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Vitamin D intake, serum 25-hydroxy vitamin D and pulmonary function in paediatric patients with cystic fibrosis: a longitudinal approach

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Abstract

Pancreatic-insufficient children with cystic fibrosis (CF) receive age-group-specific vitamin D supplementation according to international CF nutritional guidelines. The potential advantageous immunomodulatory effect of serum 25-hydroxy vitamin D (25(OH)D) on pulmonary function (PF) is yet to be established and is complicated by CF-related vitamin D malabsorption. We aimed to assess whether current recommendations are optimal for preventing deficiencies and whether higher serum 25(OH)D levels have long-term beneficial effects on PF. We examined the longitudinal relationship between vitamin D intake, serum 25(OH)D and PF in 190 CF children during a 4-year follow-up period. We found a significant relationship between total vitamin D intake and serum 25(OH)D ($\beta = 0{\cdot}02$; 95 % CI 0·01, 0·03; $P = 0{\cdot}000$). However, serum 25(OH)D decreased with increasing body weight ($\beta = -0{\cdot}79$; 95 % CI −1·28, −0·29; $P = 0{\cdot}002$). Furthermore, we observed a significant relationship between serum 25(OH)D and forced expiratory volume in 1 s ($\beta = 0{\cdot}056$; 95 % CI 0·01, 0·102; $P = 0{\cdot}018$) and forced vital capacity ($\beta = 0{\cdot}045$; 95 % CI 0·008, 0·082; $P = 0{\cdot}017$). In the present large study sample, vitamin D intake is associated with serum 25(OH)D levels, and adequate serum 25(OH)D levels may contribute to the preservation of PF in children with CF. Furthermore, to maintain adequate levels of serum 25(OH)D, vitamin D supplementation should increase with increasing body weight. Adjustments of the international CF nutritional guidelines, in which vitamin D supplementation increases with increasing weight, should be considered.

Key words: Cystic fibrosis: Serum 25-hydroxy vitamin D: Pulmonary function: Paediatric patients: Vitamin D

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive disorder in the Caucasian population, with an incidence of one in 3600 births in the Netherlands[1]. CF is characterised by progressive pulmonary dysfunction. In addition, most patients have pancreatic insufficiency, which can lead to fat malabsorption and deficiencies of fat-soluble vitamins such as vitamin D[2,3]. International CF nutritional guidelines therefore recommend age-group-specific vitamin D supplementation to maintain optimal serum 25-hydroxy vitamin D (25(OH)D) levels[2,4].

An association between serum 25(OH)D and pulmonary function (PF) was observed in the general population[4], in paediatric patients with asthma[5] and in adults with chronic obstructive pulmonary disease[6,7]. However, whether this beneficial effect also applies to paediatric patients with CF is unknown, as the study results were inconclusive[8] or limited to a cross-sectional design[9,10].

Furthermore, little is known about the daily practice of vitamin D intake, vitamin D supplementation and its association with serum 25(OH)D in paediatric CF patients, as previous studies lacked data on dietary vitamin D intake[11–14], were limited by a cross-sectional design[12,15] or were conducted in the context of a trail in which the study sample was prescribed very high dosages of vitamin D, far above those used in current clinical practice[14,16–19]. We therefore set out to record the dietary vitamin D intake, vitamin D supplementation and the long-term relationship with serum 25(OH)D. In addition, we describe the

Abbreviations: % pred., percentage of the predicted value for a given height, age and sex; 25(OH)D, 25-hydroxy vitamin D; CF, cystic fibrosis; CFRD, cystic fibrosis-related diabetes; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; PF, pulmonary function.

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association between serum 25(OH)D and PF in a large study sample of paediatric patients with CF during a 4-year follow-up.

Methods

Study sample

This retrospective study included Dutch children and adolescents with proven CF and proven pancreatic insufficiency who received medical care at the CF centre of the University Medical Centre Utrecht between January 2012 and March 2016. The diagnosis CF was confirmed by a positive sweat test and/or the presence of a known CF gene mutation on each cystic fibrosis transmembrane conductance regulator gene. Pancreatic insufficiency was defined by a documented history of fat malabsorption with a coefficient of fat absorption of <85 % and/or a faecal elastase of <15 μg/g stool or chymotrypsin activity <3 U/g per stool. Included patients had at least one serum 25(OH)D measurement obtained between January 2012 and March 2016 during the annual CF check-up. Excluded were one transplanted patient and two patients with serum 25(OH)D values above 200 nmol/l, as we suspected that these values were the result of measurement errors. Written informed consent was given by all patients or by parents or guardians of young patients. The study was performed according to the guidelines of the Medical Ethics Committee of the University Medical Centre Utrecht.

Dietary intake assessment

Yearly, patients were asked to complete a 3-d record of their food and beverage intake, consisting of two consecutive weekdays and one weekend day whenever possible. The dietary vitamin D intake was calculated for each assessment according to a standardised approach using the Dutch food composition table (2010) established by the Dutch Nutrition Centre.

The prescribed vitamin D supplements as documented in medical records were considered as supplementary vitamin D intake. The prescribed dosages were based upon the European Union guideline of 2002, which advices a daily supplementary vitamin D intake of 10–50 μg (400–2000 IU) for all ages[20]. In patients with an insufficient serum 25(OH)D level, the supplement dosage was adjusted, the increase being subject to the opinion of the physician in charge. Total vitamin D intake was calculated by adding dietary and supplementary intake.

The vitamin D intake (dietary intake, prescribed supplementation and total intake) was expressed as μg/d. Owing to the wide body weight range of the study sample (5·0–84·5 kg), we subsequently expressed the dietary, supplementary and total intake as μg/kg body weight per d.

Clinical measurements

Serum 25(OH)D levels in blood were routinely measured as part of the annual check-up and analysed by electrochemiluminescence sandwich immunoassay (Cabas E411; Roche) which was calibrated against National Institute of Standards and Technology standard material; performance was monitored daily using Lyphochek control material (Bio-Rad Laboratories). Mean CV% was within 8·7 %. Measurements were classified according to months with high (June–October) and low (November–May) UVB exposure[15].

Height and weight were measured to the nearest 0·1 cm and 0·1 kg, respectively, during annual check-ups. Weight, height and BMI were compared with reference values using *z*-scores as calculated by specialised software of the Dutch Growth Foundation (Growth Analyser 4 RCT, 2010, Dutch Growth Foundation). Yearly, patients from 10 years of age onwards were screened for glucose tolerance by the modified oral glucose tolerance test (1·75 g/kg glucose, maximum dosage 75 g). An overnight fasting plasma glucose level and a 2-h postprandial glucose level were measured. Those having glucose levels >11·1 mmol/l after oral glucose tolerance test, or fasting glucose >7·0 mmol/l were categorised as CF-related diabetes (CFRD)[21]. CF-related liver disease (CFLD) was diagnosed according to the Colombo criteria[22]. Serum IgG, as a marker of chronic inflammation, was measured concurrently with serum 25(OH)D and expressed as g/l. The use of systemic corticosteroids in each year was recorded.

PF was assessed as forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) and expressed as a percentage of the predicted value for a given height, age and sex (% pred.) using the Global Lung Function Initiative reference values[23]. For each child, the highest PF measured in the preceding calendar year was used, beginning at the age of 6 years. PF tests up to 2016 were included.

Statistical analysis

Categorical variables were examined using descriptive statistics. Continuous variables were assessed on normality and skewness. Due to repeated measures on individual patients in different years of age, children were stratified according to age year (year 0 = birth to <1 year, year 1 = 1 to <2 years, etc.) and measurements of dietary, supplemental and total vitamin D intake, intake per kg body weight and serum 25(OH)D were described accordingly.

To assess whether the initial measurements of total vitamin D intake and PF were related to serum 25(OH)D levels, children were categorised based on their serum 25(OH)D as having levels <50 nmol/l (deficient), levels between 50 and 75 nmol/l (sufficient) or >75 nmol/l (high sufficient), based upon current European Union guidelines in which serum 25(OH)D levels ≥50 nmol/l are considered sufficient[3]. Age, vitamin D intake (dietary, prescribed supplementation and total) and PF were compared cross-sectionally amongst the categorised serum 25(OH)D levels using one-way ANOVA or the Kruskal–Wallis test. To evaluate the effect of total vitamin D intake on serum 25(OH)D over time, linear mixed-effect regression models were used. These models allow inclusion of varying numbers of measurements per child, irregular observation times and missed observations. Age, sex, body weight and season were included as fixed effects. A random intercept and a random slope for age

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per child accounted for associations between measurements within children.

We also examined the longitudinal effect of serum 25(OH)D on PF (FEV_1% pred. and FVC% pred.), using linear mixed-effect regression. Included were age, sex, *z*-score BMI, IgG, CFLD, CFRD, corticosteroid use and season as fixed effects and a random intercept and slope for age. Sample size was determined by the availability of data from the medical records. Exact effect sizes for longitudinal data are difficult to estimate and require many assumptions, so the current study presents a conservative estimate here. A sample size of 190 would provide 80 % power to detect a correlation of at least 0·20 between serum 25(OH)D and PF using a two-sided hypothesis test with a significance level of 0·05. Statistical analysis was performed using the Statistical Package for the Social Sciences Computer Software version 21 (IBM).

Results

Patient characteristics

Data of 190 paediatric patients (95 % Caucasian) were eligible for inclusion. In these patients, we obtained 545 measurements of serum 25(OH)D and 353, 532 and 346 measurements of dietary, supplementary and total vitamin D intake, respectively. A total of 408 measurements of PF were obtained in 157 children aged 6 years and older. Demographic and clinical characteristics of patients at the time of inclusion are described in Table 1.

Descriptive baseline results

Median dietary intake at time of inclusion was 4·1 (interquartile range (IQR) 2·3–8·0) μg/d, supplementary intake was 10 (IQR 10–11·3) μg/d and total intake was 14·7 (IQR 12–21) μg/d. All remained relatively constant over the subsequent age-years (online Supplementary Table S1). Dietary, supplementary and total vitamin D intake are expressed as μg/kg per d, and serum 25(OH)D decreased with increasing age (Fig. 1).

A total of 76/190 (40 %) patients had deficient, 73/190 (38·4 %) patients had sufficient and 41/190 (21·6 %) had high-sufficient serum 25(OH)D levels at time of inclusion. The distribution of dietary vitamin D intake was comparable among the serum 25(OH)D classes ($P=0·170$), while the distribution of supplementary and total vitamin D intake was significantly higher in classes with higher serum 25(OH)D levels ($P=0·010$ and $P=0·018$, respectively). Children in the lower serum 25(OH)D classes were significantly older ($P=0·000$). Further, the distribution of FEV_1% pred. and FVC% pred. did not differ among the serum 25(OH)D classes ($P=0·075$ and $P=0·149$, respectively).

Longitudinal analysis of vitamin D intake and serum 25-hydroxy vitamin D

Longitudinally, there was a significant relationship between total vitamin D intake and serum 25(OH)D ($\beta=0·02$; 95 % CI 0·01, 0·03), which remained significant after correction for potential confounders (Table 2). In our study sample, on average, each 100 IU (2·5 μg) increase in vitamin D resulted in a 2 nmol/l

Table 1. Demographical and clinical characteristics of 190 children and adolescents with cystic fibrosis at the time of inclusion (Medians and interquartile ranges (IQR); numbers of subjects and percentages)

Continuous variables	Median	IQR	Total number of patients
Serum 25(OH)D (nmol/l)	55	34–70	190
Dietary vitamin D intake (μg/d)	4·1	2·3–8	126
Supplementary vitamin D intake (μg/d)	10	10–11·3	186
Total vitamin D intake (μg/d)	14·7	12–21	125
Pulmonary function			
FEV_1% of predicted*	89	78–100	157
FVC% of predicted*	94	86–103	157
Age (years)	11·14	6·01–14·47	190
Age at diagnosis (years)	0·30	0·02–0·80	188
BMI (*z*-score)	–0·34	–0·85–0·21	190
IgG (g/l)	9·96	7·53–12·70	168

Categorical variables	Number of subjects	Percentage of total (%)	Total number of patients
Sex (male)	91	47·9	190
Genotype			188
Df508del homozygote	120	63·8	
Df508del heterozygote	57	30·3	
Other	11	5·9	
Season of 25(OH)D measurement			190
Low UVB month†	101	53·2	
High UVB month†	89	46·8	
CFRD	10	5·3	190
CFLD	46	24·2	190
Systemic corticosteroid use	55	34·8	158

25(OH)D, 25-hydroxy vitamin D; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; CFRD, cystic fibrosis-related diabetes mellitus; CFLD, cystic fibrosis-related liver disease.
* Percentage of predicted as calculated according to the Global Lung Function Initiative reference values[23].
† Low UVB months, November–May; high UVB months, June–October.

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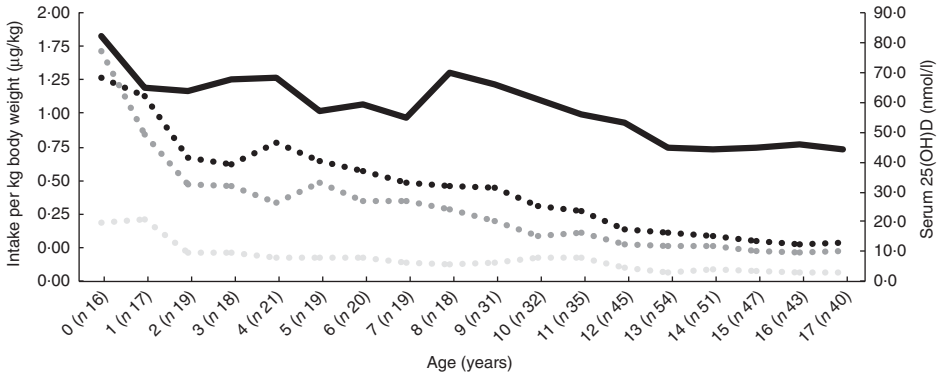

Fig. 1. Median serum 25-hydroxy vitamin D (25(OH)D) and dietary, supplementary and total vitamin D intake at the time of inclusion, expressed as µg/kg body weight per d in 190 patients with cystic fibrosis, stratified according to year of age. • • • • , Total vitamin D (µg/kg per d); • • • • , supplementary vitamin D (µg/kg per d); • • • • , dietary vitamin D (µg/kg per d); ——, serum 25(OH)D.

Table 2. Predictive factors of change in serum 25-hydroxy vitamin D expressed as nmol/l in 190 children and adolescents with cystic fibrosis, using a mixed effect regression model
(Regression coefficients and 95 % confidence intervals)

Variables	Regression coefficient	95 % CI	*P*
Total vitamin D intake (µg/d)	0·82	0·54, 1·10	<0·001
Age (years)	0·87	–0·84, 2·58	0·317
Sex (male)	–3·47	–9·47, 2·81	0·277
Weight (kg)	–0·79	–1·20, –0·29	0·002
Season (high UVB months)	9·01	4·84, 13·18	<0·001

(95 % CI 1·0, 3·0) increase in serum 25(OH)D. Further, each kg increase in body weight resulted in a 0·79-nmol/l decline (95 % CI –1·28, –0·29) in serum 25(OH)D. Serum 25(OH)D was significantly higher in months with high UVB (June–October) ($\beta = 9{\cdot}01$ nmol/l; 95 % CI 4·84, 13·18). Age and sex were not significantly associated with serum 25(OH)D.

Longitudinal analysis of serum 25-hydroxy vitamin D and pulmonary function

We observed a significant relationship between serum 25(OH)D and PF, expressed as FEV_1% pred. and FVC% pred. after adjustment for age, sex, *z*-score BMI, IgG, CFLD, CFRD and corticosteroid usage. In our study sample, each 20-nmol/l increase in serum 25(OH)D resulted in an increase of 1·12 % (95 % CI 0·2, 2·04) of FEV_1% pred. and 0·9 % (95 % CI 0·16, 1·64) FVC% pred. (Table 3). Furthermore, we found a negative association between PF and age and CFRD, while PF and BMI had a positive association.

Discussion

This longitudinal study in a large cohort of children and adolescents with CF, with a 4-year follow-up, showed a significant relationship between total vitamin D intake (dietary and supplemental intake) and serum 25(OH)D and between serum 25(OH)D and PF.

To the best of our knowledge, this is the first longitudinal study on serum 25(OH)D in paediatric patients with CF, including both dietary vitamin D intake and vitamin D supplementation dosages as prescribed in daily clinical CF care. In our study sample, and in accordance with other North-European CF populations[10], the dietary vitamin D intake attributed one-third of the total vitamin D intake. In our study, the median dietary vitamin D intake remained fairly constant throughout the age-years, while serum 25(OH)D significantly decreased with age. We found no relationship between dietary vitamin D intake and serum 25(OH)D as reported previously[15]. However, total vitamin D intake was clearly related to serum 25(OH)D, indicating the importance of vitamin D supplementation to obtain and maintain adequate serum 25(OH)D.

Longitudinally, we found a relationship between total vitamin D intake and serum 25(OH)D. This is in line with a previous study in 360 adults with CF with a mean initial serum 25(OH)D of 47 nmol/l and a mean initial supplemental vitamin D intake of 16·2 µg/d (646 IU/d) in which an increase of 10–25 µg/d (400–1000 IU/d) or counselling led to high sufficient serum 25(OH)D values in 82 % of the subjects[13]. Several intervention studies in paediatric CF patients, with serum 25(OH)D levels <75 nmol/l, found an increase in serum 25(OH)D to >75 nmol/l in 54–94 % of the study sample when prescribed extreme amounts of vitamin D supplements (1250 µg/week (50 000 IU/week) up to 15 000 µg (600 000 IU) stoss therapy)[16–19]. In contrast to these findings, Hillman *et al.*[24] found no extra effect of 50 µg (2000 IU) vitamin D/d supplementation in a small crossover trial in 15 paediatric CF patients. However, these patients had significantly higher serum 25(OH)D levels at baseline (median 83 nmol/l) than our study sample. It is questionable whether an increase in the already high serum levels can be expected, as previous studies have indicated that vitamin D intake has to increase exponentially, as higher serum 25(OH)D levels are to be reached[13,25].

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Table 3. Predictive factors of respectively forced expiratory volume in 1 s (FEV_1)% of predicted and forced vital capacity (FVC)% of predicted in 158 children and adolescents with cystic fibrosis, using a mixed effect regression model (Regression coefficients and 95 % confidence intervals)

	FEV_1% of predicted			FVC% of predicted		
	Regression coefficient	95 % CI	*P*	Regression coefficient	95 % CI	*P*
Serum 25(OH)D (nmol/l)	0·06	0·01, 0·10	0·018	0·05	0·01, 0·80	0·017
Age (years)	−1·58	−2·11, −1·05	<0·001	−0·53	−0·99, −0·08	0·022
Sex (male)	−2·18	−6·57, 2·21	0·328	0·31	−3·43, 4·05	0·870
BMI (*z*-score)	1·87	0·36, 3·38	0·002	1·67	0·44, 2·90	0·008
IgG (g/l)	−0·42	−0·85, 0·02	0·060	−0·30	−0·66, 0·05	0·096
CFRD	−7·75	−12·55, −2·95	0·002	−6·26	−10·19, −2·34	0·002
CFLD	−2·36	−6·14, 1·41	0·219	−1·90	−5·05, 1·25	0·236
Systemic corticosteroid use	−1·23	−3·03, 0·58	0·182	0·19	−1·26, 1·64	0·801

25(OH)D, 25-hydroxy vitamin D; CFRD, cystic fibrosis-related diabetes mellitus; CFLD, cystic fibrosis-related liver disease.

Previous studies also reported an inverse association between age and serum 25(OH)D[8,11,26–28] in paediatric patients with CF, although no conclusive explanation was given. We found that children with higher levels of serum 25(OH)D were significantly younger, with the highest serum 25(OH)D levels in patients below the age of 4 years old. While having a fairly constant absolute vitamin D intake, the intake per kg body weight of patients below the age of 4 years was more than double compared with adolescents, leading to the assumption that body weight might influence serum 25(OH)D levels. Our longitudinal model indeed indicated that an increasing body weight is related to a decreasing serum 25(OH)D. This might be due to the dilution of vitamin D in larger body volumes[29,30] which occurs as children grow and weight increases[25,31]. As increasing age was not sufficiently matched by a concurrent increase in (supplementary) vitamin D intake, a downward trend of serum 25(OH)D with age was observed.

To note, current CF guidelines provide recommendations for large age-groups (age ≤1 year, >1–10 years, 10 years onwards); although direct extrapolation of our results, which were based upon the 2002 guidelines, should be done with caution, children of different ages, and with large differences in body weight, still share the same recommendation. It might be more appropriate to use smaller age intervals or body weight, with yearly evaluation as described in the CF-specific guidelines[3].

We and others found a significant relationship between serum 25(OH)D and PF in children and adolescents with CF, which remained after correcting for multiple confounders known to affect PF[9]. Several studies have addressed the relationship between vitamin D intake and PF although with conflicting results[9–12,32]. Cross-sectional studies in both paediatric and in mixed paediatric and adult populations found a relationship between FEV_1% pred. and serum 25(OH)D[9–11]. The only previous longitudinal study in 130 paediatric patients with CF with a median follow-up of 4 years did not find a longitudinal relationship with PF[8]. However, this study did not account for confounders that significantly affect the PF such as age, *z*-score BMI and CFRD, as we and others found these variables are indeed correlated with PF. Therefore, a positive effect of serum 25(OH)D on PF in the study by McCauley *et al.*[8] may have been blurred.

A recent pilot study by Pincikova *et al.*[14] in sixteen patients (10 adults) did find a positive relationship between change in serum 25(OH)D and PF (FEV_1 and FVC). Our study seems to indicate that this relationship is also present in paediatrics with CF.

Any beneficial effect of serum 25(OH)D on PF has been attributed to the immunomodulatory potentials of vitamin D[33]. Metabolised serum 25(OH)D in airway epithelia exhibits anti-microbial effects by regulation of anti-microbial peptides[34] and anti-inflammatory effects by pro-inflammatory cytokines[35]. This could reduce chronic pulmonary colonisation and thereby aid in the long-term preservation of PF[12].

Several limitations of this study can be mentioned. First, keeping food records might lead to alterations of the diet and to over- and/or under-reporting. Second, differences in seasonal variation in individuals might not be detected as the time of year in which the dietary intake recorded remained fairly constant over the study years. In addition, we followed the clinical practice and thereby did not measure adherence to vitamin D supplementation or accounted for missed dosages. Finally, as this study was retrospective in design, the causal effect of serum 25(OH)D on PF we found should ideally be reproduced in a prospective randomised trial.

Conclusion

In conclusion, in this large study sample, a significant relationship between total vitamin D intake (dietary and supplemental) and serum 25(OH)D and an inverse relationship between body weight and serum 25(OH)D were described in paediatric CF patients. In addition, higher serum 25(OH)D levels were associated with higher FEV_1% pred. and FVC% pred. These findings suggest that vitamin D supplementation should increase with increasing body weight, as adequate serum 25(OH)D levels may contribute to the preservation of PF. Adjustments of the recommendations in which vitamin D supplementation increases with increasing weight, to maintain adequate serum 25(OH)D levels in children with CF, should be considered.

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The authors declare that there are no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114518003021

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