Vitamin D for glycemic control: A multicenter, double-blind, randomized, placebo-controlled trial in adults with cystic fibrosis.

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Abstract

Individuals with cystic fibrosis (CF) often incur damage to pancreas tissue due to a dysfunctional cystic fibrosis transmembrane conductance regulator (CFTR) protein, leading to altered chloride transport on epithelial surfaces and subsequent development of cystic fibrosis-related diabetes (CFRD). Vitamin D deficiency has been associated with the development of CFRD. The purpose of this study was to examine the impact of a high-dose bolus of cholecalciferol (vitamin D_3) on glycemic control. This was a secondary analysis of a multicenter, double-blind, randomized, placebo-controlled study in adults with CF hospitalized for an acute pulmonary exacerbation (APE). Glycemic control was assessed by hemoglobin A1c (HbA1c) and fasting blood glucose levels before and 12 months after the study intervention. Within 72 hours of hospital admission, participants were randomly assigned to a single dose of oral vitamin D_3 (250,000 IU) or placebo, and subsequently, received 50,000 IU of vitamin D_3 or placebo every other week, beginning at month 3 and ending on month 12. Fifty of the 91 participants in the parent study were eligible for the secondary analysis. There were no differences in 12-month changes in HbA1c or fasting blood glucose in patients randomized to vitamin D or placebo. A high-dose bolus of vitamin D_3 followed by maintenance vitamin D_3 supplementation did not improve glycemic control in patients with CF.

1. Introduction

Cystic fibrosis-related diabetes (CFRD) is the most common non-pulmonary co-morbidity associated with cystic fibrosis (CF) with a prevalence of up to 40-50% of adults with CF [1]. CF is a multi-organ disease caused by altered chloride transport on epithelial surfaces, leading to thick mucus secretions in organs such as the lung and pancreas, resulting in chronic infection, inflammation, and damage [2, 3]. Thickened mucous secretions in the pancreatic ducts can result in obstruction and damage of pancreatic tissue leading to CFRD [1, 4]. Destruction of exocrine pancreas tissue leads to fat malabsorption, which can result in undernutrition and vitamin deficiencies, including fat-soluble vitamins like vitamin D [5-7, 22]. Destruction of endocrine pancreas tissue contributes to disturbances in insulin secretion, and ultimately CFRD in some individuals [1, 4].

Vitamin D deficiency has been associated with prediabetes, insulin resistance, and an increased likelihood of developing diabetes [8-15]. Vitamin D deficiency causes intestinal malabsorption of calcium [16]. Adequate calcium absorption may be beneficial to decrease the risk of CFRD due to its ability to stimulate insulin release to the blood and its possible indirect effect on weight loss [17-20]. Further, vitamin D_3 (cholecalciferol) supplementation has been associated with improved insulin secretion and decreased risk for CFRD [21, 22]. Hyperglycemia and insulin resistance can occur after illness, however, prior studies have not examined changes in glycemic control after treatment of a high-dose bolus of vitamin D_3 supplementation following an acute pulmonary exacerbation (APE).

This study aimed to examine changes in glycemic control, quantified by changes in hemoglobin A1c (HbA1c) and fasting blood glucose values after administration of a high-dose

bolus of vitamin D in adults with CF. This study was a secondary analysis of the Vitamin D in the Immune System in Cystic Fibrosis (DISC) study [23]. The DISC study was a multicenter, double-blind, randomized, placebo-controlled clinical trial in which adults with CF were hospitalized for APE therapy and concurrently treated with a single high-dose vitamin D bolus followed by maintenance supplementation of vitamin D_3 [23, 24].

2. Methods

2.1. Study design

This was a pre-planned secondary analysis of Vitamin D for the Immune System in Cystic Fibrosis (DISC) trial [23], registered at clinicaltrials.gov as NCT01426256. Briefly, the parent DISC trial was a multicenter, double-blind, placebo-controlled, intent-to-treat clinical trial, spanning five Cystic Fibrosis Foundation Therapeutics Development Network Centers: Emory University and Emory University Hospital (Atlanta, GA), Case Western Reserve University and Rainbow Babies and Children's Hospital (Cleveland, OH), The University of Alabama Hospital at Birmingham (Birmingham, AL), the University of Cincinnati and University of Cincinnati Medical Center (Cincinnati, OH), and the University of Iowa and University of Iowa Hospitals and Clinic (Iowa City, IA). All study sites received human studies approval from their local Institutional Review Boards before participation in the trial. Participants were randomized to receive a single dose of vitamin D_3 (250,000 IU) orally or placebo within 72 hours of hospital admission for APE of CF. At the 3-month study visit, participants randomized to oral vitamin D_3 took 50,000 IU of vitamin D_3 orally every 2 weeks, and participants randomized to placebo took matching placebo orally every 2 weeks. Participants continued their regular vitamin D

supplementation if the amount did not exceed 2000 IU daily as recommended by their healthcare providers.

2.2. Trial eligibility

As previously reported, participants were eligible for the DISC trial if they were 16 years or older, admitted to the hospital for treatment of an APE of CF and enrolled into the study within 72 hours of admission, able to tolerate oral medication, and expected to survive hospital admission [24]. Patients were ineligible if they were unable to provide informed consent, their serum total 25(OH)D concentration was <10 ng/mL or >55 ng/mL within the previous 12 months, had vitamin D intake >2000 IU daily or >10,000 IU vitamin D bolus within the past 60 days, had plans for pregnancy in the next 12 months, had conditions that could be exacerbated by vitamin D such as current hypercalcemia, had conditions that affected vitamin D metabolism such as chronic kidney disease or nephrolithiasis with active symptoms, had conditions that affect survival (such as history of organ transplantation, HIV/AIDS, illicit drug use, etc.), took oral or intravenous glucocorticoids in the past month, forced expiratory volume in 1-second present predicted (FEV1%) <20%, current hepatic dysfunction with total bilirubin >2.5 mg/dL with direct bilirubin >1.0mg/dL, current use of cytotoxic or immunosuppressive drugs, or were enrolled in any other interventional trial. Participants in this secondary analysis were included if they had HbA1c and fasting blood glucose measured at baseline and month 12. Participants were excluded if there was no available data on HbA1c or fasting blood glucose level at baseline or the 12-month visit.

2.3. Blood Analysis

Routine blood work was collected at the baseline visit during an APE and at the 12-month visit after APE recovery. Values for HbA1c and fasting blood glucose levels were extracted from the electronic medical record.

2.4. Statistical analysis

Demographics, HbA1c, and fasting blood glucose levels of participants were reported by mean and their respective standard deviation. P-values for continuous variables were calculated using a two-sample t-test assuming equal variances with significance set at 0.05. A p-value was calculated to detect differences in change in HbA1c and fasting blood glucose between the two groups. Categorical variables were listed as counts and their respective percentages.

3. Results

3.1. Study participants

Ninety-one participants were enrolled in the parent DISC trial, and 50 participants were eligible for this secondary analysis on glycemic control. The baseline demographic characteristics between the vitamin D_3 and placebo groups were similar were similar for this sub-group (Table 1). Participants randomized to vitamin D_3 or placebo had similar baseline serum 25(OH)D, HbA1c, and fasting blood glucose levels (Table 1).

3.2. Change in HbA1c after administration of a bolus dose of vitamin D_3 or placebo.

The mean change in HbA1c for all enrolled study participants was -0.055% ± 0.66. The mean change in HbA1c over 12 months for study participants was not statistically significantly different by treatment group (Table 2). Participants treated with the vitamin D_3 bolus (n = 22)

had a mean HbA1c change of -0.0318% ± 0.949 vs participants treated with placebo (n = 27) had a change of -0.0740% ± 0.290 (p = 0.827) (Table 2).

3.3. Change in fasting blood glucose after administration of a bolus dose of vitamin D_3 or placebo.

The mean change in fasting blood glucose for all eligible participants was 4.82 mg/dL ± 33.57 (Table 2). The mean change in fasting blood glucose over 12 months for participants was not significantly different by treatment group. Participants randomized to vitamin D_3 bolus (n = 8) had a mean fasting blood glucose change of 0.75 mg/dL ± 39.19 vs participants treated with placebo (n = 3) had a change of 15.67 mg/dL ± 3.79 (p = 0.54) (Table 2).

4. Discussion

The purpose of this secondary analysis was to determine the role of a single high-bolus dose and maintenance vitamin D dosing of vitamin D_3 on glycemic control in participants with CF. We found that administration of a single vitamin D_3 bolus in participants with CF at the time of APE followed by bi-weekly bolus doses of vitamin D for one year did not result in significant changes in HbA1c and fasting blood glucose levels compared to placebo. Of the 9 patients with CFRD status recorded, 5 participants had normal glycemic control at baseline and the 12-month follow-up regardless of treatment group. Of those remaining within the vitamin D group, one participant's glycemic control remained the same, one had worsened glycemic control, and one had improved glycemic control. However, patients randomized to vitamin D_3 showed trends towards improved fasting blood glucose levels, although, these results were underpowered. Although the secondary analysis for fasting blood glucose was underpowered, the group

randomized to vitamin D_3 showed trends toward decreased fasting blood glucose levels. These findings suggest that the administration of a vitamin D_3 bolus dose may not be beneficial for long-term glycemic control in patients with CF or that the duration and method of vitamin D administration were not adequate.

Several studies show that vitamin D is needed for optimal glucose metabolism and homeostasis [19, 25, 26]. Vitamin D intake is believed to decrease the prevalence of type 2 diabetes through stimulation of gene expression of insulin receptors and improving transport of glucose from the intestine [27, 28]. A study in human promonocytic cells showed that insulin receptor capacity and insulin-stimulated glucose transport increased when activated by $25(OH)_2D_3$ [18, 28, 29]. Vitamin D supplementation was seen to improve glycemic control in only patients with vitamin D deficiency and had no therapeutic effects for patients already within the normal range of 25(OH)D [30]. These studies suggest that vitamin D may be important for glucose metabolism in people who have vitamin D deficiency and who are at risk for diabetes. This may be the reason for the lack of therapeutic effects in this secondary analysis.

However, prior research supports our findings that vitamin D supplementation does not improve glycemic control. A study showed that vitamin D_3 supplementation normalizes 25(OH)D concentration in patients with diabetes but may not have long-term effects on glycemic control [31]. The large-scale Vitamin D and Type 2 Diabetes (D2d) study (n = 2423) showed that two-year vitamin D supplementation, 4000 IU daily, in patients with vitamin D deficiency did not result in significantly lower risk of diabetes as compared to placebo, despite differences in $25(OH)D_3$ at month 24 (54.3 ng/mL in vitamin D group vs 28.8 ng/mL in placebo group) [18]. Further, a systematic review of 13 randomized controlled trials on the role of vitamin D supplementation in the prevention of type 2 diabetes showed that vitamin D supplementation had

no statistically significant impact on the incidence of type 2 diabetes in six of the seven trials that identified type 2 diabetes incidence as a research outcome [32]. Additionally, 10 of the trials analyzed the impact of vitamin D supplementation on insulin resistance using the Homeostatic Model Assessment for Insulin resistance (HOMA-IR). In six of the trials, patients who received vitamin D supplementation had lowered and improved insulin resistance while the four remaining trials had opposing results [32]. Therefore, the results from our secondary analysis of the DISC study support prior findings that vitamin D supplementation may not improve glycemic control despite its possible effect on insulin resistance. However, these trials ranged from 12 weeks to 60 months, in which vitamin D dosage, vitamin D-deficient status, diabetes status, and body mass index (BMI) varied widely, possibly contributing to conflicting results on the efficacy of vitamin D [32]. In a separate review, where over 15 RCTs were reviewed, vitamin D supplementation did not improve HbA1c, insulin resistance, or fasting blood glucose [32]. However, in four of the trials, prediabetic subjects who received vitamin D supplementation had improved fasting plasma glucose [32]. Thus, prior findings have indicated conflicting results regarding the therapeutic effects of vitamin D on glycemic control. It remains unresolved whether specific populations, such as those with prediabetes, may benefit from vitamin D supplementation.

Study limitations here include the small number of participants eligible within the secondary study, the timing of vitamin D_3 intervention, the severity of the APE, and baseline vitamin D status. As a secondary analysis, the sample size may not have been large enough to conclude statistically significant changes in glycemic control. The participants involved in the study were admitted following an APE, in which the timing of the bolus dose of vitamin D_3 may not be appropriate for improvement in glycemic control Following hospital admission, many patients

were recovering from the effects of APE and still receiving antibiotics. Additionally, at baseline, participants in both groups had a mean 25(OH)D_3 level considered adequate (>20 ng/mL). Previous studies show that vitamin D_3 supplementation was only beneficial in instances where patients were vitamin D deficient (25(OH)D <20 ng/mL) [30].

In conclusion, high-dose bolus vitamin D_3 treatment upon hospital admission for an APE, followed by maintenance vitamin D dosing, did not improve glycemic control after 1 year in adults with CF. More adults with CF are developing CFRD due to increasing rates of survival and an increased incidence of overweight and obesity. The findings from this secondary analysis suggest that high-dose bolus vitamin D_3 administration (during hospital admission of an APE) and patient population (not deficient in vitamin D_3 and/or CFRD status) did not impact glycemic control. Further research with rigorous evaluation of blood glucose control with continuous glucose monitoring and more frequent measurements of HgA1C over time is required to investigate the impact of vitamin D_3 on patients with vitamin D deficiency and at high risk for CFRD.

Author Contributions

The authors' contributions were as follows – VT and JAA: designed the study and obtained funding; VT, JAA, TRZ: performed and supervised the conduct of the trial and revised the manuscript; AS and VT: performed secondary analysis, verified, interpreted the data, and revised the manuscript; AS performed statistically analyses and drafted the manuscript.

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Conflicts of Interest

All the authors read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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Table 1. Baseline demographics of participants.

	Total (n = 49)	**Vitamin D_3 (n = 22)**	**Placebo (n = 27)**	**P-value**
Age (years)	29.2 ± 8.1	29.1 ± 8.0	29.3 ± 8.3	0.5
BMI (kg/m^2)	21.4 ± 4.0	21.8 ± 4.6	21.0 ± 3.5	0.2
Gender (%)				
- Male	29 (58%)	11 (47.8%)	18 (66.7%)	
- Female	21 (42%)	12 (52.2%)	9 (33.3%)	
Race (%)				
- Caucasian	45 (90%)	20 (87.0%)	25 (92.6%)	
- African American	5 (10%)	3 (13.0%)	2 (7.4%)	
CFTR mutation				
- Homozygous for f508del	45 (90%)	20 (87.0%)	25 (92.6%)	
- No copies of f508del	2 (4%)	2 (8.7%)	0 (0%)	
- Unknown	3 (6%)	1 (4.3%)	2 (7.4%)	
Baseline 25(OH)D (ng/mL)	26.8 ± 9.8	28.8 ± 10.8	25.2 ± 8.8	0.1
Baseline HbA1c (%)	6.3 ± 1.4	6.7 ± 1.8	6.1 ± 1.0	0.1
Baseline fasting blood glucose level (mg/dL)	100 ± 29.7 (n = 11)	105.1 ± 33.7 (n = 8)	87.3 ± 8.5 (n = 3)	0.4

Table 2. Baseline to month 12 change in HbA1c and fasting blood glucose levels in participants randomized to vitamin D_3 or placebo.

	Vitamin D_3 (n = 22)	**Placebo (n = 27)**	**P-value**
Δ HbA1c (%)	-0.03 ± 0.9	-0.07 ± 0.3	0.8
Δ Fasting blood glucose level (mg/dL)	0.8 ± 39.2 (n = 8)	15.7 ± 3.8 (n = 3)	0.5

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Fig. 1. Twelve-month change in HbA1c in study participants with an APE of CF randomized to vitamin D_3 or placebo.

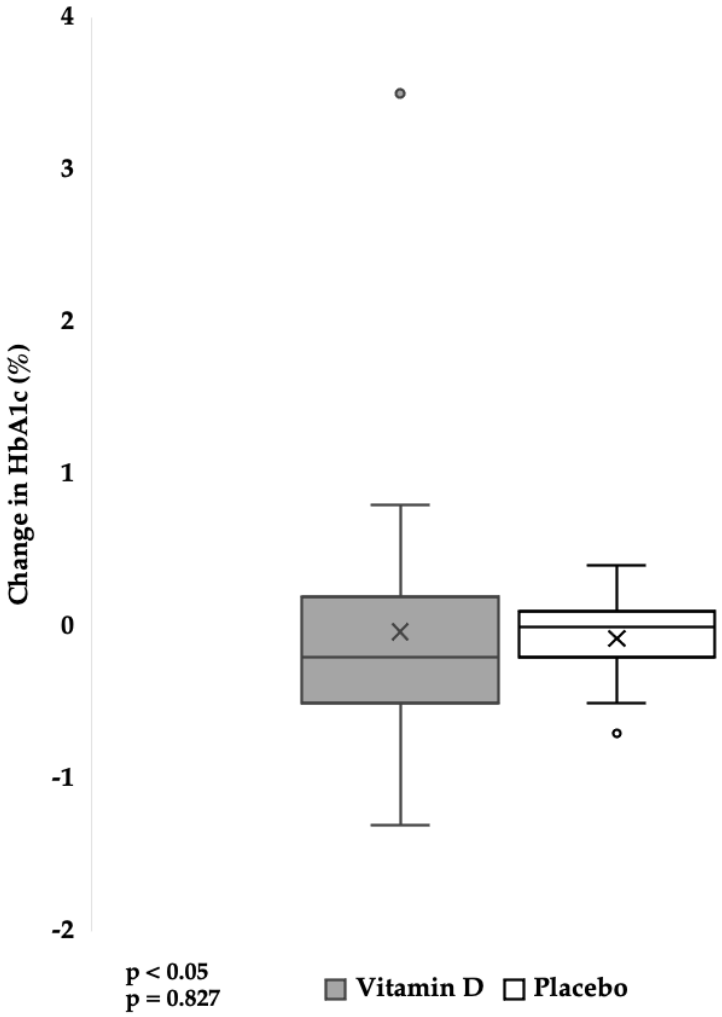
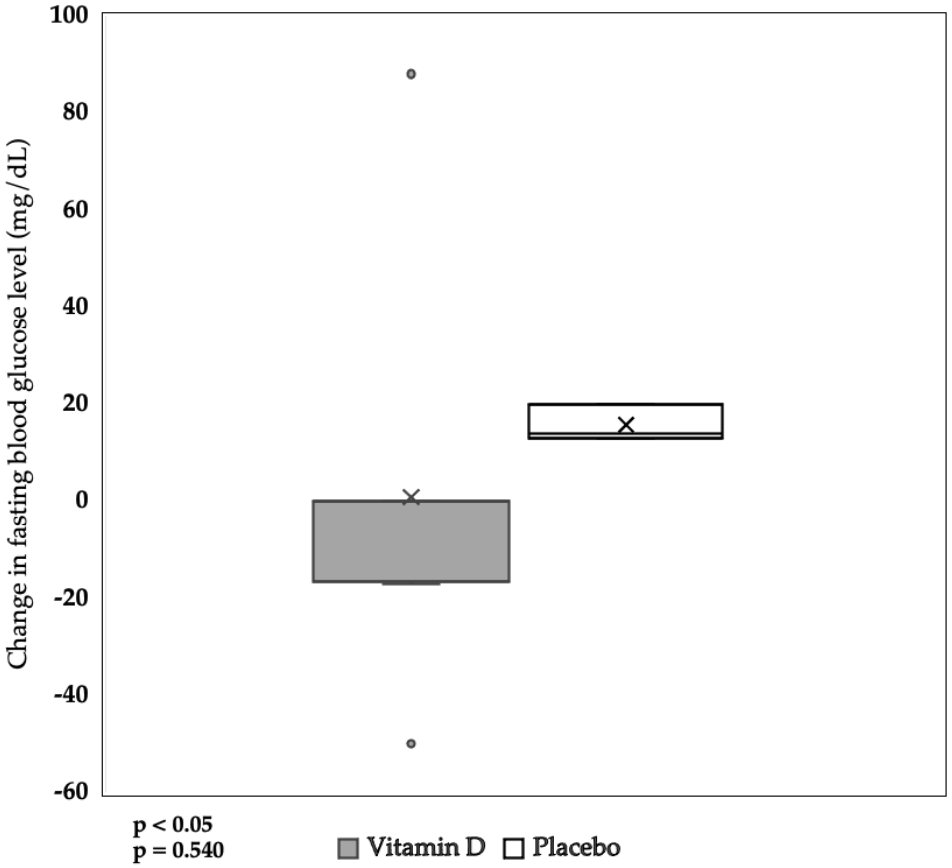
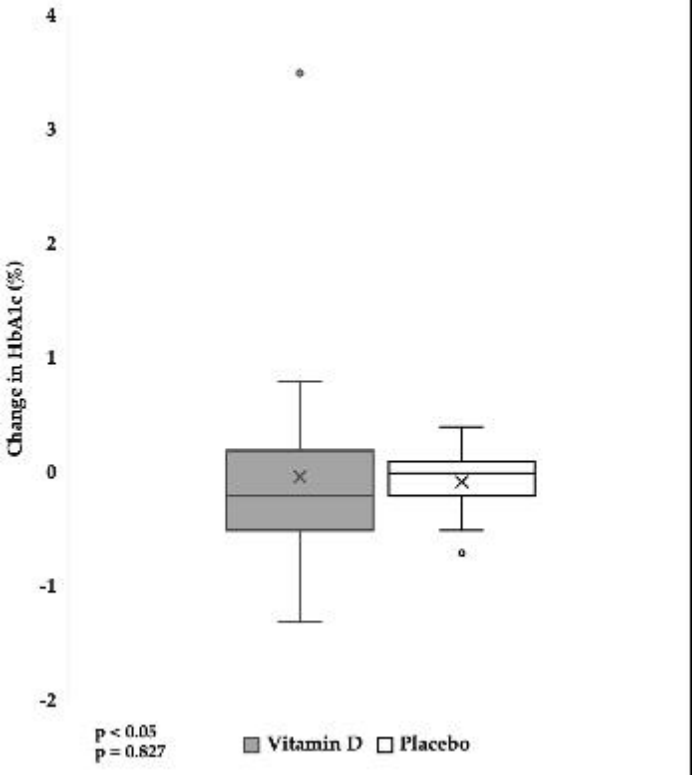


Fig. 2. Twelve-month change in fasting blood glucose in study participants with an APE of CF randomized to vitamin D_3 or placebo.

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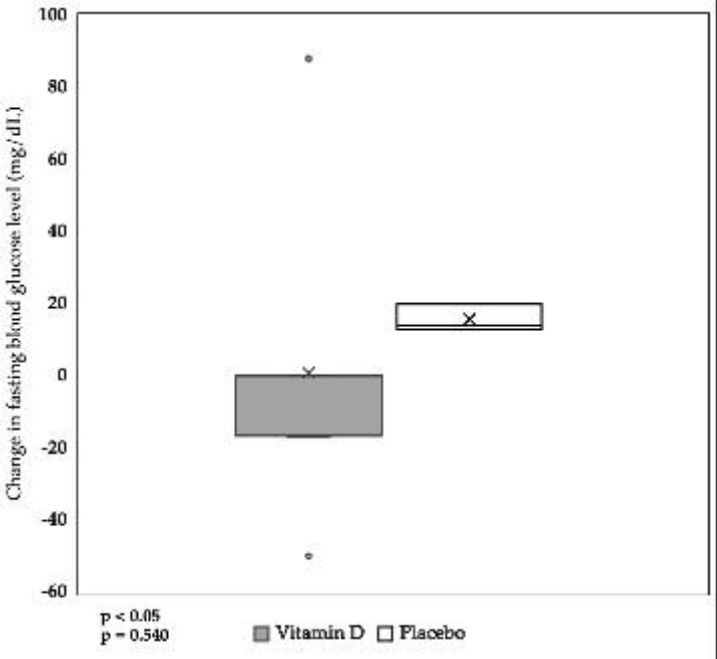
2
1
0
-1
-2
Change in HbA1c (%)
p < 0.05
p = 0.827
Vitamin D
Placebo


100
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40
20
0
-20
-40
-60
Change in fasting blood glucose level (mg/dL)
p < 0.05
p = 0.540
Vitamin D
Placebo