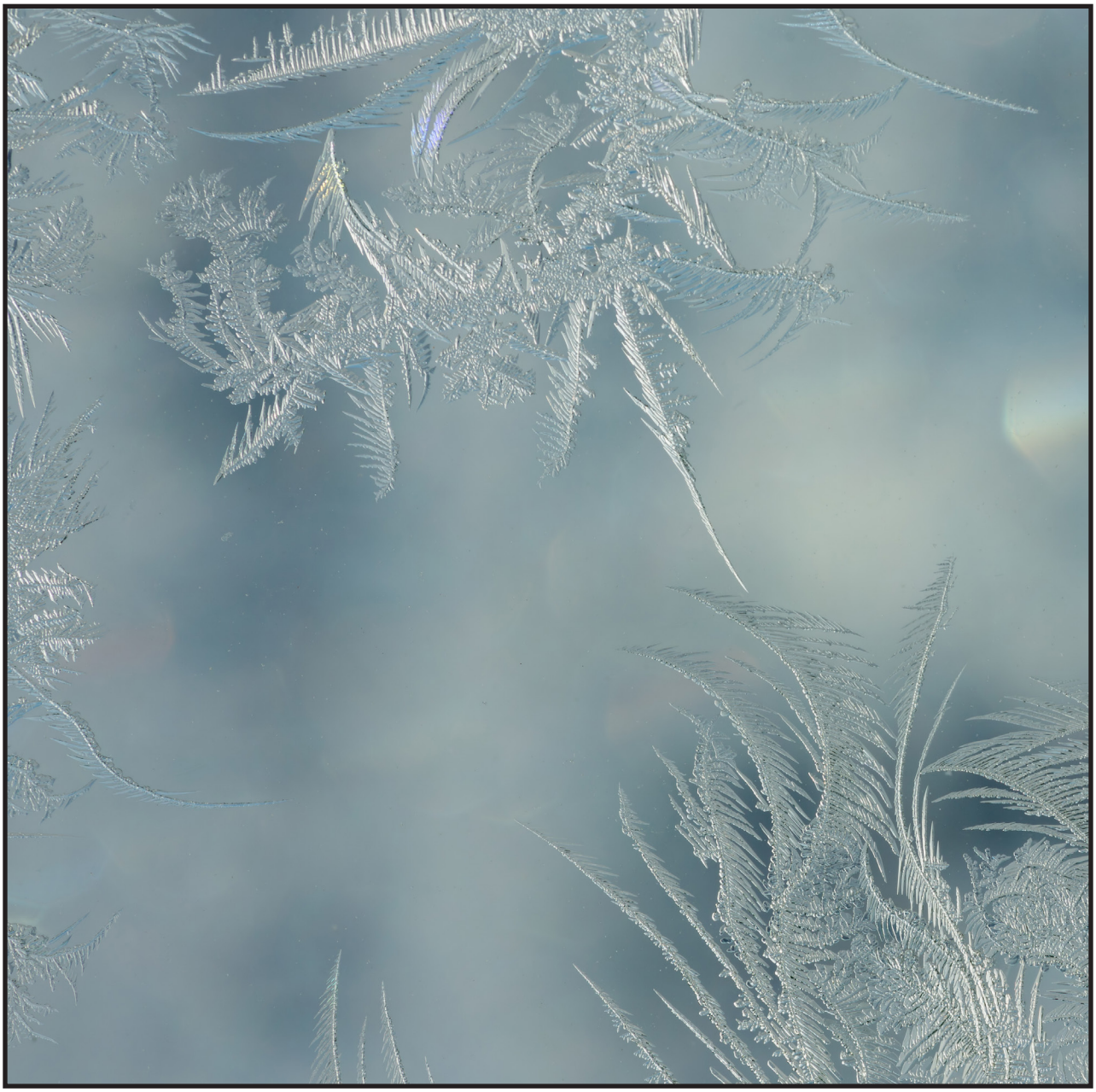
DECEMBER 2019/JANUARY 2020 • VOL. 18 NO. 6

IMCJ

Integrative Medicine: A Clinician's Journal



PERSECPTIVE

Highlighting The Substantial Body Of Evidence Confirming The Importance Of Vitamin K_2 As A Cardio-Support Nutrient, And How The Right K_2 Makes All The Difference

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In an ideal world, Vitamin K_2 would have the same association with cardiovascular health that folic acid has with pregnancy. Optimal Vitamin K_2 intake is crucial to avoid the calcium plaque buildup of atherosclerosis, thus keeping the risk and rate of calcification as low as possible.[1-3]

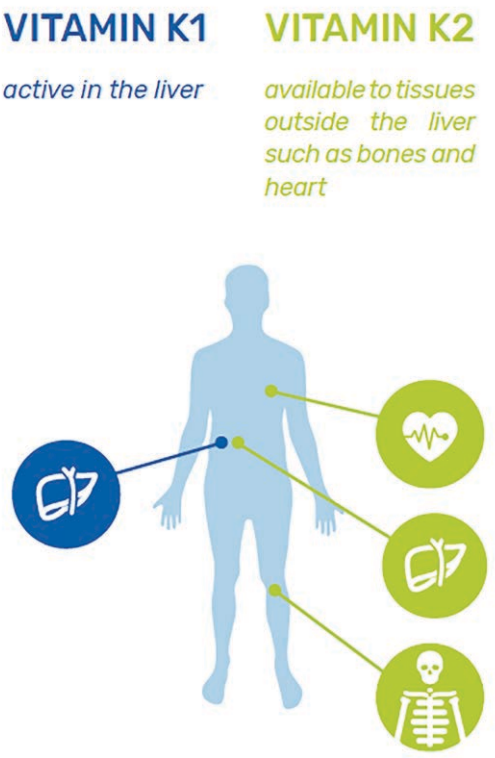
Matrix GLA protein (MGP)—found in the tissues of the heart, kidneys, and lungs—plays a dominant role in vascular calcium metabolism. Its production is stimulated by Vitamin D_3, but it requires adequate Vitamin K_2 intakes to be activated (similar to the bone-building protein osteocalcin). Once activated by Vitamin K_2, MGP can bind calcium and escort it out of the areas where this mineral is destructive, namely arteries and soft tissues.[1,4]

No other productive mechanism for maintaining flexible blood vessels walls has been discovered, which makes MGP the only known and most potent existing inhibitor of cardiovascular calcification.

That is why Vitamin K_2 is crucial as a cardiovascular health nutrient. Here we will endeavor to clear up considerable confusion about Vitamin K_2, ensuring the right form is identified, as well as provide the substantial body of evidence confirming its role as a cardiovascular-support nutrient.

Why Vitamin K_2 as MK-7 Matters Most

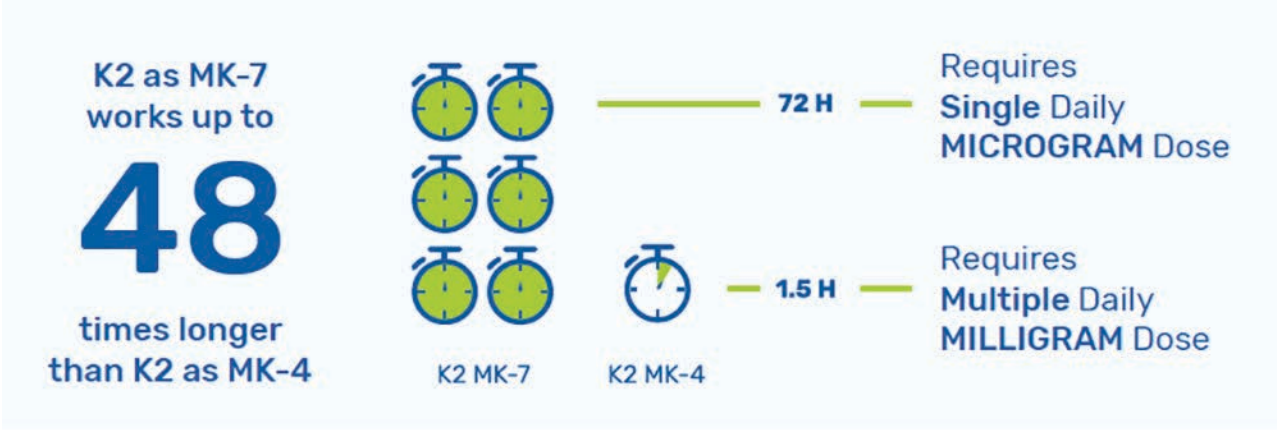
Vitamin K is a family of vitamins, the most important being Vitamins K_1 (phylloquinone) and K_2 (menaquinones).



Think of them as fraternal twins. They have similarities, such as working in the liver for blood clotting, and chemically they share a quinone ring called menadione.

But that is where their similarities end.

Vitamin K_2 has several molecules, called menaquinones, which make K_2 available beyond the liver for other systems. Vitamin K_1 is the principle source of dietary Vitamin K and is needed for proper blood coagulation. Meanwhile, Vitamin K_2 is essential to avoid calcium deposits in the arteries as well as to build and maintain strong bones. (A more detailed breakdown of Vitamin K_1 and Vitamin K_2, is in the review paper, "Vitamin K: Double Bonds beyond Coagulation Insights into Differences between Vitamin K_1 and K_2 in Health and Disease," published in *The International Journal of Molecular Sciences*.[5])



Not all forms of Vitamin K_2 are created equal. The two most commonly commercialized forms of Vitamin K_2 are MK-4 and MK-7. Due to its side chain, MK-7 has a much longer half-life in the body than MK-4, allowing it greater access to tissues beyond the liver.

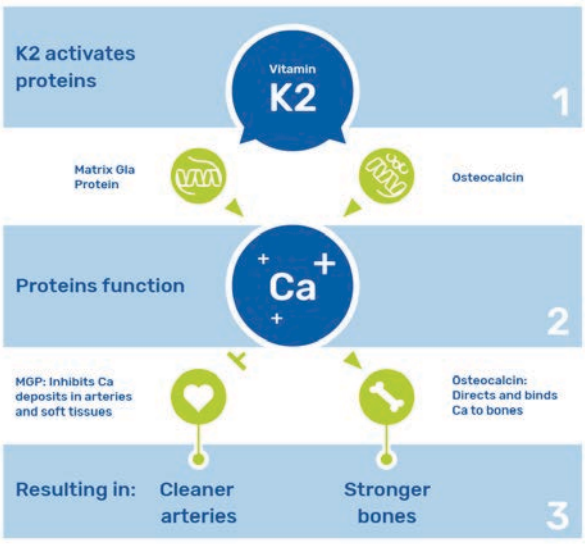
Further, the serum half-life of MK-4 has been shown to last a few hours compared to a 3+ day half-life for MK-7.

So although they have the same molecular mechanism of action, MK-7 is more bioavailable than MK-4. And due to MK-4's short half-life and poor bioavailability, it requires multiple doses per day at *milligram* levels–versus MK-7's *microgram* levels–for measurable efficacy.

How Vitamin K_2 "Turns On" MGP

So, how does MK-7 get MGP to reach its full potential?

Vitamin K_2, specifically MK-7, activates special proteins, allowing the body to properly utilize calcium. Two of these proteins are osteocalcin (OC) and MGP. The former attracts calcium to where it *is needed most*, namely into bones and teeth; the latter keeps calcium away from where it *is not needed*, namely soft tissues.



Proteins already present in the body rely on cofactors. Vitamin K_2 is the cofactor for an enzyme called vitamin-K-dependent carboxylase. The vitamin K-dependent proteins are activated by gamma-carboxylation, during which the structures of OC and MGP are altered by adding another carboxyl group to allow those proteins to bind calcium. In the case of Vitamin K_2 deficiency, they remain "under-carboxylated," or inactive.[1]

What MK-7 does better than any form of vitamin K is activate proteins made in different organs in the body, including the MGP in the vasculature. MGP is the most potent modulator of vascular calcification known, provided the body has enough Vitamin K_2 to activate it.

The collateral damage of a deficit carries tragic significance. A five-year study among 10000 asymptomatic individuals published in *Arteriosclerosis* found that survival rates were linked with the amount of calcium in blood vessels. The differences were vast: "A calcium score less than 10 correlated with 10 years younger biological age than the 'real age' in individuals older than 70 years. A calcium score above 400 correlated–on the other side–with a biological age up to 30 years older than the real age in younger patients."[6]

It is important to note that recent evidence highlights the benefits of active MGP extend beyond the heart and bone. In late 2018, The *Journal of Alzheimer's Disease* and *Scientific Reports* published papers that examined the role of aortic stiffness due to calcification as a contributing factor to dementia and retinal arteriolar health, respectively. Both conditions are impacted by the status of active MGP.

According to "Aortic Stiffness Associated with Increased Risk of Dementia in Older Adults,"[7] cardiovascular disease risk factors—including age, hypertension, and diabetes—contribute to aortic stiffness and subclinical cardiovascular and brain disease, increasing dementia risk.

In "Inactive Matrix Gla Protein is a Novel circulating Biomarker Predicting Retinal Arteriolar Narrowing in Humans,"[8] researchers studied a randomly recruited Flemish population. The conclusion: circulating inactive MGP (dp-ucMGP) is a long-term predictor of smaller retinal arteriolar diameter in the general population.

"Our observations highlight the possibility that vitamin K supplementation might promote retinal health," the researchers said.

Further, a 2019 study published in *Arteriosclerosis, Thrombosis, and Vascular Biology* observed that, based on the activation of MGP, Vitamin K_2 has the ability to scavenge free radicals and reduce oxidative stress.[9]

Vitamin K_2's Cardiovascular Connection

Evidence linking Vitamin K_2 intakes to cardiovascular benefits truly started to come to light in 2004. NattoPharma ASA saw this early observational evidence and carried it further, sponsoring intervention trials confirming this association and illuminating the actual mechanism. There is now a substantial bank of research, and most of the research used NattoPharma's MenaQ7® Vitamin K_2 as MK-7 as the actual source material.

The heart-healthy relationship between Vitamin K_2 and MGP first emerged in the landmark Rotterdam Study, which showed that high dietary intake of Vitamin K_2–but not Vitamin K_1–has a strong protective effect on cardiovascular health.

Findings from this 10-year population-based study indicated that eating foods rich in natural Vitamin K_2 (at least 32 mcg/day) resulted in 50 percent reduction of arterial calcification, 50 percent reduction of cardiovascular risk, and 25 percent reduction of all-cause mortality.[10] In 2009, these findings were confirmed by another population-based study with 16 000 subjects (ranging in age from 49 to 70) from the Prospect-EPIC cohort population. After following female participants for up to eight years, the researchers found that for every 10 mcg Vitamin K_2 (MK-7, MK-8, and MK-9) consumed—again, not Vitamin K_1—the risk of coronary heart disease was reduced by 9 percent. Vitamin K_1 intake had no effect.[11]

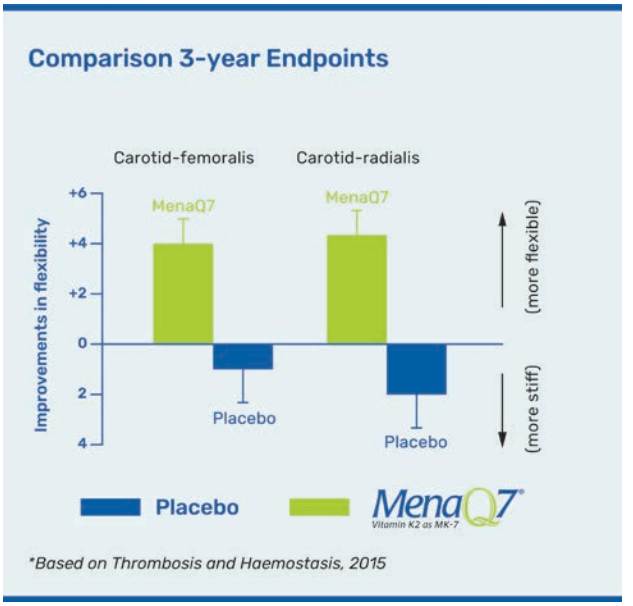
The Rotterdam Study (2004) and the Prospect-EPIC Study (2008) were the first population-based evidence that a high dietary intake of Vitamin K_2–but not vitamin K_1–offered a strong positive reduction in cardiovascular risk.

This important observational data highlighted the need for further examination, which is why NattoPharma sponsored a groundbreaking intervention study with cardiovascular endpoints where MenaQ7® Vitamin K_2 as MK-7 was the source material.

Scientists performed a double-blind, randomized, intervention study of 244 postmenopausal women given either 180 mcg of Vitamin K_2 as MK-7 (as MenaQ7® by NattoPharma) or a placebo daily for 3 years.

This first intervention trial on MK-7 supplements and cardiovascular endpoints showed that 3-year supplementation with a daily, nutritional dose of MenaQ7® was enough to actually decrease arterial stiffness in healthy post-menopausal women.

Using ultrasound and pulse-wave velocity measurements (recognized as standard measurements for cardiovascular health), researchers determined that carotid artery distensibility was significantly improved for a 3-year period in the MenaQ7® group as compared with that of a placebo group, especially in women having high arterial stiffness. Also, pulse-wave velocity showed a statistically significantly decrease after 3 years for the Vitamin K_2 (MK-7) group, but not for the placebo group, demonstrating an increase in the elasticity and reduction in age-related arterial stiffening, again, especially in women having high arterial stiffening.



This study had historical impact. It was the first intervention trial where the results confirmed the association made by previous population-based studies: Vitamin K_2 intake is linked to cardiovascular risk. A nutritional dose of Vitamin K_2, in fact, *promotes* cardiovascular health. No other compound to date has been shown to deliver the same cardiovascular protection as Vitamin K_2 as MK-7.[12]

Two studies in 2019 further strengthened (and reconfirmed) the relationship between Vitamin K_2 and cardiovascular disease.

First, researchers investigated the causal relationship between genetically predicted K concentrations and the risk of coronary heart disease in more than 103 000 cases in Europe. They found that K_1 had no impact on MGP, but that Vitamin K_2 had a positive impact on cardiovascular health.[13]

Second, the American Health Association's "Central Hemodynamics in Relation to Circulating Desphospho-Uncarboxylated Matrix Gla Protein: A Population Study," evaluated vitamin K status (dp-ucMGP) in 835 randomly recruited Flemish individuals. Researchers observed that higher inactive Vitamin K was associated with greater pulse wave velocity, central pressure, forward pulse wave, and backward pulse wave.

"Stiffening and calcification of the large arteries are forerunners of cardiovascular complications," the authors said. "MGP, which requires vitamin K-dependent

activation, is a potent locally acting inhibitor of arterial calcification. We hypothesized that the central hemodynamic properties might be associated with inactive desphospho-uncarboxylated MGP (dp-ucMGP)."[14]

A Silver Lining to a Perpetually Dark Forecast

Despite all the illuminating research, the news on cardiovascular health remains morbid.

What the consistent, grim statistics usually hide is that poor cardiovascular health is not an issue reserved for the middle-aged or elderly. A 2019 study of 22 346 young adults, ages 30 to 49, undergoing coronary artery calcium (CAC) testing for clinical indications, found that 34.4% had CAC, and those with elevated CAC scores had significantly higher rates of coronary heart disease and coronary vascular disease mortality.[15]

Traditional prescriptions for cardiovascular conditions include anticoagulants and statins, and both have important links to Vitamin K_2 that should be considered.

Anticoagulants. The most common treatment for poor blood flow is to prescribe a vitamin K antagonist, like Coumarin or warfarin. These prescribed drugs interfere with vitamin K activity in the liver, by inhibiting enzymes, resulting in the blood's inability to form an undesired blood clot. Yet recent studies have found association between long-term anticoagulant treatment and reduced bone quality due to reduction of active osteocalcin, as well as two-fold more arterial calcification compared to patients not receiving K vitamin antagonists.

Thankfully, the standard of care has improved with a new class of oral anticoagulants emerging that are *not* vitamin K antagonists and relatively devoid of major safety considerations.

Statins. Statins are a common recommendation for lowering LDL-C levels (cholesterol), and their use has been on the rise over the last few decades. However, a 2015 paper stated statins may act as "mitochondrial toxins" with negative effects on the heart and blood vessels via the depletion of coenzyme Q_{10} (CoQ_{10}) and by inhibiting Vitamin K_2 synthesis.[16]

This new paper speaks directly to statins interrupting the mechanism of action by which Vitamin K_2 inhibits calcification. Yet while CoQ_{10} and Vitamin K_2 are both affected by statins, no recommendation currently exists for supplemental Vitamin K_2 to be given to statin patients.

Vitamin K_2 may serve as an excellent option for keeping the benefits of these pharmaceuticals while tamping down the deleterious effects. That means more treatment options for patients who can continue to support their cardiovascular health with Vitamin K_2 supplementation.

K_2 as MK-7 is a Complementary Cardio Nutrient

It is also important to note that Vitamin K_2 works in concert with other nutrients that might already be a part of one's cardiovascular regimen.

A 2013 study examined Vitamin K_2's influence on vessel calcification in 3.- 5. stage chronic kidney disease patients over six months. This prospective randomized human clinical trial evaluated the cardiovascular effects of oral administration of Vitamin K_2 (as MenaQ7®) plus vitamin D or vitamin D alone.

The progression of coronary artery calcification index (CAC) and common carotid intima media thickness (CCA-IMT)—both markers of calcium deposits in arteries detected with computerized tomography—showed a slower progression of the calcification in the MenaQ7®/vitamin D group than in the D-alone group, an encouraging sign to use this possibly potent duo.[17]

Further, Omega-3 has been recognized for cardiovascular support, with qualified health claims for the reduction in risk of Coronary Heart Disease in the US. While Omega-3's mechanism of action is linked to supporting healthy inflammation, triglycerides, blood pressure, and the promotion of arterial health, it is not recognized for impacting vascular calcification. This is what makes Vitamin K_2 a perfect complementary nutrient–providing the final piece of the heart-health puzzle.

NattoPharma ASA has been awarded a Canadian patent (no. 2,657,748) that covers pharmaceutical and nutraceutical products providing Vitamin K_2 in combination with one or more polyunsaturated fatty acids, including fish and/or krill oil, for benefits related to bone, cartilage, and the cardiovascular system.

Proven Bone Benefits of K_2 as MK-7: Simultaneous Support

Aside from co-existing peacefully with other nutrients, patients who take Vitamin K_2 also get the potent bone health benefits that arise from its effect on osteocalcin. This has been established in a raft of studies, highlighted by a breakthrough double-blind randomized clinical trial published in 2013 in *Osteoporosis International*.

The study demonstrated for the first time clinically statistically significant protection of the vertebrae and the hip (femoral neck) against bone loss. This was attained with a nutritional dose of Vitamin K_2 as MK-7 (again, MenaQ7® from NattoPharma) taken daily for three years.

In this study of 244 healthy post-menopausal women, the MenaQ7® group took 180 mcg daily and showed significantly decreased circulating uncarboxylated osteocalcin (ucOC). After three years, both bone mineral content and bone mineral density, as well as bone strength were statistically significantly better for the MK-7 group compared to the placebo group.[18]

Vitamin K_2's effect on bone health on children is particularly notable, since childhood is the most important time for the building of healthy bones. Here are some highlights:

- 2009: Healthy children aged 6-10 years who took 45 mcg of MenaQ7® K_2 a day resulted in more active

osteocalcin, leading to stronger, denser bones.[19]

- 2012: Children and adults over the age of 40 express the greatest K deficiency and had the strongest response to MenaQ7® K_2 supplementation (45 mcg for children; 90 mcg from adults).[20]
- 2013: Children and teens given MenaQ7® K_2 (50 mcg) and vitamin D (5 mcg calcitriol) daily showed improvements in bone mineral density.[21]

Conclusion

In less than 20 years, more than 19 human clinical trials with Vitamin K_2 have been published confirming bone and cardiovascular health benefits in both healthy and patient populations, in young and old. The research will only grow. These trials have used NattoPharma's MenaQ7® as the actual source material, which further cements the need to use MenaQ7® as *your source* of Vitamin K_2 as MK-7, especially as cardiovascular health wreaks havoc on the world's population.

NattoPharma has led the charge for a Vitamin K_2 RDI, but practitioners can play a more immediate role in increasing the awareness of Vitamin K_2 as MK-7. You can explain—and further simplify—the power of Vitamin K_2 to your patients and colleagues.

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