



THE CF SUPPLEMENT

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FAT-SOLUBLE VITAMINS

"The CF Supplement," originally known as "CF Nutrition Source," began publication in 2003. The first set of newsletters focused on fat-soluble vitamins (FSV). Since then many papers were published, especially about vitamins K and D. This issue of "The CF Supplement" summarizes the newer knowledge and its potential clinical application. To review all issues of the newsletter go to: www.SourceCF.com.

FEATURED PAPERS:

Vitamin K and cystic fibrosis. Conway SP. 2004 J R Soc Med. 97(Suppl. 44):48-51. This paper provided a concise review. The author detailed the various methods of assessing vitamin K status and the evidence for vitamin K supplementation. Concluded that PIVKA-II be used to assess adequacy and vitamin K routinely be supplemented.

Preventing early, prolonged vitamin E deficiency: An opportunity for better cognitive outcomes via early diagnosis through neonatal screening. Kosciak RL, et al. 2005 J Pediatr. 147:S51-6. **Objective:** Evaluated relationship of early vitamin E status to later cognitive function. **Methods:** Cognitive Skills Index (CSI), as related to vitamin E levels at diagnosis, was used to assess children diagnosed by neonatal screening vs. traditional methods. **Results:** CSI was significantly higher in the screened group. **Conclusions:** Prolonged alpha-tocopherol deficiency in infancy was associated with lower subsequent CSI scores.

Current treatment recommendations for correcting vitamin D deficiency in pediatric patients with cystic fibrosis are inadequate. Green D, et al. 2008 J Pediatr. 153:554-9. **Objectives:** Determine prevalence of vitamin D deficiency; elucidate contributing factors; and determine efficacy of D2 repletion strategies. **Study design:** Retrospective chart review. **Results:** D2 did not significantly decrease deficiency when compared to "no treatment" group. **Conclusions:** 50,000 IU of D2 once weekly did not correct vitamin D deficiency.

Vitamin A levels in patients with CF are influenced by the inflammatory response. Greer RM, et al. J Cyst Fibros. 2004 3:143-9. **Objective:** Determine serum retinol association with inflammation and disease severity. **Methods:** FSV levels, weight, DXA, and C-reactive protein (CRP) measured at time of hospital admission. **Results:** CF subjects with low serum retinol had low FEV1, weight, and bone density and higher CRP levels. **Conclusions:** Serum vitamin A levels are inversely correlated with CRP. Important to distinguish between low serum vitamin A due to the inflammatory response or to inadequate nutritional status.

REVIEW

The early goal of FSV recommendations was to avoid overt deficiencies. More recently the goal is to address the more subtle functions. The reader is encouraged to review the consensus recommendations available from the international CF organizations.^{1,2,3,4,5,6,7} The reports' conclusions are somewhat dissimilar, reflecting their various publication dates. In the United States, patients are maintained on CF-specific multivitamins with individual FSV supplementation as indicated.

SPECIAL POINTS OF INTEREST:

- *Early, prolonged vitamin E deficiency is associated with poorer cognitive outcomes later in life.*
- *Recommendations for form, amount, and frequency of individual fat-soluble vitamins over and above the content of a patient's CF-specific multivitamin are dynamic and best if based on individual patient needs.*

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REVIEW (CONT.)

Vitamin K

Conway^{Featured paper} provided a comprehensive review. Vitamin K's role in coagulation is well documented and although there are occasional reports of coagulopathies, they are in infants prior to the CF diagnosis.^{8,9} Since 2003 a number of studies, using a variety of assessment techniques, focused on vitamin K in unsupplemented subjects. Conway, et al.¹⁰ Fewtrell, et al.¹¹ Grey, et al.¹² and Nicolaidou, et al.¹³ found evidence of suboptimal vitamin K nutrition and suboptimal bone status. Several researchers attempted to determine optimal vitamin K dosing in CF. In an uncontrolled study, van Hoorn, et al.¹⁴ assessed markers of bone health in patients receiving: no vitamin K, <0.25 mg/day, and ≥ 1 mg/day and found improved results in those receiving the higher dose. Nicolaidou, et al.¹³ provided 10 mg in a single dose weekly for one year and found that vitamin K may have a beneficial role in bone health. Drury, et al.¹⁵ provided either 1 mg or 5 mg daily for one month and reported a significant improvement in vitamin K status bio-markers, but the majority of patients remained in the suboptimal range. Urquhart, et al.¹⁶ reported heterogeneity in the vitamin K prescribing patterns in the UK. As more is learned about the vitamin K needs of the general population, more work in the area of vitamin K and CF is indicated. Based on current knowledge, the amount of vitamin K recommended in the 2002 US CFF Nutrition Consensus Report¹ may no longer meet the needs of the majority of persons who have CF, yet there is no conclusive evidence as to the optimal dose. Supplemental vitamin K dose, in addition to what is contained in CF-specific multivitamins, needs to be individualized, based on PIVKA-II results.

Vitamin E

The most clinically applicable evidence was provided by Koscik, et al.^{Featured paper} Based on a review of research studies, the importance of initiating FSV supplementation especially vitamin E, in infants at the time of diagnosis appears to be paramount.⁷ A review of vitamin E's possible role as an antioxidant was provided in the US CFF Antioxidant Report.⁴ Several pilot studies with small numbers of CF subjects and of short duration assessed the efficacy of multinutrient supplements containing vitamin E to lung function; results varied.^{17,18,19} Two studies looked specifically at vitamin E; serum vitamin E levels did not correlate with lung function.^{20,21} Using the vitamin E to cholesterol ratio, Huang, et al.²² reported high serum vitamin E levels in CF patients when compared to NHANES

data; the clinical significance of this finding is unknown. The use of this ratio to measure vitamin E status versus the vitamin E to total lipid ratio continues to be debated.²³ To avoid detrimental effects of deficiency, vitamin E as contained in CF-specific multivitamins, is started at diagnosis.

Vitamin D

The numerous nonskeletal actions of vitamin D, including maintenance of pulmonary health, is generating great interest. For the non-CF population, both the daily recommendations and blood "normal" values may be insufficient.²⁴ The American Academy of Pediatrics has modified their vitamin D recommendations for healthy infants and children.²⁵ In CF, the exact form, dose, and frequency of vitamin D supplementation continues to be unknown. Numerous reports of vitamin D insufficiency or deficiency in CF have been published.^{12,26,27} The recommendations provided in the US CFF Bone Consensus Report⁶ may be inadequate.^{Featured paper, 28} Stephenson, et al.²⁹ reported improved serum vitamin D levels with D3 and routine adherence counseling by registered dietitians. Several researchers^{30,31} assessed the effectiveness of ultraviolet light (sunlamps); results varied. Vitamin D levels are affected by many variables including: sun exposure due to season, geographic location, and use of sunscreen; malabsorption; and overall health status. Therefore, supplemental vitamin D dosing needs to be personalized and based on blood levels.

Vitamin A

When reviewing vitamin A papers, the reader is challenged to compare the descriptive nomenclature used and the form of vitamin A studied. The role of retinol and eye health is well known, yet papers focused on this topic in CF are limited.³² The role of high serum retinol levels to increased risk for bone complications in the non-CF population was described by Michaelsson, et al.³³ Graham-Maar, et al.³⁴ and Maqbool, et al.³⁵ addressed concern regarding bone health in CF and high serum retinol levels. Aird, et al.³⁶ assessed the relationship of vitamins A, D, and E to lung function and found vitamin A to be the only vitamin with a significant positive correlation with lung function, although Bines, et al.²⁰ did not find a similar relationship in infants. Since retinol is an acute phase reactant, serum levels are lower during times of inflammation. Greer, et al.^{Featured paper} found, that when compared to controls, CF subjects had lower serum vitamin A levels which correlated with higher CRP levels. In post lung transplant CF patients, Stephenson et al.³⁷ reported elevated serum vitamin A

REVIEW (CONT.)

and E levels. Greer, et al. ^{Featured paper} postulated that this finding may be related to decreased overall inflammation, resulting in reduced retinol needs. Hakim, et al. ²¹ noted lower serum retinol and tocopherol levels with exacerbations, independent of pancreatic status. Greer, et al. ^{Featured paper} suggested that prior to prescribing retinol, it is imperative to distinguish between low serum retinol due to inflammation or other causes, including inadequate dietary intake.

ABOUT EURAND

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CLINICAL APPLICATIONS

Recommendations for form, amount, and frequency of FSV prescriptions are dynamic both for the general public and for individuals who have CF. Researchers and clinicians alike are disadvantaged since study designs vary tremendously and few are controlled making dosages recommendations difficult. Thus, RDs are challenged to compare studies to determine individual assessment and treatment care plans best-suited for each patient. Differences and similarities to identify in studies include: 1.) Length of study; 2.) Sample: age, gender, severity of disease, pancreatic status, overall health status including liver and renal disease; 3.) Definitions of exacerbation and disease severity; 4.) Genetic profile; 5.) Laboratory assay methods and their standard reference values; 6.) Nutrient intake measurement methods; 7.) Nutrient intake recommendations (country or continent specific); and 8.) Form, dose, and frequency of supplement provided. When generalizing non-CF population findings to those with CF, care must be taken to compare blood level data in addition to all the other variables inherent in persons who have CF.

The goal of this issue of "The Supplement" is to summarize FSV information published in the last 5 years. For patient care, a reasonable approach by the RD might be to: 1.) Assess each patient as an individual; and 2.) Make recommendations based on the patient's genotype and phenotype; and current age, pancreatic status, medical conditions, level of inflammation, dietary intake, vitamin supplement content and adherence, and interval blood levels. With this information in hand, the RD is able to make the best recommendations for each patient at each outpatient and inpatient encounter.

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