

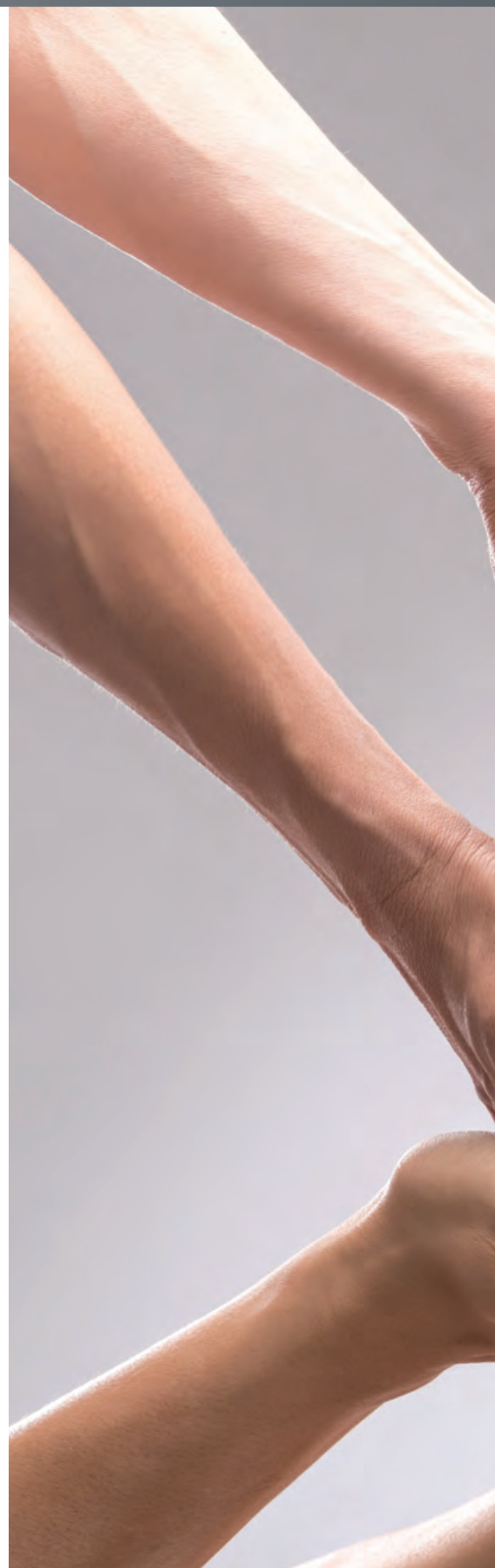
THE PERFECT  PAIR
VITAMIN K2 + VITAMIN D3
KAPPA ACADEMY

Calcium metabolism is closely linked to vitamins D3 and K2. While calcium and D3 have long been regarded as being complimentary, the scientific knowledge that vitamin K2 is also essential for healthy calcium balance has only been utilized in commercial applications for a few years. Since 2016, market launches for new products with calcium, D3 – and vitamin K2 MK-7 have increased disproportionately. A solid scientific foundation proves that K2 ‘puts calcium in balance’. K2 removes calcium from soft tissue, where it can be harmful. K2 additionally enables calcium to be stored in the bone mass. K2 works in synergy with D3. In the following paper, we will guide you through the scientific aspects of this synergy and clarify why K2 has evolved from an overlooked nutrient to a leading ingredient in dietary supplement and fortified food launches. K2 drives product effectiveness and commercial innovation. No wonder that more than 400 new K2 MK-7 products were launched to market in 2019, globally.




Calcium is the most abundant mineral in the human body, with about 99% of it occurring in bones and teeth where it serves as a major structural element. The remaining 1% is found in the blood and soft tissues.

Sufficient dietary calcium is essential for bone health. Calcium helps bones grow during childhood and adolescence. Adequate intake of calcium combats the decline of bone mass and prevent fractures. Studies have shown that strong, healthy bones formed in early life set a higher baseline for when



THE PERFECT PAIR



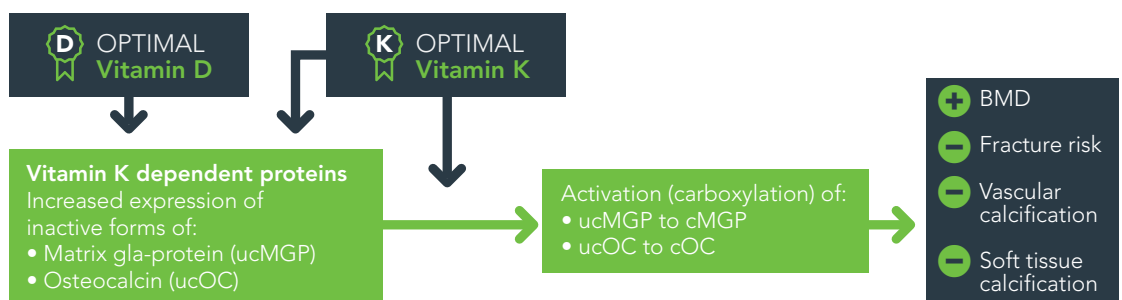
THE
FASCINATING
SYNERGY OF
VITAMINS D3
AND K2

a natural decline of bone mass begins. This is especially true for women. Just a 10% increase in peak bone mass at the end of adolescence leads to a 50% decrease in the risk of osteoporotic fracture later in life. This underscores the importance of an adequate dietary intake of calcium throughout all stages of life, especially among individuals with higher needs, such as post-menopausal women, children and older adults.

VITAMIN D3 REGULATES CALCIUM METABOLISM

Vitamin D3, sometimes known as the “sunshine vitamin” is naturally synthesized when our skin is exposed to sunlight. Although classified as a vitamin, D3 is actually a hormone. It plays a vital role in calcium absorption in the intestine, but is also involved in the expression of two major calcium-binding proteins, osteocalcin and matrix Gla protein (MGP). Almost 99% of our vitamin D supply is used to regulate calcium; the remaining part is used to strengthen the immune system and maintain muscle strength.

VITAMIN K2 FOR AN EXHAUSTIVE SOLUTION



van Ballegooijen et al., Int J Endocrinol 2017; 7454376

While vitamin D3 increases the expression of osteocalcin and MGP, these proteins are synthesized in an inactive form – they are not able to effectively bind calcium. Without sufficient levels of vitamin K, they will remain inactive and calcium will not be integrated into our skeletal system. When not integrated to build bones, excess calcium can be deposited in cardiovascular system, where it can have harmful effects. Vitamin K2 puts calcium in balance.

THE PERFECT PAIR

SCIENCE-BASED EVIDENCE OF D3+K2 SYNERGY

Several experimental, observational studies and clinical trials illustrate the vital role of vitamin K2 in combination with D3 for bone and cardiovascular health through the activation of K-dependent proteins osteocalcin and MGP.

Bone health – Important clinical trials combining vitamin K2 and D

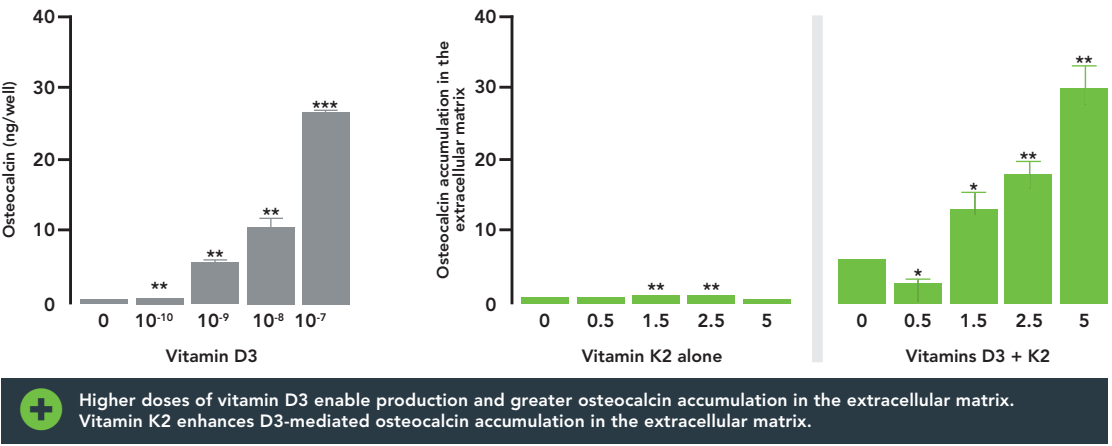
| Author/year | Participants | Intervention | Duration | Results |
|------------------------|---|---|----------|--|
| Iwamoto et al. 2000 | Osteoporotic women ≥ 5 y after menopause, N=92, mean age 64 years | 1. Calcium lactate, 2 g/d 2. Vitamin D3, 0.75 µg/d 3. Vitamin K2 (MK-4), 45 mg/d 4. Vitamin K2 + D3 | 2 years | Combined D and K2 increased the BMD |
| Ushiroyama et al. 2002 | Postmenopausal women with osteopenia and osteoporosis, N=126, mean age 53 years | 1. Diet 2. Vitamin D, 1 µg/d 3. Vitamin K2 (MK-4), 45 mg/d 4. Vitamin K2 + D | 2 years | Combined D and K2 increased the BMD |
| Yonemura et al. 2004 | Patients with glomerulonephritis, N=60, mean age 32 years | 1. Control 2. Vitamin D, 0.5 mg 3. Vitamin K2 (MK-4), 45 mg/d 4. Vitamin K2 + D | 8 weeks | The preventive effects in groups D, K2 and D + K2 were similar |
| Binkley et al. 2009 | Postmenopausal women, N=381, mean age 62 years | 1. Calcium 315 mg/d + Vit D3 200 IU/d 2. Vitamin K1 1 mg/d, Ca, Vit D3 3. Vitamin K2 (MK-4) 45 mg/d, Ca, Vit D3 | 1 year | Similar effects in all groups |
| Je et al. 2011 | Postmenopausal women, N=78, mean age 68 years | 1. Calcium 630 mg/d, Vitamin D 400 IU/d 2. Ca + Vit D + Vitamin K2 (MK-4) 45 mg/d | 6 months | BMD increased significantly in the Vitamin D + K2 group |
| Rønn et al. 2016 | Postmenopausal women with osteopenia, N=148, mean age 67y | 1. Calcium 800 mg/d + Vitamin D 38 µg/d 2. Ca + Vit D + Vitamin K2 (MK-7) 375 µg/d | 1 year | Vitamin K2 + D + Ca group preserves trabecular structures |

D3 + K2 and osteocalcin. Osteocalcin is a protein present in bones secreted by osteoblasts – the so-called “bone building cells”. Osteocalcin levels have widely been accepted as a good biomarker for the bone formation process. Higher serum osteocalcin levels are correlated to increases in bone mineral density. But only osteocalcin in its carboxylated form (activated) is able to bind calcium, and this carboxylation is vitamin K dependent.

In 1997, Koshihara and Hoshi ⁽¹⁾ investigated the role of vitamins D3 and K2 in osteocalcin accumulation within the extracellular matrix of human osteoblasts. The researchers conducted *in vitro* experiments, which ultimately demonstrated that vitamin K2 promoted osteocalcin car-

boxylation and mineralization performed by osteoblasts. As can be seen on the graph, a combination of both vitamins D3 and K2 showed the best efficiency in osteocalcin accumulation in the bone extracellular matrix.

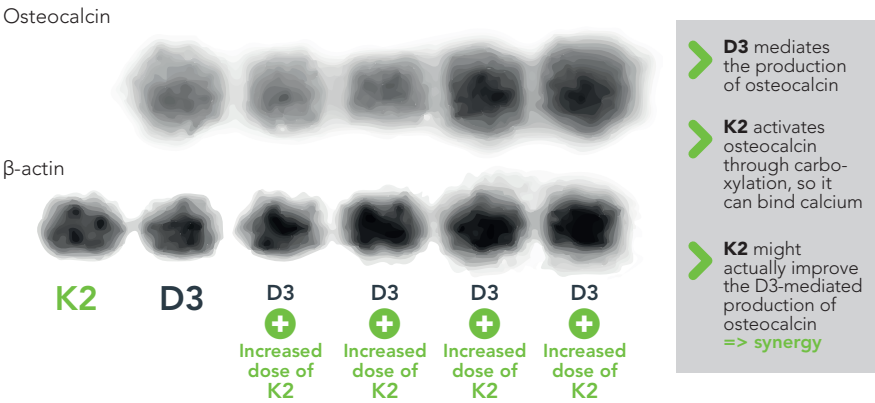
EFFECT OF VITAMIN K ON OSTEOCALCIN
IN THE PRESENCE OR ABSENCE OF 10⁻⁹ M VITAMIN D



Koshihara, Y., & Hoshi, K. (1997). Vitamin K2 enhances osteocalcin accumulation in the extracellular matrix of human osteoblasts in vitro. *Journal of Bone and Mineral Research*, 12(3), 431-438.

K2+D3 mediation of osteocalcin gene expression. But not only can vitamin K2 enhance the accumulation of carboxylated osteocalcin in the bone extracellular matrix, it also might improve the D3-mediated production of osteocalcin. Indeed, while vitamin K alone is not involved in the expression of the protein, the researchers observed that, present D3, the expression of osteocalcin mRNA was increasing correlative with vitamin K2 concentrations. (1)

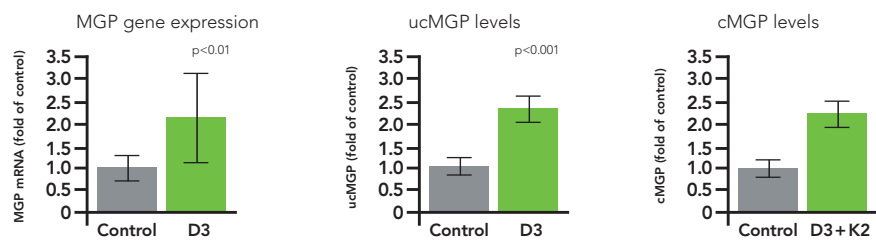
NORTHERN BLOT HYBRIDIZATION
OF OSTEOCALCIN mRNA



Koshihara, Y., & Hoshi, K. (1997). Vitamin K2 enhances osteocalcin accumulation in the extracellular matrix of human osteoblasts in vitro. *Journal of Bone and Mineral Research*, 12(3), 431-438.

THE PERFECT PAIR

D3 + K2 and MGP. Matrix Gla protein (MGP) is another vitamin K dependent protein of which production is D3-mediated. Like osteocalcin, MGP has high affinity for calcium and is able to bind it via its Gla domains. MGP therefore plays an important role in bone organization, but also inhibits vascular mineralization.



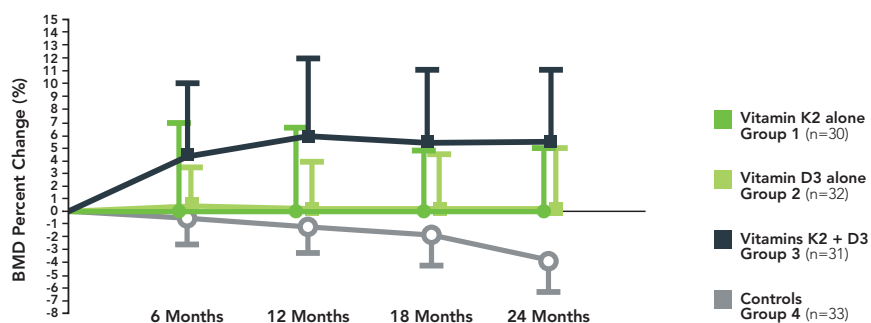
Fu, X., Wang, X. D., Memitz, H., Wallin, R., Shea, M. K., & Booth, S. L. (2008). 9-Cis Retinoic Acid Reduces 1 α , 25-Dihydroxycholecalciferol-Induced Renal Calcification by Altering Vitamin K-Dependent γ -Carboxylation of Matrix γ -Carboxyglutamic Acid Protein in A/J Male Mice. *The Journal of nutrition*, 138(12), 2337-2341. <https://academic.oup.com/jn/article/138/12/2337/4670156>

Vitamin D3 activates the expression of gene coding for MGP. As with osteocalcin, it is synthesized in uncarboxylated form (ucMGP), which is not active. If sufficient amounts of vitamin K2 are present, MGP will be carboxylated (cMGP) on its Gla domains, thus able to bind calcium. (2)

K2, D3 AND BONE HEALTH

K2 alongside vitamin D3 improves vertebral bone mass. Looking to investigate the therapeutic effect of the combined use of vitamins K2 and D3 on vertebral BMD, Ushiroyama et al. (3) enrolled 172 women with osteopenia or osteoporosis. Subjects were randomized into 4 groups, each receiving either vitamin K2 or D3 alone, or a combination of K2 and D3, or placebo for 2 years. Participants' bone mineral density was measured prior to trial, and after 6, 12, 18 and 24 months of supplementation.

BMD EVOLUTION OVER TIME



Ushiroyama, T., Ikeda, A., & Ueki, M. (2002). Effect of continuous combined therapy with vitamin K2 and vitamin D3 on bone mineral density and coagulofibrinolysis function in postmenopausal women. *Maturitas*, 41(3), 211-221.



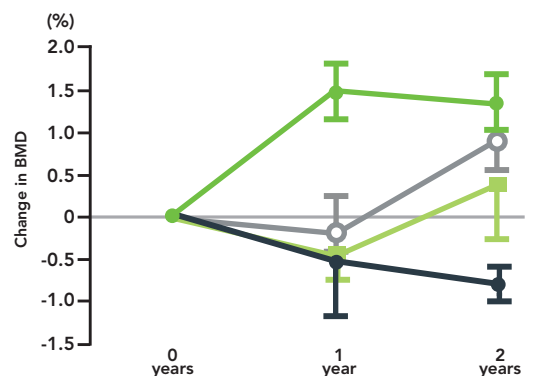
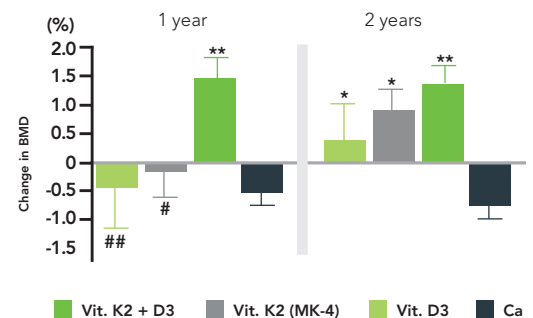
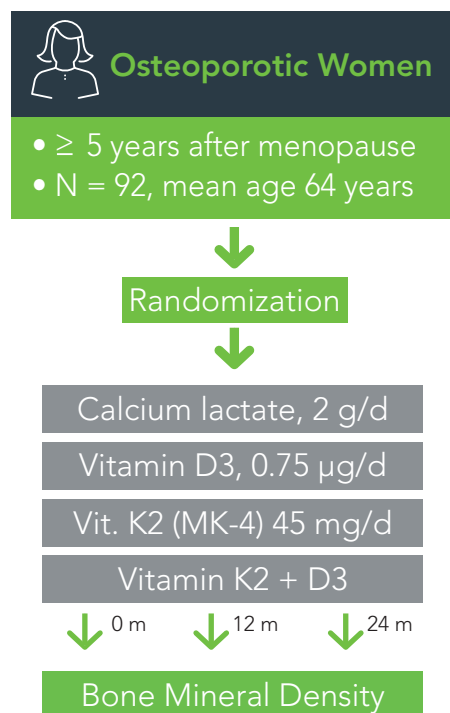
K2 alongside
vitamin D3 improves
vertebral bone mass.

Though supplementation with vitamin K2 alone was associated with a slight increase in bone mineral density, combined treatment with vitamins D3 and K2 for 24 months showed a greater increase in BMD. The bone markers measured demonstrated stimulation of both bone formation and resorption activity. The authors concluded that continuous combination therapy with vitamins K2 and D3 may be useful for increasing vertebral bone mass in postmenopausal women.

THE PERFECT PAIR

K2 and D3 and osteoporosis. A Japanese clinical trial (4) researched the effect of the combined administration of vitamin D3 together with K2 in postmenopausal women with osteoporosis, all of whom had similar BMD before trial. The 92 subjects were randomized to take either vitamin D3, vitamin K2, calcium, or a combination of vitamins D3 and K2. Results analysis showed a significantly decreased BMD for the women supplemented with calcium only, compared to those supplemented with vitamins D3 or K2 alone, who exerted significantly higher levels of BMD. The group given the combination of vitamin D3 together with K2 reported a greater increase in BMD compared to all others. The authors noted: "These findings indicate that combined administration of vitamin D3 and vitamin K2 compared with calcium administration appears to be useful in increasing the BMD of the lumbar spine in postmenopausal women with osteoporosis." Studies performed on non-healthy patients, with osteopenia or osteoporosis, cannot be used as substantiation for a health claim.

EFFECT OF COMBINED ADMINISTRATION OF VITAMIN K2 AND VITAMIN D ON BONE MINERAL DENSITY OF THE LUMBAR SPINE IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS



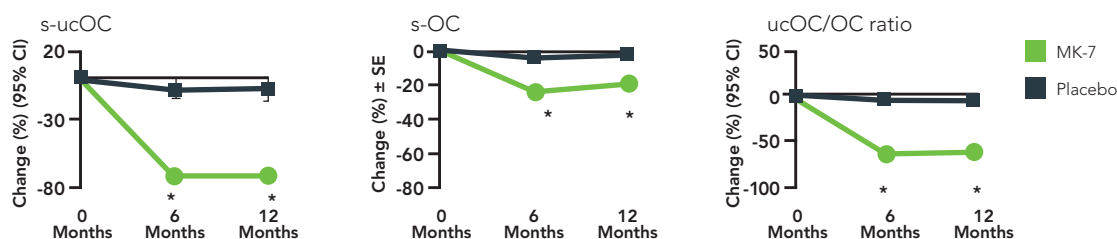
Authors' Conclusion:

These findings indicate that combined administration of vitamin D3 and vitamin K2 compared with calcium administration appears to be useful in increasing the BMD of the lumbar spine in postmenopausal women with osteoporosis.

Effect of MK-7 on bone microarchitecture. Another double-blind, randomized, placebo-controlled clinical trial conducted (5) on 148 postmenopausal women investigated the effect of vitamin K2 MK-7 on age-related deterioration of trabecular bone structure. One inclusion criterion being osteopenia, these subjects were known to be at risk of developing osteoporosis. For a year, they were assigned to supplement their diet with either calcium and D3 (control group), or with a combination of calcium, D3 and K2 MK-7.

While women who were not given K2 MK-7 observed changes in terms of trabecular numbers, spacing and thickness in their tibia, this was not the case for those taking the formulation including K2 MK-7. These three factors are used in bone research to characterize the 3-dimensional structure of cancellous bone. The changes in bone microarchitecture observed in the control group are consistent with the age-related deterioration of trabecular structure. This suggests vitamin K2 MK-7 has a protective effect in preserving trabecular bone structure in the tibia.

EFFECT OF MK-7 ON BIOCHEMICAL MARKERS OF BONE TURNOVER



Rønn, S. H., Harsløf, T., Pedersen, S. B., & Langdahl, B. L. (2016). Vitamin K2 (menaquinone-7) prevents age-related deterioration of trabecular bone microarchitecture at the tibia in postmenopausal women. *Eur J Endocrinol*, 175(6), 541-549.

Effect of MK-7 on biochemical markers of bone turnover. Over time, authors report a significant difference in changes in the ratio between serum levels of undercarboxylated osteocalcin (s-ucOC) and of total osteocalcin (s-OC). After 6 months, this ratio had decreased by -63% in the MK-7 group, compared with -3% in the control group. This change in serum levels of both forms of osteocalcin indicates an increased carboxylation of osteocalcin. The team of researchers noted: "The decrease in s-OC is more likely to be explained by increased carboxylation and thereby a change in distribution from serum to bone matrix. We speculate that the decrease in s-ucOC promotes mineralization, which may explain the preservation of trabecular structure in response to MK-7."

THE PERFECT PAIR

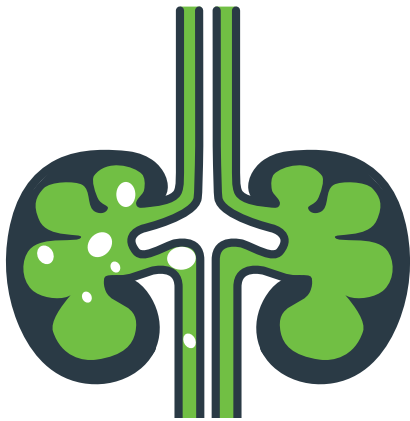


A trial conducted on 148 postmenopausal women investigated the effect of vitamin K2 MK-7 on age-related deterioration of trabecular bone structure. It suggests that vitamin K2 MK-7 has a protective effect in preserving trabecular bone structure in the tibia.



ONE PLUS ONE EQUALS THREE: FROM BONE TO HEART HEALTH

**INADEQUATE INTAKE OF K2
COULD INCREASE THE RISK
OF DEVELOPING KIDNEY STONES**



Both calcium and vitamin D3 are important nutrients for bone health, and while combining them in a supplement is synergistic, the better combination is calcium, D3 and K2. This combination is ideal – a trifecta – for bone health.

Calcium alone or with D3 is not enough. An American study (6) performed on 36,282 postmenopausal women enrolled in a Women's Health Initiative (WHI) investigated whether the combined supplementation of calcium together with vitamin D3 could reduce the risk of fractures through improvement in hip bone mineral density. While this supplementation did result in a small improvement in hip bone density, it didn't effectively reduce hip fracture. Actually, the use of combination supplements of calcium (1,000 mg/day) and vitamin D (400 IU) in postmenopausal women was even associated with a +17% increase in the risk of developing kidney stones.

Several studies have identified a higher risk of heart disease associated with calcium. Calcium can accumulate in artery and blood vessel walls causing them to harden and become less flexible. Cardiovascular risk increases because calcified arteries and vessels become narrower, more rigid and cannot expand when the heart needs to deliver higher blood flow. The heart must work harder. These types of calcification (atherosclerosis and arteriosclerosis) are associated with some of the leading causes of cardiac incident and mortality, including heart attack and stroke.

Excessive vitamin D levels can raise blood levels of calcium, which in turn leads to vascular and tissue calcification, with subsequent damage to the heart, blood vessels, and kidneys. Vitamin K, through the activation of matrix Gla protein (MGP), prevents vascular mineralization. The perfect combination for both bone and heart health therefore should include vitamin K, together with vitamin D3.

PROGRESSION OF ATHEROSCLEROSIS

Normal Artery



Atherosclerosis



Atherosclerosis with Blood Clot



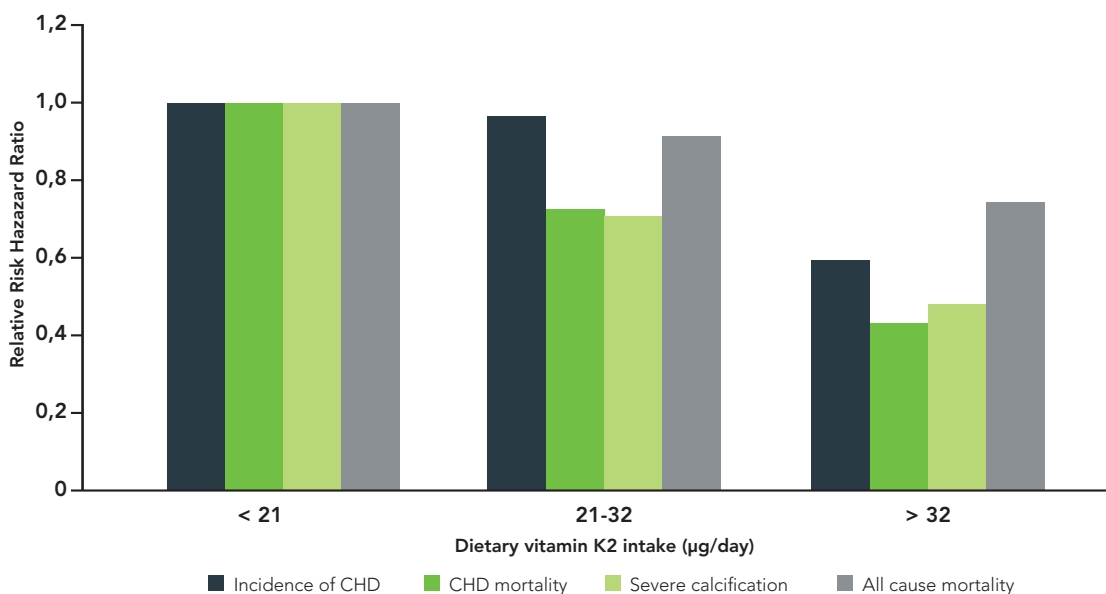
THE PERFECT PAIR



K2, D3 AND HEART HEALTH

According to the World Health Organization (WHO), cardiovascular disease (CVD) causes more than half of all deaths across the European region (7). Yet, WHO asserts that 80% of premature heart disease and stroke are preventable. Population-based studies, such as The Rotterdam Study (8), have established a link between vitamin K2 intake and cardiovascular health (9). Finally, in May 2015, the breakthrough Knapen et al. trial (10) with cardiovascular endpoints was published, confirming the association that previous studies had established.

INTAKE OF MENAQUINONE FOR CORONARY HEART DISEASE (CHD)



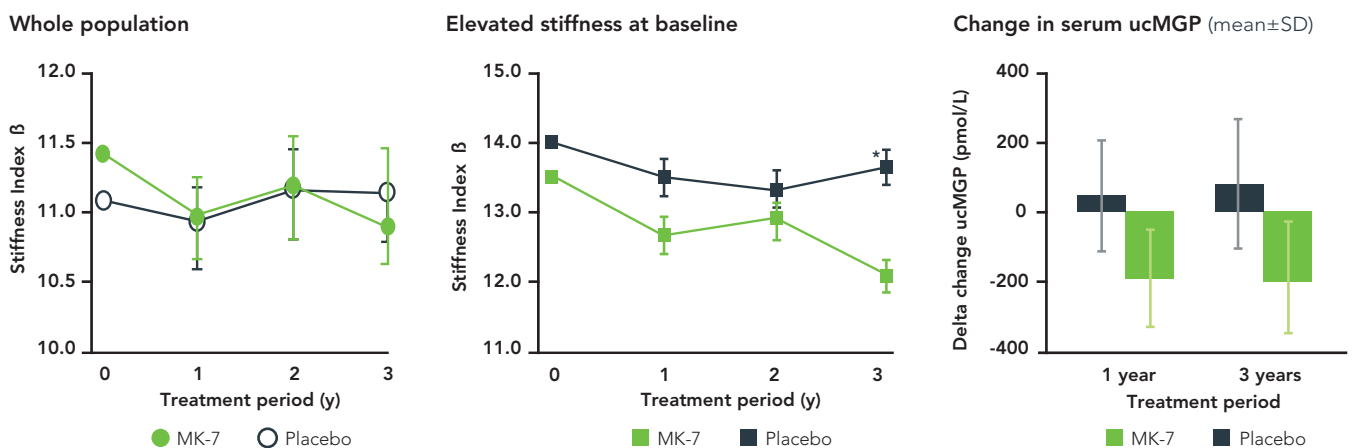
J.M. Geleijnse, et al., "Dietary Intake of Menaquinone is Associated with a Reduced Risk of Coronary Heart Disease: The Rotterdam Study," J. Nutr. 134, 3100-3105 (2004).

Studies suggest optimal concentrations of both vitamin D and vitamin K are beneficial for bone and cardiovascular health, as supported by genetic, molecular, cellular and human studies.



THE PERFECT PAIR

LONG-TERM USE OF MK-7 SUPPLEMENTS IMPROVES ARTERIAL STIFFNESS IN HEALTHY POSTMENOPAUSAL WOMEN



M.H. Knapen, et al., "Menaquinone-7 Supplementation Improves Arterial Stiffness in Healthy Postmenopausal Women: Double-Blind Randomised Clinical Trial," *Thrombosis and Haemostasis* 113(5), 1135–1144 (2015).

Both vitamins D and K are beneficial for bone and cardiovascular health. Beyond vitamins D and K being essential for bone health, studies have revealed synergistic impact for D and K on heart health. For example, in 2000 the paper, "Warfarin-Induced Artery Calcification Is Accelerated by Growth and Vitamin D," by Price, et al. (11) showed that high doses of vitamin D enhance the extent of artery calcification in rats given sufficient doses of warfarin. Warfarin is a vitamin K antagonist – it inhibits the molecule so that vitamin K no longer plays its role. For this action, it is used as a blood thinner, to prevent and treat blood clots in humans. Although they reported that further studies were required to better explain their results, it could be concluded that the extent of arterial calcification by warfarin-induced vitamin K deficiency is dramatically accelerated by high doses of vitamin D.

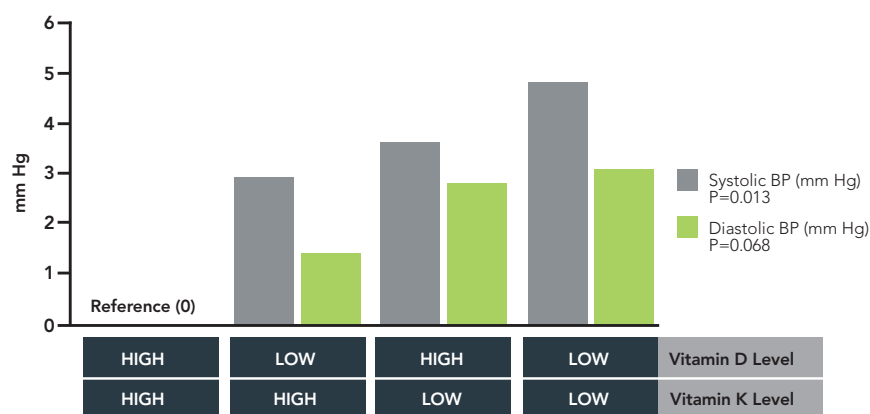
Several prospective studies have demonstrated low vitamin D and K status to be both associated with an increased risk of developing cardiovascular diseases. In 2012, a meta-analysis of 19 prospective studies reviewing the connection between circulating vitamin D and the risk of cardiovascular disease concluded a linear, inverse association between circulating levels of vitamin D and the risk of CVD (12).

In addition high menaquinone intakes have been associated with a significant reduction in the incidence of coronary heart disease (13). Notably, van Ballegooijen et al. (14) reviewed the synergistic interplay between both vitamins for bone and cardiovascular health. They cited that animal and human studies suggest optimal concentrations of both vitamins D and K are beneficial for bone

and cardiovascular health, as supported by genetic, molecular, cellular and human studies. “Long-term vitamin D supplementation could promote the production of large amounts of vitamin K dependent proteins, which remain inactive because there is not enough vitamin K to carboxylate”. The authors noted: “The disbalance between vitamin D and vitamin K promotes an environment in which excess calcium will be deposited into our vascular tissue instead of bones. The migration of calcification into the vascular tissue is described by the double burden of atherosclerosis and osteoporosis.”

Low status in both vitamin D and K means increased blood pressure and a greater risk of hypertension. In an observational trial performed on over 400 healthy Dutch men and women aged 55-65, researchers explored the role of vitamin D and vitamin K statuses on blood pressure and hypertension (15). Participants with low status of both vitamins D and K displayed the highest blood pressure, followed by those with high vitamin D level but insufficient vitamin K level. After adjustments for age and sex, participants in low vitamins D and K status group had a 69% higher risk of developing hypertension, compared with those of high vitamins D and K levels.

VITAMINS D AND K STATUS WITH BLOOD PRESSURE



The combination of low **vitamins D and K status** was associated with increased **blood pressure** and a trend for greater hypertension risk

van Ballegooijen et al., Hypertension 2017; 69(6):1165-1172

Low status of both vitamin D and vitamin K has been associated with increased risk for arterial stiffness. In 2017, a cross-sectional study evaluated the synergistic effect of low vitamins D and K status on arterial stiffness in 1,023 healthy subjects (16). Aortic pulse wave velocity (aPWV) is a classic indicator of aortic stiffness. This parameter was calculated for every participant. The initial population of healthy volunteers was divided into 16 groups depending on the participants' vitamins D

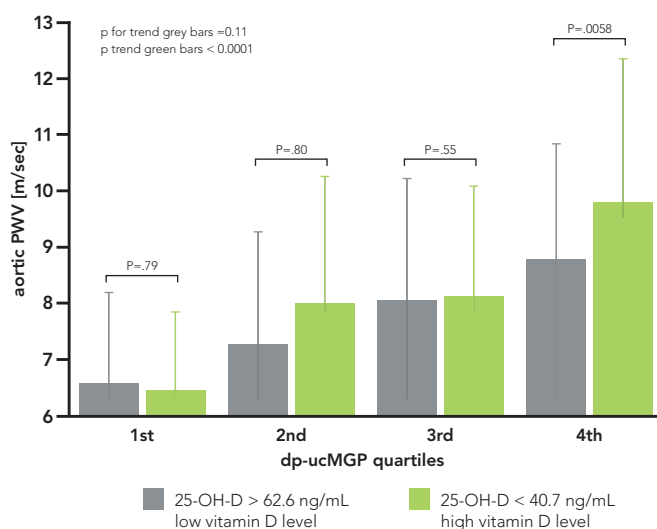
THE PERFECT PAIR

Studies showed participants in low vitamins D and K status group had a 69% higher risk of developing hypertension, compared with those of high vitamins D and K levels.



and K status. Results show that aortic PWV increases with a lower vitamin K status, the highest aPWV is measured for subjects of lowest status of both vitamin D and vitamin K. When comparing participants with the lowest vs. highest vitamin D status, researchers noted a significant difference in aPWV with co-incident low vitamin K status.

CARDIOVASCULAR HEALTH



Mayer Jr, O., Seidlerová, J., Wohlfahrt, P., Filipovsky, J., Cifková, R., Cerná, V., ... & Jardon, K. M. (2017). Synergistic effect of low K and D vitamin status on arterial stiffness in a general population. *The Journal of nutritional biochemistry*, 46, 83-89.

D3 + K2: the perfect pair to put calcium in balance. In summary, while vitamin D supplementation can effectively promote the production of vitamin K-dependent proteins, these will not be able to bind calcium unless sufficient amounts of vitamin K are also present to achieve carboxylation. An imbalance between vitamin D and vitamin K might create the propitious environment for excess calcium to be deposited into vascular tissues instead of the skeletal system, increasing the risk of developing hypertension.

THE COMMERCIAL CASE FOR K2/D3: DOSE


Depending on local health regulation, recommended doses of calcium range from 200-330 mg for infants to 600-1300 mg in children and teenagers, 1000 mg in adults (including pregnant and lactating women), and up to 1200 mg in seniors. For vitamin D, these doses are set at 10 mcg (400 IU) in infants, 15-20 mcg (600-800 IU) in children and adults, and 20 mcg (800 IU) in seniors aged 70+.

Because of the lack of data to estimate an average requirement, the Institute of Medicine set adequate intake (AI) for vitamin K, based on representative dietary intake data from healthy individuals. The AI for infants varies between 2-2.5 mcg, 30-60 mcg in children and 75 mcg in adolescents. For adults and seniors, it is of 90 and 120 mcg in women and men, respectively.



D3 and K2 offer unlimited dose and formulation opportunities. Enabling product convenience and customer satisfaction is key. Daily doses of 2–120 mcg are small enough to facilitate their inclusion into all delivery systems. By adding D3+K2, brands can offer smaller, easy-to-swallow forms that deliver bone and heart health benefits, in consumer-friendly forms such as drops, water-soluble sachets or chewable gummies.

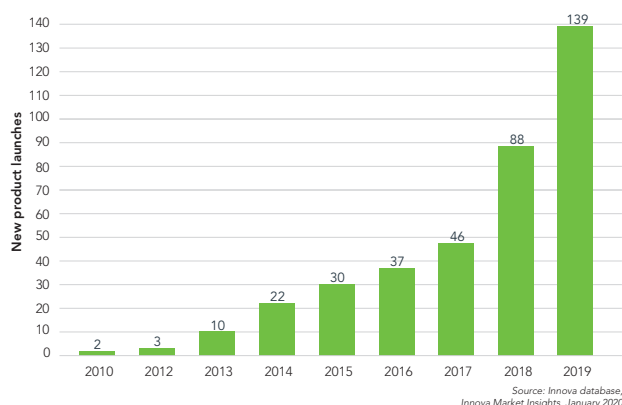
THE PERFECT PAIR

| | Market forecast | Intent to purchase | High Probability of Success |
|---|-----------------|--------------------|---|
| Vitamins K2 + D3 | 82 | 10% |  In the benchmark, "The Perfect Pair" (K2 + D3) outperformed the category and concept averages for well-established supplements such as calcium and D3. |
| Calcium <i>(with and without D3)</i> | 78 | 12% | |
| Vitamin D <i>(concept average)</i> | 75 | 9% | |
| Vitamin K1 <i>(concept average)</i> | 70 | 8% | |

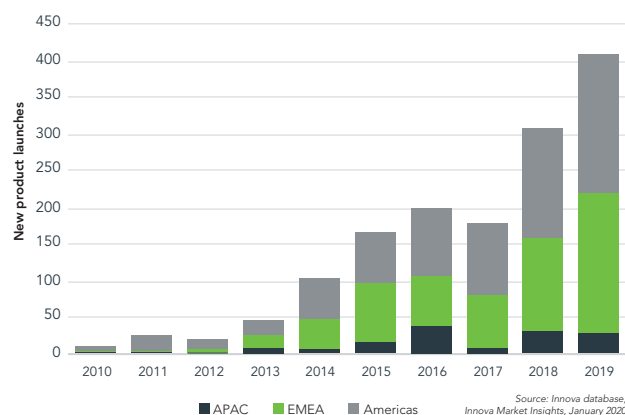
Source: Custom Concept Report prepared for Kappa Bioscience AS by New Hope Network, 2018

Vitamins K2 and D3 are biologically the Perfect Pair for bone health. In 2018, more than 2000, consumers scored the Perfect Pair higher than calcium or D3 for bone health and agreed that D3 plus K2 would be a market success that would outperform other popular bone health formulations. The Market Prediction Score for this formulation exceeded all other bone health concepts, underscoring the high probability of market success. The Purchase Intend Score reached 10% for the Perfect Pair formulation. In comparison, the average Purchase Intend Score for all bone health products is 8% only.

New products combining D3 with K2 (EU 2010 - 2019)



K2 retail launches (Globally 2010 - 2019)



CONCLUSION

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 risk factor in heart disease. Vitamin K2 MK-7 achieves both bone and heart health via its impact 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 into the vascular system.

As consumers likely don't meet the dietary recommended intakes for vitamins D3 and K2, either as a result of the poor bioavailability of these molecules in food, insufficient consumption, or because of absorption issues, combined supplementation happens to be the best fit for a comprehensive nutritional solution.

Combining vitamin D3 and vitamin K2

to promote healthy skeletal

and cardiovascular systems

is the best solution on the market.

THE PERFECT PAIR



The small amounts of required vitamins D3 and K2, within the microgram range, make it easy for manufacturers to include them in any kind of formulation. As awareness about the vital role of K2 grows, formulations targeting bone health that would not include this vitamin will increasingly look inconsistent. Progressively, the educated consumer is switching for more complete compositions, offering all the nutrients necessary for the intended effect.

Market cases in many regions have demonstrated that D3 + K2 product innovations increase the attractiveness and excitement for consumers resulting in a market share shift to such new concepts. The K2 market grows very fast. K2's usage is on track to duplicate D3's growth. K2's household penetration will match D3 due to major brands featuring K2 and driving the awareness and benefits knowledge. K2 demonstrated +133% CAGR between 2014 and 2018.

Furthermore, the Ingredient Comparative Survey 2018, a commissioned study conducted by Trust Transparency Center on behalf of the Vitamin K2 Association in May 2018, indicates that consumers are willing to invest more for K2 than for D3 or calcium. Kappa Bioscience supports fast-to-market launches. Meanwhile, more than 160 K2 white-label products have been developed in partnership with leading contract manufacturers around the globe. These products are backed with stability data and analytical services. Also, Kappa Bioscience conducted a vast amount of consumer research trials. At Kappa, we understand which consumer groups show a high interest in K2 formulations and which health application is in demand. Brand owners willing to look into new K2 product launches are invited to EXPERIENCE K2VITAL[®]ITY. Send an email: info@kappabio.com

K2VITAL[®]

Puts Calcium in Balance

References

1. Koshihara, Y., & Hoshi, K. (1997). Vitamin K2 enhances osteocalcin accumulation in the extracellular matrix of human osteoblasts in vitro. *Journal of Bone and Mineral Research*, 12(3), 431-438.
2. Fu, X., Wang, X. D., Mernitz, H., Wallin, R., Shea, M. K., & Booth, S. L. (2008). 9-Cis Retinoic Acid Reduces 1 α , 25-Dihydroxycholecalciferol-Induced Renal Calcification by Altering Vitamin K-Dependent γ -Carboxylation of Matrix γ -Carboxyglutamic Acid Protein in A/J Male Mice. *The Journal of nutrition*, 138(12), 2337-2341.
3. Ushiroyama, T., Ikeda, A., & Ueki, M. (2002). Effect of continuous combined therapy with vitamin K2 and vitamin D3 on bone mineral density and coagulofibrinolysis function in postmenopausal women. *Maturitas*, 41(3), 211-221.
4. Iwamoto, J., Takeda, T., & Ichimura, S. (2000). Effect of combined administration of vitamin D3 and vitamin K2 on bone mineral density of the lumbar spine in postmenopausal women with osteoporosis. *Journal of orthopaedic science*, 5(6), 546-551.
5. Rønn, S. H., Harsløf, T., Pedersen, S. B., & Langdahl, B. L. (2016). Vitamin K2 (menaquinone-7) prevents age-related deterioration of trabecular bone microarchitecture at the tibia in postmenopausal women. *Eur J Endocrinol*, 175(6), 541-549.
6. Jackson, R. D., LaCroix, A. Z., Gass, M., Wallace, R. B., Robbins, J., Lewis, C. E., ... & Bonds, D. E. (2006). Calcium plus vitamin D supplementation and the risk of fractures. *New England Journal of Medicine*, 354(7), 669-683.
7. World Health Organization. (2014). Global status report on noncommunicable diseases 2014 (No. WHO/NMH/NVI/15.1). World Health Organization.
8. J.M. Geleijnse, et al., "Dietary Intake of Menaquinone is Associated with a Reduced Risk of Coronary Heart Disease: The Rotterdam Study," *J. Nutr.* 134, 3100–3105 (2004).
9. G.C. Gast, et al., "A High Menaquinone Intake Reduces the Incidence of Coronary Heart Disease," *Nutr. Metab. Cardiovasc. Dis.* 19, 504–510 (2009).
10. M.H. Knapen, et al., "Menaquinone-7 Supplementation Improves Arterial Stiffness in Healthy Postmenopausal Women: Double-Blind Randomised Clinical Trial," *Thrombosis and Haemostasis* 113(5), 1135–1144 (2015).
11. Price, P. A., Faus, S. A., & Williamson, M. K. (2000). Warfarin-induced artery calcification is accelerated by growth and vitamin D. *Arteriosclerosis, thrombosis, and vascular biology*, 20(2), 317-327.
12. Wang L, Song Y, Manson JE, Pilz S, Ma W, Michaelsen K, Lundqvist A, Jassal SK, Barrett-Connor E, Zhang C, Eaton CB, May HT, Anderson JL, Sesso HD. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. *Circ Cardiovasc Qual Outcomes*. 2012;5:819–829. doi: 10.1161/CIRCOUTCOMES.112.967604.
13. Gast GC, de Roos NM, Sluijs I, Bots ML, Beulens JW, Geleijnse JM, Witterman JC, Grobbee DE, Peeters PH, van der Schouw YT. A high menaquinone intake reduces the incidence of coronary heart disease. *Nutr Metab Cardiovasc Dis*. 2009;19:504–510. doi: 10.1016/j.numecd.2008.10.004.
14. Van Ballegooijen, A. J., Pilz, S., Tomaschitz, A., Gröbler, M. R., & Verheyen, N. (2017). The synergistic interplay between vitamins D and K for bone and cardiovascular health: a narrative review. *International journal of endocrinology*, 2017.
15. Van Ballegooijen, A. J., Cepelis, A., Visser, M., Brouwer, I. A., Van Schoor, N. M., & Beulens, J. W. (2017). Joint association of low vitamin D and vitamin K status with blood pressure and hypertension. *Hypertension*, 69(6), 1165-1172.
16. Mayer Jr, O., Seidlerová, J., Wohlfahrt, P., Filipovský, J., Cífková, R., Černá, V., ... & Jardon, K. M. (2017). Synergistic effect of low K and D vitamin status on arterial stiffness in a general population. *The Journal of nutritional biochemistry*, 46, 83-89.

Disclaimer

This document exclusively addresses experts in science and research or industry professionals. Consumers cannot derive or gain any knowledge about vitamin K2 or other ingredients and formulations from this document, which is not intended as consumer information. The content has not been validated by any regulatory authority, including FDA and EFSA. It contains scientific and technical information on vitamin K2 and any explicit and/or implied claims included within this document may not necessarily be appropriate to support marketing purposes. The information is the exclusive property of Kappa Bioscience and is believed to be reliable. However, manufacturers of foods or dietary supplements should seek their own independent advice on regulatory, scientific and related matters to ensure all requirements are followed in the respective market. Our products are not intended to prevent, cure, treat, or diagnose any disease. We recommend all people to consult a licensed health care professional before starting any dietary or exercise program. Kappa Bioscience recommends that products containing Vitamin K2 MK-7 (K2VITAL®) provide a labeling notice, making consumers aware of the potential interference with anti-coagulant treatment therapies.

THE PERFECT PAIR

K2VITAL® DELTA from Kappa Bioscience is the only market-proven solution vitamin K2 that meets the requirements of finished products that contain either calcium or magnesium. K2VITAL® DELTA contains pure all-trans K2 MK-7, ensuring your product meets its K2 label claim.

Test protocols are available upon request: Kappa would be happy to help you evaluate K2VITAL® DELTA by confidentially testing your current K2-plus-minerals products.

K2VITAL® DELTA – standard in vitamin K2 MK-7.
Contact the specialists at Kappa Bioscience to learn more about K2VITAL® DELTA and vitamin K2 stability.



Kappa Bioscience is the pioneer in development and production of the exceptionally pure synthetic and biologically active all-trans menaquinone-7 (vitamin K2 MK-7), marketed under the K2VITAL® brand name.

Kappa's innovation of MK-7 synthesis marked the commercial milestone where this fat-soluble vitamin could begin to attain widespread consumer adoption. Effective synthesis production drives scalability, price reduction and a secure supply chain - with unmatched ingredient purity and documentation.

Combined with other Kappa innovations such as the patented K2VITAL® DELTA microencapsulation process, which provides K2 stability in mineral formulations, K2VITAL® offers brands and manufacturers a path to broader market segments.

GET IN CONTACT

Sales & Finished Product Development

Tel. +49 (0) 40 6094087-0

sales@kappabio.com

Kappa Ingredients GmbH, Hamburg

A Member of the Kappa Bioscience Group



Kappa Bioscience AS

Silurveien 2 | Building B | 0380 Oslo | Norway

Kappa Ingredients GmbH – A Member of the Kappa Bioscience Group

Friesenweg 4 | Building 13 | 22763 Hamburg | Germany | Office +49 40 6094087-0

info@kappabio.com | www.kappabio.com | www.k2vital.com

Copyright © by Kappa Bioscience AS, 2020. All rights reserved. Without the written permission of Kappa Bioscience AS it is prohibited to integrate the protected contents published into any media or food stuff consumer product. This brochure may contain elements that are protected by copyright and by other laws that are subject to the copyright of third parties and that are correspondingly protected for these third parties. Pictures: © by Kappa Bioscience AS. K2VITAL® is a trademarks by Kappa Bioscience AS. © DragonImages, Wavebreak-mediaMicro, crevis, focusandblur, dusanpetkovic1, chika_milan, REDPIXEL / adobe.stock.com