



THE SUPPLEMENT

VOLUME 1, ISSUE 2 JUNE 2003



VITAMIN K AND CYSTIC FIBROSIS

Vitamin K, identified in 1929, exists in several forms. Its role as “the antihemorrhagic” vitamin was quickly defined, but it wasn’t until 1979 that its role in bone health was discovered. Vitamin K activates a carboxylase enzyme to convert glutamic acid residues on the vitamin K dependent proteins to an active form called gamma-carboxyglutamate (Gla). This process is called gamma-carboxylation. The gamma-carboxylated proteins are able to bind calcium very effectively. These unique Gla residues on the vitamin K–dependent proteins aid blood-clotting factors. Gla was discovered in other body tissues including the bone vitamin-K dependent protein osteocalcin, thereby making vitamin K essential for optimal bone health. Two direct assays of functional vitamin K are 1.) osteocalcin gamma-carboxylation and 2.) Proteins Induced by Vitamin K Absence (PIVKA). An indirect, and less sensitive, measure is prothrombin time (PT).

It has long been thought that the bacteria in the GI tracts of healthy persons could synthesize sufficient vitamin K and only those persons who had had extensive bowel surgery or were taking antibiotics required supplemental vitamin K. Thus, the CF community recommended supplemental vitamin K for persons who had liver disease (CFLD) or were on extended antibiotic therapy. Recently, vitamin K research for both healthy persons and persons with CF has revealed data that may change the way we look at vitamin K requirements and need for oral supplementation. This issue of The Supplement reviews three vitamin K papers—one related to the general public and two related to CF.

FEATURED PAPERS:

Binkley NC, Krueger DC, Kawahara TN, Engelke JA, et al. A high phylloquinone intake is required to achieve maximal osteocalcin gamma-carboxylation. *Am J Clin Nutr* 76:1055 – 60, 2002. Researchers wanted to identify the lowest amount of vitamin K₁ necessary to maximize serum osteocalcin gamma-carboxylation. One hundred healthy adults, (mean age 25.6 yrs; range 19-36) enrolled in this single-blind, placebo-controlled, 2-week trial. The

experimental group received 250 to 1000 mg of supplemental vitamin K₁ daily. As measured by the percentage of undercarboxylated osteocalcin, normal values were achieved at a daily intake of about 1000 mg of supplemental vitamin K₁.

Beker LT, Ahrens RA, Fink RJ, O’Brien ME, Davidson KW, et al. Effect of vitamin K₁ supplementation on vitamin K status in cystic fibrosis patients. *JPGN* 24:512-517, 1997. Eighteen clinically stable CF patients (mean age 20 yrs; range 13-35) participated in an 8-week crossover study to determine the effect of 5000 mg weekly of oral vitamin K₁. Using PIVKA-II, at the end of the 4-week supplementation period, subjects had significantly higher plasma vitamin K₁ levels, but did not achieve normal levels.

Wilson DC, Rashid M, Durie PR, Tsang A, Kalinins D, Andrew M, et al. Treatment of vitamin K deficiency in cystic fibrosis: Effectiveness of a daily fat-soluble vitamin combination. *J Pediatr* 138:851-5, 2001. Seventy-five CF patients (mean age 15 yrs; range 0.6-46) with documented pancreatic insufficiency (PI) enrolled in the supplement study. Subjects were provided a daily fat-soluble vitamin combination formulated for persons who have CF. Mean daily vitamin K intake from the supplement was 180 mg (SD = 100, range= 0 to 300). At baseline, 81% of the subjects had elevated PIVKA-II levels. Following supplementation, 40% continued to have elevated levels. Elevated prothrombin times (PT) were found in only four subjects, two of whom had CFLD.

SPECIAL POINTS OF INTEREST:

- *Recently, vitamin K research for both healthy persons and persons with CF has revealed data that may change the way we look at vitamin K requirements and need for oral supplementation.*
- *In an 8-week crossover study to determine the effect of 5000 mg weekly of oral vitamin K₁, at the end of the 4-week supplementation period, subjects had significantly higher plasma vitamin K₁ levels, but did not achieve normal levels.*

Volume 1, Issue 2:

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DISCUSSION

Theoretically it would seem that persons with CF would be at risk for vitamin K deficiency due to fat malabsorption and/or antibiotic use. Until recently little research on the optimal dose of vitamin K has been available. The 1992 Nutrition Consensus Report (1) recommended supplemental vitamin K to be given twice weekly to patients receiving antibiotics or with CFLD. The 2002 US Consensus Committee on Nutrition for Pediatric Patients with CF (2) based their recommendation of 300 to 500 mg daily on the amount of vitamin K in multivitamins on the market at the time the report was written. The report also noted, "Clinicians should try to follow these recommendations as closely as possible until better dosage forms are available (2, pg. 251)." The 2002 European Consensus Report (3) recommends 1000 mg daily to a total of 10,000 weekly in the presence of PI or CFLD and for patients with suspected or demonstrated vitamin K deficiency.

In the early 1990s, several researchers evaluated the status of vitamin K nutrition in people with CF. The studies of older children or young adults often presented conflicting results due to limited information regarding routine vitamin supplementation of subjects prior to the study or non-standardized assessment techniques (4,5,6). In 1999 Rashid (7) used the PIVKA-II test to evaluate vitamin K levels in 98 CF patients. Seventy-eight percent of subjects with PI and 33% of those with PS had abnormal (elevated) PIVKA-II levels; subjects with PI and CFLD had more

abnormal levels. It is of interest to note that even though the majority of subjects had abnormal PIVKA-II levels, only four PI subjects and 3 PI/CFLD subjects had abnormal (elevated) PTs, indicating that by the time the PT is elevated the patient may have been experiencing long-term deficiency. No correlation was found between PIVKA-II and severity of fat malabsorption or antibiotic use.

The three papers featured in this issue, in context with previous published research and the current consensus reports, cause the clinician to rethink vitamin K nutrition for persons who have CF. Of great interest is Binkley's paper indicating that healthy adults may require 1000 mg daily of vitamin K to normalize blood levels. This amount is far greater than what has been recommended in the past. If adults with normal digestion and absorption require 1000 mg daily, the person with malabsorption should need additional amounts of vitamin K. Beker carefully defined the study sample, used standardized assessment methods, and controlled for vitamin K intake from both supplements and food. None of the subjects had CFLD and those on antibiotic therapy remained on antibiotics. Subjects were given 5000 mg in one weekly dose. None of the subjects achieved normal K levels as measured by PIVKA-II. Wilson studied the effectiveness of a multivitamin containing fat-soluble vitamins for persons with CF. Subjects took the vitamin daily, yet 40% failed to achieve normal vitamin K levels, as measured by PIVKA-II.

CLINICAL APPLICATIONS

Evidence-based practice requires practitioners to monitor Vitamin K nutrition for persons who have CF. Assessing vitamin K nutrition is a challenge since few labs provide PIVKA-II. It often is necessary to use the PT test as an indirect measure of vitamin K status. As with some other lab results, such as hematocrit and hemoglobin, an abnormal PT indicates an established deficiency. Keep in mind that Rashid (7) rarely found elevated PT levels even though abnormal PIVKA-II levels were found, suggesting early signs of a developing deficiency.

Although the US Consensus Statement recommends checking vitamin K status at diagnosis, with hemoptysis or hematemesis, or in CFLD, it may be prudent to check the PT at annual evaluations. Based on the papers summarized in this newsletter and others, vitamin K supplementation of 500 to 1000 mg daily may be necessary for patients who have CF.

Patients with liver disease, bowel resection, or other complications of CF may require higher doses.

Some patients may prefer to increase their vitamin K intake through the diet. To consume an adequate amount of vitamin K from food sources can be a challenge. The best sources of vitamin K are green leafy vegetables. Per 100 grams raw (\pm .5 cup cooked), broccoli contains about 147 mg, collards 440, turnip greens 650, and kale 726 (8).

Circulating blood concentrations of vitamin K may be improved when supplements are taken daily rather than twice weekly as is traditionally prescribed. Additionally, vitamin K, like all the fat-soluble vitamins, is better absorbed when taken with a fat-containing meal and enzymes (9). Therefore, it is important to teach patients the best way to take their supplemental vitamins.

REFERENCES

1. Ramsey BW, Farrell PM, and Pencharz P. Nutritional assessment and management in cystic fibrosis: a consensus report. *Am J Clin Nutr* 55:108-116, 1992.
2. Borowitz D, Baker RD, and Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. *JPGN* 35:246-259, 2002.
3. Sinaasappel M, Stern M, et al. Nutrition in patients with cystic fibrosis: a European Consensus. *J of CF* 1:51-75, 2002. (www.elsevier.com/locate/jcf)
4. Choonara IA, Winn MJ, Park BK, et al. Plasma vitamin K1 concentrations in cystic fibrosis. *Arch Dis Child* 64:732-734, 1989.
5. Cornelissen EAM, van Lieburg AF, Notohara K, et al. Vitamin K status in cystic fibrosis. *Acta Paediatr* 81:658-661, 1992.
6. DeMonalembert M, Lenoir G, Sain-Raymond A, et al. Increased PIVKA-II concentrations in patients with cystic fibrosis. *J Clin Pathol* 45:180-181, 1992.
7. Rashid M, Durie P, Andrew M, Kalnins D, Shin J, and Corey M, et al. Prevalence of vitamin K deficiency in cystic fibrosis. *Am J Clin Nutr* 70:378-82, 1999.
8. Shils, ME, Olsaon, JA, Shike, M Ross, AC. Modern Nutrition in Health and Disease. 9th ed. Baltimore: Williams & Wilkins, 1999;365.
9. Cystic Fibrosis Adult Care Consensus Conference Report. Consensus Conferences, Volume 9; Section 3, 1999. CFF, Bethesda, Maryland.



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Printed in USA NT 0601 6/03