Vitamin D insufficiency in children, adolescents, and young adults with cystic fibrosis despite routine oral supplementation

Alisha J Rovner, Virginia A Stallings, Joan I Schall, Mary B Leonard, and Babette S Zemel

ABSTRACT
Background: Cystic fibrosis (CF) with pancreatic insufficiency is associated with poor absorption of fat and fat-soluble vitamins, including vitamin D. Pancreatic enzyme supplementation does not completely correct fat malabsorption in CF patients.

Objective: The objective of the study was to compare the vitamin D status of children, adolescents, and young adults with CF who were treated with routine vitamin D and pancreatic enzyme supplements with the vitamin D status of a healthy reference group from a similar geographic area.

Design: Growth, dietary intake, and serum concentrations of 25-hydroxyvitamin D [25(OH)D], 1,25-dihydroxyvitamin D [1,25(OH)2D], and parathyroid hormone (PTH) were measured in 101 white subjects with CF and a reference group of 177 white subjects.

Results: The median daily vitamin D supplementation in the CF group was 800 IU. The mean ± SD serum concentrations of 25(OH)D were 20.7 ± 6.5 ng/mL in the CF group and 26.2 ± 8.6 ng/mL in the reference group (P < 0.001). Vitamin D deficiency and insufficiency were defined as 25(OH)D concentrations < 11 ng/mL, and < 30 ng/mL, respectively. Seven percent of the CF group and 2% of the healthy reference group were vitamin D deficient (P < 0.03). Ninety percent of the CF group and 74% of the healthy reference group were vitamin D insufficient (P < 0.01). Twenty-five percent of the CF group and 9% of the healthy reference group had elevated PTH (P < 0.006). The odds of vitamin D insufficiency in the CF group, compared with the healthy reference group, were 1.2 (95% CI: 1.1, 1.3) after adjustment for season and age.

Conclusion: Despite daily vitamin D supplementation, serum 25(OH)D concentrations remain low in children, adolescents, and young adults with CF.

KEY WORDS Cystic fibrosis, vitamin D, fat-soluble vitamins, children, adolescents, young adults

INTRODUCTION

Cystic fibrosis (CF), the most common autosomal recessive disease in whites, affects multiple organ systems, including the lungs, the exocrine pancreas, and the hepatobiliary system. Approximately 90% of persons with CF have pancreatic insufficiency (PI), which causes malabsorption of fat (1). Treatment of PI includes supplementation with pancreatic enzymes; however, supplementation does not completely correct the fat malabsorption. In addition, in persons with CF and PI, fat-soluble vitamins (ie, vitamins A, D, E, and K) are malabsorbed. With the recognition that CF patients are at risk of osteopenia and osteoporosis, attention has been given to optimizing the intakes of vitamins and minerals that are important in bone mineralization, including vitamin D.

Current Cystic Fibrosis Foundation (CFF) guidelines on vitamin D recommend supplementation with ≥800 IU/d for children >1 y old(2, 3), an amount that is 4 times the Adequate Intake (4). However, weekly or biweekly doses of up to 12 000 IU (children <5 y old) or 50 000 IU (children >5 y old) may be needed to achieve normal 25(OH)D concentrations, which the CFF defines as between 30 and 60 ng/mL (75–150 nmol/L) (2). The CFF further recommends that 25(OH)D concentrations should be checked in the late autumn or winter when cutaneous synthesis is low.

Previous studies in the United States and the United Kingdom have reported low 25(OH)D concentrations in children with CF, despite routine vitamin D supplementation (5–8). However, not all of those studies included control groups or examined vitamin D status by season. Reports of frequent vitamin D insufficiency in otherwise healthy children have underscored the importance of including in a study a healthy comparison group to improve the understanding of the magnitude of the problem in CF (9–11). In addition, consideration of seasonal fluctuations in vitamin D concentrations is essential in evaluating the prevalence of hypovitaminosis D. Studies in adults with CF have reported low vitamin D concentrations also, which suggests that the vitamin D concentration is a concern for CF patients throughout life (12, 13). The purpose of the present study was to compare the vitamin D status in children, adolescents, and young adults with CF who were being treated with routine vitamin D and pancreatic enzyme supplements with the status in a healthy, white, reference group from a similar geographic area.

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VITAMIN D INSUFFICIENCY IN CYSTIC FIBROSIS

SUBJECTS AND METHODS

Subjects

Subjects with CF aged 8–25 y were recruited from 3 CFF-accredited CF centers (2 pediatric and 1 adult) in Pennsylvania (latitude: 39° 43' N to 42° N) between November 2000 and February 2002. A diagnosis of CF was established either by clinical signs confirmed by a sweat test > 60 mEq/L or by a positive genotype analysis of pancreatic insufficiency. Exclusion criteria were forced expiratory volume in 1 s (FEV1) < 40% of that predicted, CF-related diabetes, or any other medical illness known to affect growth or bone health. Study-related measurements were taken while the subjects were in their usual state and when they had not had an exacerbation within the previous 2 wk.

The reference group included children aged 6–21 y who were recruited from the greater Philadelphia area between December 2000 and April 2004 as part of a study of skeletal development in healthy children (11). The exclusion criterion for the reference group was the presence of any disease or the use of any medication known to affect growth, nutritional status, or bone health. For the purposes of this study, the reference group was restricted to the 177 white subjects, because most persons with CF are white (1), and vitamin D concentrations vary significantly with race (11).

Subjects > 18 y old provided written informed consent, as did the parent or guardian of each subject < 18 y old; in addition, assent was obtained from children 7–18 y old. The institutional review boards of The Children’s Hospital of Philadelphia and of each participating institution approved the protocol.

Anthropometry

Body weight was measured with an electronic scale that is accurate to 0.1 kg (Scalatronix Inc, Wheaton, IL), and standing height was measured with a stadiometer that is accurate to 0.1 cm (Holtain, Crymych, United Kingdom); standard research techniques were used (14). Measurements were taken in triplicate by a research anthropometrist, and the average was used. Weight, height, and body mass index (in kg/m2) were compared with the Centers for Disease Control and Prevention 2000 growth charts (15), and age- and sex-specific z scores were calculated.

Pulmonary function

Pulmonary status was evaluated in the CF group by using standard pulmonary function methods. FEV1 was compared with reference values and reported as the percentage of the predicted value (16). Wang equations were used for the males < 18 y old and the females < 16 y old, and Hankinson equations were used for the males > 18 y old and the females > 16 y old (17, 18).

Vitamin D metabolites and parathyroid hormone

A nonfasting blood sample was drawn between 0800 and 1700 for measurement of serum concentrations of 25-hydroxyvitamin D [25(OH)D], 1,25-dihydroxyvitamin D [1,25(OH)2D], and parathyroid hormone (PTH). Intact PTH was analyzed in the Clinical Laboratory of The Children’s Hospital of Philadelphia. Serum for vitamin D analysis was stored in aliquots at −70 °C and shipped in batches for analysis. The serum vitamin D concentrations in both groups were analyzed by using the same radioimmunoassay (DiaSorin, Inc, Stillwater, MN) with a radioiodinated tracer (19). Serum 25(OH)D and 1,25(OH)2D concentrations in the CF group were analyzed by the Bruce W Hollis Laboratory Services (Mount Pleasant, SC), and those in the healthy reference group were analyzed at the Nichols Research Institute (NRI; Quest Diagnostics, San Juan Capistrano, CA).

To assess agreement between the 2 laboratories, the 25(OH)D and 1,25(OH)2D concentrations in 81 samples from the same subjects were analyzed at both laboratories. Although the values were highly correlated between laboratories (r = 0.96 for 25(OH)D; r = 0.92 for 1,25(OH)2D), values for both vitamin D assays from the NRI laboratory were systematically higher than those from Bruce W Hollis Laboratory Services. Because the head of that laboratory (Bruce Hollis) developed the radioimmunoassays, the results from that laboratory were used as the reference, and an adjustment was made to 25(OH)D and 1,25(OH)2D results from the NRI laboratory to account for differences. On the basis of regression models, the values from the NRI laboratories were adjusted with the use of the following equations:

Adjusted 25(OH)D Quest Diagnostics values

\[ = -2.03 + \text{Quest Diagnostics values} (0.83) \quad (1) \]

and

Adjusted 1,25(OH)2D Quest Diagnostics values

\[ = 24.73 + \text{Quest Diagnostics values} (0.30) \quad (2) \]

Dietary and supplemental intakes

Dietary intake was collected by using 3-d prospective weighed food records in the CF group and three 24-h recalls in the healthy reference group. All diet records were analyzed with NUTRITION DATA SYSTEM for RESEARCH software (NDS-R, version 4.04; Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN) and vitamin D and calcium intakes were compared with the Dietary Reference Intakes and reported as a percentage of the Adequate Intake (4).

Information on the use of vitamin and mineral supplements was obtained by questionnaire. The nutrient content and the dose of each supplement were used to calculate the supplemental calcium and vitamin D intakes.

Statistical analysis

Continuous variables were expressed as means ± SDs if normally distributed or as medians with interquartile (25–75%) ranges if nonnormally distributed. Categorical variables were presented by frequency distributions. Vitamin D deficiency was defined as 25(OH)D concentrations < 11 ng/mL, according to the Institute of Medicine’s definition in the Dietary Reference Intakes (4). Vitamin D insufficiency was defined as < 30 ng/mL, because J the most advantageous serum concentrations for multiple health outcomes are > 30 ng/mL (20), and 2) the CFF recommends that 25(OH)D concentrations should be maintained at > 30 ng/mL (2). Vitamin D sufficiency was defined as 25(OH)D concentrations ≥ 30 ng/mL.

Vitamin D concentrations were reported by season; the seasons were categorized as winter (December, January, and February), spring (March, April, and May), summer (June, July, and August), and fall (September, October, and November). Normal
TABLE 1
Characteristics of subjects with cystic fibrosis (CF) and the healthy reference group

<table>
<thead>
<tr>
<th></th>
<th>Subjects with CF (n = 101)</th>
<th>Healthy reference group (n = 177)</th>
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<tbody>
<tr>
<td>Females [n (%)]</td>
<td>50 (50)</td>
<td>104 (58)</td>
</tr>
<tr>
<td>Males [n (%)]</td>
<td>51 (50)</td>
<td>73 (42)</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.8 ± 4.2</td>
<td>12.5 ± 3.5</td>
</tr>
<tr>
<td>Weight-for-age z score</td>
<td>−0.57 ± 1.00</td>
<td>0.34 ± 0.74</td>
</tr>
<tr>
<td>Height-for-age z score</td>
<td>−0.53 ± 1.00</td>
<td>0.25 ± 0.79</td>
</tr>
<tr>
<td>BMI z score</td>
<td>−0.36 ± 0.92</td>
<td>0.28 ± 0.79</td>
</tr>
<tr>
<td>FEV1, (% of predicted)</td>
<td>84 ± 19%</td>
<td></td>
</tr>
<tr>
<td>25(OH)D concentration (ng/mL)</td>
<td>20.7 ± 6.5</td>
<td>26.2 ± 8.6</td>
</tr>
<tr>
<td>1,25(OH)2D concentration (pg/mL)</td>
<td>36.1 ± 8.1</td>
<td>43.0 ± 4.8</td>
</tr>
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1 FEV1, forced expiratory volume in 1 s; 25(OH)D, 25-hydroxyvitamin D; 1,25(OH)2D, 1,25-dihydroxyvitamin D. Student’s t test was used to assess group differences.

RESULTS

A CF group (n = 101; n = 50 females) and a healthy reference group (n = 177; n = 104 females) participated in the study. Characteristics of the study sample are presented in Table 1. The growth deficits of this sample are consistent with patterns seen in children and young adults with CF in the United States (1). The mean serum concentrations of 25(OH)D were 20.7 ± 6.5 ng/mL in the CF group and 26.2 ± 8.6 ng/mL in the reference group (P < 0.001). There were seasonal fluctuations in 25(OH)D concentrations in both groups; during every season, 25(OH)D concentrations were significantly (P < 0.01) lower in the CF group than in the healthy reference group (Figure 1).

Seven percent of subjects with CF and 2% of healthy subjects were vitamin D deficient [ie, 25(OH)D concentrations < 11 ng/mL (P < 0.01)]. Ninety subjects with CF (90%) and 130 subjects in the reference group (74%) were vitamin D insufficient (<30 ng/mL). There were no sex differences in vitamin D insufficiency in either group. Mean 1,25(OH)2D concentrations were significantly (P < 0.001) lower in the CF group than in the healthy subjects (36.1 ± 8.1 and 43.0 ± 4.8 pg/mL, respectively).

There were no significant associations between 25(OH)D concentrations and FEV1, liver function, or growth measurements in the CF group. Serum 25(OH)D concentrations were negatively associated with age in the healthy reference group but not in the CF group. Logistic regression analysis indicated that the odds of vitamin D insufficiency in the CF group were 1.2 (95% CI: 1.1, 1.3) greater than those in the healthy subjects after adjusting for season and age (Table 2).

Serum 25(OH)D concentrations were examined in relation to PTH concentrations (Figure 2). Twenty-five subjects with CF (25%) and 16 subjects in the reference group (9%) had elevated PTH. There was no significant correlation between PTH and 25(OH)D concentrations (r = −0.16, P = 0.17) in the CF group. However, there was a significant, negative correlation between PTH and 25(OH)D in the healthy reference group (r = −0.23, P < 0.002).

TABLE 2
Multiple logistic regression model for vitamin D insufficiency

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio2 (95% CI)</th>
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<tbody>
<tr>
<td>Cystic fibrosis</td>
<td>1.2 (1.1, 1.3)</td>
</tr>
<tr>
<td>Age</td>
<td>1.0 (0.9, 1.0)</td>
</tr>
<tr>
<td>Season (summer as reference group)</td>
<td></td>
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<tr>
<td>Fall</td>
<td>1.1 (0.8, 1.2)</td>
</tr>
<tr>
<td>Winter</td>
<td>1.3 (1.1, 1.4)</td>
</tr>
<tr>
<td>Spring</td>
<td>1.0 (1.0, 1.3)</td>
</tr>
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1 Defined as serum 25-hydroxyvitamin D concentrations < 30 ng/mL (2, 20).

2 Logistic regression analysis was used to calculate the odds of vitamin insufficiency. To avoid overestimation of the relative risk for frequent outcomes, the odds ratio was adjusted by the method described by Zhang and Yu (21).
All CF patients provided labels from their dietary supplements, and 70 (70%) of these patients returned the 3-d diet records. Dietary and supplement data for vitamin D and calcium are shown in Table 3. All CF patients were taking a supplement that contained vitamin D, and 16% were taking one that contained calcium. Nine percent of subjects in the reference group were taking a supplement that contained calcium, and 23% were taking one that contained vitamin D. There was no significant relation between the dietary intake of vitamin D and the serum 25(OH)D concentrations in either group.

DISCUSSION

In this sample of children, adolescents, and young adults with CF, PI, and mild-to-moderate lung disease, 7% had vitamin D deficiency and 90% had vitamin D insufficiency, despite routine supplementation with vitamin D and pancreatic enzymes. Vitamin D deficiency and insufficiency occurred most often during the winter. However, vitamin D deficiency also occurred in the spring and fall, and insufficiency occurred in all seasons.

Reports suggested that vitamin D insufficiency is common in healthy children and that it varies by season and ethnicity (9–11). A study of 11–18-y-olds from an adolescent outpatient center in Boston, MA, found that 42% had vitamin D insufficiency and that 25(OH)D concentrations were 24% lower in the winter than in the summer (10). Another study of participants (12–19 y old) in the third National Health and Nutrition Examination Survey found that 25% of males and 47% of females living at lower latitudes and 21% of males and 28% of females living at higher latitudes had vitamin D insufficiency in the winter (9). The present study, which used a healthy reference group of whose ethnicity and latitude of dwelling were similar to those of the CF group, and which adjusted for seasonal fluctuations, showed 20% increase in vitamin D insufficiency in children, adolescents, and young adults with CF on routine treatment with pancreatic enzyme replacement and vitamin D supplementation.

Data from the present study and from previously published studies showing low vitamin D concentrations in CF patients suggested either that this vitamin is inadequately absorbed, even

<table>
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<tr>
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<th>Dietary intake</th>
<th>Supplemental intake</th>
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<tbody>
<tr>
<td></td>
<td>Cystic fibrosis group</td>
<td>Healthy reference group</td>
</tr>
<tr>
<td>Energy (kcal/d)</td>
<td>2644 (2056, 4780)</td>
<td>1823 (1525, 2618)²</td>
</tr>
<tr>
<td>Calcium (mg/d)</td>
<td>1423 (1016, 3130)</td>
<td>848 (619, 1685)²</td>
</tr>
<tr>
<td>(%AI)</td>
<td>110 (78, 241)</td>
<td>65 (48, 130)²</td>
</tr>
<tr>
<td>Vitamin D (IU/d)</td>
<td>329 (212, 957)</td>
<td>189 (120, 474)²</td>
</tr>
<tr>
<td>(%AI)</td>
<td>164 (106, 479)</td>
<td>95 (60, 237)²</td>
</tr>
</tbody>
</table>

¹ All values are median; 25th and 75th percentiles in parentheses. AI, adequate intake. Wilcoxon-Mann-Whitney test was used to assess group differences.
² Significantly different from cystic fibrosis group, P < 0.0001.
in the presence of pancreatic enzyme replacement, or that current
doses are not high enough to achieve target 25(OH)D concentra-
tions (5). A recent study of 134 adults with CF (19–64 y old)
in Baltimore, MD, found that 109 (81%) of the 134 had 25(OH)D
concentrations <30 ng/mL (median: 21.5 ± 10.8 ng/mL) (13).
Sixty-six of those 109 adults underwent the CFF’s vitamin D-
repletion protocol—ie, supplementation with 50 000 IU ergocal-
ciferol (vitamin D₂)/wk for 2 mo—and only 8% had serum
25(OH)D concentrations that rose to >30 ng/mL (13). Aris et al
(12) compared the absorption of ergocalciferol in 10 adults with
CF (18–45 y old) and PI with that in 10 healthy, age-, sex-, and
race-matched controls. Even though the CF patients took their
pancreatic enzymes with the dose of vitamin D, they absorbed
less than half the amount of vitamin D that was absorbed by the
control subjects. In addition, absorption was quite erratic in the
CF patients: 20% absorbed virtually no vitamin D₂. It has been
shown that cholecalciferol (vitamin D₃) increases serum
25(OH)D more efficiently than does ergocalciferol in healthy
people (22, 23); therefore, it is possible that absorption would
have been greater in the abovementioned studies if cholecalcif-
erol were the form of vitamin D used. To date, no study has
examined vitamin D absorption in children with CF.

With the increased life expectancy of CF patients, osteopenia
and osteoporosis have become major concerns (2). Although
the cause of bone disease in CF patients is likely to be multifactorial,
one of the modifiable factors that influences bone mass is vitamin
D status. Suboptimal vitamin D status may prevent children from
reaching their genetic potential for peak bone mass. The com-
parative secondary hyperparathyroidism mobilizes calcium
from the skeleton and thus reduces bone mass. Therefore, opti-
mizing vitamin D status in CF patients is critical, especially in
light of the other risk factors they have for metabolic bone dis-
ease, including glucocorticoid therapy, decreased physical ac-
tivity, reduced body weight, and hypogonadism. There is an
increasing recognition of the role of vitamin D in muscle function,
nutrient immunity, and the development of cardiovascular disease,
diabetes, and some cancers (24). The broader effects of vitamin
D insufficiency in CF patients remain to be determined.

The CFF recommends supplementation with 800 IU vitamin
D/d for children and young adults (2). The subjects in this study
reported vitamin D supplementation intakes in keeping with this
recommendation. Data from our study, as well as from studies by
others, suggest that this dose of vitamin D is too low to maintain
the desired 25(OH)D concentrations between 30 and 60 ng/mL in
CF patients. Cutaneous synthesis from sunlight exposure is an
alternative way of increasing vitamin D concentrations. Unfor-
lunately, for those who live above ~35° latitude, vitamin D
synthesis in the skin does not occur during the winter months (25,
26). Ultraviolet B radiation from a home unit or a tanning bed can
be used to synthesize vitamin D. To date, one published Swedish
study has examined changes in 25(OH)D concentrations in re-
response to ultraviolet B radiation from fluorescent lamps in 30
children and adults (9–40 y old) with CF and mild-to-moderate
lung disease (27). Although this was a small study, it provides
initial evidence that ultraviolet B lamps may be used to improve
serum 25(OH)D concentrations in CF patients, and future larger-
scale studies are warranted.

Our data suggest that vitamin D insufficiency was present in
most of the children, adolescents, and young adults with CF in all
seasons, despite routine vitamin D supplementation. Future ef-
forts should focus on identifying the optimal dose needed to
maintain 25(OH)D concentrations between 30 and 60 ng/mL. In
light of the many risk factors that CF patients have for osteopenia
and osteoporosis, careful attention should be given to maintain-
ing adequate vitamin D status.

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collection and management of the data; MBL: provision of the data on
laboratory comparisons and assistance in writing the manuscript; and BSZ:
the designing of the study, analysis of the data, and writing of the manuscript.
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