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Relationship Between Fat-Soluble Vitamin Supplementation and Blood Concentrations in Adolescent and Adult Patients With Cystic Fibrosis

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Abstract

Background—Pancreatic insufficiency is common in patients with cystic fibrosis (CF) and leads to malabsorption of fat-soluble vitamins. Multivitamins, including vitamins A, D, E, and K, are routinely prescribed to patients with CF to prevent vitamin deficiencies. Our objective was to examine the relationship between fat-soluble vitamin supplements and their impact on blood concentrations.

Methods—This was a retrospective chart review of patients with CF who were treated at Emory Clinic and Emory University Hospital during 2008–2012. The amount of fat-soluble vitamin supplementation, serum markers of fat-soluble vitamin concentrations, CF transmembrane conductance regulator genotype, and other demographic information were recorded from electronic medical records. Mixed-effects models were used to investigate the trends over time of fat-soluble vitamin supplements and serum vitamin concentrations.

Results—In total, 177 charts were eligible. Mean (SD) age was 26.1 (10.2) years. Ninety-two percent of patients had pancreatic insufficiency and 52% had the homozygous F508 mutation. Recorded fat-soluble vitamin supplementation increased in the past 5 years ($P < .001$ for all).

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Serum 25-hydroxyvitamin D increased slightly (3% increase; $P < .01$); however, there were no changes in the blood concentrations of vitamins A, E, and K ($P = .26-.96$).

Conclusions—Despite a near doubling of recorded fat-soluble vitamin supplementation over the past 5 years, there was no parallel increase in blood concentrations of these vitamins. Potential reasons include suboptimal dosages, low adherence, or ongoing issues with malabsorption.

Keywords

cystic fibrosis; vitamin D; vitamin A; vitamin E; vitamin K; avitaminosis

Background

Cystic fibrosis (CF), caused by mutations in the CF transmembrane conductance regulator (CFTR) protein, is the most common lethal genetic disease occurring in whites in the United States. The major organs affected by CF disease include the lungs and pancreas.¹ It is well established that nutrition management is a critical component for CF health care and is directly associated with lung function, long-term outcome, and survival rate of these patients.^{2,3} Of patients with CF, 85%–90% have exocrine pancreatic insufficiency, which is a major contributing factor for malabsorption of fat and fat-soluble vitamins.⁴ Furthermore, exocrine pancreatic function continues to decline over time.^{5,6} Despite optimizing and maximizing pancreatic enzyme replacement therapy, patients with CF continue to have some degree of fat malabsorption.^{7,8}

Fat-soluble vitamin deficiency is commonly found in CF and may exist at a very early age,^{9–13} despite the availability and widespread use of CF-specific fat-soluble multivitamins. A previous study reported that deficiency of 1 or more vitamins was present in 45.8% of newly diagnosed patients, with more than one-third having multiple vitamin deficiencies.⁹ Surveys of patients with CF reported a biochemical deficiency of vitamin A in 20%–40%,^{9,10,14} vitamin D in 25%–90%,^{1,15–17} vitamin E in 23%–38%,^{9,10,18} and vitamin K in 60%–70%.^{19–21}

Consensus guidelines have been formulated to address fat-soluble vitamin deficiency in patients with CF.^{4,22–26} However, the efficacy and validity of these guidelines remain unclear. Whereas some studies report high prevalence of vitamin A deficiency,^{27–29} other recent studies have reported unexpectedly high serum retinol concentration in patients taking vitamin A supplements as recommended.^{30–32} Similarly, suboptimal, normal, or even unexpectedly high vitamin E status has been observed in patients with CF who are receiving vitamin E supplementation.^{27,33,34} Several reports have described difficulty with achieving the target serum 25-hydroxyvitamin D (25(OH)D, a marker of vitamin D status) with routine supplementation with vitamin D.^{35–37} The response of serum vitamin K concentrations to vitamin K supplementation has demonstrated suboptimal vitamin K status despite routine supplementation.^{19–21,38,39} In addition, several studies have demonstrated that there was no correlation between the quantity of fat-soluble vitamin (A, D, E, and K) and the serum markers of that vitamin.^{5,30,31} Therefore, there still is an ongoing lack of knowledge about the relationship between intake of vitamin supplements and their impact on blood concentrations of these vitamins.

The objective of this study was to examine the relationship between fat-soluble vitamin supplements and the circulating concentrations of the markers of these fat-soluble vitamins. We aimed to determine whether fat-soluble vitamin supplementation in adults with CF over a 5-year period correlated with serum concentrations of fat-soluble vitamins. We conducted a retrospective review of data at our specialized CF care center over a 5-year period.

Materials and Methods

Subjects and Protocol

This was a retrospective chart review of all adolescent and adult patients with CF treated at Emory Clinic and Emory University Hospital between 2008 and 2012. All patients who were seen in our CF center were eligible for this study and had confirmed CF by sweat chloride measurements and/or genotyping. We excluded patients who did not have serum fat-soluble vitamin concentration data in the electronic medical records. Data extracted from the medical record included serum fat-soluble vitamin concentrations and/or their established serum markers to determine sufficiency, fat-soluble vitamin supplementation, *CFTR* genotype, and other demographic information deemed as potential confounders. Data was collected by 1 recorder. Patients in our clinic are routinely seen (annually, at minimum) for adherence to national guidelines on vitamins. The study was approved by the Institutional Review Board at Emory University.

Fat-Soluble Vitamin Supplementation and Serum Concentration

The amount of prescribed or reported fat-soluble vitamin supplements and serum fat-soluble vitamin concentrations was recorded from the electronic medical records. Serum fat-soluble vitamin concentrations are routinely measured at our clinic on an annual basis. Markers of circulating fat-soluble vitamins included serum levels of retinol and retinyl palmitate (vitamin A), α -tocopherol and β/γ -tocopherol (vitamin E), 25(OH)D (vitamin D), and vitamin K. Suboptimal concentrations were defined as the following: vitamin A, serum retinol <0.3 mg/L (1.05 μ mol/L); vitamin D, serum 25(OH)D <30 ng/mL (75 nmol/L); vitamin E, serum α -tocopherol <5 mg/L (12 μ mol/L); and vitamin K, serum vitamin K <0.1 ng/mL (0.22 nmol/L).⁴⁰

For vitamin A, E, and K supplements, we divided the supplement intake range into tertiles and created the categories of low intake, normal intake, and high intake. For vitamin D, the categories of low, normal, and high intake corresponded to <1000 IU, between 1000 and 2000 IU, and 2000 IU, respectively.

Other Factors Influencing Fat-Soluble Vitamin Concentrations

We evaluated type of mutation in the *CFTR* gene as a potential independent variable. The categories were homozygous F508 mutation, heterozygous F508 mutation, and CF genetic variants different from the F508 mutation. Age, sex, race, body mass index (BMI), and pancreatic insufficiency status were also incorporated in the analysis to account for potential confounding. Patients were considered to have pancreatic insufficiency if they were prescribed pancreatic enzymes. BMI was categorized as underweight (BMI <22 kg/m² for women and BMI <23 kg/m² for men; defined according to the CF Foundation nutrition care

guidelines),⁴¹ normal weight ($22 \leq \text{BMI} < 30$ for women and $23 \leq \text{BMI} < 30$ for men), or overweight ($\text{BMI} \geq 30 \text{ kg/m}^2$). Since it is well established that vitamin D status may fluctuate by season in patients with CF, we created a variable for season, which had 2 levels: “sunny” for March through September and “dark” for October through February of the following year.

Statistical Analysis

The serum levels and vitamin supplements were log-transformed due to the right skewness of their distributions and the presence of outliers. The statistical analysis was conducted separately for each vitamin serum level and vitamin supplements. Profile plots of each patient did not suggest a major departure from a linear trend of the log-transformed serum levels with time. To investigate the statistical significance of the linear trend, a mixed-effects model was fit, which took into account the within-subject correlational structure of the repeated measurements.⁴² The model then provided an estimate of the annual percentage change in the geometric mean of serum level of the vitamin being considered. Similarly, a mixed-effects model was fit to investigate the trend over time of supplementation of a particular vitamin and generated an estimate of annual percentage change in the geometric mean of supplements of the vitamin being considered. The *P* value associated with the estimate of annual percentage change (ie, slope) determined whether there was a linear change in log scale in that particular vitamin serum level or supplementation between 2008 and 2012.

In subsequent analyses, serum vitamin level was treated as the dependent variable; vitamin supplements and type of mutation in the *CFTR* gene were the independent variables. Rates of change for both unadjusted models and models adjusted for age, sex, race, BMI, and status of pancreatic insufficiency were calculated.

SAS version 9.3 (SAS Institute, Cary, NC) was used in the data analysis, and all tests were 2-sided, conducted with a 5% level of significance.

Results

Patients

We enrolled all 243 adolescent and adult patients attending the Emory Clinic and Emory University Hospital between 2008 and 2012. In total, 177 patients were eligible for our study. Demographic characteristics of the sample are displayed in Table 1. The population consisted of 96 (54%) males and 81 (46%) females and 167 (94%) whites, 9 (5%) blacks, and 1 (1%) Asian. Baseline characteristics of the population revealed a mean $\pm$ SD age of 26.11 ± 10.24 years, body weight of 62.39 ± 13.02 kg, and BMI of $22.05 \pm 3.71 \text{ kg/m}^2$. Ninety-two percent of patients were diagnosed as having pancreatic insufficiency. With respect to the *CFTR* gene mutation, 52% of patients were homozygous for the F508 mutation, 38% were heterozygous for the F508 mutation, and 10% carried another CF mutation. Rates of change for both unadjusted models and model adjusted for age, sex, race, BMI, and status of pancreatic insufficiency are reported.

Vitamin Supplements and Serum Levels

Vitamin A, D, E, and K supplements and corresponding serum levels of retinol, retinyl palmitate, 25(OH)D, α -tocopherol, β/γ -tocopherol, and vitamin K are displayed in Tables 2 and 3.

The mean baseline vitamin A supplement was $10,184.93 \pm 10,736.27$ IU in 2008 and $20,464.25 \pm 16,879.71$ IU in 2012. Twenty-six percent of patients had suboptimal serum vitamin A levels at baseline. Vitamin A supplement, on average, increased by 11.8% annually ($P < .0001$) in contrast to serum markers of vitamin A in which retinol and retinyl palmitate level did not change significantly over the past 5 years ($P = .77$ and $P = .30$).

The mean baseline vitamin D supplement was 962.67 ± 693.95 IU in 2008 and 2045.21 ± 1427.59 IU in 2012. Fifty-seven percent of patients had suboptimal serum 25(OH)D levels at baseline. Vitamin D supplement, on average, increased by 16% annually ($P < .0001$), in contrast to serum 25(OH)D, which, on average, increased by 3% per year ($P < .01$). Forty-eight percent of patients had suboptimal serum 25(OH)D levels at 5 years.

The baseline vitamin E supplement was 218.38 ± 224.11 IU in 2008 and 351.58 ± 295.99 IU in 2012. Twenty-four percent of patients had suboptimal serum vitamin E levels at baseline. Vitamin E supplement, on average, increased by 12.2% annually ($P < .0001$) in contrast to the α -tocopherol and β/γ -tocopherol level, which did not change significantly over the past 5 years ($P = .26$ and $P = .96$).

The baseline vitamin K supplement was 410.85 ± 577.74 μ g in 2008 and 849.89 ± 690.45 μ g in 2012. Six percent of patients had suboptimal serum vitamin K levels. Vitamin K supplement, on average, increased by 20.8% annually ($P < .0001$); in contrast, the vitamin K level did not change significantly over the past 5 years ($P = .71$) (Figure 1).

Influence of CFTR Gene and Vitamin Intake on Serum Fat-Soluble Vitamin Concentrations

The association of the type of *CFTR* gene with vitamin status was examined. We found that serum 25(OH)D levels in patients with the F508 heterozygous mutation increased by 5% annually over a 5-year period with statistical significance in both the unadjusted model and the model adjusting for potential confounding variables such as age, sex, race, BMI, status of pancreatic insufficiency, and seasonal effect (95% CI, 0.02–0.08; Table 4). In contrast, no significant change in 25(OH)D level over time was found in patients who had the F508 homozygous and other genotype mutation. There was no significant association between type of *CFTR* gene mutation and the concentration of other serum fat-soluble vitamins, including retinol, retinyl palmitate, α -tocopherol, β/γ -tocopherol, and vitamin K. No significant association between the level of vitamin intake and the corresponding concentration of the serum fat-soluble vitamin was found in any type of the vitamins studied.

Discussion

The results from this study have demonstrated that a substantial increase in fat-soluble vitamin supplementation in adults with CF over the past 5 years was not associated with a

significant increase in serum concentrations of these vitamins. Despite increased recognition of fat-soluble vitamin deficiency as an important problem in individuals with CF, suboptimal fat-soluble vitamin concentrations in blood remain highly prevalent.^{27–29,36–39} We found suboptimal fat-soluble vitamin status (A, D, E, and K) in approximately 25% of adults with CF in our clinic.

The role of fat-soluble vitamins on morbidity and mortality in individuals with CF has been documented in a number of studies.⁴³ Vitamin A and its metabolites are important for vision, epithelial differentiation, and immune function.⁴⁴ Visual impairment in relation to vitamin A deficiency has been reported in CF.⁴⁵ Many studies have demonstrated a protective effect of vitamins A and E on respiratory status in CF.^{34,46,47} Vitamin E deficiency also has an effect on the central nervous system; declines in cognitive function and neurologic diseases have been reported in patients with CF who have vitamin E deficiency.^{48,49} Vitamin D deficiency has been associated with low bone mineral density and increased fracture rates and may have an impact on immunity in patients with CF.^{26,50–52} Deficiency of vitamin K may lead to hemorrhagic episodes and decreased bone mineralization in these patients.^{39,53,54} These studies reinforce the importance of fat-soluble vitamin status on CF health care.

We show that despite a near doubling of reported fat-soluble vitamin supplementation over the past 5 years, the changes of these vitamins' serum concentrations were not clinically significant. Our findings support previous studies investigating vitamins A, D, E, and K.^{35,36,38} One interesting finding is that the mean supplementation for vitamin D increased to the initial recommended daily intake values by the CF Foundation. Despite an increase above 2000 IU of vitamin D daily, the serum 25(OH)D concentrations increased only modestly, with approximately half of the patients still with suboptimal concentrations of serum 25(OH)D. Potential reasons for the discrepancy between vitamin supplementation and blood vitamin levels include suboptimal supplement doses, low adherence to these vitamins, or ongoing issues with malabsorption.

Correction of fat-soluble vitamin insufficiency is challenging in patients with CF. Either under- or overcorrection is potentially associated with significant complications.^{43,55,56} Clifton et al⁵⁵ reported a case study on an adolescent with CF who presented with hypercalcemia due to hypervitaminosis A when taking vitamin A at a dose of 12,000 IU/d. Cialdella et al⁵⁶ presented a patient with CF who was diagnosed with osteopenia and was treated with 2200 IU/d of vitamin D plus 1000 mg/d of calcium. One year later, she developed severe abdominal pain from nephrocalcinosis. Her laboratory values revealed hypercalciuria and an increased serum 25(OH)D level at 75 ng/mL (187 nmol/L). No patients in our study had a serum 25(OH) D above the suggested level of the CF Foundation (100 ng/mL or 250 nmol/L).²⁶ Although a few patients had a serum 25(OH) D higher than 75 ng/mL (187 nmol/L), no related adverse events were documented. One patient in our study had a serum retinol level higher than the upper limit at 1.2 mg/L (4.2 μ mol/L), although no adverse events were noted with this retinol level. Similarly, high vitamin E and vitamin K status, defined by a serum α -tocopherol and vitamin K level higher than 18 mg/L (42 μ mol/L) and 6 mg/L (13.2 nmol/L), respectively, was found in a few patients in our

study; however, no symptoms of hypervitaminosis E and K were documented in the medical records.

Patients who have the F508 homozygous mutation of the *CFTR*, the most severe of the CF mutations, typically have more impaired exocrine pancreatic function.^{5,57–60} We present a novel finding showing a significant association between genotype and serum 25(OH)D, such that serum 25(OH)D concentrations increased only in patients with the F508 heterozygous mutation. We did not identify any significant association between genotype and serum concentrations of any other fat-soluble vitamins.

The limitations of this study include its retrospective study design, which did not allow us to assess adherence to prescribed vitamin supplements or the reasons for the increase in the amount of recorded fat-soluble vitamin supplementation over the past 5 years. We can only speculate that increases in the fat-soluble vitamin supplements were in response to recent guidelines and/or improved provider adherence to national guidelines. It is also possible that providers increased vitamin supplementation to compensate for the lack of change in blood vitamin concentrations. We could not assess the adherence to fat-soluble vitamins or fat-soluble vitamin intakes from dietary sources given the limitation of our study design. It is reported that adherence to multivitamin supplements is often low in the CF population.^{61,62} Also another limitation is that serum vitamin K level is not an ideal method to represent vitamin K storage compared with undercarboxylated osteocalcin. Our study included only adolescents and adults, and as such, the findings may not be applicable to other age groups, such as infants and children. Another limitation of our study is lack of comparative data for serum concentrations of fat-soluble vitamins from a control group.

Conclusions

In conclusion, despite an increase in reported fat-soluble vitamin supplement over the past 5 years, the changes of these vitamins' serum concentrations were not clinically significant. Future studies should focus on what constitutes an optimal vitamin concentration and focus on clinical outcomes in addition to blood concentrations in patients with CF.

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Figure 1.
Vitamin supplement vs serum vitamin level. 25(OH)D, 25-hydroxyvitamin D.

Table 1

Demographics of the Study Population (N = 177).

Characteristics	Mean [SD] or No. (%)
Age, y	26.11 [10.24]
Race	
White	167 (94.4)
Black	9 (5.1)
Asian	1 (0.6)
Sex	
Male	96 (54.2)
Female	81 (45.8)
Body weight, kg	62.39 [13.02]
Body mass index	
Overall, kg/m ²	22.05 [3.71]
Underweight	106 (59.9)
Normal	68 (38.4)
Overweight	3 (1.7)
Pancreatic insufficiency	163 (92.1)
Genotype	
Homozygous F508 mutation	92 (52.0)
Heterozygous F508 mutation	67 (37.9)
Others	18 (10.2)

Table 2

Fat-Soluble Vitamin Supplements in Study Participants Treated at the Emory Clinic and Emory University Hospital Between 2008 and 2012.

Year	Vitamin A, Mean $\pm$ SD, IU	Vitamin D, Mean $\pm$ SD, IU	Vitamin E, Mean $\pm$ SD, IU	Vitamin K, Mean $\pm$ SD, μ g
2008	10,184.93 $\pm$ 10,736.27 (n = 73)	962.67 $\pm$ 693.95 (n = 75)	218.38 $\pm$ 224.11 (n = 74)	410.85 $\pm$ 577.74 (n = 71)
2009	15,101.85 $\pm$ 15,140.58 (n = 108)	1583.19 $\pm$ 2383.83 (n = 113)	282.25 $\pm$ 289.03 (n = 108)	583.71 $\pm$ 637.17 (n = 105)
2010	18,021.72 $\pm$ 14,860.96 (n = 132)	1814.39 $\pm$ 1965.56 (n = 139)	330.52 $\pm$ 299.92 (n = 134)	759.58 $\pm$ 662.44 (n = 130)
2011	19,494.52 $\pm$ 15,480.08 (n = 152)	1999.50 $\pm$ 1919.80 (n = 161)	343.47 $\pm$ 289.14 (n = 152)	813.85 $\pm$ 686.77 (n = 148)
2012	20,464.25 $\pm$ 16,879.71 (n = 138)	2045.21 $\pm$ 1427.59 (n = 142)	351.58 $\pm$ 295.99 (n = 138)	849.89 $\pm$ 690.45 (n = 134)
Pvalue	<.0001	<.0001	<.0001	<.0001

A small *P* value suggests a nonzero slope for fat-soluble vitamin supplement or serum fat-soluble vitamin concentration. A mixed-effects model was employed that accounted for repeated measurements. Both fat-soluble vitamin supplement or serum fat-soluble vitamin concentration were log transformed.

Serum Fat-Soluble Vitamin Concentrations in Study Participants Treated at the Emory Clinic and Emory University Hospital Between 2008 and 2012.

Year	Retinol, Mean $\pm$ SD, mg/L ^a	Retinyl Palmitate, Mean $\pm$ SD, mg/L ^b	25(OH)D, Mean $\pm$ SD, ng/mL ^c	α -Tocopherol, Mean $\pm$ SD, mg/L ^d	β / γ -Tocopherol, Mean $\pm$ SD, mg/L	Vitamin K, Mean $\pm$ SD, ng/mL ^e
2008	0.46 $\pm$ 0.21 (n = 57)	0.03 $\pm$ 0.04 (n = 56)	29.23 $\pm$ 13.10 (n = 87)	8.93 $\pm$ 4.46 (n = 84)	0.97 $\pm$ 0.68 (n = 83)	0.85 $\pm$ 1.10 (n = 59)
2009	0.40 $\pm$ 0.17 (n = 94)	0.03 $\pm$ 0.04 (n = 93)	28.69 $\pm$ 10.82 (n = 112)	8.93 $\pm$ 4.20 (n = 103)	1.04 $\pm$ 0.62 (n = 101)	0.73 $\pm$ 0.77 (n = 46)
2010	0.44 $\pm$ 0.19 (n = 114)	0.02 $\pm$ 0.01 (n = 112)	31.86 $\pm$ 12.19 (n = 123)	8.04 $\pm$ 3.85 (n = 119)	0.82 $\pm$ 0.61 (n = 118)	1.22 $\pm$ 2.16 (n = 11)
2011	0.44 $\pm$ 0.22 (n = 128)	0.03 $\pm$ 0.02 (n = 124)	32.92 $\pm$ 14.96 (n = 136)	8.35 $\pm$ 3.96 (n = 131)	0.88 $\pm$ 0.59 (n = 127)	1.02 $\pm$ 0.08 (n = 2)
2012	0.42 $\pm$ 0.19 (n = 101)	0.03 $\pm$ 0.02 (n = 100)	31.42 $\pm$ 13.33 (n = 108)	8.15 $\pm$ 3.87 (n = 98)	1.00 $\pm$ 0.92 (n = 93)	NA (n = 0)
Pvalue	.77	.30	<.01	.26	.96	.71

A small *P* value suggests a nonzero slope for fat-soluble vitamin intake or serum fat-soluble vitamin concentration. A mixed-effects model was employed that accounted for repeated measurements. Both fat-soluble vitamin intake or serum fat-soluble vitamin concentration were log transformed. NA = not applicable.

^aTo convert mg/L serum retinol to μ mol/L, multiply mg/L by 3.496. To convert μ mol/L serum retinol to mg/L, multiply μ mol/L by 0.286.

^bTo convert mg/L serum retinyl palmitate to μ mol/L, multiply mg/L by 1.904. To convert μ mol/L serum retinyl palmitate to mg/L, multiply μ mol/L by 0.525.

^cTo convert ng/mL serum 25-hydroxyvitamin D (25(OH)D) to nmol/L, multiply ng/mL by 2.496. To convert nmol/L serum 25(OH)D to ng/mL, multiply nmol/L by 0.401.

^dTo convert mg/L serum α -tocopherol to μ mol/L, multiply mg/L by 2.322. To convert μ mol/L serum α -tocopherol to mg/L, multiply μ mol/L by 0.431.

^eTo convert ng/mL serum vitamin K to nmol/L, multiply ng/mL by 2.22. To convert nmol/L serum vitamin K to ng/mL, multiply nmol/L by 0.45.

Table 4

Association of *CFTR* Gene With Serum 25-Hydroxyvitamin D Level Among Patients With CF Treated at the Emory Clinic (Atlanta, GA) From 2008–2012.

Variable	Unadjusted Model, % Change (95% CI)	Adjusted Model, ^a % Change (95% CI)
Genotype		
Homozygous F508	0.03 (–0.01 to 0.07)	0.03 (–0.01 to 0.07)
Heterozygous F508	0.05 (0.02 to 0.08)	0.05 (0.02 to 0.08)
Others	0.00 (–0.06 to 0.07)	0.00 (–0.06 to 0.07)
Vitamin D supplement ^b		
Low supplement	0.03 (–0.01 to 0.08)	0.03 (–0.01 to 0.07)
Normal supplement	0.05 (0.00 to 0.11)	0.04 (–0.01 to 0.10)
High supplement	0.05 (0.00 to 0.09)	0.05 (0.01 to 0.10)

CF, cystic fibrosis; CI, confidence interval.

^aModel adjusts for age, sex, race, body mass index, status of pancreatic insufficiency, and seasonal effect.

^bLow vitamin D supplement, <1000 IU; normal vitamin D supplement, 1000–2000 IU; and high vitamin D supplement, ≥2000 IU.