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Mini Review

Vitamin K2 Deficiency: Is It Real?

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Abstract

In this mini-review the role of vitamin K2 in normal health and research into the effects of supposed vitamin K2 'deficiency' in osteoporosis and vascular calcification are discussed. Vitamin K2 deficiency has no clinical substrate or reliable prevalence and incidence figures and seems largely a created disease leading to a new hype in the OTC vitamin business with a global market value of U.S. $33 billion. Serious research suggests a minor role for vitamin K2 in osteoporosis and vascular calcification.

INTRODUCTION

Vitamin K deficiency is actually rare in the absence of the use of vitamin K antagonists as e.g anticoagulants in adults, severe liver disease, malabsorption etc., but is very common in newborn infants (vitamin K deficiency bleeding, VDKB), who get standard a vitamin K injection at birth.[1]

Vitamin K is a fat-soluble vitamin that exists in two forms of vitamin K1 (phylloquinone), mainly found in green leafy vegetables, and vitamin K2 (menaquinone), mainly found in fermented dairy and produced by Lactobacillus bacteria in the intestine.[1] Vitamin K1 is transported to the liver, while vitamin K2 is transported to extra hepatic tissues, such as bone and the vascular wall, regulating the activity of matrix Gla protein (MGP) and osteocalcin bone Gla protein.[2]

As vitamin K2 deficiency or insufficiency is assayed indirectly by measuring undercarboxylated matrix Gla-protein (ucMGP) no reliable prevalence and incidence figures are available. Only one study reported a prevalence of 97% in a research setting.[3,4] So, is vitamin K2 deficiency the new hype? What to do with a 'disease' of which no one knows symptoms and prevalence? Is it real? Nevertheless, there is a flourishing market in vitamin K2 OTC supplements and serious research investigating the role of vitamin K2 in osteoporosis, cardiovascular disease, diabetes, arthritis, renal calculi and warfarin therapy.[5] So, vitamin K2 deficiency is like a rolling stone. In this mini-review the role of vitamin K2 in normal health and research into the effects of vitamin K2 'deficiency' is discussed for osteoporosis and vascular calcification. The other subjects are beyond the scope of this mini-review and level of evidence.[5]

Vitamin K2 in Normal Health

Vitamin K2 (menaquinone) compounds share a naphtoquinone ring and a side chain with variable length. The chemical formulation of vitamin K2 is MK-n (MK-2 to MK-14) where 'n' is the number of remaining chains of isoprenoid. Most of these isoprene residues are unsaturated, but some forms of menaquinones which are produced by bacteria have saturated prenyl units.[6]

Menaquinones, except for MK-4 are synthesized by bacteria. Anaerobic bacteria in the colon synthesize MK-10- to MK-13.Present in fish, liver, milk, vegetables and eggs, MK-4 is the dominant form of vitamin K in the body, primarily produced from menadione (vitamin K3), and directly synthesized from the dietary phylloquinone.[7,8]

Absorbed in small quantities by the small intestine vitamin K is delivered to the liver and other tissues via the lymphatic system. In humans, MK-4 to MK-10 vitamins are absorbed in greater amounts and show a higher biological activity than vitamin K1.Mainly stored in the liver, vitamin K is found in small quantities in the body. The liver stores Vitamin K1-and long-chain forms of vitamin K2. Brain, pancreas and genital organs store MK-4.[9] The liver is the last organ to be affected in cases of deficiency or insufficiency.[10]

Required daily vitamin K2 intake is estimated at 120 ug/daily based on measurements of improving osteocalcin-gamma-carboxylation in clinical studies.[11] Large scale worldwide population studies to define vitamin K2 deficiency or insufficiency are not available as vitamin K2 cannot be measured directly.[1,4,6,12] As mentioned before prevalence and incidence rates of vitamin K2 deficiency are not known, therefore. Vitamin K2 insufficiency is even worse defined and is mainly a popular term in the commercial vitamin supplements market.

There are multiple biomarkers indicative of vitamin K status, but no single biomarker is the 'gold standard'.[13] Circulating phylloquinone is a global indicator of vitamin K status and can be measured as plasma phylloquinone. Plasma phylloquinone has been evaluated in re-

lation to inflammation In the Framingham Offspring Study. Higher plasma phylloquinone levels were associated with a lower inflammatory burden. Higher serum phylloquinone was also associated with lower inflammation in the Multi-Ethnic Study of Atherosclerosis (MESA; n=662).[14,15] Measurement of uncarboxylated osteocalcin is another indirect vitamin K status indicator, as discussed above.

Symptoms and Diagnosis

Deficiency of vitamin K2 has been linked with vascular calcification and osteoporosis.[16] However, it is not surprising vitamin K2 deficiency is not manifested by clinical symptoms. So there is also no clinical diagnosis in the classic way as e.g., in vitamin C deficiency (scurvy). It seems therefore vitamin K2 deficiency is largely a created disease and not even a disease in a blood tube'. Of course there is no objection to study vitamin K2 metabolism in relation to diseases. Some of these studies are discussed below.

Vitamin K2 and Osteoporosis

Vitamin K affects the proliferation and differentiation of osteoblasts. It prevents the induction of apoptosis and improves osteoblast function.[17,18] Vitamin K2 performs it osteoprotective function by the gamma-carboxylation pathway and up regulating bone marker genes.[19-23]

Vitamin K2 supports bone formation and suppresses bone resorption by stimulating the expression of cytokines such as osteoprotogerin (OPG) and inhibiting the expression of receptor activator of nuclear kappa B ligand (RANKL) on osteoblasts and osteoclasts and improves by this way osteoblast differentiation.[18,24]

Vitamin K2 has been reported to inhibit bone resorption in animal models via several mechanisms.[25-29] It prevents osteoclast formation either directly or indirectly. It could interfere with the expression of RANKL and up regulate the expression of OPG on osteoclast precursors. In addition, vitamin K decreases both proliferation and tartrate-resistant acid positive (TRAP) cells and TRAP activity in osteogenic culture mediums. Moreover, vitamin K2 inhibits bone resorption, induced by bone resorbing factors such as PGE2, IL-1-alpha and 1.25 (OH2 D3 in a dose dependent manner. So vitamin K2 reduces osteoclastic activity via different strategies and has an anabolic effect on bone. Vitamin K2 (MK-7) from fermented soybeans has an anabolic effect on bone calcification.

A systematic review regarding level of evidence has shown vitamin K2 to prevent fractures in vertebra by 66%, hip fractures (77%) and non-vertebral fractures by 81% in Japanese patients.[30] This is nearly equivalent to conventional bisphosphonate treatment. A bone-density study (n=241) showed that patients treated with vitamin K2 (45ug/daily) along with calcium maintained lumbar bone density compared to a 2,5% loss on placebo and had 65% fewer fractures.[31] In clinical studies, vitamin K2 maintains lumbar bone mineral density (BMD), reduces age-related osteoporotic fractures and reduced corticosteroid induced (CIOP) vertebral fractures.[32] Supplementing vitamin K2 at 180 ug/daily reduced the age-related decline in BMD of the lumbar spine and femoral neck, but not the total hip. Vitamin K2 (MK-7) also prevented the loss in vertebral height in the lower thoracic spine.[33]

In contrast, supplementation of vitamin K1 (500 ug/daily) for 3-years did not improve BMD in the treatment group.[34] Another vitamin K1 supplementation study for 2-years showed no significant BMD changes compared to placebo but noted a 60% reduction of fractures in the treatment group, suggesting improved bone quality.[35] It seems vitamin D, calcium and vitamin K2 supplementation reduces under carboxylated osteocalcin (ucMGP) and improves lumbar BMD.[36]

Vitamin K2 and Vascular Calcification

Menaquinone (vitamin K2) seems to be involved also in vascular calcification.[37-41] In the ongoing Danish Cardiovascular Screening (DANCAVAS) trial patients on vitamin K antagonists had an increased aortic valve calcification score.[42] Considerations of vitamin K supplementation with anticoagulants should include dose and type of vitamin K used.[42] The evidence that coumadin may increase fractures, arterial calcification and mortality is still in debate.[43,44] Nevertheless, the global vitamin K market value is estimated at U.S $33 billion in 2018 with an expected yearly growth rate of 4,3%.[45]

CONCLUSION

It is obvious there is no clinical substrate for supposed "vitamin K2 deficiency" manifested by clinical signs and symptoms in contrast to e.g vitamin C deficiency. When using a normal diet, vitamin K2 deficiency is not real. It is largely a created disease and not even 'a disease in a blood tube' Reliable prevalence and incidence figures are not known. Serious research suggests a minor role for vitamin K2 in osteoporosis and vascular calcification. With a global market value of U.S. $33 billion the only one who benefits of vitamin K2 'deficiency or insufficiency' is the OTC vitamin business.

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