

Important Facts About Various Forms of Vitamin K & Studies Review

Addendum to tech sheet "Tri-K The Synergy of Three Forms of Vitamin K" by Cristiana Paul, MS

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Vitamin K occurs in nature in two basic forms K1 and K2, which are similar in the fact that they contain the same core molecule called naphthoquinone. K1 contains an additional phytail tail. K2 occurs in a variety of forms called menaquinones that contain additional unsaturated side-chains of isoprenoid units varying in length from 1 to 14 repeats, named correspondingly K2 (MK-1) to K2 (MK-14).

More than 90% of the Vitamin K2 occurring in animal and human tissue is the K2 (MK-4) form [40]. Currently there are only two commercially available forms of K2: K2(MK-4) (menaquinone-4 or menatrenone) and K2(MK-7) (or menaquinone-7), and they are both incorporated in Tri-K.

Vitamin K1 (Phylloquinone or Phytoanadione)

Vitamin K1 occurs in vegetables including algae and vegetable oils and seeds. For example, 1000mcg of vitamin K1 could be provided by either of the following: about 1 cup cooked kale/collards/spinach or 2 cups of beets or 4 cups of cooked broccoli/Brussels sprouts or 4 cups raw onions or 6-7 cups of raw spinach or 6-7 cups cooked cabbage/asparagus or 8 cups iceberg lettuce or 13 cup raw broccoli or 20 cups of raw cabbage or 20 cucumbers. Absorption of vitamin K1 from a nutritional supplement taken with fat was found to be 3- 6 times better than that from foods (raw or cooked), probably because the food matrix impairs the release of naturally occurring K1. One study showed that 1-2mg of vitamin K1 was shown to be the optimal dose for the maximal activation of the bone building protein osteocalcin [24]. Another study showed that older patients may have an increased need for vitamin K1 in order to get similar optimal activation (carboxylation) of their osteocalcin [8, 25]. Also, genetic polymorphisms of K1 activation may require a higher vitamin K intake [75].

Foods with high vitamin K1 content	weight in grams	measure	mcg of K1
Kale, cooked drained	130	1 cup	1062
Collards, cooked drained	170	1 cup	1059
Spinach, cooked drained	180	1 cup	889
Beets, cooked drained	144	1 cup	697
Broccoli, cooked drained	156	1 cup	220
Brussels, cooked drained	156	1 cup	219
Onions, raw	100	1 cup	207
Parsley, raw	10	10 sprigs	164
Cabbage, cooked drained	150	1 cup	163
Spinach, raw	30	1 cup	145
Asparagus, cooked drained	180	1 cup	144
Lettuce, iceberg	129	1 head	129
Broccoli, raw	88	1 cup	89
Cabbage, raw	70	2 cups	53
Cucumber, raw	301	1 large	49

Another way of estimating the modern vitamin K1 requirements might take into consideration typical K1 intake from a Paleolithic diet. This has not been evaluated yet in studies but it is plausible to have been around 1mg of K1 or higher because the Paleolithic diet was abundant in plant derived foods.

Vitamin K2 (menaquinone)

Vitamin K2 (menaquinone) is the predominant form of vitamin K found in human and animal tissues. The K2 found in the human body can be derived from various sources [11]:

- 1) Occurs in the liver and other tissues throughout the body from the conversion of K1 (from diet and/or supplements) to K2 in the form of K2(MK-4)
- 2) Absorbed from animal foods like liver (0.5-5 mcg/100g), yolk (10mcg/one egg yolk) or meats (2-3mcg/100g)
- 3) Absorbed from fermented foods (animal/vegetarian) rich in K2 (MK-4 to MK-12) produced by bacteria in foods like: cheese, natto (soybean and rice, mostly K2(MK-7), Kimchi or sauerkraut (pickled cabbage), etc.
- 4) Produced by the human intestinal tract bacteria, mostly as K2 (MK-4). These bacteria were identified as *Bacteroides Fragilis* and a friendly *E. Coli* strain. Certain strains of lactobacilli were also found to produce it as well, although these are not the commonly known lactobacillus probiotics. [12].

Antibiotic therapy or the antibiotics found in the animal food supply may diminish the vitamin K producing bacteria in the human gut. Also, poor conversion of K1 to K2 in some patients due to age or various metabolic challenges [23] may make supplementation with K2 very beneficial.

Vitamin K2 in the MK-4 form, K2(MK-4)

Vitamin K2 in the MK-4 form, K2(MK-4) was used in many Japanese studies in doses of 15mg-45mg/day with success for the treatment of osteoporosis. Increases in BMD (Bone Density Markers) were as high as 1.1%, 5.2% and 7.5% after 6, 12, 24 months, respectively, using a dose of 45mg/day of K2(MK-4). Other studies have shown a reduction in the rate of bone loss in post-menopausal women or bone fracture risk was reduced even when the BMD did not show an impressive change [3]. K2(MK-4) is used in Japan as a pharmaceutical because the dose of 15-45mg is well above that which can be derived naturally. No side-effects have been observed so far in studies using high dose K2(MK-4) [3] for the last 10 years. **DFH Tri-K was designed to include only 1mg of K2-MK-4 per dose, which is in physiological range, because its purpose is primarily to correct nutritional deficiencies with high safety margin.**

The practitioner has the liberty to review the available studies [3] and use DFH Tri-K at higher dosages based on the individual clinical need, while monitoring the patient closely. To put the vitamin K2 dose in perspective, keep in mind that while it is possible to derive 1-2mg of vitamin K1 from a Paleolithic diet, we can also consider that K1 converts to a similar amount (or less) of vitamin K2 (MK-4) in the body. 1mg of K2 (MK-4) may be a reasonable physiological daily dose that humans may have obtained in Paleolithic conditions coming from two sources: one is K2 converted from dietary K1 and the other is K2 from animal foods and bacteria in the intestinal tract. One study showed that in modern humans the GI bacteria can provide, at times about 50 % of the total Vitamin K in the body [12], but this varies based on dietary vitamin K intake.

Vitamin K2 in the MK-7 form, K2(MK-7) or menaquinone-7

K2 (MK-7) is a product of bacterial food fermentation found in foods such as cheeses, cabbage, fermented soy or natto, but it is most economically derived from natto (a traditional soy and rice fermented mixture).

The supplemental form of K2(MK-7) is purified and free of soy allergens by removing the soy protein. The range of vitamin K intake in Japanese women consuming a diet rich in soy and natto was found to be 35-247mcg [39] out of which K2(MK-7) is typically contributing 50-100mcg [39]. K2(MK-7) is thought to convert in the body to K2(MK-4) very slowly [18], which is an advantage because it provides a continuous plasma reservoir of vitamin K2 between supplementation times. This is the main reason K2 (MK-7) was added in the Tri-K formula, as it complements the metabolism of K1 and K2 (MK-4).

How does vitamin K perform its various functions?

The vitamin K function of supporting blood clotting is well known. However Vitamin K is essential in activating a large number of vitamin K-dependent proteins (VKD) throughout the body, by carboxylating certain glutamate residues and changing them to gamma-carboxyglutamate residues, abbreviated Gla. Gla has the property of binding calcium, and so as soon as VKD proteins get their glutamate residues carboxylated by vitamin K, they become able to bind calcium as well.

The more vitamin K is available in the body, the better the chance that all the VKDs needing gamma-carboxylation will end up with a maximum amount of Gla residues in them, or close to a 100% carboxylation. The activity of these proteins is proportional to how many of their glutamate residues are carboxylated. Until now, vitamin K adequate intake has been defined as the amount needed to completely carboxylate thrombin (a clotting protein) but with the discovery new roles for various VKDs throughout the body, many researchers propose that vitamin K status be considered adequate only when all VKDs are maximally carboxylated.

The following vitamin K dependent proteins are currently known:

- blood coagulation factors: factors II (prothrombin), VII, IX, and X, the anticoagulant proteins C, S and Z [92].
- osteocalcin is a protein produced by osteoblasts (bone building cells) and fixates calcium in the mineral structure of bone [10, 22, 103] and tooth dentin [59].
- Matrix Gla Protein or MGP is found mostly in the arterial walls/veins and cartilage (associated with chondrocytes) but also associated with cells of other soft tissues: brain, kidney, lung, skin, testes, sperm, salivary glands. One identified role of MGP is to reject calcium deposition in these tissues.
- Activated vitamin D, 1,25(OH)D₃ stimulates the synthesis of osteocalcin and MGP [63].
- Vitamin A (retinoic acid) stimulates the synthesis of osteocalcin but inhibits that of MGP [60,64]. **Vitamin K works in synergy with vitamin D and vitamin A, and in order for vitamin K to perform its functions efficiently, vitamin D and vitamin A statuses have to be optimized as well** [60].
- Gas-6 protein (Growth Arrest Specific) is believed to regulate cell growth and apoptosis, and was shown to support the survival of cells in various tissues such as arterial muscle, epithelial eye lens, brain and possibly others.
- GST (Galactocerebroside Sulfotransferase) enzyme is involved in sulfatide synthesis, which is an important component of myelin. This is important for the health of nerves and the brain and may be helpful to maximize this process for patients suffering from in Multiple Sclerosis, ALS or CIDP. [38]
- Four transmembrane Gla proteins (TMGPs) have been identified and their function is at presently unknown. [11]

In addition to being an enzyme cofactor for the carboxylation of all above mentioned proteins, Vitamin K₂ has a transcription regulation activity:

- increases the transcription of collagen type I by osteoblasts [102]
- it stimulates the SXR (Steroid and Xenobiotic Receptor), which upregulates detoxification pathways and the expression of various bone osteoblastic markers [58].
- inhibits the expression of osteoclast differentiation factor (ODF)/RANKL [105, 106] through its geranylgeraniol component
- inhibits adipogenesis [105] (the production of new fat cells)

Vitamin K₂ was shown to reduce inflammation, autoimmune disease activity and may be able to reduce CRP.

This may be due to the inhibition of PGE₂, COX-2 and IL-6) [3, 30]. Vitamin K₂ was shown to reduce the activity of rheumatoid arthritis (by inhibiting the proliferation of the rheumatoid synovial cells) [20]. A correlation was found between vitamin K status (plasma Vitamin K₁) and osteoarthritis disease activity in hands and knees [31]. Plasma Vitamin K₁ was shown in the Framingham study to correlate with CRP (a marker of inflammation). [104]

How can Vitamin K improve bone health?

The regulation of bone mass is the result of the actions of osteoblasts (bone building cells) and osteoclasts (bone-resorbing or bone breaking down cells). Mechanisms by which K2 may improve bone density are:

- 1) The osteoblasts make osteocalcin, which binds calcium into the bone matrix and during bone building and remodeling. As mentioned above, osteocalcin activity is dependant on its degree of carboxylation, which in turn is determined by the adequacy of vitamin K status in the body.
- 2) Osteoblasts production of collagen type I is increased by Vitamin K [102]) (through upregulation of collagen type I genetic expression)
- 3) Decreasing bone resorption by inhibiting osteoclast cells formation (inhibits the expression of osteoclast differentiation factor (ODF)/RANKL [105]), as well preventing osteoclast activation by inflammation (reduced IL-6, [30] PGE2, COX-2 [3]).
- 4) Minimizing osteoblasts apoptosis (cell death) [10, 11, 22, 48].
- 5) Activation of SXR (Steroid Xenobiotic Receptor), which modulates the expression of osteoblastic bone markers: bone alkaline phosphatase, osteoprotegerin and osteopontin [58]. This was shown specifically for Vitamin K2 [58].
- 6) Vitamin K dependent proteins MGP and Protein S are also believed to have a role in bone health (which is not clear at this time) because their deficiency has been shown to cause osteoporosis. [103].

Vitamin K1 or K2 supplementation was shown to increase or prevent a decline in BMD and reduce the risk of fracture due to its effect on bone remodeling and improvement of bone architecture [5, 6, 22] as follows:

- increases in BMD (Bone Density Markers) were 1.1%, 5.2% or 7.5% after 6, 12 or 24 months respectively, after taking 45mg/day of K2(MK-4).
- supplementation with 1mg/day of K1 was shown to increase BMD only by 1.3% after 3years.

However, none of these studies maximized the patient's status of vitamin D, used an adequate combination of minerals in their most absorbable forms (calcium, magnesium, boron etc) or optimized acid/alkaline balance (with diet, green extracts, adequate mineral intake of Ca, Mg, K.

Vitamin K may need to be supplemented to children in order to achieve maximum bone mass during development [55, 56, 57]. Osteocalcin is also involved in tooth mineralization and dental bone metabolism which means that vitamin K plays a role in these functions as well [59]. Bone ultrasound tests are now available and can be performed on the heel in order to evaluate the elastic properties of the bone. The ultrasound score may be a better predictor of the risk of bone fracture than BMD. Vitamin K supplementation is more likely to improve the bone ultrasound scores than the BMD numbers [41].

What have the studies shown in regards to arterial calcification or stiffness prevention and reversal?

Arterial calcification is thought to be initiated by inflammation (through TNF-alpha), oxidized or glycated LDL, hyperglycemia or arterial cell death (due to injuries from hypertension for example) [69-72]. Gas-6 vitamin K dependent proteins may support arterial cell survival while MGP proteins, found in the arterial wall and inside the arterial plaque (right along where calcification occurs), have the role of preventing calcium deposition in those tissues. Vitamin K2 supplementation was shown to reduce inflammation and vitamin K1 was found to correlate with CRP [3, 30, 104].

In a study from 2007 [17], rats developed arterial calcification within a few months of taking Warfarin (a vitamin K deficient state). Vitamin K1 or K2(MK-4) supplementation right after warfarin discontinuation was able to reverse the arterial calcification by 35% in 6 weeks. The effective dose for a similar effect in humans is not known, but some researchers hypothesize that it be the vitamin K dose able to completely carboxylate the MGP proteins. This is because human studies have observed a correlation between uncarboxylated MGP and arterial calcification [10]. It is not

known at the present time what is the ideal dose of vitamin K that is able to completely carboxylate all the MGP proteins found throughout the body, but it may be similar to the dose shown to completely carboxylate osteocalcin (1mg-2mg K1 with additional K2 needed for patients with poor K1 to K2 conversion).

One study, that gave postmenopausal women 1mg K1 along with vitamin D and minerals, has shown that vitamin K1 was able to prevent an increase in arterial stiffness, which was observed in the group of women taking vitamin D and minerals without vitamin K [68]. The researchers concluded that Vitamin K supplementation was responsible for maintaining the elastic properties of the arteries, which was assessed by measuring arterial compliance. This finding is in line with other studies showing that vitamin K reduces arterial calcification which is thought to be one potential cause of decreased arterial elasticity. One animal study showed that high dose vitamin K2 (1mg or 10mg/kg) "suppressed progression of arterial plaque, intima thickening, pulmonary atherosclerosis, reduced total cholesterol and lipid peroxidation and did not promote coagulative tendencies". [50].

Vitamin K deficiency may cause hypertension through increased arterial stiffness, which may be due calcifications in the arterial wall either within the medial muscle cells and/or around the elastic fibers) [73,74]. Heart valve calcifications may be a contributor to hypertension as well. Vitamin D supplementation can cause increased arterial calcification and stiffness when vitamin K is deficient (due to deficient intake of vitamin K or warfarin/coumadin treatment, which creates a vitamin K deficiency). This may be due to vitamin D increasing calcium absorption and transport, and upregulating MGP and osteocalcin expression [17,60].

Thyroid hormones influence the synthesis of MGP proteins such that arterial calcification is increased and MGP expression is decreased in hypothyroidism [76].

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