

Vitamin K2 and the calcium connection

Calcium intake requires adequate vitamin K2 to protect and promote cardiovascular health.

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OVERVIEW

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 (i.e., porous bones), particularly in elderly and postmenopausal women (1,2). However, recent scientific evidence suggests that elevated calcium consumption accelerates calcium deposits in blood vessel walls and soft tissues, which may raise the risk for heart disease (Table I) (3-8).

In contrast, vitamin K2 has been shown to prevent arterial calcification and arterial stiffening (9,10), which means increased vitamin K2 amounts in the body could be a means of lowering calcium-associated health risks. With the human diet lacking vitamin K2, taking vitamin K2 supplements is one way to secure adequate intake. By striking the right balance between calcium and vitamin K2 intake, it may be possible to fight osteoporosis and at the same time prevent the calcification and stiffening of the arteries. A new clinical study pending publication with vitamin K2 supplementation showed an improvement in arterial elasticity and regression in age-related arterial stiffening (data pending publication) (50). Most important, vitamin K2 could optimize calcium utilization in the body preventing any potential negative health impacts associated with increased calcium intake.

Calcium plays many important roles in the human body (see box below). It provides structure and hardness to bones and teeth; allows muscles to contract and nerves to send signals; makes blood vessels expand and contract; helps blood to clot; and supports protein function and hormone regulation (11). Average daily recommended intakes of calcium differ with age, with children, teens and the

aging population needing the most. Even though dairy products represent a rich source of calcium, approximately 43% of the U.S. population and 70% of older women regularly take calcium supplements (12). Calcium supplementation is supported by several studies backing its benefits for bone health and osteoporosis prevention, as well as for overall health.

Calcium's ability to lower blood pressure (13) and lower blood cholesterol levels (14-16) contributes to heart health. Indeed, a prospective cohort study (i.e., observation of individuals over time) of postmenopausal women from Iowa (US) connected higher calcium intake to lower risk of death due to heart disease through restricted blood supply (17). Meanwhile, a prospective longitudinal cohort study – i.e. observation of individuals over long period of time – in Sweden reported that older women at $\geq 1,400$ mg/day calcium intakes were at higher risk for heart disease death than women taking 600-1,000 mg/day (6). However, other prospective studies have revealed no link between high calcium intake and cardiac events (18-20) and cardiac death (18,21,22). The effects of calcium on stroke are also inconsistent since some publications associate high calcium intakes with lowered stroke risk, while others found no connection between the calcium and incidence of stroke (19,20). Most recently, several studies have cast doubt on the notion that "more is better" when it comes to calcium intake and cardiovascular disease prevention (23).

A study published by Xiao *et al.* discussed

- Calcium is the most abundant nutrient in humans.
- Bones and teeth store most of the calcium (99%), where it provides hardness and structure.
- Muscles, nerves and blood vessels depend on the remaining 1% of calcium for their function structure.
- Low calcium intake is linked to fractures, stroke and fatal ischemic heart disease in the elderly.
- **The Paradox:** supplemental calcium has also been linked to higher risk of ischemic heart disease and stroke incidence in some studies. It has also been linked to overall health and cardiovascular mortality rates, as well as increased heart disease risk.

Calcium facts.

Health concerns with calcium supplementation	Population characteristics	Main findings	Ref
Use of calcium supplements and the risk of coronary heart disease in 52-62-year-old women: The Kuopio Osteoporosis Risk Factor and Prevention Study. <i>Maturitas</i> 2009	Women (52-62 y)	Increased risk of CVD with calcium or calcium+vitamin D supplement	7
Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. <i>BMJ</i> 2010	Men and women (>40 y)	Increased heart attack risk with calcium supplements	3
Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. <i>BMJ</i> 2011	Postmenopausal women	Calcium or calcium+vitamin D supplement increases heart attack risk	4
Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). <i>Am.J.Clin.Nutr.</i> 2003	Men and women (35-64 y)	Increased risk of heart attack with calcium supplements and even higher risk when taken without other supplements	18
Long term calcium intake and rates of all-cause and cardiovascular mortality: community-based prospective longitudinal cohort study. <i>BMJ</i> 2013	Women (>40 y)	High calcium intake is linked to higher death rates from all causes and CVD	6
Dietary and supplemental calcium intake and cardiovascular disease mortality: the National Institutes of Health-AARP diet and health study. <i>JAMA</i> 2013	Men and women (50-71 y)	High supplemental calcium increases risk of CVD death in men only	8
Health benefits of vitamin K 2 supplementation	Population characteristics	Main findings	Ref
Japanese fermented soybean food as the major determinant of the large geographic difference in circulating levels of vitamin K2: possible implications for hip-fracture risk. <i>Nutrition</i> 2001	Postmenopausal women	Increased intake of MK-7 helps to reduce hip fracture risk	40
Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study. <i>J Nutr.</i> 2004	Men and women (>55 y)	High menaquinone intake reduces risk of CVD mortality, all-cause mortality and severe aortic calcification	10
Regression of warfarin-induced medial elastocalcinosis by high intake of vitamin K in rats. <i>Blood</i> 2007	Rats	Vitamin K2 reduces aortic calcium levels and increases arterial distensibility in an induced arterial calcification model	43
High dietary menaquinone intake is associated with reduced coronary calcification. <i>Atherosclerosis</i> 2009	Postmenopausal women	High dietary vitamin K2 reduces coronary calcium deposits	9
A high menaquinone intake reduces the incidence of coronary heart disease. <i>Nutr. Metab. Cardiovasc. Dis.</i> 2009.	Women (49-70 y)	High vitamin K2 intake (MK-7, -8, -9) is linked to lower CVD risk	45
Effect of vitamin K2 supplementation on functional vitamin K deficiency in hemodialysis patients: a randomized trial. <i>Am. J. Kidney Dis.</i> 2012.	Hemodialysis patients (≥18 y)	Vitamin K2 supplementation improves activity of a protein involved in calcium removal in arterial wall (MK-7) (MenaQ7®)	48
Three-year low-dose menaquinone-7 supplementation helps decrease bone loss in healthy postmenopausal women. <i>Osteoporosis Int.</i> 2013.	Postmenopausal women	MK-7 supplement may help to prevent bone loss (MenaQ7®)	49
Menaquinone-7 supplementation improves vascular properties in healthy postmenopausal women: a randomized controlled trial. Submitted, Pending.	Postmenopausal women	MK-7 supplement regressed age-related arterial stiffening (MenaQ7®)	50

Table 1

the outcome of the National Institutes of Health (NIH)–AARP Diet and Health Study, which evaluated the role of supplemental calcium on cardiovascular health (8). This prospective study involved a large group of 219,059 men and 169,170 women whose health was tracked over 12 years. The researchers found that men – but not women – taking more than 1,000 mg/day of calcium supplements had a 20% higher risk of total cardiovascular death compared to those taking no calcium supplements.

Other published studies have found a detrimental impact of calcium supplementation on women's cardiovascular health, too. The data from the Women's Health Initiative showed that those taking 1,000 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 15-22%, especially in women who at the beginning of study did not take calcium supplements (4). Moreover, a 24% increased risk of coronary heart disease was detected in a group of 10,555

Finish women who used calcium supplements with or without vitamin D (7). Also, researchers from the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg) concluded that in the 23,980 participants, those regularly taking a calcium supplement had an 86% higher risk for heart attack compared to those not taking a supplement (5). The effect was even more pronounced when no supplements other than calcium were taken – heart attack risk more than doubled in these cases.

In patients with kidney failure, supplemental calcium has also been linked to increased hardening of the arteries through calcification, as well as higher mortality (24,25). A metaanalysis – i.e., combining and analyzing the

results from different studies – of kidney disease also linked calcium supplementation with a 22% increased risk of cardiovascular death (26).

A possible explanation for the negative effects of high dose, long-term calcium

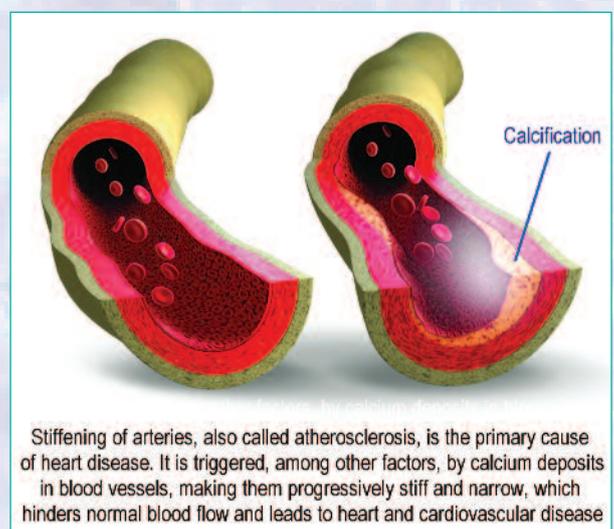


Figure 1 – Atherosclerosis development.

VITAMIN K2 (menaquinones)

- Vitamin K2 is a fat-soluble substance.
- It can render special proteins (vitamin K-dependent proteins) functional by the addition of carboxyl (-COOH) groups.
- Vitamin K2 is needed for normal blood coagulation (in German and Nordic languages: "Koagulation" from where the "K" originated).
- It is made by bacteria, which give fermented foods like cheese and the Japanese natto (fermented soybeans) a high K2 content.
- Vitamin K2 is also involved in bone formation and repair.
- It is associated with reduced risk for heart disease and hip fractures.
- Vitamin K2 can prevent and even reverse blood vessel calcium deposits (i.e., calcification) and increase flexibility.

Table II – Vitamin K2 facts.

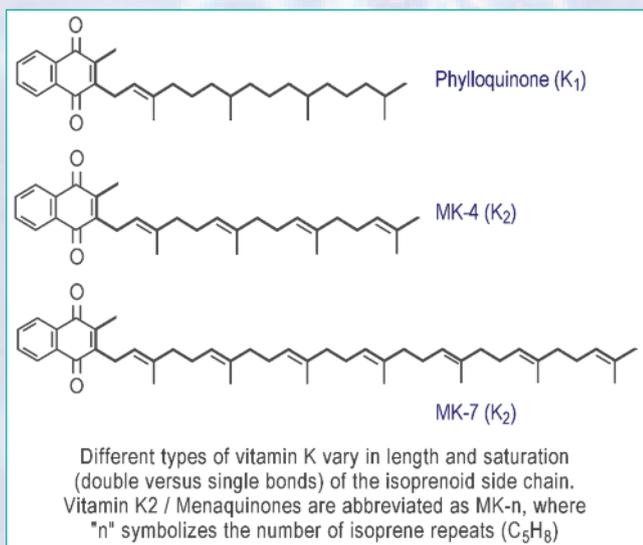


Figure 2 – Chemical structure of vitamin K1 and K2 (MK-4 and MK-7).

intake on cardiovascular health is that it renders the normal homeostatic control of blood calcium concentrations ineffective (6). In other words, increased blood calcium levels have been correlated with elevated blood clotting and calcium deposition in blood vessels leading to arterial hardening, both of which increase the risk of heart disease (Figure 1) (4,8,27,28).

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 bleeding tendencies in chickens could be prevented when a regular fat diet was restored and vitamin K was added to their diet. From this point forward, vitamin K became known as the coagulation vitamin – the "K" coming from the German word "Koagulation" (Table II) (29).

Later it was found that this fat-soluble compound needed for blood clotting exists in two forms: phylloquinone (vitamin K1) and menaquinone (vitamin K2) (Figure 2) (30). Vitamin K1 is made in plants and algae – green leafy vegetables are a particularly rich source of it. 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) (31,32).

Even though the side chains of isoprenoid units of vitamin K differ in length from 1 to 14 repeats, 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. Vitamin K (K1 and K2) is essential in maintaining blood homeostasis and optimal bone and heart health through the role it plays in inducing calcium use by proteins. Vitamin K, particularly vitamin K2, is essential for calcium utilization, helping build strong bones and inhibit arterial calcification.

people vitamin K2-deficient (34,35).

Children in particular need more vitamin K2 since they have a much higher bone metabolism than adults. From the late 20s to mid-30s peak bone mass is reached, after which bone mineral content slowly diminishes. Thus, the higher the peak bone mass attained at a younger age, the longer the bone mass can be preserved (Figure 4).

Population-based studies and clinical trials have linked higher blood vitamin K2 concentrations to stronger bones. Further, studies in adults have revealed that vitamin K2 supplementation helps promote bone health and maintain bone mineral density (36-38,42). A study in children also showed that improving vitamin K2 intake over a two-year period led to stronger and denser bones (39).

Form definitely matters. In fact, studies on natto – a vitamin K2-rich traditional Japanese food based on fermented soy beans – support the importance of vitamin K2 in the form of menaquinone with seven isoprene residues (MK-7). Kaneki and colleagues have showed 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 (40). These results were confirmed in a three-year

ACHIEVING OPTIMAL BONE HEALTH

Bone relies on calcium for its structure, function and health. It is also a living tissue that contains blood vessels, nerves and cells. Bone structure is secured by two type of cells – osteoblasts which build bones and osteoclasts which remodel bones (Figure 3). Osteoblasts produce the protein osteocalcin, which needs to be activated by vitamin K2 to bind calcium to the bone's mineral matrix, thereby strengthening the skeleton (33).

If there is a lack of vitamin K2 over a long period of time, then calcium will not be integrated into the bone and poor bone quality will result. Populations that consume enough vitamin K2 have stronger, healthier bones. The Western diet, however, does not contain sufficient vitamin K2 leaving many

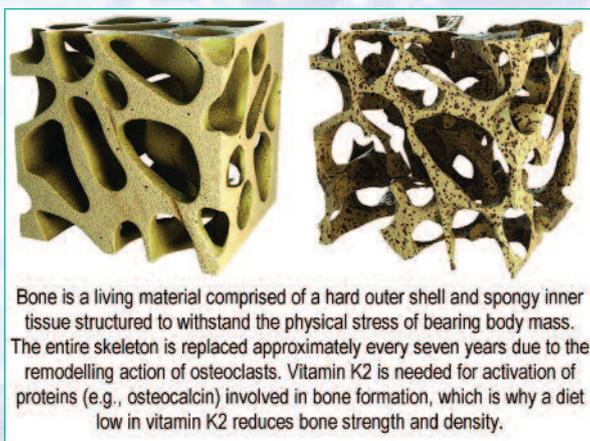


Figure 3 – Healthy bone structure vs. poor bone structure.

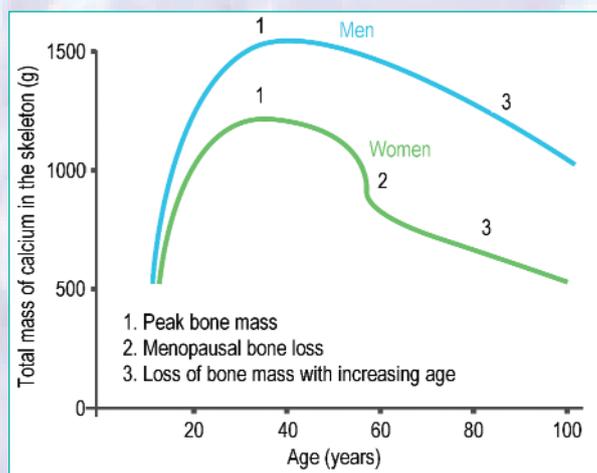


Figure 4 – Calcium loss increases with age.

study with 944 women (aged 20-79) showing that intake of MK-7-rich natto helps preserve bone mineral density (41).

One recent double-blind, randomized clinical trial investigated the effect of supplemental MK-7 (MenaQ7®) over three years in a group of 244 post-menopausal Dutch women (49). Researchers found that a daily dose of 180 µg was enough to improve bone mineral density, bone strength and cardiovascular health. They also showed that achieving a clinically relevant improvement required at least two years of supplementation.

THE IDEAL STATE OF HEART HEALTH

Adequate intake of vitamin K2 has been shown to lower the risk of vascular damage because it activates Matrix Gla

from the Prospect-EPIC cohort population (45). After eight years, the data showed that high intake of natural vitamin K2, but not vitamin K1, helps protect against cardiovascular events; for every 10 µg of vitamin K2 (in the forms of MK-7, MK-8 and MK-9) consumed, the risk of coronary heart disease was reduced by 9%.

A study on 564 post-menopausal women also revealed that vitamin K2 intake decreases coronary calcification, whereas vitamin K1 does not (9).

A study pending publication on 244 post-menopausal women supplemented with 180 µg of vitamin K2 as MK-7 actually showed a significant improvement in cardiovascular health as measured by ultra-sound and pulse-wave velocity, which are recognized standard measurements for cardiovascular health. In this trial, carotid artery distensibility (i.e., elasticity) – the ability for a blood vessel to stretch or dilate – was significantly improved over a

vitamin K2 is present in the diet, then the risk for blood vessel calcification and heart problems is significantly lowered (10) and elasticity of the vessel wall is increased (47). On the contrary, 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 adequately activate MGP, which means about 30% of vitamin K2-activated proteins remain inactive. This amount only increases with age.

Vitamin K, especially as vitamin K2, is nearly non-existent in “junk” food, and even in a healthy Western diet. The only exception seems to be the Japanese diet, particularly in the portion of the population consuming high quantities of vitamin K-rich foods, such as natto (Figure 6).

It appears that suboptimal vitamin K2 levels in the body may disadvantage the vitamin K2-dependent activation of

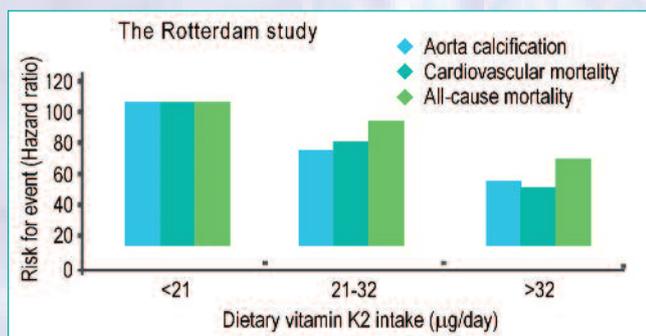


Figure 5 – High vitamin K2 consumption promotes cardiovascular health.

Protein (MGP), which inhibits calcium from depositing in the vessel walls (arterial calcification).

Hence, calcium is available for other multiple roles in the body, leaving the arteries healthy and flexible (43). However, vitamin K deficiency results in inadequate activation of MGP, which greatly impairs the calcium removal process and increases the risk of blood vessel calcification (44). Since this process occurs in the vessel wall, it leads to the wall thickening via calcified plaques (i.e., typical atherosclerosis progression), which is associated with higher risk of cardiovascular events.

The population-based Rotterdam study evaluated 4807 healthy men and women over age 55 and 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 µg per day) and not vitamin K1, reduced arterial calcification by 50%, cardiovascular death by 50%, and all-cause mortality by 25% (Figure 5).

These findings were supported by another population-based study with 16,000 healthy women (aged 49-70)

three-year period as compared to the placebo group. Also, pulse-wave velocity was significantly decreased in the vitamin K2 (MK-7) group, but not the placebo group, demonstrating an increase in the elasticity and reduction in age-related arterial stiffening (50).

VITAMIN K2 AND CALCIUM: PERFECT TOGETHER KEEP THE CALCIUM... JUST ADD VITAMIN K2

The studies presented in Table I 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, 16).

Dysfunctional calcium-regulatory proteins such as MGP correlate with the development of arterial calcification. To render these proteins active, a sufficient amount of vitamin K2 has to be present in the body (46). If at least 32 µg of

specific proteins. If these proteins cannot perform their function by keeping calcium in the bones and preventing calcium deposits in soft tissues (e.g. arterial walls) during situations of increased calcium intake, then general health – and in particular cardiovascular health – may suffer due to an inefficient and misdirected utilization of calcium in the body.

CONCLUSION

Dietary calcium is linked to many benefits, especially bone health. This is why recommended daily intakes for calcium have been established. Because diets often fall short of these guidelines, in

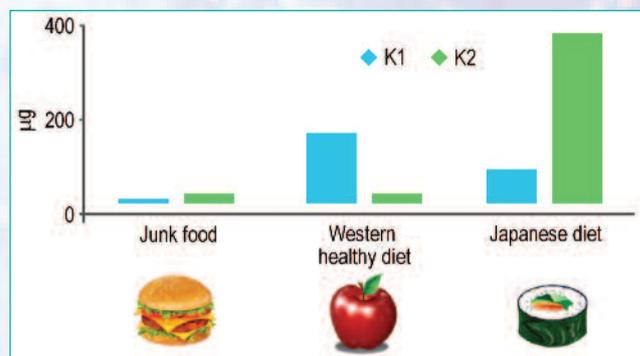


Figure 6 – Vitamin K deficiencies in Western diets.

- At elevated levels, calcium may increase the risk for heart disease, possibly by forming calcium deposits in blood vessels.
- Vitamin K2 has the ability to reverse arterial stiffening since it is a key regulator of the proteins that are involved in calcium use.
- Vitamin K2 might therefore neutralize the potential health problems associated with high calcium intakes.
- Calcium taken together with vitamin K2 may improve bone and vascular health.

Table III – Importance of calcium + vitamin K

particular in individuals with higher needs (e.g. children, the elderly and postmenopausal women), dietary supplementation can help address the body's demands. Although the study outcomes of high calcium consumption are controversial, several studies do suggest caution when it comes to over supplementing, especially since some evidence points to health problems at elevated levels (3-8).

This issue could be remedied, however, if the right amount of vitamin K2 is added to regimen (Table III). Vitamin K2 promotes arterial by preventing arterial calcium accumulation (10,43,48,50), which could correct the calcium in the body. Thus, calcium vitamin K2 may well be the solution necessary bone benefits while circumventing increased risk for heart disease.

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