Effect of Vitamin D Supplementation on Glycemic Control in Patients With Type 2 Diabetes (SUNNY Trial): A Randomized Placebo-Controlled Trial

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OBJECTIVE

Low vitamin D status has been associated with impaired glycemic control in patients with type 2 diabetes. The purpose of our study was to evaluate the effect of vitamin D supplementation on glycemic control in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

This randomized, double-blind, placebo-controlled trial was conducted in 275 adult patients with type 2 diabetes without insulin treatment. Patients were randomly assigned to receive either vitamin D_3 (50,000 IU/month) or placebo for 6 months. To assess the primary outcome of the study, change in HbA_{1c}, we performed a linear regression analysis.

RESULTS

Mean baseline serum 25-hydroxyvitamin D [25(OH)D] increased from 60.6 ± 23.3 to 101.4 ± 27.6 nmol/L and 59.1 ± 23.2 to 59.8 ± 23.2 nmol/L in the vitamin D and placebo group, respectively. Mean baseline HbA_{1c} was 6.8 ± 0.5% (51 ± 6 mmol/mol) in both groups. After 6 months, no effect was seen on HbA_{1c} (mean difference: β = 0.4 [95% CI −0.6 to 1.5]; *P* = 0.42) and other indicators of glycemic control (HOMA of insulin resistance, fasting insulin, and glucose) in the entire study population. Subgroup analysis in patients with a serum 25(OH)D <50 nmol/L or an HbA_{1c} level >7% (53 mmol/mol) did not differ the results.

CONCLUSIONS

In a well-controlled group of patients with type 2 diabetes, intermittent high-dose vitamin D supplementation did not improve glycemic control.

Type 2 diabetes, characterized by peripheral insulin resistance and pancreatic β-cell dysfunction, represents a worldwide epidemic with significant comorbidity and mortality due to microvascular and macrovascular complications (1). Although therapies for type 2 diabetes have improved over the last few decades, new insights for the prevention and management of type 2 diabetes remain necessary due to the increased prevalence of the disease.

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Over the past decade, vitamin D has attracted substantial interest toward extraskeletal outcomes in various disease conditions, including diabetes (2,3). Vitamin D deficiency (defined as serum 25-hydroxyvitamin D [25(OH)D] <50 nmol/L) is highly prevalent in patients with type 2 diabetes (4,5). Several potential mechanisms involving vitamin D might affect glycemic control in patients with type 2 diabetes. Most cells, including the pancreatic β-cells, contain the vitamin D receptor, and most of them also have the capability to produce the biologically active 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], which allows intracrine and paracrine functions. In vitro studies have shown that the active vitamin D metabolite 1,25$(OH)_2$D stimulated insulin release by the pancreatic β-cells (6,7). In addition, vitamin D is known to have immunomodulatory and anti-inflammatory effects and might reduce peripheral insulin resistance by altering low-grade chronic inflammation (8,9). Furthermore, insulin secretion and insulin sensitivity are both calcium-dependent processes.

A large number of cross-sectional studies generally demonstrated an inverse association between vitamin D status and prevalence of hyperglycemia (4,10). Longitudinal studies have reported that low vitamin D status is a predictor for incident type 2 diabetes (11,12). Still, it remains unclear whether vitamin D deficiency and insulin resistance are causally related or whether they constitute two independent features of patients with type 2 diabetes. Results from previous intervention studies with vitamin D supplementation have been conflicting. A systematic review and meta-analysis of 15 studies examining the effect of vitamin D supplementation concluded that there is currently insufficient evidence of beneficial effect to recommend vitamin D supplementation as a means of improving glycemia or insulin resistance in patients with diabetes, impaired glucose tolerance, or normal fasting glucose (13). A weak positive effect of vitamin D supplementation was seen on fasting glucose and insulin resistance in patients with type 2 diabetes. Inconsistency in these results may be due to the fact that many of the included reviewed studies used a different supplementation regimen, had a lack of power, did not have glycemic control as primary outcome, or did not include patients with type 2 diabetes.

Taken together, the causality of the association between vitamin D status and glycemic control in patients with type 2 diabetes has not yet been proven. We therefore designed this double-blind, randomized, placebo-controlled trial to determine the effect of vitamin D supplementation on glycemic control in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The SUNNY trial (acronym for the *stu*dy on the effect of vitami*n* D supplemen*n*tation on gl*y*cemic control in type 2 diabetes) is a double-blind, randomized, placebo-controlled clinical trial in which the effect of vitamin D supplementation on glycemic control was examined in patients with type 2 diabetes. A detailed description of the protocol can be found elsewhere (14).

In brief, the trial was conducted in five general practices in and around Alkmaar, the Netherlands, at latitude 52°. Adult patients (≥18 years) with type 2 diabetes treated with lifestyle advice, metformin, or sulfonylurea (SU) derivatives, whether or not in combination, were invited by letter for participation in the study. Serum HbA_{1c} had to be stable and ≤8.0% (64 mmol/mol) for the last 3 months without recent changes in hypoglycemic agents. All patients were included between July 2012 and April 2013. This trial was approved by the Medical Ethics Committee of North Holland, the Netherlands, and was conducted according to the principles of the Declaration of Helsinki.

The main exclusion criteria were as follows: an impaired renal function (estimated glomerular filtration rate <30 mL/min/1.73 m^2, calculated from serum creatinine using the modification of renal disease formula), any granuloma forming disorder, hypercalcemia (serum calcium >2.65 nmol/L) of any reason, serum 25(OH)D <15 or >150 nmol/L, and urolithiasis. The patients were not allowed to take vitamin D supplements during the study. Throughout the study, drug alterations regarding hypoglycemic agents and statins were not allowed. All patients gave written informed consent. Withdrawal criteria for premature termination of the trial were as follows: onset of hypercalcemia, serum 25(OH)D <15 or >250 nmol/L, hypersensitivity to cholecalciferol or placebo, onset of urolithiasis, any change in hypoglycemic agents, or HbA_{1c} >8.5% (69 mmol/mol).

Intervention

All participants were randomized according to either an oral dose of cholecalciferol 50,000 IU once a month or an identically looking placebo 50,000 IU once a month for 6 months (Meander Medical Center, Amersfoort, the Netherlands). The patients were randomized 1:1 according to the method of block randomization with a block size of 10. No stratification was used. The randomization procedure was performed by the pharmacist. The participants and the research team remained blinded till the end of the study.

Outcome Measures

The primary outcome of the study was the change in serum HbA_{1c} between the vitamin D and placebo group after 6 months of intervention. Secondary outcomes were insulin resistance and β-cell function, measured through the HOMA of insulin resistance (HOMA-IR) and β-cell function (HOMA-B), quantitative insulin sensitivity index (QUICKI), lipid profile, blood pressure, and safety profiles. Furthermore, prespecified subgroup analysis in patients with serum 25(OH)D <50 nmol/L or HbA_{1c} between 7 and 8% (53–64 mmol/mol) at baseline were performed. An exploratory subgroup analysis was performed in patients with severe vitamin D deficiency [serum 25(OH)D <30 nmol/L]. Outcome measurements were obtained at baseline (immediately prior to dosing) and at 3 and 6 months. Venous blood samples for serum 25(OH)D, HbA_{1c}, fasting blood glucose and insulin, lipid profile, serum calcium, albumin, creatinine, and parathyroid hormone (PTH) were collected after an overnight fast at 8:00–9.30 A.M. Serum 25(OH)D was measured on an iSYS automated immunoanalyzer (IDS GmbH, Frankfurt, Germany). PTH was determined using an Access Intact PTH assay on a Beckman Coulter UniCel DxI immunoanalyzer (Beckman Coulter Nederland B.V., Mijdrecht, the Netherlands). All assays were performed according to the manufacturer's instructions and carried out by the clinical chemistry laboratory of the Medical Center Alkmaar, the Netherlands. This laboratory is CCKL certified.

Statistical Analysis

We calculated that 126 patients with type 2 diabetes would be required in this trial to demonstrate a significant difference at 80% power and 5% significance. Power calculations were based on the literature and aimed at a difference of 0.5% in HbA_{1c} value in the treated group as compared with the placebo group with an SD of 1.0% (15). With an expected rate of 50% of the subjects having a serum 25(OH)D <50 nmol/L, 252 subjects would be required to draw conclusions in vitamin D subgroups (deficient vs. sufficient). According to an expected drop out rate of 20%, 300 subjects were recruited.

All data were analyzed using the Statistical Package of the Social Sciences (SPSS software, version 20.0; SPSS Inc., Chicago, IL). Baseline characteristics were presented as means ± SD), frequencies (%), or as median (interquartile range [IQR]) in case of a skewed distribution. According to the guidelines of the Institute of Medicine, vitamin D deficiency was defined by a serum 25(OH)D <50 nmol/L (16). Severe vitamin D deficiency is defined by a serum 25(OH)D <30 nmol/L according to the Dutch Health Council. The efficacy analyses to explore the intervention effect on glycemic control were based on a modified intent-to-treat protocol, in which all randomized patients with at least one available postbaseline HbA_{1c} value were included. For patients with missing data at 6 months, the last measurement was carried forward. Per-protocol analysis was also performed including all patients who completed the trial. Linear regression analysis was used to assess the mean difference between intervention and placebo groups after 6 months (mean difference is reported as β). Change in HbA_{1c} was analyzed as primary outcome with randomization group and baseline values as explanatory measures. All effects were adjusted for baseline value, sex, season of measurement, baseline age and BMI, and ethnicity in line with earlier literature. For the prespecified subgroup analysis among patients with vitamin D deficiency and an HbA_{1c} level >7% (53 mmol/mol) at baseline, the same analyses were used. For the exploratory analysis among patients with a severe vitamin D deficiency, the results were solely adjusted for baseline value, age, and season of measurement, due to the small sample size with a lack of statistical power. Skewed continuous variables were natural log transformed before analysis. A two-sided *P* value <0.05 was considered as statistically significant.

RESULTS

Of the 787 patients who were screened for eligibility, 423 were invited for participation. Of these, 300 potential participants were recruited for the study, of whom 275 showed up at the first visit and were randomized (139 and 136 in the placebo and vitamin D group, respectively). In total, 261 (95%) (132 in the placebo group and 129 in the vitamin D group) accomplished the 3 months measurement and were included in the intent-to-treat analysis (Fig. 1). The main reasons for premature termination between start and completion of the trial were as follows: any alteration in oral hypoglycemic agents (*n* = 10), serum 25(OH)D <15 or >150 nmol/L (*n* = 2), lost to follow-up (*n* = 10), and HbA_{1c} level >69 mmol/mol (8.5%) (*n* = 5). Baseline demographic, anthropometric, and biochemical characteristics of both groups are presented in Table 1. The mean age of all patients was 67 ± 8 years and 65% were male. The mean diabetes duration was 6 ± 5 years with a mean baseline HbA_{1c} value of 6.8 ± 0.5% (51 ± 6 mmol/mmol). The antidiabetic treatment regimen did not differ between both groups. Overall mean serum 25(OH)D was 59.8 ± 23.2 nmol/L. Vitamin D deficiency was present in 98 of 261 patients (38%), 102 patients (39%) had a serum 25(OH)D level between 50 and 74 nmol/L, and 61 patients (23%) had a 25(OH)D level between 75 and 150 nmol/L at baseline. No differences were reported in diet (dairy products and fish intake) at baseline between both groups. Statin use was high in both groups (84%).

Serum 25(OH)D increased significantly in patients who received vitamin D supplementation (60.6 ± 23.3 to 101.4 ± 27.6 nmol/L at 6 months), compared with no change in the placebo group [serum 25(OH)D: 59.1 ± 23.2 to 59.8 ± 27.4 nmol/L]. Seventy-five percent of the patients in the intervention group achieved a serum 25(OH)D level ≥75 nmol/L at 3 months, and 85% after

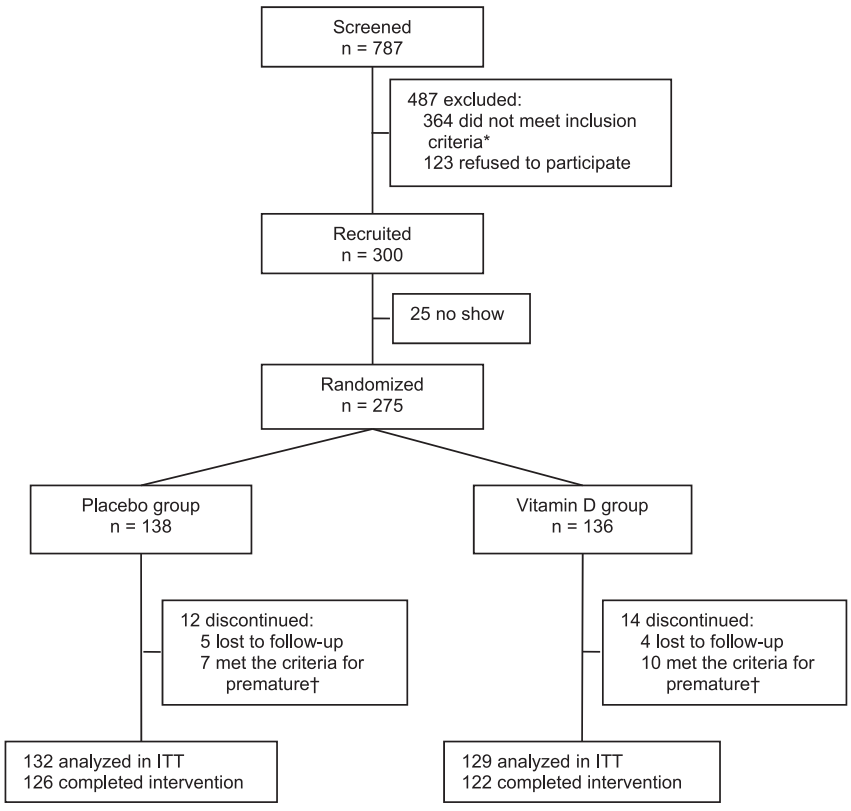

Figure 1—Participant flowchart. *Most patients did not meet the inclusion criteria because of insulin therapy; †criteria for premature termination of the trial: increase of HbA_{1c} (*n* = 5), change in antidiabetic medication (*n* = 10), or serum 25(OH)D <15 or >150 nmol/L (*n* = 2). ITT, intent to treat.

Table 1—Patient demographics and baseline characteristics

	Vitamin D group (n = 129)	Placebo group (n = 132)
Demographic parameters		
Male, *n* (%)	88 (68)	82 (62)
Age (years)	67 ± 8	67 ± 9
Diabetes duration (years)	6 ± 4	6 ± 5
White skin color, *n* (%)	122 (95)	122 (93)
Antidiabetic treatment, *n* (%)		
Lifestyle adjustments	4 (3)	7 (5)
Metformin	91 (71)	75 (57)
SU derivatives	3 (2)	5 (4)
Metformin + SU derivatives	31 (24)	45 (34)
Microvascular complications ≥1, *n* (%)*	35 (27)	16 (12)
Cardiovascular disease, *n* (%)	35 (27)	48 (36)
Current smoker, *n* (%)	18 (14)	19 (14)
Alcohol use ≤2 units/day, *n* (%)	114 (88)	114 (86)
Dairy intake ≥2 units/day, *n* (%)	85 (66)	100 (76)
Fish intake >1 servings/week, *n* (%)	45 (35)	56 (42)
Vitamin D supplements, *n* (%)†	18 (14)	12 (9)
Exposure to sun, *n* (%)		
<5 h/week	50 (39)	52 (39)
5–10 h/week	57 (44)	59 (45)
>10 h/week	22 (17)	21 (16)
Physical activity, *n* (%)		
<2 h/week	40 (31)	38 (29)
2–5 h/week	56 (43)	67 (51)
>5 h/week	33 (26)	27 (20)
Season of blood collection, *n* (%)		
Spring	15 (12)	12 (9)
Summer	31 (24)	32 (24)
Autumn	63 (49)	64 (45)
Winter	20 (15)	24 (18)
Clinical characteristics		
BMI (kg/m^2)	28.7 ± 4.6	28.5 ± 4.5
Systolic blood pressure (mmHg)	146 ± 18	146 ± 18
Diastolic blood pressure (mmHg)	81 ± 10	81 ± 9
Waist circumference (cm), median (IQR)	105 (97–111)	103 (95–109)
Fasting glucose (mmol/L)	7.7 ± 1.1	7.6 ± 1.1
Fasting insulin (mU/L)	15.6 ± 9.9	16.6 ± 10.1
HbA_{1c} (%/mmol/mol)	6.8 ± 0.5/51 ± 6	6.8 ± 0.5/51 ± 5
HOMA-IR, median (IQR)	4.63 (2.61–6.78)	4.59 (3.1–7.0)
QUICKI	0.31 ± 0.03	0.31 ± 0.03
HOMA-B, median (IQR)	64.8 (43.3–102.6)	66.7 (46.9–122.9)
Cholesterol (mmol/L)	4.4 ± 1.0	4.4 ± 1.0
HDL cholesterol (mmol/L), median (IQR)	1.1 (1.0–1.3)	1.1 (1.0–1.3)
Triglycerides (mmol/L), median (IQR)	1.5 (1.1–2.0)	1.4 (1.0–2.1)
LDL cholesterol (mmol/L)	2.5 ± 0.9	2.5 ± 0.9
Total cholesterol-to-HDL ratio (mmol/L)	3.88 ± 1.06	3.92 ± 1.28
Serum 25(OH)D (nmol/L)	60.6 ± 23.3	59.1 ± 23.2
Serum creatinine (μmol/L)	83 ± 18	81 ± 18
Serum calcium (mmol/L), median (IQR)	2.32 (2.28–2.38)	2.33 (2.28–2.40)
Serum PTH (pmol/L)	5.4 ± 2.2	5.6 ± 2.1

Data are presented as mean ± SD, unless indicated otherwise. *Including nephropathy, neuropathy, and retinopathy. †Maximum dose of 400 IU vitamin D supplement daily before start of the trial.

6 months of vitamin D supplementation. A significant inverse association was found between baseline serum 25(OH)D and the increase in serum 25(OH)D at 6 months in both groups (r = −0.42 and P = <0.001, and r = −0.38 and P = <0.001, in vitamin D and placebo groups, respectively). No significant association was found between baseline BMI and the change in serum 25(OH)D.

Serum 25(OH)D and Glycemic Control

Concerning the primary outcome, the change in HbA_{1c} from baseline to 6 months including all patients did not differ significantly between both groups (β = 0.4 [95% CI −0.6 to 1.5]; P = 0.42) (Table 2*A*). Regarding mean change of the secondary outcomes, no significant differences between both groups were seen in other indicators of glycemic control (HOMA-IR, HOMA-B, fasting glucose, fasting insulin, and QUICKI) and anthropometric variables (Table 2*A*). A significant difference, to the detriment of the vitamin D group, was observed in the total cholesterol-to-HDL ratio. This result, however, remained no longer significant after adjustment for the change in BMI over 6 months and baseline total cholesterol-to-HDL ratio (data not shown). Serum 25(OH)D and PTH significantly differed between both groups. Systolic blood pressure fell significantly in both groups (−6.4 ± 17.7 mmHg and P < 0.001 in the vitamin D group; −6.8 ± 17.2 mmHg and P < 0.001 in the placebo group), but the difference between the intervention and control groups was not significant. Per protocol analysis did not change the results (data not shown).

Prespecified subgroup analysis in patients with a serum 25(OH)D <50 nmol/L (n = 98) did not reveal any change in HbA_{1c} between both groups (β = 0.07 [95% CI −2.0 to 1.9]; P = 0.95) or in the other indicators of glycemic control (Table 2*B*). In addition, no effect was seen in subgroups with reduced glycemic control (baseline HbA_{1c} >7.0% [53 mmol/mol]) (data not shown).

Performing an exploratory subgroup analysis in severe vitamin D–deficient patients (n = 19) demonstrated a significant mean difference of 3.1 mmol/mol in HbA_{1c} after 6 months of vitamin D supplementation between both groups (β = −3.1 [95% CI −6.0 to −0.1]; P = 0.04). This result remained significant after adjustments for baseline HbA_{1c}, season of measurement, and age (β = −3.5 [95% CI −6.6 to −0.4]; P = 0.02) (Table 2*C*). In the safety profiles, one patient in the treatment group experienced new-onset urolithiasis who was excluded after 3 months. No other side effects were seen in the vitamin D group; in particular, none of the patients developed hypercalcemia during the study.

CONCLUSIONS

In this double-blind, placebo-controlled, randomized clinical trial, the effect of 6 months

Table 2—Comparison of characteristics before and after treatment in both groups in *A*: the entire study population, *B*: subgroup of patients with baseline serum 25(OH)D <50 nmol/L, and *C*: subgroup of patients with serum 25(OH)D <30 nmol/L

	Vitamin D group (n = 129)		Placebo group (n = 132)			
	0 months	6 months	0 months	6 months	Adjusted β (95% CI)†	*P* value
A: Entire study population						
Characteristics						
Serum 25(OH)D (nmol/L)	60.6 ± 23.3	101.4 ± 27.6	59.1 ± 23.2	59.8 ± 27.4	41.4 (36.5 to 46.2)	<0.01
HbA_{1c} (%/mmol/mol)	6.8 ± 0.5/51 ± 6	6.8 ± 0.6/51 ± 6	6.8 ± 0.5/51 ± 5	6.8 ± 0.6/50 ± 7	0.4 (−0.6 to 1.5)	0.42
BMI (kg/m^2)	28.7 ± 4.6	29.0 ± 4.6	28.5 ± 4.5	28.6 ± 4.6	0.23 (0.04 to 0.43)	0.02
Systolic blood pressure (mmHg)	146 ± 18	140 ± 16	146 ± 18	139 ± 14	−0.2 (−3.5 to 3.1)	0.91
Diastolic blood pressure (mmHg)	81 ± 10	79 ± 10	81 ± 9	79 ± 9	−0.2 (−2.3 to 1.9)	0.87
Fasting glucose (mmol/L)	7.7 ± 1.1	8.1 ± 1.4	7.6 ± 1.1	7.8 ± 1.2	0.2 (−0.1 to 0.5)	0.16
Fasting insulin (mU/L)	15.6 ± 9.9	16.3 ± 11.1	16.6 ± 10.1	16.3 ± 9.8	0.5 (−1.1 to 2.1)	0.52
HOMA-IR, median (IQR)*	4.63 (2.61–6.78)	4.99 (3.29–6.98)	4.59 (3.10–7.00)	4.83 (3.37–7.24)	0.06 (−0.05 to 0.17)	0.31
HOMA-B, median (IQR)*	64.8 (43.3–102.6)	64.8 (46.1–93.8)	66.7 (46.9–122.9)	67.4 (42.5–102.7)	−0.02 (−0.11 to 0.07)	0.64
QUICKI	0.31 ± 0.03	0.31 ± 0.03	0.31 ± 0.03	0.31 ± 0.03	−0.00 (−0.01 to 0.00)	0.39
Total cholesterol-to-HDL ratio (mmol/L)	3.88 ± 1.06	3.99 ± 1.16	3.92 ± 1.28	3.85 ± 1.24	0.19 (−0.03 to 0.35)	0.10
Serum PTH (pmol/L)	5.4 ± 2.2	5.4 ± 2.3	5.6 ± 2.1	6.3 ± 2.9	−0.87 (−1.32 to −0.42)	<0.01
Serum calcium (mmol/L), median (IQR)*	2.32 (2.28–2.38)	2.32 (2.29–2.38)	2.33 (2.28–2.40)	2.33 (2.29–2.38)	0.00 (−0.01 to 0.02)	0.48
	Vitamin D group (n = 44)		Placebo group (n = 54)			
	0 months	6 months	0 months	6 months	Adjusted β (95% CI)†	*P* value
B: Subgroup of patients with baseline serum 25(OH)D <50 nmol/L						
Characteristics						
Serum 25(OH)D (nmol/L)	36.6 ± 7.7	90.3 ± 22.2	37.7 ± 8.2	48.4 ± 26.2	44.5 (36.4 to 52.3)	<0.01
HbA_{1c} (%/mmol/mol)	6.8 ± 0.5/51 ± 5	6.8 ± 0.5/51 ± 6	6.8 ± 0.5/51 ± 6	6.8 ± 0.7/50 ± 7	−0.07 (−2.0 to 1.9)	0.95
BMI (kg/m^2)	30.2 ± 5.2	30.4 ± 5.0	29.4 ± 4.1	29.6 ± 4.3	−0.01 (−0.31 to 0.32)	0.97
Fasting glucose (mmol/L)	7.6 ± 0.9	8.0 ± 1.4	7.5 ± 1.1	7.9 ± 1.3	0.05 (−0.44 to 0.53)	0.85
Fasting insulin (mU/L)	16.1 ± 8.8	18.2 ± 14.4	16.4 ± 9.3	17.1 ± 10.8	0.56 (−2.8 to 3.9)	0.74
HOMA-IR, median (IQR)*	5.29 (3.14–7.27)	5.57 (3.37–7.37)	4.85 (3.10–6.69)	5.14 (3.25–7.48)	0.02 (−0.18 to 0.03)	0.84
	Vitamin D group (n = 8)		Placebo group (n = 11)			
	0 months	6 months	0 months	6 months	Adjusted β (95% CI)‡	*P* value
C: Subgroup of patients with serum 25(OH)D <30 nmol/L						
Characteristics						
Serum 25(OH)D (nmol/L), median (IQR)*	25.0 (22.0–26.5)	85.0 (68.5–95.5)	25.0 (22.0–29.0)	18.0 (16.0–27.0)	1.22 (0.60 to 1.85)	<0.01
HbA_{1c} (%/mmol/mol)	7.0 ± 0.5/53 ± 5	6.8 ± 0.6/51 ± 7	6.7 ± 0.4/50 ± 5	6.7 ± 0.5/51 ± 6	−3.5 (−6.6 to −0.4)	0.02
BMI (kg/m^2), median (IQR)*	29.8 (26.0–31.1)	29.6 (26.5–31.0)	29.8 (27.6–30.5)	29.1 (28.0–30.8)	0.01 (−0.02 to 0.04)	0.62
Fasting glucose (mmol/L), median (IQR)*	8.0 (7.0–8.3)	7.9 (6.9–10.2)	7.2 (6.3–8.2)	8.1 (6.6–8.3)	0.07 (−0.10 to 0.24)	0.40
Fasting insulin (mU/L)	14.7 ± 6.8	15.1 ± 8.0	22.0 ± 13.6	24.9 ± 14.8	−2.5 (−12.1 to 7.1)	0.58
HOMA-IR, median (IQR)*	4.27 (3.33–6.75)	5.38 (3.05–7.17)	5.10 (3.91–9.47)	7.94 (3.71–11.66)	−0.05 (−0.66 to 0.56)	0.87

Data are expressed as mean ± SD, unless otherwise stated. Significance between groups was tested with linear regression analysis. *Analyses based on natural logarithms. †Analyses adjusted for baseline value, age, BMI, ethnicity, sex, and season of measurement. ‡Analyses adjusted for baseline value, age, and season of measurement.

of oral vitamin D_3 supplementation on glycemic control was investigated in patients with well-controlled type 2 diabetes. We did not find a significant effect of vitamin D supplementation on glycemic control and metabolic profile in the entire study population, despite a significant increase in serum 25(OH)D in patients who received vitamin D. A significant effect of vitamin D supplementation on HbA_{1c} was seen after 6 months in severe vitamin D–deficient patients. However, despite adjusting for the baseline HbA_{1c} value, this significant result may be explained by the imbalance in the baseline HbA_{1c} value between the group receiving vitamin D compared with placebo.

The current study adds to an increasing body of evidence that vitamin D supplementation in vitamin D–sufficient patients with type 2 diabetes does not improve glycemic control. Unfortunately, studies or subgroup analyses in patients

with a vitamin D–deficient status regarding glycemic indices in patients with type 2 diabetes are limited (17–19). Three studies included solely vitamin D–deficient [serum 25(OH)D <50 nmol/L] patients with type 2 diabetes, of which one reported endothelial function as primary outcome (19). In a study performed among 129 Korean patients with a mean serum 25(OH)D level of 26.1 ± 11.2 nmol/L, the patients were randomized into either vitamin D_3 2,000 IU/day combined with calcium 200 mg or placebo. After a follow-up of 24 weeks, no difference was seen in the intervention group on HbA_{1c} or insulin resistance, despite a significant rise in serum 25(OH)D (25.2 ± 9.7 to 75.4 ± 25.2 nmol/L) (18).

Our findings are consistent with a recent meta-analysis that reported that there is insufficient evidence of a beneficial effect to recommend vitamin D supplementation as a means of improving glycemic control in patients with type 2 diabetes (13). Most studies that investigated the effect of vitamin D supplementation in patients with type 2 diabetes did not find a significant effect on glycemic control (20–24). However, in one study performed by Nikooyeh et al. (25) in which patients were randomized into plain yogurt drink or vitamin D3–fortified yogurt drink (~1,000 IU/day), after 12 weeks, there was a significant reduction in HbA_{1c}, HOMA-IR, fasting insulin, and glucose.

Intervention studies among other study populations than type 2 diabetes yielded conflicting results (26–29). Possible reasons for the lack of an effect found in intervention studies might be related to the patient characteristics [e.g., baseline serum 25(OH)D and HbA_{1c}], duration of the study, sample size, dosage or formulation of vitamin D supplement, and primary outcome of the studies.

The discrepancy between epidemiologic studies and intervention studies regarding vitamin D status is remarkable; almost all epidemiologic studies reported a significant association between vitamin D status and glycemic control or incident diabetes, whereas almost all intervention studies did not show an effect of vitamin D supplementation on glycemic indices. This observation suggests that vitamin D status could be more an expression of ill health rather than a cause of poor glycemic control.

Strengths of our study are the randomized, double-blind, placebo-controlled study design, the use of a large sample size with similar characteristics at baseline in the intervention and control groups, and the relatively high dose of vitamin D supplementation leading to adequate target levels of serum 25(OH)D.

Our study also has important limitations, which may partly be responsible for the lack of an effect found on glycemic control in the whole study population. First, our study population consisted of patients who were relatively well controlled in their diabetes regulation, treated with lifestyle advice whether or not in combination with oral hypoglycemic agents, with the majority of the patients having no cardiovascular complications. Moreover, only 37% of our included patients had a serum 25(OH)D <50 nmol/L, instead of the estimated 50% to have enough power for a subgroup analysis of patients with a serum 25(OH)D <50 nmol/L. It is imaginable that vitamin D supplementation is only effective in patients with vitamin D deficiency and that due to a power problem we did not find an effect on glycemic control in the subgroup with a serum 25(OH)D <50 nmol/L (type II error).

Second, an important limitation is the use of a large intermittent dose of vitamin D supplementation, which is currently not promoted. Debate is ongoing whether vitamin D supplementation has to be given in a lower oral dosage once daily instead of a higher dose once a month (30). We believe that another supplementation regimen would not have altered our results because the intervention group achieved a rise in serum 25(OH)D from 60.6 to 101.4 nmol/L, indicating an optimal increase. Another limitation of our study is the use of HOMA-IR to measure insulin resistance instead of hyperinsulinemic-euglycemic clamp, which is the gold standard method to assess insulin sensitivity.

In conclusion, a large intermittent dose of vitamin D supplementation at a level optimizing serum 25(OH)D did not improve glycemic control in patients with well-controlled type 2 diabetes. Further research among vitamin D–deficient patients with poorly regulated type 2 diabetes will be necessary to elucidate the question of whether vitamin D supplementation is effective on glycemic control or if it appears to be a marker of ill health.

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