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Hot topic in geriatric medicine

Vitamin K and bone metabolism in the elderly with normal and reduced kidney function

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ABSTRACT

Vitamin K plays a key role in the synthesis of several blood coagulation factors, but it is also involved in bone metabolism and vascular calcification. There are two forms of vitamin K: K1 and K2, which may behave differently. Oral anticoagulation with warfarin inhibits the vitamin K system. Although warfarin reduces ischemic stroke, there are concerns on hemorrhagic complications and, due to the impaired activity of other vitamin K-dependent proteins such as osteocalcin (or BGP, bone Gla protein) and MGP (matrix Gla protein), on an increased burden of bone fractures and vascular calcifications. These in turn may be significant determinants of morbidity and mortality. The geriatric population, who is often affected by bone disorders frequently related to aging itself, could benefit from a supplementation of vitamin K, but further studies are necessary to prove actual benefits, both in CKD patients and in the general population. In patients at risk of vascular calcifications and fractures, in particular elderly patients affected by CKD, the possible beneficial role of vitamin K supplementation, as well as more a selected administration of vitamin K inhibitors for anticoagulation should be considered.

1. Introduction

Since its discovery in the 1930s, vitamin K was found to play a key role in the synthesis of several blood coagulation factors. However, it was subsequently recognized to be also involved in bone metabolism and vascular calcifications [1].

Bone disorders affecting elderly patients are very common. Osteoporosis, in particular, is characterized by reduced bone mineral density (BMD) and increased risk of fractures. Wedge, biconcave or crush fractures, depending on whether the reduction affects the anterior, central or posterior dimension of the vertebra, can be diagnosed [2,3]. The association between vertebral fracture and vascular calcification is common in postmenopausal females and in patients affected by chronic kidney disease (CKD), with increased morbidity [4,5]. Fig. 1 illustrates an example of a patient affected by vertebral fractures and vascular calcifications.

In CKD patients the risk of bone disease is increased; in fact, the majority of patients with CKD from stage 3 to stage 5 is affected by "chronic kidney disease - mineral bone disorder" (CKD-MBD), a syndrome characterised by specific biochemical abnormalities, renal bone disorders with either high (secondary to hyperparathyroidism) or low (adynamic) bone turnover, and vascular calcifications [6].

Dietary intake of vitamin K is often insufficient. Moreover, some elderly patients are treated with anticoagulation therapy, which inhibits the recycling of vitamin K and consequently reduces its activity (Fig. 2). Low vitamin K intake is associated with bone disorders in the elderly population [7], and vitamin K deficiency has been linked to vascular calcifications [8]. This article summarises how vitamin K may have an important role in bone metabolism in the elderly with normal and reduced kidney function.

2. Physiology of vitamin K

Vitamin K exists in two main natural forms: K1 (or phylloquinone) and K2 (or menaquinones, MKs). Vitamin K1 is found in green and leafy vegetables such as spinach, broccoli, lettuce, kale, and cabbage; vitamin K2 is contained mainly in cheese and fermented foods, such as natto (fermented soybean, common in Japan), or produced by the intestinal microflora through bacterial fermentation. The MKs are classified according to the length of their unsaturated side chains into 15 different types denominated as MK-n, when "n" defines the number of isoprenyl residues in the side chain. The most common MKs in humans are the short-chain MK-4, which is principally produced by systemic conversion of K1 to K2, and the long-chain vitamers, MK-7 through MK-10, which are exclusively synthesized by bacteria in humans [9]. Finally, vitamin K3 (menadione), is a synthetic form of vitamin K, which

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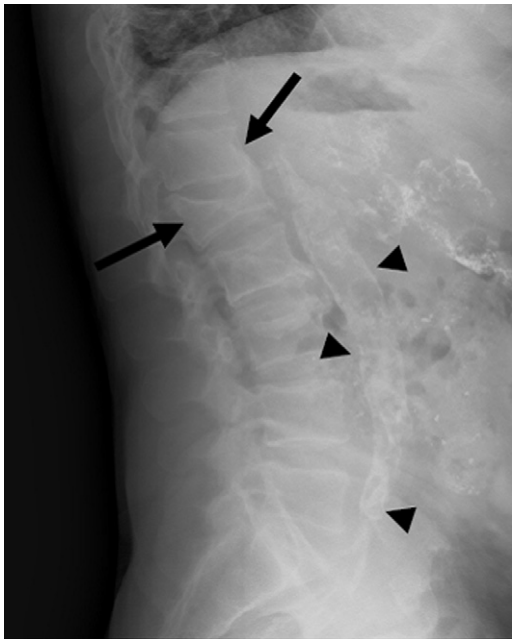

Fig. 1. Assessment of vascular calcifications and prevalent vertebral fractures with quantitative vertebral morphometry in a 54-year-old man in hemodialysis treatment for 44 months. Two vertebral fractures are present (arrows), affecting L1 (biconcave type, severe, with central height reduction of 46%) and T12 (wedge type, moderate, with anterior height reduction of 29%). In addition, aortic and iliac arteries calcifications are clearly visible (arrowheads). The patient had hyperphosphatemia and hypercalcemia with low PTH, which can be observed in cases of reduced bone turnover defining the condition of adynamic bone disease.

shares the same naphthoquinone ring with K1 and K2, but lacks a side chain.

Absorption of vitamin K takes place in the jejunum and ileum in the form of mixed micelle complexes with bile salts [10]. The predominant dietary form of vitamin K in the Western Countries is vitamin K1, while the major form in Japan is vitamin K2, especially MK-7, which is the main component of "natto".

The daily intake of vitamin K in a western diet ranges from 60 to 200 μg, about 90% of it being vitamin K1. However, only 10% of K1 is absorbed from food because of the tight binding to the chloroplast membranes in green vegetables. There are no exact data on the amount of vitamin K2 intake, but it is estimated about 10% of total vitamin K intake.

Vitamin K affects the coagulation system by regulating the introduction of a carboxyl group into the glutamic acid residue in four of the blood coagulation factors (II, VII, IX, X) to yield γ-glutamic carboxyl (Gla) residues [11]. In addition, extra-hepatic vitamin K-dependent proteins are osteocalcin (bone Gla protein; BGP) and matrix Gla protein (MGP) [12]. These proteins are known to be involved in bone mineralization and inhibition of vascular calcifications, respectively. In case of vitamin K deficiency, these proteins are sub-optimally carboxylated and they are not able to bind calcium, so that the process of vascular calcification is enhanced. The amount of under-carboxylated osteocalcin (ucOC) is considered a sensitive marker of vitamin K status in humans [13].

There is no precise recommendation for daily intake of vitamin K. COMA (the UK Department of Health's Committee on Medical Aspects of Food Policy) has suggested that a daily intake of 1 μg/kg body weight is probably adequate for blood clotting, but may be suboptimal for bone health [14].

Deficiency of vitamin K occurs when dietary intake is insufficient or when intestinal bacterial production of vitamin K2 is disrupted by prolonged treatment with antibiotics. Vitamin K deficiency may also occur in patients with fat malabsorption (Table 1). There is also evidence suggesting that oestrogen levels in women may influence vitamin K status [15]. Even if vitamin K is contraindicated in patients on anticoagulant therapy for its pro-coagulant effect, it has been observed that the stability of anticoagulation was not significantly affected by vitamin K supplements at doses below 100 μg/d [16].

3. Vitamin K and bone metabolism

Bone disorders frequently affect elderly men and women, the most common being osteoporosis.

Although it is accepted that vitamin K is an important cofactor for the post-translational activation of proteins involved in bone

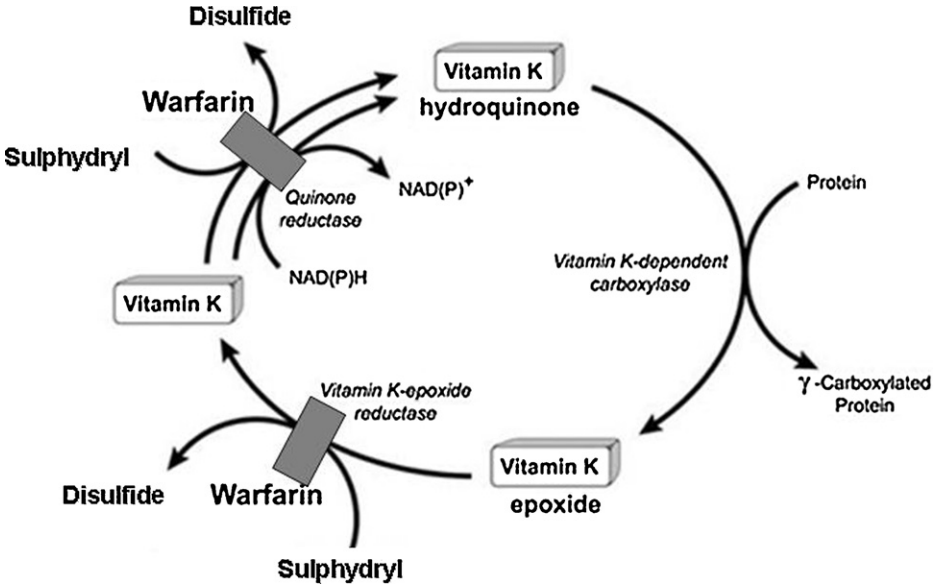

Fig. 2. Warfarin and the vitamin K cycle. Warfarin inhibits two key enzymes of the vitamin K system, quinone reductase and vitamin K-epoxide reductase, thus blocking the vitamin recycling and inactivating vitamin K-dependent proteins.
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