See corresponding article on page 660.

Vitamin K and cystic fibrosis: give me a double, please[1,2]

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Since the work of Dam, Doisy, and others in the 1930s, it has been known that vitamin K is essential for the normal process of blood coagulation. What is less well known, however, are more recent discoveries of its role in bone formation and the regulation of inflammation and energy metabolism (1). Thus, for patients with cystic fibrosis (CF), vitamin K may play a number of important roles that remain to be fully explored.

Newborn infants and patients with advanced liver disease, bowel resection, and pancreatic insufficiency are at particular risk for vitamin K deficiency. Infants are born with a relatively sterile gut and do not get adequate quantities of vitamin K from placental transfer prepartum or breast milk. In patients with bowel disease, CF, or other causes of pancreatic insufficiency, vitamin K is depleted due to low dietary intake, malabsorption, and the use of antibiotics that diminish the intraluminal production of vitamin K by gut microorganisms.

Biochemically, vitamin K is a cofactor for the enzyme γ-glutamyl carboxylase, which converts glutamic acid residues to γ-carboxyglutamic residues. These ''gla'' residues are present on prothrombin (as well as clotting factors VII, IX, X, and proteins C and S), and the bone protein, osteocalcin. Undercarboxylated prothrombin leads to abnormal clotting and bleeding, whereas undercarboxylated osteocalcin has been associated with osteopenia and osteoporosis. Serum concentrations of undercarboxylated osteocalcin (ucOC or Glu-OC) and prothrombin [plasma prothrombin in vitamin K absence (PIVKA-II)] are highly sensitive measures of vitamin K status (2, 3), unlike prothrombin time which is only prolonged in advanced deficiency states. PIVKA-II is also a more sensitive marker of early deficiency.

It has been known for some time that vitamin K insufficiency or deficiency is highly prevalent in CF patients with pancreatic insufficiency, with and without liver disease (2). However, there has been debate on how much supplemental vitamin K should be provided on a daily basis to achieve sufficiency. Although it has been shown that routine oral fat soluble vitamin supplementation significantly reduced the prevalence of vitamin K insufficiency in CF patients, it remained highly prevalent among these study subjects (4). Not surprisingly, given current dietary habits with regard to consumption of green leafy vegetables and vegetable oils, vitamin K insufficiency also appears to be common among otherwise healthy subjects, and daily supplements of $\leq$1000 μg have been needed to normalize γ-carboxylated osteocalcin concentrations (5).

In this issue of the Journal, Dougherty et al (6) examined those factors that might predict vitamin K insufficiency in patients with CF and the daily dose of supplemental vitamin K needed to produce sufficiency in the study population. Subjects between the ages of 8–25 y with CF and pancreatic insufficiency, and mild-to-moderate lung disease were recruited. Very importantly, a contemporary comparison group of healthy subjects aged 8–21 y was also recruited for this study. Anthropometric measures, body composition, sexual maturation, pulmonary function, and CF transmembrane conductance regulator genotype were obtained. Total osteocalcin and undercarboxylated osteocalcin (%ucOC) were determined in both healthy and CF subjects with pancreatic insufficiency. PIVKA-II and serum 25-hydroxyvitamin D were obtained in the CF patients only. Dietary intake was assessed by using 3-d weighed food records. Cystic fibrosis patients were divided into 3 groups according to vitamin K supplementation: $<$150 μg/d (low), 150–900 μg/d (mid), and $>$1000 μg/d (high).

Overall, there was a higher prevalence of subjects with CF who were deficient in vitamin K (on the basis of %ucOC) compared with healthy subjects. They also had median daily dietary intakes of vitamin K below the recommended Adequate Intake for age and sex of healthy children. Fifty-nine percent of CF subjects also did not meet their recommended daily energy intake. Only those children with CF and pancreatic insufficiency who received $>$1000 μg/d of vitamin K achieved a status similar to healthy subjects. Only the vitamin K supplementation dose predicted vitamin K status for CF patients with pancreatic insufficiency.

Now that we know patients with CF and pancreatic insufficiency require higher doses of vitamin K supplementation than has been recommended in the past to achieve carboxylated osteocalcin concentrations similar to healthy individuals, what does this mean for our CF patients? Indeed it seems reasonable to supplement with higher vitamin K doses, but what amount is needed and how will this affect bone health and overall morbidity and mortality in the CF patient? This study does not provide the data from body composition dual-energy X-ray absorptiometry analyses, but the z scores of these patients' anthropometric measurements, along with the median serum concentrations of

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25-hydroxyvitamin D, suggest that significant further attention to macronutrient as well as micronutrient intakes is warranted, even in CF patients such as these with reasonably well-preserved pulmonary function. Analyses of bone mineralization were also unavailable and thus we have no direct information on the relation between vitamin K insufficiency and bone health in these individuals. Others have not shown a cause-effect relation between vitamin K concentrations and low bone mass. In one study vitamin K concentrations showed a significant negative correlation with %ucOC, but there was no significant correlation between vitamin K concentrations and markers of bone turnover or measurements of bone mineral status (7).

Thus, Dougherty et al have added significantly to the current evidence base to reinforce the need for daily supplemental vitamin K (and perhaps vitamin D as well) in patients with CF, at doses at least twice those currently recommended. However, further prospective intervention studies will be required to determine the optimal daily dose of supplemental vitamin K in patients with CF. In addition, longitudinal studies that examine the relation of vitamins A, D, and K status on bone mineralization and lung inflammation will also prove critically important as we continue to evolve nutritional management guidelines for patients with CF and malabsorption.

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