VITAMIN K STATUS IN CYSTIC FIBROSIS PATIENTS

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Abstract. Vitamin K belongs to the family of fat-soluble vitamins and plays an important role in hemostasis, bone metabolism and may affect cerebral sphingolipid synthesis. It is a cofactor necessary for posttranslational γ-carboxylation of glutamyl residues in selected proteins such as the osteocalcin, and procoagulation factors II, VII, IX, X. Vitamin K deficient individuals appear to have more undercarboxylated proteins, which are functionally defective. The vitamin K deficiency has been frequently documented in patients with cystic fibrosis. The main possible causes of this deficiency include: fat malabsorption due to pancreatic exocrine insufficiency, cholestatic or noncholestatic liver disease, reduced production of vitamin K by colonic flora related to chronic antibiotic treatments, bowel resections and increased mucous accumulation in the bowel. CF patients are more prone to osteopenia, caused by chronic vitamin K shortage, than to coagulopathy. Despite available evidence, which strongly suggests that all CF patients are at risk for developing vitamin K deficiency, its supplementation doses have not been established. Recent recommendations from Europe and the UK have suggested varied doses ranging from 0.3 mg/day to 10 mg/week. Further studies, both cross sectional and longitudinal interventional, are still required to determine routine and therapeutic supplementation doses.

Key words: cystic fibrosis, vitamin K, osteocalcin, undercarboxylated prothrombin, PIVKA-II

Vitamin K belongs to the family of fat-soluble vitamins [Rashid et al. 1999]. The term vitamin K is used as a group name for a number of structurally related compounds including phylloquinone (vitamin K_1) and menaquinones (vitamin K_2) [Schurgers et al. 2007]. The former is the major form found in plants whereas the latter is synthesized by intestinal bacteria [Weber 2001]. A synthetic form of vitamin K is menadione (vitamin K_3) [Durie 1994]. Vitamin K plays an important role in hemostasis, bone metabolism and may affect cerebral sphingolipid synthesis [Mager et al. 2006]. It is a cofactor necessary for posttranslational γ-carboxylation of glutamyl residues in selected proteins [Kalkwarf et al. 2004]. Vitamin K deficient individuals appear to have more undercar-

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boxylated proteins, which are functionally defective [Wilson et al. 2001]. The common risk factors for vitamin K deficiency include inadequate dietery intake, malabsorption syndromes, liver disease, antibiotic therapy and renal insufficiency [Shearer 2009]. Another clinical entity where vitamin K deficiency is frequently observed in cystic fibrosis (CF) individuals [Rashid et al. 1999].

CF is the most common autosomal recessive genetic disease in the Caucasian population [Hecker and Aris 2004]. It is caused by a mutation in the *CFTR* gene (cystic fibrosis transmembrane conductance regulator). The product of this gene – CFTR protein – is a chloride ion channel found in epithelial tissues in the lungs, pancreas, gastrointestinal tract and skin. CFTR modulates the transport of salt and water across these organs epithelia. *CFTR* mutations lead to alterations in host defense in the respiratory tract and can cause an increase in chronic, progressive infections with *Pseudomonas aeruginosa*, *Staphylococcus aureus* and other pathogens, pancreatic duct obstruction and pancreatic insufficiency, biliary obstruction, cirrhosis and distal intestinal obstruction syndrome [Aris et al. 2005]. The main possible causes of vitamin K deficiency in CF patients include: fat malabsorption due to pancreatic exocrine insufficiency, cholestatic or non-cholestatic liver disease, reduced production of vitamin K by colonic flora related to chronic antibiotic treatments, bowel resections and also via increased mucous accumulation in the bowel [Drury et al. 2008, Durie 1994].

Vitamin K deficiency decreases the liver's production of vitamin K-dependent coagulation factors such as II, VII, IX, X and predisposes CF patients to easy bruising, bleeding and potentially life-threatening hemorrhage [McPhail 2010]. The deficiency can be detected by the measurement of undercarboxylated prothrombin – PIVKA-II (prothrombin inducted by vitamin K absence) [Mosler et al. 2003]. PIVKA-II has been found to be a much more sensitive index of vitamin K deficiency than the commonly measured prothrombin time, because just 50% of the normal prothrombin concentration is still sufficient to produce a normal prothrombin time [Conway 2004, Urquhart et al. 2007]. As early as 1960, Schwachman reported that vitamin K deficiency and abnormal bleeding may be an early sign of CF. In 1970, Torstenson et al. described life-threatening bleeding in three babies with undiagnosed CF. Prothrombin times ranged from 47 second to 13 minutes and was correlated with the babies vitamin K concentrations. Two years later, Walters and Koch [1972] reported on four infants aged 1 to 4 months with abnormal bleeding times which were associated with vitamin K deficiency and hypoprothrombinaemia. In 1981, Corrigan et al. described coagulopathy in 17 out of 24 adolescents and young adults with CF. Vitamin K deficiency and liver disease were suggested to be the underlying causes in 14 and 3 patients, respectively. In 2003, Verghese and Beverley reported a baby girl with coagulopathy and large haematomas at the injection sites of immunizations. All symptoms appeared to resolve after intravenous vitamin K supplementation. Coagulopathy caused by vitamin K deficiency is unusual in CF patients without liver disease who are receiving adequate pancreatic enzyme supplementation. The liver can uptake vitamin K from blood and can maintain sufficient concentrations in tissues, even if the serum vitamin K concentration is low. In contrast to this, bone metabolism is strictly dependent on normal serum vitamin K levels and hence has a higher susceptibility to vitamin K deficiency. Therefore, since CF patients are at a high risk of vitamin K deficiency and low serum vitamin K levels they are more prone to decreased bone mineral density (BMD) than to coagulopathy [Mosler et al. 2003].

Decreased BMD was first reported in CF patients in 1979 [Hahn et al. 1979, Mischler et al. 1979]. Low BMD can lead to kyphosis and may result in pathological fractures. Many of the expected clinical manifestations occur in CF patients very early [Hecker and Aris 2004]. The etiology of CF bone disease is likely to be multifactorial. Poor nutritional status, malabsorption, chronic inflammation and infections, physical inactivity, hypogonadism, glucocorticoid therapy and delayed puberty are all potential contributing factors [Fewtrell et al. 2008, Hecker and Aris 2004]. Recently, the role of suboptimal vitamin K status has been also discussed. Vitamin K is a cofactor required for the posttranslational conversion of glutamyl residues to γ-carboxyglutamyl residues in osteocalcin. Osteocalcin is producted by osteoblasts and is the major non-collagenous protein in bones. Carboxylated osteocalcin binds to hydroxyapatite in bone and in this way plays a regulatory role in bone formation, mineralization, and resorption. The binding of undercarboxylated osteocalcin to hydroxyapatite is less effective [Fewtrell et al. 2008]. The presence of the undercarboxylated form of the protein is the most sensitive marker of a vitamin K deficiency. Osteocalcin is the first protein to become undercarboxylated in vitamin K deficiency, and the last to become fully carboxylated when vitamin K becomes sufficient [Urquhart et al. 2007].

Vitamin K deficiency has been clearly documented in CF toddlers, preschool and schoolchildren as well as in aldolescents and adults [Montalembert et al. 1992, Mosler et al. 2003, Rashid et al. 1999, Wilson 2001]. However, there is no clinical evidence clearly describing vitamin K status in the youngest CF population – neonates. Despite available evidence, which strongly suggests that all CF patients are at risk for developing vitamin K deficiency [Hoorn et al. 2003], its supplementation doses have not been well established [Kalnins et al. 2007]. In a group of 18 CF aldolescent and adults patients a supplementary dose of 5 mg vitamin K_1/week improved their vitamin K status (undercarboxylated osteocalcin and PIVKA-II). However, full normalization was not achieved [Beker et al. 1997]. On the other hand, in X patients aged 7 months to 25 years Mosler et al documented that some patients receiving vitamin K supplementation (between 6 and 20 mg per week) had even supranormal vitamin K plasma concentrations. PIVKA-II levels in these individuals were normal [Mosler et al. 2003]. In a subsequent study, one year of vitamin K supplementation (10 mg vitamin K_1/week), resulted in increased levels of carboxylated osteocalcin in a group of CF schoolchildren [Nicolaidou et al. 2006]. In turn, Drury et al. [2008] investigated 14 children with similar ages receiving either 1 or 5 mg/day vitamin K_1 for one month. Such supplementation resulted in a normalization of undercarboxylated osteocalcin levels in 3 of the 14 patients. No trend towards in the dosage difference was observed. The authors finally concluded that a longer period of supplementation might be necessary in order to normalize the vitamin K status in the studied patients.

Despite available evidence, which strongly suggests that all CF patients are at risk for developing vitamin K deficiency, its supplementation doses have not been clearly established. Recent recommendations from Europe and the UK have suggested varied dose ranging from 0.3 mg/day to 10 mg/week [Cystic Fibrosis... 2002, Sinaasappel et al. 2002]. Further studies, both cross sectional and longitudial interventional, are still required to determine routine and therapeutic supplementation doses.

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ZASOBY USTROJOWE WITAMINY K U CHORYCH NA MUKOWISCYDOZĘ

Streszczenie. Witamina K należy do witamin rozpuszczalnych w tłuszczach, odgrywa ważną rolę w utrzymywaniu hemostazy i metabolizmie kości, może wpływać na proces syntezy sphingolipidów. Jest niezbędnym kofaktorem posttranslacyjnej γ-karboksylacji reszt glutaminowych wybranych białek takich, jak osteokalcyna i czynniki krzepnięcia krwi II, VII, IX, X. U osób z niedoborem witaminy K pojawia się więcej białek w formie niekarboksylowanej, które nie spełniają swojej funkcji biologicznej. Niedobór witaminy K został wielokrotnie udokumentowany u pacjentów z mukowiscydozą (CF). Do głównych przyczyn jej niedoboru należą: zaburzenia wchłaniania tłuszczów związane z niewydolnością zewnątrzwydzielniczą trzustki, cholestatyczne i niecholestatyczne choroby wątroby, zmniejszenie produkcji witaminy K przez jelitową florę bakteryjną spowodowane przewlekłą antybiotykoterapią, resekcją jelita cienkiego oraz zwiększonym nagromadzeniem śluzu w jelitach. Pacjenci z CF, ze względu na przewlekły niedobór witaminy K, są bardziej predysponowani do osteopenii, niż wystąpienia zaburzeń koagulologicznych. Pomimo dostępnych danych, sugerujących występowanie ryzyka niedoboru witaminy K u wszystkich pacjentów z CF, jej dawki suplementacyjne nie zostały jednoznacznie określone. Najnowsze zalecenia z Europy i Wielkiej Brytanii sugerują stosowanie różnych dawek, od 0,3 mg/dobę do 10 mg/tydzień. W celu określenia rutynowych i terapeutycznych zaleceń suplementacyjnych jest wskazane prowadzenie dalszych badań zarówno przekrojowych, jak i długofalowych interwencyjnych.

Słowa kluczowe: mukowiscydoza, witamina K, osteokalcyna, niekarboksylowana protrombina, PIVKA-II