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Changes in bone turnover after high-dose vitamin D supplementation during acute pulmonary exacerbation in cystic fibrosis

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A B S T R A C T

In people with cystic fibrosis (CF), chronic inflammation and infection increase the risk for low bone mineral density and CF-related bone disease. During acute pulmonary exacerbations (APE), people with CF have increases in markers of bone resorption. Vitamin D has been proposed as a potential nutrient to lower inflammation. In this ancillary analysis of the Vitamin D for the Immune System in CF study, we hypothesized that vitamin D administered at the time of APE would have favorable changes on bone turnover markers compared to placebo. Participants with CF were randomized to receive a single dose of 250,000 IU of vitamin D or placebo during an APE and followed for 1 year for the primary outcome of APE or death after randomization. Bone turnover markers: C-terminal telopeptide (CTX-1) and procollagen type 1 intact N-terminal propetide (P1NP) were assessed at randomization (during APE) and after recovery from the APE in 45 participants. Participants randomized to vitamin D had significant decreases in markers of bone turnover; participants who received placebo had non-significant increases in markers of bone turnover. Vitamin D supplementation during an APE may help reduce the risk for CF-related bone disease.

1. Introduction

Up to a quarter of adults living with cystic fibrosis (CF) have CF-related bone disease (CFBD) [1], characterized by low bone mineral density and increased risk for fractures. CFBD increases in prevalence with increasing age [1]. People with CF have multiple factors that may increase their risk for CFBD including vitamin D deficiency compounded by exocrine pancreatic insufficiency, use of systemic glucocorticoids, undernutrition, inflammation, sex steroid deficiency, decreased exercise and CF transmembrane conductance regulator (CFTR) dysfunction [2–4]. Even with normal bone density, people with CF have uncoupled bone turnover, favoring bone resorption [5], abnormal bone micro-architecture [6] and increased risk of fractures compared to people without CF [7,8].

Acute pulmonary exacerbations (APE) are associated with decreased bone mineral density in people with CF [9]. During APE, levels of inflammatory cytokines rise, which is in turn associated with increased bone resorption [10,11]. Whole blood collected from adults with CF during APE has increased potential to form osteoclasts from hematopoietic precursors [12]. During APE, markers of bone resorption rise before decreasing after recovery from APE [13], which likely contributes to the decreases in bone density associated with APE [9]. Ways to reduce this bone loss associated with APE are focused on prevention and aggressive treatment of APE [14,15].

Vitamin D has been proposed as a potential nutrient to lower inflammation [16]. In a single-center pilot study, a single high-dose vitamin D bolus administered to adults admitted to the hospital for an APE was associated with decreased plasma inflammatory markers, improved survival, and recovery of lung function compared to placebo [17,18]. Two recent single-center pilot studies enrolling patients with CF at baseline health found that treatment with vitamin D or its analogues was associated with decreased inflammatory markers and pleiotropic immunomodulatory effects [19–21]. As inflammation mediates bone loss [3,7,22], it is possible that the anti-inflammatory effect of vitamin D may mitigate the bone loss associated with APEs in people with CF. Few clinical studies, however, have studied changes in bone

Abbreviations: cystic fibrosis, (CF); acute pulmonary exacerbation, (APE); CF-related bone disease, (CFBD); 25-hydroxyvitamin D, (25(OH)D); C-terminal telopeptide, (CTX-1); procollagen type 1 intact N-terminal propeptide, (P1NP); Vitamin D in the Immune System in Cystic Fibrosis, (DISC); CF transmembrane conductance regulator, (CFTR); forced expiratory volume in one second, (FEV1).

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turnover markers before and after APE, and whether any treatments are effective in decreasing the bone turnover markers in people with CF [10,11,13].

The objective of this study was to examine the impact of high dose vitamin D on changes in bone turnover markers in adults with CF admitted with an APE. This was a secondary analysis of The Vitamin D in the Immune System in Cystic Fibrosis (DISC) study which was a multi-center, randomized, placebo-controlled clinical trial of a single high-dose vitamin D bolus followed by maintenance vitamin D supplementation for adults with CF during an APE, with the primary endpoint of recurrent APE or death in the following 12 months [23]. The hypothesis of this ancillary study was that vitamin D administered at the time of APE would have favorable changes on bone turnover markers compared to placebo.

2. Methods

2.1. Study design

This was a secondary analysis of the DISC trial which has been previously described [23,24]. In brief, DISC was a multi-center, double-blind, placebo-controlled randomized study (NCT01426256) conducted by five Cystic Fibrosis Foundation Therapeutics Development Network Center study sites in the United States. Participants were randomized to receive a single dose of vitamin D_3 (250,000 IU) orally or placebo within 72 h of admission for management of an APE. Three months after the bolus dose, participants randomized to oral vitamin D_3 began 50,000 IU every other week for the next 9 months; those randomized to placebo took oral matching placebo for 9 months. Participants would continue their habitual vitamin D supplementation as long as it did not exceed 2000 IU daily as per their primary team.

2.2. Participant eligibility

In brief, patients with CF were eligible for DISC if they were at least 16 years old and enrolled within 72 h of being admitted to the hospital for management of APE. Patients were ineligible if they were taking >2000 IU vitamin D daily, most recent 25(OH)D < 10 ng/mL or > 55 ng/mL, had conditions that could be exacerbated by vitamin D supplementation including hypercalcemia, conditions affecting vitamin D metabolism such as chronic kidney disease, or conditions affecting expected 12-month survival [24]. Participants were included in this analysis if they were enrolled at the coordinating site (Emory University, Atlanta, GA) and had a pulmonary function test and serum collection at a follow-up study visit after recovery from APE.

2.3. Laboratory analysis

Samples were collected during an APE at the baseline study visit and after recovery from the APE. Stored serum from the 3-month study visit was used, unless the participant did not have a pulmonary function test and stored serum available from that study visit; in which case stored serum from another study visit at least 1-month after randomization was used. Samples were collected in the fasting state when possible and stored at −80 °C until batch processing. C-terminal telopeptide (CTX-1), a marker of bone resorption, and procollagen type 1 intact N-terminal propeptide (P1NP), a marker of bone formation, were analyzed by chemiluminescent immunoassay with the IDS-iSYS system (Immunodiagnostic Systems, Gaithersburg, MD).

2.4. Statistical analysis

Continuous variables were examined for normality. Characteristics of participants randomized to high-dose vitamin D and placebo were compared with Mann Whitney *U* test if continuous, Chi-square test if categorical and Fisher's exact test if counts were infrequent. Bone turnover markers during and after recovery from APE were compared pairwise with Wilcoxon signed rank test. Change in bone turnover markers were compared between intervention arms with Mann Whitney *U* test. Two sensitivity analyses were performed: including only participants whose follow-up study visit was at 3 months and another excluding participants whose follow-up study visit was at 1 month. Analysis was performed with Stata 17 (StataCorp LLC, College Station, TX), and 0.05 significance.

3. Results

3.1. Study participants

Of the 91 participants in the parent study, 48 participants were enrolled at the coordinating site. Three participants were excluded due to not having pulmonary function testing and blood collected at the follow-up study visit. A total of 45 participants were included in this secondary analysis. No participants had used oral or intravenous glucocorticoids in the month prior to enrollment, and their median baseline 25(OH)D level was 26.4 ng/mL. Participants randomized to placebo had higher baseline 25(OH)D than participants randomized to high-dose vitamin D (28.3 ng/mL vs 21.40 ng/mL, $p = 0.006$, Table 3). Participants were otherwise similar in their baseline demographics (Table 1). The follow-up study visits for 71 % of participants were 3 months after enrollment during APE. Follow-up was at 6 months for seven participants (16 %), at 12 months for three participants (7 %), and at 1 month for three participants (7 %).

Table 1
Baseline characteristics of participants.

	Total	Placebo	High Dose Vitamin D	*p*-value
	N = 45	*N* = 23	*N* = 22	
Male	19 (42.2 %)	10 (43.5 %)	9 (40.9 %)	0.86[a]
Race				0.29[b]
White	38 (84.4 %)	21 (91.3 %)	17 (77.3 %)	
African American	6 (13.3 %)	2 (8.7 %)	4 (18.2 %)	
Asian	1 (2.2 %)	0 (0.0 %)	1 (4.6 %)	
CFTR mutation				0.51[b]
No copies of f508del	9 (20.0 %)	3 (13.0 %)	6 (27.3 %)	
Heterozygous for f508del	16 (35.6 %)	9 (39.1 %)	7 (31.8 %)	
Homozygous for f508del	20 (44.4 %)	11 (47.8 %)	9 (40.9 %)	
Cystic fibrosis-related diabetes*				
No CFRD	11 (29.0 %)	6 (30.0 %)	5 (27.8 %)	0.85[a]
Impaired fasting glucose or Impaired glucose tolerance	11 (29.0 %)	5 (25.0 %)	6 (33.3 %)	
CFRD	16 (42.1 %)	9 (45.0 %)	7 (38.9 %)	
Use Systemic Glucocorticoids	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	
Exocrine Pancreatic Insufficiency	41 (91.1 %)	22 (95.7 %)	19 (86.4 %)	0.35[b]
Age (years)	33.7 (31.5,38.9)	33.7 (30.9,40.2)	34.3 (31.9,38.8)	0.73[c]
Baseline FEV_1 (% pred)**	47.0 (37.0,61.0)	51.0 (43.0,64.0)	40.5 (35.0,60.0)	0.08[c]
Body mass index (kg/m^2)	20.0 (18.7,21.3)	20.3 (19.2,22.5)	19.6 (18.0, 21.0)	0.23[c]

Baseline demographics of participants. Categorical variables are reported as count (%). Continuous variables are reported as median (interquartile range).
* Missing data: 7 participants had indeterminant or unknown CFRD status.
** FEV_1: forced expiratory volume in one second (percent predicted).
[a] Chi-square test.
[b] Fisher's exact test.
[c] Mann Whitney *U* test.

3.2. Change in CTX-1 and P1NP during and after APE

The average change over time of participants' CTX-1 (participants treated with high-dose vitamin D: −0.034 ng/mL vs participants treated with placebo: 0.025 ng/mL, $p = 0.02$) and P1NP (participants treated with high-dose vitamin D: −10.4 ng/mL vs participants treated with placebo: 5.5 ng/mL, $p = 0.01$) were significantly different by treatment group. Participants randomized to high-dose vitamin D had significant decreases in their median CTX-1 ($p = 0.003$) and P1NP ($p = 0.008$) after recovering from APE (Fig. 1). Participants randomized to placebo had no significant changes in their median CTX-1 or P1NP after recovering from APE. Median bone turnover markers before and after intervention are reported in Table 2. In sensitivity analyses, when including only participants whose post-APE recovery study visit was at 3 months ($N = 32$) or excluding participants whose post-APE recovery study visit was before 3 months ($N = 42$), the findings were similar.

3.3. Change in 25(OH)D during and after APE

In the parent study, the vitamin D arm significantly increased serum 25(OH)D by 1 month compared to placebo. Three months following the vitamin D or placebo intervention, there was no significant difference in 25(OH)D between groups [23]. Similar to the parent study, participants in this analysis who were randomized to high dose vitamin D had significantly higher median 25(OH)D by 1 month compared to participants randomized to placebo (53.0 ng/mL vs 31.3 ng/mL, $p = 0.002$, Table 3). The post-recovery 25(OH)D was similar in both arms ($p = 0.33$, Table 3).

4. Discussion

In this study, participants with CF had significant reductions in markers of bone resorption and formation after recovering from admission for APE when treated with high-dose vitamin D during the admission. In contrast, participants with CF had non-significant increases in markers of bone resorption and formation after recovering from admission for APE when treated with standard of care for APE. These findings suggest that use of high-dose vitamin D supplementation during an APE may mitigate the bone loss suffered by people with CF with each APE.

People with CF are at risk for low bone mineral density and fractures compared to people without CF. Pubertal adolescents and young adults with CF in baseline health, not in an APE, have uncoupled markers of bone turnover: increased markers of bone resorption and reduced markers of bone formation compared to matched controls without CF [5]. In vitro models of human osteoblast cultures treated with CFTR inhibitor have reduced osteoprotegerin (OPG), an inhibitor of osteoclastogenesis, and increased PGE_2, an inducer of inflammatory bone loss [25]. Bone turnover is uncoupled at baseline and further perturbed during APE [10,11,13].

APE are associated with increased inflammatory cytokines, including cytokines that stimulate bone resorption. Our findings are similar to previous studies of bone turnover markers during APE, that markers of bone resorption rise during APE before decreasing after recovery from APE [13]. This mechanism may be independent from quelling inflammation with high-dose vitamin D, as there was not a significant difference in markers of inflammation (plasma LL-37) in the parent study

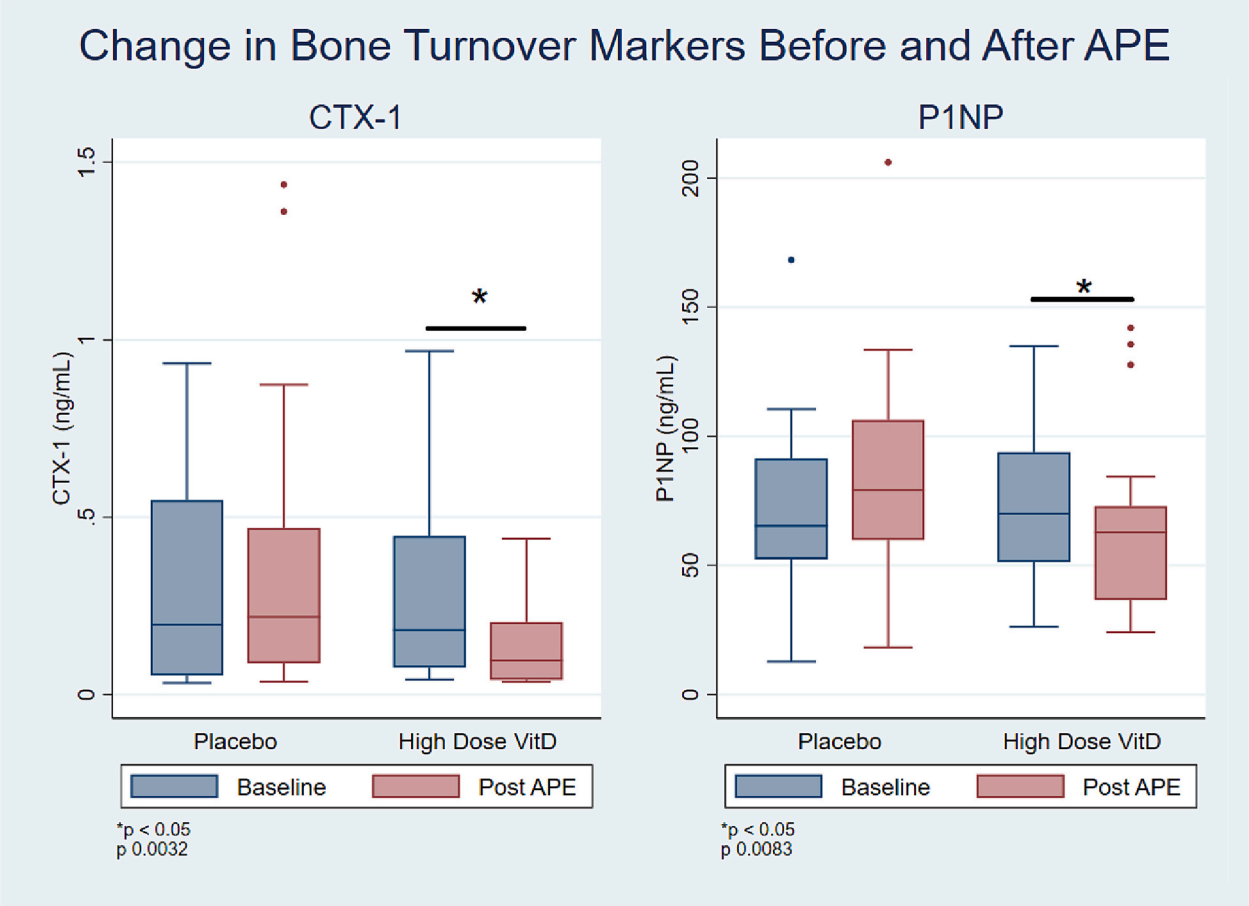

Fig. 1. Change in bone turnover markers during and after APE
Bone turnover markers during APE (baseline) and after recovery from APE (post APE). Baseline to post APE levels are compared with Wilcoxon Singed Rank test. *$p < 0.05$.

Table 2
Bone turnover markers and vitamin D levels.

		Placebo	N = 23		High-dose Vitamin D	N = 22
	Baseline	Post	p-value	Baseline	Post	p-value
25(OH)D (ng/mL)	28.3 (24.3,36.3)	37.4 (28.5,48.9)	0.03	21.4 (15.1,28.2)	39.1 (29.4,53.1)	<0.001
CTX-1 (ng/mL)	0.197 (0.054,0.548)	0.218 (0.089,0.469)	0.52	0.182 (0.076,0.447)	0.096 (0.041,0.204)	0.003
P1NP (ng/mL)	65.31 (52.35,91.33)	79.05 (59.80,106.27)	0.12	70.04 (51.33,93.82)	62.86 (36.61,72.87)	0.008

Bone turnover markers and vitamin D levels during APE (baseline) and after recovery from APE (post). Baseline to post APE levels are compared with Wilcoxon Singed Rank test. Variables are reported as median (interquartile range).

Table 3
25(OH)D level in participants.

	Total	N	Placebo	N	High Dose Vitamin D	N	p-value
Baseline 25(OH)D (ng/mL)	26.4 (19.5,32.0)	45	28.3 (24.3,36.3)	23	21.4 (15.1,28.2)	22	0.006
1 month 25(OH)D (ng/mL)	39.7 (31.3,53.0)	24	31.3 (29.5,40.6)	12	53.0 (39.0,64.0)	12	0.002
Post APE 25(OH)D (ng/mL)	38.8 (29.0,48.9)	45	37.4 (28.5,48.9)	23	39.1 (29.4,53.1)	22	0.33

25(OH)D at baseline during APE, 1 month after high-dose vitamin D or placebo, and at after recovery from APE (post). 25(OH)D in the high-dose vitamin D and placebo arms are compared by Wilcoxon Signed Rank test. Variables are reported as median (interquartile range).

[23]. However, when examining participants who received standard of care without high-dose vitamin D supplementation, their markers of bone resorption were similar during APE and after recovery. Work by Shead et al, examining whole blood collected from adults with CF during APE found increased potential to form osteoclasts from hematopoietic precursors [12], increased osteoclast activity which correlated with serum IL-6, and increased osteoclast formation which correlated with serum TNF-alpha [11]. Similar to our findings in the placebo arm, other groups have found that markers of bone formation were stable during an APE and after recovery [10,11].

Vitamin D supplementation would be expected to decrease markers of bone turnover, as vitamin D is necessary for optimal dietary calcium absorption and renal reabsorption to minimize parathyroid hormone-mediated bone resorption to maintain calcium homeostasis. Studies of "high-dose" and "standard-dose" vitamin D supplementation for children and young adults with human immunodeficiency virus (HIV) infection – disease in which bone turnover is uncoupled similar to CF, have found decreases in CTX-1 and P1NP with high-dose vitamin D supplementation [26,27]. Similarly, in postmenopausal osteoporosis where there is net bone loss due to increased bone resorption, postmenopausal women randomized to high-dose (20,000 IU twice weekly in addition to 800 IU daily) or standard-dose (800 IU daily) vitamin D supplementation found a similar significant decrease in CTX-1 in both arms and significant decreases in P1NP in both arms, but more pronounced reduction in P1NP in the standard-dose arm [28]. In these studies, the dose of vitamin D supplementation considered high-dose varied, but was well above the typical upper limit of recommended daily allowance for vitamin D supplementation by the Institute of Medicine [29].

In contrast to these findings, a dose-finding study of safe vitamin D bolus dose for elderly individuals with vitamin D deficiency found that elderly individuals who received a single dose of 600,000 IU or 300,000 IU vitamin D had significant increases in their CTX-1, which returned to baseline by the 90 day follow-up [30]. The elevation of CTX-1 was higher and more sustained in the arm that received 600,000 IU compared to the arm that received 300,000 IU vitamin D. There was no change in the marker of bone formation (bone specific alkaline phosphatase) or in CTX-1 in the arm that received a single dose of 100,000 IU vitamin D [30]. These findings are similar to previous studies suggesting dose dependent changes in bone turnover markers. However, these data suggest that there is a limit to beneficial megadosing of vitamin D. In our study, participants received 250,000 IU vitamin D as their single bolus dose at baseline.

The current study is limited by design to only evaluate association and not causation or mechanism of perturbance of bone turnover markers. Bone turnover markers themselves are surrogates for changes in bone biology that ultimately lead to increased risk for fracture. Furthermore, as a secondary analysis, the sample size of this study may not have been powered to evaluate changes. This study also did not examine changes in bone turnover markers in the context of highly effective CFTR modulators. As participants were enrolled from 2012 to 2016, only two participants enrolled in DISC were using highly effective CFTR modulator therapy; neither were enrolled at the coordinating site and so were not included in this secondary analysis. Another limitation is that CTX-1 has some circadian variation and varies relative to fed/fasting state. While >80 % of baseline samples were collected fasting in the morning, approximately 40 % of post APE samples were not collected fasting.

In conclusion, participants treated with a high-dose bolus of vitamin D during admission for APE had declines in bone turnover markers not seen in participants who received standard of care. With increasing survival of people living with CF, the prevalence of CFBD is also increasing. It is important to continue to investigate therapeutic options to prevent and treat CFBD even in the era of highly effective CFTR modulators, as the effects on bone health by CFTR modulators are not yet known. These findings suggest that use of high-dose vitamin D supplementation during an APE may mitigate the bone loss suffered by people with CF with each APE. This mechanism may be independent from vitamin D's hypothesized immunomodulatory benefits. Further research is needed to confirm these changes in bone turnover in people regardless of their use of highly effective modulator therapy and also examine if there are noticeable changes in bone histomorphometry, microarchitecture, or bone density. Further research is needed to explore doses of vitamin D that may be helpful without potentially exacerbating increases in bone resorption.

CRediT authorship contribution statement

Malinda Wu: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing, Funding acquisition. **Anirudh Bhimavarapu:** Investigation, Conceptualization, Writing – review & editing. **Jessica A. Alvarez:** Writing – review & editing, Methodology. **William R. Hunt:** Writing – review & editing, Resources. **Vin Tangpricha:** Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Visualization, Writing – review & editing, Project administration.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2023.116835.

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