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ORIGINAL ARTICLE

Lack of effect of subtherapeutic vitamin D treatment on glycemic and lipid parameters in Type 2 diabetes: A pilot prospective randomized trial

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Abstract

Background: Epidemiological studies suggest a higher prevalence of metabolic syndrome and its components among individuals with vitamin D deficiency. The aim of the present study was to determine whether vitamin D treatment improves glucose control and insulin sensitivity in Type 2 diabetes mellitus (T2DM).

Methods: Subjects with T2DM and serum 25-hydroxyvitamin D (25(OH)D) concentrations <25 ng/mL were randomized to receive 400 IU (Group 1) or 1200 IU (Group 2) cholecalciferol for 4 months. Fasting plasma glucose, glycosylated hemoglobin (HbA1c), Quantitative Insulin Sensitivity Check Index (QUICKI), serum lipid levels and serum adiponectin were measured at baseline and at 4 months.

Results: Mean 25(OH)D levels increased in both groups (from 17.6 ± 1.5 to 25.5 ± 1.8 ng/mL in Group 1 and from 15.6 ± 1.4 to 27.4 ± 2.4 ng/mL in Group 2; $P \leq 0.001$ vs baseline for each group). No significant differences were noted in fasting plasma glucose, HbA1c, QUICKI, serum adiponectin, and lipid levels compared with baseline within groups or between the two groups.

Conclusions: In the present pilot study, conventional vitamin D treatment at a level improving, but not optimizing, serum 25(OH)D did not improve glycemia, insulin sensitivity, or lipid profile. However, diabetes and lipids were relatively well controlled at baseline. Future studies should be designed to achieve optimal concentrations of serum 25(OH)D (at least >32 ng/mL) and should include subjects showing more abnormal parameters of glycemia, lipid, and insulin sensitivity at baseline.

Keywords: insulin resistance, Type 2 diabetes, vitamin D deficiency.

Introduction

Type 2 diabetes mellitus (T2DM) is caused by insulin resistance and pancreatic islet insufficiency. Vitamin D deficiency and T2DM share common demographic characteristics for their risk groups (elderly, dark-skinned individuals, obese), and patients with T2DM are reported to have higher rates of vitamin D deficiency.[1] Epidemiological studies also suggest a higher prevalence of metabolic syndrome and its components (central obesity, hypertension, dyslipidemia, and glucose intolerance) among individuals with low circulating vitamin D concentrations.[2]

Experimentally, vitamin D receptors have been identified in pancreatic islets and administration of vitamin D increases insulin secretion in vitamin D-deficient animals.[3] Vitamin D levels are inversely related to percentage body fat [4] and vitamin D supplementation has been shown to improve hypertension, a component of the insulin resistance syndrome.[5] A small study involving 10 women with T2DM treated with cholecalciferol 1332 IU daily for 1 month showed increased

first-phase insulin secretion.[6] Fasting and post-challenge (75 g glucose) insulin levels were also decreased with increased vitamin D concentrations in 142 elderly non-diabetic Dutchmen.[7]

In the present study, we hypothesized that vitamin D treatment in vitamin D-deficient T2DM patients will improve insulin sensitivity and glycemic control.

Methods

Patients with T2DM and normal renal and hepatic function whose glycosylated hemoglobin (HbA1c) was $<9\%$ were screened for the study. Patients on stable diabetes treatment for at least 1 month were recruited to the study; however, patients on thiazolidinediones were required to be on a stable dose for 6 months before entering the study. Individuals who met these criteria and whose serum 25-hydroxyvitamin D (25(OH)D) levels were <25 ng/mL were randomized to receive cholecalciferol (CVS Pharmacy, Woonsocket, RI, USA) 400 IU (Group 1) or 1200 IU (Group 2) daily for 4 months.

The present study was approved by the Institutional Review Board at Beth Israel Medical Center and written informed consent was obtained from all patients prior to their enrolment in the study.

Medications and calcium and vitamin D intake were assessed at monthly visits, along with serum 25(OH)D, intact parathyroid hormone (PTH), and calcium concentrations. Fasting plasma glucose, HbA1c, serum lipid profile, serum adiponectin (ELISA; Linco Research, St Charles, MO, USA), and serum insulin concentrations (radioimmunoassay (RIA); Linco Research) were determined at baseline and at the final study visit (after 4 months treatment). Quantitative Insulin Sensitivity Check Index (QUICKI), a measure of insulin sensitivity,[8] was calculated for patients not on insulin therapy. Body mass index (BMI) was calculated at each visit.

Statistical analysis

Data are presented as the mean ± SD. Statistical analysis was performed using SPSS software (SPSS, Chicago, IL, USA). Comparisons between groups were made using two-tailed independent samples t-tests. Paired t-tests were used to compare all parameters from baseline to the end of the study. $P < 0.05$ was considered significant.

Secondary analyses were performed to determine whether improvements in serum 25(OH)D concentrations from baseline to final visit were related to changes in other parameters. Pearson's correlation coefficient was used to assess the relationship between changes in 25(OH)D and changes in fasting plasma glucose and serum adiponectin. An analysis of variance was also performed using quartiles of change in vitamin D concentration in order to look at non-linear relationships with changes in the remaining parameters.

Results

Of the 32 patients who were screened, 24 completed the study. Five patients dropped out due to personal reasons and three patients were not eligible on repeat testing at first visit. Thirteen patients were randomized to receive 400 IU cholecalciferol daily (Group 1) and 11 patients were randomized to receive 1200 IU cholecalciferol daily (Group 2). Both groups were comparable in terms of baseline 25(OH)D and HbA1c levels (Table 1). Patients in Group 2 had a significantly shorter duration of diabetes compared with those in Group 1 (4.1 ± 1.1 vs 11.5 ± 2.2 years, respectively; $P < 0.05$). Based on the values obtained at baseline, the power estimate approached 99% for detecting a clinically meaningful difference of either 0.5% in HbA1c or 20% in triglycerides with $\alpha = 0.05$.

Table 2 describes the biochemical parameters of patients at baseline and after 4 months of vitamin D treatment in the entire study group as well as in Groups 1 and 2 individually. Twenty-two of 24 patients exhibited an increase in serum 25(OH)D levels. The mean serum 25(OH)D levels in the entire

Table 1 Patient characteristics at baseline

Characteristics	Group 1 (n = 13)	Group 2 (n = 11)	Groups 1 and 2 (n = 24)
Vitamin D daily dose (IU)	400	1200	
Mean age (years)	61 ± 4	54 ± 3	58.4 ± 2.5
Gender			
Female (n)	10	7	17
Male (n)	3	4	7
Ethnicity			
Hispanic (n)	7	4	11
Non-Hispanic White (n)	2	2	4
Non-Hispanic Black (n)	4	3	7
Asian Indian (n)	0	2	2
Mean duration of diabetes (years)	11.5 ± 2.2	4.1 ± 1.1*	8.2 ± 1.5
Mean HbA1c (%)	6.7 ± 0.3	6.7 ± 0.2	6.7 ± 0.2
Mean 25(OH)D (ng/mL)	17.6 ± 1.5	15.6 ± 1.4	16.7 ± 1.0
No. using insulin	4	3	7

Data are the mean ± SEM. HbA1c, glycosylated hemoglobin; 25(OH)D, 25-hydroxyvitamin D.
*$P < 0.01$ compared with Group 1.

Table 2 Biochemical parameters at baseline and after 4 months of vitamin D treatment

	No. patients with complete data	Entire group (n = 24)		Group 1 (n = 13)		Group 2 (n = 11)	
		Baseline	4 months	Baseline	4 months	Baseline	4 months
25(OH)D (ng/mL)	24	16.7 ± 1.0	26.4 ± 1.3*	17.6 ± 1.5	25.5 ± 1.8*	15.6 ± 1.4	27.4 ± 2.4*
Intact PTH (pg/mL)	24	35.2 ± 3.7	36.0 ± 3.4	38.7 ± 5.0	41.2 ± 4.2	31.1 ± 5.4	29.9 ± 4.9
Calcium (mg/dL)	24	9.5 ± 0.1	9.4 ± 0.1	9.5 ± 0.1	9.5 ± 0.1	9.4 ± 0.1	9.2 ± 0.1
Fasting glucose (mg/dL)	22	122.9 ± 6.6	114.5 ± 7.7	122.9 ± 10.3	110.3 ± 12.0	124.8 ± 9.6	124.1 ± 9.3
HbA1c (%)	24	6.7 ± 0.2	6.9 ± 0.2	6.8 ± 0.3	6.9 ± 0.3	6.7 ± 0.2	7.0 ± 0.4
Insulin (μU/mL)	13	8.6 ± 1.3	8.9 ± 1.9	6.4 ± 0.9	8.9 ± 3.6	10.6 ± 2.2	8.9 ± 2.1
QUICKI	11	0.35 ± 0.01	0.35 ± 0.01	0.36 ± 0.01	0.34 ± 0.01	0.34 ± 0.02	0.35 ± 0.02
Adiponectin (μg/mL)	22	15.2 ± 3.0	14.5 ± 2.5	17.9 ± 5.2	16.1 ± 3.9	12.6 ± 3.3	12.9 ± 3.1
Cholesterol (mg/dL)	23	167.7 ± 6.5	171.8 ± 9.1	169.2 ± 11.1	180.5 ± 15.6	166.2 ± 6.7	162.3 ± 8.4
HDL (mg/dL)	23	55.1 ± 3.8	54.5 ± 3.5	57.8 ± 5.8	55.3 ± 4.7	52.2 ± 4.8	53.7 ± 5.4
LDL (mg/dL)	21	83.4 ± 5.5	89.0 ± 7.9	81.3 ± 9.4	93.5 ± 13.0	85.7 ± 5.8	84 ± 9
Triglycerides (mg/dL)	23	150.9 ± 22.5	132.5 ± 21.1	141.5 ± 29.8	122.9 ± 22.4	161 ± 35	143.0 ± 37.8
BMI (kg/m^2)	23	32.3 ± 1.4	32.6 ± 1.4	32.9 ± 2.0	32.9 ± 2.0	31.8 ± 2.1	32.1 ± 2.1

Data are the mean ± SEM. 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; HbA1c, glycosylated hemoglobin; QUICKI, Quantitative Insulin Sensitivity Check Index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.
*$P \leq 0.001$ compared with baseline.

group increased from 16.7 ± 1.0 ng/mL at baseline to 26.4 ± 1.3 ng/mL after 4 months treatment ($P \leq 0.001$; Table 2). Mean 25(OH)D levels increased significantly in both Group 1 (from 17.6 ± 1.5 to 25.5 ± 1.8 ng/mL; $P < 0.001$) and Group 2 (from 15.6 ± 1.4 to 27.4 ± 2.4 ng/mL; $P < 0.001$) over the 4 months of treatment. There was no significant difference in the percentage increase in serum 25(OH)D levels between the two groups.

Fasting plasma glucose, HbA1c, and QUICKI remained unchanged from baseline until the end of the study. Serum adiponectin concentrations also remained unchanged after vitamin D treatment. There was no correlation between changes in serum 25(OH)D levels and changes in fasting plasma glucose or serum adiponectin concentrations. There was also no correlation among the quartiles of vitamin D groups and glycemic outcomes.

Although there was a trend for mean serum triglycerides to decline in the entire group (from 150.9 ± 22.5 to 132.5 ± 21.1 mg/dL) over the course of the 4 months treatment, as well as in both subgroups (from 141.5 ± 29.8 to 122.9 ± 22.4 mg/dL in Group 1 and from 161 ± 35 to 143.0 ± 37.8 mg/dL in Group 2), the decreases did not reach statistical significance ($P = 0.08$ for the entire group). Serum cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein concentrations remained unchanged in both groups after vitamin D treatment.

Baseline and final serum calcium (9.5 ± 0.1 and 9.4 ± 0.1 mg/day, respectively) and serum intact PTH (35.2 ± 3.7 and 36.0 ± 3. 4 pg/mL, respectively) concentrations did not change significantly over the course of the study. Furthermore, there was no change in BMI after vitamin D treatment (from 32.3 ± 1.4 to 32.6 ± 1.4 kg/m^2).

Discussion

The rationale for vitamin D treatment in patients with T2DM is based on studies that suggest some benefit on insulin secretion or insulin sensitivity. Vitamin D receptors are present on pancreatic β-cells[9] and vitamin D treatment improves insulin secretion.[10] Furthermore, individuals with higher vitamin D levels are more insulin sensitive compared with individuals with lower vitamin D levels.[11,12] In a recently published study involving patients without diabetes,[13] vitamin D concentrations were inversely correlated with fasting glucose and insulin concentrations, as well as homeostasis model assessment of insulin resistance (HOMA-IR), after adjusting for age, sex, BMI, and waist circumference. Positive associations with vitamin D concentration and adiponectin, HDL, and insulin sensitivity index, and a negative association with triglycerides after adjustments for sex and age were no longer significant after adjustment for BMI or waist circumference.[13] In the present study, we did not see any changes in serum adiponectin levels or QUICKI, and the trend for a decrease in serum triglycerides did not reach statistical significance. Furthermore, there was no evidence of improved

insulin sensitivity with vitamin D supplementation in the present study.

Multiple observational studies have shown increased prevalence of T2DM in individuals with vitamin D deficiency.[14,15] A large, 20-year observational study reported a decreased incidence of T2DM in women using vitamin D and calcium supplements.[14] However, a randomized placebo-controlled trial did not show a reduction in the development of T2DM,[15] although that study used a lower dose of vitamin D than that used in the observational study (400 vs 800 IU, respectively; note, the dose of calcium supplementation was similar in both studies). In a rare prospective study, men aged 40–74 years who were in the highest quartile of baseline vitamin D concentration had a 72% reduced risk of developing T2DM over 22 years of follow-up.[16]

Intervention studies investigating vitamin D supplementation for the prevention or treatment of T2DM have shown no or minimal effect.[1] The studies vary in patient characteristics (such as duration of diabetes vs patients with prediabetes), formulations of vitamin D used (cholecalciferol or vitamin D analog), duration of intervention (from days to months), and number of participants, making comparisons and conclusions difficult to make. In one study involving 10 women,[6] cholecalciferol 1332 IU was given daily for 1 month in the winter, when vitamin D levels are the lowest. In that study, 25(OH)D concentrations increased by 75% and first-phase insulin secretion (measured during an i.v. glucose tolerance test) increased by 34.3%. Improvements in second-phase insulin secretion and peripheral insulin resistance were not significant.[6] In another study, treatment with 1,25(OH)D for 4 months in 20 subjects with T2DM and low vitamin D levels did not improve fasting glucose concentrations.[17] Among individuals with impaired glucose tolerance, α-calcidol supplementation for 3 months did not change fasting blood glucose, HbA1c, or response to i.v. glucose load.[18] In the present study, vitamin D administration did not alter fasting plasma glucose or HbA1c concentrations. Furthermore, neither 400 nor 1200 IU cholecalciferol was effective in achieving serum 25(OH)D concentrations >30 ng/mL, a level considered optimal by most experts.[19]

In addition to achieving only suboptimal levels of vitamin D, there may be several reasons for the failure to observe improved glycemia and insulin sensitivity in the present study. We did not supplement calcium, which may be required in addition to vitamin D treatment.[1] Our study patients had excellent glucose and lipid values at baseline, which may be difficult to improve further. We note that one group had a significantly longer duration of diabetes. Given that the other baseline parameters did not show significant difference (e.g. HbA1c, fasting insulin, and glucose concentrations), we do not think this discrepancy in diabetes duration affected the study results. Finally, among African American individuals, we did not observe the inverse association between vitamin D levels and insulin sensitivity that has been reported previously.[12] More than one-quarter of our patients were African American.

A limitation of our study is a small number of patients, which may not be sufficient to show an effect. We also chose not to have a placebo group (for ethical reasons) and, thus, compared two different replacement doses of vitamin D. Many patients take 400 IU cholecalciferol because it is commonly available in this form, although 400 IU/day is insufficient to maintain optimal vitamin D levels.[20] It appears that in vitamin D-deficient individuals, daily doses of both 400 and 1200 IU cholecalciferol over a 4-month period are insufficient to achieve optimal D concentrations. A dose of 2000–3000 IU cholecalciferol daily is likely necessary to achieve optimal vitamin D status when the initial 25(OH)D concentration is <20 ng/mL.

The strengths of the present study are its prospective design, stable diabetes regimen throughout the duration of the study, and assessment of objective endpoints of diabetes. It is unclear at this point whether vitamin D treatment can significantly improve insulin sensitivity or glycemic control in individuals with T2DM or impaired glucose tolerance. We conclude that in this pilot prospective randomized trial, vitamin D supplementation did not improve glucose levels in individuals with T2DM and vitamin D deficiency. Until further data are available supporting this hypothesis, vitamin D supplementation cannot be expected to improve glycemia or parameters of insulin resistance.

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Disclosure

This study has not been published previously. EL has received support from Abbott Pharmaceuticals to conduct another study, although the funds were not used for the present study.

References

1. Pittas A, Lau J, Hu F, 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**: 2017–29.
2. Ford ES, Ajani UA, McGuire LC, Liu S. Concentrations of serum vitamin D and the metabolic syndrome among U.S. adults. *Diabetes Care*. 2005; **28**: 1228–30.
3. Norman AW, Frankel JB, Heldt AM, Grodsky GM. Vitamin D deficiency inhibits pancreatic secretion of insulin. *Science*. 1980; **209**: 823–5.
4. Arunabh S, Pollack S, Yeh J, Aloia JF. Body fat content and 25-hydroxyvitamin D levels in healthy women. *J Clin Endocrinol Metab*. 2003; **88**: 157–61.
5. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short term vitamin D and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab*. 2001; **86**: 1633–7.
6. Borissova A, Tankova T, Kirilov G, Dakovska L, Kovacheva R. The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. *Int J Clin Pract*. 2003; **57**: 258–61.
7. Baynes KC, Boucher BJ, Feskens EJ, Kromhout D. Vitamin D, glucose tolerance and insulinaemia in elderly men. *Diabetologia*. 1997; **40**: 344–7.
8. Katz A, Nambi SS, Mather K et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab*. 2000; **85**: 2402–10.
9. Clark S, Stumpf W, Madhabananda S, DeLuca H, Tanaka Y. Target cells for 1, 25 dihydroxyvitamin D3 in the pancreas. *Cell Tissue Res*. 1980; **209**: 515–20.
10. Bourlon P, Billaudel B, Faure-Dussert A. Influence of vitamin D3 deficiency and 1, 25 dihydroxyvitamin D3 on de novo insulin biosynthesis in the islets of the rat endocrine pancreas. *J Endocrinol*. 1999; **160**: 87–95.
11. Chiu K, Chu A, Go V, Saad M. Hypovitaminosis D is associated with insulin resistance and beta cell dysfuncftion. *Am J Clin Nutr*. 2004; **79**: 820–5.
12. Scragg R, Sowers M, Bell C. Serum 25- hydroxyvitamin D, diabetes and ethnicity in the third national health and nutrition examination survey. *Diabetes Care*. 2004; **27**: 2813–8.
13. Liu E, Meigs JB, Pittas AG et al. Plasma 25-hydroxyvitamin D is associated with markers of the insulin resistant phenotype in nondiabetic adults. *J Nutr*. 2009; **139**: 329–34.
14. Pittas A, Dawson-Hughes B, Li T et al. Vitamin D and Calcium Intake in Relation to Type 2 Diabetes in Women. *Diabetes Care*. 2006; **29**: 650–6.
15. Boer I, Tinker L, Connelly S et al. Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative. *Diabetes Care*. 2008; **31**: 701–7.
16. Knekt P, Laaksonen M, Mattila C et al. Serum vitamin D and subsequent occurrence of type 2 diabetes. *Epidemiology*. 2008; **19**: 666–71.
17. Orwoll E, Riddle M, Prince M. Effects of vitamin D on insulin and glucagon secretion in non-insulin dependent diabetes mellitus. *Am J Clin Nutr*. 1994; **59**: 1083–7.
18. Ljunghall S, Lind L, Lithell H et al. Treatment with one-alpha-hydroxycholecalciferol in middle-aged men with impaired glucose tolerance-prospective randomized double-blind study. *Acta Med Scand*. 1987; **222**: 361–7.
19. Vieth R. Vitamin D supplementation, 25- hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr*. 1999; **69**: 842–56.
20. Heaney R, Davies K, Chen T, Holick M, Barger-Lux M. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr*. 2003; **77**: 204–10.