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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.