



# THE SUPPLEMENT

VOLUME 1, ISSUE 3 SEPTEMBER 2003



## VITAMIN D AND CYSTIC FIBROSIS

The sunshine vitamin! The cod liver oil vitamin! For years parents seemed to know that getting sunshine or taking cod liver oil was important for their children. In early 1920s, to address the public health problem of rickets, the governments of the United States and Canada mandated the addition of 400 IU vitamin D to each quart of milk (1). Recently, vitamin D deficiency and insufficiency has reemerged as a public health problem and of particular concern for persons who have cystic fibrosis. The proposed CF Foundation (CFF) Bone Consensus Statement recommends that persons with CF maintain serum levels no less than 30 ng/ml and that measures should be done in fall or spring. Review of vitamin D research is complicated by varying definitions of deficiency, type of vitamin D supplemented and/or measured, and geographic location of subjects.

### FEATURED PAPERS:

**Vitamin D insufficiency among free-living healthy young adults. Tangpricha V, Pearce EN, Chen TC, and Holick MF. Am J Med 112:659 – 662, 2002.** The objective of this study was to determine the prevalence of vitamin D insufficiency in a group of free-living healthy adults. Study population consisted of 302 employees of, or visitors to, a Boston, Mass hospital. Sixty-one percent were women, 60% white, 165 were evaluated at the end of the winter and 142 at the end of the summer. Age range was reported as 18 to over 50. Milk intake and multivitamin use were assessed. Using 25(OH)D<sub>3</sub> to assess vitamin D nutrition, 36% of young adults (18-29 yrs) were found to have insufficient levels of vitamin D. Significant differences were noted between the winter vs. summer groups. Taking a multivitamin was associated with a higher 25(OH)D<sub>3</sub>, while drinking less than two cups of milk (mean intake 1.6 ± 1.0 servings) was not associated with adequate vitamin D levels.

**Bone mineral status in prepubertal children with cystic fibrosis. Mortensen LA, Chan GM, Alder SC, and Marshall BC. J Peds 136(5):648 – 652, 2000.**

The objective of this study was to determine if osteopenia was evident in young children with CF and if so what was the cause. Subjects included 11 children with CF and non-CF matched controls. Mean age was 9 yrs (range 6-12). Researchers assessed

bone density, serum calcium and vitamin D, parathyroid hormone (PTH) and dietary intake. Nutrient intake (calories, calcium, phosphorus, vitamin D) was significantly higher in the CF group. 25(OH)D<sub>3</sub> was significantly lower in the CF group; 1,25(OH)<sub>2</sub>D<sub>3</sub> was lower in 7 CF subjects and 2 control subjects. PTH level was high normal in 4 CF subjects and 1 control subject. The authors concluded that although significant bone mineral deficits were not present in the sample of CF subjects, chronic lower vitamin D levels may place this group at risk for bone disease in adolescence and adulthood. Bone disease may begin near or immediately after adolescence, therefore overall bone health should be carefully monitored.

**Diminished and erratic absorption of ergocalciferol in adult cystic fibrosis patients. Lark RK, Lester GE, Ontjes DA, Blackwood AD, Hollis BW, Hensler MM, and Aris RM. Am J Clin Nutr 73:602 – 606, 2001.** The objective of this study was to assess absorption of oral vitamin D<sub>2</sub> in 10 subjects who had CF and 10 healthy control subjects. In this pair-matched pharmacokinetic study subjects were given 2500 µg (100,000 IU) D<sub>2</sub> with a meal. CF subjects were given supplemental pancreatic enzymes. CF subjects absorbed less than half of the vitamin when compared to the control subjects. The rise in 25(OH)D<sub>3</sub> over time was significantly lower in the CF group suggesting that in addition to poor absorption of vitamin D, the CF subjects converted vitamin D to 25(OH)D<sub>3</sub> at reduced rates. Among the CF subjects absorption was highly variable with 2 subjects showing virtually no absorption.

### SPECIAL POINTS OF INTEREST:

- *Recently, vitamin D deficiency and insufficiency has reemerged as a public health problem and of particular concern for persons who have cystic fibrosis.*
- *The proposed CF Foundation (CFF) Bone Consensus Statement recommends that persons with CF maintain serum levels no less than 30 ng/ml and that measures should be done in fall or spring.*

Volume 1, Issue 3:

Author: Suzanne H. Michel, MPH, RD, LDN

Editor: Donna H. Mueller, PhD, RD, FADA, LDN

## DISCUSSION

As the life expectancy for persons who have CF increases so do the challenges to maintain optimal health, particularly bone health (2,3). Bone health is multifactorial, including nutrient intake, absorption and biosynthesis plus weight, sun exposure, medication use, inflammation, exercise, and genetics. Research interest in vitamin D and its relationship to bone health in CF has been evident for over 20 years (4,5,6,7). The three papers featured in this issue of *The Supplement* provide evidence for continued research into the daily requirement of Vitamin D for both people with or without CF.

Tangpricha, et al found vitamin D insufficiency in the younger subjects they studied. It is of interest to note that drinking milk did not make a difference in vitamin D levels. The authors attributed this to the small amount of milk that was consumed and the variability of the vitamin D content of milk (8,9).

The study site for the Tangpricha research was Boston, which is at the 42<sup>oN</sup> latitude. Researchers have found that the body is incapable of producing cutaneous vitamin D in winter months at latitudes at and above the 40<sup>oN</sup> or at or below 40<sup>oS</sup> (10, 11). It has been thought that people who live between 40<sup>oN</sup> and 40<sup>oS</sup> are exposed to sufficient sunshine to support Vitamin D synthesis for the majority of the year. Researchers using NHANES III data learned that this may not necessarily be the case (12). Subjects living in what should be considered a "safe" area were found to be Vitamin D insufficient. Some attribute the prevalence of vitamin D insufficiency to the increased use of sunscreen, pollution, and type of clothing worn (13,14). Reiter et al (15) documented geographic and seasonal variations in vitamin D nutrition in adolescents and adults who have CF.

A number of papers have identified deficient and/or insufficient 25(OH)D<sub>3</sub> in persons who have CF (16,17,18, 19). Mortensen et al were interested in learning more about the prevalence and cause of osteopenia in prepubertal children with CF. The findings were similar to other researchers (16,17,18, 19). Based on their findings and supported by the work of other researchers the authors suggested that early intervention may decrease the prevalence and/or severity of bone disease.

The paper by Lark et al can give cause for concern when prescribing vitamin D. Vitamin D absorption over time was markedly different between the CF group and controls. The wide variability of absorption within the CF group is worrisome. The authors concluded that there may be a difference in the way persons with

**THERE MAY BE A DIFFERENCE IN THE WAY  
PERSONS WITH CF ABSORB VITAMIN D  
COMPARED TO CONTROL SUBJECTS . . .  
(LARK, ET AL 2001)**

CF absorb vitamin D compared to control subjects and that persons with CF may not convert absorbed vitamin D to the active form in the same manner as persons without CF. The authors suggested that the current recommendations for daily vitamin D supplementation for adults (20µg/800IU) may not be adequate and a more appropriate dose may be 25µg/1000IU. The authors advised vitamin D levels be evaluated annually and individual doses adjusted as needed based on lab results. They also noted that more potent forms of vitamin D, such as calcidiol or calcitriol, may be necessary to correct vitamin D deficiency. These preparations require careful monitoring of biochemical parameters.

## CLINICAL APPLICATIONS

It is evident from this review of vitamin D and CF research that there is a great deal to learn about how persons who have CF digest, absorb, synthesize, and utilize the vitamin. What should the clinician do to promote optimal bone health nutrition, specifically vitamin D nutrition?

The CFF Pediatric Consensus report and the European Nutrition Consensus Statement (20, 21) include recommendations of 400 IU for infants to 12

months of age and 400 to 800 IU vitamin D for anyone over 12 months of age. A draft of the CFF Bone Health Consensus (22) statement provides specific recommendations related to vitamin D health. Recommendations related to vitamin D are: 1.) Monitor 25(OH)<sub>3</sub> annually, preferably prior to winter months; 2.) Target circulating 25(OH)D<sub>3</sub> levels from 30 to 60 ng/ml; and 3) Replete with vitamin D as indicated. Screening patients for vitamin D levels may

## CLINICAL APPLICATIONS (CONT.)

identify patients who require supplemental vitamin D in doses greater than is currently recommended in the CFF Nutrition Consensus Statement. Vitamin D, as all fat-soluble vitamins, should be taken with supplemental pancreatic enzymes.

It is important to recognize that the vitamin D content of milk can be quite variable. In work done 10 years ago, Chen and Holick (8,9) found that samples of milk could contain almost no vitamin D to extremely high levels of vitamin D so that one cannot assume that patients drinking one quart of fortified milk daily are getting 400 IU of vitamin D. Even though the vitamin D content of fortified milk can vary, patients should be encouraged to consume milk for its many nutrient benefits. Keep in mind that foods made from milk, such as cheese and yogurt, are usually not made with vitamin D fortified milk. Patients should be advised to check the product nutrient label. Few foods contain naturally occurring vitamin D; some examples are fatty fish such as herring, salmon, and sardines and fish liver oils.

The role of sunshine for the well being of patients cannot be ignored. Henderson (18) noted in patients with CF, intestinal uptake may account for only a small portion of circulating vitamin D and sunshine may play an important roll. Clinicians are advised to be sensitive to the geographic location of their patients in terms of appropriate sun availability. Patients living at

or below the 40<sup>oN</sup> theoretically should have access to appropriate sunshine for 8 to 9 months annually, while those located above the 42<sup>oN</sup> will only have 6 months of available sunshine (10, 11) Recommendations for daily exposure range from 15 to 30 minutes daily without sunscreen and, when possible, with legs, arms and face exposed. Patients need to be counseled regarding appropriate exposure time as to not increase risk for skin cancer.

Clinicians also must keep in mind that medications such as glucocorticoids and anticonvulsants can interfere with vitamin D metabolism. Liver and kidney disease will interfere with normal vitamin D nutrition.

In summary, persons who have CF are at risk for abnormal bone status. Vitamin D plays a crucial role in maintaining optimal bone health. Vitamin D requirements for persons who have CF need to be individualized thereby necessitating monitoring of serum vitamin D levels, dietary intake, exposure to sunlight, medications, medical status, and supplementation. Patients will need to be: 1. Evaluated annually; 2. Dosed and monitored individually; 3. Guided as to the use of sunshine as a source of vitamin D; 4. Advised about the importance of weight-bearing exercise; 5. Educated regarding dietary intake; and 6. Instructed to take all vitamin supplements with food and enzymes.

## REFERENCES

1. Steenbock H, Black A. The reduction of growth-promoting and calcifying properties in a ration by exposure to ultraviolet light. *J Biol Chem.* 1924; 61:408-422.
2. Aris RM, Renner JB, Winders AD, Buell HE, Riggs DB, Lester GE, Ontjes DA. Increased rate of fractures and severe kyphosis: Sequelae of living into adulthood with cystic fibrosis. *Ann Intern Med.* 1998;128:186-193.
3. Donovan DS, Papadopoulos A, Staron RB, Adesso B, Schulman L, McGregor C, Cosman F, Lindsay RL. Bone mass and vitamin D deficiency in adults with advanced cystic fibrosis lung disease. *Am J Respir Crit Care Med.* 1998;158:1892-1899.
4. Mischler EH, Chesney PJ, Chesney RW, et al. Demineralization in cystic fibrosis. *Am J Dis Child.* 1979;133:632-635.
5. Farrell PM, di Sant'Agnese PA. Vitamin D levels in the serum of cystic fibrosis patients. *Pediatr Res.* 1977;11:443.
6. Hubbard VS, Farrell PM, diSant'Agnese PA. 25-Hydroxycholecalciferol levels in patients with cystic fibrosis. *J Pediatr.* 1979;94:84.
7. Weisman Y, Reiter E, Stern R, Root A. Serum concentrations of 25-hydroxyvitamin D and 24,25-dihydroxyvitamin D in patients with cystic fibrosis. *J Pediatr.* 1979;95:416.
8. Holick MF, Shao Q, Liu WW, Chen TC. The vitamin D content of fortified milk and infant formula. *N Engl J Med.* 1992;326:1178-1181.

## REFERENCES (CONT.)

9. Chen TC, Shao A, Heath H III, Holick MF. An update on the vitamin D content of fortified milk from the United States and Canada. *N Engl J Med.* 1993;329:1507.
10. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: Exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. *J Clin Endocrinol Metab.* 1988;67:373-378.
11. Ladizesky M, Lu Z, Oliveri B, San Roma N, Diaz S, Holick MF, Mautalen C. Solar ultraviolet B radiation and photoproduction of vitamin D3 in central and southern areas of Argentina. *J Bone Miner Res.* 1995;10:545-549.
12. Looker AC, Dawson-Hughes B, Calvo MS, Gunter EW, Sahyoun NR. Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulation from NHANES III. *Bone.* 2002;30:771-777.
13. Matuska LY, Ide L, Wortsman J, MacLaughlin JA, Holick MF. Sunscreens suppress cutaneous vitamin D3 synthesis. *J Clin Endocrinol Metab.* 1987;64:1165-1168.
14. Holick MF. Environmental factors that influence the cutaneous production of vitamin D. *Am J Clin Nutr.* 1995;61(3 Suppl):638S-645S.
15. Reiter EO, Brugman SM, Pike JW, Pitt M, Dokoh S, Haussler MR, Gerstle RS, Taussig LM. Vitamin D metabolites in adolescents and young adults with cystic fibrosis: Effects of sun and season. *J Pediatr.* 1984;106:21-25
16. Hahn TJ, Squires AE, Halstead LR, Strominger DB: Reduced serum 25-hydroxyvitamin D concentration and disordered mineral metabolism in patients with cystic fibrosis. *J Pediatr.* 1979;94:38-42.
17. Hanly JG, McKenna MJ, Quigley C, Freaney R, Muldowney FP, Fitzgerald MX. Hypovitaminosis D and response to supplementation in older patients with cystic fibrosis. *Quarterly J Med.* 1985;New Series 56:377-385.
18. Friedaman HZ, Langman CB, Favous, MJ. Vitamin D metabolism and osteomalacia in cystic fibrosis. *Gastro.* 1085;88:808-813.
19. Henderson RC, Lester G. Vitamin D levels in children with cystic fibrosis. *S Med J.* 1997;90:378-383.
20. Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. *JPGN.* 2002;35:246-259.
21. Sinaasappel M, Stern M, et al. Nutrition in patients with cystic fibrosis: a European consensus. *J of CF.* 2002;1:51-75. ([www.elsevier.com/locate/jcf](http://www.elsevier.com/locate/jcf))
22. Aris RM, Joseph PM, Haworth CS. Pathogenesis, screening and treatment of CF bone disease, summary of presentations. *Ped Pulm.* 2002;Suppl 24:177-181.



### EURAND PHARMACEUTICALS, INC.

790 Township Line Road  
Suite 250  
Yardley, PA 19067

Phone: 267-759-9400  
E-mail: [newsletterinfo@eurand.com](mailto:newsletterinfo@eurand.com)

---

Visit our Web Site  
[www.eurand.com](http://www.eurand.com)

---

The Supplement is an educational service provided by Eurand Pharmaceuticals, Inc. If you would like to be added or removed from our mailing list, please email us at [newsletterinfo@eurand.com](mailto:newsletterinfo@eurand.com)

The information in this publication is presented for educational and guidance purposes only. It should not be used as the basis for any medical diagnosis, prognosis or treatment plan. Anyone seeking medical advice, diagnosis or treatment should consult a qualified medical doctor. We are not responsible for any loss or damage that you, your beneficiaries or your estate may suffer, as reliance on our information is not reasonable for all the forgoing reasons. Please direct any inquiries regarding the same to: [newsletterinfo@eurand.com](mailto:newsletterinfo@eurand.com)

Eurand Pharmaceuticals, Inc., © 2008 All rights reserved.  
Printed in USA NT 0601 9/03