Vitamin K2

Two Important Forms of Vitamin K2 for Bone Health

- Helps your bones use calcium more effectively
- Supports normal blood clotting and cardiovascular health
- Provides both MK-4 and MK-7 for greater effectiveness

Details
Vitamin K is an essential vitamin needed for cardiovascular, bone and liver health. Vitamin K2 is more effective than vitamin K1, the form found in plants, for these specific health effects. There are two effective and popular forms of Vitamin K2: namely MK-4 and MK-7. While MK-4 is the active form of vitamin K2 used by the body and has been used clinically in Japan for decades with good results, MK-7 has also been shown to provide good results at low doses in a sustained-release manner. AOR’s Vitamin K2 provides a 50/50 blend of MK-4 and MK-7 to ensure the best of both worlds.

The most popular, albeit recently highlighted, use for vitamin K2 is for bone health. Vitamin K, along with vitamin D, is essential for proper calcium absorption and usage in the bones. Vitamin K2 also stimulates the synthesis of proteins that regulate bone growth, and has been shown to reduce the incidence of osteoporotic fractures and improve bone quality.

Vitamin K is also essential to cardiovascular health. It is an important blood clotting factor: without adequate amounts, the risk of bruising and excessive bleeding increases substantially. By the same token, vitamin K enhances calcium absorption from the bloodstream into the bones, preventing arterial calcification and promoting healthy blood vessel function and heart health. Ultimately, Vitamin K2 is an excellent adjunct to conventional osteoporosis medications and is essential for those taking calcium supplements. Vitamin K2 may also be useful for those with a family history of osteoporosis, cardiovascular disease, arterial calcification or for people who bruise or bleed easily.
Discussion
Vitamin K2 from AOR™ provides MK-4 and MK-7, the two optimal forms of Vitamin K2 that help maintain bone health. Although it interferes with "blood thinning" medications, it does not cause excessive or abnormal blood clotting.

Product Variation
Product Code | Size
---|---
AOR04143 | 60 VEGI-CAPS

Supplements Facts
Serving Size: 1 Capsule

<table>
<thead>
<tr>
<th>Amount</th>
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<tbody>
<tr>
<td>Vitamin K2</td>
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<tr>
<td>MK-4</td>
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<tr>
<td>MK-7 (may contain soy)</td>
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Non-medical ingredients:

Guarantees
AOR™ guarantees that all ingredients have been declared on the label. Contains no wheat, gluten, corn, nuts, peanuts, sesame seeds, sulphites, mustard, dairy, eggs, fish, shellfish or any animal byproduct.

Adult Dosage
Take 1 capsule daily with food, or as directed by a qualified health care practitioner.

Cautions
Do not use if taking anticoagulant ("blood thinning") medications such as warfarin (Coumadin®) or if pregnant or breastfeeding.

Source
Pharmaceutical synthesis

Main Application
Bone health
Cardiovascular health
Calcium absorption

Disclaimer
The information and product descriptions appearing on this website are for information purposes only, and are not intended to provide or replace medical advice to individuals from a qualified health care
professional. Consult with your physician if you have any health concerns, and before initiating any new diet, exercise, supplement, or other lifestyle changes.

**Research**

**Background**

Vitamin K is an essential component for health, and deficiency can cause serious consequences in cardiovascular, bone and liver health. Vitamin K was discovered in the early part of the last century. Originally, it was thought mostly to contribute to blood clotting. However, the latter half of the 1900s saw vitamin K clinically used in Japan to reduce the risk of osteoporosis and bone fractures in women.

**AOR’s New 50/50 K2 Blend**

Over 90% of all studies on bone health have been done with MK-4, and 40 to 50 of these were of large scale and long duration. MK-7 has been the subject of more research over the past several years, and the most recent bioavailability comparison study has answered several questions that previously cast doubt on the efficacy of MK-7. While this research is promising, there are still many unanswered questions. Due to the strong historical clinical use and effectiveness of MK-4 and the significance of the new research on MK-7, AOR has opted to provide a 50/50 blend of both forms in order to provide the full range of benefits of vitamin K2.

**The Vitamin K Family**

Vitamin K constitutes a family of compounds that exist as natural vitamin K1 (phylloquinone) and vitamin K2 (menaquinones) and the synthetic form vitamin K3 (menadionone). Vitamin K1 is the more prevalent form in our diet and is found in leafy green vegetables (lettuce, broccoli, cabbage, spinach etc) and vegetable oils. Vitamin K2 has several forms, two of which are commonly used as supplements: menatetrenone (MK-4), which is found in animal tissue, and menaquinone-7 (MK-7) which is abundant in fermented soy foods like natto. The chemical structure consists of a benzene ring (napthoquinone) and a side chain with various numbers of isoprenyl groups. The suffix numbers 4, 7, 8 and 9 refer to the position of these groups.

**Bone Health**

Bone is a living tissue that continually undergoes remodeling via synthesis and degradation of bone tissue by osteoblast and osteoclast cells respectively. In addition to other key nutrients for proper bone-remodeling e.g. calcium, vitamin D, vitamin C, zinc, magnesium and manganese, vitamin K plasma status is important for maintaining healthy bone. Osteocalcin is a small protein and the degree of its carboxylation (hence vitamin K status) is a measure of bone health. There is a direct correlation between carboxylation of osteocalcin and bone health.

**Pharmacological functions:**

The chief function of vitamin K is to act as a co-factor (an adjunct) for vitamin K-dependent proteins in the body and convert the glutamate residues of these proteins into gamma-carboxyglutamate group via an enzymatic process of carboxylation. Such proteins include bone turnover molecules (osteocalcin and protein S), vascular repair proteins (Matrix GLA) and proteins responsible for cell-cycle arrest, signal transduction and cell-cell adhesion.
Research

Comparing MK-4 & MK-7

Bioavailability

Although no studies have directly compared the distribution, metabolism and excretion of MK-4 and MK-7, the first bioavailability study comparing their absorption into the bloodstream has been published. This study showed that amounts of MK-4 lower than 420 mcg did not result in detectable levels in the bloodstream at 0, 2 and 4 hours and beyond while amounts of MK-7 as low as 60 mcg resulted in measurable levels in the blood, peaking at 6 hours. However, no measurements were taken within the first two hours.

Dose

Most of the best studies on MK-4 have been conducted using doses ranging from 15-90 mg. These studies have shown positive results for various health indications. High doses of MK-4 were found to reduce fracture risk in postmenopausal osteoporosis, and some researchers suggest that those doses are much higher than what is required to carboxylate bone proteins like osteocalcin which is a marker of bone quality. Other studies have shown that doses of MK-4 at least 500-1500 mcg are required for the carboxylation of osteocalcin, while doses of 45-90 mcg of MK-7 accomplish this task.

Benefits unique to MK-4

It is thought that all forms of vitamin K are converted into MK-4 for use. Interestingly, levels of MK-4 but not MK-7 rise significantly in breast milk and bone tissue when supplementing with MK-7. It is also thought that MK-4 has other specific functions that are not related to gamma-carboxylation. Indeed, studies with MK-4 have found that it suppresses the inflammatory factor NF-kB. MK-4 alone also appears to activate genes in osteoblasts (cells that build bone) while MK-7 did not. To this point, MK-7 has been studied uniquely for gamma-carboxylation of osteocalcin, so it is unclear whether supplementing with MK-7 exerts the same additional effects as MK-4.

Bone Health

In human studies low serum vitamin K levels have been associated with increased incidence of osteopenia (pre-osteoporotic condition) and full blown osteoporosis. Japanese studies have shown that in areas where there is high consumption of natto (Eastern Japan- Tokyo) the incidence of osteoporosis and hip fractures is significantly lower compared to Western Japan (Hiroshima) where the incidence of natto consumption is low (hence low vitamin K levels).

A study comparing the bioavailability of MK-4 to MK-7 head to head has finally been published. This study showed a dose of 60 mcg of MK-7 is sufficient to significantly activate osteocalcin. However, there are a wealth of studies demonstrating the benefits of MK-4, benefits that are not shown by MK-7. MK-4 has been extensively clinically studied for its effects on bone metabolism and other areas of health.
**Market Trends**

It is now known that Vitamin K2 produces superior results and is better absorbed and utilized in the body than the plant form vitamin K1 found in green leafy vegetables. MK-4 is the form of vitamin K2 found in animal tissue, has been clinically used in Japan for decades and has dozens of quality clinical trials supporting its effectiveness for bone health. A second form of supplemental vitamin K2 has recently emerged onto the market, namely MK-7. MK-7 has been found to activate an important bone protein at low doses and in a sustained-release manner.

**AOR Advantage**

Driven by research, AOR’s new formulation offers a 50/50 blend of 60 mcg each of both forms of vitamin K2 in order to provide an adequate dose for the absorption benefits of MK-7 while still providing MK-4, which has been successfully clinically studied and used for bone health for decades and is the primary form found in the human body.

**References**


Iwamoto J, Takeda T, Sato Y. Menatetrenone (vitamin K2) and bone quality in the treatment of postmenopausal osteoporosis. Nutr Rev. 2006 Dec;64(12):509-17.


Sato T, Schurgers LJ, Uenishi K. Comparison of menaquinone-4 and menaquinone-7 bioavailability in

Abstract


Theuwissen E, Teunissen KJ, Spronk HM, Hamulyák K, Ten Cate H, Shearer MJ, Vermeer C, Schurgers LJ.

Despite the worldwide use of vitamin K antagonists (VKAs), there is limited knowledge of the influence of dietary vitamin K on anticoagulation control. In view of the increasing nutraceutical availability of menaquinone-7 (MK-7; vitamin K2) and its promotion for bone and cardiovascular health, it is important to determine the posology for the interference of supplemental MK-7 with VKA therapy. Eighteen healthy men and women were anticoagulated for 4 weeks with acenocoumarol, and 15 of them attained a target International Normalized Ratio (INR) of 2.0. In the six subsequent weeks, subjects were given increasing doses of MK-7 (10, 20 and 45 ?g day(-1)) while continuing acenocoumarol treatment at established individual doses. Apart from the INR, acenocoumarol treatment significantly increased the levels of uncarboxylated factor II (ucFII), uncarboxylated osteocalcin (ucOC), and desphospho-uncarboxylated matrix Gla-protein (dp-ucMGP), and decreased endogenous thrombin generation (ETP). A daily intake of 45 ?g of MK-7 significantly decreased the group mean values of both the INR and ucFII by ~ 40%. Daily intakes of 10 and 20 ?g of MK-7 were independently judged by two hematologists to cause a clinically relevant lowering of the INR in at least 40% and 60% of subjects, respectively, and to significantly increase ETP by ~ 20% and ~ 30%, respectively. Circulating ucOC and dp-ucMGP were not affected by MK-7 intake. MK-7 supplementation at doses as low as 10 ?g (lower than the usual retail dose of 45 ?g) significantly influenced anticoagulation sensitivity in some individuals. Hence, the use of MK-7 supplements needs to be avoided in patients receiving VKA therapy.

Three-year low-dose menaquinone-7 supplementation helps decrease bone loss in healthy postmenopausal women.

Osteoporos Int. 2013 Sep;24(9):2499-507.

Knapen MH, Drummen NE, Smit E, Vermeer C, Theuwissen E.

We have investigated whether low-dose vitamin K2 supplements (menaquinone-7, MK-7) could beneficially affect bone health. Next to an improved vitamin K status, MK-7 supplementation
significantly decreased the age-related decline in bone mineral density and bone strength. Low-dose MK-7 supplements may therefore help postmenopausal women prevent bone loss. Despite contradictory data on vitamin K supplementation and bone health, the European Food Safety Authorities (EFSA) accepted the health claim on vitamin K’s role in maintenance of normal bone. In line with EFSA’s opinion, we showed that 3-year high-dose vitamin K1 (phytolquinone) and K2 (short-chain menaquinone-4) supplementation improved bone health after menopause. Because of the longer half-life and greater potency of the long-chain MK-7, we have extended these investigations by measuring the effect of low-dose MK-7 supplementation on bone health. Healthy postmenopausal women (n=244) received for 3 years placebo or MK-7 (180 ?g MK-7/day) capsules. Bone mineral density of lumbar spine, total hip, and femoral neck was measured by DXA; bone strength indices of the femoral neck were calculated. Vertebral fracture assessment was performed by DXA and used as measure for vertebral fractures. Circulating uncarboxylated osteocalcin (ucOC) and carboxylated OC (cOC) were measured; the ucOC/cOC ratio served as marker of vitamin K status. Measurements occurred at baseline and after 1, 2, and 3 years of treatment. MK-7 intake significantly improved vitamin K status and decreased the age-related decline in BMC and BMD at the lumbar spine and femoral neck, but not at the total hip. Bone strength was also favorably affected by MK-7. MK-7 significantly decreased the loss in vertebral height of the lower thoracic region at the mid-site of the vertebrae. MK-7 supplements may help postmenopausal women to prevent bone loss. Whether these results can be extrapolated to other populations, e.g., children and men, needs further investigation.

Comparison of menaquinone-4 and menaquinone-7 bioavailability in healthy women.

Sato T, Schurgers LJ, Uenishi K.


Vitamin K2 contributes to bone and cardiovascular health. Therefore, two vitamin K2 homologues, menaquinone-4 (MK-4) and menaquinone-7 (MK-7), have been used as nutrients by the food industry and as nutritional supplements to support bone and cardiovascular health. However, little is known about the bioavailability of nutritional MK-4. To investigate MK-4 and MK-7 bioavailability, nutritional doses were administered to healthy Japanese women. Single dose administration of MK-4 (420 ?g; 945 nmol) or MK-7 (420 ?g; 647 nmol) was given in the morning together with standardized breakfast. MK-7 was well absorbed and reached maximal serum level at 6 h after intake and was detected up to 48 h after intake. MK-4 was not detectable in the serum of all subjects at any time point. Consecutive administration of MK-4 (60 ?g; 135 nmol) or MK-7 (60 ?g; 92 nmol) for 7 days demonstrated that MK-4 supplementation did not increase serum MK-4 levels. However, consecutive administration of MK-7 increased serum MK-7 levels significantly in all subjects. We conclude that MK-4 present in food does not contribute to the vitamin K status as measured by serum vitamin K levels. MK-7, however significantly increases serum MK-7 levels and therefore may be of particular importance for extrahepatic tissues.

Vitamin K(2) supplementation improves hip bone geometry and bone strength indices in postmenopausal women.
Knapen MH, Schurgers LJ, Vermeer C.

Vitamin K mediates the synthesis of proteins regulating bone metabolism. We have tested whether high vitamin K(2) intake promotes bone mineral density and bone strength. Results showed that K(2) improved BMC and femoral neck width, but not DXA-BMD. Hence high vitamin K(2) intake may contribute to preventing postmenopausal bone loss.

INTRODUCTION: Vitamin K is involved in the synthesis of several proteins in bone. The importance of K vitamins for optimal bone health has been suggested by population-based studies, but intervention studies with DXA-BMD as a clinical endpoint have shown contradicting results. Unlike BMC, DXA-BMD does not take into account the geometry (size, thickness) of bone, which has an independent contribution to bone strength and fracture risk. Here we have tested whether BMC and femoral neck width are affected by high vitamin K intake.

METHODS: A randomized clinical intervention study among 325 postmenopausal women receiving either placebo or 45 mg/day of vitamin K(2) (MK-4, menatetrenone) during three years. BMC and hip geometry were assessed by DXA. Bone strength indices were calculated from DXA-BMD, femoral neck width (FNW) and hip axis length (HAL).

RESULTS: K(2) did not affect the DXA-BMD, but BMC and the FNW had increased relative to placebo. In the K(2)-treated group hip bone strength remained unchanged during the 3-year intervention period, whereas in the placebo group bone strength decreased significantly.

CONCLUSIONS: Vitamin K(2) helps maintaining bone strength at the site of the femoral neck in postmenopausal women by improving BMC and FNW, whereas it has little effect on DXA-BMD.

Menatetrenone (vitamin K2) and bone quality in the treatment of postmenopausal osteoporosis.

Iwamoto J, Takeda T, Sato Y.

Menatetrenone (vitamin K2) reduces the incidence of vertebral fractures but has only modest effects on bone mineral density (BMD) in postmenopausal women with osteoporosis. Combined treatment with bisphosphonates and menatetrenone may be more effective than treatment with bisphosphonates alone in preventing vertebral fractures, despite the lack of an additive effect of menatetrenone on the BMD increase by bisphosphonates. Menatetrenone improves bone architecture in ovariectomized rats, and the mineral/ matrix ratio of the bone in terms of matrix volume and bone strength (without increasing bone mass) in rats with magnesium deficiency. Thus, available evidence supports an effect of menatetrenone on bone quality during osteoporosis treatment.
Beneficial effect of pretreatment and treatment continuation with risedronate and vitamin K2 on cancellous bone loss after ovariectomy in rats: a bone histomorphometry study.


Iwamoto J, Takeda T, Sato Y, Shen CL, Yeh JK.

The purpose of the present study was to examine the effect of pretreatment with risedronate and/or vitamin K2 and treatment continuation with reduced dosing frequency of the drugs on the early cancellous bone loss induced by ovariectomy (OVX) in rats. Eighty female Sprague-Dawley rats, 4 mo of age, were randomized by the stratified weight method into eight groups (n= 10 in each group); rats subjected to OVX, but not sham-operated rats, were treated with vehicle, risedronate, vitamin K2 (menatetrenone), or risedronate vitamin K2 for 4 wk before the surgery, and the treatment was either discontinued (pretreatment groups) or continued after the surgery (treatment continuation groups) for 2 wk. Sham-operated rats (controls) were treated with the vehicle throughout the experimental period. During the 4 wk prior to the surgery (pretreatment), risedronate and vitamin K2 were administered five times a week either subcutaneously at a dose of 2.5 microg/kg body weight (risedronate) or orally at the dose of 30 mg/kg body weight (vitamin K2). During the 2 wk after the surgery (treatment continuation), the dosing frequency of the drugs was reduced to twice a week. Risedronate and vitamin K2 had an anti-resorptive effect on the bone. Pretreatment with risedronate alone, but not vitamin K2 alone, prevented the loss of the cancellous bone volume/total volume (BV/TV) of the proximal tibial metaphysis after OVX. Treatment continuation with vitamin K2 alone prevented the loss of the cancellous BV/TV after OVX, while treatment continuation with risedronate alone increased the cancellous BV/TV to beyond the values in controls. Pretreatment with risedronate vitamin K2 had a more beneficial effect in increasing the cancellous bone mass than pretreatment with risedronate alone. Treatment continuation with risedronate and/or vitamin K appeared to have a more beneficial effect in increasing the cancellous bone mass than the respective pretreatment. Neither the total tissue area nor the cortical area of the tibial diaphysis was affected by any treatment. The present study demonstrated that pretreatment with risedronate had a beneficial effect on the early cancellous bone loss after OVX in rats, with a more beneficial effect when combined with vitamin K2. Moreover, even though the dosing frequency of the drugs was reduced after OVX, treatment continuation appeared to be more beneficial than pretreatment for increasing the cancellous bone mass.

Vitamin K2 treatment for postmenopausal osteoporosis in Indonesia.


Purwosunu Y, Muharram , Rachman IA, Reksoprodjo S, Sekizawa A.

AIM:To investigate the effect of vitamin K2 (menatetrenone) treatment on bone mineral density (BMD) and a bone metabolic marker (osteocalcin) in postmenopausal women with osteoporosis living in Indonesia.

METHODS: A double-blind randomized placebo-controlled study of 63 postmenopausal women with osteoporosis. The vitamin K2 group (n = 33) received 45 mg menatetrenone and 1500 mg calcium
carbonate per day and the control group (n = 30) received placebo and 1500 mg calcium carbonate per day for 48 weeks. BMD of lumbal spine (L2-L4), osteocalcin (OC) and undercarboxylated OC were measured before, 24 and 48 weeks after initiation of the treatment.

RESULTS: After 48 weeks of treatment, the mean percentage change of lumbar BMD in the vitamin K2 group was significantly higher (P < 0.05) than that of the control group. The undercarboxylated OC level decreased by 55.9% in the menatetrenone group and 9.3% in the control group compared with the baseline level. The difference between the two groups was significant (P < 0.01). The adverse events were three minor gastrointestinal cases, which subsided after temporary cessation of therapy.

CONCLUSIONS: Treatment with 45 mg vitamin K2 with 1500 mg calcium per day for postmenopausal women with osteoporosis for 48 weeks resulted in a significant increase in lumbar BMD and a significant decrease in undercarboxylated OC levels.