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KAPPA ACADEMY

kappa BIOSCIENCE

K2VITAL®
VITAMIN K2 MK-7 – SCIENTIFIC FUNDAMENTALS AND IMPORTANT STUDIES

Bone and cardiovascular health have a common connection to calcium. Calcium is required to build and maintain healthy bones, whereas excess calcium deposited in arteries leads to arterial stiffening - a leading co-factor in heart disease. Vitamin K2 MK-7 links bone and heart health via its action on calcium. K2 activates osteocalcin to incorporate calcium into bones. K2 also activates matrix Gla protein (MGP) which binds excess calcium to prevent its deposition in arteries. Vitamin K2 deficiency is common in most populations. As such, K2 supplementation is necessary to maintain optimal bone and heart health for both genders and all age groups. K2VITAL® is the brand name for the synthetic all-*trans* form of MK-7, a superior form of K2 with regards to bioavailability and half-life. K2VITAL® *trans* is 100% equal to fermentation-derived MK-7 with similar uptakes into the body and vitamin K activity. Several clinical and epidemiological studies show a positive health benefit for MK-7 and the numbers are growing rapidly.

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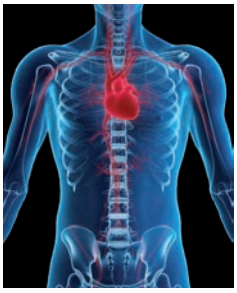
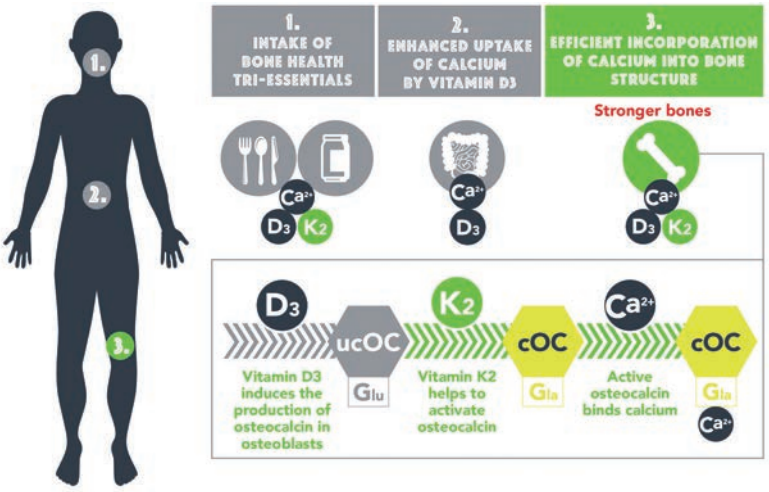
VITAMIN K2 FOR BONES AND HEART: BIOMARKERS OF DEFICIENCY

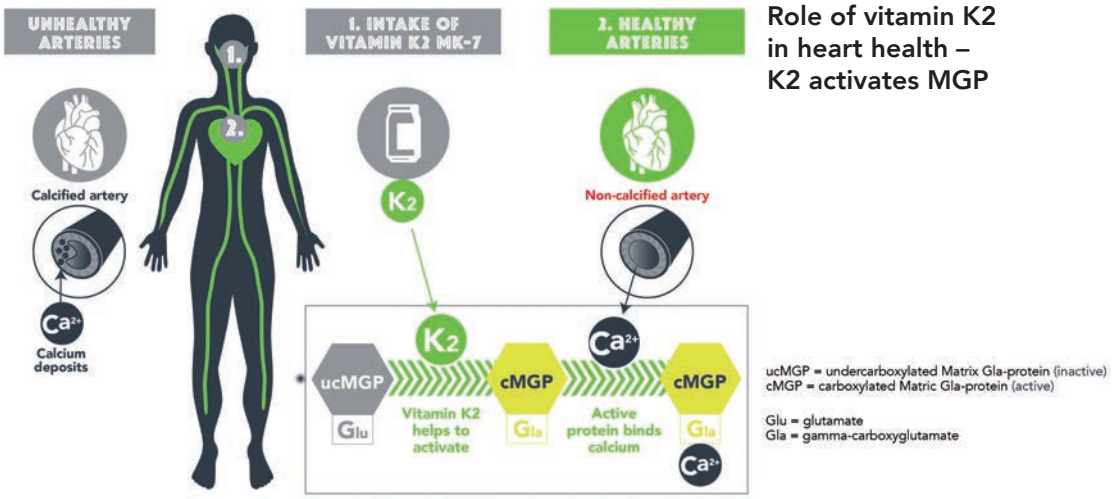


> Skeleton and heart (circulatory system)

Vitamin K2 is vital for bone-building and optimal funtioning of the cardiovascular system. Vitamin K2 is used by the body to activate osteocalcin, a protein that helps build bones by integrating calcium into the bone matrix *[1]*. If vitamin K2 levels are low, then activation of osteocalcin is insufficient and as a consequence bone formation is reduced. Similarly, vitamin K2 activates MGP in cartilage and the smooth muscle cells of the vascular system. Activated MGP binds excess calcium and removes it, reducing the risk of calcium deposits in the vessel wall and arterial stiffening, which is a risk factor for heart disease *[2]*.



Role of vitamin K2 in bone health – K2 activates osteocalcin



Role of vitamin K2 in heart health – K2 activates MGP

Inactive proteins are the biomarkers of vitamin K2 deficiency. Vitamin K2 deficiency is common in Western populations. Because of low dietary vitamin K2 intake, a high proportion of osteocalcin and MGP proteins is in the inactive (uncarboxylated) form as demonstrated by blood samples from healthy subjects. Many studies have documented the beneficial effects of vitamin K2 supplementation in reducing levels of inactive osteocalcin and MGP, and thereby improving bone and cardiovascular health *[2, 3]*. The statuses of carboxylated and uncarboxylated osteocalcin and MGP in the blood are important biomarkers for the vitamin K2 status in the human body.

Studies on vitamin K2 biomarkers

Publication	Participants	Population	Duration	Results
Aoun et al. 2017 *[4]*	50	Hemodialysis patients	4 weeks	86% reduction in ucMGP. Significant correlation between ucMGP and calcification score
Knapen et al. 2016 *[5]*	107	Healthy, 45-65 years	6 weeks	Significantly higher MK-7 in blood when MK-7 is given in yogurt compared to capsules
Knapen et al. 2015 *[6]*	60	Healthy	12 weeks	Significant reduction of ucOC and ucMGP
Inaba et al. 2015 *[7]*	60	Healthy postmenopausal women	4 weeks	Significant increase in the cOC:ucOC ratio
	120	Healthy	12 weeks	Significant reduction of ucOC. Significant increase in the cOC:ucOC ratio
Caluwe et al. 2014 *[8]*	200	Chronic hemodialysis patients	8 weeks	Dose-dependent change on ucMGP
Theuwissen et al. 2013 *[9]*	18	Healthy	6 weeks	Low doses of MK-7 influences anticoagulation sensitivity
Sato et al. 2012 *[10]*	10	Healthy women	1 dose	Serum MK-7 significantly higher
	10	Healthy women	7 days	Serum MK-7 significantly higher
Theuwissen et al. 2012 *[11]*	42	Healthy	12 weeks	Significant increase of cOC Significant reduction of ucOC and ucMGP
Dalmeijer et al. 2012 *[12]*	60	Healthy	12 weeks	Significant and dose-dependent change in o/uc ratio for OC and MGP
Westenfeld et al. 2012 *[13]*	53	Long-term dialysis patients in stable condition	6 weeks	Significant reduction for ucOC and ucMGP
Abdel-Rahman et al. 2012 *[14]*	84	Rheumatoid arthritis	12 weeks	Positive effects on biomarkers for disease activity (DAS28, CRP, sedimentation)
Bruge et al. 2011 *[15]*	12	Healthy	4 weeks	Significant reduction of ucOC Significant increase of cOC
Schurgers et al. 2007 *[16]*	15	Healthy	1 dose	Pharmacokinetics of MK-7
	10	Healthy	1 dose	Linear relationship: dose-MK-7 in serum
	18	Healthy	6 weeks	Steady state level of MK-7 in serum after 20 days
	12	Healthy	2 weeks	MK-7 plays a role in coagulation by changing the INR
Kamao et al. 2007 *[17]*	125	Healthy women	Habitual intake	MK-7 in serum is higher in natto eaters compared to people not eating natto
Homma et al. 2006 *[18]*	32	Healthy	3 days	Natto gives increase of MK-7 in serum
Tsukamoto et al. 2000 *[19]*	48	Healthy	2 weeks	Significant increase on cOC
Sato et al. 2000 *[10]*	4	Women (long distant runners)	4 weeks	Significant reduction on ucOC
Tsukamoto et al. 2000 *[20]*	134	Healthy	21 days	Significant correlation between increase in MK-7 and cOC
Sumi 1999 *[21]*	6	Healthy	1 dose	Dose dependent increase of MK-7 in serum

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DIFFERENT VITAMIN K FORMS PROVIDE DIFFERENT HEALTH CONTRIBUTIONS

Vitamin K2 (menaquinone) is different from vitamin K1 (phylloquinone) and represents a family of compounds with isoprenoid side chains of varying lengths. These side chains consist of 4 to 13 isoprenyl units named MK-4 to MK-13. EFSA vitamin K approval is limited to the K1 and K2 MK-7 forms, making MK-7 the default commercial standard (MK-6 may be present to a 'minor extent' as per Commission Implementing Regulation (EU) 2017/2470). While other MK forms are used for dietary supplementation or may be present in K2 products, their presence is non-EFSA approved or fundamentally an impurity.

Biologically, MK-7 is the superior form for supplementation. Studies demonstrated that intestinal uptake/absorption of MK forms are different, and this affects the efficacy of each form as measured by effectiveness in activating osteocalcin and MGP proteins. One study found that MK-7 is better absorbed than MK-4 *[22]*, two clinical trials demonstrated that MK-4 and MK-9 are less-effectively absorbed than K1 *[23, 24]*, but that MK-7 is better absorbed than K1 *[16, 25]*. Based on these studies the EFSA Scientific Opinion concluded that the uptake of MK-4, MK-7 and MK-9 is different and that 'MK-7 is more efficiently absorbed' than other MK forms *[26]*.

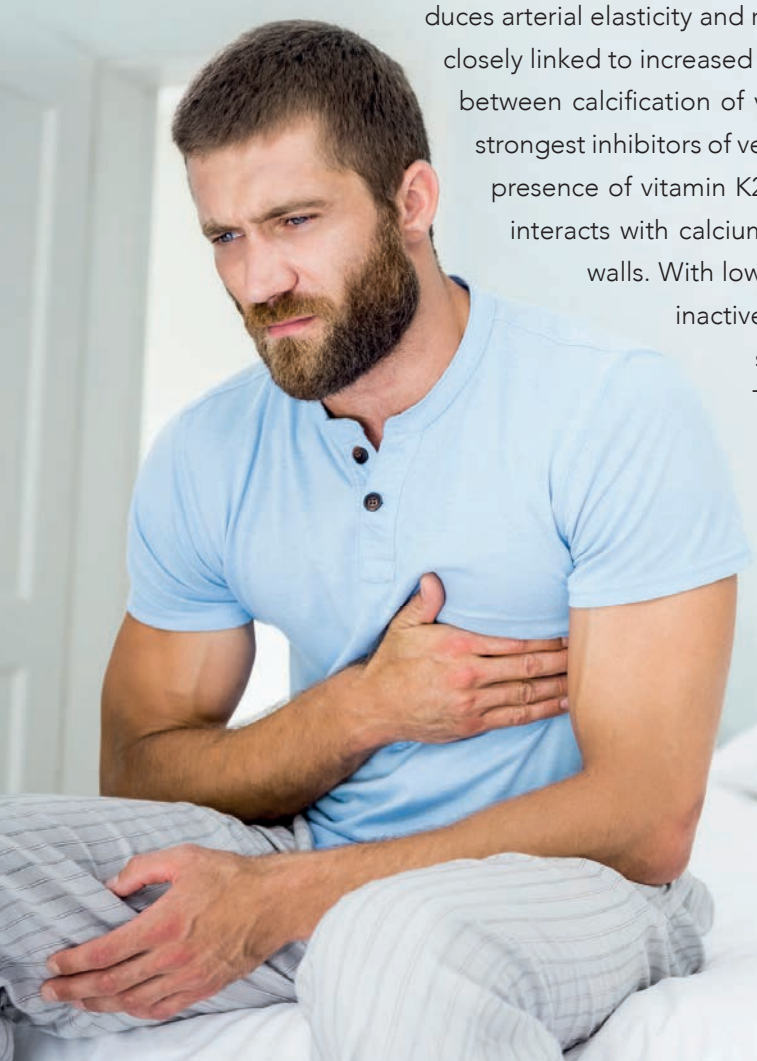
Because of MK-7's superior biological efficacy that resulted in the current EFSA regulatory status, any attempt to manufacture K2 should require MK-7 as the standard. Other MK forms do not deliver equal benefits and their presence is fundamentally undesirable.

> Throughout life, it is important to consume enough calcium to maintain a healthy skeleton

VITAMIN K2
FOR BETTER HEART HEALTH

Cardiovascular disease (CVD) is caused by disorders of the heart and blood vessels. CVD includes coronary heart disease (heart attacks), cerebrovascular disease (stroke), high blood pressure, peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure. Heart attacks and stroke are usually acute events and are mainly caused by a blockage that prevents blood flow to the heart or brain. The most common reason for this is a build-up of fatty calcium-rich deposits on and in the inner walls of the blood vessels that supply the heart or brain, known as atherosclerosis.

Studies on the effect of vitamin K2 MK-7 on cardiovascular health demonstrate a significant reduction in arterial stiffness and slower progression of calcification. Vascular calcification reduces arterial elasticity and results in stiffening of the vessels. Calcification of the arteries is closely linked to increased risk of cardiovascular disease *[27-30]* and an inverse relationship between calcification of vessels and survival was observed in patients *[31]*. One of the strongest inhibitors of vessel calcification is the vitamin K-dependent MGP *[32, 33]*. In the presence of vitamin K2, MGP is activated by carboxylation to become cMGP, which interacts with calcium in the bloodstream and regulates calcification in the vessel walls. With low levels of vitamin K2 in the bloodstream, MGP is present in its inactive form, which is in a de-phosphorylated and undercarboxylated state (dp-ucMGP) and will not be able to interact with calcium. This may lead to a higher calcification in the vessel wall *[32-35]*.



> Calcification of the arteries is closely linked to increased risk of cardiovascular disease

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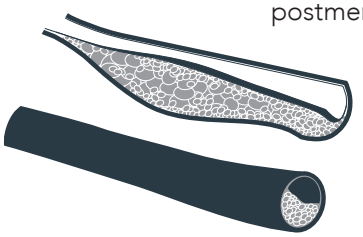


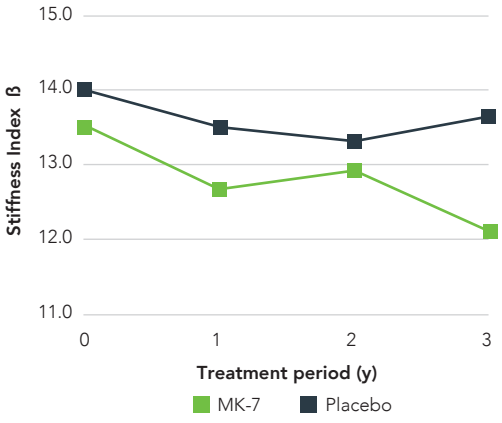
Calcified Vessel
A lack of vitamin K2 leads to calcium being deposited in vessels.

Arterial stiffness was reduced with a 3-year MK-7 supplementation. In a double-blinded, randomized, placebo-controlled clinical trial, arterial stiffness was investigated in 244 healthy postmenopausal women over a period of 3 years, supplemented with either 180 µg of MK-7 or a placebo *[36]*. Among the participants with an elevated arterial stiffness at baseline, the stiffness index was significantly improved compared to the placebo group ($p<0.05$). A beneficial effect of MGP activation was also seen among the participants taking MK-7, which experienced a 50% decrease in circulating dp-ucMGP compared to the placebo group ($p<0.0001$).

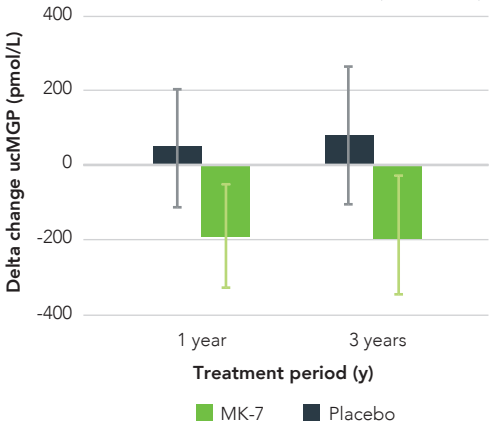
Studies on vitamin K2 biomarkers

Publication	Participants	Population	Duration	Results
Mansour et al. 2017 *[37]*	60	Renal transplant recipients	8 weeks	Reduction in arterial stiffness
McFarlin et al. 2017 *[38]*	26	Athletes	8 weeks	12% increase in maximal cardiac output
Knapen et al. 2015 *[36]*	244	Healthy postmenopausal women	3 years	Significant reduction in arterial stiffness
Kurnatowska et al. 2015 *[39]*	42	Kidney patients	9 months	Slower progression of calcification by MK-7

Elevated stiffness at baseline



Change in serum ucMGP
(mean±SD)



VAN BALLEGOOIJEN ET AL. 2017. A REVIEW OF K2 AND CARDIOVASCULAR ENDPOINTS

Cardiovascular disease is a general term that describes heart diseases based on blood vessels that have become stiff, narrow or blocked, which can lead to a heart attack or stroke. Risk factors for heart disease are numerous and include chronic kidney disease, diabetes, sedentary lifestyle, obesity, age, family history, smoking, etc. Risk factors such as age and family history cannot be changed, but steps can be taken to prevent blood vessel calcification and stiffness. If dietary supplementation with vitamin K2 has the potential to be one of these steps, was investigated in a literature review of observational and clinical studies by Van Ballegooijen and colleagues *[40]*. While there are no pharmacological treatments available to ameliorate vascular calcification, vitamin K2 may provide a cheap and low-risk option, because of its involvement in the activation of a protein present in vessel walls, called matrix GLA-protein (MGP). The biological rationale is that optimized activation of MGP is linked to better vascular health since calcium is used for the formation of bones instead of deposition in blood vessel walls. On the other hand, a lack of vitamin K2 is associated with increased inactive MGP concentrations, which leads to calcium deposition, artery calcification and eventually cardiovascular disease.
The authors have used inactive MGP as a biomarker for a low vitamin K status and have screened all available published literature, where inactive MGP and cardiovascular endpoints have been studied (see Table). Taken together, observational studies indicate that low vitamin K status, measured by high inactive MGP concentrations, plays a role in cardiovascular disease. This suggests that in particular chronic kidney disease or other high-risk groups might benefit from vitamin K2 supplementation for cardiovascular health benefits. Furthermore, there might be a synergistic effect of vitamin K2 with vitamin D for hearth health, implying that their combination will benefit arteries most by keeping them flexible and calcium plaque-free.

Studies on circulating ucMGP and cardiovascular-related outcomes

Author, year	Country	Participants	Outcome measure	Results and conclusion
Cross-sectional studies				
Ueland 2010	Norway	N=147 calcific vulvular aortic stenosis patients, age 74 ± 10, 45% female	Echocardiographic measures	Circulating ucMGP was associated with decreased cardiac function
Ueland 2011	Norway	179 heart failure patients and 33 health individuals, age 56±12, 22% female	Systolic function	Circulating ucMGP was associated with increased heart failure
Dalmeijer 2013	Netherlands	N=195, post-menopausal women, age 67±6	Coronary artery calcification (CAC) score	A trend (p=0.06) was found on the association between high circulation ucMGP and CAC
Liabeuf 2014	France	N=198, type 2 diabetes, men>50 and women >60 years	Peripheral arterial calcification score	Circulating ucMGP was associated with peripheral arterial calcification score
Pivin 2015	Switzerland	N=1001, age 47±17, 52% female	Aortic pulse wave velocity	Circulating ucMGP was associated with increased arterial stiffness
Mayer 2016	Czech Republic	N=1087, age 55±14, female	Aortic and distal pulse wave velocity	Circulating ucMGP was associated with increased aortic pulse wave velocity
Sardana 2016	USA	N=66, type 2 diabetes, age 62±12 years, 9% female	Carotid-femoral pulse wave velocity	Circulating ucMGP was associated with increased arterial stiffness
Longitudinal studies				
Dalmeijer 2013	Netherlands	N=518, type 2 diabetes, age 58±7, 82% female, 11 years follow-up	Cardiovascular disease (CVD)	Circulating ucMGP was associated increased CVD risk
Dalmeijer 2013	Netherlands	N=508, post-menopausal women, age 56±6, 8.5 years follow-up	CAC	Circulating ucMGP was associated with increased CAC
Van den Heuvel 2014	Netherlands	N=577, age 60 years, 56% female, 5.6 years follow-up	CVD	Circulating ucMGP was associated with increased risk of CVD
Dalmeijer 2014	Netherlands	N=2985, age 49.5±12 years, 56% female, 11.5 years follow-up	CVD and stroke	An association between ucMGP and risk for CVD and stroke was not seen in this health population
Liu 2015	Belgium	N=2318, age 44, 51% female, 14.1 years follow-up	CVD and mortality	Circulating ucMGP was associated with increased coronary events and cardiovascular mortality
Longitudinal studies among cardiac patients				
Ueland 2010	Norway	N=147 calcific vulvular aortic stenosis patients, age 74 ± 10, 45% female, 23 months follow-up	All-cause mortality	Circulating ucMGP was associated with long-term mortality
Ueland 2011	Norway	179 heart failure patients and 33 health individuals, age 56±12, 22% female, 2.9 years follow-up	Mortality due to heart failure	Circulating ucMGP was associated with decreased long-term heart-transplant-free survival
Mayer 2014 & 2016	Czech Republic	N=799, prior CVD patients, age 65 years, 29% female, 5.6 years follow-up	All-cause mortality, CVD mortality	Circulating ucMGP was associated with increased risk of mortality

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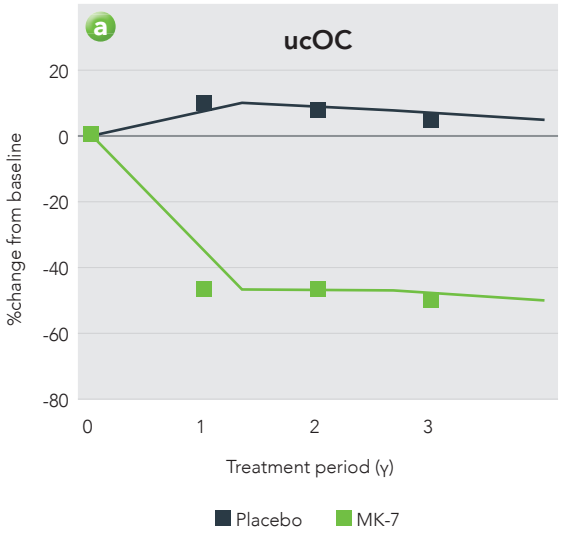
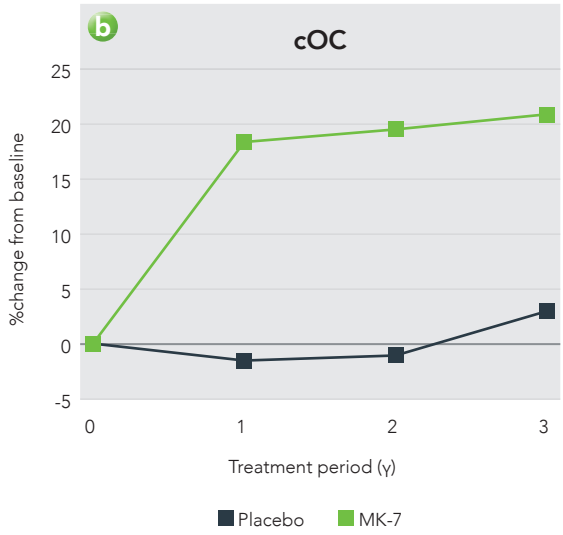
DENSER AND STRONGER BONES WITH MK-7 SUPPLEMENTATION

Throughout life, it is important to consume enough calcium to maintain a healthy skeleton. Bone mass increases until the early twenties, but from 30-40 years onwards, bone mass gradually decreases in both men and women. This indicates that sufficient calcium intake is particularly important in childhood/puberty and from age 35 onwards. The risk of broken bones increases with age and the ability to recover decreases. Post-menopausal women are particularly vulnerable to fractures.

Western diets are deficient in vitamin K2. Fermented food products are the primary sources of vitamin K2. In Western populations, the daily intake of vitamin K2 via food has decreased over the past hundred years. Japan, on the other hand, shows a lower frequency of bone and cardiovascular diseases, especially in certain regions in the north *[41]*. What is so special about these regions? The Japanese, in the northern regions, eat a dish called natto. It is fermented soybeans containing a high amount of MK-7. Natto food has been eaten for hundreds of years and is approved as a health food in Japan. Many epidemiological *[42, 43]* and clinical studies have pointed to the beneficial effects of MK-7 for bone health.

MK-7 reduces the level of inactive osteocalcin (ucOC) and increases the level of active osteocalcin (cOC), which led to changes in bone mineral density (BMD) in the lumbar spine during a 3-year intervention





MK-7 supplementation helps postmenopausal women against bone loss. In a double-blinded, randomized, placebo-controlled clinical trial, the bone strength was investigated in 244 healthy postmenopausal women over a period of 3 years, supplemented with either 180 µg of MK-7 or placebo *[44]*. MK-7 supplementation significantly reduced the level of inactive osteocalcin (ucOC) and increased the level of active osteocalcin (cOC). In addition, the intake of MK-7 significantly decreased the age-related decline in bone mineral content (BMC) and density (BMD) at the end of the thighbone (femoral neck) and the lower back spine (lumbar spine). Also, MK-7 significantly reduced the loss in vertebral height in the lower chest region.

Studies on vitamin K2 biomarkers

Publication	Participants	Population	Duration	Results
Ronn et al. 2016 *[42]*	148	Women with osteopenia	1 year	MK-7 preserves bone microstructure compared to control
Knapen et al. 2013 *[44]*	244	Healthy postmenopausal women	3 years	Significant improvement of BMD and BMC, Significant reduction of ucOC, Significant increase of cOC
Fujita et al. 2012 *[45]*	1662	Healthy elderly men	Habitual intake	Habitual intake of natto was significantly associated with higher BMD and low ucOC
Genius and Bouchard 2012 *[46]*	77	Postmenopausal women with comprised bone health	1 year	Significant increase of BMD
Kanellakis et al. 2012 *[47]*	173	Healthy postmenopausal women	1 year	Significant increase of BMD
Michalek et al. 2011 *[48]*	176	Healthy	6 months	Significant increase of BMD
Førli et al. 2010 *[49]*	94	Patients post heart or lung transplantation	1 year	Significant increase of BMD
Emaus et al. 2010 *[50]*	334	Healthy postmenopausal women	1 year	No significant increase of BMD, Significant increase of cOC, Significant reduction of ucOC
Ikeda et al. 2006 *[51]*	944	Healthy women	3 years	Significant association between natto intake and BMD in femoral neck
Katsuyama et al. 2004 *[52]*	73	Healthy postmenopausal women	1 year	No significant changes in stiffness index, Significantly lower ucOC
Katsuyama et al. 2002 *[53]*	117	Healthy young women	Habitual intake	Bone stiffness positively associated with natto intake
Kaneki et al. 2001 *[54]*	105	Healthy women	Habitual intake	Significant inverse association between natto intake and hip fractures

MK-7 preserves bone structure at the shinbone or tibia. In another double-blinded, randomized, placebo-controlled clinical trial, the bone microarchitecture was investigated in 148 postmenopausal women with osteopenia, a condition characterized by low bone mineral density *[42]*. After one year of intervention, Rønn and colleagues showed that MK-7 preserves the bone microstructure compared to the placebo group. These studies demonstrate the beneficial effects of MK-7 on bone strength as a prevention strategy for fractures.

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VITAMIN K2 AND CHILDREN – VITAMIN K2 FOR GROWING BONES

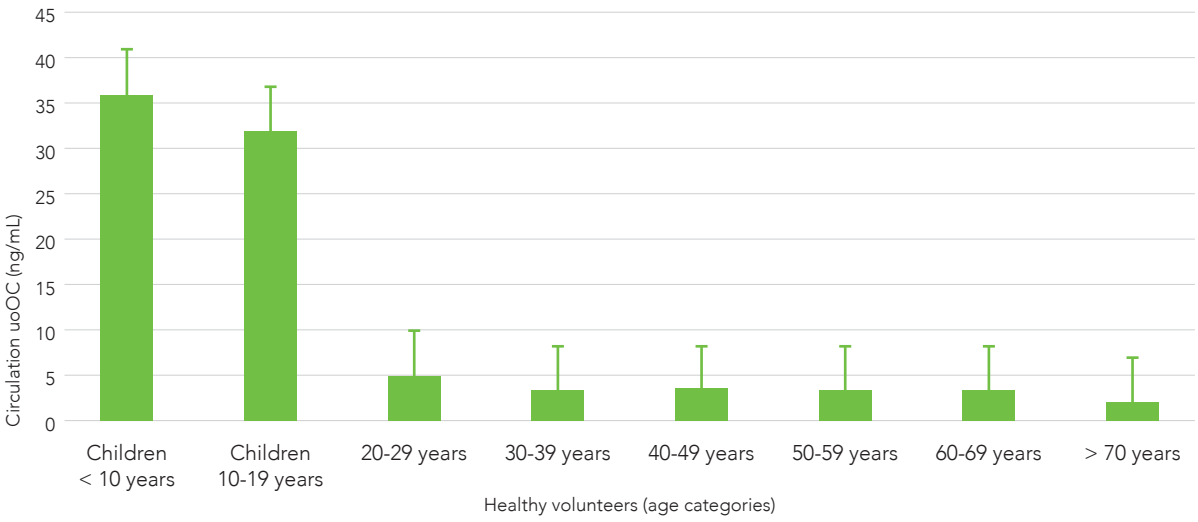
Vitamin K2 is crucial for bone development and is the best choice of vitamin K supplement to promote bone health in children. K2 deficiencies can go unnoticed in healthy children, who can benefit from daily K2VITAL® supplementation to maintain life-long bone health. This is particularly true for children suffering from diseases in which the intestine absorbs too little vitamin K, such as cystic fibrosis and biliary atresia, and the blood disorder thalassemia characterized by thin and brittle bones. These patient groups could benefit from vitamin K supplementation. Sufficient intake of vitamin K2 in the early years helps ensure good bone health later in life. A growing number of studies have been carried out looking at vitamin K levels in relation to bone health in children.

There is a positive relationship between vitamin K status and bone mineral density in children. One study by O'Connor et al. included 223 healthy Danish girls aged 11-12 to investigate the relationship between vitamin K status (measured as ucOC) and bone mineral content (BMC) *[55]*. The researchers concluded that low ucOC status was positively associated with BMC of the total body and lumbar spine.

Children could benefit from higher vitamin K intake. Another study by van Summeren et al. included 281 healthy children (mean age 11.2 years, 139 boys and 142 girls) for measurements of ucOC, cOC and BMC of lumbar spine, femoral neck, total body at baseline and after a two-year observation period *[56]*. At baseline, vitamin K status was associated with markers of bone formation – vitamin D, and sex steroids. After two years, improvements in vitamin status were associated with marked increase in total body BMC, a measure that takes into account bone size and shape of all skeletal regions. They also looked at vitamin K status by measuring the amount of active/inactive OC in adult and children *[57]*. A much higher level of ucOC in the circulation was found in the majority of children between 6 and 18 years old compared to adults, pointing to low vitamin K levels. Even if the children were subdivided into two age groups, the ratio of ucOC to cOC was higher than for adults. The authors raise the question whether children would benefit from higher vitamin K intake.

MK-7 intake reduces uncarboxylated osteocalcin (ucOC) levels in children. In a double-blinded, randomized, placebo-controlled clinical trial, the effect of 45 µg/day of MK-7 over eight weeks was investigated by studying the levels of ucOC and cOC in the blood of 55 healthy pre-pubertal children (6 to 10 years old) *[58]*. During this short intervention period, there was a significant reduction in both ucOC and the ucOC:cOC ratio for the participants that received MK-7. In addition, no changes in the coagulation parameters were found, indicating no safety concerns for the dose applied in the study.

Circulating inactive osteocalcin (ucOC) across age groups



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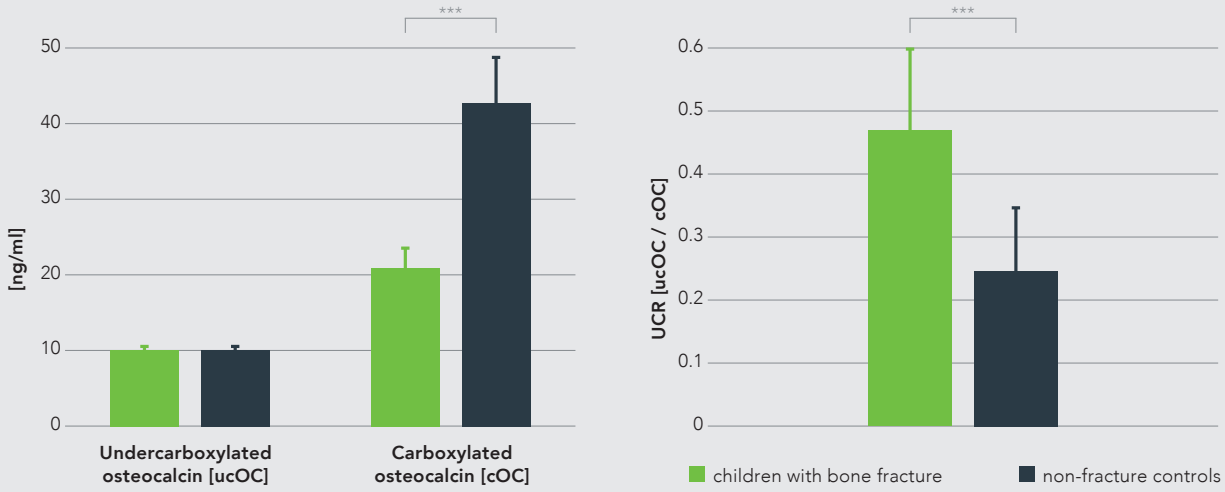
DECREASED LEVELS OF CIRCULATING CARBOXYLATED OSTEOCALCIN IN CHILDREN WITH LOW ENERGY FRACTURES: A PILOT STUDY *[59]*

There is accumulating evidence that vitamin K and D are involved in the regulation of bone health and the prevention of fractures. The aim of the study was to assess the vitamin D and vitamin K status in children with low-energy fractures and in children with no fractures. A total of 39 children were included in the trial. The study group contained 20 children, 5 to 15 years of age, 14 boys and 6 girls with low energy fracture. The control group contained 19 children, 7 to 17 years of age, 9 boys and 10 girls with no fracture. A blood sample was collected for assessment of vitamin K status by cOC and ucOC level, and total vitamin D level (25(OH)D3 plus 25(OH)D2).
The level of activated osteocalcin (cOC) was significantly higher in the group with no fractures. The UCR (ucOC/cOC ratio) was significantly higher in the group with bone fractures. No difference in vitamin D status was found between the groups.

Significant correlation between fractures and activation status of osteocalcin



K2 supplementation can improve bone health of both mother and child. Pregnant women undergo substantial skeletal remodeling in preparation for giving birth and can suffer from calcium deficiency due to the unborn child's high demand for calcium. In extreme cases, this can result in pregnancy-associated osteoporosis, a condition characterized by severe pain because of vertebral fractures. K2 supplementation has been shown to relieve this pain *[60]*. Besides, vitamin K2 is poorly transported from a mother to her unborn child *[61]*. However, the situation can be improved through K2 supplementation. In a controlled Japanese study, women given 20 mg of vitamin K2 about a week before they gave birth had more K2 in their blood compared to women who were not given K2 *[62]*. Crucially, the K2 level was also elevated in umbilical cord blood, indicating increased transfer of K2 to the child. Thus, none of the children born to K2-treated mothers showed signs of vitamin K deficiency at birth, compared to 90% of the children whose mothers were not given vitamin K. Interestingly, levels of vitamin K2 in breast milk on day five after birth were significantly higher in those women who were given K2 before they gave birth. So, the direct benefits of K2 supplementation during pregnancy may extend to early infancy.

Studies on the significance of vitamin K during maternity, infancy, and childhood

Publication	Participants	Population	Duration	Results
Popco et al. 2017 *[59]*	39	Children with fracture (n=20) compared to children with no fracture (n=19)	Correlation study	Significantly higher level of cOC in children with no fractures
O'Connor et al. 2007 *[55]*	223	Healthy Danish girls aged 11-12	12 months	Better vitamin K status (low ucOC status) was associated with decreased bone turnover
Theuwissen et al. 2014 *[57]* **van Summeren et al. 2009** *[58]*	55	Healthy children, 6-10 years	8 weeks	Significant reduction of ucOC in serum
Ozdemir et al. 2013 *[68]*	20	Children suffering from thalassemia major undergoing regular blood transfusions	1 year	Significant improvement on BMD
Motohara et al. 1990 *[62]*	33	Japanese mothers and their newborn	Before and after delivery	Increased transfer of K2 from mother to fetus

Infants are often deficient in vitamin K. During pregnancy, placental transfer is inadequate, and after birth, vitamin K levels in breast milk are low *[61, 63]*. While bacteria in the colon may contribute to the pool of K2 *[64]*, neonates produce less K2 since their bacterial colonies are not yet fully developed. Evidence indicates that lactating mothers may increase levels of vitamin K2 in their breast milk by taking K2 supplementation *[65, 66]*. One study further showed increased vitamin K levels in the breast milk of new mothers who took 5 mg/day of vitamin K1. Additionally, vitamin K levels were also elevated in the blood of their breastfed children *[67]*. K2 delivery via breast milk might not be adequate. Direct K2 supplementation in neonates using a formula containing K2VITAL® may be an effective option.

> K2VITAL® can fill the gap between what our bodies need and what our diets provide

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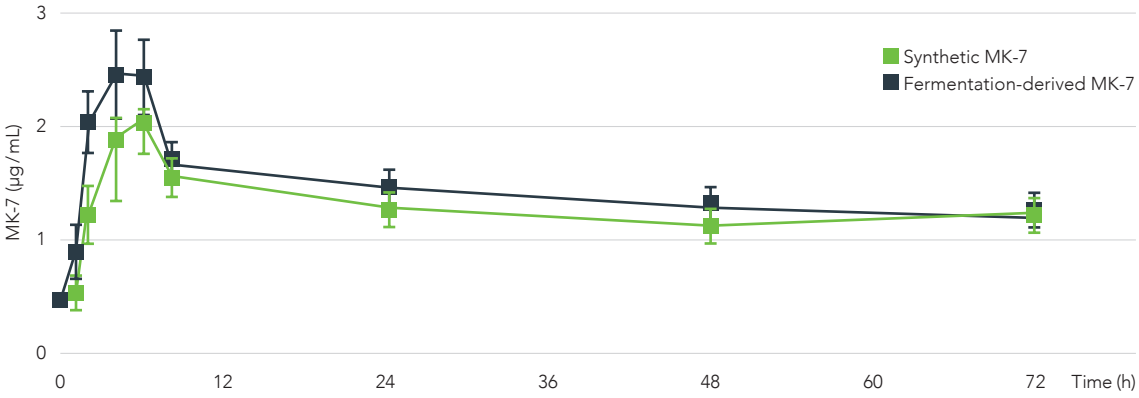
K2VITAL® IS BIOEQUIVALENT TO FERMENTATION-PRODUCED MK-7

Fermentation-derived K2 products have been shown in clinical studies to prevent and reverse arterial calcification *[36]* **and improve bone mineral density** in healthy postmenopausal women *[44]*. Since K2VITAL® is a synthetic MK-7 form, two studies were performed to determine whether synthetically-derived MK-7 is equally effective as fermentation-derived MK-7 at raising blood vitamin K2 levels and activity.

K2VITAL® and fermentation-derived MK-7 have the same bioavailability. In the first cross-over design trial, K2VITAL® and fermentation-derived MK-7 were administered to 16 healthy volunteers as a single 180 µg dose to determine whether they are equally well absorbed and demonstrate similar detection levels in blood samples during the three days after consumption. Blood analysis of the two treatment groups throughout the study period indeed demonstrated that the two MK-7 forms are bioequivalent. The results fall within a confidence range of 90% for AUC (area under the concentration time curve; 0-72 h) and Cmax (maximum concentration observed) *[69]*.

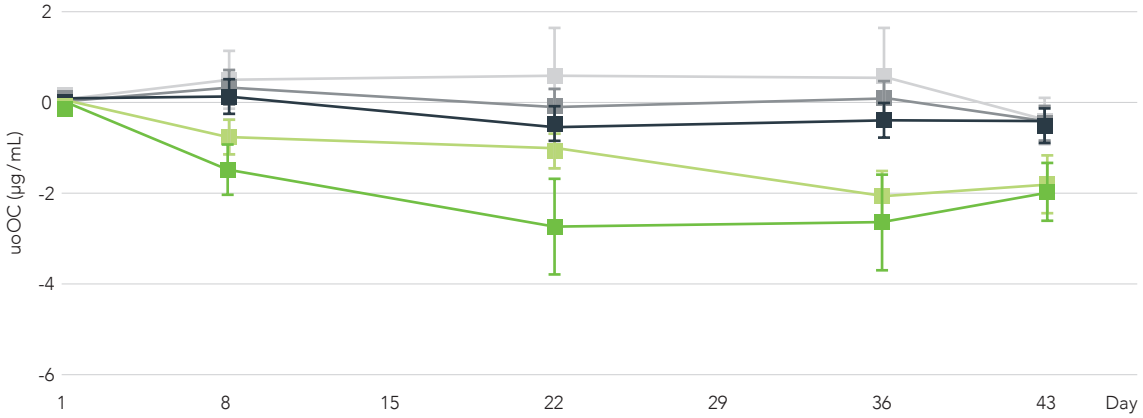


K2VITAL® and fermentation-derived MK-7 demonstrated equal reduction of inactive osteocalcin (ucOC). In the second trial, a placebo, three K2VITAL® doses (45, 90 or 180 µg) and one dose (90 µg) of natural-fermented MK-7 were given daily to healthy adults over a period of 43 days *[69]*. To investigate MK-7 activity, researchers measured how much of the uncarboxylated osteocalcin (ucOC) was transformed into the carboxylated form (cOC) after activation by MK-7. As expected from known K2 activity, blood concentrations of ucOC decreased at the end of the study, when compared to study start, while cOC levels increased. The observed cOC increase at the end of

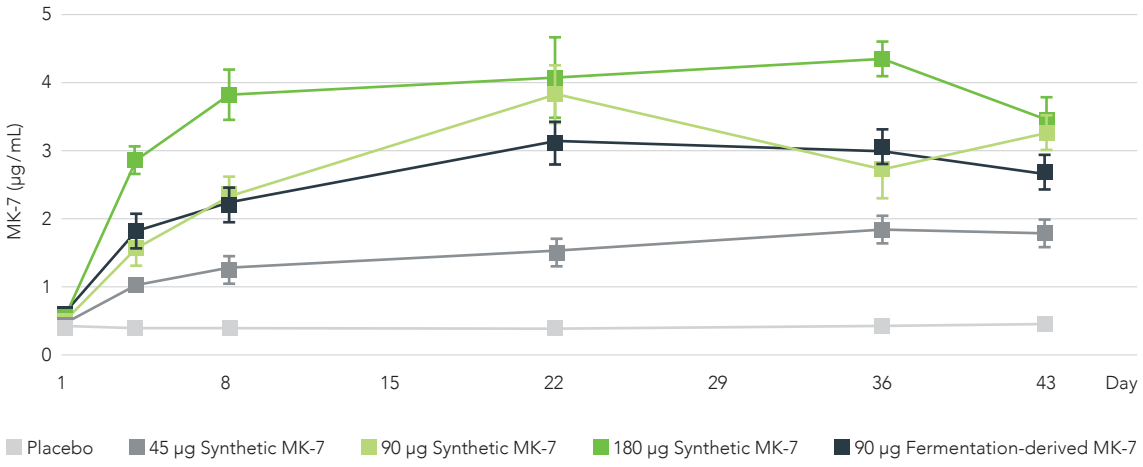
the study was equal for the 90 µg synthetic and natural K2. Furthermore, an equal increase of MK-7 in blood by supplementation of K2VITAL® and fermentation-derived MK-7 was observed.

These results prove that the synthetic form of MK-7 as K2VITAL® is bioequivalent to natural-fermented MK-7. Which means that all benefits obtained with the natural MK-7 supplement are equally valid for K2VITAL®.

Equal reduction of inactive osteocalcin (ucOC) by K2VITAL® and fermented derived MK-7



Equal increase of MK-7 in blood by supplementation of K2VITAL® and fermentation-derived MK-7



Placebo | 45 µg Synthetic MK-7 | 90 µg Synthetic MK-7 | 180 µg Synthetic MK-7 | 90 µg Fermentation-derived MK-7

Studies on K2VITAL(R) Bioequivelence

Publication	Participants	Population	Duration	Results
Møller et al. 2016 *[69]*	17	Healthy	One dose	Synthetic MK-7 and fermentation-derived MK-7 have the same bioavailability
	48	Healthy	6 weeks	No differences between synthetic and fermentation-derived MK-7 on biological activity

SCIENCE

SAFETY OF VITAMIN K2 MK-7

MK-7 has also been evaluated in several pre-clinical toxicology trials up to very high doses. The highest dose tested was a single dose of 2000 mg per kg body weight in mice *[70]*. For repeated dosing, the highest dose investigated was 10 mg per kg body weight per day in rats for 90 days. No animal study reports any safety concern or adverse effects. It can be concluded that K2VITAL® is safe. The recommended daily dose of vitamin K2 MK-7 for infants and children is not yet determined. There is evidence of benefits in children given 45 µg of K2 MK-7 a day *[58]*. Therefore, optimal doses of K2 MK-7 must be established for children.

K2VITAL® can fill the gap between what our bodies need and what our diets provide. Many clinical and pre-clinical studies have explored the health effects of vitamin K2 intake and have demonstrated benefits ranging from improved cardiovascular health to better bone health in all age groups.

MARLES ET AL. 2017: A SAFETY EVALUATION OF MK-7

The US Pharmacopeial Convention recently performed a safety evaluation of MK-7, where all relevant aspects were assessed including the chemistry, dietary sources, intake levels, and pharmacokinetics, together with nonclinical toxicity data and data on clinical outcomes related to safety (adverse events) *[71]*.
14 clinical trials, where adverse events were reported, were identified. Treatment with MK-7 at levels of up to 180 µg/d for 3 years, of up to 360 µg/d for 12 weeks, or of up to 1080 µg thrice weekly for 8 weeks with populations of up to 120 individuals was associated with no significant adverse effects compared to placebo (summarized in table). In a study in rats MK-7 was tested up to 10mg/kg/d for up to 90 days with no significant adverse effects and was shown to have no genotoxic or mutagenic potentials. The authors concluded that there is a risk between MK-7 and anticoagulant drugs, which are vitamin K antagonists. However, as long as the patient's vitamin K intake is known, dose titration and patient counselling will allow the physician or pharmacist to mitigate any risk and maintain stable anticoagulation control.
The authors concluded from the reviewed data that **MK-7, when taken as a dietary supplement, is not associated with any serious risk to health or with other public health concerns.**

Database	Reports
FDA MedWatch program	No reports
Canada Vigilance Adverse Reaction Online Database	No reports on menaquinone-7 or MK-7 One report on "menaquinones" which was one non-serious incidence of diarrhea and vomiting associated with a "suspected" 92 ingredient product containing 6µg of vitamin K2
UK Medicines and Healthcare products Regulatory Agency Drug Analysis Prints A-Z	No reports
Australian Therapeutic Goods Administration Database of Adverse Event Notifications – medicines	Two reports associated with menaquinones: - Hot flush and blurred vision - One case of myocardial infarction and splenic infarction associated with an unspecified menaquinone-containing product taken in combination with multiple prescription drugs that include human prothrombin complex (also a suspected product in the adverse event)
New Zealand MedSafe Suspected Medicine Adverse Reaction Search	No reports

Aoun, M., et al.,

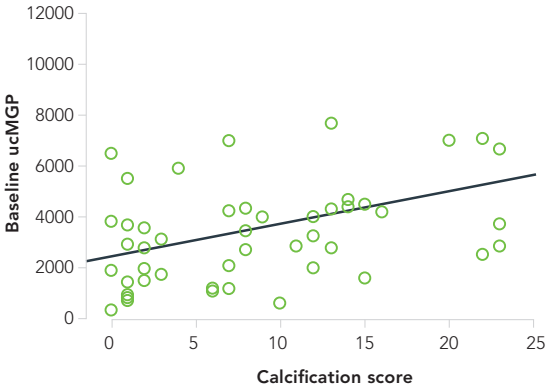
High Dephosphorylated-Uncarboxylated MGP in Hemodialysis Patients: Risk Factors and Response to Vitamin K2, a Pre-Post Intervention Clinical Trial

Objective:
Vascular calcification is very common in hemodialysis patients, a population with high levels of inactive/uncarboxylated MGP (ucMGP). This pre-post intervention clinical trial examined the correlation between the degree of calcification and ucMGP levels and assessed the reduction in ucMGP levels following MK-7 supplementation.

Method:
Fifty hemodialysis patients received a daily dose of 360 µg MK-7 for 4 weeks. At baseline, the calcification score was performed by two independent physicians, one of them was blinded. Blood samples for detection of ucMGP were collected at baseline and at the end of the trial.

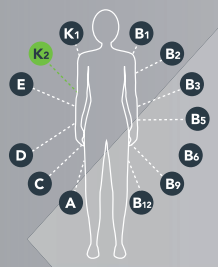
Results:
At baseline, the calcification score correlated significantly with ucMGP serum levels (p=0.002). The median level of ucMGP reduced from 3179 µM at baseline to 295 µM at the end of the trial, an 86% reduction.

Correlation between inactive MGP (ucMGP) and calcification score



4 REASONS WHY YOU NEED VITAMIN K2 MK-7

VITAMIN K2 IS AN ESSENTIAL FAT-SOLUBLE VITAMIN



Like all vitamins, it must be obtained from the diet to enable your body to function as it should.

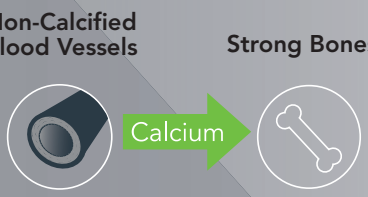
OUR DIETS TODAY DO NOT PROVIDE US WITH ENOUGH VITAMIN K2

Average vitamin content in a balanced diet

Minimum recommended intake 75 µg

It needs to be supplemented just as Vitamin D does.

VITAMIN K2 MK-7 DIRECTS CALCIUM TO THE RIGHT PLACES



It brings calcium into your bones and clears your arteries from excess calcium.

VITAMIN K2 MK-7 IS THE BEST FORM OF VITAMIN K

It absorbs easiest, reaches every part of your body and remains there longest.

EFSA approved health claim: Vitamin K contributes to the maintenance of normal bones

EXPERIENCE K2VITALITY®

THE FASTEST GROWING HEALTH INGREDIENT

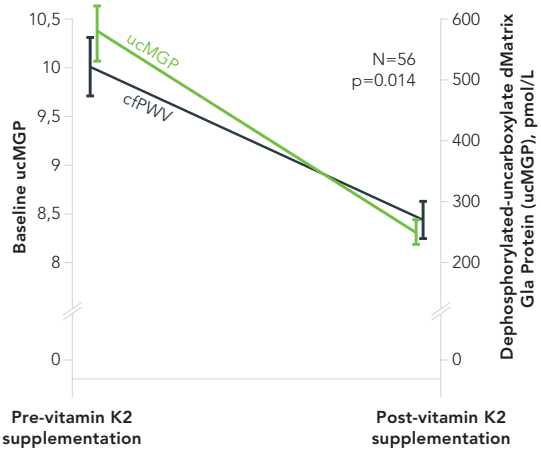
STAY HEALTHY AND STRONG THROUGHOUT LIFE!

Kappa BIOSCIENCE

Mansour, A. G., et al.,
Vitamin K2 Supplementation and Arterial Stiffness Among Renal Transplant Recipients – A Single-Arm, Single-Center Clinical Trial

Objective:
Renal transplant recipients have an increased risk of arterial stiffness and cardiovascular disease. This population also displays a subclinical vitamin K deficiency, detected by high levels of inactive, uncarboxylated matrix gla-protein (ucMGP). This prospective, single-arm clinical study examined the effects of MK-7 supplementation on arterial stiffness and ucMGP levels.

Effects of MK-7 supplementation on arterial stiffness and ucMGP levels



Method:
Sixty renal transplant recipients were supplemented with a daily dose of 360 µg MK-7 for 8 weeks. Arterial stiffness was measured using carotid-femoral pulse wave velocity (cfPWV). Blood samples were collected for assessment of ucMGP.

Results:
The patients experienced a 14.2% improvement in arterial stiffness ($P < 0.001$) and a 55.1% decrease in mean serum levels of ucMGP ($P < 0.0001$), at the end of the study. In conclusion, MK-7 supplementation improved subclinical vitamin K deficiency and arterial stiffness in renal transplant recipients with stable graft function.

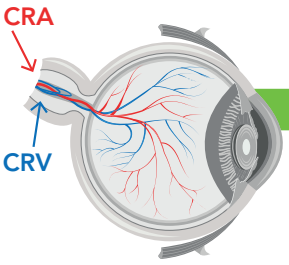
SCIENCE

Wei, F.F., et al.,
Inactive Matrix Gla-Protein is a Novel Circulating Biomarker Predicting Retinal Arteriolar Narrowing in Humans

Objective:
The diameter of retinal micro-vessels carries important prognostic information; smaller arteriolar diameter is a predictive marker for cardiovascular mortality and coronary heart disease. Matrix gla-protein (MGP) is expressed in the retinal vasculature. The trial investigated the association between inactive or uncarboxylated MGP (ucMGP) and retinal circulation (measured by retinal arteriolar and venular narrowing).

Method:
The trial recruited 935 participants (mean age of 40.9 years and 50.3% women). Retinal vascular diameters (central retinal arteriole and venule) were assessed. Blood samples were collected for ucMGP assessment.

Results:
The retinal arteriolar diameter was significantly smaller among participants with high circulating ucMGP than those with low circulating ucMGP. Therefore, circulating ucMGP is a predictor of smaller retinal arteriolar narrowing. Vitamin K supplementation might promote retinal health.



CRA - central retinal artery
CRV - central retinal vein

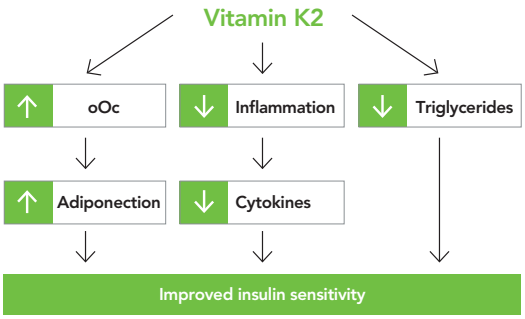
The association between inactive or uncarboxylated MGP (ucMGP9) and retinal circulation

Characteristics	Category of ucMGP			*p* Value
Limits (µg/L)	< 2.88	2.88 – 4.58	≥ 4.58	
Central retinal arteriolar calibre (µm)	152.1 (14.3)	151.0 (13.9)	148.8 (13.5)	0.005
Central retinal venular calibre (µm)	218.7 (18.4)	219.2 (18.9)	217.0 (19.9)	0.33
Arteriolar-to-venule ratio	0.70 (0.06)	0.69 (0.06)	0.69 (0.06)	0.080

Li, Y., et al.,
Effect of Vitamin K2 on Type 2 Diabetes mellitus: A Review

Objective:

Type 2 diabetes mellitus (T2DM) is a major public health problem, globally. Type 2 diabetes develops when the body becomes resistant to insulin. At first, the pancreas tries to compensate by producing more insulin, eventually, the insulin production diminishes and blood sugar increases. Prospective observational studies and clinical trials show a reduced risk of developing T2DM with vitamin K2 supplementation. The literature review assessed the effects of vitamin K2 on T2DM and its pathogenesis.



Main Evaluation:

Clinical data (one cohort study and two clinical trials) indicate that vitamin K2 intake improves insulin sensitivity and reduces the risk of T2DM.

1. Increased activation of osteocalcin (cOC) can increase adiponectin, lowering plasma glucose levels and increasing insulin sensitivity
2. Reduced inflammation leading to a reduced secretion of cytokines can enhance glucose uptake
3. Reduced serum levels of triglycerides can lead to increased glucose uptake

Results:

The authors propose vitamin K2 supplementation as a potential therapeutic strategy for T2DM in the future.

Effect of vitamin K2 on type 2 diabetes mellitus: A review

Author/year	Country	Design, Participants	Outcome measure	Results and conclusion
Beulens 2010	**Netherlands**	Prospective cohort study (N=38.094) where 918 incidents of diabetes were documented, 10.3 years of follow-up	Documented cases of T2DM were compared to intake levels of vitamin K2	Vitamin K2 may be associated with a reduced risk of T2DM
Choi 2011	**Korea**	Placebo-controlled clinical trial, N=42 healthy males aged 29 years were included, 4 weeks of intervention	Insulin sensitivity index, acute insulin response to glucose, disposition index, adiponectin, interleukin-6	Supplementation with vitamin K2 improves insulin sensitivity
Zatollah 2016	**Iran**	Double-blinded, randomized, placebo-controlled trial, N=66, patients with T2DM and coronary heart disease, aged 40-85 years, 12 weeks of intervention	Serum insulin levels, HOMA index	Significant reduction in serum insulin and HOMA-index

SCIENCE

Myneni, V.D. and E. Mezey, Regulation of Bone Remodeling by Vitamin K2

Objective:

Bone structures are tightly regulated and require amino acids, fatty acids, carbohydrates, minerals, vitamins and water for optimal development and maintenance. Vitamin K2 regulates bone remodeling, a continuous process that helps maintain bone structure, bone volume, and calcium homeostasis. This review summarizes the current data on how K2 regulates bone remodeling.

Main Evaluation:

Old and micro-damaged bone are continuously replaced through the bone remodeling cycle, which consists of five distinct and overlapping phases.

1. **Initiation:** Osteocytes sense deformed bone and secretes signaling molecules to activate osteoclast precursor cells to osteoclasts.
2. **Resorption:** Osteoclasts form bone-resorbing compartments. They secrete proteolytic enzymes and hydrogen ions to lower the pH. This facilitates the dissociation of bone minerals and the degradation of the bone matrix.
3. **Reversal:** Osteoclasts are inactivated, and osteoblasts are recruited.
4. **Formation:** Osteoblasts deposit an organic matrix that is mineralized. They secrete osteocalcin into the bone extracellular matrix where it binds to hydroxyapatite crystals.
5. **Resting:** Most of the osteoblasts that participated in the now bone formation dies, some develop to lining cells and some to osteocytes. Thereafter, the cycle is completed, followed by a resting phase.

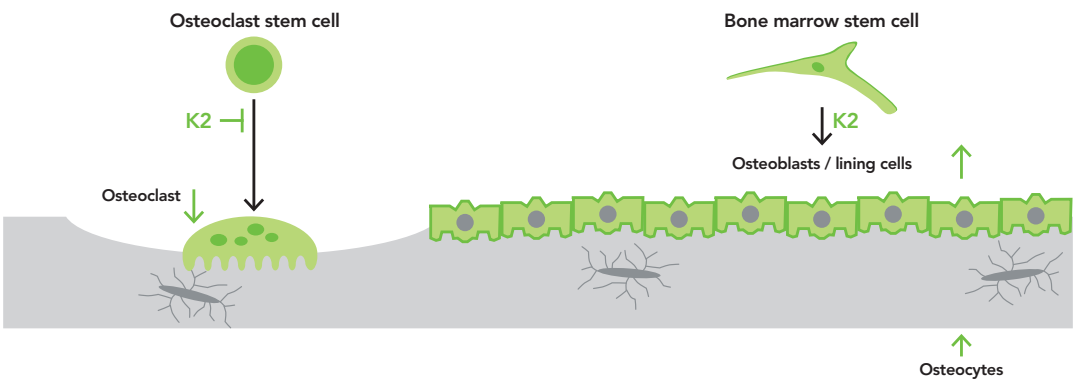
The bone remodeling cycle can be imbalanced. If less bone mass is formed than resorbed, it can evolve into osteopenia and eventually osteoporosis.

Results:

Vitamin K2 regulates the bone remodeling cycle at several levels:

1. **Osteoclasts:** Vitamin K2 inhibits osteoclast differentiation
2. **Osteoblasts:** Vitamin K2 stimulates osteoblast development and protects them from cell death leading to increased osteoblast/lining cells and osteocytes
3. **Osteocalcin:** Vitamin K2 activates or carboxylates osteocalcin that allows binding the calcium and hydroxyapatite crystals.

Regulation of bone remodeling by vitamin K2



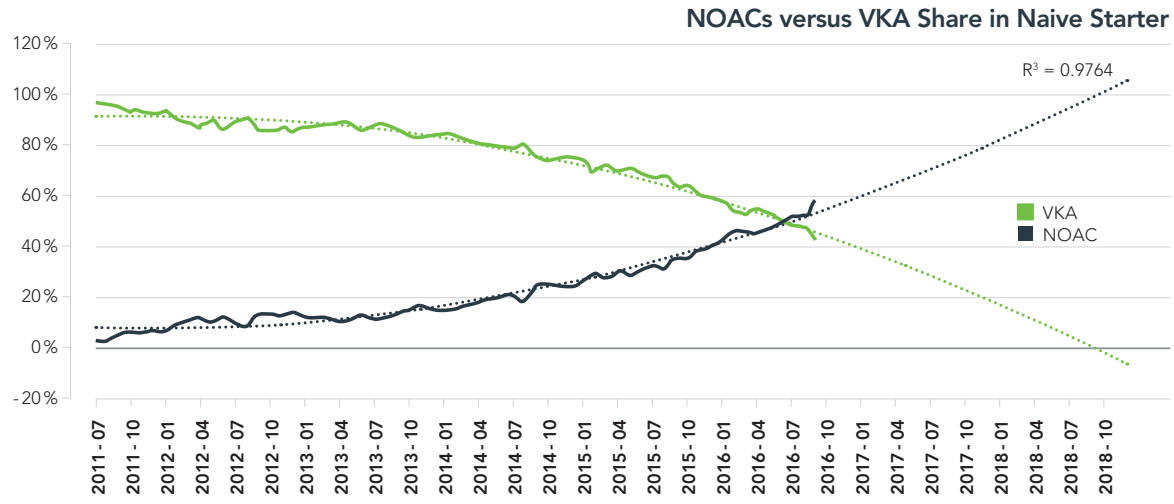
van den Heuvel, J.M., et al.,

NOACs Replace VKA as Preferred Oral Anticoagulant Among New Patients: A Drug Utilization Study in 560 Pharmacies in The Netherlands

Objective:
Vitamin K antagonists (VKA) and non-VKA oral anticoagulants (NOACs) are the two main categories of oral anticoagulants prescribed for thromboembolic diseases. VKA interferes with the vitamin K cycle and has a small therapeutic window. Treating patients with VKA requires titration of the dose, and the required dose can differ largely among patients. NOACs are a new group of drugs that entered the market in 2011. NOACs do not interfere with the vitamin K cycle and do not require frequent monitoring of the blood, which is a benefit for the patient. This study compared the use and adherence of NOACs to VKA.

Method:
Data from 560 pharmacies and 247,927 patients prescribed from 2011 to 2016 were analyzed. Use in new patients and switch from VKA to NOAC were registered. Adherence to the therapies were calculated.

Results:
Since its launch in 2011, NOACs has grown up to 57% of prescriptions to new patients. Among the NOAC users, 70% were new naïve patients and around 26% switched from VKA. 88% of all NOAC users were adherent to the therapy. In conclusion, NOAC has taken over VKA as the major treatment prescribed to new users. The number of patients starting on VKA is decreasing.



MARKET OPPORTUNITIES WITH VITAMIN K2 MK-7

BENEFICIAL FOR ALL CONSUMERS REGARDLESS OF AGE LIFE-STAGE OR GENDER

BENEFITS

VITAMIN K2 MK-7 PAIRED WITH

Vitamin K2 MK-7 is an essential vitamin, which directs calcium to the right places in the body

BENEFITS VITAMIN K2 MK-7 ONLY

- Builds strong teeth
- Builds and maintains strong bones*
- Prevents calcified arteries

MOTHERS & INFANTS

Vitamins: C, D, folic acid **Other:** DHA
Minerals: calcium, magnesium, zinc
Bone, brain & nervous system development of the baby*

Vitamins: B group, C
Minerals: calcium, magnesium
Energy and strength for the mother*

CHILDREN & TEENS

Vitamins: B group, C, D
Minerals: calcium, magnesium, zinc
Energy to play and unbreakable bones*

YOUNG ADULTS

Vitamins: B group, C, D
Minerals: calcium, magnesium, zinc
Keeping bones and muscles strong and healthy*

Vitamins: A, B6, C, D, niacin, riboflavin
Minerals: calcium, magnesium, zinc
Looking good and healthy*

MIDDLE AGERS

Vitamins: B group, C, D
Minerals: calcium, magnesium, zinc
Keeping bones and muscles strong and healthy*

Vitamins: A, B6, C, D, niacin, riboflavin
Minerals: calcium, magnesium, zinc
Looking good and healthy*

SENIORS

Vitamins: B group, C, D
Minerals: calcium, magnesium, zinc
Staying active and energetic*

Vitamins: C, thiamine
Other: DHA, EPA, phytosterols, betaglucan
Ensuring a healthy heart*

*Based on EFSA approved health claims, see http://ec.europa.eu/nuhclaims

BUSINESS OPPORTUNITIES WITH VITAMIN K2 MK-7 ARE ENDLESS AND CONSTANTLY GROWING

Bone Health | Heart Health | Other market segments

Key growth drivers:

- Aging population
- Unhealthy lifestyles and dietary habits
- Sporty lifestyles becoming mainstream
- Increasing interest for holistic health

VERSATILE APPLICATION POSSIBILITIES TO FIT WITH TARGET CONSUMER LIFESTYLES

Dietary supplement | Food | Beverage

Kappa BIOSCIENCE

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