Proper Calcium Use: Vitamin K$_2$ as a Promoter of Bone and Cardiovascular Health

Katarzyna Maresz, PhD

Abstract

Inadequate calcium intake can lead to decreased bone mineral density, which can increase the risk of bone fractures. Supplemental calcium promotes bone mineral density and strength and can prevent osteoporosis. Recent scientific evidence, however, suggests that elevated consumption of calcium supplements may raise the risk for heart disease and can be connected with accelerated deposit of calcium in blood-vessel walls and soft tissues. In contrast, vitamin K$_2$ is associated with the inhibition of arterial calcification and arterial stiffening. An adequate intake of vitamin K$_2$ has been shown to lower the risk of vascular damage because it activates matrix GLA protein (MGP), which inhibits the deposits of calcium on the walls. Vitamin K, particularly as vitamin K$_{n}$, is nearly nonexistent in junk food, with little being consumed even in a healthy Western diet. Vitamin K deficiency results in inadequate activation of MGP, which greatly impairs the process of calcium removal and increases the risk of calcification of the blood vessels. An increased intake of vitamin K$_2$ could be a means of lowering calcium-associated health risks.

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Inadequate calcium intake can lead to decreased bone mineral density, which can increase the risk of bone fractures. Supplemental calcium promotes bone mineral density and strength and can prevent osteoporosis (ie, porous bones), particularly in older adults and postmenopausal women. However, recent scientific evidence suggests that elevated consumption of calcium supplements can raise the risk for heart disease and can be connected to accelerated deposit of calcium in blood-vessel walls and soft tissues. In contrast, vitamin K$_2$ is associated with the inhibition of arterial calcification and arterial stiffening. An adequate intake of vitamin K$_2$ has been shown to lower the risk of vascular damage because it activates matrix GLA protein (MGP), which inhibits the deposits of calcium on the walls. Vitamin K, particularly as vitamin K$_{n}$, is nearly nonexistent in junk food, with little being consumed even in a healthy Western diet. Vitamin K deficiency results in inadequate activation of MGP, which greatly impairs the process of calcium removal and increases the risk of calcification of the blood vessels. An increased intake of vitamin K$_2$ could be a means of lowering calcium-associated health risks.

Abstract

Since 1950, the consumption of vitamin K has decreased gradually, and even a well-balanced diet might not provide vitamin K in amounts sufficient for satisfying the body’s needs.

Further, due to modern manufacturing processes, the vitamin K content, particularly the vitamin K$_2$ content, of the food supply today has significantly dropped, making vitamin K$_2$ supplements a more reliable way to secure adequate intake. By striking the right balance in intake of calcium and K$_2$, it may be possible to fight osteoporosis and simultaneously prevent the calcification and stiffening of the arteries. A new clinical study with vitamin K$_2$ supplementation showed an improvement in arterial elasticity and regression in age-related arterial stiffening (data pending publication). Most important, through its activation of K-dependent proteins, vitamin K$_2$ can optimize calcium use in the body, preventing any potential negative health impacts associated with increased calcium intake.

Vitamin K$_2$: Essential Role

Bone is composed of a hard outer shell and a spongy matrix of inner tissues and is a living substance. The entire skeleton is replaced every 7 to 10 years. During the
skeleton's remodeling, the body releases calcium from the bone into the bloodstream to meet an individual's metabolic needs, allowing the bone to alter size and shape as it grows or repairs from injuries. This remodeling is regulated by osteoblasts—cells that build up the skeleton—and osteoclasts—cells that break down the skeleton. As long as the bone-forming activity (ie, absorption) is greater than the breakdown of bone (ie, resorption), the process of maintaining a healthy bone structure is maintained.

Osteoblasts produce osteocalcin, which helps take calcium from the blood circulation and bind it to the bone matrix. In part, osteocalcin influences bone mineralization through its ability to bind to the mineral component of bone, hydroxyapatite, which in turn makes the skeleton stronger and less susceptible to fracture. The newly made osteocalcin, however, is inactive, and it needs vitamin K₂ to become fully activated and bind calcium.

That requirement alone makes vitamin K₂ a major player in bone health, but its importance does not stop there. Vitamin K₂ also keeps calcium from accumulating in the walls of blood vessels. The vitamin K–dependent protein, matrix GLA protein (MGP), is a central calcification inhibitor produced by the cells of vascular smooth muscles and regulates the potentially fatal remodeling of the normal range are a risk factor for vascular disease. A possible explanation for the negative effects of high-dose (1000 mcg daily), long-term intake of calcium on cardiovascular health is that it renders the normal homeostatic control of calcium concentrations in the blood ineffective. Substantial epidemiological evidence has shown that levels of serum calcium in the upper part of the normal range are a risk factor for vascular disease and that calcium supplements acutely elevate serum calcium. This combination of findings lends plausibility to the idea that supplementation can increases vascular risk. In other words, increased levels of blood calcium have been correlated with elevated blood clotting and calcium deposition in blood vessels, which leads to arterial hardening. Both of these effects increase the risk of heart disease.

Vitamin K: Form and Structure

Eighty-four years ago, while investigating the effects of a low-fat diet fed to chickens, Danish scientist Henrik Dam discovered vitamin K. He found that the bleeding tendencies found in the chickens on that diet could be prevented when a diet with normal levels of fat was restored and vitamin K was added to their diets. From that point forward, vitamin K became known as the coagulation vitamin, the "K" coming from the German word "koagulation."
Later, it was found that the fat-soluble compound needed for blood clotting existed in 2 forms: phylloquinone (vitamin K1) and menaquinone (vitamin K2).32 Vitamin K1 is made in plants and algae; green leafy vegetables are a particularly rich source. On the other hand, bacteria generate vitamin K2, which can also be found in meat, dairy, eggs, and fermented foods, such as cheese, yogurt, and natto—a Japanese dish of fermented soybeans.33,34 Even though the side chains of isoprenoid units of vitamin K differ in length, generally from 4 to 13 repeats (MK-4 to MK-13), they are all used by the enzyme γ-glutamate carboxylase to activate a specific set of proteins, including proteins involved in blood coagulation, bone formation, and inhibition of soft tissue calcification. Both forms of vitamin K, K1 and K2, are essential in maintaining blood hemostasis and optimal bone and heart health through the role they play in inducing calcium use by proteins. Vitamin K, particularly vitamin K2, is essential for calcium use, helping build strong bones and inhibiting arterial calcification.35

Vitamin K is a cofactor for 1 enzyme, γ-glutamylcarboxylase, which γ-carboxylates certain glutamic acid residues posttranslationally in a number of vitamin K–dependent (VKD) proteins. This γ-carboxylation allows VKD proteins to bind calcium. Vitamin K1 is required for the activity of coagulation and anticoagulation factors46 and for the binding of osteocalcin to hydroxyapatite in bone;47 it is generally considered to be required for the function of MGP.35

Vitamin K is not a single entity but, rather, a family of structurally related molecules derived from different sources. Major molecular forms, their primary dietary sources, and their relative contributions to vitamin K activity are shown in Table.35,37,39-44 All molecules listed in Table 1 share the same nucleus—methylated naphthoquinone (menadione)—but have side chains of differing composition and length, which results in different potencies and absorption efficiencies.44

Heart Health: Ideal State

Adequate intake of vitamin K2 has been shown to lower the risk of vascular damage because it activates MGP, which inhibits calcium from depositing in the vessel walls. Hence, calcium is available for multiple other roles in the body, leaving the arteries healthy and flexible.46 However, vitamin K deficiency results in inadequate activation of MGP, which greatly impairs the process of calcium removal and increases the risk of calcification of the blood vessels.48,52 Because that calcification occurs in the vessel walls, it leads to thickening of the wall via calcified plaques (ie, to the typical progression of atherosclerosis), which is associated with a higher risk of cardiovascular events.

### Table 1. Vitamin K: Molecular Forms, Sources, and Contributions to Vitamin K Activity

<table>
<thead>
<tr>
<th>Molecular Form of Vitamin K</th>
<th>Primary Sources</th>
<th>Dietary Contribution to Vitamin K Activity</th>
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<tr>
<td>Vitamin K₁—Phylloquinone</td>
<td>Green leafy vegetables</td>
<td>Major, close to 90%&lt;sup&gt;41&lt;/sup&gt; Well-absorbed, less active than K₂ as an MK-7 form; mainly supports homeostasis&lt;sup&gt;35&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vitamin K₂—MK-4</td>
<td>Some meats, eggs, and cheeses</td>
<td>Minor as a direct dietary source of vitamin K&lt;sup&gt;41&lt;/sup&gt; Well-absorbed, less active than K₁ as MK-7 form; activates K–dependent proteins outside the liver&lt;sup&gt;43&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vitamin K₂—MK-7</td>
<td>Natto, cheeses</td>
<td>Minor as a direct dietary source of vitamin K in Europe, the United States, and Australia&lt;sup&gt;39,41&lt;/sup&gt; Well-absorbed; provides the highest vitamin K activity; activates K–dependent proteins outside the liver&lt;sup&gt;44&lt;/sup&gt;</td>
</tr>
<tr>
<td>Long-chain menaquinones (eg, MK-10–MK-13)</td>
<td>Colon bacteria</td>
<td>Minor as a direct dietary source of vitamin K&lt;sup&gt;42&lt;/sup&gt; Poorly absorbed&lt;sup&gt;42&lt;/sup&gt; and provides little vitamin K activity&lt;sup&gt;37,40&lt;/sup&gt;</td>
</tr>
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Abbreviations: MK-4, menaquinone 4; MK-7, menaquinone 7; MK-10, menaquinone 10; MK-13, menaquinone 13.
The population-based Rotterdam study studied 4807 healthy men and women older than age 55 years, evaluating the relationship between dietary intake of vitamin K and aortic calcification, heart disease, and all-cause mortality.10 The study revealed that high dietary intake of vitamin K2—at least 32 mcg per day, with no intake of vitamin K1, was associated with a 50% reduction in death from cardiovascular issues related to arterial calcification and a 25% reduction in all-cause mortality.

Those findings were supported by another population-based study with 16,000 healthy women aged 49 to 70 years that was drawn from EPIC’s cohort population.53 After 8 years, the data showed that a high intake of natural vitamin K2 (ie, not synthetic K2, but not of vitamin K1) was associated with protection against cardiovascular events. For every 10 mcg of dietary vitamin K2 consumed in the forms of menaquinone 7 (MK-7), menaquinone 8 (MK-8), and menaquinone 9 (MK-9), the risk of coronary heart disease was reduced by 9%. A study on 564 postmenopausal women also revealed that intake of vitamin K2 was associated with decreased coronary calcification, whereas intake of vitamin K1 was not.5

One recent, double-blind, randomized clinical trial investigated the effects of supplemental MK-7, MenaQ7 (NattoPharma ASA, Hovik, Norway), within a 3-year period for a group of 244 postmenopausal Dutch women.54 The researchers found that a daily dose of 180 mcg was enough to improve bone mineral density, bone strength, and cardiovascular health. They also showed that achieving a clinically relevant improvement required at least 2 years of supplementation.

A study pending publication of 244 postmenopausal women who took supplements with 180 mcg of vitamin K2, as MK-7, for 3 years daily actually showed a significant improvement in cardiovascular health as measured by ultrasound and pulse-wave velocity, which are recognized as standard measurements for cardiovascular health.55-57 In that trial, carotid artery distensibility was significantly improved for a 3-year period as compared with that of a placebo group. Also, pulse-wave velocity showed a statistically significantly decrease after 3 years for the vitamin K2 (MK-7) group, but not for the placebo group, demonstrating an increase in the elasticity and reduction in age-related arterial stiffening.

**Calcium Concerns: Vitamin K2**

Studies illustrate that high calcium consumption helps strengthen the skeleton but, at the same time, may increase the risk of heart disease due to arterial calcification.3-8,22 Inactive proteins regulating calcium, such as MGP, correlate with the development of arterial calcification. Although vitamin K1 can activate MGP, it is much less efficient because it is transported to the liver first to activate coagulation proteins.35 To render the proteins regulating calcium active, a sufficient amount of vitamin K2 has to be present in the body.58

If at least 32 mcg of vitamin K2 is present in the diet, then the risks for blood-vessel calcification and heart problems are significantly lowered,10 and the elasticity of the vessel wall is increased.59 Moreover, the beneficial effects of vitamins D and K on the elastic properties of the vessel wall in postmenopausal women has been seen in clinical trials.59 If less vitamin K2 is present in the diet, then cardiovascular problems may arise.

In general, the typical Western diet contains insufficient amounts of vitamin K2 to activate MGP adequately, which means that approximately 30% of the proteins that can be activated by vitamin K1 remain inactive. The percentage of K deficiency increases with age.12

Vitamin K2, particularly as vitamin K2, is nearly nonexistent in junk food, with little being consumed even in a healthy Western diet. Although vitamin K2 is present in green leafy vegetables, only 10% of the total amount is absorbed from that source in the diets of people in industrialized countries.60-61 The only exception seems to be the Japanese diet, particularly for the portion of the population consuming high quantities of foods rich in vitamin K2, such as natto.

It appears that suboptimal levels of vitamin K2 in the body may disadvantage the activation of specific proteins that are dependent on vitamin K2.35 If those proteins cannot perform their function in keeping calcium in the bones and preventing calcium deposits in soft tissues (eg, in arterial walls) during situations of increased calcium intake, then general health, and—in particular—cardiovascular health, may suffer due to an inefficient and misdirected use of calcium in the body.

**Conclusions**

Dietary calcium is linked to many benefits, particularly bone health. Those benefits are why adequate daily intakes for calcium have been established. Because diets often fall short of the guidelines, in particular in individuals with higher needs, such as children, older adults, and postmenopausal women, dietary supplementation can help address the body’s demands. Although the outcomes in studies evaluating high calcium consumption are controversial, some studies do suggest caution when considering supplementation, particularly excessive supplementation, because some evidence points to health problems at elevated levels.3-8

That issue could be remedied, however, if the right amount of vitamin K2 were to be added to a high-calcium regimen. Vitamin K2 promotes arterial flexibility by preventing accumulation of arterial calcium.10,47,62 and supplementation with it could correct calcium amounts in the body that are out of balance. Thus, calcium in tandem with vitamin K2 may well be the solution for bringing necessary bone benefits while circumventing an increased risk for heart disease.
References


