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An Update on the Screening, Diagnosis, Management, and Treatment of Vitamin D Deficiency in Individuals with Cystic Fibrosis: Evidence-Based Recommendations from the Cystic Fibrosis Foundation

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Objective: The objective was to develop evidence-based clinical care guidelines for the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis (CF).

Participants: The guidelines committee was comprised of physicians, registered dietitians, a pharmacist, a nurse, a parent of an individual with CF, and a health scientist, all with experience in CF.

Process: Committee members developed questions specific to vitamin D health in individuals with CF. Systematic reviews were completed for each question. The committee reviewed and graded the available evidence and developed evidence-based recommendations and consensus recommendations when insufficient evidence was available. Each consensus recommendation was voted upon by an anonymous process.

Conclusions: Vitamin D deficiency is common in CF. Given the limited evidence specific to CF, the committee provided consensus recommendations for most of the recommendations. The committee recommends yearly screening for vitamin D status, preferably at the end of winter, using the serum 25-hydroxyvitamin D measurement, with a minimal 25-hydroxyvitamin D concentration of 30 ng/ml (75 nmol/liter) considered vitamin D sufficient in individuals with CF. Recommendations for age-specific vitamin D intake for all individuals with CF, form of vitamin D, and a stepwise approach to increase vitamin D intake when optimal vitamin D status is not achieved are delineated. **(*J Clin Endocrinol Metab* 97: 1082–1093, 2012)**

Vitamin D deficiency is common in individuals with cystic fibrosis (CF) due to impaired absorption of fat-soluble vitamins, decreased sunlight exposure, and suboptimal intake of vitamin D-containing foods and/or supplements (1). Vitamin D deficiency in CF has been associated with decreased bone mass in children, failure to achieve expected peak bone mass in young adults, and osteoporosis in mature adults, and it may impact other comorbidities common in CF (2–4). The CF Foundation established recommendations for vitamin D supplementation in 2002 (5) and again in 2005 (6); however, it soon became apparent that the amount of vitamin D recommended for treatment and prevention of vitamin D deficiency was insufficient (7–9). Similarly, the appreciation that vitamin D deficiency is widespread and represents a risk to health throughout the general population prompted the

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Abbreviations: CF, Cystic fibrosis; 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D.

Institute of Medicine (IOM) to publish new dietary reference intakes for vitamin D in November 2010 and prompted The Endocrine Society to publish a Clinical Practice Guideline on vitamin D in June 2011 (10, 11). In September 2010, the CF Foundation assembled a multispecialty *ad hoc* committee after a call for applications. The charge of the committee was to develop evidence-based guidelines on vitamin D screening, diagnosis, supplementation, and treatment. This document outlines the process for the systematic review and the recommendations regarding vitamin D in the CF population.

Methods

The CF Foundation assembled a multidisciplinary committee comprised of one adult endocrinologist, one pediatric endocrinologist, three adult pulmonologists, two pediatric gastroenterologists, five registered dietitians, one pharmacist, one registered nurse, one parent of an individual with CF, and one public health scientist, all of whom had special expertise in CF. The committee identified clinical questions that would form the basis of the guidelines. An evidence review was commissioned from The Johns Hopkins University under the leadership of an epidemiologist (K.A.R.). A report of the completed systematic reviews was provided to the guidelines committee for use in developing recommendations. Where possible, the guidelines committee developed evidence-based recommendations and graded these using the U.S. Preventive Services Task Force (USPSTF) grading system (12). The committee developed consensus recommendations for topics not included in the systematic reviews or for which limited evidence was available. Anonymous voting was conducted for each consensus recommendation considered by the committee, with 80% approval set as the threshold for acceptance of the recommendation. Draft recommendations were reviewed by endorsing organizations, publicly posted for comment by all CF centers, and revised accordingly.

Systematic review

The guidelines committee members developed and refined systematic review questions for the development of these recommendations. Members of The Johns Hopkins University evidence review team searched for existing relevant guideline documents in CF as well as in the general population. Combined controlled vocabulary terms and text words for "vitamin D" and "cystic fibrosis" were used to create comprehensive search strategies. The team searched the National Guidelines Clearinghouse (www.guidelines.gov), the existing CF Foundation guidelines, and the web sites of the CF Foundation and the United Kingdom CF Trust for relevant guideline documents (July 9, 2010) and existing Cochrane systematic reviews that addressed the management of vitamin D levels in individuals with CF (10, 11, 13–21, 23). In addition, the evidence review team identified primary studies by completing searches of MEDLINE (accessed via PubMed September 7, 2010); the Excerpta Medical Database (EMBASE, September 7, 2010); and the Cochrane Central Register of Controlled Trials (CENTRAL, September 7, 2010). Hand searching was completed through the searching of reference lists of relevant guideline documents, Cochrane systematic reviews, and all eligible articles.

Articles were independently screened by two reviewers from The Johns Hopkins evidence review team for eligibility, first using title and abstract, and subsequently using the full text. Disagreements concerning eligibility were resolved by consensus or by a third reviewer from the evidence review team. Articles were excluded from further consideration if they: 1) did not describe a study in humans; 2) provided no original data (*i.e.* were reviews, commentaries, *etc.*); 3) did not pertain directly to CF; 4) did not address vitamin D; or 5) did not address any review question.

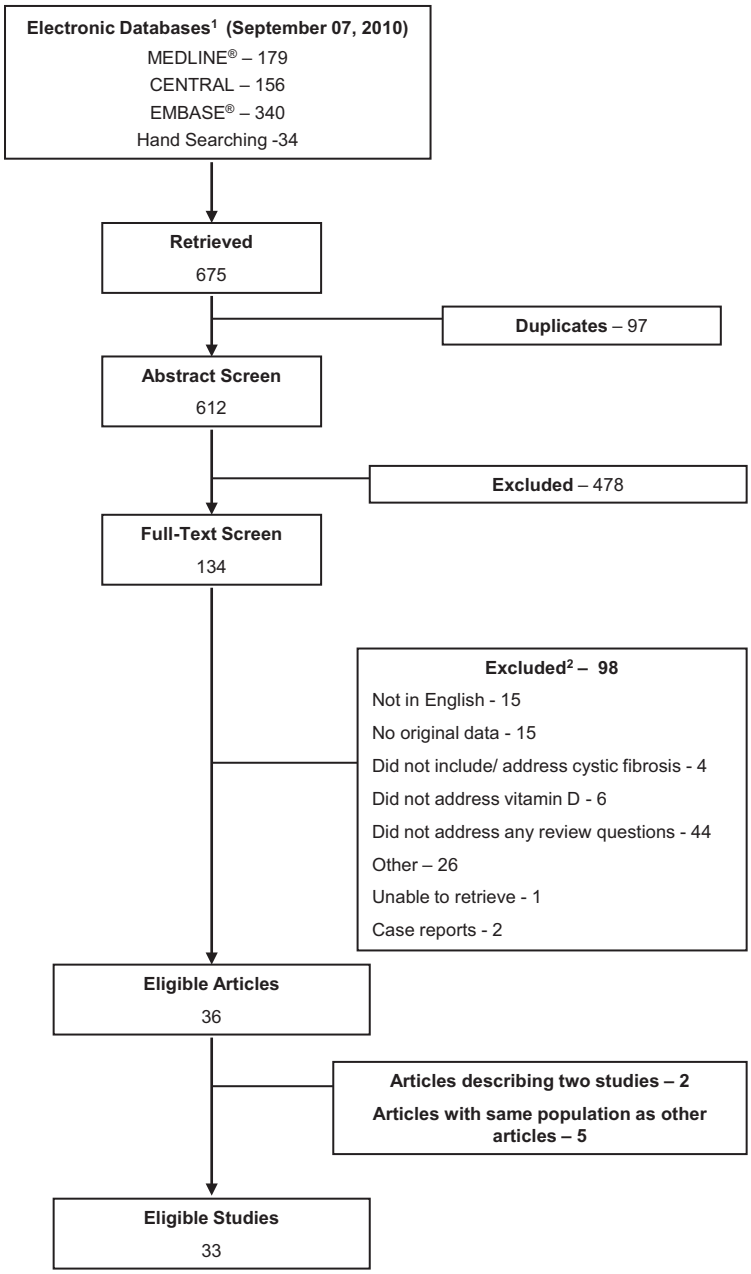
At the full-text level, the evidence review team also excluded articles if they were not in English. Article review forms were developed and pilot-tested. Using the forms, two reviewers abstracted information regarding study and participant characteristics, risk of bias, each treatment (intervention) arm, and specific outcomes addressed in each eligible article.

Results

The search process identified 36 articles, describing 33 unique studies published between 1979 and 2011, as eligible for inclusion (Fig. 1). These studies included two randomized controlled trials, two nonrandomized controlled trials, nine before-and-after studies, one retrospective cohort study, 17 cross-sectional studies, and two case series. The guideline committee members were provided with the details of the included articles in evidence tables and a report that provided a qualitative synthesis of the evidence.

Assessment of Vitamin D Status and Target Treatment Goals

The circulating level of total 25-hydroxyvitamin D [25(OH)D] is considered the best index of vitamin D nutritional status in both the CF population and the general population. Vitamin D status should be checked annually in all patients with CF, given the high prevalence of vitamin D deficiency in both the general and CF populations. Ideally, vitamin D status should be checked at the end of winter because there is sufficient evidence to suggest that vitamin D status fluctuates by season in the CF population (24, 25). As is true in other groups, CF patients have lower serum concentrations of 25(OH)D during the winter than during the summer. Ideally, vitamin D status should be assessed at the nadir to ensure that patients are receiving sufficient vitamin D supplementation throughout the entire year. Those individuals who have normal vitamin D status at the end of winter are likely to have sufficient vitamin D status throughout the year on their current vitamin D regimen. If it is not possible to obtain an end



[1]MEDLINE accessed via PubMed; EMBASE - the Excerpta Medica database, CENTRAL – Cochrane CENTRAL Register of Controlled Trials

[2]Reviewers did not need to agree on the reason for exclusion.

FIG. 1. Summary of search and review process for the vitamin D evidence-based recommendations of the CF Foundation.

of winter value, values from other times of the year should be interpreted in the context of the timing of the determination and the patient's sun exposure and use of topical sun blockers. It is unclear at this time whether there is any benefit to having patients fast before having serum 25(OH)D.

- The CF Foundation recommends that all individuals with CF have serum 25-hydroxyvitamin D measured to assess vitamin D status (consensus recommendation).
- The CF Foundation recommends that all individuals with CF have serum 25-hydroxyvitamin D measured annually, preferably at the end of winter (consensus recommendation).
- The CF Foundation is not able to make a recommendation for or against having all individuals with CF fast before the measurement of serum 25-hydroxyvitamin D (USPSTF, grade I).

Vitamin D status should be measured using serum 25(OH)D because this marker is associated with health

outcomes and is the primary circulating form of vitamin D. Serum 25(OH)D has a 2- to 3-wk half-life, and thus levels do not fluctuate acutely. Serum 25(OH)D is also recommended as the measure to use for assessment of vitamin D status by The Endocrine Society 2011 Clinical Practice Guideline (11) and the IOM Dietary Recommendation Intake Report for Calcium and Vitamin D (10). There are available assays that measure $25(OH)D_2$ and $25(OH)D_3$ in addition to total 25(OH)D. Clinically, the total 25(OH)D should be adequate to assess vitamin D status, which accounts for vitamin D produced from skin and obtained from the diet. Serum 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] should not be used to assess vitamin D status; this marker can be high, normal, or low in patients with vitamin D deficiency because circulating concentrations are more dependent on levels of PTH and fibroblast growth factor 23 than on endogenous stores of vitamin D. Moreover, serum $1,25(OH)_2D$ has a short half-life of only 4 h, and thus levels may fluctuate significantly over the day. This recommendation is consistent with the recommendation of The Endocrine Society. In addition, routine measurement of PTH, osteocalcin, alkaline phosphatase, or other indirect markers is not recommended for the routine assessment of vitamin D status. The committee determined that there was no evidence that these markers reflect vitamin D status and also considered the costs in obtaining these markers on a routine basis.

- The CF Foundation recommends that all individuals with CF have serum 25-hydroxyvitamin D measured to assess vitamin D status (consensus recommendation).
- The CF Foundation recommends against the use of serum $1,25(OH)_2D$ as the measurement to assess vitamin D status in all individuals with CF (consensus recommendation).
- The CF Foundation recommends against the routine measurement of PTH, osteocalcin, alkaline phosphatase, or other indirect markers to assess vitamin D status in all individuals with CF (consensus recommendation).

There is little consensus among professional societies and scientific organizations regarding the optimal serum concentration of 25(OH)D to ensure good health. The American Academy of Pediatrics (20) and the IOM (10) have proposed a serum 25(OH)D concentration greater than 20 ng/ml (50 nmol/liter) in otherwise healthy children as sufficient, principally with regard to prevention of rickets. By contrast, The Endocrine Society, the Canadian Society of Endocrinology and Metabolism, and the National Osteoporosis Foundation have targeted a serum 25(OH)D concentration greater than 30 ng/ml (75 nmol/liter) (11). No studies have specifically addressed the potential benefits of setting serum 25(OH)D goals of between 30 and 60 ng/ml (75–150 nmol/liter) *vs.* setting other serum 25(OH)D goals in the management of individuals with CF. However, given the association of vitamin D deficiency with lower bone density and other markers of bone health in individuals with CF (26–35) and increased fracture rates overall in the CF population (1), the guidelines committee adopted a goal for serum 25(OH)D concentration between 30 and 50 ng/ml as defining optimal vitamin D status. The safe upper limit for serum 25(OH)D has not been established for the general or CF population. The risk of hypercalcemia increases when serum 25(OH)D concentrations exceed 100 ng/ml (250 nmol/liter) (36). Therefore, serum 25(OH)D concentrations should not exceed 100 ng/ml (250 nmol/liter).

Technical challenges in the measurement of serum 25(OH)D further complicate the management of vitamin D status because serum concentrations display as much as 30% variability between laboratories (37). Moreover, some assays do not measure both $25(OH)D_2$ and $25(OH)D_3$ with equal sensitivity. Therefore, measurements of serum 25(OH)D should be conducted by a laboratory that participates in the vitamin D external quality assessment scheme (DEQAS) or some other external quality assessment testing.

- The CF Foundation recommends that all individuals with CF maintain a serum 25-hydroxyvitamin D goal of at least 30 ng/ml ($\geq$75 nmol/liter).

Management of CF patients who have low serum levels of 25(OH)D (*i.e.* $<$30 ng/ml) should begin with an assessment of adherence to their currently prescribed vitamin D intake regimen. No studies directly addressed the timing of a repeat serum 25(OH)D concentration in the CF population. Because the half-life of circulating serum 25(OH)D is approximately 2–3 wk, steady-state levels of serum 25(OH)D after institution of treatment are achieved in approximately 12 wk. This corresponds with the current recommendation for routine CF center visits and allows us to recommend that serum 25(OH)D concentrations be reassessed approximately 3 months after any change in vitamin D_3 dosing. There are no studies that directly address the timing of a repeat serum 25(OH)D concentration in the CF population.

- The CF Foundation recommends that all individuals with CF and a serum 25-hydroxyvitamin D level below 30 ng/ml ($<$75 nmol/liter) be assessed for adherence to the prescribed regimen (consensus recommendation).
- The CF Foundation recommends that all individuals with CF have serum 25-hydroxyvitamin D levels rechecked 3 months after the dose of vitamin D_3 has been changed (consensus recommendation).

Vitamin D Compounds and Treatment Strategies

Two forms of vitamin D are available for vitamin D supplementation—vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). We therefore examined evidence of the relative effectiveness of these two vitamin D preparations for treating vitamin D insufficiency (8, 38–49). One study, a cross-sectional study, did not specify which form of vitamin D supplementation (vitamin D_2 or vitamin D_3) was being assessed (48). Seven studies [six before-and-after studies (41, 42, 44–46, 50) and one retrospective cohort study (47)] specifically assessed vitamin D_2 supplementation. The other two studies [one before-and-after study (43) and one case series (49)] specifically assessed vitamin D_3 supplementation.

In the general population, debate exists as to whether vitamin D_2 or D_3 more effectively produces a sustained rise in serum 25(OH)D (51–55). This issue relates to both potential biological differences in potency between vitamin D_2/25(OH)D_2 and vitamin D_3/25(OH)D_3 as well as to differences in bioavailability of the different compounds after oral ingestion. This question surfaced in the CF literature because high doses of vitamin D_2 failed to treat hypovitaminosis D effectively in pediatric (8) and adult (7) populations. In a short-term, single-dose pharmacokinetic study, ergocalciferol absorption was erratic, and serum 25(OH)D responses were less than those of healthy controls (42). The only evidence directly comparing ergocalciferol and cholecalciferol in patients with CF is a 2009 randomized controlled trial of 28 adults that showed a greater increase in serum 25(OH)D after 50,000 IU weekly of cholecalciferol than after 50,000 IU weekly of ergocalciferol over 12 wk. Additionally, all nine subjects receiving cholecalciferol achieved a serum 25(OH)D greater than 30 ng/ml, whereas only 60% of subjects who received ergocalciferol achieved such a response. In this small study, no hypercalcemia or other adverse events were reported (56). The results of this study, the finding that most trials for osteoporosis have used cholecalciferol, and the fact that cholecalciferol is the endogenously produced vitamin D suggest that cholecalciferol should be preferred over ergocalciferol. For those individuals who are vegetarian or have dietary restriction that prohibits use of animal products, ergocalciferol may be considered, but higher doses may be required. If ergocalciferol supplementation effectively sustains serum 25(OH)D concentrations of at least 30 ng/ml, the managing CF team may elect to continue such therapy rather than switching to cholecalciferol supplementation.

- The CF Foundation recommends that all individuals with CF be treated with vitamin D_3 (cholecalciferol) to achieve and maintain serum 25-hydroxyvitamin D levels of at least 30 ng/ml (≥75 nmol/liter) (USPSTF, grade B).

In regard to the vehicle substance contained in the vitamin D supplement (oil *vs.* powder-based preparation), no eligible studies were identified to address this question in the systematic review. A 2010 systematic review of the non-CF literature found few studies comparing the influence of the vehicle substance upon vitamin D bioavailability among different populations, including those with fat malabsorption (57). In regard to the timing of the ingestion of the supplement, there may be improved absorption of fat-soluble vitamins if taken with food; therefore, it is logical that absorption would be better if supplements were taken with pancreatic enzymes in patients who need them.

- The CF Foundation is not able to make a recommendation for or against the use of an oil *vs.* a powder-based formulation of vitamin D_3 in all individuals with CF (USPSTF, grade I).

We did not find any evidence for the benefit of bolus *(e.g.* weekly, monthly, every 3 months) vitamin D (either vitamin D_2 or D_3) supplementation *vs.* daily vitamin D supplementation in the management of individuals with CF. The American Academy of Pediatrics (20) recommends daily dosing, whereas The Endocrine Society (10) suggests either daily or weekly dosing. Financial issues and treatment burden are highly relevant to individuals with CF; thus, the dosing schedule (daily *vs.* weekly) may be individualized and take into account patient/family preference. Some individuals may prefer weekly maintenance treatment with vitamin D_3 that achieves the total weekly equivalent of daily dosing. Other considerations include: 1) potential for hypervitaminosis D if high-dose weekly boluses are inadvertently continued; and 2) the potential for lack of efficacy if the weekly dose is missed too frequently.

- The CF Foundation recommends that all individuals with CF who are prescribed vitamin D_3 (in addition to their CF-specific vitamins) take once-daily vitamin D_3 therapy or its weekly equivalent to maintain serum 25-hydroxyvitamin D levels of at least 30 ng/ml (≥75 nmol/liter) (consensus recommendation).

More polar vitamin D metabolites (by addition of hydroxyl groups) and, hence, more water-soluble vitamin D compounds may be beneficial in CF because of issues with fat malabsorption. Two studies addressing the role of more polar vitamin D compounds in individuals with CF were identified but were small and not of sufficient quality to conclude that the use of more

polar vitamin D compounds is effective or safe. One study, in abstract form, compared oral 25(OH)D supplementation (0.7 μg/kg) daily *vs.* no supplementation for an unspecified time in 73 subjects (58). Significant improvements were noted in both study arms. A before-and-after study of 10 adults with CF and 10 matched controls treated with $1,25(OH)_2D$ (calcitriol) 0.5 μg/d for 14 d found lower serum PTH after treatment (59). Although the CF Foundation does not recommend the routine supplementation with polar forms of vitamin D, such supplementation may be beneficial in a carefully selected patient population. Examples include individuals with renal insufficiency or those with persistently low serum 25(OH)D and increased PTH despite good adherence to first-line vitamin D supplementation.

The committee did not find evidence for use of calcitriol or other analogs of vitamin D in individuals with CF. Individuals with difficult-to-treat vitamin D deficiency should be referred to a specialist with expertise in vitamin D therapy. This could be an endocrinologist, nephrologist, rheumatologist, or any other physician with expertise in metabolic bone disease.

- The CF Foundation recommends that all individuals with CF with difficult-to-treat vitamin D deficiency be treated with calcitriol, doxercalciferol, or paricalcitol only in consultation with a specialist with expertise in vitamin D therapy (consensus recommendation).

Management of Vitamin D Status in Infants (Birth to 1 Year) and Children (1 to 10 Years)

We did not find any evidence for specific dosing recommendations for infants based on serum 25(OH)D concentrations. The committee made consensus recommendations consistent with The Endocrine Society guidelines (10) and the pathophysiology of CF, which leads to malabsorption of fat-soluble vitamins.

For the treatment of infants with CF up to 12 months of age, the CF Foundation recommends an initial dose of 400–500 IU vitamin D_3 per day. This dose can be provided in 1 ml of CF-specific multivitamins, 1 ml of most standard infant multivitamins, and 1 ml of most over-the-counter infant liquid vitamin D_3 preparations. For infants with a serum 25(OH)D concentration of less than 10 ng/ml (<25 nmol/liter), given the higher risk of clinical rickets, urgent management and treatment are recommended, in consultation with a specialist with expertise in vitamin D therapy.

For infants with a serum 25(OH)D concentration of at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and with confirmed adherence to the prescribed regimen, the dose of vitamin D may be increased to 800–1000 IU/d. Increasing the dose of vitamin D should be accomplished by addition of vitamin D only, rather than doubling the dose of multivitamins, because the latter would result in providing excess amounts of vitamins and minerals other than vitamin D. For infants with serum 25(OH)D of less than 20 ng/ml (<50 nmol/liter) or with a persistent serum 25(OH)D concentration not in the optimal range of greater than 30 ng/ml (>75 nmol/liter) after the initial increase in vitamin D dose, the dose of vitamin D should be increased to a maximum of 2000 IU/d. In addition to the vitamin D contained in the liquid multivitamins, additional vitamin D may be administered either from infant vitamin D drops or by extracting the contents of a defined dose of a vitamin D gelcap. Infants with CF from birth to 12 months of age who are unable to achieve a serum 25(OH)D of at least 30 ng/ml (≥75 nmol/liter) after treatment with 2000 IU vitamin D per day and with confirmed adherence should be managed in consultation with a specialist with expertise in vitamin D therapy.

We did not find any evidence for benefit of vitamin D (D_2 or D_3) supplementation at 800 IU/d *vs.* vitamin D (D_2 or D_3) supplementation at other doses in the management of children more than 1 yr of age with CF; thus, a similar treatment strategy consistent with The Endocrine Society recommendations and CF pathophysiology is recommended for vitamin D therapy in children 1 to 10 yr of age.

- The CF Foundation recommends that all individuals with CF, from birth to 12 months of age, be treated with an initial dose of 400–500 IU vitamin D_3 per day (consensus recommendation).
- The CF Foundation recommends that all individuals with CF, from birth to 12 months of age, and a serum 25-hydroxyvitamin D level of less than 10 ng/ml (<25 nmol/liter) be assessed for rickets and managed urgently in consultation with a specialist with expertise in vitamin D therapy (consensus recommendation).
- The CF Foundation recommends that all individuals with CF, from birth to 12 months of age, with a serum 25-hydroxyvitamin D level of at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and with confirmed adherence to the prescribed regimen, have the dose of vitamin D_3 increased to 800–1000 IU/d (consensus recommendation).
- The CF Foundation recommends that all individuals with CF, from birth to 12 months of age, with a serum 25-hydroxyvitamin D level of less than 20 ng/ml (<50 nmol/liter) or with a persistent serum 25-hydroxyvitamin D level of at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and with confirmed adherence to the prescribed regimen, have the dose of vitamin D_3 increased to a maximum of 2000 IU/d (consensus recommendation).

- The CF Foundation recommends that all individuals with CF, from birth to 12 months of age, who are unable to achieve a serum 25-hydroxyvitamin D level of at least 30 ng/ml (≥75 nmol/liter) after treatment with 2000 IU vitamin D_3 per day, and with confirmed adherence to the prescribed regimen, be managed in consultation with a specialist with expertise in vitamin D therapy (consensus recommendation).
- The CF Foundation recommends that all individuals with CF, from more than 12 months of age to 10 yr, be treated with an initial dose of 800-1000 IU vitamin D_3 per day (consensus recommendation).
- The CF Foundation recommends that all individuals with CF, from more than 12 months of age to 10 yr, with a serum 25-hydroxyvitamin D level of at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and with confirmed adherence to the prescribed regimen, have the dose of vitamin D_3 increased to 1600–3000 IU/d (consensus recommendation).
- The CF Foundation recommends that all individuals with CF, from more than 12 months of age to 10 yr, with a serum 25-hydroxyvitamin D level of less than 20 ng/ml (<50 nmol/liter) or with a persistent serum 25-hydroxyvitamin D level of at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and with confirmed adherence to the prescribed regimen, have the dose of vitamin D_3 increased to a maximum of 4000 IU/d (consensus recommendation).
- The CF Foundation recommends that all individuals with CF, from more than 12 months of age to 10 yr, who are unable to achieve a serum 25-hydroxyvitamin D level of at least 30 ng/ml (≥75 nmol/liter) after treatment with 4000 IU vitamin D_3 per day, and with confirmed adherence to the prescribed regimen, be managed in consultation with a specialist with expertise in vitamin D therapy (consensus recommendation).

Management of Vitamin D Status of Children More Than 10 Years of Age and Adults

The IOM and The Endocrine Society suggest that the minimum dietary intake of vitamin D for healthy individuals over the age of 10 yr is 600 to 800 IU. For those individuals at risk for vitamin D deficiency, including individuals with CF, The Endocrine Society recommends a daily vitamin D requirement of 1,500–2,000 IU, with an upper limit of 4,000 IU daily for ages 1 to 18 yr and 10,000 IU daily for ages greater than 18 yr, to maintain serum 25(OH)D above 30 ng/ml (75 nmol/liter). The Endocrine Society guidelines also note that individuals with malabsorption may require two to three times more vitamin D than individuals without malabsorption (10).

The evidence review team found no CF-specific studies in children 10–18 yr of age that evaluated the appropriate dose of vitamin D supplementation to achieve serum 25(OH)D concentrations above 30 ng/ml (75 nmol/liter). In the adult CF population, three studies were identified (7, 22, 39). These studies differed in duration, formulation, and dose of vitamin D. In general, vitamin D doses in the 800-1700 IU range were inadequate to raise the serum 25(OH)D above 30 ng/ml (75 nmol/liter). Studies by Haworth *et al.* (39) and Kelly *et al.* (22) evaluated daily oral vitamin D_3. In contrast, Boyle *et al.* (7) demonstrated that subjects receiving ergocalciferol 50,000 IU twice a week did not increase their mean serum 25OH)D concentrations.

Based on these studies demonstrating that higher doses of vitamin D may be necessary to achieve serum 25(OH)D concentrations above 30 ng/ml (75 nmol/liter) in individuals with CF, specific dosing recommendations for children greater than 10 yr of age and adults are made as outlined in Tables 1, 2, and 3. Studies that specifically addressed dosing for women with CF who are pregnant or lactating were not found.

- The CF Foundation recommends that all individuals more than 10 yr of age with CF be treated with an initial dose of 800–2000 IU vitamin D_3 per day (consensus recommendation).
- The CF Foundation recommends that all individuals more than 10 yr of age with CF with a serum 25-hydroxyvitamin D level of at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and with confirmed adherence to the prescribed regimen, have the dose of vitamin D_3 increased to 1600–6000 IU/d (consensus recommendation).
- The CF Foundation recommends that all individuals more than 10 yr of age with CF with a serum 25-hydroxyvitamin D level less than 20 ng/ml (<50 nmol/liter) or with a persistent serum 25-hydroxyvitamin D level of at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and with confirmed adherence to the prescribed regimen, have the dose of vitamin

TABLE 1. USPSTF grading system used to grade the evidence for the diagnosis and treatment of vitamin D deficiency in individuals with CF

Certainty of net benefit	Estimate of net benefit (Benefit minus harms)			
	Substantial	Moderate	Small	Zero/ negative
High	A	B	C	D
Moderate	B	B	C	D
Low	I (insufficient evidence)			

TABLE 2. Diagnosis and treatment recommendations for management of vitamin D deficiency in individuals with CF

Recommendation	Strength of
Assessment of vitamin D status and target treatment goals	
1. The CF Foundation recommends that all individuals with CF have serum 25-hydroxyvitamin D measured to assess vitamin D status.	Certainty: low Consensus recommendation
2. The CF Foundation recommends that all individuals with CF maintain a serum 25-hydroxyvitamin D goal of at least 30 ng/ml (≥75 nmol/liter).	Certainty: low Consensus recommendation
3. The CF Foundation recommends that all individuals with CF and a serum 25-hydroxyvitamin D level of less than 30 ng/ml (<75 nmol/liter) be assessed for adherence to the prescribed regimen.	Certainty: low Consensus recommendation
4. The CF Foundation recommends against the use of serum $1,25(OH)_2D$ as the measurement to assess vitamin D status in all individuals with CF.	Certainty: low Consensus recommendation
5. The CF Foundation recommends against the routine measurement of PTH, osteocalcin, alkaline phosphatase, or other indirect markers to assess vitamin D status in all individuals with CF.	Certainty: low Consensus recommendation
6. The CF Foundation recommends that all individuals with CF have serum 25-hydroxyvitamin D measured annually, preferably at the end of winter.	Certainty: low Consensus recommendation
7. The CF Foundation is not able to make a recommendation for or against having all individuals with CF fast before the measurement of serum 25-hydroxyvitamin D.	Certainty: low Benefit: unknown Grade: I
8. The CF Foundation recommends that all individuals with CF have serum 25-hydroxyvitamin D levels rechecked 3 months after the dose of vitamin D_3 has been changed.	Certainty: low Consensus recommendation
Use of vitamin D compounds and treatment strategy	
9. The CF Foundation recommends that all individuals with CF be treated with vitamin D_3 (cholecalciferol) to achieve and maintain serum 25-hydroxyvitamin D levels of at least 30 ng/ml (≥75 nmol/liter).	Certainty: moderate Benefit: moderate Grade: B
10. The CF Foundation is not able to make a recommendation for or against the use of an oil *vs.* a powder-based formulation of vitamin D_3 in all individuals with CF.	Certainty: low Benefit: unknown Grade: I
11. The CF Foundation recommends that all individuals with CF who are prescribed vitamin D_3 (in addition to their CF-specific vitamins) take once-daily vitamin D_3 therapy or its weekly equivalent to maintain serum 25-hydroxyvitamin D levels of at least 30 ng/ml (≥75 nmol/liter).	Certainty: low Consensus recommendation
12. The CF Foundation recommends that all individuals with CF with difficult to treat vitamin D deficiency be treated with calcitriol, doxercalciferol, or paricalcitol only in consultation with a specialist with expertise in vitamin D therapy.	Certainty: low Consensus recommendation
Treatment of infants	
13. The CF Foundation recommends that all individuals with CF, from birth to 12 months or age, be treated with an initial dose of 400–500 IU vitamin D_3 per day.	Certainty: low Consensus recommendation
14. The CF Foundation recommends that all individuals with CF, from birth to 12 months or age, and a serum 25-hydroxyvitamin D level of less than 10 ng/ml (<25 nmol/liter) be assessed for rickets and managed urgently in consultation with a specialist with expertise in vitamin D therapy.	Certainty: low Consensus recommendation
15. The CF Foundation recommends that all individuals with CF, from birth to 12 months or age, with a serum 25-hydroxyvitamin D level of at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and with confirmed adherence to the prescribed regimen, have the dose of vitamin D_3 increased to 800–1,000 IU per day.	Certainty: low Consensus recommendation
16. The CF Foundation recommends that all individuals with CF, from birth to 12 months or age, with a serum 25-hydroxyvitamin D level of less than 20 ng/ml (<50 nmol/liter) or with a persistent serum 25-hydroxyvitamin D level of at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and with confirmed adherence to the prescribed regimen, have the dose of vitamin D_3 increased to a maximum of 2,000 IU per day.	Certainty: low Consensus recommendation
17. The CF Foundation recommends that all individuals with CF, from birth to 12 months or age, who are unable to achieve a serum 25-hydroxyvitamin D level of at least 30 ng/ml (≥75 nmol/liter) after treatment with 2,000 IU vitamin D_3 per day, and with confirmed adherence to the prescribed regimen, be managed in consultation with a specialist with expertise in vitamin D therapy.	Certainty: low
Treatment of children up to 10 yr of age	Consensus recommendation

(*Continued*)

TABLE 2. Continued

Recommendation	Strength of
18. The CF Foundation recommends that all individuals with CF, age greater than 12 months to 10 yr, be treated with an initial dose of 800–1,000 IU vitamin D_3 per day.	Certainty: low Consensus recommendation
19. The CF Foundation recommends that all individuals with CF, age greater than 12 months to 10 yr, with a serum 25-hydroxyvitamin D level of at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and with confirmed adherence to the prescribed regimen, have the dose of vitamin D_3 increased to 1,600–3,000 IU per day.	Certainty: low Consensus recommendation
20. The CF Foundation recommends that all individuals with CF, age greater than 12 months to 10 yr, with a serum 25-hydroxyvitamin D level of less than 20 ng/ml (<50 nmol/liter) or with a persistent serum 25-hydroxyvitamin D level of at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and with confirmed adherence to the prescribed regimen, have the dose of vitamin D_3 increased to a maximum of 4,000 IU per day.	Certainty: low Consensus recommendation
21. The CF Foundation recommends that all individuals with CF, age greater than 12 months to 10 yr, who are unable to achieve a serum 25-hydroxyvitamin D level of at least 30 ng/ml (≥75 nmol/liter) after treatment with 4,000 IU vitamin D_3 per day, and with confirmed adherence to the prescribed regimen, be managed in consultation with a specialist with expertise in vitamin D therapy.	Certainty: low Consensus recommendation
Treatment of children above 10 yr of age and adults	
22. The CF Foundation recommends that all individuals with CF, age greater than 10 yr, be treated with an initial dose of 800–2,000 IU vitamin D_3 per day.	Certainty: low Consensus recommendation
23. The CF Foundation recommends that all individuals with CF, age greater than 10 yr, with a serum 25-hydroxyvitamin D level of at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and with confirmed adherence to the prescribed regimen, have the dose of vitamin D_3 increased to 1,600–6,000 IU per day.	Certainty: low Consensus recommendation
24. The CF Foundation recommends that all individuals with CF, age greater than 10 yr, with a serum 25-hydroxyvitamin D level less than 20 ng/ml (<50 nmol/liter) or with a persistent serum 25-hydroxyvitamin D level of at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and with confirmed adherence to the prescribed regimen, have the dose of vitamin D_3 increased to a maximum of 10,000 IU per day.	Certainty: low Consensus recommendation
25. The CF Foundation recommends that all individuals with CF, age greater than 10 yr, who are unable to achieve a serum 25-hydroxyvitamin D level of at least 30 ng/ml (≥75 nmol/liter) after treatment with 10,000 IU vitamin D_3 per day, and with confirmed adherence to the prescribed regimen, be managed in consultation with a specialist with expertise in vitamin D therapy.	Certainty: low Consensus recommendation
Use of UV lamps	
26. The CF Foundation is not able to recommend for or against the use of UV lamps in the management of vitamin D deficiency in all individuals with CF.	Certainty: low Benefit: unknown Grade: I

All recommendations except nos. 2, 5, and 12 were unanimous. For recommendations 5 and 12, 13 of 14 committee members voted for the recommendations. For recommendation 2, 12 of 14 voted for the recommendation.

D_3 increased to a maximum of 10,000 IU/d (consensus recommendation).

- The CF Foundation recommends that all individuals more than 10 yr of age with CF who are unable to achieve a serum 25-hydroxyvitamin D level of at least 30 ng/ml (≥75 nmol/liter) after treatment with 10,000 IU vitamin D_3 per day, and with confirmed adherence to the prescribed regimen, be managed in consultation with a specialist with expertise in vitamin D therapy (consensus recommendation).

Use of UV Lamps in the Management of Vitamin D Deficiency

UV lamps used for tanning, specifically those that emit UVB radiation, can result in vitamin D production in

TABLE 3. Vitamin D intakes and treatment recommendations of vitamin D deficiency in children and adults with CF

Age	Routine dosing with CF-specific vitamins (IU)	Step 1: dose increases (IU)	Step 2: dose titration maximum (IU)	Step 3
Birth to 12 months	400–500	800–1,000	Not more than 2,000	Refer
>12 months to 10 yr	800–1,000	1,600–3,000	Not more than 4,000	Refer
>10 yr to 18 yr	800–2,000	1,600–6,000	Not more than 10,000	Refer
>18 yr	800–2,000	1,600–6,000	Not more than 10,000	Refer

the skin. Because of decreased fat absorption in CF and the fact that vitamin D production in the skin bypasses the gastrointestinal tract, use of UV lamps is potentially advantageous for this patient population. Three studies were identified in the systematic review that addressed the use of artificial tanning in the management of vitamin D deficiency in CF (50, 56, 60). Two studies evaluated the use of a desktop tanning lamp (Sperti "Del Sol"). These studies differed in the amount and duration of exposure to the UV lamp. One study by Chandra *et al.* (50) demonstrated a modest but statistically significant increase in serum 25(OH)D concentration of 6 ng/ml after 8 wk of UV lamp therapy performed five times a week. Another study did not demonstrate a significant increase in serum 25(OH)D concentration; however, half of the study subjects were nonadherent to the therapy (56). A third study evaluated exposure to whole body UV lamps administered one to three times a week for 6 months and demonstrated a statistically significant increase in 25(OH)D from 23.8 to 50.4 ng/ml in the UV radiation group compared with a nonsignificant increase in a control group ($P < 0.001$) (60).

Given the limited evidence regarding the use of UV lamps in individuals with CF, the committee considered the limited availability and potential costs of such devices. Furthermore, the committee was concerned that the type of UV light (UVA *vs.* UVB) may not be standard in such devices. The dosage and the amount of skin that needs to be exposed are not well-characterized. Thus, developing clear recommendations for individuals with CF is difficult. In addition, oral antibiotic therapy (*i.e.* fluoroquinolones, tetracyclines, sulfa drugs) commonly used in the CF population may cause photosensitivity. The risks of potential burns would also be increased in an unsupervised setting.

- The CF Foundation is not able to recommend for or against the use of UV lamps in the management of vitamin D deficiency in all individuals with CF (USPSTF, grade I).

Future Directions

A review of this type always highlights gaps in our knowledge. Future directions should include exploring the impact of vitamin D status on bone health, pulmonary outcomes, and mortality in individuals with CF. We need to define the influence of pulmonary exacerbations on vitamin D status and vice versa, and to better explore the role of vitamin D status in other aspects of this multifaceted disease, including inflammation, CF-related diabetes, and depression. As the guidelines committee noted, very few studies addressing these questions have been performed. Only the completion of appropriately powered, well-designed studies focused on vitamin D in the CF population will answer these questions.

We need a better understanding of the appropriate timing of measurement of serum 25(OH)D concentrations, the utility of measuring other vitamin D metabolites, and the influence of gene polymorphisms on vitamin D status. Our recommendations about treatment would be strengthened by exploring factors such as dosing and formulation of vitamin D and its polar compounds, and the influence of diet, pancreatic functional status, and medications on absorption. Future research is needed to compare several outcomes for daily *vs.* alternative dosing schedule regimens including adherence, impact of adherence on serum 25(OH)D, time to correction of hypovitaminosis D, and maintenance of desirable serum 25(OH)D concentrations. We need to maintain a focus on the complexity of therapy for individuals with CF and to understand which recommendations individuals with CF and their caregivers are able to implement in their daily lives.

Summary

People with CF are at risk of vitamin D deficiency due to the underlying pathophysiology of the disease that leads to malabsorption of fat-soluble vitamins. Ample evidence confirms that individuals with CF have abnormal bone metabolism. There is concern that vitamin D deficiency may contribute to other comorbidities. The CF Foundation convened a committee to update its recommendations concerning vitamin D supplementation. This review of evidence identified gaps in our knowledge; however, 26 recommendations based on both evidence and consensus opinion have been made concerning assessment of vitamin D status, target treatment goals, use of vitamin D compounds, and treatment strategies, with specific attention to the needs of infants, children, and older individuals with CF.

Review Committee Members

Members of the CF Foundation Vitamin D Evidence-Based Review Committee are (in alphabetical order): Robert Aris (University of North Carolina); Drucy Borowitz, co-chair (State University of New York at Buffalo); Ellen Bowser (University of Florida); Christine Coburn-Miller (Women and Children's Hospital of Buffalo); Jessica Enders (Emory Healthcare); Danett Guy (Vanderbilt University); Pamela Hofley (Dartmouth-Hitchcock Medical Center); Andrea Kelly (Children's Hospital of Philadelphia); Karen Maguiness (Riley Hospital for Children); Brigid Mordeson (Nebraska Regional Cystic Fibrosis

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Endorsing organizations: The Endocrine Society, Cystic Fibrosis Canada, and The Pediatric Endocrine Society.

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