Vitamin K Influence on Cardiovascular Mortality in Chronic Hemodialysed Patients

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Cardiovascular disease causes increased mortality in chronic hemodialysed patients. The decrease of vascular calcification is one of the main targets in the management of these patients. According to several experimental and clinical trials, choosing the proper diet and prescribing vitamin K2 supplements help to improve prognosis and decrease mortality, but further larger researchers are required to advocate the importance of this dietary intervention in hemodialysed population.

Keywords: vitamin K, matrix Gla protein, osteocalcin, vascular calcification

There is an increasing risk of cardiovascular death in chronic hemodialysed patients [1-3]. Mineral and bone disorders, often emphasized in patients with chronic kidney disease, have an early onset inducing cardiovascular changes; vascular calcification is one of the major risk factors that leads to increased mortality in this group of population [4-15]. To help decrease the risk of death in chronic hemodialysed individuals, prompt clinician intervention is required on risk factors that undergo cardiovascular damage [5,7-16]. Besides the usual drug treatment, nutritional intervention plays a crucial role in the prevention of the mineral-bone disorders in chronic kidney disease [5-16]. A diet with low phosphorus and carefully adjusted potassium intake is already proved to have favorable effects on chronic kidney disease progression and on mineral-bone abnormalities prevention [6-19]. Several recent literature researches have shown the potential role of dietary vitamin K deficiency and vitamin K-dependent proteins – matrix Gla protein and osteocalcin – in the pathogenesis of vascular calcification in chronic kidney disease [8-15,20].

Vitamin K supplementation in hemodialysed patients

Recent trials support the beneficial role of food vitamins in reducing the cardiovascular risk in hemodialysed patients [8-22]. Vitamin K is mentioned among the vitamins that have a role in improving cardiovascular risk by reducing calcification in chronic hemodialysed patients [1,8-15,20,23]. In 1930, *Henrik Dam* described for the first time the existence of vitamin K, and subsequent studies confirmed its role in blood coagulation (clotting) [24,25]. Vitamin K belongs to the class of fat soluble vitamins (absorbtion requires the presence of fat), naturally presenting in the following forms: vitamin K1 (phylloquinone) and different types of vitamin K2 (menaquinone) [1,8-15,25,26]. The primary structure represented by methylated naphthoquinone is specific to all the class members, differentiation being made through the aliphatic chains linked to the nucleus in different positions [25]. Vitamin K ($C_{11}H_7O_2$-R), vitamin K1 ($C_{31}H_{46}O_2$), and vitamin K2 with radicals $C_{30}H_{49}$, $C_{35}H_{57}$, $C_{45}H_{73}$ are represented in the following figures (figs.1, 2 and 3) [25,27].

The natural sources of vitamin K1 and vitamin K2 differ. Vitamin K1 synthesis occurs in plants, while vitamin K2 synthesis takes place in the human body, in the presence

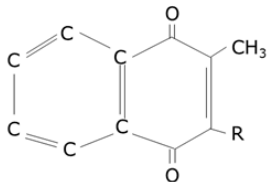

Fig. 1. Vitamin K

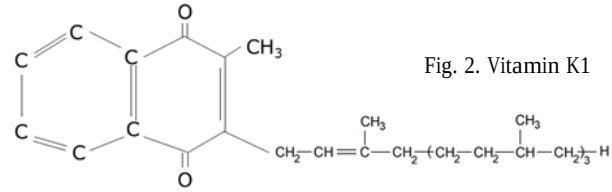

Fig. 2. Vitamin K1

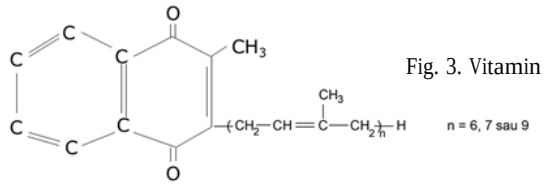

Fig. 3. Vitamin K2

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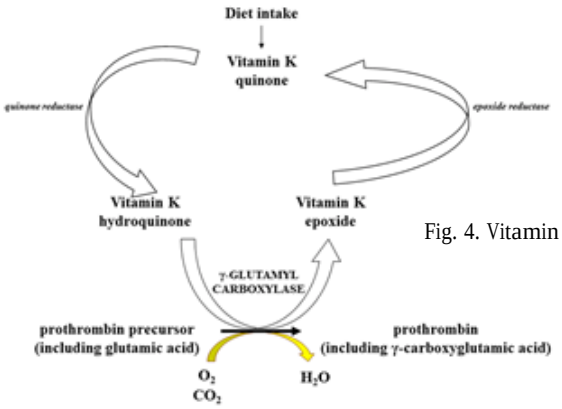

Fig. 4. Vitamin K cycle

of bacterial flora [24]. Vitamin K is useful in the glutamate (Glu) carboxylation process, present in the constitution of various proteins, resulting in gamma-carboxylglutamate (Gla) (fig. 4) [8-15,28-30].

There are various proteins which contain Gla, among which prothrombin, coagulation factors VII, IX and X, protein C, protein S, osteocalcin, matrix Gla protein *etc* [8-15,25,28].

In chronic kidney disease patients, matrix Gla protein and osteocalcin (vitamin K dependent proteins) are important in the process of vascular calcification, being recognized as some of the most potent inhibitors of vascular calcification [8-15,20,31,32]. Matrix Gla protein is present in the vascular endothelium, being produced by the smooth muscle cells [8-15,20,31,32]. It is activated in the presence of vitamin K [8-15,20,31,32]. Gla proteins are preferentially carboxylated and in patients with vitamin K deficiency extrahepatic located Gla proteins (*e.g.*: matrix Gla protein, osteocalcin) are found in carboxylated form in a lower percentage compared to those hepatic located (*e.g.*: prothrombin, coagulation factors VII, IX and X) [8-15,20,32,33]. The quantification of the level of uncarboxylated Gla proteins (especially the extrahepatic ones) helps for detecting the patients with vitamin K deficiency [1,8-15,20,32,33]. Furthermore, the increased level of uncarboxylated Gla proteins is associated with important arterial calcification and subsequently with an increased risk of cardiovascular mortality [1,8-15,20,32,33]. Osteocalcin is found in bones, being produced by osteoblasts, and it is used as a marker for bone formation [8-15,20,34,35]. The level of uncarboxylated osteocalcin is also useful in detecting patients with vitamin K deficiency [8-15,20,34,35].

In addition, there are some studies highlighting that initially increased undercarboxylated matrix Gla proteins levels decreases in advanced chronic renal failure and it does not further elevate as it would expected; therefore, reasonable doubts arouse regarding the utility of using the undercarboxylated matrix Gla protein as a marker for vitamin K deficiency [8-15,20,36]. Several explanations of this phenomena have been developed. One is that the undercarboxylated matrix Gla protein is accumulated in the calcified areas [8-15,30], but the most probable explanation is that matrix Gla protein, in contrast with osteocalcin, undergoes also concomitant vitamin K-dependent ã-glutamate carboxylation and serine phosphorylation [8-15,37]. Therefore, undercarboxylated matrix Gla protein exists under two forms: phosphorylated and nonphosphorylated, and only the nonphosphorylated fraction, which is approximately 1000 times lower than total undercarboxylated matrix Gla protein [8-15,30], is an adequate marker for vitamin K deficiency [8-15,20,36].

Gamma-carboxylated matrix protein inhibits vascular calcification by combining with insoluble salts of calcium, thus preventing vascular hydroxyapatite crystal growth [1,8-15,38,39]. Additionally, it inhibits the action of the BMP (bone morphogenetic protein) at vascular level [8-15,20,38,39]. In patients with chronic kidney disease and mineral-bone disorders, BMP promotes the phenotypic transformation of endothelial smooth muscle cells into osteoblast-like cells, and, consequently, by inhibiting it, vascular calcification is prevented [8-15,20,38,40,41].

For the carboxylation of proteins involved in vascular calcification, vitamin K serum level is an important factor. Among the types of vitamin K, vitamin K2 has the most important role in the gamma carboxylation [8-15,20,31]. Food that provide vitamin K2 are fermented food, fermented cheese, meat, meat offal, egg yolks *etc* [8-15,40,42]. In chronic hemodialysed patients, who require a diet with low phosphorus amount, vitamin K2 intake and serum levels are reduced [8-15,20,38,43]; no removal by dialysis procedure is present because vitamin K is lipophilic [26]. Although vitamin K2 may derive from vitamin K1 in the so-called vitamin K cycle [8-15,38,43], it is proved that in chronic kidney disease and end-stage renal disease, vitamin K recycling is impaired and may be restored by increased doses of vitamin K1 [8-15,20]. Supplementation with high doses of vitamin K1 is regarded with circumspection, because it is also decreases the osteocalcin; undercarboxylated osteocalcin has been associated, in experimental studies, with positive effects on glucose metabolism [8-15,34] and on regulation of male fertility [8-15,44]. Therefore, to avoid vitamin K deficiency it is important that these patients follow a low phosphorus diet, but with vitamin K2 intake [8-15,20,43]. In this category there are: goat cheese, camembert, butter cream *etc* [8-15,43]. Given the important role of vitamin K2 in reducing vascular calcification, many recent studies recommend supplements of vitamin K2 in chronic hemodialysed patients, but the optimal doses of vitamin K supplementation in hemodialysed population are not yet well established [26,43,45-48]. Following the administration of these supplements, it was noticed that the level of Gla uncarboxylated protein (inactive) was reduced and the prognostic improved in these individuals by decreasing cardiovascular death risk [1,8-15,20,43,45,46,49]. Favorable effects of vitamin K2 supplementation have been noted on bone remodeling too, including adynamic bone disease in hemodialysed patients [8-15, 20, 50].

Conclusions

Although the available data regarding the importance of vitamin K supplementation in reducing vascular calcification development in hemodialysed population are promising, further larger clinical trials are needed in order to establish the required doses for the best adequate effect.

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