Vitamin K1 and K2 as MK-7 & MK-4: Differences & Applications

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Vitamin K, particularly vitamin K2, represents a significant segment of the vitamin market. In fact, the global vitamin K2 market size was estimated at $421.1 million in 2023 and is projected to grow at a CAGR of 10.8% from 2024 to 2030.[1] Certainly, vitamin K2 as menaquinone-7 (MK-7) has been recognized for its role in bone health and cardiovascular health, and to a lesser extent MK-4 has also been recognized for its role in bone health. However, MK-7 has other benefits beyond bone and cardiovascular health, and vitamin K1 also has meaningful benefits to offer in regard to cardiovascular health. This article reviews the differences between and the applications for vitamin K1 and K2 as MK-7 and MK-4. Let's start with a little background.

Background
Discovered in 1929, vitamin K was originally identified for its role as a blood-clotting (coagulation) cofactor.[2] In the 1970s, vitamin K-dependent proteins (VKDPs) were discovered, which led to a more comprehensive understanding of vitamin K's role with respect to bone and cardiovascular health.[3]

Additionally, two forms of this fat-soluble vitamin exist: Vitamin K1 and K2. Plants synthesize phylloquinone (aka, vitamin K1), and intestinal microbiota and fermentation of some foods synthesize a range of K2 forms collectively referred to as menaquinones (e.g., MK-4 and MK-7).[4] The menaquinones have a number designation according to the number of repeating 5-carbon units in its side chain. For example, if there are seven repeating 5-carbon units, the designation will be MK-7.[5]

The cardiovascular benefits of vitamin K2 as MK-7
In 2016, I wrote an article for VRM[6] discussing research which my co-author and I previously published in a scientific journal[7]. The research showed that the primary way in which Vitamin K acts to promote cardiovascular health is by inhibiting calcification in the arteries—which would otherwise lead to atherosclerosis. Specifically, some of the seventeen VKDPs have been identified to act as calcification inhibitors. These include osteocalcin (OC), also known as bone Gla protein (synthesized by osteoblasts) and matrix Gla protein (MGP, found in cartilage, bone, and soft tissue, including blood vessel walls). These proteins are local inhibitors of calcification in the tissues in which they exert their function. Here's how it works.

Carboxylation is a process in which a carboxylic acid group is reacted with a substance such as a protein—and carboxylation is necessary for the formation of critical VKDPs that have a positive impact on arterial stiffness and bone strength. Since 10-40 % of VKDPs remain undercarboxylated, research was conducted showing that the MK-7 form of vitamin K2 was effective in increasing the carboxylation of VKDPs.[8]

In the aforementioned research, we also discussed the population-based Rotterdam study, [9] which included 4807 subjects, and which provided the first evidence for a link between vitamin K and vascular health. The results showed the relative risk of coronary heart disease mortality and calcification of the aorta (an artery in the heart) was reduced in those with high intakes of vitamin K2, compared to those with a lower intake. Another study[10] with 564 post-menopausal women also showed a decreased risk of coronary calcification with higher intakes of vitamin K2.

Even more meaningful was a three year, double-blind, placebo-controlled trial[11] in which 248 postmenopausal women received 180 mcg/day of MK-7 or a placebo for three years to examine the effect on arterial stiffness (i.e., caused by calcification). The results were that supplementation with MK-7 significantly decreased measures of aortic stiffness and improved undercarboxylated VKDPs by 50%.

The bone health benefits of vitamin K2 as MK-7 & MK-4

In another a three year, double-blind, placebo-controlled trial[12], 244 healthy postmenopausal women also received 180 mcg/day of MK-7 or a placebo for three years, this time to examine indicators of bone health. The results were that MK-7 decreased age-related decline in bone mineral content and bone mineral density, and also favorably affected bone strength and decreased loss in vertebral height. Additionally, postmenopausal women with osteopenia (bone softening) also demonstrated a preservation of bone structure with 375 mcg/day MK-7.[13]

It is important to understand that MK-4 also has significant research to support its role in bone health. In fact, it could be argued that it has more research for this purpose than MK-7. It should also be noted that the doses used of MK-4 are higher (although safe) than MK-7. For example, in one randomized, double-blind, placebo-controlled trial[14], 1.5 mg/day of MK-4 for 6-12 months in postmenopausal women improved carboxylation of VKDPs and helped maintain bone mineral density. Similar results were seen in another study[15] with 600 mcg/MK-4. When 5 mg/day MK-4 was used there was a significant improvement in carboxylation of VKDPs, with no additional benefit compared to 45 m/day MK-4[16].

This is particularly meaningful since there are seven randomized controlled trials[17] [18] [19] [20] [21] [22] [23] demonstrating that 45 mg/day of MK-4 improved carboxylation of VKDPs and bone mineral density and reduced the incidence of fracture in osteoporosis patients. Likewise, there are seven human studies[24] [25] [26] [27] [28] [29] [30] demonstrating that 45 mg/day of MK-4 improved bone quality in various population types.

Additional benefits for MK-7

In addition to its cardiovascular and bone health benefits, MK-7 has also demonstrated benefits for muscle cramps, polycystic ovary syndrome, rheumatoid arthritis, and glucose/insulin modulation.

- Muscle cramps: A randomized, placebo-controlled clinical trial[31] found that 360 mcg/day MK-7 reduced the frequency, duration, and severity of muscle cramps in 39 hemodialysis patients.
- Polycystic ovary syndrome: A randomized, double-blind, placebo-controlled clinical trial[32] found that 90 mcg/day MK-7 significantly decreased serum fasting insulin, insulin resistance, serum triglyceride, dihydrotestosterone levels, free androgen index, waist circumference, and body fat mass, as well as significantly increasing skeletal muscle and

sex hormone binding globulin in polycystic ovary syndrome patients. It also improved depression status[33].

- Rheumatoid arthritis: A randomized, cross-sectional, clinical study[34] found that 100 mcg/day MK-7 added to normal therapeutic regimen decreased erythrocyte sedimentation rate (which are increased in RA), disease activity score assessing 28 joints, C-reactive protein (CRP, an inflammation marker) and matrix metalloproteinase (a tissue damage marker) in rheumatoid arthritis patients.
- Glucose/insulin modulation: A double-blinded, placebo-controlled, randomized trial[35] found that 360 mcg/day MK-7 lowered fasting plasma glucose, glycated hemoglobin in patients with type-2 diabetes.

Cardiovascular benefits for vitamin K1

As stated at the beginning of this article, vitamin K1 also has meaningful benefits to offer for supporting cardiovascular health—specifically with regards to arterial calcification:

- Hypertension medication users: A study[36] of 296 participants with extreme coronary artery calcium (CAC) progression and 561 randomly selected participants without extreme CAC progression found that hypertension medication users with low serum vitamin K1 were more likely to have extreme CAC progression than were medication users without extreme CAC progression.
- Preexisting coronary artery calcification: A double-blind trial of 388 healthy men and postmenopausal women with preexisting coronary artery calcification found that those receiving a multivitamin with 500 mcg/day vitamin K1 had 6% less progression of CAC than did those who received the multivitamin alone.[37]
- Aortic and coronary artery calcification: A double-blind, randomized, placebo-controlled trial[38] found that 10 mg/day vitamin K1 study helped prevent the development of newly calcifying lesions within the aorta and the coronary arteries in diabetic patients.
- Lower risk of cardiovascular complications: A population study[39] found that middle-aged subjects with no history of atherosclerotic cardiovascular disease who had the highest intake of dietary vitamin K1 intake (162–800 mcg) had a 21% lower risk of CVD-related hospitalization and complications over 17-22 years when compared to those with the lowest intake (73–101 mcg).

Available forms of vitamin K & complementary/synergistic considerations

Vitamin K2 as MK-7 is available in synthetic form, as well as in both natto (soy) and chickpea-derived forms for those who prefer a soy-free option (e.g., K2Go® by Nutraland USA). Vitamin K2 as MK-4 is only available in synthetic form. Vitamin K1 is available in synthetic form and as a natural alfalfa-derived form (from Nutraland USA).

Consider that there are complementary advantages to concurrent use of the various forms of vitamin K. For example, If the goal is to support cardiovascular health, a combination of vitamin K1 and vitamin K2 as MK-7 has advantages. If the goal is to support bone health, then a combination of vitamin K2 as both MK-7 and MK-4 is a good choice.

In addition, there is a synergistic relationship between vitamin K and vitamin D. In a study[40] conducted with chronic kidney disease patients, artery thickness of the carotid intima-media was significantly lower in those receiving vitamin K2 as MK-7 and vitamin D3 compared to D3 alone. A 2-

year randomized study[41] found that the combined administration of vitamin D3 and vitamin K2 (as MK-4), was effective in increasing the bone mineral density in postmenopausal women with osteoporosis. Another study[42] in women with estrogen deficiency found that MK-4 combined with vitamin D3 partially prevented bone loss caused by estrogen deficiency.

Conclusion

Three commercially viable forms of vitamin K include K1, K2 as MK-7 and K2 as MK-4. Each form has its own distinct advantages. Research has demonstrated the cardiovascular benefits of K1 and K2 as MK-7, while other research has demonstrated the benefits of MK-7 and MK-4 for bone health. Additionally, research has demonstrated that MK-7 also has benefits for muscle cramps, polycystic ovary syndrome, rheumatoid arthritis, and glucose/insulin modulation. These various forms of vitamin K may be used together and/or in combination with vitamin D3 to maximize complementary/synergistic effects.

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