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Short Communication

Effect of vitamin D supplementation on cardiovascular risk in type 2 diabetes

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SUMMARY

Background & aims: Whether vitamin D affects lipid profile and cardiovascular disease (CVD) risk is controversial. We evaluated the effect of oral daily vitamin D supplementation on lipid profile and CVD risk in patients with well-controlled type 2 diabetes.
Methods: Secondary analysis in the vitamin D for established type 2 diabetes (DDM2) study, a double-blind, randomized, placebo-controlled clinical trial. 127 patients (mean age 60 years) with stable (HbA1c $\leq$ 7.5%) diabetes managed with lifestyle only or lifestyle plus metformin were randomized to receive 4000 IU/day of vitamin D_3 (n = 66) or placebo (n = 61) for 48 weeks. Changes in lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides [TG] and TG/HDL ratio), C-reactive protein and CVD risk (calculated according the American College of Cardiology/American Heart Association [ACC/AHA] guidelines) were assessed at week 24 and 48.
Results: The mean [±SEM] plasma 25-hydroxyvitamin D [25(OH)D] level was higher in the vitamin D vs. the placebo group (20.5 ± 1.18 vs. −1.6 ± 1.2 ng/mL respectively; $p < 0.001$). There was no statistically significant change in lipid profile, C-reactive protein or CVD risk. Among patients who were not on cholesterol medication (n = 32), vitamin D supplementation reduced TG compared to placebo at week 48 (−18.74 ± 8.91 vs. 9.69 ± 8.60 mg/dL respectively; $p = 0.032$).
Conclusion: One year supplementation with vitamin D_3 at 4000 IU/day did not affect lipid profile, C-reactive protein and CVD risk in patients with stable type 2 diabetes not selected for vitamin D deficiency, with the exception of improvement of TG among patients not on cholesterol medication.
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1. Introduction

Observational studies, summarized in systematic reviews [1–3], have reported associations between low blood 25(OH)D concentration and increased risk of cardiovascular disease (CVD). In the most recent meta-analysis, Zhang et al. reported an inverse association between serum 25(OH)D concentration and total cardiovascular events (27 studies) and cardiovascular mortality (17 studies); the reported pooled relative risks per 10 ng/mL increment were 0.90 (95% CI: 0.86, 0.94) for total cardiovascular events and 0.88 (95% CI: 0.80, 0.96) for cardiovascular mortality [3]. Results from intervention studies are contradictory but overall, findings so far indicate that vitamin D supplementation is unlikely to improve cardiovascular health [4]. Two small (<150 patients), short-term (8 weeks) trials with blood pressure as the end-point

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reported a reduction of blood pressure with vitamin D supplementation) [5,6].

Results from observational studies support a favorable association between high blood 25(OH)D concentration on lipid profile [7] but no causal relationship can be established from these studies given their observational nature. In a meta-analysis of 10 trials, Wang et al. reported no statistically significant effects for vitamin D supplementation on lipid profile [1]. However, the trials had small sizes (only 5 had more than 100 participants), and varied in quality, duration and method of vitamin D administration; therefore, firm conclusions cannot be drawn. A meta-analysis of 17 trials conducted among patients with type 2 diabetes reported that vitamin D supplementation improved serum levels of total cholesterol (TC), triglycerides (TG) and LDL; in more detail, vitamin D significantly reduced serum TC (−3.74 mg/dl, 95% CI: −7.13 to −0.34, P = 0.031) and LDL (−2.55 mg/dl, 95% CI: −4.83 to −0.26, P = 0.029), while the reduction in TG was not significant (−4.90 mg/dl, 95% CI: −15.11–5.31, P = 0.347) [8].

The aim of the present analysis was to evaluate the effect of oral daily vitamin D supplementation on lipid profile and CVD risk among patients with stable type 2 diabetes.

2. Materials and methods

2.1. Study design

This is a secondary analysis using data from the vitamin D for established type 2 diabetes (DDM2) study, a double-blind, placebo-controlled, randomized trial investigating the effect of oral daily vitamin D supplementation on cardiometabolic outcomes in patients with stable type 2 diabetes [9]. The study was approved by the Institutional Review Board of Tufts Medical Center and University of Cincinnati and all participants provided written informed consent.

2.2. Setting and participants

Patients were 25–75 years old; had a BMI 23–42 kg/m^2; had type 2 diabetes defined by being on a stable dose of metformin monotherapy or meeting laboratory criteria for diabetes at screening according to the American Diabetes Association criteria (fasting glucose ≥ 126 mg/dL, HbA1c ≥ 6.5% or glucose ≥ 200 mg/dL two hours after a 75-gram oral glucose load [2hPG]); had stable diabetes defined by HbA1c ≤ 7.5% without any anticipated change in diabetes therapy in the next 24 weeks. Key exclusion criteria included being on any diabetes pharmacotherapy other than metformin; history of type 1 diabetes or secondary diabetes, recent history of hyperparathyroidism, nephrolithiasis or hypercalcemia.

2.3. Intervention

Patients were randomly assigned (1:1 ratio) to receive either one pill of 4000 IU of vitamin D_3 (cholecalciferol) or placebo daily for 48 weeks. We performed a computer-generated randomization, in random blocks of 4 or 8, and stratified by BMI (<30 or ≥30 kg/m^2), race (White or non-White [e.g., American Indian, Asian, Pacific Islander, Black]) and diabetes therapy (lifestyle only or lifestyle plus metformin). Adherence was assessed by pill counts at every visit. Participants completed a food frequency questionnaire at baseline.

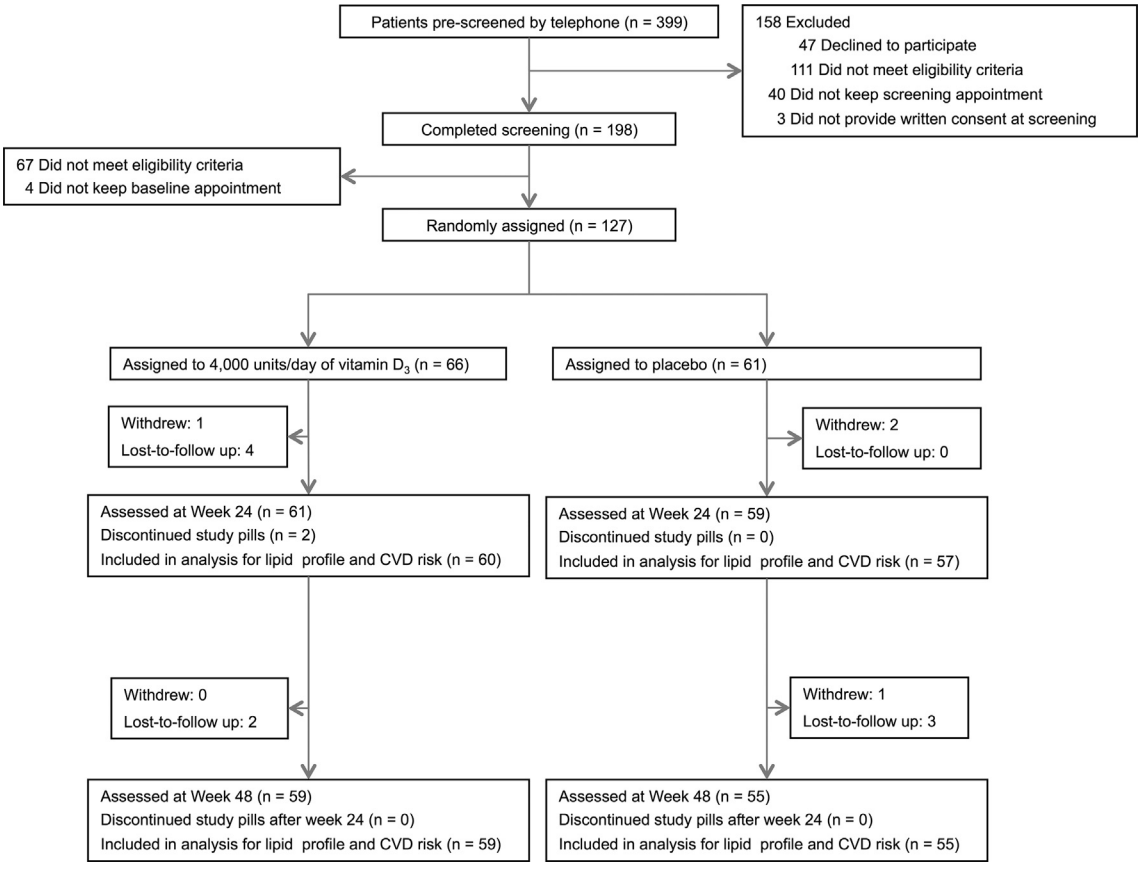

Fig. 1. Flow of participants.

2.4. Follow up and measurements

Blood was drawn after an 8-hour overnight fast. Patients held their study pill (vitamin D or placebo) and any other medications until after testing was completed. Screening and safety labs were analyzed on the same day at each site's clinical laboratory. Serum for lipid outcomes was processed and stored at −80 °C until analyses, which were done by the central laboratory (Tufts Medical Center) in pairs (before/after intervention) in the same analytical run to reduce systematic error and inter-assay variability. TC, LDL, HDL-C, and TG levels were measured at baseline, week 24 and 48 by Abbott Architect c8000 (7D62-21, 1E31-20, 3K33-21 and 7D74-21 respectively). C-reactive protein was measured by Abbott Architect c8000 (1.68% CV). Plasma 25(OH)D was measured by liquid chromatography-mass spectrometry with calibrators that are traceable to NIST (from the Bureau of Standards).

2.5. Outcomes

We evaluated the effect of vitamin D supplementation on lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides [TG] and TG/HDL ratio), C-reactive protein and CVD risk, calculated according the ACC/AHA guidelines [10]. Variability of response to vitamin D supplementation was also assessed in subgroups defined by baseline characteristics of race (White vs. non-White) and 25(OH)D concentration (<20 vs. ≥20 ng/mL).

2.6. Statistical methods

Analyses were by intention-to-treat, defined as all participants in their randomly assigned treatment group and including all available measurements irrespective of adherence to assigned treatment. Difference between treatment groups at week 24 and 48 was assessed using linear regression. Analyses were adjusted for the stratification variables ([BMI <30 or ≥30 kg/m^2], race [White vs. non-White], diabetes therapy [lifestyle only vs. lifestyle plus metformin]) and baseline value of the outcome variable. Sample size calculations were not done for the CVD outcomes because they are secondary outcomes. The sample size was based on the primary outcome [9].

3. Results

From February 2013 through July 2014, a total of 399 patients were pre-screened by telephone and 198 completed in-person screening (Fig. 1).

127 patients met eligibility criteria and were randomized to vitamin D_3 (n = 66) or placebo (n = 61). Patient characteristics at baseline were balanced between the two groups (Table 1).

Mean age was 60.2 years, BMI was 30.9 k/m^2 and plasma 25(OH)D concentration was 26.6 ng/mL. About two thirds of patients were on cholesterol medication [statin only (n = 66), statin plus another cholesterol medication (n = 10), non-statin alone (n = 4)].

Of the 127 patients, 94% (n = 120) and 90% (n = 114) completed the week 24 and week 48 visit respectively (Fig. 1). Mean adherence to study pills was 94% for vitamin D and 93% for placebo. At week 24, plasma 25(OH)D concentration was 47.1 ng/mL (increase by 20.5 ng/mL from baseline) in the vitamin D group vs. 25.5 ng/mL (decrease by 1.6 ng/mL) in the placebo group (p < 0.001). Plasma 25(OH)D concentration remained constant at week 48.

Change in TG, TG/HDL ratio, LDL, C-reactive protein and CVD risk at week 24 and 48 were not statistically different between the two groups. No statistically significant change was observed in TC and HDL in both groups at week 24 and 48 (Table 2).

Table 1
Baseline characteristics.

Characteristics	Total (N = 127)	Vitamin D (N = 66)	Placebo (N = 61)
Demographics			
Age, years	60.2 (8.4)	60.1 (8.4)	60.3 (8.5)
Women, n (%)	38 (29.9)	17 (25.8)	21 (34.4)
Race, n (%) [a]			
White	79 (62.2)	41 (62.1)	38 (62.3)
Black or African-American	38 (29.9)	17 (25.8)	21 (34.4)
Asian	6 (4.7)	4 (6.1)	2 (3.3)
Other	4 (3.1)	4 (6.1)	0 (0)
Hispanic or latino ethnicity, n (%)[a]	3 (2.4)	2 (3.0)	1 (1.6)
Season at study entry, n (%)			
January to March	33 (26.0)	15 (22.7)	18 (29.5)
April to June	45 (35.4)	27 (40.9)	18 (29.5)
July to September	32 (25.2)	17 (25.8)	15 (24.6)
October to December	17 (13.4)	7 (10.6)	10 (16.4)
Self-reported vitamin D intake, units/day[b]	399 (343)	407 (381)	391 (301)
Self-reported calcium intake, mg/day[b]	931 (513)	1006 (597)	852 (394)
Smoking status, n (%)			
Never smoked	48 (37.8)	22 (33.3)	26 (42.6)
Currently smoking	14 (11.0)	8 (12.1)	6 (9.8)
Formerly smoked	64 (50.4)	35 (53.0)	29 (47.5)
Prefer not to answer	1 (0.8)	1 (1.5)	0 (0)
Clinical characteristics			
Weight, kg	92.0 (15.5)	91.2 (15.9)	92.9 (15.1)
Body Mass Index, kg/m^2	30.9 (3.8)	30.7 (3.9)	31.2 (3.8)
Metformin use, n (%)	99 (78.0)	51 (77.3)	48 (78.7)
Cholesterol medication, n (%)	80 (63.0)	41 (62.1)	39 (63.9)
Statin only	66 (52.0)	35 (53.0)	31 (50.8)
Statin plus another cholesterol medication	10 (12.5)	6 (9.1)	5 (8.2)
Non-statin alone	3 (2.4)	0	3 (4.9)
Laboratory			
Vitamin D status			
25OHD, ng/mL	26.6 (11.1)	25.8 (10.3)	27.5 (12.0)
25OHD <20 ng/mL, n (%)	33 (26.0)	19 (28.8)	14 (23.0)
25OHD <30 ng/mL, n (%)	80 (63.0)	42 (63.6)	38 (62.3)
Cholesterol, mg/dL			
Total	161.4 (39.7)	166.6 (45.0)	155.7 (32.5)
HDL, mg/dl	41.6 (10.4)	40.5 (10.5)	42.7 (10.4)
LDL	90.7 (34.8)	95.7 (40.5)	85.4 (26.6)
Triglycerides	154.8 (109.3)	162.9 (112.1)	146.0 (106.5)
Triglycerides/HDL ratio	4.2 (3.5)	4.5 (3.5)	3.8 (3.5)
C-reactive protein, mg/L	3.60 (6.67)	2.85 (3.60)	4.42 (8.83)
CVD Risk[c]	25.2 (13.7)	25.3 (12.0)	25.0 (15.4)

Values are means (standard deviation) unless otherwise specified; percentages may not total 100 because of rounding; to convert 25(OH)D from ng/mL to mmol/L, multiply by 2.456; to convert vitamin D intake from international units to mcg, divide by 40.

[a] Race and ethnicities were self-reported and followed NIH guidelines. Participants could check multiple categories. Asian includes "Chinese" (n = 3) and "Other Asian" (n = 3). Other includes "Native Hawaiian or Other Pacific Islander" (n = 1) and "Other" (n = 3).

[b] Data are derived from the food frequency questionnaire.

[c] Cardiovascular risk was calculated according the ACC/AHA guidelines [10-year and lifetime risks for atherosclerotic cardiovascular disease (ASCVD), defined as coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke].

After excluding 15 participants who changed cholesterol medications during the study, results did not change (not shown). In subgroup analyses by race (white vs. non-white) or 25(OH)D concentration at baseline (<20 vs. ≥20 ng/mL), results did not change (not shown).

Among patients who were not on cholesterol medication at baseline or during follow up (n = 32), vitamin D supplementation reduced TG in vitamin D vs placebo group at week 24 (−9.454 vs 8.047 mg/dL; p = 0.26) and 48 (−18.74 vs 9.690 mg/dL; p = 0.032) (Table 3). Favorable changes were seen in HDL, TG/HDL ratio and CVD risk, but these were not statistically significant.

Table 2
Effects of vitamin D supplementation on lipid profile and cardiovascular risk.

		Adjusted mean change from baseline[a]		P value[b]
	N used in analysis	Vitamin D, N = 61	Placebo, N = 59	
Total cholesterol, mg/dL				
Week 24	120	−4.05 ± 3.05	−1.70 ± 3.10	0.595
Week 48	114	2.37 ± 3.72	−2.12 ± 3.86	0.412
HDL, mg/dL				
Week 24	120	−0.36 ± 0.74	−0.53 ± 0.75	0.870
Week 48	114	1.93 ± 0.78	1.17 ± 0.81	0.503
TG, mg/dL				
Week 24	120	−10.97 ± 6.70	−10.83 ± 6.81	0.988
Week 48	114	−0.26 ± 8.59	−14.67 ± 8.90	0.251
TG/HDL ratio				
Week 24	120	−0.31 ± 0.21	−0.33 ± 0.22	0.966
Week 48	114	−0.18 ± 0.27	−0.52 ± 0.28	0.389
LDL, mg/dL				
Week 24	120	−1.91 ± 2.64	−0.43 ± 2.68	0.699
Week 48	114	−0.07 ± 3.26	−1.98 ± 3.39	0.691
C-reactive protein, mg/L				
Week 24	120	−0.18 ± 0.50	−0.83 ± 0.51	0.371
Week 48	114	−0.79 ± 0.28	−0.58 ± 0.29	0.600
CVD risk[c]				
Week 24	119	−1.64 ± 0.57	−0.38 ± 0.58	0.128
Week 48	113	−0.35 ± 0.65	−0.85 ± 0.67	0.594

[a] Values are mean ± SEM after adjustment for stratified variables [(BMI <30 or ≥30 kg/m^2), race (White vs. non-White), diabetes therapy [metformin or lifestyle]) and baseline value of the outcome variable.
[b] P values for the difference at each time-point.
[c] Cardiovascular risk was calculated according the ACC/AHA guidelines [10-year and lifetime risks for atherosclerotic cardiovascular disease (ASCVD), defined as coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke].

Table 3
Effects of vitamin D supplementation on cardiovascular risk among participants not on cholesterol medications at baseline and during the follow up.

		Adjusted mean change from baseline[a]		P value[b]
	N used in analysis	Vitamin D, N = 15	Placebo, N = 17	
Total cholesterol, mg/dL				
Week 24	32	−0.01 ± 5.69	−0.11 ± 5.34	0.990
Week 48	29	4.56 ± 5.48	7.94 ± 5.29	0.666
HDL, mg/dL				
Week 24	32	0.78 ± 2.06	0.49 ± 1.93	0.920
Week 48	29	5.48 ± 2.21	2.35 ± 2.14	0.323
TG, mg/dL				
Week 24	32	−9.45 ± 10.99	8.05 ± 10.31	0.260
Week 48	29	−18.74 ± 8.91	9.69 ± 8.60	0.032
TG/HDL ratio				
Week 24	32	−0.26 ± 0.35	0.21 ± 0.32	0.329
Week 48	29	−0.75 ± 0.24	−0.08 ± 0.23	0.056
LDL, mg/dL				
Week 24	32	1.30 ± 4.97	−1.15 ± 4.66	0.726
Week 48	29	3.28 ± 4.83	3.28 ± 4.66	0.99
C-reactive protein, mg/L				
Week 24	32	0.66 ± 1.86	−1.59 ± 1.74	0.398
Week 48	29	−1.51 ± 0.64	−1.77 ± 0.62	0.774
CVD risk[c]				
Week 24	31	−1.66 ± 1.22	−0.55 ± 1.10	0.513
Week 48	28	−2.17 ± 1.44	−0.05 ± 1.34	0.297

[a] Values are mean ± SEM after adjustment for stratified variables [(BMI <30 or ≥30 kg/m^2), race (White vs. non-White), diabetes therapy [metformin or lifestyle]) and baseline value of the outcome variable.
[b] P values for the difference at each time-point.
[c] Cardiovascular risk was calculated according the ACC/AHA guidelines [10-year and lifetime risks for atherosclerotic cardiovascular disease (ASCVD), defined as coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke].

4. Discussion

In this secondary analysis of a completed trial [9], we investigated the effect of daily vitamin D supplementation on cardiometabolic outcomes in patients with stable type 2 diabetes, not selected for vitamin D deficiency.

Despite a significant increase in plasma 25(OH)D concentration, there was no statistically significant effect on lipid profile levels, C-reactive protein or CVD risk after 48 weeks of vitamin D supplementation compared with placebo. One explanation for the negative result is that the study cohort was not selected for vitamin D deficiency and the baseline 25(OH)D concentration was 26 ng/mL, which may indicate an adequate vitamin D status for CVD. Another explanation is that most patients were on cholesterol-lowering therapy, which may have masked a small effect of vitamin D supplementation on outcomes. Among the small subgroup of patients who were not on cholesterol medication (n = 32), we observed a statistically significant reduction in TG concentration and a near statistically significant trend in the TG/HDL ratio in the vitamin D group compared to the placebo group. This finding is consistent with other clinical trials conducted among patients with diabetes [11–13], although a different method of administration (food fortification) was used compared to our study (supplementation) and use of lipid-lowering medication was not provided.

The results of the present analysis indicate that any effect of vitamin D supplementation on lipid profile is expected to be relatively small and would be most noticeable among patients not requiring cholesterol therapy.

5. Conclusion

Compared to placebo, vitamin D at 4000 IU/day did not improve the lipid profile and the CVD risk among patients with well-controlled, stable type 2 diabetes not selected for vitamin D deficiency. Favorable trends were observed among patients who were not on cholesterol medication.

Conflicts of interest

The authors disclose no conflict of interest.

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Additional contribution

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AGP, DD and BDH designed the study; EA and JN analyzed data; EA wrote draft; all authors contributed to the writing and critical

review of the manuscript. ED and AGP are the guarantors of this work and, as such, had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

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