

Proper Calcium Use: Vitamin K₂ as a Promoter of Bone and Cardiovascular Health

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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 K₂ is associated with the inhibition of arterial calcification and arterial stiffening. An adequate intake of vitamin K₂ 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 K₂, 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 K₂ 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.^{1,2} 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.³⁻⁸

In contrast, vitamin K₂ is associated with the inhibition of arterial calcification and arterial stiffening,^{9,10} which means that increased vitamin K₂ intake could be a means of lowering calcium-associated health risks. However,

since 1950, the consumption of vitamin K has decreased gradually,¹¹ 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 K₂ content, of the food supply today has significantly dropped, making vitamin K₂ supplements a more reliable way to secure adequate intake.¹² By striking the right balance in intake of calcium and K₂, it may be possible to fight osteoporosis and simultaneously prevent the calcification and stiffening of the arteries. A new clinical study with vitamin K₂ 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 K₂ can optimize calcium use in the body, preventing any potential negative health impacts associated with increased calcium intake.

Vitamin K₂: 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.¹³ 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,¹⁴ 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.¹⁵

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 accumulation of calcium.¹⁶

Calcium: Mixed Messages

Calcium serves many important roles in the human body, including (1) providing structure and hardness to bones and teeth, (2) allowing muscles to contract and nerves to send signals, (3) making blood vessels expand and contract, (4) helping blood to clot, and (5) supporting protein function and hormone regulation.¹⁷ Even though dairy products represent a rich source of calcium, approximately 43% of the US population and 70% of older women regularly take calcium supplements.¹⁸ Calcium supplementation is supported by several studies that back its benefits for bone health and osteoporosis prevention as well as for overall health.

Calcium's ability to lower blood pressure¹⁹ and lower levels of blood cholesterol²⁰⁻²² contributes to heart health. Indeed, a prospective cohort study of postmenopausal women from Iowa connected higher calcium intake to lower risk of death due to heart disease through the controlled supply of calcium in the blood.²³ But most recently, several studies have cast doubt on the notion that "more is better" when it comes to calcium intake and prevention of cardiovascular disease.²⁴

A study published by Xiao et al⁸ discussed the outcome of the National Institutes of Health (NIH) AARP Diet and Health Study, which evaluated the role of supplemental calcium on cardiovascular health. This prospective study involved a large group, 219 059 men and 169 170 women, whose health was tracked for 12 years. The researchers found that men, but not women, taking

more than 1000 mg/day of calcium supplements had a risk of total cardiovascular death that was 20% higher than that of participants taking no calcium supplements.

Other published studies have found a detrimental impact for calcium supplementation on women's cardiovascular health, too. Data from the Women's Health Initiative showed that those women taking 1000 mg/day in the form of calcium supplements, with or without the addition of 400 IU/day of vitamin D, increased their risk of cardiovascular events by 15% to 22%, particularly women who at the beginning of study did not take calcium supplements.⁴ Moreover, the risk for coronary heart disease increased by 24% in a group of 10 555 Finnish women who used calcium supplements, with or without vitamin D.⁷

Further, a study by the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg) with 23 980 participants concluded that participants regularly taking a calcium supplement had an risk for heart attack that was 86% higher than that for participants not taking a supplement.⁵ The effect was even more pronounced when no supplements other than calcium were taken; the risk of heart attack more than doubled in those cases.

In patients with kidney failure, supplemental calcium has also been linked to increased hardening of the arteries through calcification as well as to higher mortality.^{25,26} A meta-analysis combining and analyzing the results from different randomized, controlled trials of kidney disease also linked calcium supplementation with a 22% increase in the risk of death from cardiovascular issues.²⁷

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.⁶ 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 increase vascular risk.²⁸ 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.^{4,8,29,30}

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*.³¹

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

Molecular Form of Vitamin K	Primary Sources	Dietary Contribution to Vitamin K Activity
Vitamin K ₁ —Phylloquinone	Green leafy vegetables	Major, close to 90% ⁴¹ Well-absorbed, less active than K ₂ as an MK-7 form; mainly supports homeostasis ³⁵
Vitamin K ₂ —MK-4	Some meats, eggs, and cheeses	Minor as a direct dietary source of vitamin K ⁴¹ Well-absorbed, less active than K ₂ as MK-7 form; activates K-dependent proteins outside the liver ⁴³
Vitamin K ₂ —MK-7	<i>Natto</i> , cheeses	Minor as a direct dietary source of vitamin K in Europe, the United States, and Australia ^{39,41} Well-absorbed; provides the highest vitamin K activity; activates K-dependent proteins outside the liver ⁴⁴
Long-chain menaquinones (eg, MK-10–MK-13)	Colon bacteria	Minor as a direct dietary source of vitamin K ⁴² Poorly absorbed ⁴² and provides little vitamin K activity ^{37,40}

Abbreviations: MK-4, menaquinone 4; MK-7, menaquinone 7; MK-10, menaquinone 10; MK-13, menaquinone 13.

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 -glutamyl 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 K is required for the activity of coagulation and anticoagulation factors³⁶ and for the binding of osteocalcin to hydroxyapatite in bone³⁷; it is generally considered to be required for the function of MGP.³⁸

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

Form definitely matters. In fact, studies on *natto* support the importance of vitamin K₂ in the form of menaquinone with 7 isoprene residues (MK-7). Kaneki and colleagues have shown that increased consumption of MK-7 leads to more activated osteocalcin, which is linked to increased bone-matrix formation and bone mineral density and, therefore, a lower risk of hip fracture.^{45,46} Those results were confirmed in a 3-year study with 944 women aged 20 to 79 years, which showed that intake of MK-7-rich *natto* was associated with the preservation of bone mineral density.⁴⁷

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.

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.⁹

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 significant 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 K₂ remain inactive. The percentage of K deficiency increases with age.¹²

Vitamin K, particularly as vitamin K₂, is nearly nonexistent in junk food, with little being consumed even in a healthy Western diet. Although vitamin K₁ 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.

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