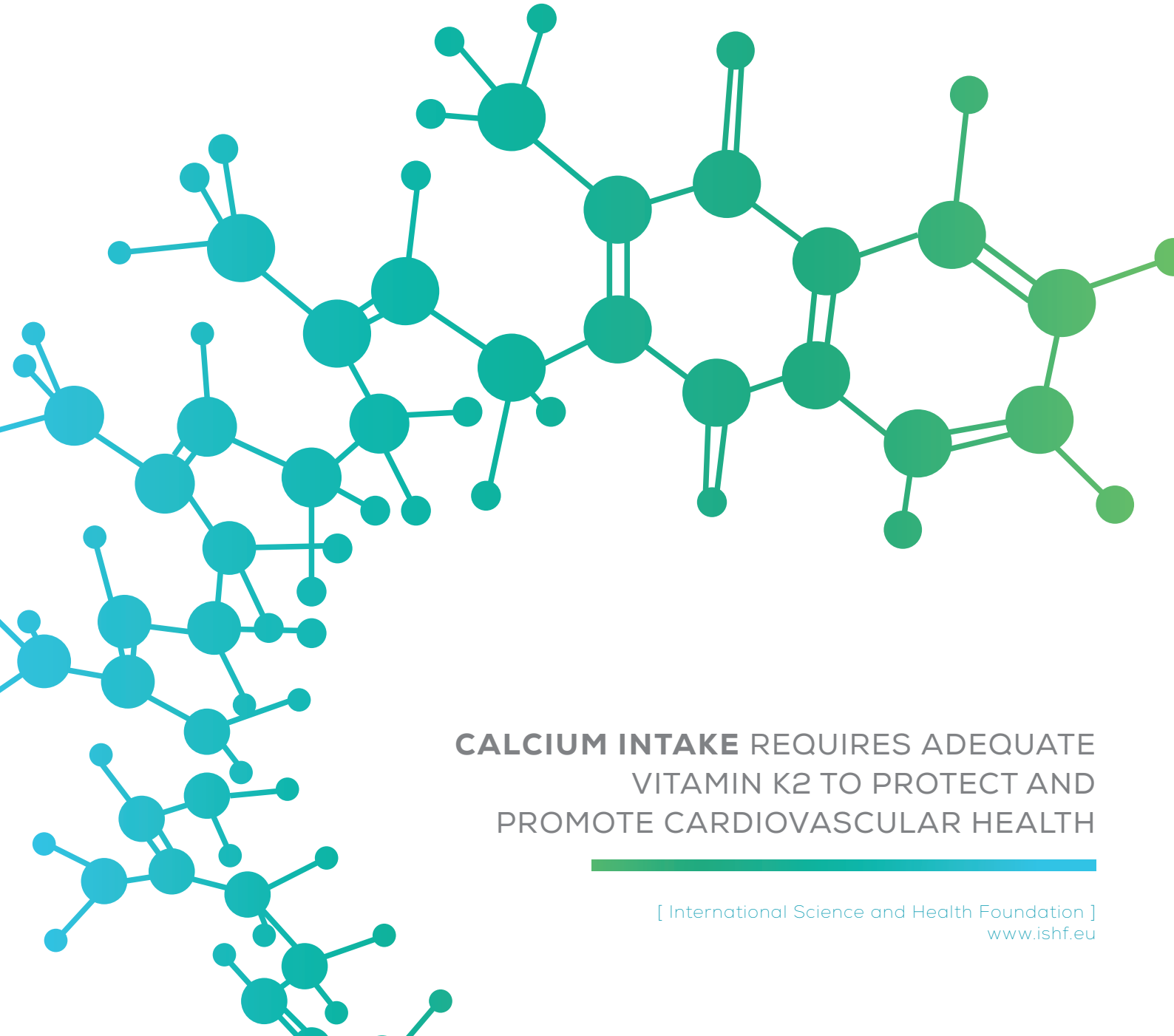
VITAMIN K2 &
THE CALCIUM CONNECTION



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[3-8] (*see Table 2*).

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 serves many important roles in the human body (*see Table 1*). 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 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 ≥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]"

TABLE 1

CALCIUM FACTS

- **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.

TABLE 2

TITLE	POPULATION-CHARACTERISTICS	MAIN FINDINGS	REFERENCE
HEALTH CONCERNS WITH CALCIUM SUPPLEMENTATION			
1. 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. **Mauritas.** 2009.	Women (52-62 y)	Increased risk of CVD with calcium or calcium+vitamin D Supplement	(7)
2. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. **BMJ.** 2010.	Men and women (>40 y)	Increased heart attack risk with calcium Supplements	(3)
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. **BMJ.** 2011.	Postmenopausal women	Calcium or calcium+vitamin D Supplements increases heart attack risk	(4)
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). **Am J Clin Nutr.** 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)
5. Long term calcium intake and rates of all-cause and cardiovascular mortality: community based prospective longitudinal cohort study. **BMJ.** 2013.	Women (>40 y)	High calcium intake is linked to higher death rates from all causes and CVD	(6)
6. Dietary and supplemental calcium intake and cardiovascular disease mortality: the National Institutes of Health-AARP diet and health study. **JAMA.** 2013.	Men and women (50-71 y)	High supplemental calcium increases risk of CVD death in men only	(8)

TITLE	POPULATION-CHARACTERISTICS	MAIN FINDINGS	REFERENCE
HEALTH BENEFITS OF VITAMIN K2 SUPPLEMENTATION			
7. 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. **Nutrition.** 2001.	Postmenopausal women	Increased intake of MK-7 helps to reduce hip fracture risk	(40)
8. Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study. **J Nutr.** 2004.	Men and women (>55 y)	High menaquinone intake reduces risk of CVD mortality, all-cause mortality and severe aortic calcification	(10)
9. Regression of warfarin-induced medial elastocalcinosis by high intake of vitamin K in rats. **Blood.** 2007.	Rats	Vitamin K2 reduces aortic calcium levels and increases arterial distensibility in an induced arterial calcification model	(43)
10. High dietary menaquinone intake is associated with reduced coronary calcification. **Atherosclerosis.** 2009.	Postmenopausal women	High dietary vitamin K2 reduces coronary calcium deposits	(9)
11. A high menaquinone intake reduces the incidence of coronary heart disease. **Nutr Metab Cardiovasc Dis.** 2009.	Women (49-70 y)	High vitamin K2 intake (MK-7, -8, -9) is linked to lower CVD risk	(45)
12. Effect of vitamin K2 supplementation on functional vitamin K deficiency in hemodialysis patients: a randomized trial. **Am J Kidney Dis.** 2012.	Hemodialysis patients (≥18 y)	Vitamin K2 Supplementation improves activity of a protein involved in calcium removal in arterial wall (MK-7) (MenaQ7®)	(48)
13. Three-year low-dose menaquinone-7 supplementation helps decrease bone loss in healthy postmenopausal women. **Osteoporosis Int.** 2013.	Postmenopausal women	Mk-7 Supplement may help to prevent bone loss (MenaQ7®)	(49)
14. 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)

OVERVIEW .

A study published by Xiao et. al. 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.[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]

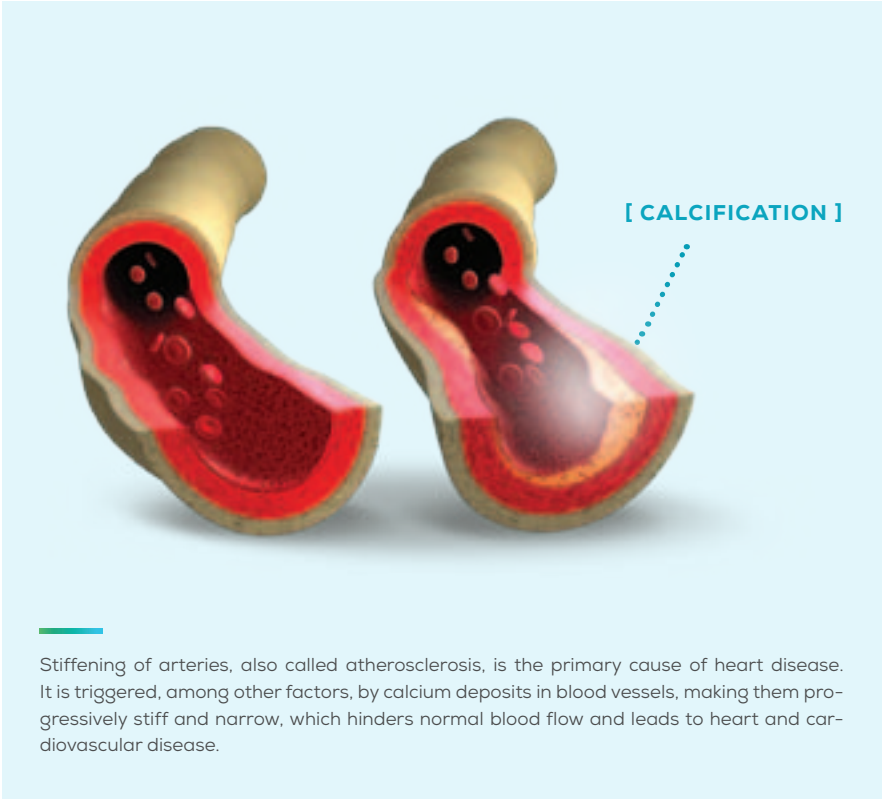
Also, researchers from the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg) concluded that in the 23,980 participants, those regularly taking a calcium supplement had an 86% higher risk for heart attack compared to those not taking a supplement.[5] The effect was even 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 meta-analysis (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 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 (*see Figure 1*).[4, 8, 27, 28]

FIGURE 1: ATHEROSCLEROSIS DEVELOPMENT



Stiffening of arteries, also called atherosclerosis, is the primary cause of heart disease. It is triggered, among other factors, by calcium deposits in blood vessels, making them progressively stiff and narrow, which hinders normal blood flow and leads to heart and cardiovascular disease.

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" (*see Table 3*).[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) (*see 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."

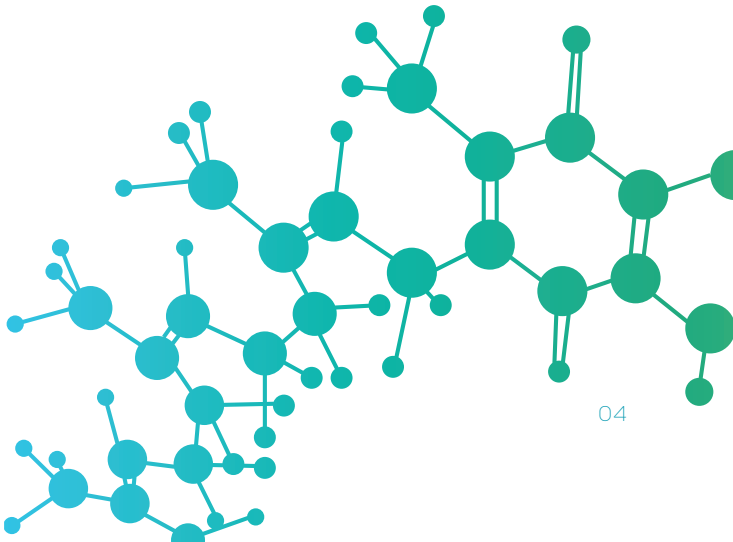
Vitamin K, particularly vitamin K2, is essential for calcium utilization, helping build strong bones and inhibit arterial calcification.

TABLE 3

VITAMIN K2 FACTS

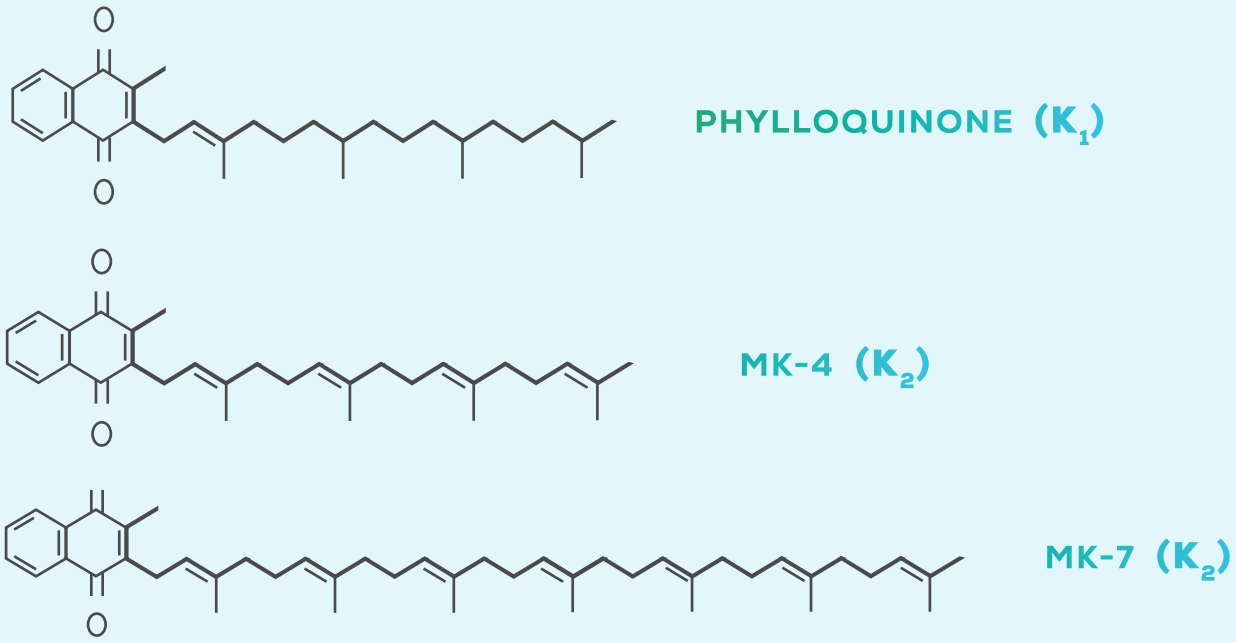
VITAMIN K2 (menaquinones)

- **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.**



VITAMIN K2 .

FIGURE 2: CHEMICAL STRUCTURE OF VITAMIN K1 & K2 (MK-4 & MK-7)



Different types of vitamin K vary in length and saturation (double versus single bonds) of the isoprenoid side chain. Vitamin K2/Menaquinones are abbreviated as MK-n, where "n" symbolizes the number of isoprene repeats (C_5H_8).

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 (*see 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 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 (*see 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]

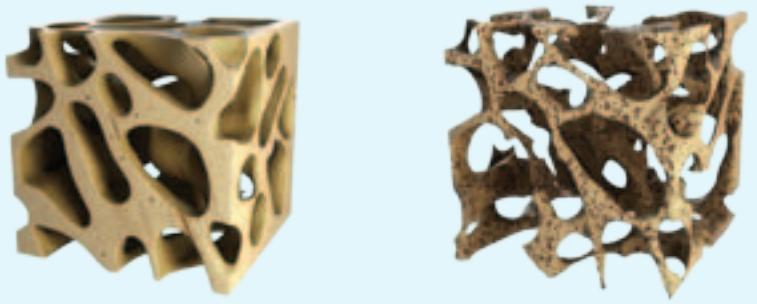
"A study in children also showed that improving vitamin K2 intake over a two-year period led to stronger and denser bones.[39]"

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

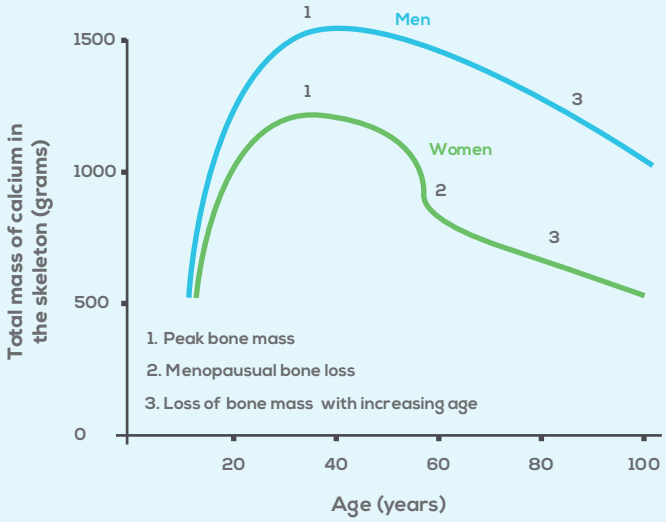
One recent double-blind, randomized clinical trial investigated the effect of supplemental MK-7 (MenaQ7®) over three years in a group of 244 post-menopausal Dutch women.[49] Researchers found that a daily dose of 180 mcg was enough to improve bone mineral density, bone strength and cardiovascular health.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

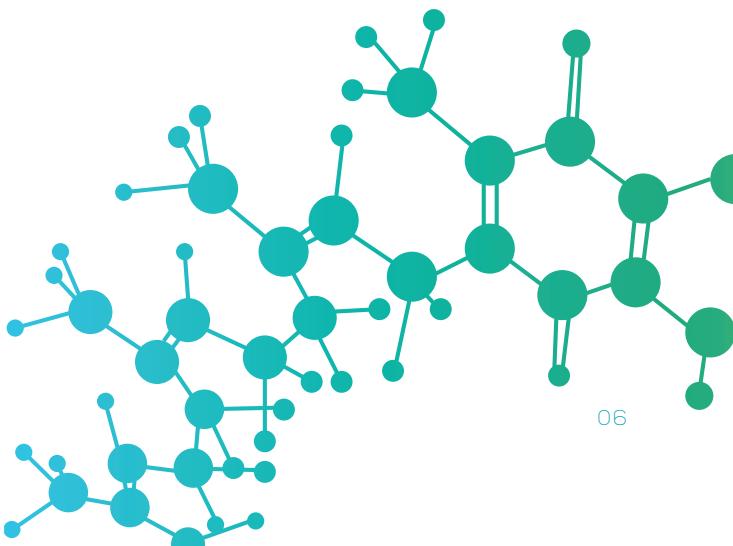
FIGURE 3: HEALTHY BONE STRUCTURE VS. POOR BONE STRUCTURE



Bone is a living material comprised of a hard outer shell and spongy inner tissue structured to withstand the physical stress of bearing body mass. The entire skeleton is replaced approximately every seven years due to the remodelling action of osteoclasts. Vitamin K2 is needed for activation of proteins (e.g., osteocalcin) invovled in bone formation, which is why a diet low in vitamin K2 reduces bone strength and density.

FIGURE 4: CALCIUM LOSS INCREASES WITH AGE





THE IDEAL STATE OF HEART HEALTH

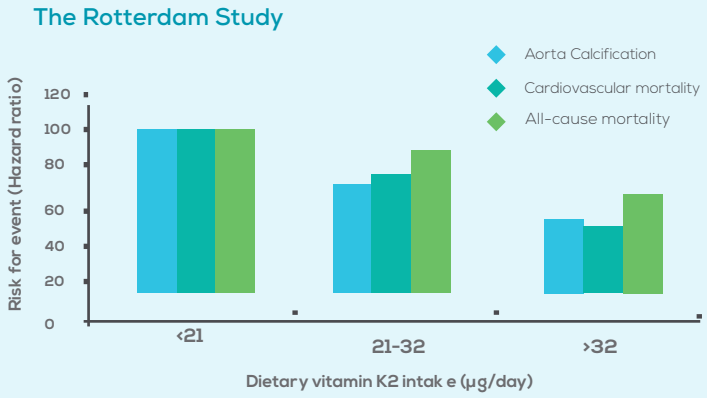
Adequate intake of vitamin K2 has been shown to lower the risk of vascular damage because it activates Matrix Gla Protein (MGP), which inhibits calcium from depositing in the vessel walls (arterial calcification).

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 mcg per day) and not vitamin K1, reduced arterial calcification by 50%, cardiovascular death by 50%, and all-cause mortality by 25% (*see Figure 5*).

These findings were supported by another population-based study with 16,000 healthy women (aged 49-70) from the Prospect-EPIC cohort population.[45]

FIGURE 5: HIGH VITAMIN K2 CONSUMPTION PROMOTES CARDIOVASCULAR HEALTH



"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 mcg 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 mcg 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 three-year period as compared to the placebo group (*see Figure 6*). 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 (*see Figure 7*).[50]

FIGURE 6: CAROTID ARTERY DISTENSIBILITY IMPROVED

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FIGURE 7: CAROTID & FEMORAL ARTERIES PULSE WAVE VELOCITY IMPROVED

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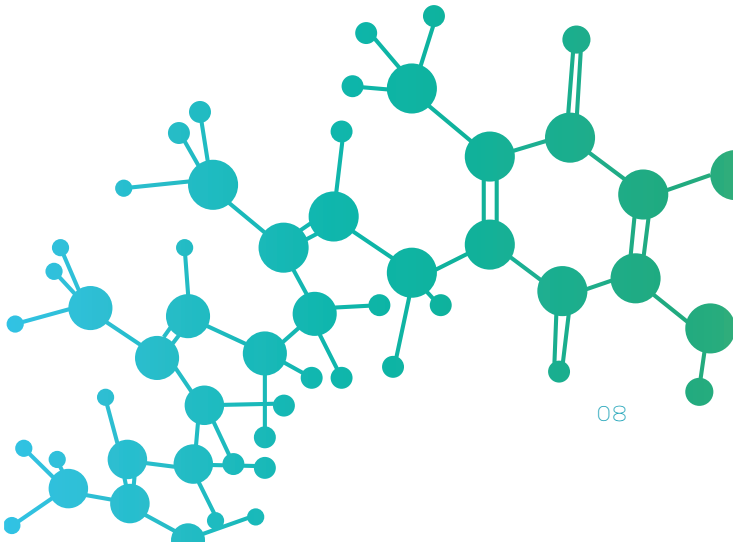


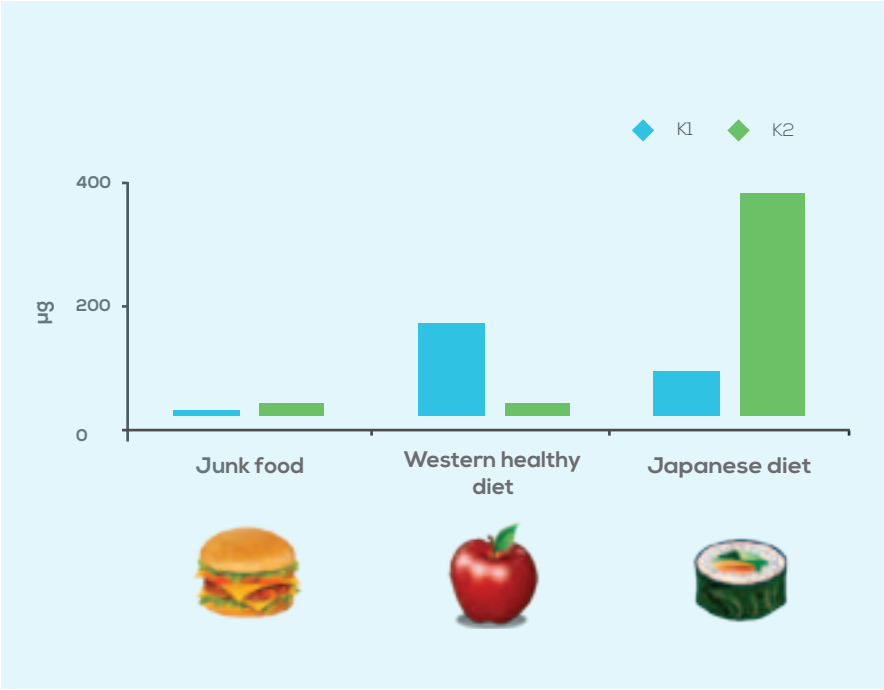
VITAMIN K2 & CALCIUM: PERFECT TOGETHER

KEEP THE CALCIUM ...JUST ADD VITAMIN K2

The studies presented in *Table 2* 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-regulatoryproteins 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 mcg of 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.

FIGURE 8: VITAMIN K DEFICIENCIES IN WESTERN DIETS



"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 (*see Figure 8*).

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

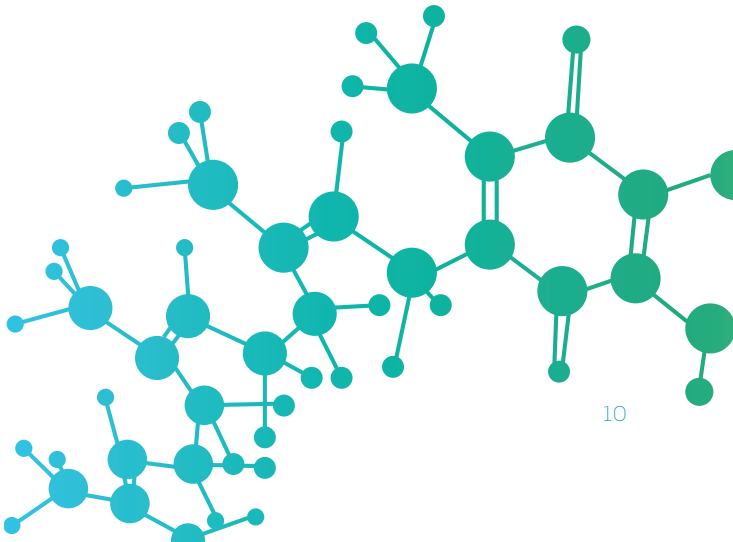
Dietary calcium is linked to many benefits, especially bone health. This is why recommended daily intakes for calcium have been established. Because diets often fall short of these guidelines, in particular in individuals with higher needs (e.g. children, the elderly and postmenopausal women), dietary 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 a high calcium regimen. Vitamin K2 promotes arterial flexibility by preventing arterial calcium accumulation[10, 43, 48, 50], which could correct the imbalance of calcium in the body. 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.

TABLE 4

IMPORTANCE OF CALCIUM + VITAMIN K2

- **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.



REFERENCES .

1. **Cumming RG, Cummings SR, Nevitt MC, et al.** Calcium intake and fracture risk: results from the study of osteoporotic fractures. Am J Epidemiol. 1997;145:926-34.

2. **Hodgson SF, Watts NB, Bilezikian JP, et al.** American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003. Endocr Pract. 2003;9:544-64.

3. **Bolland MJ, Avenell A, Baron JA, et al.** Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ. 2010;341:c3691.

4. **Bolland MJ, Grey A, Avenell A, et al.** 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. BMJ. 2011;342:d2040.

5. **Li K, Kaaks R, Linseisen J, et al.** 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). Heart. 2012;98:920-5.

6. **Michaelsson K, Melhus H, Warensjo Lemming E, et al.** Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. BMJ. 2013;346:f228.

7. **Pentti K, Tuppurainen MT, Honkanen R, et al.** 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. Maturitas. 2009;63:73-8.

8. **Xiao Q, Murphy RA, Houston DK, et al.** Dietary and supplemental calcium intake and cardiovascular disease mortality: the National Institutes of Health-AARP diet and health study. JAMA Intern Med. 2013;173:639-46.

9. **Beulens JW, Bots ML, Atsma F, et al.** High dietary menaquinone intake is associated with reduced coronary calcification. Atherosclerosis. 2009;203:489-93.

10. **Geleijnse JM, Vermeer C, Grobbee DE, et al.** Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study. J Nutr. 2004;134:3100-5.

11. **Edwards SL.** Maintaining calcium balance: physiology and implications. Nurs Times. 2005;101:58-61.

12. **Bailey RL, Dodd KW, Goldman JA, et al.** Estimation of total usual calcium and vitamin D intakes in the United States. J Nutr. 2010;140:817-22.

13. **van Mierlo LA, Arends LR, Streppel MT, et al.** Blood pressure response to calcium supplementation: a meta-analysis of randomized controlled trials. J Hum Hypertens. 2006;20:571-80.

14. **Ditscheid B, Keller S, Jahreis G.** Cholesterol metabolism is affected by calcium phosphate supplementation in humans. J Nutr. 2005;135:1678-82.

15. **Major GC, Alarie F, Dore J, et al.** Supplementation with calcium + vitamin D enhances the beneficial effect of weight loss on plasma lipid and lipoprotein concentrations. Am J Clin Nutr. 2007;85:54-9.

16. **Reid IR, Mason B, Horne A, et al.** Effects of calcium supplementation on serum lipid concentrations in normal older women: a randomized controlled trial. Am J Med. 2002;112:343-7.

17. **Bostick RM, Kushi LH, Wu Y, et al.** Relation of calcium, vitamin D, and dairy food intake to ischemic heart disease mortality among postmenopausal women. Am J Epidemiol. 1999;149:151-61.

18. **Al-Delaimy WK, Rimm E, Willett WC, et al.** A prospective study of calcium intake from diet and supplements and risk of ischemic heart disease among men. Am J Clin Nutr. 2003;77:814-8.

19. **Marniemi J, Alanen E, Impivaara O, et al.** Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects. Nutr Metab Cardiovasc Dis. 2005;15:188-97.

20. **Umesawa M, Iso H, Ishihara J, et al.** Dietary calcium intake and risks of stroke, its subtypes, and coronary heart disease in Japanese: the JPHC Study Cohort I. Stroke. 2008;39:2449-56.

21. **Umesawa M, Iso H, Date C, et al.** Dietary intake of calcium in relation to mortality from cardiovascular disease: the JACC Study. Stroke. 2006;37:20-6.

22. **Van der Vijver LP, van der Waal MA, Weterings KG, et al.** Calcium intake and 28-year cardiovascular and coronary heart disease mortality in Dutch civil servants. Int J Epidemiol. 1992;21:36-9.

23. **Reid IR.** Cardiovascular effects of calcium supplements. Nutrients. 2013;5:2522-9.

24. **Goodman WG, Goldin J, Kuizon BD, et al.** Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000;342:1478-83.

25. **Russo D, Miranda I, Ruocco C, et al.** The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. Kidney Int. 2007;72:1255.

26. **Jamal SA, Vandermeer B, Raggi P, et al.** Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. Lancet. 2013.

27. **Seely S.** Is calcium excess in western diet a major cause of arterial disease? Int J Cardiol. 1991;33:191-8.

28. **Wang L, Manson JE, Sesso HD.** Calcium intake and risk of cardiovascular disease: a review of prospective studies and randomized clinical trials. Am J Cardiovasc Drugs. 2012;12:105-16.

29. **Zetterstrom R. H. C. P. Dam (1895-1976) and E. A. Doisy (1893-1986):** the discovery of antihaemorrhagic vitamin and its impact on neonatal health. Acta Paediatr. 2006;95:642-4.

30. **Beulens JW, Booth SL, van den Heuvel EG, et al.** The role of menaquinones (vitamin K2) in human health. Br J Nutr. 2013:1-12.

31. **Bolton-Smith C, Price RJ, Fenton ST, et al.** Compilation of a provisional UK database for the phylloquinone (vitamin K1) content of foods. Br J Nutr. 2000;83:389-99.

32. Schurgers LJ, Vermeer C. Determination of phylloquinone and menaquinones in food. Effect of food matrix on circulating vitamin K concentrations. Haemostasis. 2000;30:298-307.

33. Shearer MJ, Newman P. Metabolism and cell biology of vitamin K. Thromb Haemost. 2008;100:530-47.

34. Kalkwarf HJ, Khoury JC, Bean J, et al. Vitamin K, bone turnover, and bone mass in girls. Am J Clin Nutr. 2004;80:1075-80.

35. O'Connor E, Molgaard C, Michaelsen KF, et al. Serum percentage undercarboxylated osteocalcin, a sensitive measure of vitamin K status, and its relationship to bone health indices in Danish girls. Br J Nutr. 2007;97:661-6.

36. Iwamoto J, Takeda T, Ichimura S. Effect of combined administration of vitamin D3 and vitamin K2 on bone mineral density of the lumbar spine in postmenopausal women with osteoporosis. J Orthop Sci. 2000;5:546-51.

37. Shiraki M, Shiraki Y, Aoki C, et al. Vitamin K2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis. J Bone Miner Res. 2000;15:515-21.

38. Ushiroyama T, Ikeda A, Ueki M. Effect of continuous combined therapy with vitamin K(2) and vitamin D(3) on bone mineral density and coagulofibrinolysis function in postmenopausal women. Maturitas. 2002;41:211-21.

39. van Summeren MJ, van Coeverden SC, Schurgers LJ, et al. Vitamin K status is associated with childhood bone mineral content. Br J Nutr. 2008;100:852-8.

40. Kaneki M, Hodges SJ, Hosoi T, et al. 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. Nutrition. 2001;17:315-21.

41. Ikeda Y, Iki M, Morita A, et al. Intake of fermented soybeans, natto, is associated with reduced bone loss in postmenopausal women: Japanese Population-Based Osteoporosis (JPOS) Study. J Nutr. 2006;136:1323-8.

42. Knapen MH, Schurgers LJ, Vermeer C. Vitamin K2 supplementation improves hip bone geometry and bone strength indices in postmenopausal women. Osteoporos Int. 2007;18:963-72.

43. Schurgers LJ, Spronk HM, Soute BA, et al. Regression of warfarin-induced medial elastocalcinosis by high intake of vitamin K in rats. Blood. 2007;109:2823-31.

44. Cranenburg EC, Vermeer C, Koos R, et al. The circulating inactive form of matrix Gla Protein (ucMGP) as a biomarker for cardiovascular calcification. J Vasc Res. 2008;45:427-36.

45. Gast GC, de Roos NM, Sluijs I, et al. A high menaquinone intake reduces the incidence of coronary heart disease. Nutr Metab Cardiovasc Dis. 2009;19:504-10.

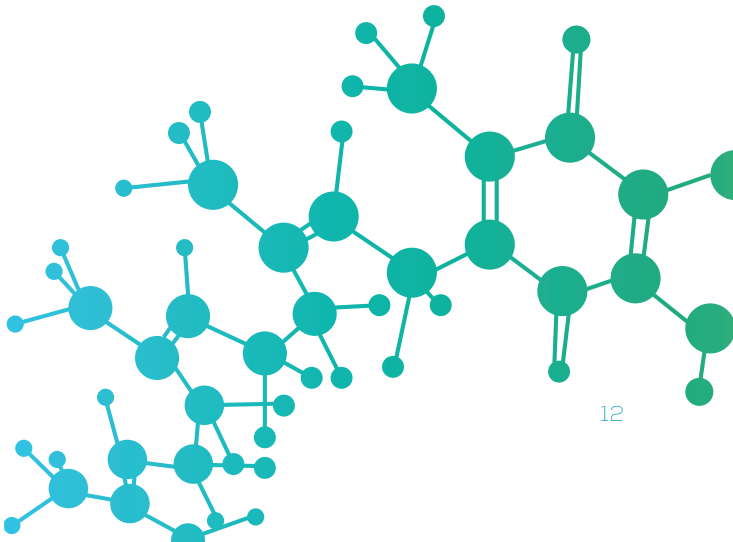
46. Berkner KL, Runge KW. The physiology of vitamin K nutriture and vitamin K-dependent protein function in atherosclerosis. J Thromb Haemost. 2004;2:2118-32.

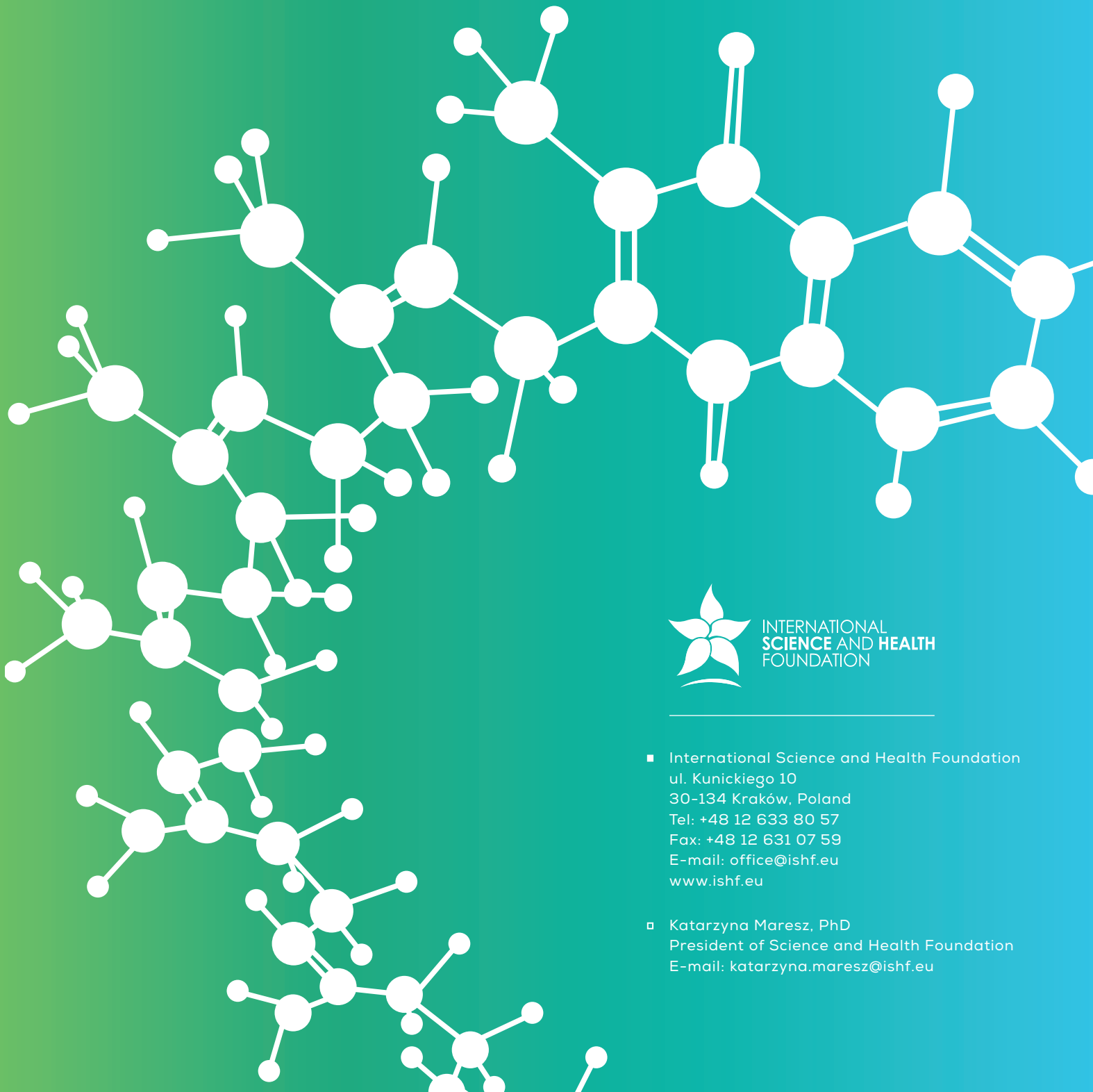
47. Braam LA, Hoeks AP, Brouns F, et al. Beneficial effects of vitamins D and K on the elastic properties of the vessel wall in postmenopausal women: a follow-up study. Thromb Haemost. 2004;91:373-80.

48. Westenfeld R, Krueger T, Schlieper G, et al. Effect of vitamin K2 supplementation on functional vitamin K deficiency in hemodialysis patients: a randomized trial. Am J Kidney Dis. 2012;59:186-95.

49. Knapen MH, Drummen NE, Smit E, et al. Three-year low-dose menaquinone-7 supplementation helps decrease bone loss in healthy postmenopausal women. Osteoporosis Int. 2013.

50. Proprietary study on MenaQ7® Vitamin K2 pending publication. Submitted. Contact NattoPharma, Oslo, for details.





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