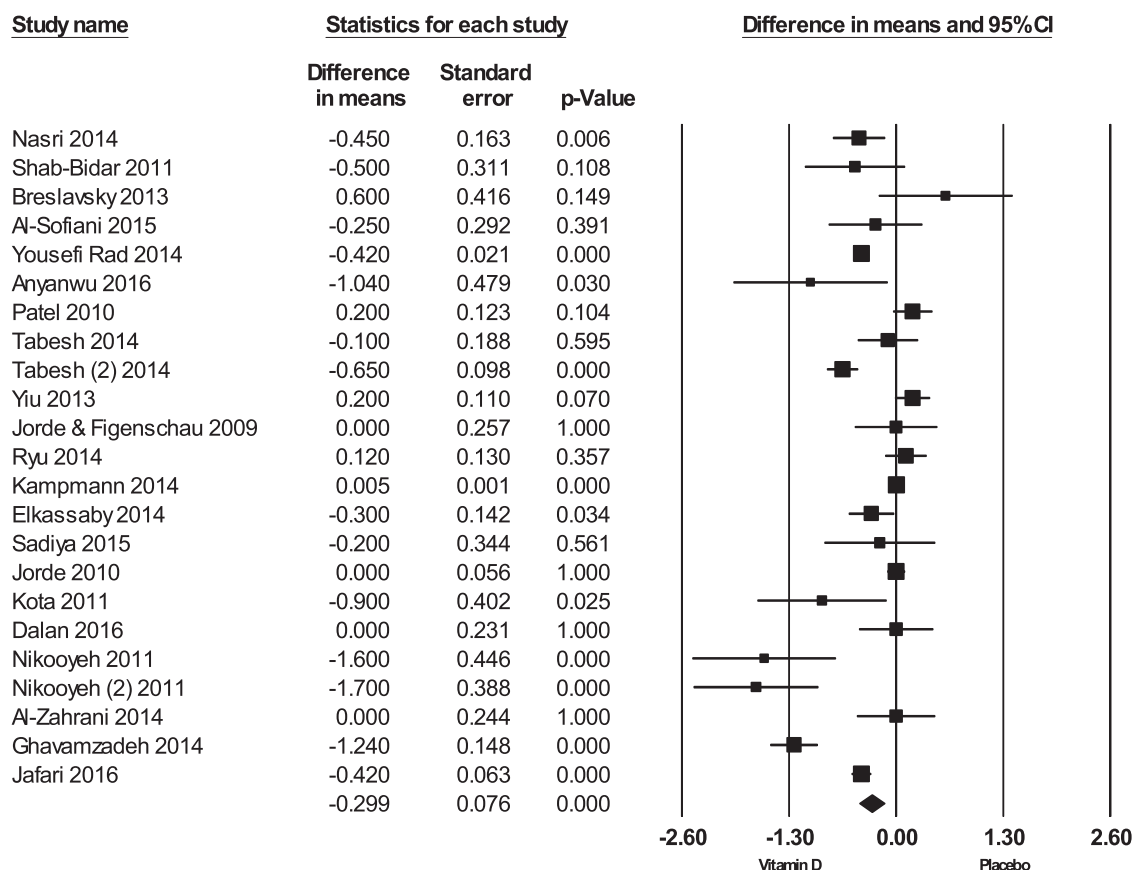| Study name	Statistics for each study			Difference in means and 95%CI
	Difference in means	Standard error	p-Value	
Nasri 2014	-0.450	0.163	0.006	
Shab-Bidar 2011	-0.500	0.311	0.108	
Breslavsky 2013	0.600	0.416	0.149	
Al-Sofiani 2015	-0.250	0.292	0.391	
Yousefi Rad 2014	-0.420	0.021	0.000	
Anyanwu 2016	-1.040	0.479	0.030	
Patel 2010	0.200	0.123	0.104	
Tabesh 2014	-0.100	0.188	0.595	
Tabesh (2) 2014	-0.650	0.098	0.000	
Yiu 2013	0.200	0.110	0.070	
Jorde & Figenschau 2009	0.000	0.257	1.000	
Ryu 2014	0.120	0.130	0.357	
Kampmann 2014	0.005	0.001	0.000	
Elkassaby 2014	-0.300	0.142	0.034	
Sadiya 2015	-0.200	0.344	0.561	
Jorde 2010	0.000	0.056	1.000	
Kota 2011	-0.900	0.402	0.025	
Dalan 2016	0.000	0.231	1.000	
Nikooyeh 2011	-1.600	0.446	0.000	
Nikooyeh (2) 2011	-1.700	0.388	0.000	
Al-Zahrani 2014	0.000	0.244	1.000	
Ghavamzadeh 2014	-1.240	0.148	0.000	
Jafari 2016	-0.420	0.063	0.000	
	-0.299	0.076	0.000	

Figure 2. Mean difference in the change of HbA1c (%) for vitamin D–supplemented and control groups. Data from (12, 28–32, 52–66).

Table 2. Meta-Analysis and Subgroup Analysis of Primary and Secondary Outcomes

Subgroup Analysis	No. of Study	No. of Subjects		Mean Difference (95% CI)	P Value
		Vitamin D	**Placebo**		
Concomitant use of Ca					
HbA1c (%)					
D vs placebo	18	643	642	−0.25 ± 0.08 (−0.41 to −0.09)	0.003
D + Ca vs placebo	6	239	228	−0.50 ± 0.2 (−0.89 to −0.09)[a]	0.01
FPG (mg/dL)					
D vs placebo	16	598	596	−6.7 ± 2.2 (−11.0 to −2.2)	0.003
D + Ca vs placebo	6	239	228	−9.5 ± 4.9 (−18.9 to −0.2)[a]	0.04
HOMA-IR					
D vs placebo	8	212	208	−0.62 ± 0.3 (−1.2 to −0.05)	0.03
D + Ca vs placebo	4	174	163	−0.69 ± 0.3 (−1.34 to −0.04)	0.04
Obesity					
HbA1c (%)					
Obese	5	173	157	−0.16 ± 0.15 (−0.45 to 0.132)	0.2
Nonobese	19	709	713	−0.34 ± 0.08 (−0.51 to −0.18)[a]	< 0.001
FPG (mg/dL)					
Obese	5	173	157	−5.0 ± 1.8 (−8.6 to −1.3)	0.009
Nonobese	17	664	667	−8.1 ± 2.7 (−13.3 to −2.7)[a]	0.003
HOMA-IR					
Obese	3	104	92	−0.28 ± 0.16 (−0.60 to 0.04)	0.09
Nonobese	9	388	389	−0.74 ± 0.26 (−1.25 to −0.22)[a]	0.005
25(OH)D level at baseline					
HbA1c (%)					
<20 ng/mL	12	382	381	−0.29 ± 0.13 (−0.55 to −0.03)	0.02
≥20 ng/mL	12	500	489	−0.29 ± 0.09 (−0.46 to −0.12)	0.001
FPG (mg/dL)					
<20 ng/mL	11	367	365	−1.1 ± 1.4 (−4.0 to 1.6)	0.4
≥20 ng/mL	11	470	459	−8.6 ± 2.7 (−13.9 to −3.4)[a]	0.001
HOMA-IR					
<20 ng/mL	6	312	313	−0.43 ± 0.29 (−0.99 to 0.14)	0.1
≥20 ng/mL	6	180	168	−0.82 ± 0.32 (−1.44 to −0.20)[a]	0.01

Abbreviation: Ca, calcium.

[a]Significant difference between groups (t-test, $P < 0.05$).

mean reduction in HbA1c was observed in nonobese participants (−0.34%; 95% CI: −0.51 to −0.18, $P < 0.001$) compared with obese group (−0.16%; 95% CI: −0.45 to 0.13, $P = 0.2$). The average vitamin D supplementation dose in obese patients was 4220 IU/d, and, although still below the optimal level (40 ng/mL), serum 25(OH)D levels doubled (from 18 to 34 ng/mL). Serum 25(OH)D level at baseline [<20 ng/mL (<50 nmol/L) vs ≥20 ng/mL (≥50 nmol/L)] did not affect the changes in HbA1c after vitamin D supplementation (Table 2).

Risk of bias assessment based on inclusion of the studies that were characterized as good quality, based on Cochrane score ≥9, did not change the overall result (mean change: −0.31; 95% CI: −0.47 to −0.15, $P < 0.001$). Heterogeneity was present ($I^2 = 96\%$), and visual inspection of funnel plot symmetry did suggest potential publication bias [Fig. 3(a)], which was confirmed by Egger's linear regression (intercept = −2.6; SE = 1.03; 95% CI: −4.75 to −0.43, t = −2.5, $P = 0.02$). We adjusted the effect size for potential publication bias using the trim and fill correction (with no

potentially missing study to be imputed in the funnel plot) and found an overall reduction in HbA1c with vitamin D supplementation (with or without calcium) of 0.30% [95% CI: −0.45 to −0.15, $P < 0.001$; Fig. 3(b)].

Effect on FPG

There were 21 studies that reported FPG as an outcome measure (12, 28–33, 52–61, 63, 65). Six studies reported a significant reduction in FPG (52, 54, 56, 61, 63, 65), whereas three studies demonstrated a decreasing trend in FPG after vitamin D supplementation (55, 59, 60).

A pooled meta-analysis including 1386 patients with type 2 diabetes (n = 701 treated with vitamin D and n = 685 with placebo) was performed to compare the mean change in FPG between the beginning and the end of study. Vitamin D supplementation resulted in a significant reduction of FPG with a standardized mean difference of −4.9 mg/dL (−0.27 mmol/L) [95% CI: −8.2 to −1.7 (−0.45 to −0.09 mmol/L), $P = 0.003$, $I^2 = 52\%$; Supplemental Fig. 3].
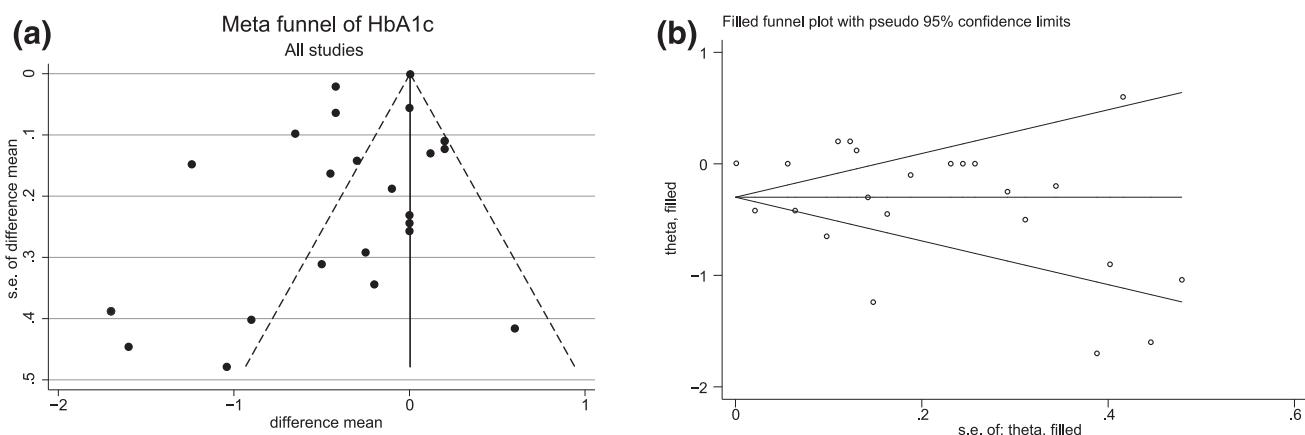
Figure 3. Funnel plot detailing publication bias in the selected studies for HbA1c analysis. (a) Funnel plot of SE by standardized mean difference; closed circles represent observed published studies. (b) Trim-and-fill method to impute for potentially missing studies; open circles represent observed published studies.

No evidence of publication bias was detected using funnel plot [Supplemental Fig. 4(a)] or Egger's test (intercept = −0.53; SE = 0.43; 95% CI: −1.44 to 0.37, t = −1.24, $P = 0.23$). Effect size was adjusted for potential publication bias (trim and fill correction) with no potentially missing study to be imputed in the funnel plot. The adjusted effect size of vitamin D supplementation on FPG was −4.9 mg/dL (−0.27 mmol/L) [95% CI: −8.2 to −1.7 (−0.45 to −0.09 mmol/L), $P = 0.003$; Supplemental Fig. 4(b)]. The result did not differ when only the good quality studies (Cochrane score ≥9) were assessed [mean change of −5.0 mg/dL (−0.28 mmol/L); 95% CI: −8.8 to −1.4 (−0.49 to −0.08 mmol/L), $P = 0.006$].

Subgroup analysis of FPG is shown in Table 2. Coadministration of calcium significantly promoted the effect of vitamin D supplementation on FPG. Patients supplemented with both vitamin D and calcium demonstrated greater reduction in FPG [−9.5 mg/dL (−0.53 mmol/L); 95% CI: −18.9 to −0.2 (−1.05 to −0.01 mmol/L), $P = 0.04$] compared with those who received vitamin D alone [−6.7 mg/dL (−0.37 mmol/L); 95% CI: −11.0 to −2.2 (−0.61 to −0.12 mmol/L), $P = 0.003$]. Nonobese patients showed a greater reduction in FPG [−8.1 mg/dL (−0.45 mmol/L); 95% CI: −13.3 to −2.7 (−0.74 to −0.15 mmol/L), $P = 0.003$] compared with obese group [−5.0 mg/dL (−0.28 mmol/L); 95% CI: −8.6 to −1.3 (−0.48 to −0.07 mmol/L), $P = 0.009$]. The impact of vitamin D supplementation on FPG was influenced by serum 25(OH)D status at the beginning of the intervention. Diabetic patients who were vitamin D insufficient at baseline did not show any significant reduction in FPG after vitamin D supplementation [−1.1 mg/dL (−0.06 mmol/L); 95% CI: −4 to −1.6 (−0.22 to 0.09 mmol/L), $P = 0.4$), but those with serum 25(OH)D level ≥20 ng/mL (≥50 nmol/L) had a significant reduction in FPG over time [−8.6 mg/dL

(−0.48 mmol/L); 95% CI: −13.9 to 3.4 (−0.77 to −0.19 mmol/L), $P = 0.001$].

Effect on insulin resistance (HOMA-IR)

Twelve studies provided sufficient data to measure the overall effect of vitamin D supplementation on insulin resistance using HOMA-IR (12, 32, 33, 53, 54, 56–59, 65). The total number of included diabetic patients was 757, of whom 386 were included in the vitamin D group and 371 in the placebo group. Seven of the 12 studies observed a significant reduction in insulin resistance after vitamin D intervention compared with placebo (12, 33, 54, 56, 57, 65) and five did not.

We found a significant lowering effect of vitamin D supplementation on insulin resistance compared with controls (standardized difference in means: −0.66; 95% CI: −1.06 to −0.26, $P = 0.001$; Supplemental Fig. 5).

Asymmetry of funnel plot was suggestive of potential publication bias [Supplemental Fig. 6(a)], but Egger's test did not find a publication bias (intercept = −1.76; SE = 2.6; 95% CI: −7.5 to 3.98, t = −0.68, $P = 0.51$). To evaluate potential publication bias, the effect size was adjusted using the trim and fill correction, and one missing study was imputed in the funnel plot [Supplemental Fig. 6(b)]. The adjusted mean difference was −0.72 (95% CI: −1.11 to −0.33, $P < 0.001$).

Calcium was coadministered with vitamin D in four studies (33, 56–58) with no significant effect on HOMA-IR changes (Table 2). Obesity inversely influenced insulin resistance. The reduction in HOMA-IR was significant in nonobese (−0.74; 95% CI: −1.25 to −0.22, $P = 0.005$) but not in obese participants (−0.28; 95% CI: −0.60 to 0.04, $P = 0.09$). The impact of vitamin D supplementation on insulin resistance was influenced by baseline serum 25(OH)D status. Patients who were vitamin D insufficient at baseline did not show any significant reduction in

HOMA-IR after vitamin D supplementation (−0.43; 95% CI: −0.99 to 0.14, $P = 0.1$), whereas HOMA-IR was significantly reduced in those with serum 25(OH)D levels ≥20 ng/mL (≥50 nmol/L) (−0.82; 95% CI: −1.44 to −0.20, $P = 0.01$).

Sensitivity analysis

Using the leave-one-out method, the pooled effect of vitamin D supplementation on HbA1c, FPG, and HOMA-IR remained similar across all included studies. This confirmed that the significant effect of vitamin D supplementation on glycemic measures was the overall effect of all included studies.

After removing the nine trials conducted in Iran, HbA1c (−0.105%; 95% CI: −0.27 to 0.06, $P = 0.2$), FPG (−1.6 mg/dL; 95% CI: −4.47 to 1.35, $P = 0.2$), and HOMA-IR (−0.09; 95% CI: −0.41 to 0.23, $P = 0.4$) were not significantly reduced following vitamin D supplementation compared with the placebo. Removing these studies decreased the power such that 69.5%, 67.0%, and 52.8% of the population remained for HbA1c, FPG, and insulin, respectively. However, glycemic parameter changes were in the same direction with vitamin D supplementation.

Discussion

We conducted a systematic review and meta-analysis of 24 RCTs to determine the efficacy of vitamin D supplementation on glycemic control and insulin sensitivity in diabetic patients. This unique meta-analysis was comprised of well-designed clinical trials centered on diabetic patients from diverse countries with high prevalence of vitamin D deficiency and poorly controlled type 2 diabetes. Extended follow-up periods (average of 7 months) and high daily doses (average of 4200 IU/d) increased the chances of achieving physiologically favorable levels of serum 25(OH)D (100 to 130 nmol/L), which is essential for better glycemic controls. Our meta-analysis found that vitamin D supplementation and subsequent increased serum 25(OH)D levels improved glucose control and insulin resistance in type 2 diabetic patients. Significant reductions in HbA1c, FPG, and HOMA-IR were found with vitamin D supplementation.

Overall, vitamin D supplementation seems to be efficacious as an adjuvant treatment of diabetes-related glucose metabolism disorders. The results of the current meta-analysis suggest that a minimum dose of 100 μg/d (4000 IU/d), which is equivalent to the tolerable upper intake level of vitamin D for adults (66), is required to have a protective effect on glucose homeostasis in type 2 diabetic patients.

Vitamin D deficiency, like other nutritional deficiencies, may compromise different body functions like glucose homeostasis (67). A majority of diabetic patients have been found to be vitamin D insufficient (68). Observational studies demonstrate an inverse association between serum 25(OH)D levels and the incidence of type 2 diabetes (69). In agreement with our findings, other studies have reported that vitamin D supplementation improves glycemic control and insulin sensitivity (7, 14, 54, 61, 65).

However, as may be expected with varied study designs (such as dose, duration, population characteristics, concomitant medications, etc.), results from numerous other RCTs have conflicted. A recent meta-analysis by Krul-Poel et al. (70), for instance, did not recover any beneficial effect of short-term vitamin D supplementation in a diverse population with type 2 diabetes. Yet, it is notable that these authors principally included trials that used single or monthly vitamin D supplementation, despite evidence that the two are not equivalent and daily doses are recommended (71). Krul-Poel et al. (70) also included clinical trials with relatively short follow-up periods, often <3 months. This is particularly problematic because HbA1c has a life span of ~100 days (72), meaning that any change induced would take longer to detect. In our meta-analysis, studies shorter than 2 months in duration were excluded to account for biology, and the average of follow-up periods was 7 months. As a result of the study inclusion criteria, the average vitamin D supplementation dose in the study by Krul-Poel et al. (70) was lower than that used in the present meta-analysis (3600 IU/d compared with 4200 IU/d), and the average increase in serum 25(OH) levels was less (12 ng/mL compared with 17 ng/mL).

Krul-Poel et al. (70) did, however, find beneficial effect of vitamin D in diabetic patients with poor glycemic control. Previous works had noted that in compromised conditions (high and poorly controlled HbA1c), vitamin D supplementation might improve glycemic measures even with lower doses and shorter period of supplementation (70, 72). The results of our meta-analysis further corroborate these findings.

Our systematic review showed that baseline vitamin D insufficiency had a negative influence on glycemic measure outcomes such that positive outcomes were found with higher baseline 25(OH)D levels (Table 2). The authors posit that optimal glucose homeostasis is enabled by a physiological vitamin D status achieved through targeted supplementation and/or regular sun exposure containing UVB, a level that may be reflected by serum 25(OH)D concentrations >40 ng/mL (100 nmol/L) (73). In the current study, we found that 100 μg/d (4000 IU/d) vitamin D was required for efficacy.

There is evidence that body weight loss improves some biomarker concentrations, including cholesterol, glucose, and insulin (74). As such, the positive results observed in single vitamin D supplementation trials could be seen as a consequence of energy restriction and weight loss; the lack of appropriate response in obese individual might also be related to weight control failure (75). However, a closer examination of the trials included in our meta-analysis revealed that there were no significant weight reductions that could have boosted glycemic control. In addition, the diet and medications of the supplemented and placebo groups in the included trials were comparable, and even a slight decrease in BMI over time might be attributed to improved serum 25(OH)D levels in vitamin D–supplemented group. Significant reductions in FPG and HOMA-IR were also recorded in obese individuals; therefore, the lack of a response in obese diabetic patients might be related to lack of vitamin D repletion [serum 25(OH)D levels ≥75 nmol/L] rather than controlling weight (25, 76). von Hurst *et al.* (12) similarly showed significant improvement in insulin resistance among insulin-resistant women, despite there being no effect on body weight or C-reactive protein level after 6 months of 4000 IU/d vitamin D supplementation. Overall, improved serum 25(OH)D levels have shown promising results for glycemic control, although other parameters such as age, season, ethnicity, obesity, and physical activity level should be taken into consideration.

We found that reductions in HbA1c, FPG, and HOMA-IR were all significantly greater in nonobese patients (Table 2). This may be due to the influence of body mass (fat mass) on the required vitamin D dose to achieve the same serum 25(OH)D. Maintaining the physiological levels of serum 25(OH)D [40 (100 nmol/L) to 52 ng/mL (130 nmol/L)] is essential for many body organs and their proper function, including the pancreas and β cell function and, subsequently, glycemic control. Serum 25(OH)D values >40 ng/mL (100 nmol/L) require a total vitamin D intake in the range of 100 to 150 µg/day (4000 to 6000 IU/d) in normal populations (77). Overweight and obese individuals need an average dose of 150 µg/day (6000 IU/d) to achieve serum 25(OH)D concentrations of 20 ng/mL (50 nmol/L) (36). To obtain physiological levels, obese individuals require doses in excess of 150 µg/day (two to three times as much vitamin D as normal weight individuals). It is postulated that higher doses of vitamin D may be required to compensate for vitamin D trapped in fat mass and/or inadequate vitamin D status (73, 78, 79).

The recommended vitamin D supplementation dose suggested by this meta-analysis [100 µg/d (4000 IU/d)] is likely to result in serum 25(OH)D levels of >40 ng/mL (100 nmol/L) in normal weight and possibly overweight

patients; however, these doses should be adjusted in obese diabetic patients (78). The overall increase in 25(OH)D was substantial at 17 ng/mL (42 nmol/L) (Supplemental Fig. 1). If we consider that nonobese subjects, who experience greater increases in 25(OH)D and higher baseline 25(OH)D concentrations, had improved glycemic control, and the adequate vitamin D dose was found to be >100 µg/d (4000 IU/d), one may conclude that studies with inconclusive results simply fail to reach the physiological vitamin D status. In support, if we look at the population characteristics of the trials that reported HbA1c (n = 23), the negative trials included participants who were vitamin D insufficient and/or obese (12, 28–33, 52, 53, 58, 60, 62, 63).

The studies included in this meta-analysis were not totally heterogeneous (high I^2) and used radioimmunoassay, high-performance liquid chromatography, chemiluminescence immunoassay, enzyme-linked immunosorbent assay, and liquid chromatography mass spectrometry—methods that are not fully harmonized. Coefficients of variation ranged between 11% and 25% (80), which may over- or underestimate serum 25(OH)D levels (81). The physiological 25(OH)D concentration may vary based on the method of measurement. A combined analysis of individual level data from the studies analyzed in this work may elucidate an optimal serum 25(OH)D level for glycemic homeostasis as it would allow the use of standardized 25(OH)D concentrations and to take into account body weight. Overall, type 2 diabetic patients need more vitamin D than what is recommended for general population recommended daily allowance, for better glycemic control.

The prevalence of vitamin D deficiency is high in both developed (42% in United States, 32% in Canada, 40% in Europe) and developing countries (60% in Iran, 85% in India, 79% in Saudi Arabia) (82–86), although substantially higher in developing countries. Baz-Hecht and Goldfine (87) have shown that the vitamin D supplementation improves glucose control and benefits insulin resistance in different vitamin D–deficient populations. Yet, the benefits of vitamin D supplementation and improved serum 25(OH)D levels on glycemic control are better highlighted in developing countries. In the current meta-analysis, we found improved glycemic control in different populations, including Iran, Norway, Australia, India, and Nigeria, suggesting that the effects of vitamin D are not unique to specific populations.

Vitamin D was found to improve insulin response and glycemic control. Pancreatic β cell impairment is crucial for the development and progression of type 2 diabetes (88). Vitamin D plays an important role in the regulation of cellular calcium signaling with an indirect effect on regulating insulin secretion from pancreatic β cells (14, 89, 90). Vitamin D may influence C-peptide secretion, an

indicator of insulin secretion (91, 92), and suppress renin-angiotensin activity to preserve β cell function (93). We found that coadministration of calcium with vitamin D improved the impact on glycemic measures, which may be due to the fact that calcium increases insulin sensitivity and improves glucose homeostasis (94, 95). Moreover, vitamin D may improve glucose metabolism systemically through its anti-inflammatory and immunomodulatory effects (96).

The standard of care for diabetes, established by the American Diabetes Association, recommends intensive lifestyle intervention and metformin for diabetes prevention (97). Because of insufficient evidence, vitamin D supplementation in diabetic patients was not recommended to improve glycemic control (98). We compared the changes from baseline of HOMA-IR, FPG, and HbA1c between vitamin D (current meta-analysis) and metformin from the study by Haffner *et al.* (99) to evaluate the clinical significance of vitamin D impact on glycemic control. The average intervention period was 6 to 7 months for vitamin D and 1 year for metformin; however, the lowering effect of vitamin D was half of that of metformin for HOMA-IR (-0.66 vs -1.46), similar to that of metformin for FPG (-0.27 mmo/L vs -0.27 mmol/L) and one-third of metformin for HbA1c (-0.3% vs -1%). However, we believe that vitamin D is not a medication, but, based on our findings, should be included as an adjunct option to help improve glycemic control and provide an assortment of other health benefits.

Although these changes are somewhat modest, considering the differences in study design, sample size, and doses of vitamin D among individual clinical trials, the statistical significance of the pooled data demonstrates its clinical importance. Furthermore, in nutritional epidemiology, not all factors can be controlled for to mimic the real-life situation, and high effect sizes are not expected; rather, more consistent significance is preferred (100). Hence, the current meta-analysis provides promising results for vitamin D as an adjuvant therapy for type 2 diabetes prevention and treatment.

There are several strengths of the current study. Higher numbers of studies included in this analysis, high-dose supplementation in more than half of the included studies, and longer period of trials have added to the value of this meta-analysis, compared with previous published ones. This review is based on an up-to-date literature search representing the most available data on this topic. All included studies were placebo-controlled randomized trials with acceptable methodological quality and the least probable chance of bias. Strength is added by including three different glycemic outcomes measures: HbA1c, FPG, and HOMA-IR. The majority of included studies had been designed for glycemic outcomes and included studies

covering a diverse population. Furthermore, we relied on duplicate independent judgment in which two different reviewers independently performed the systematic review process. However, limitations exist in that the trials included in this review were heterogeneous according to the type of outcomes measured, vitamin D dosage, duration of supplementation, and comorbid conditions. A few studies were underpowered (16 to 30 participants per intervention group). We used random model in meta-analysis to overcome these limitations. Most of the included studies did not describe dietary intake and sun exposure contributing to vitamin D synthesis. It was, therefore, difficult to interpret results based solely on vitamin D supplementation. However, we accounted for this by including only studies that measured serum 25(OH)D at baseline and follow-up were included. There were a small number of studies that used calcium in parallel with vitamin D that were included in the meta-analysis for which subgroup analyses were conducted, but statistical significance may be affected by the number of included studies.

Conclusion

This systematic review showed that vitamin D supplementation can improve glycemic control, through lowering HbA1c, FPG, and HOMA-IR. A minimum dose of 100 μg/d (4000 IU/d), which brings serum 25(OH)D values to >40 ng/mL (100 nmol/L), is recommended to improve glycemic measures in type 2 diabetic patients. It seems that the effect of vitamin D was exerted mainly through promoting insulin sensitivity, with the major impact of supplementation on the reduction of HOMA-IR. Our study suggests that vitamin D supplementation could be recommended as adjunct therapy for patients suffering from type 2 diabetes. Clinical trials that examine the effects of vitamin D supplementation with coadministration of diabetic medications should be considered for future investigation to give an unequivocal response to whether vitamin D supplementation can improve glycemic measures in type 2 diabetic patients.

Author contributions: N.M. and S.M.K. designed the study. N.M. and M.M. searched databases and performed the selection of studies. N.M., H.V., and S.M.K. wrote the manuscript. N.M. and M.M. analyzed the data. S.M.K., H.V., and M.M. critically evaluated the review, commented on it, and approved the last version. All authors reviewed and approved the final manuscript. S.M.K. is the guarantor of this study.

Disclosure Summary: The authors have nothing to disclose.

References

1. Zhang P, Zhang X, Brown J, Vistisen D, Sicree R, Shaw J, Nichols G. Global healthcare expenditure on diabetes for 2010 and 2030. *Diabetes Res Clin Pract*. 2010;**87**(3):293–301.
2. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care*. 2013;**36**(4):1033–1046.
3. Canadian Diabetes Association. *The Burden of Out-of-Pocket Costs for Canadians With Diabetes*. Toronto, ON, Canada: Canadian Diabetes Association; 2016.
4. Hux JE, Booth GL, Slaughter PM, Laupacis A, eds. *Diabetes in Ontario: An ICES Practice Atlas*. Toronto, ON, Canada: Canadian Diabetes Association; 2003.
5. Canadian Diabetes Association. *2015 Report on Diabetes: Driving Change*. Toronto, ON, Canada: Canadian Diabetes Association; 2015.
6. Zhuo X, Zhang P, Barker L, Albright A, Thompson TJ, Gregg E. The lifetime cost of diabetes and its implications for diabetes prevention. *Diabetes Care*. 2014;**37**(9):2557–2564.
7. Mitri J, Muraru MD, Pittas AG. Vitamin D and type 2 diabetes: a systematic review. *Eur J Clin Nutr*. 2011;**65**(9):1005–1015.
8. Song Y, Wang L, Pittas AG, Del Gobbo LC, Zhang C, Manson JE, Hu FB. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: a meta-analysis of prospective studies. *Diabetes Care*. 2013;**36**(5):1422–1428.
9. Palomer X, González-Clemente JM, Blanco-Vaca F, Mauricio D. Role of vitamin D in the pathogenesis of type 2 diabetes mellitus. *Diabetes Obes Metab*. 2008;**10**(3):185–197.
10. Pittas AGSQ, Sun Q, Manson JE, Dawson-Hughes B, Hu FB. Plasma 25-hydroxyvitamin D concentration and risk of incident type 2 diabetes in women. *Diabetes Care*. 2010;**33**(9):2021–2023.
11. Di Cesar DJ, Ploutz-Snyder R, Weinstock RS, Moses AM. Vitamin D deficiency is more common in type 2 than in type 1 diabetes. *Diabetes Care*. 2006;**29**(1):174.
12. von Hurst PR, Stonehouse W, Coad J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient: a randomised, placebo-controlled trial. *Br J Nutr*. 2010;**103**(4):549–555.
13. Pittas AG, Dawson-Hughes B, Li T, Van Dam RM, Willett WC, Manson JE, Hu FB. Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care*. 2006;**29**(3):650–656.
14. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2007;**92**(6):2017–2029.
15. Chagas CE, Borges MC, Martini LA, Rogero MM. Focus on vitamin D, inflammation and type 2 diabetes. *Nutrients*. 2012;**4**(1):52–67.
16. Hewison M. An update on vitamin D and human immunity. *Clin Endocrinol (Oxf)*. 2012;**76**(3):315–325.
17. Selvaraj P, Harishankar M, Afsal K. Vitamin D: immuno-modulation and tuberculosis treatment. *Can J Physiol Pharmacol*. 2015;**93**(5):377–384.
18. Maestro B, Molero S, Bajo S, Dávila N, Calle C. Transcriptional activation of the human insulin receptor gene by 1,25-dihydroxyvitamin D(3). *Cell Biochem Funct*. 2002;**20**(3):227–232.
19. Wolden-Kirk H, Overbergh L, Christesen HT, Brusgaard K, Mathieu C. Vitamin D and diabetes: its importance for beta cell and immune function. *Mol Cell Endocrinol*. 2011;**347**(1-2):106–120.
20. Dunlop TW, Väisänen S, Frank C, Molnár F, Sinkkonen L, Carlberg C. The human peroxisome proliferator-activated receptor delta gene is a primary target of 1alpha,25-dihydroxyvitamin D3 and its nuclear receptor. *J Mol Biol*. 2005;**349**(2):248–260.
21. Cheng Q, Li YC, Boucher BJ, Leung PS. A novel role for vitamin D: modulation of expression and function of the local renin-angiotensin system in mouse pancreatic islets. *Diabetologia*. 2011;**54**(8):2077–2081.
22. Ferder M, Inserra F, Manucha W, Ferder L. The world pandemic of vitamin D deficiency could possibly be explained by cellular inflammatory response activity induced by the renin-angiotensin system. *Am J Physiol Cell Physiol*. 2013;**304**(11):C1027–C1039.
23. Fadda GZ, Akmal M, Lipson LG, Massry SG. Direct effect of parathyroid hormone on insulin secretion from pancreatic islets. *Am J Physiol*. 1990;**258**(6 Pt 1):E975–E984.
24. George PS, Pearson ER, Witham MD. Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis. *Diabet Med*. 2012;**29**(8):e142–e150.
25. Jamka M, Woźniewicz M, Jeszka J, Mardas M, Bogdański P, Stelmach-Mardas M. The effect of vitamin D supplementation on insulin and glucose metabolism in overweight and obese individuals: systematic review with meta-analysis. *Sci Rep*. 2015;**5**:16142.
26. Niqil Haroon N, Anton A, John J, Mittal M. Effect of vitamin D supplementation on glycemic control in patients with type 2 diabetes: a systematic review of interventional studies. *J Diabetes Metab Disord*. 2015;**14**:3.
27. Seida JC, Mitri J, Colmers IN, Majumdar SR, Davidson MB, Edwards AL, Hanley DA, Pittas AG, Tjosvold L, Johnson JA. Clinical review: effect of vitamin D3 supplementation on improving glucose homeostasis and preventing diabetes: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2014;**99**(10):3551–3560.
28. Breslavsky A, Frand J, Matas Z, Boaz M, Barnea Z, Shargorodsky M. Effect of high doses of vitamin D on arterial properties, adiponectin, leptin and glucose homeostasis in type 2 diabetic patients. *Clin Nutr*. 2013;**32**(6):970–975.
29. Patel P, Poretsky L, Liao E. Lack of effect of subtherapeutic vitamin D treatment on glycemic and lipid parameters in type 2 diabetes: a pilot prospective randomized trial. *J Diabetes*. 2010;**2**(1):36–40.
30. Yiu YF, Yiu KH, Siu CW, Chan YH, Li SW, Wong LY, Lee SW, Tam S, Wong EW, Lau CP, Cheung BM, Tse HF. Randomized controlled trial of vitamin D supplement on endothelial function in patients with type 2 diabetes. *Atherosclerosis*. 2013;**227**(1):140–146.
31. Kampmann U, Mosekilde L, Juhl C, Moller N, Christensen B, Rejnmark L, Wamberg L, Orskov L. Effects of 12 weeks high dose vitamin D3 treatment on insulin sensitivity, beta cell function, and metabolic markers in patients with type 2 diabetes and vitamin D insufficiency: a double-blind, randomized, placebo-controlled trial. *Metabolism*. 2014;**63**(9):1115–1124.
32. Jorde R, Figenschau Y. Supplementation with cholecalciferol does not improve glycaemic control in diabetic subjects with normal serum 25-hydroxyvitamin D levels. *Eur J Nutr*. 2009;**48**(6):349–354.
33. Jorde R, Figenschau Y, Emaus N, Hutchinson M, Grimnes G. Serum 25-hydroxyvitamin D levels are strongly related to systolic blood pressure but do not predict future hypertension. *Hypertension*. 2010;**55**(3):792–798.
34. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Res Clin Pract*. 2014;**105**(2):141–150.
35. Teegarden D, Donkin SS. Vitamin D: emerging new roles in insulin sensitivity. *Nutr Res Rev*. 2009;**22**(1):82–92.

36. Veugelers PJ, Pham TM, Ekwaru JP. Optimal vitamin D supplementation doses that minimize the risk for both low and high serum 25-hydroxyvitamin D concentrations in the general population. *Nutrients*. 2015;**7**(12):10189–10208.

37. Vimaleswaran KS, Berry DJ, Lu C, Tikkanen E, Pilz S, Hiraki LT, Cooper JD, Dastani Z, Li R, Houston DK, Wood AR, Michaëlsson K, Vandenput L, Zgaga L, Yerges-Armstrong LM, McCarthy MI, Dupuis J, Kaakinen M, Kleber ME, Jameson K, Arden N, Raitakari O, Viikari J, Lohman KK, Ferrucci L, Melhus H, Ingelsson E, Byberg L, Lind L, Lorentzon M, Salomaa V, Campbell H, Dunlop M, Mitchell BD, Herzig KH, Pouta A, Hartikainen AL, Streeten EA, Theodoratou E, Jula A, Wareham NJ, Ohlsson C, Frayling TM, Kritchevsky SB, Spector TD, Richards JB, Lehtimäki T, Ouwehand WH, Kraft P, Cooper C, März W, Power C, Loos RJ, Wang TJ, Järvelin MR, Whittaker JC, Hingorani AD, Hyppönen E; Genetic Investigation of Anthropometric Traits-GIANT Consortium. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. *PLoS Med*. 2013;**10**(2): e1001383.

38. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009; **151**(4):264–269, W64.

39. Phan K, Tian DH, Cao C, Black D, Yan TD. Systematic review and meta-analysis: techniques and a guide for the academic surgeon. *Ann Cardiothorac Surg*. 2015;**4**(2):112–122.

40. Vieth R. Critique of the considerations for establishing the tolerable upper intake level for vitamin D: critical need for revision upwards. *J Nutr*. 2006;**136**(4):1117–1122.

41. Mazidi M, Gao HK, Rezaie P, Ferns GA. The effect of ginger supplementation on serum C-reactive protein, lipid profile and glycaemia: a systematic review and meta-analysis. *Food Nutr Res*. 2016A;**60**:32613.

42. Higgins JPT, Green SE. Cochrane Handbook for Systematic Reviews of Interventions. *Version 5.0.2*. London, UK: Cochrane Collaboration; 2009.

43. Mazidi M, Karimi E, Rezaie P, Ferns GA. Treatment with GLP1 receptor agonists reduce serum CRP concentrations in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *J Diabetes Complications*. 2017;**31**(7):1237–1242.

44. Borenstein MHL, Higgins J, Rothstein H. *Comprehensive Meta-Analysis*. Version 2. Englewood Cliffs, NJ: Biostat; 2005.

45. Sutton AJAK, Jones DR, Sheldon TA, Song F. *Methods for Meta-Analysis in Medical Research*. West Sussex, UK: John Wiley & Sons; 2000.

46. Higgins J, Thompson S, Deeks J, Altman D. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. *J Health Serv Res Policy*. 2002;**7**(1): 51–61.

47. Ferretti G, Bacchetti T, Sahebkar A. Effect of statin therapy on paraoxonase-1 status: a systematic review and meta-analysis of 25 clinical trials. *Prog Lipid Res*. 2015;**60**:50–73.

48. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; **315**(7109):629–634.

49. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;**56**(2):455–463.

50. Institute of Medicine, Food and Nutrition Board. Dietary reference intakes for calcium and vitamin D. Washington, DC: National Academies Press. Available at: http://books.nap.edu/openbook.php?record_id=13050. Accessed 18 March 2017.

51. Nasri H, Behradmanesh S, Maghsoudi AR, Ahmadi A, Nasri P, Rafieian-Kopaei M. Efficacy of supplementary vitamin D on improvement of glycemic parameters in patients with type 2

52. Shab-Bidar S, Neyestani TR, Djazayery A, Eshraghian MR, Houshiarrad A, Gharavi A, Kalayi A, Shariatzadeh N, Zahedirad M, Khalaji N, Haidari H. Regular consumption of vitamin D-fortified yogurt drink (Doogh) improved endothelial biomarkers in subjects with type 2 diabetes: a randomized double-blind clinical trial. *BMC Med*. 2011;**9**:125.

53. Al-Sofiani ME, Jammah A, Racz M, Khawaja RA, Hasanato R, El-Fawal HA, Mousa SA, Mason DL. Effect of vitamin D supplementation on glucose control and inflammatory response in type II diabetes: a double blind, randomized clinical trial. *Int J Endocrinol Metab*. 2015;**13**(1):e22604.

54. Yousefi Rad E, Djalali M, Koohdani F, Saboor-Yaraghi AA, Eshraghian MR, Javanbakht MH, Saboori S, Zarei M, Hosseinzadeh-Attar MJ. The effects of vitamin D supplementation on glucose control and insulin resistance in patients with diabetes type 2: a randomized clinical trial study. *Iran J Public Health*. 2014; **43**(12):1651–1656.

55. Anyanwu AC, Fasanmade OA, Odeniyi IA, Iwuala S, Coker HB, Ohwovoriole AE. Effect of vitamin D supplementation on glycemic control in type 2 diabetes subjects in Lagos, Nigeria. *Indian J Endocrinol Metab*. 2016;**20**(2):189–194.

56. Nikooyeh B, Neyestani TR, Farvid M, Alavi-Majd H, Houshiarrad A, Kalayi A, Shariatzadeh N, Gharavi A, Heravifard S, Tayebinejad N, Salekzamani S, Zahedirad M. Daily consumption of vitamin D- or vitamin D+ calcium-fortified yogurt drink improved glycemic control in patients with type 2 diabetes: a randomized clinical trial. *Am J Clin Nutr*. 2011;**93**(4):764–771.

57. Tabesh M, Azadbakht L, Faghihimani E, Tabesh M, Esmaillzadeh A. Effects of calcium-vitamin D co-supplementation on metabolic profiles in vitamin D insufficient people with type 2 diabetes: a randomised controlled clinical trial. *Diabetologia*. 2014;**57**(10): 2038–2047.

58. Ryu OH, Lee S, Yu J, Choi MG, Yoo HJ, Mantero F. A prospective randomized controlled trial of the effects of vitamin D supplementation on long-term glycemic control in type 2 diabetes mellitus of Korea. *Endocr J*. 2014;**61**(2):167–176.

59. Elkassaby S, Harrison LC, Mazzitelli N, Wentworth JM, Colman PG, Spelman T, Fourlanos S. A randomised controlled trial of high dose vitamin D in recent-onset type 2 diabetes. *Diabetes Res Clin Pract*. 2014;**106**(3):576–582.

60. Sadiya A, Ahmed SM, Carlsson M, Tesfa Y, George M, Ali SH, Siddieg HH, Abusnana S. Vitamin D supplementation in obese type 2 diabetes subjects in Ajman, UAE: a randomized controlled double-blinded clinical trial. *Eur J Clin Nutr*. 2015;**69**(6): 707–711.

61. Kota SK, Jammula S, Kota SK, Tripathy PR, Panda S, Modi KD. Effect of vitamin D supplementation in type 2 diabetes patients with pulmonary tuberculosis. *Diabetes Metab Syndr*. 2011;**5**(2): 85–89.

62. Dalan R, Liew H, Assam PN, Chan ES, Siddiqui FJ, Tan AW, Chew DE, Boehm BO, Leow MK. A randomised controlled trial evaluating the impact of targeted vitamin D supplementation on endothelial function in type 2 diabetes mellitus: the DIMENSION trial. *Diab Vasc Dis Res*. 2016;**13**(3):192–200.

63. Al-Zahrani MK, Elnasieh AM, Alenezi FM, Almoushawah AA, Almansour M, Alshahrani F, Rahman SU, Al-Zahrani A. A 3-month oral vitamin D supplementation marginally improves diastolic blood pressure in Saudi patients with type 2 diabetes mellitus. *Int J Clin Exp Med*. 2014;**7**(12):5421–5428.

64. Ghavamzadeh S, Mobasseri M, Mahdavi R. The effect of vitamin D supplementation on adiposity, blood glycated hemoglobin, serum leptin and tumor necrosis factor-α in type 2 diabetic patients. *Int J Prev Med*. 2014;**5**(9):1091–1098.

65. Jafari T, Faghihimani E, Feizi A, Iraj B, Javanmard SH, Esmaillzadeh A, Fallah AA, Askari G. Effect of vitamin D-fortified low fat yogurt on glycemic status, anthropometric indexes,

inflammation, and bone turnover in diabetic postmenauposal women: a randomised controlled clinical trial. *Clin Nutr*. 2016; **35**(1):67–76.

66. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab*. 2011;**96**(1):53–58.

67. Ruiz-Núñez B, Pruimboom L, Dijck-Brouwer DA, Muskiet FA. Lifestyle and nutritional imbalances associated with Western diseases: causes and consequences of chronic systemic low-grade inflammation in an evolutionary context. *J Nutr Biochem*. 2013; **24**(7):1183–1201.

68. Dalgård C, Petersen MS, Weihe P, Grandjean P. Vitamin D status in relation to glucose metabolism and type 2 diabetes in septuagenarians. *Diabetes Care*. 2011;**34**(6):1284–1288.

69. Ramos-Trautmann G, González L, Díaz-Luquis G, Pérez CM, Palacios C. Inverse association between vitamin D status and diabetes in a clinic-based sample of Hispanic adults in Puerto Rico. *Diabetes Res (Fairfax)*. 2015;**1**(1):5–11.

70. Krul-Poel YH, Westra S, ten Boekel E, ter Wee MM, van Schoor NM, van Wijland H, Stam F, Lips PT, Simsek S. Effect of vitamin D supplementation on glycemic control in patients with type 2 diabetes (SUNNY trial): a randomized placebo-controlled trial. *Diabetes Care*. 2015;**38**(8):1420–1426.

71. Chel V, Wijnhoven HA, Smit JH, Ooms M, Lips P. Efficacy of different doses and time intervals of oral vitamin D supplementation with or without calcium in elderly nursing home residents. *Osteoporos Int*. 2008;**19**(5):663–671.

72. Soric MM, Renner ET, Smith SR. Effect of daily vitamin D supplementation on HbA1c in patients with uncontrolled type 2 diabetes mellitus: a pilot study. *J Diabetes*. 2012;**4**(1):104–105.

73. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;**96**(7):1911–1930.

74. Harris SS, Pittas AG, Palermo NJ. A randomized, placebo-controlled trial of vitamin D supplementation to improve glycaemia in overweight and obese African Americans. *Diabetes Obes Metab*. 2012;**14**(9):789–794.

75. Stelmach-Mardas M, Mardas M, Warchoł W, Jamka M, Walkowiak J. Successful maintenance of body weight reduction after individualized dietary counseling in obese subjects. *Sci Rep*. 2014; **4**:6620.

76. Mason C, Xiao L, Imayama I, Duggan C, Wang CY, Korde L, McTiernan A. Vitamin D3 supplementation during weight loss: a double-blind randomized controlled trial. *Am J Clin Nutr*. 2014; **99**(5):1015–1025.

77. Heaney RP. Toward a physiological referent for the vitamin D requirement. *J Endocrinol Invest*. 2014;**37**(11):1127–1130.

78. Ekwaru JP, Zwicker JD, Holick MF, Giovannucci E, Veugelers PJ. The importance of body weight for the dose response relationship of oral vitamin D supplementation and serum 25-hydroxyvitamin D in healthy volunteers. *PLoS One*. 2014;**9**(11):e111265.

79. Kimball SM, Mirhosseini N, Holick MF. Evaluation of vitamin D3 intakes up to 15,000 international units/day and serum 25-hydroxyvitamin D concentrations up to 300 nmol/L on calcium metabolism in a community setting. *Dermatoendocrinol*. 2017;**9**(1):e1300213.

80. Carter GD. Accuracy of 25-hydroxyvitamin D assays: confronting the issues. *Curr Drug Targets*. 2011;**12**(1):19–28.

81. Le Goffa CCE, Souberbielleb JC, Gonzalez-Antunaa A, Delvinc E. Measurement of circulating 25-hydroxyvitamin D: a historical review. *Practical Laboratory Medicine*. 2015;**2**:1–14.

82. Al-Mogbel ES. Vitamin D status among adult Saudi females visiting primary health care clinics. *Int J Health Sci (Qassim)*. 2012;**6**(2):116–126.

83. G R, Gupta A. Vitamin D deficiency in India: prevalence, causalities and interventions. *Nutrients*. 2014;**6**(2):729–775.

84. Cashman KD, Dowling KG, Škrabáková Z, Gonzalez-Gross M, Valtueña J, De Henauw S, Moreno L, Damsgaard CT, Michaelsen KF, Mølgaard C, Jorde R, Grimnes G, Moschonis G, Mavrogianni C, Manios Y, Thamm M, Mensink GB, Rabenberg M, Busch MA, Cox L, Meadows S, Goldberg G, Prentice A, Dekker JM, Nijpels G, Pilz S, Swart KM, van Schoor NM, Lips P, Eiriksdottir G, Gudnason V, Cotch MF, Koskinen S, Lamberg-Allardt C, Durazo-Arvizu RA, Sempos CT, Kiely M. Vitamin D deficiency in Europe: pandemic? *Am J Clin Nutr*. 2016;**103**(4):1033–1044.

85. Statistics Canada. Vitamin D blood levels of Canadians. Available at: http://www.statcan.gc.ca/pub/82-624-x/2013001/article/11727-eng.htm. Accessed 2 February 2017.

86. Forrest KY, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. *Nutr Res*. 2011;**31**(1):48–54.

87. Baz-Hecht M, Goldfine AB. The impact of vitamin D deficiency on diabetes and cardiovascular risk. *Curr Opin Endocrinol Diabetes Obes*. 2010;**17**(2):113–119.

88. Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. *J Clin Invest*. 1981;**68**(6):1456–1467.

89. Sergeev IN, Rhoten WB. 1,25-Dihydroxyvitamin D3 evokes oscillations of intracellular calcium in a pancreatic β-cell line. *Endocrinology*. 1995;**136**(7):2852–2861.

90. Bergsten P. Slow and fast oscillations of cytoplasmic Ca2+ in pancreatic islets correspond to pulsatile insulin release. *Am J Physiol*. 1995;**268**(2 Pt 1):E282–E287.

91. Wahren J, Ekberg K, Johansson J, Henriksson M, Pramanik A, Johansson BL, Rigler R, Jörnvall H. Role of C-peptide in human physiology. *Am J Physiol Endocrinol Metab*. 2000;**278**(5): E759–E768.

92. Marques RG, Fontaine MJ, Rogers J. C-peptide: much more than a byproduct of insulin biosynthesis. *Pancreas*. 2004;**29**(3): 231–238.

93. Takiishi T, Ding L, Baeke F, Spagnuolo I, Sebastiani G, Laureys J, Verstuyf A, Carmeliet G, Dotta F, Van Belle TL, Gysemans CA, Mathieu C. Dietary supplementation with high doses of regular vitamin D3 safely reduces diabetes incidence in NOD mice when given early and long term. *Diabetes*. 2014;**63**(6):2026–2036.

94. Pikilidou MI, Lasaridis AN, Sarafidis PA, Befani CD, Koliakos GG, Tziolas IM, Kazakos KA, Yovos JG, Nilsson PM. Insulin sensitivity increase after calcium supplementation and change in intraplatelet calcium and sodium-hydrogen exchange in hypertensive patients with type 2 diabetes. *Diabet Med*. 2009;**26**(3):211–219.

95. Sánchez M, de la Sierra A, Coca A, Poch E, Giner V, Urbano-Márquez A. Oral calcium supplementation reduces intraplatelet free calcium concentration and insulin resistance in essential hypertensive patients. *Hypertension*. 1997;**29**:531–536.

96. Kolb H, Mandrup-Poulsen T. An immune origin of type 2 diabetes? *Diabetologia*. 2005;**48**(6):1038–1050.

97. American Diabetes Association. Standards of medical care in diabetes–2013. *Diabetes Care*. 2013;**36**(Suppl 1):S11–S66.

98. Evert AB, Boucher JL, Cypress M, Dunbar SA, Franz MJ, Mayer-Davis EJ, Neumiller JJ, Nwankwo R, Verdi CL, Urbanski P, Yancy WS Jr; American Diabetes Association. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care*. 2013;**36**(11):3821–3842.

99. Haffner S, Temprosa M, Crandall J, Fowler S, Goldberg R, Horton E, Marcovina S, Mather K, Orchard T, Ratner R, Barrett-Connor E. Diabetes Prevention Program Research Group. Intensive lifestyle intervention or metformin on inflammation and coagulation in participants with impaired glucose tolerance. *Diabetes*. 2005;**54**(5):1566–1572.

100. Willett W. Overview of nutritional epidemiology. *Nutritional Epidemiology*. 3rd ed. New York, NY: Oxford University Press; 2013:1–16.