Introduction

Malabsorption of fat soluble vitamins is likely in most patients with CF, particularly those who are pancreatic insufficient. Biochemical evidence of fat soluble vitamin deficiency has been found by two months of age in untreated screened infants with CF (Sokol et al, 1989; Feranchak et al, 1999). Patients should have plasma levels checked annually (Borowitz et al, 2002; Cystic Fibrosis Trust, 2002; Sinaasappel et al, 2002) and receive supplementation with the fat soluble vitamins A, D and E. Frequent and serial monitoring of serum vitamin levels is essential (Feranchak et al, 1999). Pancreatic sufficient patients need to be monitored annually to ensure continuing adequacy of plasma vitamin levels or the need for supplementation.

The recommended daily supplements of the fat soluble vitamins for pancreatic insufficient patients are:

• Infants: Vitamin A 4,000 IU (1,200 mcg), vitamin D 400 IU (10 mcg) and vitamin E 37-75 IU (25-50 mg)

• Children over 1 year of age: Vitamin A 4,000 -10,000 IU (1,200 -3,000 mcg), vitamin D 400 -800 IU (10-20mcg) and vitamin E 150-300 IU (100-200 mg)

• Adolescents and adults: Vitamin A 4,000 -10,000 IU (1200-3,000 mcg), vitamin D 800-2,000 IU (20-50mcg) and vitamin E 150-300 IU (100-200 mg)

These doses are considerably higher than the usual dietary intake and should be titrated against plasma levels (Cystic Fibrosis Trust, 2002). The need for routine vitamin K supplementation in CF remains the subject of discussion and there is little international consensus. It is likely that all patients with CF need routine vitamin K supplements for optimal bone health and the current recommendations are vitamin K1 (phytomenadione) 300 µg/kg/day for babies, 5 mg/day for children aged two to seven years, and 10 mg/day for older children and adults (Cystic Fibrosis Trust, 2007).

Plasma levels of the fat soluble vitamins A, D and E, total cholesterol, vitamin E: cholesterol ratio and a prothrombin time should be checked as part of an annual assessment. Ideally, this should be carried out at a time of clinical stability. Retinol binding protein (RBP), plasma zinc levels and C-reactive protein (CRP) should be measured at the same time to help in the interpretation of plasma vitamin A levels.

Vitamin K status is more difficult to assess. Plasma vitamin K levels alone are unreliable for assessment of vitamin K status (Durie, 1994; Rashid et al, 1999). Vitamin K status should be considered in relation to individual tissues (Vermeer et al, 1998; Mosler et al, 2003). Vitamin K deficiency of the liver and bone may occur independently. Prothrombin levels do not always correlate with plasma vitamin K levels (De Montalembert et al, 1992). A plasma sample that has only 50% of the normal concentration of prothrombin still has a normal prothrombin time (Suttie, 1992). Although it is not widely available, PIVKA II (protein induced by vitamin K absence or antagonism) levels are a more sensitive measure of vitamin K status of the liver (Alexander et al, 1998). Undercarboxylated osteocalcin is the most accurate method of assessing vitamin K adequacy for bone metabolism but is used only as a research tool.

Vitamin A

Vitamin A, also known as retinol or preformed vitamin A, comes from animal sources such as liver, dairy produce and fish oils. Vitamin A can also be formed from pro vitamin A carotenoids, (beta carotene is probably the most well known), which are found mainly in yellow fruit and vegetables and carrots. Vitamin A deficiency may cause night blindness in older patients (Rayner et al, 1989) and can progress to severe xerophthalmia if not checked (Campbell et al, 1998). Vitamin A is also important because of its role in the maintenance of mucus secreting epithelial cells. Low vitamin A levels are associated with worse clinical status (Rayner & Littlewood, 1989), impaired lung function (Greer et al,
2004; Aird et al, 2006) and lower weight standard deviation scores and bone mineral density (Greer et al, 2004). As patients get older there is an increasing disparity in vitamin A levels between patients with CF and controls suggesting an association with disease progression (Greer et al, 2004). When supplements are adequate and blood levels are checked at annual assessment we found no ophthalmological evidence of vitamin A deficiency (Ansari et al, 1999). There is currently much interest in the role of beta carotene as an antioxidant.

High serum levels of vitamin A (Graham-Maar et al, 2006) have been documented in people with CF and are especially common following transplantation (Stephenson et al, 2005). Care is therefore needed in the interpretation of low plasma levels and in monitoring intake and supplementation. Retinol binding protein is often lower in clinically stable people with CF than in controls (Mrugacz et al, 2005) and we have observed this in our clinic. A positive correlation between RBP and zinc status has been found (Navarro & Desquibel, 1998). Vitamin A is a negative acute phase reactant. Serum levels of vitamin A and RBP fall transiently during the acute phase response due to decreased release from the liver whilst acute phase proteins such as CRP increase (Thurnham et al, 2003; Greer et al, 2004). Vitamin A levels and RBP levels increase during the treatment of infection in CF (Greer et al, 2004). Plasma vitamin A levels should therefore be measured at a time of clinical stability and alongside a marker of infection (Duggan et al, 1996; Cawood et al, 2002). Oral supplements should not be increased indiscriminately. Causes of low vitamin A levels other than malabsorption, e.g. patient adherence, should be considered.

Vitamin D

The two main forms of vitamin D are ergocalciferol (vitamin D2) and colecalciferol (vitamin D3). Only a small amount of vitamin D actually comes from the diet (Holick, 2002). Rich sources of vitamin D are fish liver oils, e.g. cod liver oil, and fatty fish such as herring, mackerel, pilchards, sardines and fresh tuna. Other sources are eggs and fortified foods. The main source of vitamin D is sunlight exposure to the skin which causes the conversion of 7-dehydrocholesterol to colecalciferol (Vitamin D3).

Vitamin D deficiency may cause rickets (Scott et al, 1977) and osteomalacia (Friedman et al, 1985; Elkin et al, 2002). Clinical evidence of overt vitamin D deficiency is rare but CF related low bone mineral density (osteoporosis & osteopenia) and low levels of vitamin D metabolites are increasingly recognised in both children and adults with CF (Stamp & Geddes, 1993; Bachrach et al, 1994; Bhudhikanok et al, 1996; Henderson & Madsen, 1996; Haworth et al, 1999; Conway et al, 2000; Elkin et al, 2001). Suboptimal vitamin D levels may occur due to fat and vitamin D malabsorption (Lark et al, 2001), low vitamin D binding protein (Coppenhaver et al, 1981), poor adherence with prescribed vitamin supplements, and inadequate sunlight exposure due to hospitalisation, illness or through advice regarding photosensitivity from antibiotic therapy.

Serum vitamin D levels largely depend on sunlight exposure and considerable seasonal variation is seen despite oral supplementation (Elkin et al, 1999; Wolfe et al, 2001), though with close attention to serum levels and enhanced supplementation the seasonal effect can be reduced (Wolfe et al, 2001).

The frequency of vitamin D deficiency in different studies varies considerably (Henderson & Madsen, 1999) depending on the diagnostic criteria used (Ott & Aitkin, 1998). The term vitamin D insufficiency is
now more widely used but there is no consensus on its definition. A minimum desirable level has been described and we currently aim to achieve plasma levels greater than 30ng/ml or 75nmol/L (Dawson-Hughes et al, 2005; Bischoff-Ferrari et al, 2006) at all times of the year. This is in line with the recommendations for patients with CF from the UK (Cystic Fibrosis Trust, 2007) and North America (Aris et al, 2005).

Vitamin D levels should be measured and reviewed at least annually and three to six months after changes in vitamin D dosing (taking into account seasonal variations). Vitamin D supplementation should be individualised with the aim of achieving levels greater than 30ng/ml or 75nmol/L. It is often necessary to give much higher doses of vitamin D than those suggested above to achieve adequate levels (Kelly et al, 2002; Boyle et al, 2005).

As vitamin D is usually given in combination with vitamin A (as multivitamin preparations or vitamin A & D capsules) care should be taken when increasing the dose of supplement as a high intake of vitamin A may contribute to poor bone mineralisation (Promislow et al, 2002). A separate vitamin D preparation may be required.

Vitamin E

There are eight similar compounds with vitamin E activity. Alpha-tocopherol is the most active form. Vitamin E is found in vegetable oils, nuts, fortified margarines and cereals, broccoli and spinach.

Severe vitamin E deficiency may cause neurological problems in older patients with CF (Willison et al, 1985). It may also contribute to anaemia and correction of vitamin E deficiency improves haemoglobin levels (Kelleher et al, 1987). Vitamin E is present in all cell membranes. It acts as an important antioxidant reducing the effects of free radicals produced by infection and chronic inflammation, thus helping to protect cell membranes from oxidative damage. Therefore, vitamin E may be important in controlling the progression of lung disease. Studies suggest that people with CF have inadequate antioxidant defences to cope with elevated oxidative stress (Brown et al, 1996).

More recently it has been suggested that vitamin E plays a role in cognitive function. The prevention of prolonged vitamin E deficiency by neonatal screening and early active nutritional intervention in infants with CF is associated with better cognitive function (Koscik et al, 2005).

With modern intervention and monitoring, high plasma vitamin E levels have been reported in pancreatic insufficient patients (Huang et al, 2006) and are especially common following transplantation (Stephenson et al, 2005). This emphasises the need for regular nutritional assessment and surveillance.

Hypervitaminosis E only occurs with very large supplemental doses and may cause bruising and

Figure 2. Xray of a rib fracture following coughing
bleeding with increased prothrombin time. This is due to inhibition of vitamin K dependent carboxylase and can be reversed by administering vitamin K. Other symptoms may include fatigue, weakness and gastrointestinal upset.

**Vitamin K**

Vitamin K is a fat soluble vitamin and its absorption from the gut is dependent on bile salt and pancreatic lipase secretion stimulated by dietary fat (Vermeer *et al.*, 1995). People with CF are at risk of developing vitamin K deficiency due to fat malabsorption as a consequence of pancreatic insufficiency and bile salt deficiency. Other risk factors include CF related liver disease, frequent antibiotic therapy, inadequate dietary intake and short gut syndrome resulting from bowel resection (Durie, 1994).

Regular vitamin K supplements are not currently given unless there is chronic liver disease, a prolonged prothrombin time or a proposed surgical operation when we would give an oral daily supplement of 5-10mg for a week prior to the operation, or 10mg intramuscularly prior to the procedure. Vitamin K deficiency and subclinical vitamin K deficiency (as shown by elevated PIVKA II levels) are common (Rashid *et al.*, 1999; Wilson *et al.*, 2001; Conway *et al.*, 2005). Deficiency is almost universal in pancreatic insufficient children with CF, occurs in all patients with CF liver disease and is found in about one third of pancreatic sufficient patients. There is increased attention on the role of vitamin K in bone health in both the general population and in people with CF (Weber, 2001; Nicolaidou *et al.*, 2006). Vitamin K is required for the carboxylation, and thereby the optimal activity, of osteocalcin which plays an important role in bone formation (Weber, 1997). A cause and effect relationship between vitamin K deficiency and low bone mass in CF has not been proven (Conway *et al.*, 2005), but subclinical vitamin K deficiency may be important in the development of CF related low bone mineral density and is being researched. The need for routine vitamin K supplementation in CF remains the subject of discussion. Having identified that vitamin K deficiency is common in our paediatric patients we now plan to undertake further research to determine the optimal supplemental dose of vitamin K for people with CF.

**Water soluble vitamins**

Routine supplementation of water soluble vitamins is unnecessary in CF (Congden *et al.*, 1981; Peters & Rolles, 1993) unless there is documented evidence of a poor dietary intake. However, deficiencies can occur and have been reported for B vitamins (McCabe, 2001; McCabe *et al.*, 2004). Parenteral vitamin B12 may be required for patients who have had extensive surgery for meconium ileus (Sinaasappel *et al.*, 2002).

**Antioxidants**

Oxidative stress is increased in patients with CF, despite normal dietary antioxidant intakes (Wood *et al.*, 2001). Improved antioxidant status is associated with improved lung function (Wood *et al.*, 2003) and antioxidant levels increase when respiratory exacerbations are treated (Range *et al.*, 1999). As yet there is insufficient evidence to recommend routine supplementation with antioxidants though vitamin C, beta carotene and vitamin E are areas of current research in CF (Winklhofer-Roob *et al.*, 1997; Madarasi *et al.*, 2000; Wood *et al.*, 2001).

**Key points**

- Suboptimal vitamin D levels are very common
- Fat soluble vitamin replacement is essential in patients with pancreatic insufficiency
- Vitamin A deficiency may cause night blindness and can progress to severe xerophthalmia
- Vitamin D deficiency may cause rickets, osteomalacia and reduced bone density
- Severe vitamin E deficiency may cause neurological problems
- It is likely that all patients require vitamin K supplementation but the appropriate dose is unknown
- Further research is needed on vitamin supplementation and antioxidants
• All patients should have their fat soluble vitamin levels checked at least annually

• Pancreatic insufficient patients should receive oral supplementation of the fat soluble vitamins A, D and E and the dose of supplement should be guided by plasma levels and supporting information e.g. retinol binding protein level

• Pancreatic sufficient patients should receive fat soluble vitamin supplementation

References


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