Why bother to take vitamins?

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Introduction

The first clear description of ‘fibrocystic disease of the pancreas’ or Cystic Fibrosis (CF) came in the late 1930s and evidence of vitamin A deficiency was reported in 10 of 49 patients as early as 1939. Indeed, this paper recommended ‘generous dosages’ of vitamin A for these patients.

Biochemical evidence of fat-soluble vitamin deficiency occurs early in infants diagnosed with CF by newborn screening. Sokol et al. reported the fat-soluble vitamin status of 36 infants diagnosed by newborn screening between 1984 and 1987 with the initial evaluation being undertaken at around seven weeks of age. There was an inverse correlation between three-day faecal fat excretion and serum α-tocopherol levels (vitamin E). Twenty-one percent of patients had low vitamin A levels, 35% low vitamin D, 38% low vitamin E and vitamin E:lipid ratio though none had an elevated PIVKA-II (protein induced by vitamin K absence or antagonism) – one indicator of vitamin K deficiency. Introduction of pancreatic enzyme replacement therapy, and standard fat-soluble vitamin supplementation corrected vitamin A and D status at 6 and 12 months of age. However, 10% of patients remained vitamin E deficient.

Feranchak et al. reported that 44 of 96 (45.8%) infants diagnosed by newborn screening between 1984 and 1997 had a deficiency of one or more of the fat-soluble vitamins by 4–8 weeks of age. Vitamin A deficiency occurred in 29% of patients, vitamin D deficiency in 22.5% and vitamin E deficiency in 22.8%. Bines et al. reported low serum retinol in 20 out of 39 (51%) infants and low α-tocopherol in nine of 38 (24%) infants diagnosed by newborn screening between 1991 and 1994.

These studies are supported by more contemporaneous data. Neville and Ranganathan reported 58 infants diagnosed by newborn screening between 2001 and 2006. Median age of diagnosis was 1 month (range 0–3 months). Vitamin D deficiency was described in 11 of 30 infants (37%), vitamin E deficiency in seven of 45 (16%) and vitamin A deficiency 27 of 45 (60%). Vitamin A and E levels were significantly lower in pancreatic insufficient patients. Vitamin A and E status was significantly correlated with pancreatic status though there was no significant correlation with pancreatic status and vitamin D deficiency.

Why bother to take vitamins? Firstly, because at the time of diagnosis of CF there is clear biochemical evidence of vitamin A deficiency in up to 60% of infants and vitamin D and E deficiency in up to 37% and 38%, respectively. Untreated, the incidence of biochemical and later clinical vitamin deficiencies will increase.

Most people with CF are at risk of fat-soluble vitamin deficiencies due to fat malabsorption and mal-digestion as a consequence of pancreatic insufficiency and bile salt deficiency. Patients treated with pancreatic enzyme replacement therapy may still experience refractory steatorrhoea due to enzyme inactivation as a consequence of high intestinal pH, small bowel bacterial overgrowth, the presence of a mucus barrier lining the intestine, short gut syndrome due to previous bowel resection and CF-related liver disease. Adherence rates are difficult to assess but non-adherence to pancreatic enzyme replacement is commonly reported and contributes to malabsorption. We know that some patients do not bother to take their prescribed vitamins as adherence rates in people with CF of 47% of the recommended vitamin prescription have been reported. Modi et al. compared different methods of assessing adherence to vitamin therapy. Adherence was variable and ranged...
from 22% when recorded in a diet diary to 94% for self-report by children. Non-adherence to therapy, poor dietary intake either due to anorexia or poor dietary sources of vitamins can also contribute to fat-soluble vitamin deficiency in CF. All of these factors put people with CF at high risk of vitamin deficiencies and in addition there are vitamin-specific risk factors detailed below.

Advances in the clinical and medical management of people with CF have led to improved life expectancy and new and emerging co-morbidities. The introduction of newborn screening allowing for earlier and more aggressive intervention together with improved pancreatic enzyme replacement therapy, the early introduction of appropriate fat soluble vitamin supplementation and an overall improvement in nutritional status together with advances in our understanding of fat-soluble vitamin metabolism mean we need to consider fat-soluble vitamin status in the context of modern disease. The emphasis of how vitamin status is defined has shifted. Traditionally vitamin status was discussed in terms of overt deficiency resulting in the classically recognized deficiency symptoms such as night blindness and xerophthalmia in vitamin A deficiency. Now vitamin status is also considered in terms of subclinical deficiencies which are defined as low serum, tissue or airway surface liquid vitamin levels with no visible signs or symptoms of deficiency. It is increasingly recognized that subclinical deficiencies in CF may play a significant role. Vitamin status may now be considered in the context of health outcomes rather than overt deficiency with levels being described as deficient, insufficient, adequate, optimal and toxic.

**Vitamin A**

The term vitamin A refers to a group of fat-soluble compounds known as the retinoids. Preformed vitamin A refers to retinol or the fatty acid ester derivative. This is the active form of the vitamin and in health it is well absorbed from the gut. Preformed vitamin A is found in liver, fortified margarines, dairy products, oily fish and fish oils. The carotenoids are precursors of vitamin A and the most common is beta carotene. Beta carotene is found in green leafy vegetables such as spinach and broccoli, carrots, red peppers, tomatoes and yellow fruits such as peaches and mangoes. Beta carotene is less efficiently absorbed from the gut and the conversion rate decreases as oral intake increases therefore there is less risk of toxicity.

Why bother to take vitamin A? Firstly, in addition to malabsorption of fat there are a number of risk factors for vitamin A deficiency in CF. Ahmed et al. reported a significant increase in faecal losses of retinol in CF unrelated to the degree of fat loss in the stools. They concluded that there may be a specific retinol handling defect in the gastrointestinal tract in people with CF possibly unrelated to digestion and absorption of dietary fat. Also beta carotene is an antioxidant and oxidative stress and increased free radical formation may contribute to a conditional deficiency due to increased needs.

Assessment of vitamin A status in CF is not without some inherent difficulties. Serum retinol is one indicator of vitamin A status but it is an insensitive indicator and remains normal until hepatic stores are almost depleted. In addition, serum retinol concentrations decrease transiently during the acute phase response to infection which can make interpretation of levels in CF difficult. Retinol binding protein (RBP) is important for the transfer of retinyl esters to the tissues and synthesis of RBP is responsible for the homeostatic control of plasma retinol concentrations. Synthesis of RBP decreases during the acute phase response so assessment of RBP and retinol may be helpful in CF. Plasma zinc deficiency depresses the synthesis of RBP and reduces mobilization from hepatic stores. Therefore assessment of vitamin A in CF would be aided by serum retinol levels, retinol binding protein, plasma zinc and an assessment of a positive acute phase protein such as C-reactive protein (CRP). These difficulties in assessing vitamin status and interpreting plasma levels in people with CF have been highlighted in three studies. Duggan et al. reported that vitamin A levels were significantly lower on admission for an acute respiratory exacerbation (1.14±0.1 μmol/L) than at discharge (1.70±0.6 μmol/L) (paired t-test: P <0.0001) with 23% of patients being considered deficient on admission. The mean value for retinol binding protein increased significantly during treatment for an acute respiratory exacerbation from 1.46 to 2.24 μmol/L. (P = 0.0003) and CRP concentrations fell from 25.7 to

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**Further readings**

9.8 mg/L (P = 0.002). Univariate-regression analysis found retinol concentration on admission correlated best with RBP on admission (r = 0.87). There was a negative correlation between plasma retinol concentration and both peak body temperature on admission (r = −0.41) and CRP concentration (r = −0.44).20

Lindblad et al. investigated 15 patients with CF (aged 8–34 years). Five (33%) had serum concentrations of retinol below the reference range and seven (47%) had decreased serum levels of retinol binding protein. There was a strong correlation between serum levels of retinol and retinol binding protein. There was a strong correlation (rs = 0.90, P = 0.01).21

Greer et al. used multiple regression analysis for predictors of vitamin A status and found CRP was negatively correlated with vitamin A in patients with CF (rs = −0.37, p < 0.0001).22

Biologically, vitamin A is important for dark adaptation and normal vision, epithelial cell proliferation and differentiation, maintenance of mucus-secreting epithelia and maintaining integrity of epithelial cells, apoptosis, immune regulation and immunocompetence; and its precursor beta carotene has antioxidant properties.

The major consequence of vitamin A deficiency is ocular with abnormal dark adaptation (night blindness), conjunctival and corneal xerosis that can lead to blindness. Historically, xerophthalmia and night blindness have been reported in patients with CF and have been reported as presenting features leading to a diagnosis of CF.24,25 Asymptomatic conjunctival xerosis with associated night blindness or abnormal dark adaptation despite vitamin A supplementation has also been reported.26–29

More recently, Morkeberg et al. investigated 35 adult patients with CF who were receiving the recommended daily supplemental dose of vitamin A. None of the patients had serum vitamin A levels indicative of deficiency and none of the patients had clinical (ocular) signs of vitamin A deficiency. They however report a high incidence (26%) of keratoconjunctivitis sicca (dry eye).30 Ansari et al. compared 28 adults with CF to 25 age- and sex-matched controls. With appropriate supplementation none of the patients had biochemical vitamin A deficiency, dark adaptation was normal compared to controls and only two patients (7%) had clinical evidence of dry eye.31 Whatham et al. compared electroretinograms in 29 pancreatic insufficient patients with CF supplemented with vitamin A and compared them with 12 pancreatic sufficient patients with CF aged 4–17 years. They reported no significant difference in vitamin A or retinol binding protein and reported similar levels of retinal function (electroretinogram amplitudes and implicit times).32 Taking appropriate vitamin A supplements can prevent the development of the ocular signs of deficiency.

In people with CF the roles of vitamin A in the maintenance of mucus secreting epithelia and immunocompetence together with the role of beta carotene as an antioxidant and how this may impact on respiratory health is important. Vitamin A is important in the maintenance of mucus-secreting epithelia including the respiratory epithelia. Mild or subclinical vitamin A deficiency may impair respiratory epithelium integrity.53 It leads to a loss of ciliated cells and an increase in mucus-secreting goblet-cells which impairs muco-ciliary clearance and favours bacterial adherence.34–36 In addition, bacterial adhesion to nasopharyngeal epithelial cells is increased in vitamin A deficiency37 and may permit increased colonization. In severe vitamin A deficiency squamous epithelium replaces the mucus-secreting ciliated epithelium resulting in squamous metaplasia. Vitamin A also plays a role in immunity and suggested mechanisms include T-cell subset depression, cell differentiation, cytokine modulation and phagocyte stimulation.38–40 Beta carotene also has antioxidant properties, it acts as a ‘free-radical’ scavenger and may help to prevent or slow oxidative damage in the lung. This suggests subclinical vitamin A deficiency may be of importance in CF.

Linking subclinical vitamin A deficiency and lung function is difficult due to the impact of the acute phase response on plasma vitamin A levels and the multifactorial basis of respiratory exacerbations. However, in a retrospective review of 102 patients with CF, mean age of 11.1 ± 6.4 years (range 1.5–27 years) experiencing 597 pulmonary exacerbations there was a direct correlation between increased number of exacerbations and lower vitamin A levels. This correlation was sustained within normal serum levels, across all lung function and in both pancreatic sufficient and insufficient patients.41 Aird et al. reported a significant correlation between serum vitamin A...
concentration and forced expiratory volume in one second (% predicted) \((r = 0.37, P = 0.02)\), forced vital capacity \((r = 0.39, P = 0.02)\) and peak expiratory flow \((r = 0.41, P = 0.01)\) in 38 patients with CF (mean age 15.3 years [range 6.1–25.2 years]).42

More recently interest has turned to increased levels of vitamins in patients with CF. Hypervitaminosis A has been reported in patients with CF following lung transplantation.43 Two retrospective studies highlighted elevated serum retinol concentrations in children and young adults with CF. Graham-Maar et al. compared intakes of 73 pancreatic insufficient children (aged 8.0–11.9 years) with CF to data from the 1999–2000 National Health and Nutrition Examination Survey (NHANES). Mean serum retinol was 52±13 μg/dl \((\text{range } 26–98 \mu g/dl)\) in patients with CF with no patients being in the deficient range. Mean serum retinol concentrations were significantly higher in patients with CF 52±13 μg/dl \((\text{range } 26–98 \mu g/dl)\) compared to NHANES 37±10 μg/dl \((\text{range } 17–63 \mu g/dl)\) \((p < 0.001)\).44 In a second study from Maqbool et al. reported 78 pancreatic insufficient patients with CF (aged 8–25 years) median serum retinol was 80 μg/dl \((\text{range } 33–208 \mu g/dl)\) with 58% of patients having serum retinol levels above the NHANES reference range.45 These studies highlight the importance of regular assessment and adjustment of supplemental doses.

Current recommendations for vitamin A supplementation in pancreatic insufficient patients are based on historical data and vary between countries.46–49 In the UK the recommended starting doses are less than 1 year old 4000 IU (1200 μg), older than 1 year 4000–10,000 IU (1200–3000 μg/day).47 Doses should be guided by individuals’ serum levels accepting that some people will need more and some less.

### Vitamin E

Vitamin E is a generic term for a group of eight lipid soluble compounds synthesized by plants. There are two classes; tocopherols (\(\alpha\), \(\beta\), \(\gamma\), \(\delta\)) and tocotrienols (\(\alpha\), \(\beta\), \(\gamma\), \(\delta\)) which exhibit differing levels of activity. Alpha-tocopherol has the highest biological potency and is the standard against which other forms are compared. Most vitamin E in the diet is derived from vegetable oils particularly corn, soya and sunflower seed oil, margarines and fat spreads depending on the base oil used and fortification, some nuts and foods such as crisps and savoury snacks in which fat is a major ingredient.

Why bother to take vitamin E? In addition to malabsorption which increases the risk of vitamin E deficiency. Vitamin E requirements may be increased due to the role of vitamin E as an antioxidant.

Serum or plasma vitamin E levels are most commonly used to assess vitamin E status. Vitamin E circulates in the blood bound to lipoproteins and as a consequence more accurate assessment of status may be assessed using the vitamin E to total lipid ratio. Normal ratios of \(\alpha\)-tocopherol to total lipid are >0.6 mg and >0.8 mg \(\alpha\)-tocopherol/gram total lipid in children and adults, respectively.50 In a study carried out in people without CF 47% of low vitamin E levels were normal when re-evaluated using vitamin E to lipid ratio and 58% with elevated plasma vitamin E were normal or low when re-evaluated with lipid ratio. Elevated triglyceride levels in non-fasting specimens were the most common reason for abnormal results when lipid was not considered.51 In people with CF, low plasma vitamin E levels may be a reflection of low total lipid levels and the vitamin E to total lipid ratio may actually be within the normal range.

Vitamin E is present in all cell membranes and is important in maintaining neurological function. It is an important antioxidant. Antioxidants protect cells from the damaging effects of free radicals. Free radicals are highly reactive molecules and react with oxygen to form reactive oxygen species. The body forms reactive oxygen species when it converts food to energy and the body is also exposed to environmental sources of free radicals, e.g. air pollution. In CF, bacterial infection and chronic inflammation may also contribute to increased free radical production. Vitamin E stops the production of reactive oxygen species formed when fat undergoes oxidation. The antioxidant properties of vitamin E may therefore help to reduce the effects of free radicals and help to protect cell membranes from oxidative damage.

Severe vitamin E deficiency is rare but leads to neurological degeneration, muscle weakness, hyporeflexia, ataxia and abnormal brainstem evoked auditory potential. Vitamin E deficiency
also causes haemolytic anaemia due to decreased erythrocyte survival time and increased red blood cell fragility with susceptibility to haemolysis. Neurological symptoms of vitamin E deficiency have been described in children and adults with CF including peripheral neuropathy, areflexia, ataxia, and pigmentary retinopathy, abnormal somatosensory and visual evoked potentials. Haemolytic anaemia has been reported as occurring as early as 6 weeks in three infants with CF and also as a presenting feature of CF. More recently, there has been interest in the role of vitamin E in cognitive function. Koscik et al. reported that patients with prolonged vitamin E deficiency due to delayed diagnosis had significantly lower Cognitive Skills Index and cognitive factor scores. This suggests that early diagnosis, prevention of prolonged periods of malnutrition and minimizing the duration of vitamin E deficiency, as seen in newborn screening programmes, is associated with better cognitive function in children with CF.

Why bother to take vitamin E? Taking vitamin E in people with CF is important to prevent overt deficiency symptoms but also for its potentially protective roles in cognitive function and for its antioxidant properties.

However, as with vitamin A high plasma levels of vitamin E have been reported in patients with CF following lung transplantation. In a cross-sectional study vitamin E levels of 69 children with CF (aged 6.0–10.0 years) were compared to levels from 222 children from the NHANES Survey III sample (aged 6.0–11.9 years). Forty-eight percent of patients with CF had serum vitamin E levels greater than the NHANES 95th percentile (high levels) and 83% had high vitamin E to cholesterol ratios. While vitamin E deficiency is our primary concern in patients with CF, care givers should be aware that with early diagnosis and improved treatments high levels can occur. The consequence of exposure to high vitamin E levels in people with CF is unknown. Plasma levels should be monitored regularly and the dose should be adjusted accordingly.

Current recommendations for vitamin E supplementation in pancreatic insufficient patients are based on historical data and vary between countries. In the UK the recommended starting doses are less than 1 year 10–50 mg, older than one year 50–100 mg, adults 100–200 mg. Doses should be guided by serum levels accepting that some people will need variable doses.

Vitamin D

There are several compounds with vitamin D activity. Two nutritionally significant compounds are ergocalciferol (vitamin D2) and colecalciferol (vitamin D3). Dietary intake of ergocalciferol is very low as few foods are naturally rich in vitamin D2, e.g. fatty fish and fish oils, liver. In many countries foods may be fortified with vitamin D, e.g. margarine, fat spreads and breakfast cereals, and this may make a significant contribution to dietary intake. Both colecalciferol and ergocalciferol are used to fortify foods. Most of the vitamin D required by humans is produced photochemically by exposure of the 7-dehydrocholesterol present in the skin to sunlight or ultraviolet light irradiation which causes the production of vitamin D3 (colecalciferol). Specific wavelengths of light are required for this process and as a consequence seasonal variation is reported in both people with CF and the general population with those living at higher latitudes being most at risk of low levels. In addition, the prescription of supplemental vitamin D as either ergocalciferol or colecalciferol is significant in CF.

Why bother to take vitamin D? In addition to malabsorption and maldigestion people with CF are at increased risk of vitamin D deficiency due to suboptimal levels of vitamin D binding protein, reduced sunlight exposure because of illness and photosensitivity related to prescribed medications, and reduced stores in some due to depleted fat mass.

The conventional marker of vitamin D status is plasma 25-hydroxyvitamin D as it is most readily available and it reflects the main storage form of the precursor substrate for 1, 25 dihydroxyvitamin D. Measurement of 1, 25 dihydroxyvitamin D is possible but less commonly performed. It is important to take into account seasonal variation in vitamin D levels. In addition, it is essential to ensure that the assay includes both ergocalciferol and colecalciferol and when interpreting results to recognize that inter-assay and inter-laboratory variability have been reported.
status is not thought of solely in terms of deficiency but is considered in terms of sufficiency and insufficiency in relation to overall health outcomes with levels greater than 75 nmol/L being considered by some optimal for health outcomes, though this remains controversial.

Absorbed vitamin D is hydroxylated in the liver to 25-hydroxyvitamin D further hydroxylation occurs in the kidney to produce the active metabolite 1,25-dihydroxyvitamin D (calcitriol). The active metabolite 1,25-dihydroxyvitamin D is a steroid hormone which regulates calcium and phosphate metabolism. In the kidney, 1,25-dihydroxyvitamin D regulates calcium transport in the proximal tubule and it regulates calcium and phosphate absorption from the small intestine. 1,25-dihydroxyvitamin D is also involved in the maintenance of plasma calcium levels via bone resorption and accrual under the regulation of parathyroid hormone which is secreted in response to low calcium levels.

Vitamin D is classically thought of for its role in calcium absorption, metabolism and bone mineralization. However, there is increasing recognition and interest in the non-skeletal roles of vitamin D in muscle function, innate immunity, diabetes, cardiovascular disease and some forms of cancer.

Vitamin D deficiency leads to reduced calcification of bones and causes rickets in children and osteomalacia in adults. Overt vitamin D deficiency in CF is rare but both rickets and osteomalacia have been reported.

Reduced bone mineral density is common in patients with CF with pooled prevalence rates for osteoporosis being reported as 23.5% and for vertebral and non-vertebral fractures being 14% and 19.7%, respectively. Reduced bone mineral density is of consequence in people with CF as it is associated with higher fracture rates, kyphosis, and pain which may limit physiotherapy; it may also be a contraindication to transplantation.

Reduced bone mineral density in patients with CF was first described in 1979 and since these initial reports more than 40 published studies have reported low vitamin D level in patients with CF and reduced bone mineral density. There are numerous recently published studies showing that levels remain suboptimal in most paediatric and adult patients with CF despite routine and high dose supplementation. Despite the evidence of extensive vitamin D insufficiency in people with CF most studies do not report a direct link between low vitamin D levels and low bone density because CF-related low bone mineral density is complex and multifactorial. However, it appears highly likely that low vitamin D levels do play a role in low bone mineral density in CF as they do in the general population.

An emerging consideration is the relationship between vitamin D status and lung function. In the third National Health and Nutritional Examination Survey a strong relationship was found between serum 25-hydroxyvitamin D levels and lung function. Green and colleagues reported that a higher FEV1 (implying improved lung function) was associated with higher levels of 25-hydroxyvitamin D in children. For each 10% increase in FEV1, the 25-hydroxyvitamin D level increased by 1.0 ng/mL. Wolfenden et al. reported a small but significant positive association between serum 25-hydroxyvitamin D levels and FEV1 percent predicted in adults with CF. Stephenson et al. reported a trend towards increasing FEV1 percent predicted with higher vitamin D levels and a significant difference in FEV1 percent predicted between patients with a plasma vitamin D level less than 25 nmol/L and those with a plasma vitamin D level greater than 50 nmol/L.

Why bother to take vitamin D? Optimizing vitamin D status and minimizing the risk factors for CF-related low bone mineral density would seem prudent in view of the prevalence data and potential consequences. In addition, the increasing recognition and interest in the non-skeletal roles of vitamin D in respiratory function, muscle function, innate immunity, diabetes, cardiovascular disease and some forms of cancer may also have relevance in people with CF.

Current recommendations for vitamin D supplementation are based on historical data and vary between countries. It is recognized that this level of supplementation is not sufficient to achieve adequate levels in many patients with CF. In the UK the recommended starting doses are less than 1 year 400 IU (10 μg), older than 1 year 400–800 IU (10–20 μg/day), adults 800–2000 IU (20–50 μg) per day. Doses should be guided by serum levels accepting that many people will need a higher dose.
Vitamin K

Vitamin K is a fat-soluble vitamin that exists naturally in multiple dietary forms. It is not a single compound but a group of homologous fat-soluble compounds. Vitamin K₁ (phylloquinone) is synthesized by plants and in the diet is present in dark green leafy vegetables such as spinach, broccoli, cabbage and kale. Some vegetable oils such as rapeseed, soy bean and olive oil are rich sources. Dairy products, meat and eggs also contain vitamin K though in lesser amounts. Vitamin K₂ (menaquinone) is synthesized by Gram-positive bacteria present in the jejunum and ileum. It is unclear how much the bacterial flora contributes to overall vitamin K status. Vitamin K₃ (menadione) and vitamin K₄ (menadiol) are synthetic forms of the vitamin but it is recommended that K₄ is best avoided in humans as it is linked to haemolysis and liver damage in the newborn and has the potential for mutagenicity.

Vitamin K is an essential nutrient but even in the general population recommendations on adequate intake have not been precisely established due to the uncertainty of the contribution of Vitamin K₂. Absorption of vitamin K from the gut is dependent on bile salts and pancreatic lipase secretion stimulated by dietary fat. In addition to fat malabsorption and maldigestion, risk factors for vitamin K deficiency in CF include bile salt deficiency, liver disease, chronic antibiotic use, short gut due to bowel resection and inadequate dietary intake.

Vitamin K is an essential cofactor in the post-translational conversion of glutamyl (Glu) residues to γ-carboxyglutamyl (Gla) residues. Under-carboxylated Gla-dependent proteins are functionally inactive. Major Gla-proteins (active) include prothrombin, osteocalcin and other bone metabolism-related proteins. Hence vitamin K is important for blood coagulation, bone health and mineralization and more recently interest has been shown in its role in energy metabolism and inflammation which may be of importance in CF.

Prothrombin time is not a very sensitive marker of vitamin K status as just 50% of the normal prothrombin concentration produces a normal prothrombin time. Therefore a prolonged prothrombin time is a marker of advanced subclinical vitamin K deficiency. It also reflects only vitamin K deficiency of the liver. Protein or prothrombin induced by vitamin K absence or antagonism (PIVKA II) is the under-carboxylated form of prothrombin and is a more sensitive indicator of vitamin K deficiency of the liver. Under-carboxylated osteocalcin is the most sensitive indicator of vitamin K status of the bone and is the first Gla protein to occur in the undercarboxylated form. Under-carboxylated osteocalcin is the most sensitive indicator of vitamin K status.

PIVKA II and under-carboxylated osteocalcin are not readily available in many CF centres and currently tend to be used mainly as research tools.

Fifty years ago Shwachman, and Di Sant’Agnese and Vidaurreta reported that bleeding and vitamin K deficiency may be an early sign of CF. Since that time numerous authors have reported coagulopathies including haematomas, intracerebral haemorrhage and severe life-threatening bleeding in people with CF and vitamin K deficiency. Subclinical deficiency of vitamin K as assessed by PIVKA II is common in CF. Rashid et al. published a prospective study assessing vitamin K status using PIVKA II in 98 patients (83 pancreatic insufficient) and 62 healthy controls. None of the controls but 78% of pancreatic insufficient patients, 33% of pancreatic sufficient patients and all those with CF-related liver disease had elevated PIVKA II levels. Conway et al. reported elevated PIVKA II in 42% of 93 children with CF.

A number of studies have also been published which indicate subclinical vitamin K deficiency despite supplementation with varying doses of vitamin K suggesting the appropriate dose of vitamin K has yet to be established. De Montebert et al. reported 14 (33%) of 43 patients supplemented with 5–10 mg vitamin K daily had elevated PIVKA II levels. Wilson et al. reported 58 (81%) of 72 patients had abnormal PIVKA II levels. After supplementation with a mean vitamin K intake of 0.18 mg/day for a minimum of four months 20 (40%) still had abnormal PIVKA II levels. Van Hoorn et al. compared 39 healthy subjects with 20 patients with CF
receiving either no vitamin K supplementation \((n = 10)\), low dose vitamin K supplementation \((<0.25 \text{ mg/day}) \) \((n = 6)\) and ‘high’ dose supplementation \( (>1 \text{ mg/day}) \) \((n = 4)\). Only patients in the high dose supplementation group had normal PIVKA II levels.\(^{105}\)

Similar findings have recently been reported by Dougherty et al., who compared patients supplemented with what they defined as low \((<150 \mu\text{g/day})\), middle \((150–999 \mu\text{g/day})\) and high \((1000 \mu\text{g/day})\) dose supplementation. Despite supplementation 50\% of patients \((n = 60)\) had PIVKA II in the deficient range. In addition to PIVKA II this study determined vitamin K status as defined by under-carboxylated osteocalcin, the most sensitive indicator of vitamin K status of the bone. Seventy-four percent of the population has shown that low vitamin K status contributes to lung damage.\(^{105}\)

Despite supplementation 50\% of patients \((n = 60)\) had PIVKA II in the deficient range. In addition to PIVKA II this study determined vitamin K status as defined by under-carboxylated osteocalcin, the most sensitive indicator of vitamin K status of the bone. Seventy-four percent of the patients had under-carboxylated osteocalcin levels in the insufficient or deficient range. Vitamin K supplementation was negatively associated with the percentage of under-carboxylated osteocalcin.\(^{106}\)

Increased levels of under-carboxylated osteocalcin have been reported in other studies and have been associated with reduced lumbar spine bone mineral content,\(^{107}\) reduced levels of bone markers for bone mineral accrual\(^{80,102,107}\) and increased levels of markers for bone turnover.\(^{102}\)

These studies suggest subclinical vitamin K deficiency is common in CF. In the general population vitamin K intervention studies have reported increased bone mineral density, reduced fracture rates and improved bone strength. However, as with vitamin D because of the multifactorial nature of low bone mineral density in CF cause and effect will be difficult to establish.

A recent observational study in the non-CF population has shown that low vitamin K status is inversely associated with circulating measures of inflammation.\(^{108}\) The mechanism underlying the potential influence of vitamin K on inflammatory cytokine production is unclear but and it has been suggested that vitamin K may suppress inflammation by decreasing expression of genes for individual cytokines. This may be of importance in CF where inflammation and infection contribute to lung damage.

Why bother to take vitamin K? Overt deficiency can lead to life-threatening bleeding. Subclinical deficiency is common and may contribute to cystic fibrosis low bone mineral density. In addition, vitamin K and vitamin K dependent proteins may play a role in energy metabolism and inflammation which may be of relevance in CF.

Supplementation with vitamin K is not currently universal. Current recommendations for vitamin K supplementation are based on historical data and vary between countries.\(^{46–49}\) In the UK the recommended doses are less than 2 years 300 \(\mu\text{g/kg/day} \) rounded to the nearest \(mg\), 2–7 years 5 \(mg/day\) and older than 7 years 10 \(mg/day\).\(^{87}\) As vitamin K is metabolized within 24 hours a daily dose appears most appropriate.

**Conclusion**

Why bother to take vitamins? Correcting fat-soluble vitamin deficiencies is an early management goal. Prevention of overt deficiency is the primary goal but optimizing fat-soluble vitamin status in people will influence health outcomes. Our understanding of these vital nutrients continues to expand. Further research is needed to determine optimal supplemental doses in the context of modern disease. High levels are reported so continuous monitoring and adjustment of doses is essential.

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