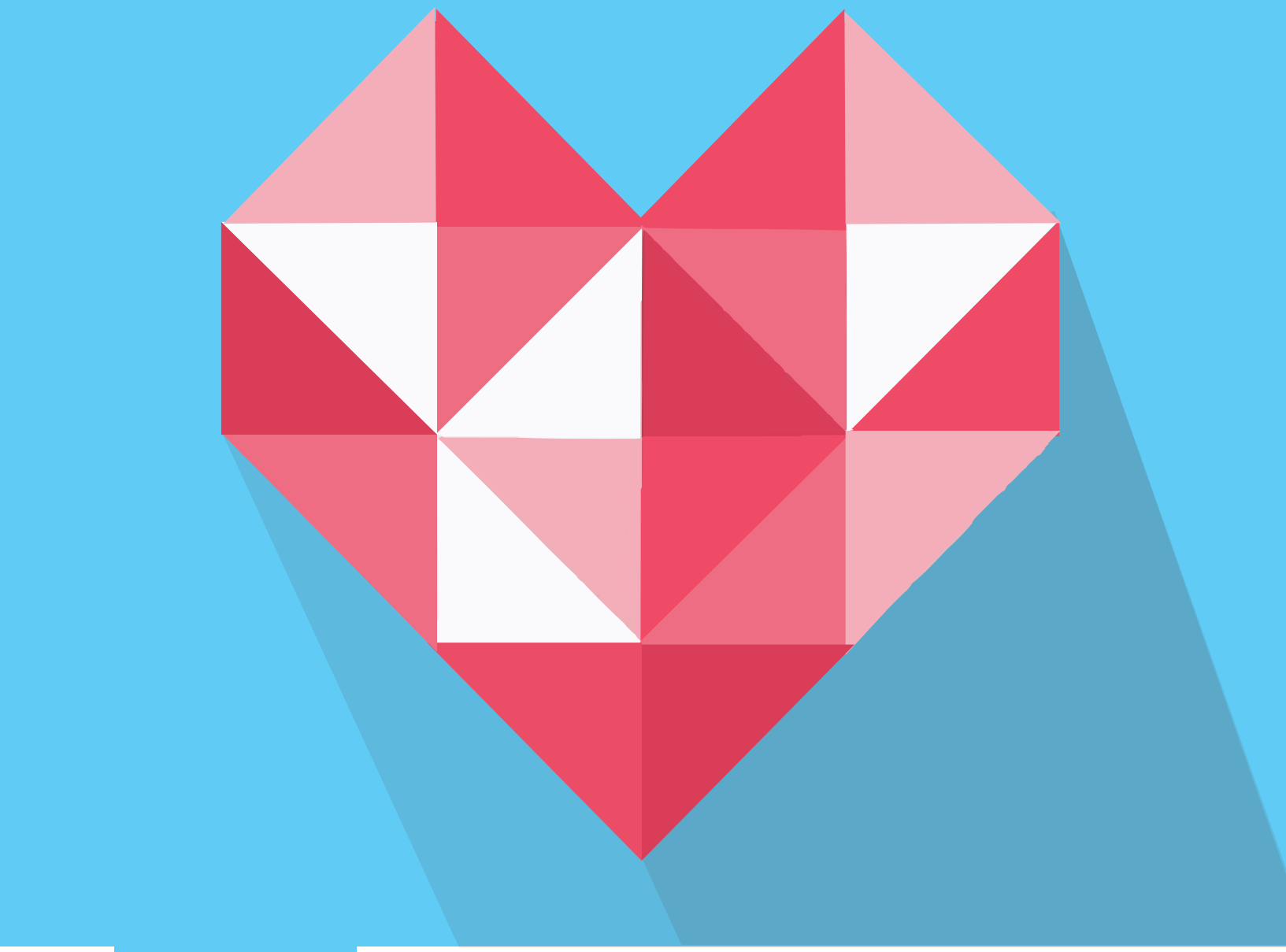


Vitamin K2:

An Essential Nutrient in the Pursuit of Heart Health

Calcification is believed to be an unfortunate result of aging, but studies show that arterial calcification is, in fact, an actively regulated process. Recognized as the most potent modulator of vascular calcification, Matrix Gla Protein (MGP) can only fulfill its heart-protecting role if the body has adequate amounts of Vitamin K2 to activate it.

While observational data suggest a link between Vitamin K2 intake and cardiovascular health, a newly published breakthrough study has confirmed this nutrient as absolutely essential in combating age-related cardiovascular decline.

Calcified Arteries

The first stage of cardiovascular disease (CVD) is usually characterized by atherosclerosis. This is a process that develops over many years wherein cardiovascular arteries clog and harden as a result of plaque formation where calcium is the main mineral component.

Calcification contributes to vascular disease by increasing vessels' stiffness and fragility, impeding healthy blood flow to and from the heart, thus also increasing the workload on the heart.[1] Scientific studies have confirmed that the amount of calcium stored in the arteries is an indicator of one's cardiovascular health.[2]

Population-based research shows that the survival rate is associated with the size of calcified areas present within the vasculature. Significant calcification makes one older than what their birth certificate states; while with little or no calcification, it has been suggest that one may deduct up to 10 years from one's chronological age.[3] In short, you are as old as your arteries.

Key Facts

- **Cardiovascular disease (CVD)** is the main cause of global mortality and morbidity.
- **Calcium deposition in the arteries** is actively regulated by many factors, including Matrix Gla Protein (MGP), the most potent modulator of calcification known today.
- **To perform its preventative functions, MGP** must be activated by the vitamin K-dependent enzyme: gammaglutamyl carboxylase. Thus, vitamin K deficiency leads to the synthesis of inactive MGP species, which cannot inhibit calcification.
- **Findings from the Rotterdam study** by Geleijnse et al. (2004) and the Prospect study by Gast et al. (2008) show that significant intake of vitamin K2, but not K1, has a strong protective effect on heart health. This Rotterdam study publication showed that daily consumption of more than 32 µg dietary vitamin K2 reduces the risk of both arterial calcification and cardiovascular death by as much as 50%. The Prospect study emphasized this finding by showing that for every 10 µg vitamin K2 consumed, there is a reduction in risk of coronary heart disease (CHD) by 9%.
- **Study performed by Westenfeld** et al. (2012) showed that inactive MGP levels in patients can be decreased markedly by daily vitamin K2 supplementation.
- **The recently published breakthrough 3-year study** by Knapen et al. (2015) shows substantial benefits in preventing age-related stiffening of arteries resulting in increase of pulse wave velocity (PWV) in the placebo group, but not in the vitamin K2-group. Most remarkably, vitamin K2 (MK-7 as MenaQ7®) not only inhibited stiffening, it also resulted in an unprecedented statistically significant improvement of vascular elasticity both measured by ultrasound techniques and PWV.

Matrix Gla Protein

Calcification was until recently believed to be an irreversible process and a consequence of aging. As such it is often associated with the final stage of CVD. However, it is now known that calcium accumulation is an actively regulated process, strongly influenced by the vitamin K-dependent Matrix Gla Protein (MGP) – the most potent natural inhibitor of calcification presently known.[4] Animal studies show that the highest levels of MGP are expressed in the heart, lungs, kidneys, and cartilage. The unquestionable role of MGP in calcification inhibition was demonstrated by Lou et al. in 1997.[5] They used MGP knock-out mice to show that animals without the ability to make MGP died after only six to eight weeks due to massive calcification of the arteries.

This experiment – and later other studies – shows that MGP is a key inhibitor of soft vascular tissue calcification.[6-9] MGP can be measured in blood, but studies indicate that its primary effect is in tissues where it binds calcium and prevents it from crystallizing in the vessel walls.

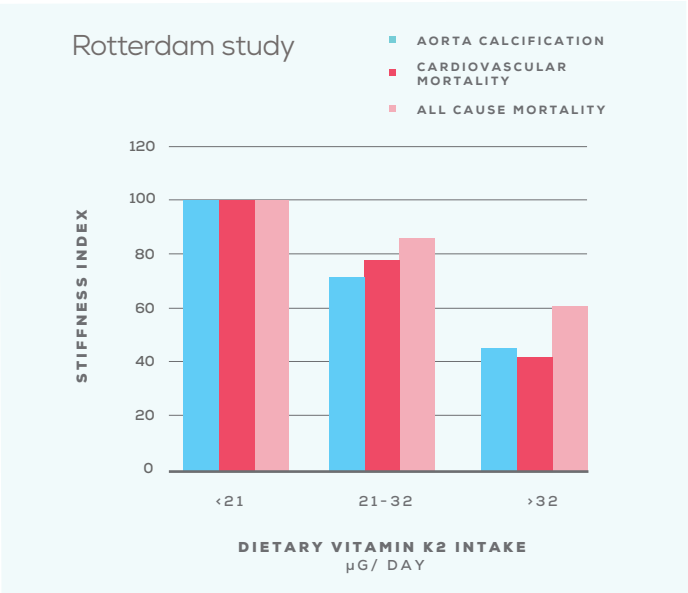
However, to properly perform its inhibitory function, MGP must be activated by vitamin K in a carboxylation reaction. Vitamin K deficiency results in undercarboxylation of MGP (creating ucMGP species) impairing MGP's biological function. Consequently, without adequate vitamin K in tissues dependent upon activated MGP, ucMGP accumulates in tissues at the sites of calcium deposition as well as being released into the bloodstream. However, ucMGP (according to present knowledge) is basically inert as it cannot bind calcium and thus hardly any inhibition of further calcium crystallization takes place. This, in turn, has consequences for progression towards atherosclerosis – an independent risk factor of fatal cardiovascular events.

Scientific evidence has shown that measurement of serum ucMGP is an interesting a biomarker for identification of persons at risk for developing atherosclerosis even before symptoms are evident.[10,11] However, further studies are needed to fully explore this option.

Vitamin K2
& Vascular Calcification

What can be done in order to identify persons at risk? Can calcifications be arrested – or even reversed? So far only animal studies have been conducted. However, these show that calcifications can be arrested, and preformed calcifications leading to atherosclerotic plaques might even be reversed.[12-14] Moreover, case reports indicate that high intake of vitamin K2 may restore the arterial walls, as well as decrease circulating cholesterol levels.[15] It has been shown that in cases of CVD, people with diseased aortas showed absence of K vitamins in this tissue. In healthy aortas, however, a high level of vitamin K2 was found.[16] Research performed in Maastricht University strongly suggests that vitamin K2 is a major contributing factor to preserve and possibly restore a healthy cardiovascular system through the concerted action of MGP, soluble proteins, and cellular activities.[17]

The Rotterdam Study published by Geleijnse et al. (2004) showed that dietary vitamin K2 is beneficial for prevention of heart disease. This study is based on a 10-year follow-up of an initial healthy Dutch population consisting of 4,807 men and women aged 55 and older at inclusion. The results suggest that high dietary vitamin K2 intake has a protective effect on arterial calcification, cardiovascular events, and risk of dying from such events. What is interesting is that dietary vitamin K1, obtained from green vegetables, had no influence on excessive calcium accumulation even when taken in large quantities.[18]



The hypothesis of protective potential of vitamin K2 was also shown in 2008 by Gast et al. Scientists examined the relationship between dietary vitamin K1 versus vitamin K2 with regards to the incidence of coronary heart disease (CHD). A group of 16,057 women (all free of CVDs at baseline) aged 49-70 years were followed up for 8 years and the data from this Prospect-EPI cohort study showed that K2 vitamins can help prevent CVDs. The scientists found significant correlation in the case of MK-7, MK-8, and MK-9, and they concluded that for every 10µg vitamin K2 intake (MK-7, MK-8, and MK-9), the risk of CHD was reduced by 9%. The intake of vitamin K1 did not have this effect.[19]

Hemodialysis patients experience severe vascular calcifications, and most of them have a functional vitamin K deficiency. Study performed by Westenfeld et al. (2012) showed that inactive MGP levels can be decreased markedly by daily vitamin K2 supplementation. The study provided for the first time evidence for a functional vitamin K deficiency in hemodialysis patients, and that the deficiency could be treated effectively by vitamin K2 supplementation.[20]

Results of a newly published, double-blind, randomized clinical trial (Knapen et al. 2015)[21] shows that when taken daily in nutritional doses (180 µg as MenaQ7®) for 3 years, Vitamin K2 (MK-7) improves cardiovascular health. In this study 244 healthy post-menopausal Dutch women, 55 to 65 years old, where randomly assigned to receive daily either MK-7 or placebo capsules. The trial showed substantial benefits in inhibiting age-related stiffening of arteries resulting in increase of the pulse wave velocity (PWV) in the placebo group, but not in the MK-7 group. Most remarkably, MK-7 not only inhibited arterial stiffening, but it also resulted in an unprecedented statistically significant improvement of vascular elasticity both measured with ultrasound techniques and PWV.

A U.S. study in army personnel did not find any preventive effect of vitamin K1 in daily doses varying from 35 µg to 200 µg (Villines et al. 2005)[22], while another prospective Dutch study (Beulens et al. 2008) in postmenopausal women did find a preventive effect of relatively small doses of vitamin K2 (estimated average daily intake of 31.6 µg/day). No effect of vitamin K1 was seen in this latter study even if the average daily consumption of vitamin K1 was estimated to be 217 µg.[23]

Vitamin K & Coagulation

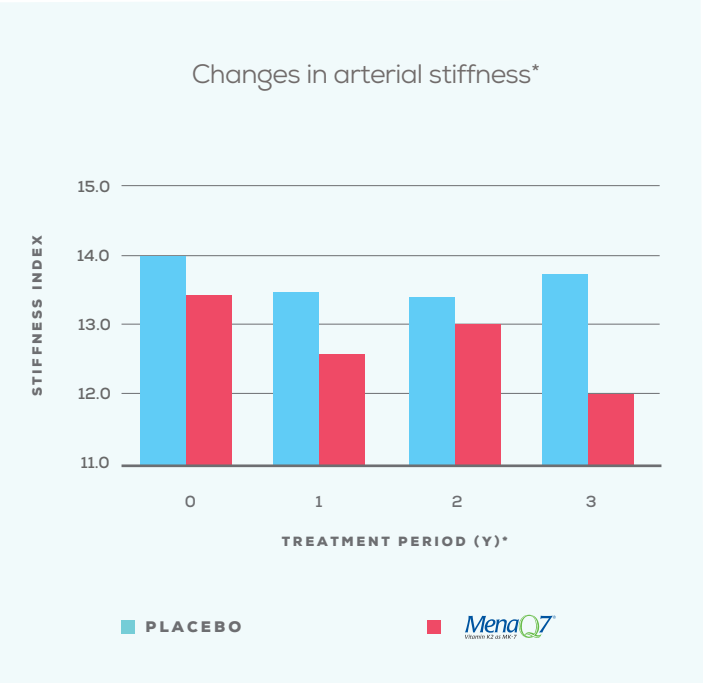
Coagulation is an important process in preventing blood loss and in restoring normal hemodynamic activities after injuries. When vessels are damaged, the platelets stimulate plasma coagulation factors to form a fibrin clot that prevents bleeding. Formation of platelet aggregates and fibrin clots are strictly restricted to the sites of the injury. After the wound healing process is finished, the fibrin clot breaks down. Vitamin K is essential for the activation of several coagulation proteins synthesized in the liver-including factors II (prothrombin), VII, IX, X, as well as the anticoagulation proteins S, C, and Z. All of these proteins contain inactive Glu (glutamic acid) residues when synthesized. The activation turns non-functional Glu residues into active Gla species as a result of a carboxylation process. The carboxylation is carried out by a vitamin K-dependent enzyme. The transformation makes them capable of binding calcium, and thus be ready to take part in the coagulation cascade when there is an extrinsic or intrinsic event triggering coagulation.

Under normal conditions, all coagulation proteins are fully carboxylated, which means they are ready to take part in clotting process whenever this is necessary. The supply of vitamin K is secured by recycling process vitamin K as it is poorly stored in the liver. Through the concept of the "vitamin K cycle," vitamin K can be used many times.[24] It is estimated that one molecule of vitamin K is able to activate several hundred thousand proteins molecules. Vitamin K deficiency may however result in cases of extremely inadequate intake, fat malabsorption including severe gastrointestinal diseases or long-term use of antibiotics. In such cases supplementation of vitamin K is very important.

Vitamin K & Anticoagulant Treatment

Anticoagulant treatment is necessary to avoid life-threatening diseases: It decreases the risk of hypercoaguability-related disorders such as myocardial infarction, stroke, and pulmonary embolism. Coumarins such as warfarin inhibit clotting activity by inhibiting the vitamin K recycling process. Consequently, use of oral anticoagulants lead to an inadequate gamma-carboxylation of vitamin K-dependent coagulation proteins. Hence, it inhibits clot formation and helps prevent unwanted blood "thickening," which may block the flow of blood in the arteries.

Unfortunately, the inhibitory activity of coumarins is not restricted to only vitamin K-dependent activities in the liver. Other extra-hepatic Gla-proteins, such as osteocalcin and MGP, are also affected by oral anticoagulant treatment. Recent studies found clear association between long-term anticoagulant treatment (OAC) and reduced bone quality due to reduction of active osteocalcin. OAC might lead to an increased incidence of fractures, reduced bone mineral density (BMD) and bone mineral content (BMC), osteopenia, and increased serum level of undercarboxylated osteocalcin.[25,26] It has been shown that BMD is significantly lower in stroke patients with long-term warfarin treatment in comparison to untreated patients. Additionally, osteopenia is probably an effect of warfarin-induced reduction in vitamin K activity.[27]



Furthermore, OAC is often linked to undesired soft-tissue calcification in both children and adults. The consequences of anticoagulant treatment might be an increased aortic obstruction, coronary insufficiency, ischemia, and even heart failure. Arterial calcification might also contribute to systolic hypertension and ventricular hypertrophy. Coumarins, by interfering with vitamin K metabolism, might also lead to an excessive calcification of cartilage and tracheobronchial arteries.[28-30] It is known that the high intake of vitamin K might overcome the anticoagulant effect. Patients on coumarin treatment have been advised by physicians not to consume vitamin K-rich diets in order to avoid the interference between oral anticoagulants and vitamin K. However, recent research suggests combining an appropriate concentration of vitamin K with OAC, and that the best choice of vitamin K supplementation during OAC treatment is MK-7.[31] The combination of vitamin K2 intake and OAC treatment is still under investigation

In May 2013, a study was published by Theuwissen et al. showing that if measured at group level, a daily intake of 45 µg/day of MK-7 does not lead to a statistically significant decrease of the INR value, but that 10-20% of the population belongs to the "quick responders", i.e. that they even show effects on their INR value at 10 µg/day.[32] It must be stressed that all patients on OAC treatment must contact their physicians before taking vitamin K2 supplements. All vitamin K2 dietary products must carry a warning of this on the label.

Vitamin K2 Deficiency: An Unrecognized Health Problem

A calcium-rich diet and an active lifestyle are commonly thought to be the strategy for keeping the bones strong and healthy. However, recent scientific discoveries indicate that there is one more piece of the puzzle that is essential for ensuring proper utilization of calcium, namely vitamin K. Vitamin K – a family of compounds widely known but thus far underestimated – has been shown to play a key role in calcium utilization, required for maintaining strong bones and smooth, flexible vasculature. Unfortunately, the majority of the Western population seems to be vitamin K deficient.

Benefits Beyond Coagulation

Vitamin K refers to a family of vitamins responsible for several vital processes that occur in the body. Primarily, it has been known as "the coagulation vitamin" because of its essential effect on the blood-clotting process. However, vitamin K's function is not limited to the activation of important coagulation factors. A growing body of scientific evidence points to the special roles of vitamin K2 (especially in the form of menaquinone-7) in maintaining both bone and cardiovascular health. Simplified, vitamin K2 as MK-7 is an optimal form for proper carboxylation (i.e. activation) of extrahepatic Gla proteins that can inhibit calcium deposition in the arteries thus lower the risk for development of arterial stiffness and calcification, and in bones - bind calcium to the mineral structure of bone to make them stronger.

Two Types of Vitamin K Deficiency

There are two types of vitamin K deficiency: acute and chronic, which can equally affect populations of both sexes and at different stages in life. Acute deficiency is characterized by unusual bleeding from gums, nose, or the gastrointestinal tract. Likewise, consequences of deficiencies due to anticoagulant therapy can be severe and even fatal – especially if intracranial bleeding episodes occur.[33]

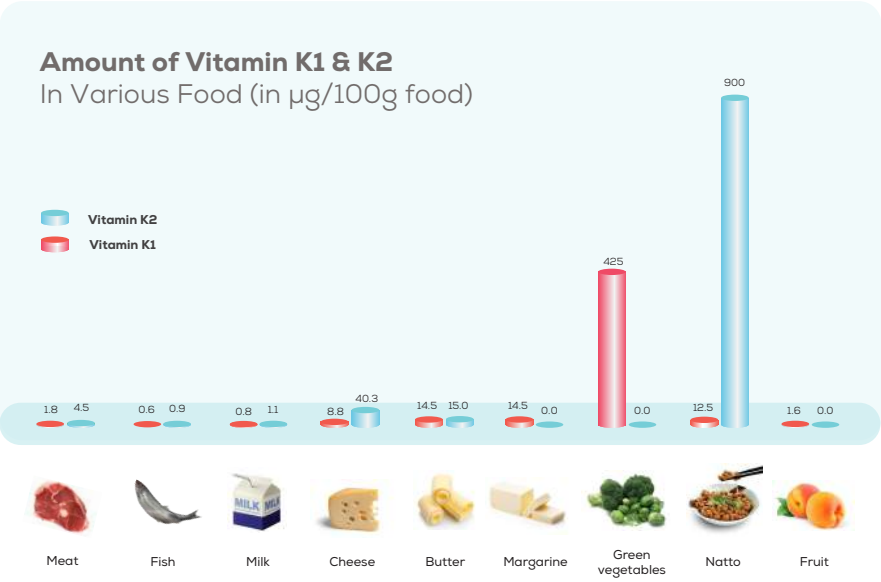
Newborn infants are especially exposed to acute vitamin K deficiency because fetuses do not produce vitamin K themselves and vitamin K is not transported sufficiently through the placenta. Additionally, the newborn gut is sterile at birth, and there are therefore no intestinal bacteria that potentially could produce the amount of vitamin K needed.

Lack of vitamin K may also be caused by anticoagulant drugs (such as warfarin or other coumarins), prolonged use of antibiotics, gallbladder disease, and also Crohn's disease. These conditions will either block the effect of vitamin K, or reduce the uptake of intestinal dietary vitamin K. Chronic vitamin K deficiency is less obvious than the acute deficiency. It is actually more dangerous as there are no clear alarming symptoms and the results – impairment in bone and cardiovascular health – might be severe.

Commonly it has been the belief that vitamin K deficiency is rare as requirements easily can be met by both diet and microbial biosynthesis by bacteria living in the gut. In the latter case, scientists do not agree to the importance of this supply as bacteria that produce vitamin K are mainly found in the colon, while the absorption of vitamin K takes place in the intestines. Bile salts required for vitamin K are also not present in the colon. Thus, the efficacy of intestinal K-vitamin absorption might be questionable.

Dietary Vitamin K

Recent scientific data also show that the amount of vitamin K is not as abundant in the diet as once thought. Even a well-balanced diet might not provide vitamin K in the amounts sufficient for satisfying the body's needs. This is especially of concern given that, according to researcher CJ Prynne, the daily consumption of vitamin K has decreased gradually since 1950.[34] This shortage can partly be explained by alterations in food composition as people eat less green leafy vegetables rich in vitamin K1. The change in preparation practices also influences the low vitamin K status. Traditionally food was made in the presence of various bacteria species (synthesizing vitamin K2), international standards of food manufacturing stop microorganisms, including beneficial flora, from multiplying and entering also changed over decades. For example, children in 1950 derived around 15% of their vitamin K intake from fats and oil sources and 55% from vegetables (excluding potatoes), compared to 35% from fats and oils and 30% from vegetables in the 1990s.[34]



Recommended Dose of Vitamin K2 in Health & Disease

A number of population-based studies have investigated the beneficial health effects of high vitamin K intake. In all published population surveys the maximal health benefit was obtained in the highest tertile or quartile for vitamin K2 intake with an average vitamin K2 intake of 45 micrograms per day (µg/day). That is the reason why tablets or capsules containing 45 µg/day are most widely marketed. The obvious question is whether this dose provides optimal benefit.

In healthy volunteers the minimal dose required to see a biochemical effect (i.e.: increased carboxylation of osteocalcin) is 10 µg/day while 45 µg/day is the usual dose showing effect. For effective carboxylation of MGP a somewhat higher dose is required. The vitamin K2 doses needed depend on the food matrix in which MK-7 is given and the size of the study cohort in which it is investigated. The effects of very low doses are however modest. Maximal MGP activation was observed at a daily intake ≥180 µg/day of vitamin K2 from menaquinone-7 (as MenaQ7®).[35] In some patients, the circulating levels of inactive MGP are much higher and some patients need maybe even 500 or 1,000 µg/day to fully activate their circulating MGP, depending on the starting value of inactive MGP. In chronic kidney disease and hemodialysis these levels may be 10-20 fold the normal level. Obviously very high doses of menaquinone-7 are required in such condition.

In the United States, the recommended daily dose (RDI) of vitamin K1 for adults is 120 µg/day for men and 90 µg/day for women. In the EU, it is 1µg/kg of body mass daily.[36]

Research has revealed that the actual need for K vitamins may be higher than current recommendations.

Present RDI is not sufficient for adequate activation of all K-dependent proteins like osteocalcin and MGP, which affect bone and cardiovascular health, respectively. The current Daily Value (DV) is based upon vitamin K1 may in fact be too low, as it has been based on hepatic requirements only, and is not sufficient for other tissues that need vitamin K as well.

1 Doherty TM, Asotra K, Fitzpatrick LA, Qiao J, Wilkin DJ, Detrano RJ, Dunstan CR, Shah PK, Rajavashisth TB. Calcification in atherosclerosis: bone biology and chronic inflammation at the arterial crossroads. Proc Natl Acad Sci USA. 2003; 100:11201-11206.

2 Rosenhek, R, Binder T, Porenta G, Lang I, Christ G, Schemper M, Maurer G, Baumgartner H. Predictors of outcome in severe asymptomatic aortic stenosis. N Engl J Med. 2000; 343:611-617.

3 Shaw LJ, Raggi P, Berman DS, Callister TQ. Coronary artery calcium as a measure of biologic age. Atherosclerosis. 2006;188(1):112-119.

4 Price PA, Urist MR, Otawara Y. Matrix Gla protein; a new gamma-carboxyglutamic acid-containing protein which is associated with the organic matrix of bones. Biochem Biophys Res Commun. 1983; 117: 765-771.

5 Luo G, Ducy P, McKee MD, Pinero GJ, Loyer E, Behringer RR, Karsenty G. spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. Nature. 1997;386 (6620):78-81.

6 Schurgers LJ, Cranenburg EC, Vermeer C.: Matrix Gla-protein: The calcification inhibitor in need of vitamin K. Thromb Haemost. 2008; 100: 593-603.

7 Proudfoot D, Skepper JN, Shanahan CM, Weissberg PL. Calcification of human vascular cells in vitro is correlated with high levels of matrix Gla protein and low levels of osteopontin expression. Arterioscler Thromb Vasc Biol. 1998;18(3):379-88.

8 Spronk HM, Soute BA, Schurgers LJ, Cleutjens JP, Thijssen HH, De Mey JG, Vermeer C. Matrix Gla protein accumulates at the border of regions of calcification and normal tissue in the media of the arterial vessel wall. Biochem Biophys Res Commun. 2001; 289(2):485-90.

9 Schurgers LJ, Dissel PE, Spronk HM, Soute BA, Dhore CR, Cleutjens JP, Vermeer C.: Role of vitamin K and vitamin K dependent proteins in vascular calcification. Z Kardiol. 2001 90: Suppl 3, 57 –63.

10 Schurgers LJ, Teunissen KJ, Knapen MH, Geusens P, van der Heijde D, Kwaijtaal M, van Diest R, Ketteler M, Vermeer C.: Characteristics and performance of an immunosorbent assay for human matrix Gla-protein. Clin Chim Acta. 2005: 351 (1-2):131-13.

11 Cranenburg EC, Vermeer C, Koos R, Boumans ML, Hackeng TM, Bouwman FG, Kwaijtaal M, Brandenburg VM, Ketteler M,Schurgers LJ.: The Circulating Inactive Form of Matrix Gla Protein (ucMGP) as a Biomarker for Cardiovascular Calcification. J Vasc Res. 2008; 45(5):427-436.

12 Essalihi R, Dao HH, Gilbert LA, Bouvet C, Semerjian Y, McKee MD, Moreau P.: Regression of medial elastocalcification in rat aorta: anew vascular function for carbonc anhydrase. Circulation. 2005; 112:1628-1635.

13 Bas A, Lopez I, Perez J, Rodriguez M, Aguilera-Tejero E.: Reversibility of calcitriol-induced medial artery calcification in rats with intact renal function. J Bone Min Res. 2006; 21:484-490.

14 Schurgers LJ, Spronk HM, Soute BA, Schiffers PM, DeMey JG, Vermeer C. Regression of warfarin-induced medial elastocalcinosis by high intake of vitamin K in rats. Blood. Nov 30 2006

15 Kawashima H, Nakajima Y, Matubara Y, Nakanowatari J, Fukuta T, Mizuno S, Takahashi S, Tajima T, Nakamura T. Effects of vitamin K2 (menatetrenone) on atherosclerosis and blood coagulation in hypercholesterolemic rabbits. Jpn J Pharmacol. 1997;75(2):135-43.

16 Data collected by Dr. LJ Schurgers (not published), 2006.

17 Schurgers LJ, Cranenburg EC, Vermeer C. Matrix Gla-protein: The calcification inhibitor in need of vitamin K. Thromb Haemost. 2008; 100: 593-603.

18 Geleijnse JM, Vermeer C, Grobbee DE, Schurgers LJ, Knapen MH, van der Meer IM, Hofman A, Witteman JC.: Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study. J Nutr. 2004; 134(11):3100-5.

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

20 Westenfeld R, Krueger T, Schlieper G, Cranenburg EC, Magdeleyns EJ, Heidenreich S, Holzmann S, Vermeer C, Jahnen-Dechent W, Ketteler M, Floege J, Schurgers LJ. Effect of vitamin K2 supplementation on functional vitamin K deficiency in hemodialysis patients: a randomized trial.Am J Kidney Dis. 2012 Feb;59(2):186-95.

21 Knapen MHJ, Braam LAJL, Drummen NE, Bekers O, Hoeks APG, Vermeer C. Menaquinone-7 supplementation improves arterial stiffness in healthy postmenopausal women: double-blind randomised clinical trial. Thromb Haemost. 2015 May: 0340-6245, http://dx.doi.org/10.1160/TH14-08-0675. Epub 2015 Feb 19.

22 Villines, TC et al.: Vitamin K1 intake and coronary calcification. Coronary Artery Disease. 2005;16:199-203.

23 Beulens JW, Bots ML, Atsma F, Bartelink ML, Prokop M, Geleijnse JM, Witteman JC, Grobbee DE, van der Schouw YT.: High dietary menaquinone intake is associated with reduced coronary calcification. Atherosclerosis. 2008 doi:10.1016/j.atherosclerosis.2008.07.010.

24 Stafford, DW: The vitamin K cycle. J Thromb Haemost. 2005; 3:1873-1878.

25 Caraballo PJ, Gabriel SE, Castro MR, Atkinson EJ, Melton LJ 3rd.: Changes in bone density after exposure to oral anticoagulants: a meta-analysis. Osteoporos Int. 1999;9(5):441-8.

26 Vermeer C, Hamulyák K. Pathophysiology of vita- min K-deficiency and oral anticoagulants. Thromb Haemost. 1991;66(1):153-9.

27 Sato Y, Honda Y, Kunoh H, Oizumi K. Long-term oral anticoagulation reduces bone mass in patients with previous hemispheric infarction and nonrheumatic atrial fibrillation. Stroke. 1997;28(12):2390-4.

28 Taybi H, Capitanio MA. Tracheobronchial calcification: an observation in three children after mitral valve replacement and warfarin sodium therapy. Radiology. 1990; 176 (3):728-730.

29 Moncada RM, Venta LA, Venta ER, Fareed J, Walenga JM, Messmore HL. Tracheal and bronchial cartilaginous rings: warfarin sodiuminduced calcification. Radiology. 1992:184(2):437-439.

30 Thoongsuwan N, Stern EJ.: Warfarin-induced tracheobronchial calcification. J Thorac Imaging. 2003; 18 (2):110-112.

31 Stafford DW, Roberts HR, Vermeer C. Vitamin K supplementation during oral anticoagulation: concerns. Blood. 2007 Apr 15;109(8):3607; author reply 3607-8.

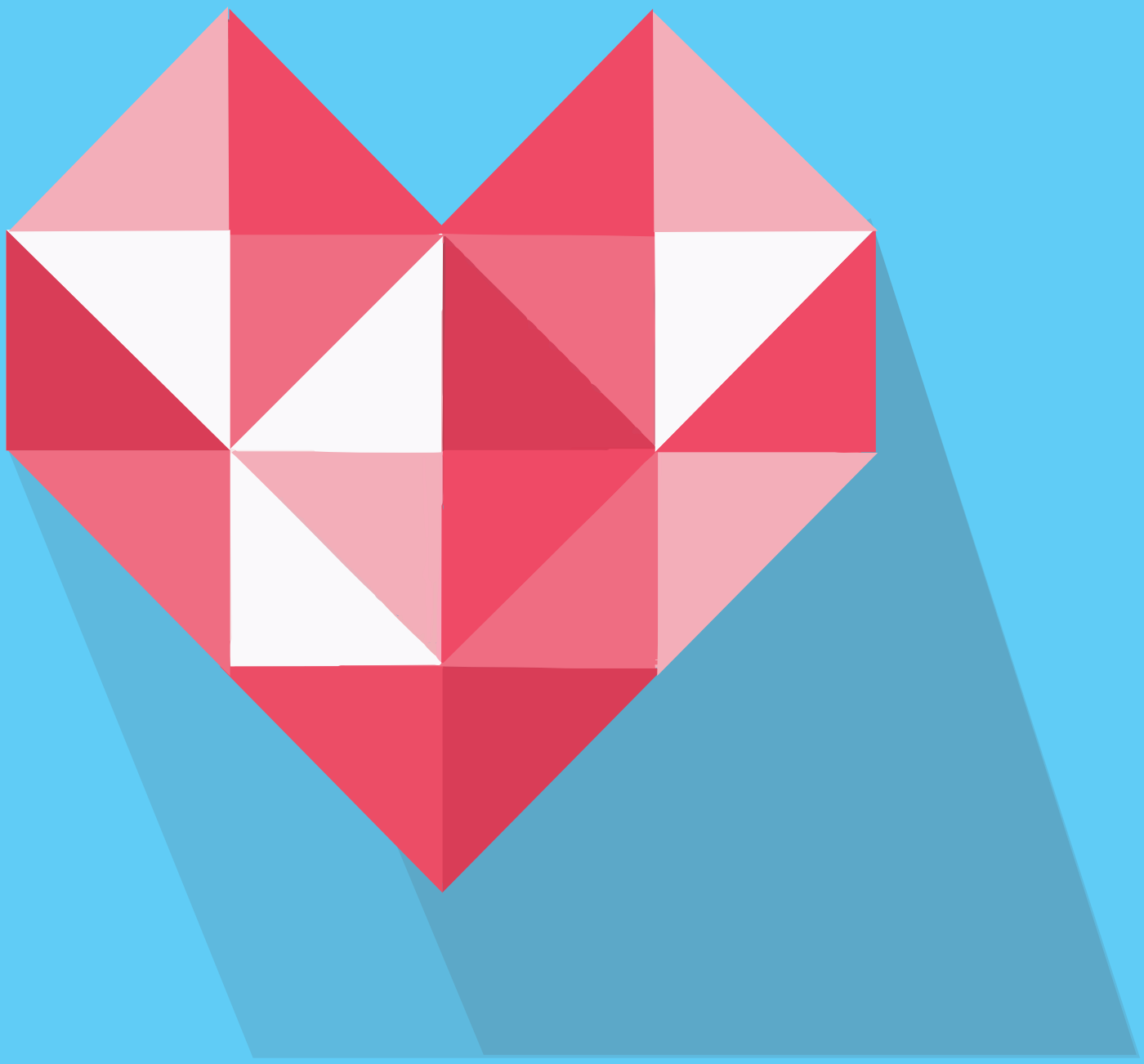
32 Theuwissen E, Teunissen KJ, Spronk HM, Hamulyák K, Ten Cate H, Shearer MJ, Vermeer C, Schurgers LJ., Effect of low-dose supplements of menaquinone-7 (vitamin K2) on the stability of oral anticoagulant treatment: dose-response relationship in healthy volunteers. J. Thromb. Haemostas. 2013.

33 Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism. A meta –analysis. Annals of Internal Medicine. 2003; 139:893-900.

34 Prynne CJ, Thane CW, Prentice A, Wadsworth ME. Intake and sources of phylloquinone (vitamin K(1)) in 4-year-old British children: comparison between 1950 and the 1990s. Public Health Nutr. 2005;8(2):171-80.

35 Theuwissen, E., Cranenburg, E.C.M., Knapen, M.H.J., Magdeleyns, E.J., Teunissen, K.J., Schurgers, L.J., Vermeer, C. Low dose menaquinone-7 supplementation improved extra-1 hepatic vitamin K 2 status, but had no effect on thrombin generation in healthy subjects. Brit. J. Nutr. 2013.

36 EFSA Scientific Opinion for vitamin K2. EFSA Journal. 2008, 822, p. 1-31.



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