Cystic fibrosis (CF) is the most prevalent fatal, autosomal, recessive genetic disease in white people, affecting approximately 1 in 3400 live births.

Children with CF are at high risk for developing vitamin K deficiency because of fat malabsorption. The prevalence of vitamin K deficiency in CF is not precisely known, but it is common in unsupplemented patients with pancreatic insufficiency.\(^1\)

Besides its function in blood clotting, accumulating evidence suggests that vitamin K plays a key role in improving bone health.\(^3\) Vitamin K is a cofactor in the post-translational \(\gamma\)-carboxylation of glutamic acid residues (Glu) to form \(\gamma\)-carboxyglutamic acid (Gla) residues which are able to bind calcium. Gla containing proteins are found in the clotting cascade (vitamin K dependent clotting factors) and in bone (osteocalcin). In the absence of vitamin K, Gla residues remain undercarboxylated, resulting in a strongly decreased affinity for calcium. Undercarboxylated coagulation factors are known as PIVKAs (protein induced by vitamin K absence); notably PIVKA-II (undercarboxylated prothrombin) serves as a sensitive marker for vitamin K status.

Circulating undercarboxylated osteocalcin (u-OC) is considered to be an even more sensitive marker for vitamin K deficiency because of fat malabsorption. The prevalence of vitamin K deficiency in CF is not precisely known, but it is common in unsupplemented patients with pancreatic insufficiency.\(^1\)

The relation between different doses of vitamin K supplementation, several bone markers, and PIVKA-II concentrations in cystic fibrosis (CF) patients compared to controls was evaluated. Results suggest that a increased vitamin K intake may have significant health benefits for children with CF.

**SUBJECTS AND METHODS**

In this uncontrolled study, 39 subjects were divided in four groups: 19 healthy subjects, 10 CF patients with no vitamin K \((\text{CF}_{\text{no}})\), six CF patients with low dose vitamin K \((<0.25 \text{ mg/day} = \text{CF}_{\text{low}})\), and four CF patients with high dose vitamin K \((\geq 1 \text{ mg/day} = \text{CF}_{\text{high}})\) supplementation. Inclusion criteria for CF patients were pancreas insufficiency without liver function disturbances. Serum or urine concentrations of different bone markers and serum PIVKA-II concentrations were determined in healthy subjects and in and CF patients on different vitamin K supplementation. Serum concentrations of the bone formation markers osteocalcin (OC, total OC (t-OC), undercarboxylated OC (u-OC) and carboxylated OC (c-OC)) and bone alkaline phosphatase (BAP) as well as the bone resorption marker N-terminal collagen type 1 (NTX) were determined. The bone resorption marker deoxypyridinoline (DPD) was determined in urine.

Data were analysed using the non-parametric Wilcoxon’s (Mann-Whitney) rank sum test (\(p<0.05\) two sided).

**RESULTS**

Serum t-OC was measured in 10 controls only and was significantly higher in CF\(_{\text{high}}\) patients \((p = 0.016)\) than in controls (see fig 1). Serum u-OC was significantly lower in CF\(_{\text{high}}\) patients than in controls \((p = 0.005)\), CF\(_{\text{no}}\) \((p = 0.011)\), and CF\(_{\text{low}}\) patients \((p = 0.033)\). Serum c-OC was significantly lower in CF\(_{\text{no}}\) \((p = 0.001)\) and CF\(_{\text{low}}\) patients \((p = 0.011)\) than in controls, whereas c-OC was significantly higher in CF\(_{\text{high}}\) patients than in CF\(_{\text{no}}\) \((p = 0.005)\) and CF\(_{\text{low}}\) patients \((p = 0.010)\).

There was no significant difference in serum BAP and urinary DPD between the four groups. Serum NTX was significantly lower in CF\(_{\text{no}}\) \((p = 0.017)\) and CF\(_{\text{low}}\) patients \((p = 0.020)\) than in controls. Serum PIVKA-II concentrations were significantly higher in CF\(_{\text{no}}\) \((p = 0.012)\) and CF\(_{\text{low}}\) patients \((p = 0.022)\) than in controls (see fig 2).

**DISCUSSION**

High u-OC, low c-OC and raised PIVKA-II concentrations in all but CF\(_{\text{high}}\) patients suggest a vitamin K dependent carboxylation defect in CF patients. In our study only CF\(_{\text{high}}\) patients showed normal PIVKA-II concentrations suggesting that all other groups were vitamin K deficient to some degree. Hence only patients receiving a high dose \((\geq 1 \text{ mg/day})\) of vitamin K had an adequate vitamin K status.

Several studies showed that vitamin K supplementation induced a decrease of serum u-OC and may alter other bone markers such as NTX and BAP.\(^4\) Our data showed a similar tendency, with the most prominent changes in the vitamin K status than PIVKA-II concentrations.\(^1\) High serum u-OC, low c-OC and raised PIVKA-II concentrations in cystic fibrosis (CF) patients compared to controls was evaluated. Results suggest that a increased vitamin K intake may have significant health benefits for children with CF.
K-dependent osteocalcin. Whether the improved vitamin K status in CF high patients is associated with improved bone health still remains unclear. If vitamin K supplementation resulted in increased bone formation, both bone formation markers t-OC and BAP would be expected to be high in the CF high group, whereas this was only found to be the case for t-OC. Similarly, low bone resorption could be regarded as a beneficial effect. Again, our data are inconsistent, because NTX was significantly lower in the CF high group, whereas DPD was not. In conclusion, our results suggest that a high dose (>1 mg/day) vitamin K supplementation is needed to improve the vitamin K status of children with CF and to prevent potential vitamin K deficiency related complications. Long term (more than one year) randomised follow up studies are required to clarify the relation between vitamin K status and bone health in CF. This aspect will be of increasing importance as CF patients grow older and have a higher frequency of pathological fractures.\textsuperscript{2,4}

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