Effects of vitamin D and calcium supplementation on pancreatic β cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial[1–4]

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ABSTRACT

Background: A suboptimal vitamin D and calcium status has been associated with higher risk of type 2 diabetes in observational studies, but evidence from trials is lacking.

Objective: We determined whether vitamin D supplementation, with or without calcium, improved glucose homeostasis in adults at high risk of diabetes.

Design: Ninety-two adults were randomly assigned in a 2-by-2 factorial-design, double-masked, placebo-controlled trial to receive either cholecalciferol (2000 IU once daily) or calcium carbonate (400 mg twice daily) for 16 wk. The primary outcome was the change in pancreatic β cell function as measured by the disposition index after an intravenous-glucose-tolerance test. Other outcomes were acute insulin response, insulin sensitivity, and measures of glycemia.

Results: Participants had a mean age of 57 y, a body mass index (BMI; in kg/m^2) of 32, and glycated hemoglobin (Hb A_{1c}) of 5.9%. There was no significant vitamin D $\times$ calcium interaction on any outcomes. The disposition index increased in the vitamin D group and decreased in the no–vitamin D group (adjusted mean change $\pm$ SE: 300 $\pm$ 130 compared with -126 ± 127, respectively; $P = 0.011$), which was explained by an improvement in insulin secretion (62 $\pm$ 39 compared with -36 ± 37 mU $\cdot$ L^{-1} $\cdot$ min, respectively; $P = 0.046$). Hb A_{1c} increased less, but nonsignificantly, in the vitamin D group than in the no–vitamin D group (0.06 $\pm$ 0.03% compared with 0.14 $\pm$ 0.03%, respectively; $P = 0.081$). There was no significant difference in any outcomes with calcium compared with no calcium.

Conclusion: In adults at risk of type 2 diabetes, short-term supplementation with cholecalciferol improved β cell function and had a marginal effect on attenuating the rise in Hb A_{1c}. This trial was registered at clinicaltrials.gov as NCT00436475. *Am J Clin Nutr* 2011;94:486–94.

INTRODUCTION

There is accumulating evidence that suggests that altered vitamin D and calcium homeostasis may play a role in the development of type 2 diabetes (1). A potential role of vitamin D has been hypothesized on the basis of animal studies (2, 3), cross-sectional studies that showed that low vitamin D status was associated with prevalent glucose intolerance or diabetes (4), and observational longitudinal studies that showed that low vitamin D status was associated with incident type 2 diabetes (5). A potential role for calcium in the development of type 2 diabetes was indirectly suggested by cross-sectional studies in which high calcium intake was shown to be inversely associated with body weight (6–8) or longitudinal observational studies in which calcium intake was inversely associated with incident type 2 diabetes (9, 10). Results from small clinical trials and post hoc analyses of larger trials on the effect of vitamin D supplementation, with or without calcium, on glucose homeostasis have been inconsistent (5).

The present randomized trial was designed to evaluate the effects of vitamin D and calcium supplementation alone or in combination on pancreatic β cell function, insulin sensitivity, and glucose tolerance in adults at high risk of type 2 diabetes.

SUBJECTS AND METHODS

Study design

The Calcium and Vitamin D for Diabetes Mellitus (CaDDM) trial was a 2-by-2 factorial, double-masked, placebo-controlled,

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randomized trial that examined the effects of vitamin D and calcium compared with matching placebos on pancreatic β cell function, insulin sensitivity, and glycemia in adults at risk of type 2 diabetes or with early type 2 diabetes who received no pharmacotherapy. The trial was conducted at the Clinical Translational Research Center at Tufts Medical Center (Boston, MA) with approval by the Institutional Review Board at Tufts University, and all participants provided written informed consent.

Participants and eligibility criteria

Participants were ambulatory adults who were $\geq$40 y of age and with a body mass index (BMI; in kg/m^2) $\geq$25 ($\geq$23 if Asian) with glucose intolerance or early diabetes that was defined as a fasting plasma glucose (FPG) concentration $\geq$100 mg/dL or 2-h glucose concentration $\geq$140 mg/dL after 75 g oral dextrose or glycated hemoglobin (Hb A_{1c}) $\geq$5.8%.

Exclusion criteria were BMI >40, Hb A_{1c} >7%, self-reported diabetes treated with pharmacotherapy, weight change >4 kg over the previous 6 mo, use of supplements that contained vitamin D or calcium in $\leq$8 wk of screening and an unwillingness to discontinue supplementation for $\geq$2 wk before the study initiation and during the study, hyperparathyroidism, hypercalcemia, nephrolithiasis, chronic kidney disease, conditions that may have affected vitamin D or calcium metabolism (eg, sarcoidosis), and regular visits to tanning booths. To increase the external validity of the study and because of a lack of consensus in defining optimal vitamin D status, the plasma 25-hydroxyvitamin D [25(OH)D] concentration was not an inclusion or exclusion criterion.

Participants were recruited from the greater metropolitan area in Boston, MA, through direct mailings and print advertisements. Potential volunteers underwent prescreening over the phone to derive a diabetes risk score (11). Persons with a high diabetes risk score who also met inclusion and exclusion criteria were invited for a full screening (visit 1, first baseline visit) where a 75-g oral-glucose-tolerance test (OGTT) was performed to measure FPG, 2-h postload plasma glucose (2hPG), and Hb A_{1c}. Eligible participants returned $\approx$1 wk later (visit 2, second baseline visit) for a frequently sampled intravenous-glucose-tolerance test (FSIVGTT) to determine insulin secretion and insulin sensitivity and calculate pancreatic β cell function (12).

Randomization and intervention

Eligible participants were randomly assigned in a 1:1 ratio to receive vitamin D [2000 IU (50 μg) cholecalciferol (vitamin D_3)/d] or matching placebo and, within each category, to receive calcium (800 mg elemental calcium as calcium carbonate in 2 divided daily doses) or matching placebos consistent with the 2-by-2 factorial design. Consistent with the double-masked design, there was no prespecified target goal for the plasma 25(OH)D concentration. Randomization was achieved by permuted blocks (block size of 4 or 8) by using a computer-generated random-number sequence with stratification by age (<55 or $\geq$55 y) and BMI (<30 or $\geq$30). The assignment was double masked. Participants were advised to maintain their usual diet and physical activity and to avoid taking supplemental vitamin D, calcium, or any other supplements on their own during the study. Vitamin D and matching placebos were manufactured by Tishcon Corp (Salisbury, MD). Quality control was conducted at the beginning and once during the study to ensure that vitamin D pills contain the stated amount without deterioration over time. Calcium and matching placebos, as chewable tablets, were manufactured and donated by GlaxoSmithKline (Parsippany, NJ). At week 16, participants came to the center twice, separated by 1 wk, for their repeat testing (OGTT at visit 4; FSIVGTT at visit 5). Physical measurements and fasting blood specimens were collected at each visit. Safety profile questionnaires and measurements of serum calcium and phosphorus were done at the 8- and 16-wk visits.

Ascertainment of exposure and adherence

Vitamin D and calcium intakes were estimated at baseline by a self-report on the basis of a food-frequency questionnaire (13). Vitamin D status was assessed at baseline (visit 1) and 16 wk (visit 5) by measuring plasma 25(OH)D concentrations. Pill adherence was assessed by a self-report on the basis of pill counts.

Prespecified outcomes

The primary endpoint was the mean change from baseline to 16 wk in the disposition index, which was the product of insulin secretion and insulin sensitivity derived from data obtained during the FSIVGTT (12). Data from the FSIVGTT were analyzed by using minimal model analysis (MinMod Millennium, version 5.18; MinMod Inc, Los Angeles, CA) to estimate insulin sensitivity [insulin sensitivity index (S_i)]. The incremental first-phase insulin secretion [acute insulin response to glucose (AIR_g)] was measured by calculating the area under the insulin curve above the baseline for the first 10 min after an intravenous glucose infusion. The disposition index is calculated as $AIR_g \times S_i$. Other outcomes included the change from baseline to 16 wk in AIR_g, S_i, and glucose tolerance (Hb A_{1c}, FPG and 2hPG).

Assessment of potential confounders

Height (to $\pm$0.1 cm) was measured at baseline with a wall-mounted stadiometer, and body weight (to $\pm$100 g) was measured at every visit with an electronic calibrated scale (Cardinal Detecto Model 758C; Cardinal Health, Webb City, MO). BMI was calculated as weight divided by the square of height (in kg/m^2). Data on age, sex, race, ethnicity, and family history of diabetes were self-reported at baseline.

Laboratory analysis

Blood measurements were done in the morning after a 12-h overnight fast. Plasma glucose was measured by an oxygen rate method with a Beckman Synchron LX System (Beckman Coulter Inc, Fullerton, CA). Hb A_{1c} was measured with a Tosoh G7 high-performance liquid chromatochraphy assay (Tosoh Bioscience Inc, San Francisco, CA), certified through the national glycohemoglobin standardization program (http://www.ngsp.org). Serum insulin was measured with a radioimmunoassay commercial kit (DPC Coat-A-Count Insulin assay; Siemens Medical Solutions Diagnostics, Los Angeles, CA). Plasma 25(OH)D was measured at Tufts Medical Center by using liquid chromatography-mass spectrometry certified through the National Institute of Standards and Technology vitamin D quality assurance program (14). Laboratory measurements were done in

a masked fashion and in pairs (before and after the intervention) in the same analytic run to reduce systematic error and interassay variability, with the exception of Hb A_{1c}, which was completed after each sample was collected.

Statistical analysis

To reduce the measurement error, the baseline value for all physical and biochemical (glucose and insulin) measurements were calculated as the mean of values obtained at the screening (visit 1) and randomization (visit 2) visits. Similarly, the end-of-study measurements were calculated as the mean of values obtained at the OGTT (visit 4) and FSIVGTT (visit 5) visits at 16-wk. To examine differences in baseline characteristics between groups, we used the analysis of variance test for differences in means for continuous data and the chi-square test for differences in proportions for categorical variables. For each comparison, we verified whether assumptions for the statistical analyses were met. To compare differences between treatment groups in outcomes over time, we used general linear models (PROC GLM procedure, SAS Software version 9.2; SAS, Cary, NC) conditioned on baseline values to avoid the potential bias that might have resulted if the magnitude of the change depended on the starting value and adjusted for the stratified variables (age and BMI) during randomization. We also adjusted for race (white compared with nonwhite) as a proxy for the different vitamin D homeostasis in persons with dark skin (15) and time at study entry (as the season of the year in 4 categories: January to March compared with April to June compared with July to September compared with October to December). We did not adjust for multiple comparisons because hypotheses were prespecified a priori (16).

The intention-to-treat analyses for the primary outcome (the change in the disposition index) and S_i included 88 participants. Four participants were excluded because the FSIVGTT was not done at baseline ($n = 1$) or because of an inability to calculate the disposition index and S_i because of the early stoppage of the test because of symptomatic hypoglycemia ($n = 3$; **Figure 1**). These 4 participants contributed data to the secondary outcomes AIR_g, Hb A_{1c}, FPG, and 2hPG. Consistent with the intention-to-treat principle, data from participants who were lost to follow-up ($n = 4$) were included in the analyses with their baseline values carried forward. We tested for the interaction between treatment group assignments (vitamin D, calcium) for the primary and secondary outcomes by including the interaction term vitamin D × calcium, in the regression model. P values were 2-sided at the 0.05 significance level. Statistical analysis was done with SAS version 9.2.

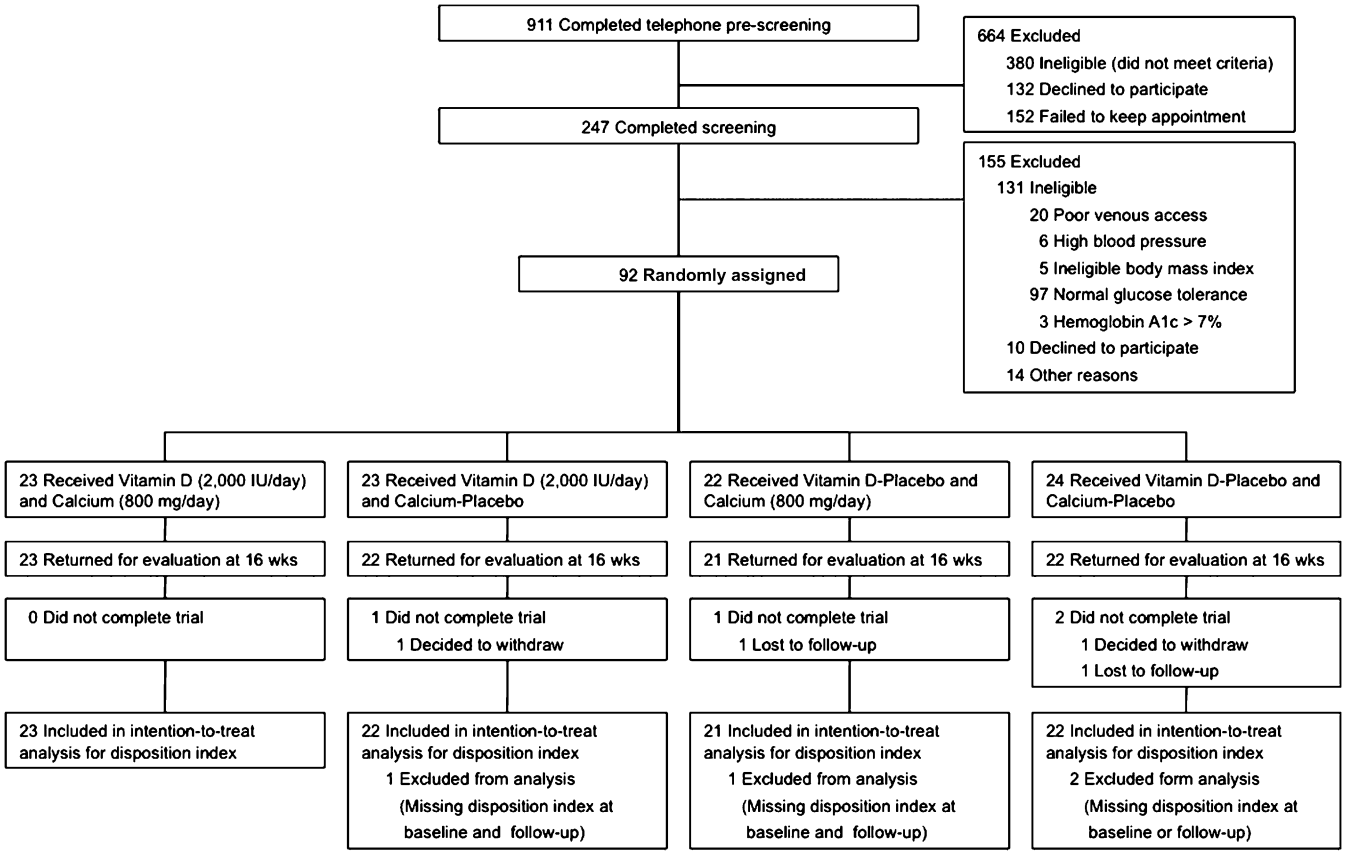

FIGURE 1. Flow of participants. Data on the primary outcome (the disposition index) were not available for 4 participants either because the frequently sampled intravenous-glucose-tolerance test was not done at baseline and follow-up ($n = 1$) or the test was stopped prematurely because of symptomatic hypoglycemia and the disposition index could not be estimated ($n = 3$). These 4 participants were excluded from the analysis of the primary outcome (the disposition index) and insulin sensitivity index, but they all contributed data to secondary outcomes (insulin secretion and measures of glycemia). Data from participants who withdrew or who were lost to follow-up were included in the analysis by carrying over their baseline values.

RESULTS

Participant characteristics and follow-up

Between October 2007 and July 2009, 247 participants were screened for eligibility, of whom 92 participants (37%) underwent randomization (Figure 1). Baseline characteristics of participants are shown in **Table 1**. Consistent with a prediabetes (glucose-intolerant) population, the mean (±SEM) age of the cohort was 57 ± 1 y, BMI was 32 ± 0, and Hb A_{1c} was 5.9 ± 0.0%. According to the 2010 American Diabetes Association diagnostic criteria for diabetes that includes Hb A_{1c} as a criterion (17), 93% of participants were at risk of diabetes, and 7% of participants had diabetes. The mean (± SEM) plasma 25(OH)D concentration at baseline was 24.5 ± 0.8 ng/mL. There was some heterogeneity in baseline values of the disposition index, AIR_g, and S_i in the 4 groups; however, values were nonstatistically

TABLE 1
Baseline characteristics of study participants[1]

Characteristics	Total (n = 92)	Vitamin D + calcium (n = 23)	Vitamin D + placebo (n = 23)	Placebo + calcium (n = 22)	Placebo + placebo (n = 24)	P
Age (y)	57 ± 1[2]	57 ± 2	57 ± 2	57 ± 2	59 ± 2	0.84
Women [n (%)]	47 (51)	12 (52)	12 (52)	10 (45)	13 (54)	0.94
Race [n (%)][3]						0.60
White	72 (78)	17 (74)	20 (87)	16 (73)	19 (79)	
Black	19 (21)	6 (26)	3 (13)	5 (23)	5 (21)	
Asian	1 (1)	0 (0)	0 (0)	1 (5)	0 (0)	
Ethnicity [n (%)][3]						0.40
Not Hispanic or Latino	89 (97)	22 (95)	22 (95)	22 (100)	23 (95)	
Hispanic or Latino	1 (1)	0 (0)	1 (4)	0 (0)	0 (0)	
Other or not reported	2 (2)	1 (4)	0 (0)	0 (0)	1 (4)	
Season of study entry [n (%)]						0.87
January to March	25 (27)	8 (35)	8 (35)	5 (23)	4 (17)	
April to June	12 (13)	3 (13)	2 (9)	2 (9)	5 (21)	
July to September	17 (18)	4 (17)	4 (17)	4 (18)	5 (21)	
October to December	38 (41)	8 (35)	9 (39)	11 (50)	10 (42)	
Family history of diabetes [n (%)]	39 (43)	12 (55)	8 (35)	6 (27)	13 (54)	0.15
Weight (kg)	93 ± 2	94 ± 3	94 ± 3	91 ± 3	92 ± 3	0.85
BMI (kg/m^2)[4]	32 ± 0	33 ± 1	32 ± 1	32 ± 1	32 ± 1	0.62
Glucose tolerance [n (%)][5]						0.54
At risk of diabetes	86 (93)	20 (87)	22 (96)	21 (95)	23 (96)	
Diabetes	6 (7)	3 (13)	1 (4)	1 (5)	1 (4)	
Vitamin D intake (IU/d)						
Total (diet + supplements)	386 ± 33	374 ± 61	403 ± 65	414 ± 87	355 ± 53	0.92
Diet only	216 ± 15	241 ± 32	236 ± 27	206 ± 37	181 ± 23	0.45
Calcium intake (mg/d)						
Total (diet + supplements)	976 ± 58	1083 ± 141	974 ± 103	971 ± 131	880 ± 89	0.67
Diet only	859 ± 49	1000 ± 125	876 ± 96	791 ± 86	770 ± 82	0.34
25-hydroxyvitamin D (ng/mL)	24.5 ± 0.8	22.4 ± 1.6	26.5 ± 1.6	25.0 ± 1.8	24.2 ± 1.3	0.30
Frequently sampled intravenous glucose tolerance test						
Disposition index: $AIR_g \times S_i$	1033 ± 124	1010 ± 229	1318 ± 210	1096 ± 376	725 ± 133	0.51
Insulin secretion: AIR_g ($mU \cdot L^{-1} \cdot min$)[6]	339 ± 42	330 ± 48	336 ± 49	421 ± 154	276 ± 45	0.74
Insulin sensitivity: S_i ($mU^{-1} \cdot L^{-1} \cdot min^{-1}$)[7]	4.16 ± 0.46	3.59 ± 0.77	5.49 ± 1.09	4.47 ± 1.25	3.20 ± 0.47	0.27
Glycemia						
Hb A_{1c} (%)	5.90 ± 0.00	5.91 ± 0.11	5.91 ± 0.06	5.89 ± 0.08	5.91 ± 0.08	0.99
Fasting plasma glucose (mg/dL)	93.2 ± 1.1	92.5 ± 2.0	92.0 ± 2.4	94.6 ± 2.6	93.8 ± 2.2	0.85
2-h postload glucose (mg/dL)[8]	133.3 ± 3.7	139.8 ± 7.5	118.6 ± 6.3	135.4 ± 6.2	139.2 ± 8.4	0.13

[1] AIR_g, acute insulin response to glucose; S_i, insulin sensitivity index; Hb A_{1c}, glycated hemoglobin. Percentages may not total 100 because of rounding. To convert from traditional units (mg/dL) to international units (mmol/L) for glucose concentrations, multiply by 0.0555; to convert insulin concentrations from milliunits per liter to picomoles per liter, multiply by 7.175; to convert 25-hydroxyvitamin D concentrations from nanograms per milliliter to nanomoles per liter, multiply by 2.456; to convert vitamin D intake from international units to micrograms, divide by 40. P values are for the ANOVA for differences between groups or for the chi-square for differences in proportions.

[2] Mean ± SEM (all such values).

[3] Self-reported, and participants could check multiple categories.

[4] Calculated as weight divided by the square of height.

[5] Defined by using the 2010 American Diabetes Association criteria (17); at risk of diabetes was defined as a fasting plasma glucose concentration of 100–125 mg/dL or plasma glucose concentration 2 h after a 75-g oral glucose load of 140–199 mg/dL or Hb A_{1c} of 5.8–6.4%; diabetes was defined as a fasting plasma glucose concentration >125 mg/dL or plasma glucose concentration 2 h after a 75-g oral glucose load >199 mg/dL or Hb A_{1c} >6.4%.

[6] Estimated as the incremental insulin area for the first 10 min after an intravenous glucose infusion.

[7] Calculated by the minimal model.

[8] Plasma glucose 2 h after a 75-g oral glucose load.

significant. Four participants did not return for their follow-up visits at 16 wk (Figure 1), but they were included in the intention-to-treat analyses.

Intervention

Supplements were well tolerated. Only 1 participant discontinued all study pills because of an intolerance to the smell of the calcium pills. Pill adherence (consumption of >80% of prescribed pills) was 89% to vitamin D pills and 85% to calcium pills without any differences between groups. At the last follow-up visit, the plasma 25(OH)D concentration was higher in the vitamin D group than in the no vitamin D group (30.6 ± 1.2 compared with 18.4 ± 1.1 ng/mL respectively; P for difference < 0.001; **Table 2**) whereas the 25(OH)D concentration did not differ between the calcium and no calcium groups (Table 2).

Change in disposition index, insulin sensitivity, and insulin secretion

After adjustment for stratified variables (age and BMI), the baseline disposition index value, race, and time of study entry, the disposition index significantly increased in the vitamin D group and decreased in the no vitamin D group (adjusted mean change ± SEM: 300 ± 130 for vitamin D compared with −126 ± 127 for no vitamin D; P = 0.011; **Figure 2**A). There was no significant difference in the change in the disposition index with calcium compared with no calcium (79 ± 130 for calcium compared with 83 ± 135 for no calcium; P = 0.979; Figure 2A). Within each individual group, combined vitamin D and calcium supplementation or vitamin D alone, compared with placebo, improved the disposition index the most, and the difference was nearly significant compared with placebos (Figure 2B). There was no significant interaction between the 2 interventions (vitamin D ×

TABLE 2
Effects of vitamin D or calcium supplementation on metabolic variables[1]

	Baseline	Change from baseline[2]	P	Adjusted change from baseline[3]	P
25(OH)D (ng/mL)					
Vitamin D (n = 46)	24.4 ± 1.1	6.3 ± 1.0	<0.001	5.0 ± 1.1	<0.001
No vitamin D (n = 46)	24.6 ± 1.1	−6.3 ± 1.0	—	−7.0 ± 1.1	—
Calcium (n = 45)	23.6 ± 1.2	0.0 ± 1.4	0.996	−1.2 ± 1.5	0.841
No calcium (n = 47)	25.3 ± 1.0	0.0 ± 1.4	—	−1.5 ± 1.5	—
Insulin secretion: AIR_g ($mU \cdot L^{-1} \cdot min$)					
Vitamin D (n = 45)	333 ± 34	34 ± 34	0.074	62 ± 39	0.046
No vitamin D (n = 46)	345 ± 77	−53 ± 34	—	−36 ± 37	—
Calcium (n = 45)	374 ± 79	5 ± 35	0.545	22 ± 38	0.605
No calcium (n = 46)	304 ± 33	−25 ± 35	—	−4 ± 40	—
Insulin sensitivity: S_i ($mU^{-1} \cdot L^{-1} \cdot min^{-1}$)					
Vitamin D (n = 45)	4.52 ± 0.67	−0.3 ± 0.3	0.161	−0.2 ± 0.3	0.145
No vitamin D (n = 43)	3.65 ± 0.64	−0.9 ± 0.3	—	−0.8 ± 0.3	—
Calcium (n = 44)	4.01 ± 0.71	−0.4 ± 0.3	0.375	−0.4 ± 0.3	0.389
No calcium (n = 44)	4.18 ± 0.60	−0.8 ± 0.3	—	−0.7 ± 0.3	—
Hb A_{1c} (%)					
Vitamin D (n = 46)	5.91 ± 0.06	0.06 ± 0.03	0.055	0.06 ± 0.03	0.081
No vitamin D (n = 46)	5.90 ± 0.06	0.14 ± 0.03	—	0.14 ± 0.03	—
Calcium (n = 45)	5.90 ± 0.07	0.07 ± 0.03	0.197	0.07 ± 0.03	0.196
No calcium (n = 47)	5.91 ± 0.05	0.13 ± 0.03	—	0.13 ± 0.03	—
Fasting plasma glucose (mg/dL)					
Vitamin D (n = 46)	92.3 ± 1.5	1.7 ± 1.6	0.149	2.4 ± 1.9	0.172
No vitamin D (n = 46)	94.2 ± 1.7	5.0 ± 1.6	—	5.6 ± 1.8	—
Calcium (n = 45)	93.6 ± 1.6	2.1 ± 1.6	0.305	2.9 ± 1.8	0.258
No calcium (n = 47)	92.9 ± 1.6	4.5 ± 1.6	—	5.5 ± 1.8	—
2-h postload glucose (mg/dL)[4]					
Vitamin D (n = 46)	129.2 ± 5.1	−7.9 ± 4.7	0.182	−7.2 ± 5.5	0.220
No vitamin D (n = 46)	137.4 ± 5.3	1.0 ± 4.7	—	1.2 ± 5.2	—
Calcium (n = 45)	137.7 ± 4.8	−4.6 ± 4.8	0.734	−3.9 ± 5.2	0.698
No calcium (n = 47)	129.1 ± 5.4	−2.3 ± 4.7	—	−1.2 ± 5.5	—

[1] All values are means ± SEMs. 25(OH)D, 25-hydroxyvitamin D; S_i, insulin sensitivity index; AIR_g, acute insulin response to glucose; Hb A_{1c}, glycated hemoglobin. To convert from traditional units (mg/dL) to international units (mmol/L) for glucose concentrations, multiply by 0.0555; to convert insulin concentrations from milliunits per liter to picomoles per liter, multiply by 7.175; to convert 25(OH)D concentrations from nanograms per milliliter to nanomoles per liter, multiply by 2.456. P values are for the ANOVA test for differences in means between active intervention and matching placebo (vitamin D compared with no vitamin D or calcium compared with no calcium).

[2] Adjusted for stratified variables (age and BMI) and the baseline value of the outcome variable.

[3] Additionally adjusted for race (white compared with nonwhite) and time of study entry (season of the year in the following 4 categories: January to March compared with April to June compared with July to September compared with October to December).

[4] Plasma glucose 2 h after a 75-g oral glucose load.

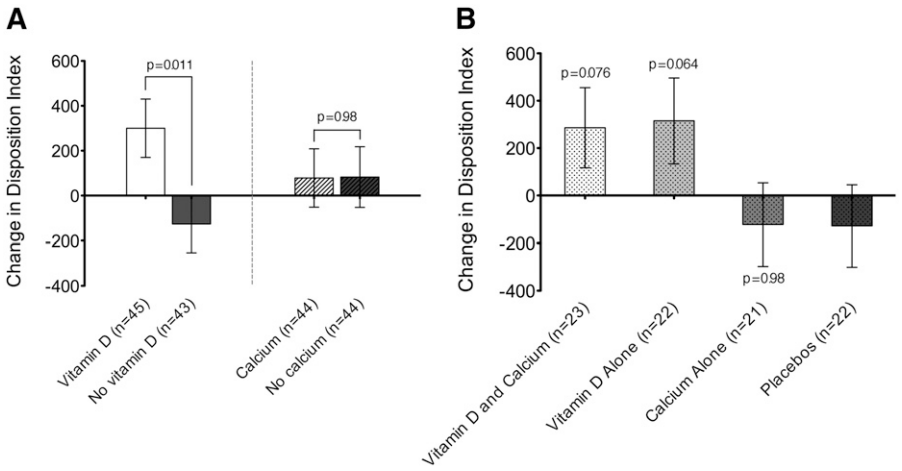

FIGURE 2. Mean (±SEM) changes in the disposition index between baseline and week 16. All data are least squares means adjusted for stratified variables (age and BMI), the baseline value of the outcome variable, race, and time of study entry. A: Changes in the disposition index between vitamin D (300 ± 130) and no vitamin D (−126 ± 127) or between calcium (79 ± 130) and no calcium (83 ± 135). *P* values are for the ANOVA test for differences in means between vitamin D and no vitamin D or between calcium and no calcium. B: Changes in the disposition index for vitamin D and calcium (286 ± 169) compared with vitamin D alone (315 ± 181) compared with calcium alone (−122 ± 176) compared with placebo (−128 ± 173). *P* values are for the ANOVA test for differences in means compared with placebo. $P = 0.92$ for the vitamin D × calcium interaction.

calcium) on the change in the disposition index (*P* for interaction = 0.92).

The change in AIR_g paralleled the change in the disposition index. Insulin secretion significantly increased in the vitamin D group and decreased in the no vitamin D group (62 ± 39 for vitamin D compared with -36 ± 37 mU · L^{-1} · min for no vitamin D; $P = 0.046$), whereas there was no significant difference with calcium compared with no calcium (Table 2). Insulin secretion increased the most in the group that received both vitamin D and calcium (76 ± 51 for vitamin D and calcium compared with -44 ± 50 mU · L^{-1} · min for placebo; $P = 0.082$; **Table 3**). There was no significant change in insulin sensitivity in any group (Tables 2 and 3). There was no interaction between the 2 interventions (vitamin D × calcium) on the change in insulin secretion (*P* for interaction = 0.87) or insulin sensitivity (*P* for interaction = 0.43).

Change in glycemia

As expected, because of the natural history of prediabetes, Hb A_{1c} increased in all groups during the study period. Hb A_{1c} tended to increase less in the vitamin D group than in the no vitamin D group, but the result was not significant (0.06 ± 0.03% for vitamin D compared with 0.14 ± 0.03% for no vitamin D; $P = 0.081$; Table 2); however, after excluding 2 outliers with a change in Hb A_{1c} >0.8%, the difference between vitamin D compared with no vitamin D became significant (0.08 ± 0.03% compared with 0.15 ± 0.02%, respectively; $P = 0.024$). There was no difference in the Hb A_{1c} change with calcium than with no calcium (Table 2). Within each individual group, the combined vitamin D and calcium supplementation, compared with the placebo, attenuated the increase in Hb A_{1c} the most (0.05 ± 0.05% for vitamin D and calcium compared with 0.18 ± 0.04% for the placebo; $P = 0.036$; Table 3). However, there was no significant interaction between the 2 interventions (vitamin D × calcium) on the change in Hb A_{1c} (*P* for interaction = 0.51).

There was no significant effect of vitamin D compared with no vitamin D or calcium compared with no calcium on FPG or 2hPG (Table 2). Vitamin D alone attenuated the increase in FPG the most compared with the placebo (2.1 ± 2.5 for vitamin D alone compared with 8.4 ± 2.3 for the placebo; $P = 0.051$; Table 3). There was no interaction between the 2 interventions (vitamin D × calcium) on FPG (*P* for interaction = 0.15) or 2hPG (*P* for interaction = 0.82).

Safety

A total of 28 adverse events were reported without difference between study groups. There were no reports of nephrolithiasis or hypercalcemia. Two participants (one patient randomly assigned to receive vitamin D and calcium and the other patient randomly assigned to receive calcium alone) were briefly hospitalized for reasons unrelated to the study but returned for follow-up visits. One participant randomly assigned to the vitamin D alone group sustained an ankle fracture and withdrew from the study. Three participants permanently discontinued all study pills during the trial (one participant did not tolerate the taste of the calcium pills and 2 participants discontinued all study pills on the advice of their physicians), but they returned for follow-up visits.

DISCUSSION

In this 2-by-2 factorial trial of vitamin D and calcium supplementation in adults at high risk of type 2 diabetes, vitamin D supplementation with or without calcium improved the disposition index and insulin secretion, and there was a trend toward an attenuation of the rise in Hb A_{1c} that occurs over time in this population. The supplementation with calcium alone did not have any significant effect, and there was no significant interaction between the 2 nutrients on primary or secondary outcomes. These results suggested that vitamin D may have a role in delaying the progression to clinical diabetes in adults at high risk of type 2 diabetes. Our results may also be relevant to patients with type 1 diabetes, which is characterized by β cell

TABLE 3
Effects of vitamin D and calcium supplementation on metabolic variables[1]

	Baseline	Change from baseline[2]	*P*	Adjusted change from baseline[3]	*P*
25(OH)D (ng/mL)					
Vitamin D and calcium (n = 23)	22.4 ± 1.6	4.8 ± 1.4	<0.001	3.7 ± 1.5	<0.001
Vitamin D only (n = 23)	26.5 ± 1.6	7.7 ± 1.4	<0.001	6.3 ± 1.5	<0.001
Calcium only (n = 22)	25.0 ± 1.8	−5.0 ± 1.4	0.242	−5.6 ± 1.5	0.181
Placebos (n = 24)	24.2 ± 1.3	−7.4 ± 1.4	—	−8.2 ± 1.4	—
AIR_g ($mU \cdot L^{-1} \cdot min$)					
Vitamin D and calcium (n = 23)	330 ± 48	53 ± 49	0.097	76 ± 51	0.082
Vitamin D only (n = 22)	336 ± 49	15 ± 50	0.270	46 ± 55	0.196
Calcium only (n = 22)	421 ± 154	−45 ± 50	0.809	−29 ± 52	0.831
Placebos (n = 24)	276 ± 45	−62 ± 48	—	−44 ± 50	—
S_i ($mU^{-1} \cdot L^{-1} \cdot min^{-1}$)					
Vitamin D and calcium (n = 23)	3.6 ± 0.8	0.0 ± 0.4	0.114	0.1 ± 0.4	0.108
Vitamin D only (n = 22)	5.5 ± 1.1	−0.7 ± 0.4	0.687	−0.6 ± 0.4	0.657
Calcium only (n = 21)	4.5 ± 1.2	−0.9 ± 0.4	0.974	−0.8 ± 0.4	0.989
Placebos (n = 22)	2.9 ± 0.4	−0.9 ± 0.4	—	−0.9 ± 0.4	—
Hb A_{1c} (%)					
Vitamin D and calcium (n = 23)	5.9 ± 0.1	0.04 ± 0.04	0.026	0.05 ± 0.05	0.036
Vitamin D only (n = 23)	5.9 ± 0.1	0.07 ± 0.04	0.073	0.08 ± 0.05	0.093
Calcium only (n = 22)	5.9 ± 0.1	0.10 ± 0.04	0.181	0.09 ± 0.05	0.177
Placebos (n = 24)	5.9 ± 0.1	0.18 ± 0.04	—	0.18 ± 0.04	—
Fasting plasma glucose (mg/dL)					
Vitamin D and calcium (n = 23)	92.5 ± 2.0	2.2 ± 2.2	0.087	2.8 ± 2.4	0.087
Vitamin D only (n = 23)	92.0 ± 2.4	1.1 ± 2.2	0.040	2.1 ± 2.5	0.051
Calcium only (n = 22)	94.6 ± 2.6	2.0 ± 2.3	0.078	2.6 ± 2.4	0.075
Placebos (n = 24)	93.8 ± 2.2	7.7 ± 2.2	—	8.4 ± 2.3	—
2-h postload glucose (mg/dL)[4]					
Vitamin D and calcium (n = 23)	139.8 ± 7.5	−9.6 ± 6.7	0.247	−8.9 ± 7.1	0.267
Vitamin D only (n = 23)	118.6 ± 6.3	−6.2 ± 6.8	0.430	−5.1 ± 7.8	0.486
Calcium only (n = 22)	135.4 ± 6.2	0.7 ± 6.8	0.944	1.0 ± 7.2	0.931
Placebos (n = 24)	139.2 ± 8.4	1.3 ± 6.5	—	1.7 ± 7.0	—

[1] All values are means ± SEMs. 25(OH)D, 25-hydroxyvitamin D; S_i, insulin sensitivity index; AIR_g, acute insulin response to glucose; Hb A_{1c}, glycated hemoglobin. To convert from traditional units (mg/dL) to international units (mmol/L) for glucose concentrations, multiply by 0.0555; to convert insulin concentrations from milliunits per liter to picomoles per liter, multiply by 7.175; to convert 25(OH)D concentrations from nanograms per milliliter to millimoles per liter, multiply by 2.456. *P* values are for the ANOVA test for differences in means between active intervention (vitamin D and calcium, vitamin D only, and calcium only) and placebo.

[2] Adjusted for stratified values (age and BMI) and the baseline value of the outcome variable.

[3] Additionally adjusted for race (white compared with nonwhite) and time of study entry (season of the year in the following 4 categories: January to March compared with April to June compared with July to September compared with October to December).

[4] Plasma glucose 2 h after a 75-g oral glucose load.

failure; however, a specific study in type 1 diabetes would be needed to test this hypothesis because the underlying defect (autoimmunity) is different from type 2 diabetes.

For type 2 diabetes to develop, impaired pancreatic β cell function and insulin resistance are often present, and there is evidence from nonhuman studies that vitamin D influences both of these mechanisms. In in vitro and in vivo studies, vitamin D deficiency impaired the glucose-mediated insulin secretion from β cells (2, 18–20), whereas vitamin D supplementation restored the insulin secretion (2, 19–22). Vitamin D may have a direct effect mediated by the binding of the active form 1,25 dihydroxyvitamin D to the vitamin D receptor, which is expressed in β cells (23, 24). The presence of the vitamin D response element in the human insulin gene promoter (25) and transcriptional activation of the human insulin gene caused by 1,25 dihydroxyvitamin D (26) further supported a direct effect of vitamin D on insulin synthesis and secretion. Alternatively, the activation of vitamin D may occur within the β cell by the 25(OH) D-1α-hydroxylase (CYP27B1), which is expressed in β cells (27). An indirect effect of vitamin D on the pancreatic β cell may be mediated via its regulation of calcium that in turn, affects insulin secretion, which is a calcium-dependent process (28). In peripheral insulin-target cells, active vitamin D metabolites may enhance insulin sensitivity in several ways, including the increase of the expression of insulin receptors (26), the activation of transcription factors important in glucose homeostasis (29), or indirectly via the regulation of calcium, which is essential for insulin-mediated intracellular processes.

In the CaDDM study, vitamin D supplementation improved the disposition index by ≈26% compared with a worsening of ≈14% in the group that received no vitamin D. The disposition index is a measure of pancreatic β cell function that captures the hyperbolic relation between insulin secretion and insulin

sensitivity (30). A low disposition index indicates an impaired pancreatic β cell function and is a validated predictor of diabetes risk (31, 32). Vitamin D improved the disposition index and insulin secretion (AIR_g), but its effect on insulin sensitivity was not significant, which indicated a predominant effect of vitamin D on the pancreatic β cell. The targeting of β cell function early in the pathogenesis of type 2 diabetes is considered a critical intervention for the prevention of the disease (33), and our results suggested that vitamin D supplementation may have a role in delaying the natural history of type 2 diabetes.

Our results were consistent with observational studies in which an association between vitamin D status and insulin secretion has been reported (34, 35). Two other small trials have reported no change in insulin secretion after vitamin D supplementation among insulin resistant (36) or healthy obese adults (37). Several observational studies have reported an association between vitamin D status and insulin sensitivity (38–41), but in our study, the effect of vitamin D supplementation on insulin sensitivity was not significant. A few other trials have reported no change in insulin sensitivity after vitamin D supplementation in healthy adults (37, 42, 43) or patients with established type 2 diabetes (44); however, vitamin D supplementation improved insulin sensitivity in persons with insulin resistance (37) or prediabetes (45).

Glycemia, as measured by Hb A_{1c}, tends to rise as part of the natural history of prediabetes (46). Although the absolute difference in Hb A_{1c} between the vitamin D and no vitamin D groups appeared to be small ($\approx$0.08%), such a difference could have a large effect at the population level, especially in individuals with prediabetes. For example, in the Diabetes Prevention Program trial, which targeted a population very similar to our population, the difference in Hb A_{1c} between the active lifestyle intervention and placebo throughout the entire duration of the study was $\approx$0.15%, which was associated with a 58% decrease in incident diabetes (46). In the CaDMM study, although not significant, FPG rose in both groups but less so in the vitamin D group, whereas 2hPG declined in the vitamin D group, which suggested that the effect of vitamin D on glycemia may have been more pronounced in the postprandial phase, consistent with the improvement in AIR_g. However, a larger study powered for glycemic outcomes would be required to confirm this hypothesis.

Several trials have reported the effect of vitamin D supplementation on glycemia (5, 43, 44) or incident diabetes by self-reports (42, 47). Seven trials included participants with normal glucose tolerance, and 3 trials had participants with established type 2 diabetes. In these trials, supplementation with vitamin D had no significant effect on glycemic measures or incident diabetes. However, several of these studies were designed for nonglycemic outcomes, and the analyses on vitamin D were post hoc, and all trials but one trial (42) were underpowered for glycemic outcomes. Moreover, several trials supplemented with infrequent (weekly or monthly) large doses of vitamin D, which may not have been a desirable physiologic method for supplementation and may have been be counterproductive (48). However, vitamin D may have beneficial effects in individuals with prediabetes, as suggested by the results of the present study and a post hoc analysis of a completed trial with combined vitamin D_3 calcium carbonate in adults with glucose intolerance at baseline (45).

In the CaDDM study, the calcium supplementation did not have any significant effect, and there was no interaction between vitamin D and calcium on outcomes. Calcium intake has been associated with lower risk of incident diabetes in previous studies (9, 10), and the combination of vitamin D and calcium may have been more beneficial than with either nutrient alone (10, 45). However, in these studies the intake of calcium that conferred a benefit was between 600 and 1000 mg calcium per day. In our study, the mean dietary calcium intake at baseline was 859 mg calcium per day, which indicated that most participants may have already reached the necessary threshold for calcium intake required for a benefit, and additional intake during the trial would not have conferred an increased benefit (49).

The strengths of our study included the study design, population with prediabetes, high retention rate, high adherence to the study interventions, the mean 25(OH)D concentration achieved in the vitamin D group ($\approx$31 ng/mL) despite the population being obese, difference between vitamin compared with no vitamin D groups ($\approx$12 ng/mL), and the use of a highly sensitive and validated measure of β cell function. Potential limitations were that participants were predominantly white, there was some heterogeneity in baseline values of the disposition index, AIR_g and S_i in the 4 groups (although not significant), and the short duration of the study; however, our analyses adjusted for race to account for skin color, for baseline values of outcomes, and for the time at study entry to account for seasonal differences in sun exposure because of 4-mo study period. We did not adjust for multiple comparisons because the hypotheses were specified a priori, which may have increased the possibility of an experiment-wise (type 1) error. Finally, because our study was conducted at a single-site, the results may not apply in geographic areas at different latitudes.

In conclusion, supplementation with vitamin D was associated with improved pancreatic β cell function in adults at high risk of type 2 diabetes, and there was a trend toward attenuating the rise in Hb A_{1c} that occurs over time in this population. Because our study was short-term and was not powered for hard clinical outcomes, our findings need to be confirmed in larger trials of longer duration to test the hypothesis that vitamin D supplementation is a safe and effective intervention to improve glycemia and retard the progression from prediabetes to diabetes in participants at high risk of the disease.

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