

Vitamin K – an update

Part 2: Medical aspects

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Abstract

In the second part of this article, the extrahepatic functions of vitamin K will be discussed in more detail. Recently, there have been numerous indications that suboptimal vitamin K status is associated with adverse effects on cardiovascular and bone health. This article will present relevant cohort and interventional studies on arterial calcification and bone mineral density (BMD) in the form of a literature review. The potential effect of vitamin K status on other diseases like osteoarthritis, type 2 diabetes mellitus, and cancer will also be mentioned briefly.

Keywords: vitamin K, matrix gla protein (MGP), osteocalcin, atherosclerosis, calcification, bone mineral density (BMD), osteoarthritis, type 2 diabetes mellitus, cancer

Vitamin K and cardiovascular health

Vitamin K appears to reduce the risk of atherosclerosis – including MÖNCKEBERG'S arteriosclerosis (medial calcific sclerosis) – by activating the matrix gla protein (MGP) which inhibits the deposition of calcium in the arterial walls. The consequences of ectopic blood vessel calcification like peripheral artery disease, heart attack, and stroke on the one hand, and hypertension and heart failure on the other hand can be life-threatening. It is assumed that MGP binds calcium ions and surrounds them like a shell that prevents the development of hydroxyapatite crystals and their ossification-like ef-

fects on the affected soft tissues [54, 61]. Whether a high proportion of carboxylation of MGP can actually protect against atherosclerotic microcalcifications and subsequent plaque ruptures still has to be investigated. The association between vitamin K intake and cardiovascular health has been investigated in both epidemiological and interventional studies (for an overview, see [86]). In these studies, as described below, the main focus of investigation was the effect of vitamin K₂ that was consumed either in the normal diet (MK-4 to MK-10) or as a supplement (MK-7), because some authors ascribe a more important role to menaquinones (vitamin K₂) than to phylloquinone (vitamin K₁) in the carboxylation of vitamin K-dependent (VKD) proteins. For instance, in the Health Professionals Follow-up Study including 40,087 men aged 48 to 83 years by ERKKILÄ et al. [87] and in the Nurses' Health Study including 72,874 midwives aged 38 to 65 years by ERKKILÄ et al. [88], no association was found between the dietary supply of vitamin K₁ – the median intakes were 163 µg/day and 165 µg/day, res-

pectively, estimated by a food frequency questionnaire (FFQ) – and the risk of coronary artery disease (CAD) or stroke over a period of 16 and 14 years, respectively. Furthermore, VILLINES et al. [89] also found no association between vitamin K₁ intake and early onset calcification of the coronary arteries in a group of 807 active US soldiers aged 39 to 45 years without coronary artery disease. However, the selected follow-up period of 1.5 years for this study was very short. SHEA et al. [90], who administered a daily dose of 500 µg of phylloquinone to 200 out of a group of 388 men and women aged 68 ± 6 years over a period of three years, observed a 6 % reduction in progression of calcification of the coronary arteries in subjects with a mild to moderate calcification (n = 81).

Epidemiological studies on vitamin K₂ intake (MK-4 to MK-10) and atherosclerosis, coronary artery disease, stroke, and mortality

It should be noted that both the cross-over study mentioned below first and the prospective cohort studies mentioned thereafter used a one-off FFQ to record vitamin K intake – an approach that has some methodological limitations.¹

BEULENS et al. [91] observed an association between vitamin K intake (FFQ) and calcification of the coronary arteries of 564 postmenopausal women aged 49 to 70 years. The

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average intake was 217 $\mu\text{g}/\text{day}$ for vitamin K_1 and 31.6 $\mu\text{g}/\text{day}$ for vitamin K_2 . In the highest dietary intake quartile, vitamin K_2 intake was 48.5 $\mu\text{g}/\text{day}$, whereas in the lowest quartile it was 18 $\mu\text{g}/\text{day}$. The subjects in the highest dietary intake quartile had a 20 % lower risk of coronary sclerosis than those in the lowest quartile. There was no statistically significant association between vitamin K_1 intake and the incidence of calcification of the coronary arteries.

In the representative Rotterdam Study conducted on 1,836 men and 2,971 women aged > 55 years, GELLEIJNSE et al. [25] investigated the effect of vitamin K intake (FFQ) on the cardiovascular system. Although a vitamin K_1 intake of around 250 $\mu\text{g}/\text{day}$ exhibited no protective effects in the 10-year follow-up, a vitamin K_2 intake of > 32.7 $\mu\text{g}/\text{day}$ (upper tertile of dietary intake) was associated with significant reductions in the relative risks of severe aortic calcification (52 % reduction), CAD incidence (41 % reduction), death due to CAD (57 % reduction) and all-cause mortality (26 % reduction) compared to an intake of < 21.6 $\mu\text{g}/\text{day}$ (lower tertile of dietary intake). However, there was no association between vitamin K_2 intake level and the incidence of non-fatal heart attacks.

GAST et al. [27] used data from the Prospect-EPIC cohort consisting of 16,057 women aged 49 to 70 years to examine the association between vitamin K intake (FFQ) and CAD incidence. The average intake of vitamin K_1 was 212 $\mu\text{g}/\text{day}$, and the average intake of vitamin K_2 29 $\mu\text{g}/\text{day}$. In the 8-year follow-up, 480 cases of coronary artery disease occurred. With every 10 $\mu\text{g}/\text{day}$ increase in MK-n intake, the risk of CAD decreased by 9 %, with MK-7, MK-8 and MK-9 contributing the most to this effect. (Taking into account the confounding variables of age, typical CAD risk factors, and fatty acid/energy intake, the significance level of $p \leq 0.05$ was reached, whereas the additional integration

of calcium resulted in $p = 0.08$.) No evidence of an association could be found for vitamin K_1 .

VISSERS et al. [26, 92] used the representative EPIC-Netherlands cohort of about 36,000 participants aged 49 ± 12 years as the basis of their research. The calculated vitamin K_1 intake (FFQ) was 200 $\mu\text{g}/\text{day}$ on the average, and the average intake of vitamin K_2 was 31 $\mu\text{g}/\text{day}$. In the 12-year follow-up, 324 ischemic strokes and 163 hemorrhagic strokes were recorded as well as 489 cases of peripheral artery disease (PAD). No association was found between vitamin K_1 intake and the risk of stroke or PAD. Nor was any association found between vitamin K_2 intake and stroke. However, compared to the study participants with the lowest MK-n intake (1st quartile: 15.6 $\mu\text{g}/\text{day}$), those with the highest intake (4th quartile: 49.3 $\mu\text{g}/\text{day}$) had a 29 % lower risk of PAD. In people suffering from hypertension and diabetes mellitus, the risk decreased by as much as 41 % and 44 %, respectively.

Interventional studies on vitamin K_2 intake (MK-7) and arterial calcification

In a randomized, double-blind study including 244 postmenopausal women aged 55 to 65 years, KNAPEN et al. [93] investigated the effect of a daily dose of 180 μg MK-7 or placebo over the course of 3 years on the arterial stiffness index (AIS) of the Arteria carotis. In the treatment group ($n = 120$), both the concentration of dephosphorylated undercarboxylated matrix gla protein (dp-ucMGP²) and the level of hardening of the arterial walls were lower than in the placebo group. In addition, in women whose arterial stiffness index was above the median value of 10.8 at the start of the study, there was a positive correlation between MK-7 intake and the elastic properties of the Arteria carotis (e. g. pulse wave velocity).


VOSSEN et al. [94] are currently conducting a randomized, double-blind study on 180 test subjects aged 18 years or over with calcification of the coronary arteries in the initial stages, who are receiving either 360 μg MK-7 per day or a placebo for a period of 24 months. The authors' aim is to determine whether supplementation with vitamin K_2 has any effect on biomarkers such as dp-ucMGP, on the morphology of existing atherosclerotic plaques, on the incidence of new plaques, and on arterial structure and functionality, as well as to determine whether MK-7 can slow or halt the progression of the calcification of the coronary arteries.

In summary, the studies mentioned here show that:

- a dietary vitamin K_2 intake of > 30 or > 45 $\mu\text{g}/\text{day}$ significantly reduces the risk of coronary artery disease and peripheral artery disease in people aged 49 years or over in contrast to an intake of < 20 $\mu\text{g}/\text{day}$, whereas there is no evidence of any effect on the incidence of stroke,
- a daily supplementation with 180 μg MK-7 in postmenopausal women and in people with incipient coronary sclerosis leads to a significant reduction in the dp-ucMGP level and to a reduction in vascular calcification compared to placebo.

Vitamin K and bone health

Vitamin K appears to counteract excessive bone loss, thus also counteracting the associated enhanced risk of fracture that can occur for instance with increasing age, during menopause (decreasing estro-

²  Part 1: ERNÄHRUNGS UMSCHAU 11/2017, section "Biomarkers for the determination of vitamin K status"

gen level), or in wasting diseases, because it directly influences the development of bone substance in the context of remodeling and indirectly influences the mineralization of the bone matrix (through activation of osteocalcin) (♦ Box “Bone metabolism”).

The association between vitamin K intake and bone health has been investigated in both epidemiological and interventional studies. The outcomes of studies on vitamin K₂ and its effects on bone mineral density (BMD) have been predominantly positive, as described in more detail below. By contrast, studies on vitamin K₁ yielded conflicting results regarding its effect on the risk of fracture were mostly positive [102]. These conclusions are based on the prospective cohort studies and cross-over studies summarized in ♦ Table 5³, and on one interventional study in which a vitamin K₁ supplement of 600 µg/day was administered [111]. VOLPE et al. [111] were unable to find any evidence of an effect on BMD in healthy premenopausal and perimenopausal women, however, the 6-month study duration was very short.

The next part of this article gives a detailed description of studies on the effect of MK-7 (vitamin K₂) from natto or supplements on BMD. APALSET et al. [105] were unable to find any evidence of an association between vitamin K₂ intake and risk of fracture (♦ Table 5).

Epidemiological studies on vitamin K₂ intake (MK-7) and BMD

In a cross-over study conducted on 1,662 Japanese men aged > 65 years who were participating in the Fujiwara-kyo Osteoporosis Risk in Men Study, FUJITA et al. [112] recorded the intake of natto (FFQ, interviews), the serum concentration of undercarboxylated osteocalcin (ucOC²), and the BMD of the hips, the femoral neck, and the lumbar spine. One 40 g pack of natto contains

Bone metabolism – remodeling and mineralization (simplified)

Bone is a dynamic tissue that is constantly being broken down and built up (a process known as remodeling) in order to adapt the bone architecture to changing loads and to repair smaller areas of structural damage (microcracks) as well as larger ones (fractures). Bone tissue consists of cells called osteoclasts (responsible for bone breakdown) and osteoblasts (responsible for bone building) on the one hand, and of the extracellular matrix, which is composed of organic material (type I collagen fibers, non-collagen proteins [e. g. osteocalcin], proteoglycans, etc.) and inorganic material (hydroxyapatite (Ca₁₀[PO₄]₆[OH]₂), hydrogen carbonate, sodium, potassium, magnesium, fluoride, etc.) on the other hand. In the case of an acute drop in plasma calcium or phosphate levels, both mineral salts can be released from the bone (which is the body's largest reservoir of calcium and phosphate) via a regulatory circuit involving parathyroid hormone and vitamin D₃ hormone [64]. By contrast, estrogens and androgens inhibit bone loss [95].

In the case of bone resorption, the osteoclasts bind firmly to the bone matrix and reduce the pH value by releasing hydrochloric acid (HCl), which removes the mineral salts from the organic material in the extracellular space. At the same time, the collagen fibrils are broken down by proteolytic enzymes, and the resulting fragments are phagocytized by the osteoclasts, which break them down further into individual amino acids. These amino acids are then released into the bone matrix, from where the osteoblasts can absorb them [36].

In order to build bone mass, the osteoblasts secrete a collagenous ground substance (osteoid) into the extracellular space, and this substance then matures – meaning it forms fibrils, fibers, and cross-connections [96]. This is followed by mineralization, i. e. the development of platelet-shaped hydroxyapatite crystals inside the organic ground substance, for which osteocalcin is required [97].

The osteoblasts produce inactive osteocalcin, which is activated by vitamin K-dependent carboxylation, and subsequently released into the extracellular space. Via three binding sites the active osteocalcin “sticks” calcium to the surface of the collagen fibrils, thus supporting the build-up of hydroxyapatite, which gives the bone its hardness [98]. Vitamin K not only appears to be involved in the mineralization of bone via osteocalcin, but it also appears to be directly involved in bone remodeling. *In vitro* studies describe vitamin K₂ as a regulator of the transcription of bone-cell-specific genes. It appears to promote osteoblastogenesis [99] and to inhibit osteoclastogenesis (by inhibiting synthesis of RANK-L [100]) [101]. RANK-L (receptor activator of NF-KB-ligand) is a cytokine synthesized in osteoblasts under the influence of parathyroid hormone and vitamin D₃ hormone. After secretion into the extracellular space it binds to the RANK receptors of monocytic osteoclast precursors, inducing their differentiation into mature osteoclasts [98].

approximately 380 µg MK-7 and 20 µg of phylloquinone. The study subjects consumed between < 1 pack per week and > 1 pack per day. A significant inverse association was found

between the level of natto consumption and the amount of ucOC in the serum. In addition, the consumption

³ Table 5 in the online supplement

of several packs of nattō per week or per day was associated with higher BMD in the hips and the femoral neck than the consumption of only one pack per week or less.

In a prospective cohort study, IKEDA et al. [113] investigated whether nattō has any effect on BMD. One 40 g pack of nattō corresponded to an equivalent of approximately 350 µg of MK-7. 944 Japanese women aged 20 to 79 years (394 of whom were premenopausal and 550 of whom were postmenopausal) provided data on their consumption of nattō in the representative Japanese Population-based Osteoporosis Study (FFQ, interviews). They were invited to have BMD measurements performed in the lumbar spine, the hips, the femoral neck, and the radial bone at the beginning of the study and 3 years later. At follow-up, premenopausal women aged 34 ± 7.1 years showed no changes in BMD, and no association could be demonstrated between nattō consumption and BMD. The postmenopausal women aged 64.2 ± 8.4 years, at the beginning of the study, demonstrated a positive association between BMD of the hips and nattō consumption when more than 4 packs per week were consumed. During the 3-year monitoring period, the BMD of these women (which was already lower than that of the premenopausal women at the beginning of the study) decreased across all study sites. The overall higher level of nattō consumption was unable to prevent this. However, the BMD of the femoral neck decreased significantly less, the more nattō was consumed during follow-up.

Interventional studies on vitamin K₂ intake (MK-7) and BMD

KNAPEN et al. [114] demonstrated in a randomized, placebo-controlled study conducted on 244 healthy, postmenopausal women aged 60 ± 3 years that daily supplementation

with 180 µg MK-7 (n = 120) over the course of 3 years significantly lowered the biomarker ucOC/cOC (58 % reduction), and also significantly attenuated age-related decrease in BMD and bone strength, both in the lumbar spine and in the femoral neck, compared to the control group. However, in both groups BMD as well as bone mineral content (BMC) decreased equally and continuously.

EMAUS et al. [115] recruited 334 women aged 50 to 60 years (1–5 years after the menopause), some of whom were affected by osteoporosis at one of the sites under focus, for a randomized, double-blind study. One group (n = 167) received a daily dose of 360 µg MK-7 in the form of nattō capsules for 12 months, and the other group received a placebo in the form of olive oil capsules. In addition to the biomarker ucOC/cOC, the BMD of the hips, femoral neck, lumbar spine, and the entire body was measured. Although ucOC/cOC decreased significantly in the group that received the supplement, the authors found no difference in bone loss rates between the two groups. They came to the conclusion that the intervention period was too short to achieve significant results.

In summary, the studies described here show that:

- **in both men and women aged 65 years or over, menaquinone consumption of > 200 µg/day in the form of MK-7 derived from nattō over the course of three years leads to a significantly lower reduction in the BMD of the femoral neck, but it does not significantly affect BMD of the hips,**
- **supplementation with 180 µg/day of MK-7 for 36 months in postmenopausal women aged 60 years significantly attenuates age-related reduction in the BMD of the femoral neck and the lumbar spine, but does not**

significantly affect that of the hips, whereas 12 months of supplementation with 360 µg/day MK-7 in women of the same age has no significant effect on BMD.

In Japan, pharmacological amounts of MK-4 (10–90 mg/day) are used routinely to treat osteoporosis. However, interventional studies and meta-analyses yield contradictory results with regard to BMD and risk of fracture, necessitating a brief discussion: Whereas BINKLEY et al. [116] and KNAPEN et al. [99] could demonstrate no effect on BMD in healthy postmenopausal North American women (12 months of supplementation) or in Dutch women with the same characteristics (3 years of supplementation), ORIMO et al. [117] found in a study involving 23 Japanese women and 3 Japanese men with osteoporosis (24 weeks of supplementation) that in the treatment group there was a significant increase in BMD – a noteworthy 2.2 % – whilst in the placebo group (2 women, 1 man) there was a reduction of 7.3 % over the same period.

A meta-analysis of Japanese studies by COCKAYNE et al. (2006) shows that pharmacological doses of MK-4 over 1–3 years have a positive effect both on BMD and on risk of fracture in elderly (postmenopausal) women both with and without various diseases, including osteoporosis [118]. HUANG et al. (2015), who mainly included studies that used high-dosed MK-4, established that this treatment has a positive effect both on risk of fracture and maintenance of the BMD of the spine, but only in postmenopausal women with osteoporosis [119]. FANG et al. (2012) found indications that vitamin K supplements affect the BMD of the lumbar spine, but not the BMD of the femoral neck. However, they took studies into account in which vitamin K₁, MK-7, or MK-4 was administered at either physiological or pharmacological doses to young or

old people with or without osteoporosis [120]. This means that some methodological limitations can be assumed here [121].

From a practical point of view, it should be noted that the doses of MK-4 used for therapeutic purposes in Japan and the doses of MK-7 used in the cited interventional studies can only be achieved with supplements (on prescription) or natto (in capsules). An increase in MK-n intake to the level that would be potentially effective as prophylaxis by means of boosting the supply of common foodstuffs rich in vitamin K₂ is neither possible nor desirable because the relevant amounts can only be found in products of animal origin (♦ Table 1 ■■■ part 1, issue 11/2017); an increased consumption of the latter would be at odds with the recommended predominantly plant-based diet.

Vitamin K and other diseases

Osteoarthritis

Osteoarthritis is characterized by the progressive deterioration of articular cartilage, bone spurs (osteophytes), narrowing of the intra-articular space, chondrocyte hypertrophy, mineralization of the extracellular matrix including the synovial membrane and synovial fluid, and signs of inflammation, culminating in impaired joint function and pain. It appears to respond to vitamin K. Vitamin K contributes to the activation of the gla-rich protein (GRP)⁴ which inhibits the mineralization of the cartilage. It has been demonstrated *in vitro* that carboxylated GRP inhibits the calcification of the extracellular matrix of the cartilage [122]. In addition, GRP down-regulates the synthesis of pro-inflammatory cytokines and other mediators of inflammation, even when under-carboxylated or bound to calcium phosphate crystals [122].

To date, there have been two cross-over studies and one prospective cohort study that suggest an association between vitamin K status and osteoarthritis. They were conducted in older people, since this group is more susceptible to degenerative diseases than young people. In the Japanese cross-over study shown in ♦ Table 6⁵, vitamin K status was estimated based on vitamin K₁ and K₂ consumption (it must be taken into account that Japanese people traditionally consume natto [MK-7]). Whilst vitamin K intake had a positive effect on the risk of osteoarthritis, other dietary factors (energy consumption, micronutrients, dietary fiber, salt, vitamins D, E, B₁, B₂, B₆, B₁₂, niacin, C) had no effect [123].

In both of the other studies, vitamin K status was determined using the concentration of phylloquinone (vitamin K₁) in the plasma². In a study on the wrists of 314 men and 358 women aged 42 to 89 years, NEOGI et al. [124] found a significant inverse association between phylloquinone levels and the prevalence of cartilage alterations, osteophytes, and narrowing of the intra-articular space, although the effect was only observed up to a plasma concentration of 1 nM. According to BOOTH et al. [19], this concentration is achieved by a vitamin K intake that matches the Dietary Reference Intake (DRI: 120 µg/day for women, 90 µg/day for men). In a study including 448 men and 732 women aged 50 to 79 years, MISRA et al. [125] investigated the association between phylloquinone levels and osteoarthritic changes in the knee joints. Suboptimal vitamin K status (plasma concentration < 0.5 nM) was associated with a 139 % increase in detection of cartilage damage and a 56 % higher risk of osteoarthritis at follow-up after 2.5-years. The risk of developing the condition in both knees was higher by 33 %.

However, no interventional studies have yet been conducted, so that the

hypothesis that vitamin K may help to prevent osteoarthritis can only be considered as speculation.

Type 2 diabetes mellitus

Based on a literature review, it has been suggested [36] that vitamin K has an influence on the synthesis and functional activity of insulin not only in mice [126], but also in humans, meaning that an increased intake via food or supplements could have a positive effect on glucose homeostasis in the case of pre-existing type 2 diabetes mellitus.

With regard to the association between vitamin K₂ intake and type 2 diabetes mellitus, only one prospective cohort study has been conducted to date [9]. Further details on this study are provided in ♦ Table 6⁵: The study participants in the highest dietary intake quartile had a 20 % lower risk of developing the disease than those in the lowest quartile. Furthermore, a placebo-controlled interventional study has been conducted in which, however, a pharmacological amount of vitamin K₂ was administered: Out of a group of 33 healthy young men with an average age of 29 years, 18 men were given a daily supplement of 30 mg of MK-4 for 4 weeks, and 15 men were given placebo. The treatment group exhibited significant improvement in insulin sensitivity [127]. As promising as these results may be, further interventional studies must be conducted before menaquinone can be recommended for diabetes prophylaxis. Studies on vitamin K₁ suggest a more minor effect on the risk of diabetes. The prospective cohort study [9] shown in ♦ Table 6 established only a trend. YOSHIDA et al. [128] found no association between vitamin K₁ intake and fasting insulin/glucose levels, HbA1c, or insulin resistance

4 ■■■ Part 1: ERNÄHRUNGS UMSCHAU 11/2017
 5 Table 6 in the online supplement

in their cross-over study including 2,719 Americans with an average age of 54 years. In an interventional study conducted on 42 women with an average age of 62 years, KUMAR et al. [129] were unable to find any evidence that a daily dose of 1,000 μg of phylloquinone over a period of 12 months caused changes in the secretion of insulin or its effects. YOSHIDA et al. [130] investigated the effect of a daily supplement of 500 μg of phylloquinone administered for 36 months to 355 subjects aged 68 years who did not have manifest diabetes. Whilst no effect was found in women, in men there was a significantly reduced progression of insulin resistance. In a cross-over study including 510 Spanish people aged > 55 years, JUANOLA-FALGARONA et al. [131] found no association between phylloquinone intake and the risk of diabetes. However, some risk markers (ghrelin, leptin, GIP, GLP-1, IL-6, TNF- α) were positively influenced by a one-year dietary adjustment towards a Mediterranean diet that provided more phylloquinone than the baseline diet.

In vitro, insulin promotes not only the differentiation and mineralization of osteoblasts, but also the dose-dependent synthesis of osteocalcin [132]. This means that vitamin K could be beneficial to diabetics in the sense that, compared to healthy people, diabetics have an increased risk of bone fractures, as shown in a meta-analysis (n = 836,941): The risk of hip fractures was 160 % higher, and the risk of other fractures was 30 % higher [133]. Interventional studies need to be conducted in order to demonstrate the potential effect of vitamin K on fracture risk in diabetic patients.

DAM et al. [134] studied patients suffering from metabolic syndrome which is characterized by a diabetic metabolism, amongst other symptoms. Among the 171 study participants who were on the average 73 years old after the 10-year fol-

low-up, there was a significant inverse association between the upper dietary intake tertile for vitamin K₂ (112.1 $\mu\text{g}/\text{day}$ vs. 44.6 $\mu\text{g}/\text{day}$ in the lower tertile) and syndrome prevalence, and between the upper vitamin K status tertile (measured as dp-ucMGP: 108 pmol/L vs. 484 pmol/L in the lower tertile) and syndrome prevalence. The vitamin K₁ intake level had no demonstrable effect.

Cancer

In animal and *in vitro* studies, vitamin K was found to have anti-carcinogenic effects. These effects appear to be associated with the proportion of carboxylated GRP because undercarboxylated GRP and pathological mineralization can be found in tumor cells from the skin and breast tissue, whereas both forms of GRP and no calcification are found in healthy cells [135]. To date, there have only been three prospective cohort studies in Europe that concentrated on the association between vitamin K intake and cancer incidence/mortality [8, 136, 137]. These are shown in \blacklozenge Table 6⁵. For Vitamin K₂, increased intake was found to have a positive effect. No interventional studies have been conducted to date.

Conclusions

There are numerous indications that vitamin K performs important functions in the body that go beyond its traditionally understood role in the activation of various blood coagulation factors. MK-7, MK-8 and MK-9 in particular appear to have anti-atherosclerotic and anti-osteoporotic properties; however, the research that is currently available is not sufficient to justify recommending that they be taken as prophylaxis in the form of food supplements. Even though in 2006, the EFSA stated that: “Since undercarboxylation of extrahepatic gla-proteins seems to

be common in the healthy adult population, the current recommended intake is probably insufficient fully to carboxylate these proteins.” ([22], p. 255), and although in 2008, they stated that there were no health concerns with regard to the use of menaquinone in foodstuffs, including food supplements [30], and although in 2009, they agreed to the health claim “Vitamin K contributes to maintenance of normal bone” ([138], p. 8), in the position paper provided in 2017 [12], the EFSA did not set out any plans to change the Adequate Intake (AI) of 1 μg per kg of body weight of phylloquinone per day, which was established in 1993 ([33], p. 148). The reason given for this is that there is no precise reference value for the proportion of carboxylation of gla proteins that can be considered optimal in association with the functions controlled by vitamin K status ([12], p. 28). It is acknowledged that MK-7 stimulates the γ -carboxylation of gla proteins more strongly than phylloquinone, but it is also noted that the available data is insufficient to establish the activation coefficients for both vitamins ([12], p. 11). The main reason given for not setting a Dietary Reference Value (DRV) for menaquinone is that: “(...) the knowledge on MK-n is limited and highly contradictory” ([12], p. 49), and the 24-year-old estimated value is retained because: “all possible approaches investigated to set Dietary Reference Values (...) have considerable uncertainties” [ibid.]. The fact that “cut-off” values for biomarkers of vitamin K status have still to be established is highlighted in particular.

Given that it will take some time for enough studies to be conducted in order to derive “cut-off” values for biomarkers such as dp-ucMGP or ucOc, it should be considered whether physician-prescribed therapeutic or even prophylactic supplementation with menaquinone (MK-7) might be indicated for certain patient groups – i. e., people

who regularly take calcium and/or vitamin D₃ – or for adults aged 40 years and older as an alternative to nattō, if there were a chance that this might slow down atherosclerotic and osteoporotic processes [139]. An MK-7 intake of 50–150 μg/day [17] or 0.5–1.0 μg per kg of body weight per day would be sufficient to increase the proportion of carboxylated extrahepatic vitamin K-dependent (VKD) proteins [140], however, in the case of pre-existing osteoporosis, 180–200 μg/day [114] or 2–4 μg per kg of body weight per day [140] would be required.

Vitamin K substitution is not expected to cause side effects: An increased risk of thrombosis can be

ruled out because the number of glutamic acid residues in the coagulation-promoting vitamin K-dependent (VKD) proteins is limited [7]. The EFSA has not set any Tolerable Upper Intake Level (UL) because the risk of unfavorable effects is considered low ([22], p. 257). Even pharmacological doses of 45 mg/day (MK-4) over a period of three years have proven safe [118]. In addition, there have been no documented cases of vitamin K intoxication [141]. However, caution is necessary when vitamin K antagonists such as Marcoumar® or Coumadin® are being used for blood thinning. Just 10 μg MK-7 per day can have a negative effect on anticoagulation treatment, meaning

that patients taking coumarin derivatives must avoid food supplements containing menaquinone [43].

The references for parts 1 and 2 can be found in issue 11/2017 at:

→ www.ernaehrungs-umschau.de

Conflict of Interest

The author declares no conflict of interest.

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