



Vitamin K2 Status and Health Concerns

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Growing evidence of a proven mechanism shows vitamin K2 can impact health conditions beyond bone and cardiovascular.

INTRODUCTION

Vitamin K2 is a vital nutrient newly recognized for supporting bone and cardiovascular health. This has been shown in observational and intervention trials, in healthy and patient populations, in adults and children. Even more recently it has come to light that K2 status and the vitamin's very mechanism of action impacts other areas of health, including but not limited to brain health, healthy joints, neuropathy, and vision health. All of this evidence lends itself to the argument that correcting a widespread vitamin K2 deficiency can greatly impact improving global health. The first step in correcting that deficiency is establishing a vitamin K2-specific recommended daily intake.

A FOUNDATION OF EVIDENCE

A need for an RDI

The discovery of the role of vitamin K-dependent proteins in processes beyond coagulation and identification of various isoforms of vitamin K in the recent decades has specifically highlighted vitamin K2 (menaquinone) as a crucial cardiovascular health nutrient mainly due to its long half-life and extrahepatic activity, compared to a shorter half-life of the dietary form vitamin K1 (phylloquinone). Health-conscious consumers are seeking to meet the optimal intake of vitamin K2 in order to avoid calcium plaque buildup of atherosclerosis, and thus keep the risk and rate of calcification as low as possible.^{1,2,3}

Researchers formulated a nine-criteria standard in 2014 for the purpose of assessing whether there are sufficient grounds for a nutraceutical to be considered for Reference Daily Intake (RDI).⁴ The following factors need to be considered: (1) an accepted definition; (2) a reliable analysis method; (3) a food database with known amounts of the bioactive; (4) cohort studies; (5) clinical trials on metabolic processes; (6) clinical trials for dose-response and efficacy; (7) safety data; (8) systematic reviews and/or meta-analyses; and lastly, (9) a plausible biological rationale. By evaluating current knowledge and studies, either performed or still

ongoing, a paper recently published in the journal *Nutrients* assessed whether vitamin K2 meets these nine criteria.⁵

There is no doubt as to the differences between the pharmacokinetics of vitamin K1 and vitamin K2 in the human body. Vitamin K2 has been widely acknowledged for its extrahepatic activity; however, a detailed mechanistic description of vitamin K2 action has not been provided in the literature so far. The *Nutrients* paper showed that Vitamin K2 clearly passes the nine criteria set out for establishing bioactive RDI recommendation. The concentration of bioactive vitamin K2 in a range of fermented foods common to Western diets depends on factorial preparation methods, namely, the type of bacteria used in fermentation processes. Results of different clinical trials that tested the influence of vitamin K2 supplementation on human health status have shown that it either significantly improved it or strongly correlated. Researchers postulate that consistent consumption of vitamin K2 can reduce the risk of occurrence of cardiovascular diseases, bone loss, and, potentially, other age-related diseases. Bearing in mind this nature of vitamin K2 action on decreasing the development of diseases commonly linked to aging, steps should be taken

by scientific and food policy makers to review the literature on the current state of vitamin K2 research and consider establishing an RDI for vitamin K2 in order to significantly improve global health and reduce the socioeconomic consequences of an aging population.

Vitamin K deficiency

To know the status of vitamin K in bone, one has to mark the level of circulating uncarboxylated osteocalcin (ucOC); in order to estimate its status in the vasculature, one has to mark the level of desphospho-uncarboxylated matrix Gla-protein (dp-ucMGP). These markers have been measured in 896 samples of healthy volunteers and, based on increased levels indicative of tissue-specific vitamin K deficiency, researchers defined target groups for vitamin K supplementation. By measuring the circulating dp-ucMGP level in samples from two short-term trials on menaquinone-7 (MK-7, vitamin K2) supplementation in 42 children and 68 adults, they analyzed the response to vitamin K supplements at different states of vitamin K deficiency. The authors of this study found that the largest tissue-specific vitamin deficiency is common among children and adults above 40 years, and thus MK-7 supplementation in their case may have a beneficial influence on improving the extra-hepatic vitamin K status.⁶

Vitamin K2 shown to reduce CV health problems

Epidemiological data, among them the well-known Rotterdam Study (2004), show that prolonged high dietary intake of vitamin K2—but not K1— has a strong protective effect on cardiovascular health. This population-based study, which took place over a 10-year period, included 4,807 men and women 55 years of age or older at the start. Findings from the study indicate that eating foods rich in natural vitamin K2 (at least 32 µg per day) reduces the

risk of both arterial calcification and cardiovascular disease by as much as 50% – with no undesirable side effects.⁷

The Rotterdam findings were confirmed in 2008 by another Dutch population-based study investigating the protective effect of vitamin K2. The Prospect-EPIC cohort study by Gast et al included 16,057 women, and after 8 years of follow-up, vitamin K2 was found to decrease the risk of coronary heart disease (CHD) by 9% for every 10 µg vitamin K2 consumed. The scientists found that the strongest correlation was seen in cases of intake of the higher menaquinones (MK-7, MK-8, and MK-9). Vitamin K1 intake was not significantly related to CHD.⁸

A study published in *Cureus* in 2016 was another milestone in the quest to deal with major cardiovascular disease (CVD) risk factors, among which the deficiency of vitamin K2 plays a crucial role. Multiple regression analysis of worldwide cohort data that was presented in this paper showed that vitamin K2 was inversely correlated with early CVD death to the same degree that tobacco use was positively correlated. Similar effect was not found in case of vitamin K1.⁹

Results of a Dutch large-scale cohort study that aimed to investigate the association of vitamin K1 and vitamin K2 intake with all-cause and cause-specific mortality that were published 12 years after the Rotterdam Study, constituted an important continuation of the previous Dutch cohort research in terms of stating that only the intake of long chain menaquinones may be associated with a reduced risk of CHD.¹⁰

Very recent publication of the results of a Norwegian prospective cohort study whose authors aimed to evaluate relations between intake of vitamin K and incident (new onset) CHD among community-dwelling middle-age adults in Western Norway during a median follow-up time of 11 years, further demonstrated that “[...] a higher energy-adjusted reported intake of K2 was associated with a lower

risk of subsequent CHD events, whereas intake of K1 was not associated with incident CHD. Similar direction of associations was observed when further adjusting for potential dietary confounders.”¹¹

Low vitamin K status correlates with mortality risk

So far it has been widely agreed among researchers that vascular calcification is independently associated with an increased risk of cardiovascular events (CV) and mortality. In the light of accumulating evidence suggesting that plasma dp-ucMGP is a useful marker of vascular calcification, several investigations have been undertaken in various populations in order to explore the possible association of dp-ucMGP with CV events and mortality.

In a study among 577 older adults of the Longitudinal Aging Study Amsterdam study (LASA) with no history of previous CVD, there was a more than 2-fold higher risk of CVD in the highest tertile of dp-ucMGP group

(HR: 2.69, 95% CI: 1.09–6.62) compared with the lowest tertile after a follow-up period of 5.6 years.¹²

In a Flemish population study of 2318 participants, higher concentrations of dp-ucMGP were an independent predictor of total, non-cancer, CV mortality after a follow-up period of 14.1 years.¹³

In a prospective cohort study consisting of 518 type 2 diabetes mellitus patients, high dp-ucMGP levels were associated with increased risk for CVD, especially with peripheral artery disease (PAD) and heart failure after a follow-up of 11.2 years.¹⁴

In a prospective cohort study conducted with 799 patients with history of myocardial infarction, stroke, or coronary artery disease, there was a higher risk of all-cause and CV mortality in the highest quartile of dp-ucMGP (HR 1.89, 95% CI: 1.32–2.72 and HR 1.88, 95% CI: 1.22–2.90, respectively).¹⁵

The above longitudinal data imply the fact that modern medicine may rely on plasma dp-ucMGP level as a novel biomarker for CV events and mortality.

LOW VITAMIN K STATUS INFLUENCES MANY HEALTH ISSUES

Bone health

Vitamin K2 activates osteocalcin (OC), which is a vitamin K-dependent protein (VKDP) synthesized by osteoblasts, and is thought to be related to bone mineralization. Vitamin K, and particularly K2, may also decrease bone resorption by reducing prostaglandin E2 synthesis in osteoclasts (cells responsible for the dissolution and absorption of bone).

In addition to OC carboxylation, which modulates the deposition of calcium in bone, vitamin K2 increases collagen accumulation [16] and production

by osteoblasts [17]. Collagen is essential for bone flexibility and elasticity, and occupies more than half the volume of bones. It is responsible for matrix production, the material on which calcium and other minerals accumulate. Therefore, along with bone minerals, collagen accumulation is critical for high-quality bone formation.

Other than OC, many VKDPs, such as MGP, protein S¹⁸, and periostin are produced in the bone matrix, suggesting a complex involvement of vitamin K and VKDPs in bone health.

Low vitamin K status and poor bone health

Low vitamin K status correlates with poor bone quality and increased risk of osteoporosis and bone fracture.^{19,20,21} The incidence of forearm fractures in children peaks around the time of the pubertal growth spurt, possibly because physical activity increases at the same time that there is less cortical bone mass due to the increased calcium demand during skeletal growth. A population-based study in Minnesota examined whether there has been a change in the incidence of forearm fractures in children over a 30-year period. The results showed that annual incidence rates of forearm fractures per 100,000 increased from 263.3 in 1969-1971 to 322.3 in 1979-1981, and to 399.8 in 1989-1991 before leveling off at 372.9 in 1999-200, which may be linked to vitamin K intake decrease in children on Western diets.²²

The Hungarian study evaluated 10-12 years old children (N = 123, 59 girls, 64 boys) according to physical activity, diet, anthropometric and bone data. The study showed that changes in the characteristics of ultrasound bone parameters among 10-12 years old children mainly depended on the amount of intense PA, adequate vitamin K intake and anthropometric variables related to age.²³

Understanding the combined approach to a healthy skeletal system in children and young adults, including the roles of vitamins D and K, particularly vitamin K2 as menaquinone-7 (MK-7), calcium, healthy diet, and exercise, is particularly important in view of reports of subclinical insufficiency of vitamins D and K in otherwise healthy pediatric populations with low-energy bone fractures.²⁴

In clinical study, researchers measured inactive osteocalcin (ucOC) in 896 samples of healthy volunteers and the response to vitamin K2 supplementation was measured in 42 children and

68 adults. Children had high ucOC levels, reflecting low vitamin K status. Children and adults with more pronounced vitamin K deficiency gave the highest responses to vitamin K2 (MK-7) supplementation. Researchers concluded that children and adults above 40 years old showed the largest tissue-specific vitamin deficiency and, accordingly, may benefit from MK-7 supplementation to improve vitamin K status.²⁵

A pilot study evaluated vitamin D and K status in children with low-energy fractures and in children without fractures. The scientists enrolled a group of 20 children (14 boys, 6 girls) aged 5 to 15 years old, with radiologically confirmed low-energy fractures and 19 healthy children (9 boys, 10 girls), aged 7 to 17 years old, without fractures. In this study, better vitamin K status expressed as the ratio of ucOC:cOC-UCR is positively and statistically significantly correlated with lower rate of low-energy fracture incidence.²⁶

Further, glucocorticoids (GCs) are widely used in pediatric practice. Long-term systemic GC therapy is associated with many side-effects, including low bone mineral density (BMD) and fragility fractures. Vitamin K2 (menatetrenone) combined with alfacalcidol has preserved BMD in children on long-term GC therapy. According to a systematic review, vitamin K2 might be a good option in the treatment used in the management of bone loss associated with glucocorticoid (GC) use among children.²⁷

Bone mineralization

Various clinical trials in adults have reported that daily supplementation with vitamin K2 improved bone mineral density (BMD), significantly reduced bone loss, and improved measures of bone strength, which may well contribute to reduced risks of fractures.^{28,29,30,31,32,33} In addition, research has demonstrated the relationship between vitamin K and bone mineralization in children and adults.

Interventional studies in children

A prospective, 1-year pilot study investigated the effects of a dietary supplement with vitamin K2 (50 mcg MenaQ7®) and vitamin D (5 mcg calcitriol) on 20 children with thalassemic osteopathy or TOSP (a blood disorder that may result in osteopenia and osteoporosis). Results showed a significant improvement in the BMD at the lumbar spine area of the patients at month 6 and month 12 of the treatment, especially in the prepubertal group. This pilot study demonstrated that vitamin K2 and calcitriol combination clearly has a positive effect on the BMD of the children with TOSP.³⁴

Further, researchers conducted an 8-week, double-blind, randomized, placebo-controlled trial in which 45 mcg vitamin K2 (as MenaQ7®) was given to healthy prepubertal children, and undercarboxylated osteocalcin (ucOC) and carboxylated osteocalcin (cOC) were measured, as well as the ucOC:cOC ratio (UCR) as an indicator of vitamin K status. Results showed that with increases in MK-7, the circulating concentration of inactive ucOC reduced and the UCR improved. There were no significant changes in the placebo group. Researchers concluded that supplementation with MenaQ7® vitamin K2 increases circulating concentrations of MK-7 and increases osteocalcin carboxylation in healthy, prepubertal children.³⁵

Interventional studies in adults

Vitamin K2 is used as a drug to treat osteoporosis in Japan. Studies show that vitamin K2 (menatetrenone) effectively prevents the occurrence of new fractures and sustains lumbar bone mineral density in osteoporosis.^[36] Moreover, vitamin K2 suppressed the decrease in spinal BMD as compared with no treatment group. Vitamin K2 therapy may be a useful method for preventing postmenopausal spinal bone mineral loss. It is recommended that the therapy should

be started early in postmenopausal period.³⁷

A clinical study demonstrated also that postmenopausal women treated with a pharmacological dose of MK-4 (45 mg/day) for three years showed no effects on BMD, but bone quality indices of the femur increased.³⁸ In addition, MK-7 (MenaQ7) (180 µg/day) was demonstrated to inhibit bone loss and helped maintain high bone strength in healthy postmenopausal women.³⁹

MK-7 has been shown to have the highest bioavailability and the most significant effect on OC carboxylation in humans among vitamin K homologs. Vitamin K1 and MK-4 at their current RDIs are not sufficient for activation of OC. Therefore, it is expected that MK-7 may promote bone health.⁴⁰

Cardiovascular and kidney health

Arterial calcification is considered an unfortunate result of aging, but fortunately we are able to actively regulate this process by providing our body with adequate amounts of vitamin K2. This nutrient is essential to activate the most potent modulator of vascular calcification – Matrix Gla Protein (MGP) – and thus lower the risk of age-related cardiovascular decline.

While observational data suggest a link between vitamin K2 intake and cardiovascular health, intervention trials with hard clinical endpoints are missing. So far, there have been two groundbreaking intervention trial studies published (a three-year and a one-year clinical study), which evaluated the effect of vitamin K2 vs. placebo on arterial stiffness in healthy people.

Results of a published, double-blind, randomized clinical trial (Knapen et al. 2015) shows that when taken daily in nutritional doses (180 µg as MenaQ7®) for 3 years by a healthy population, vitamin K2 (MK-7) improves cardiovascular health. In this study

244 healthy post-menopausal Dutch women, 55 to 65 years old, were randomly assigned to receive daily either MK-7 or placebo capsules. The trial demonstrated substantial benefits in inhibiting age-related stiffening of arteries resulting in increase of the pulse wave velocity (PWV) in the placebo group, but not in the MK-7 group. Most remarkably, MK-7 not only suppressed arterial stiffening, but it also resulted in an unprecedented statistically significant improvement of vascular elasticity both measured with ultrasound techniques and PWV in a healthy population.⁴¹

A 1-year follow-up clinical study completed by the expert researchers at VitaK also showed cardiovascular benefit after K2 supplementation in both genders. This second placebo-controlled randomized clinical trial was performed in a population of 243 subjects (40-70 years old) characterized by elevated risk for cardiovascular disease due to vitamin K-insufficiency (i.e., circulating dp-ucMGP concentrations above the median of the general population: dp-ucMGP > 400 pmol/L). Treatment was performed with either 180 µg/day of vitamin K2 as MenaQ7® or placebo for one year. Arterial stiffness was concluded from the carotid-femoral pulse-wave velocity (cfPWV), and other vascular characteristics were measured by echotracking of the common carotid artery. In the total study group, MK-7 induced a significant decrease of both dp-ucMGP and cfPWV. The participants taking MenaQ7® maintained arterial flexibility and the stiffness did not increase, whereas placebo group became stiffer and less flexible.⁴²

The significance of this clinical work has earned the attention of the medical community, which is now in process with its own trials that are using vitamin K2 as MK-7 (as MenaQ7®) as a possible therapy for patients whose conditions present symptoms of intense calcification. Worth mentioning are the following trials: the VitaK-CAC Trial, which is examining the effects of vitamin K2 on coronary artery calcification (CAC). CAC is a precursor to atherosclerosis and a strong CVD predictor.⁴³ The second study underway is BASIK2, a prospective study looking at the effect of

vitamin K2 on imaging measurements of calcification in the bicuspid aortic valve (BAV) and calcific aortic valve stenosis (CAVS). BAV is associated with early development of CAVS.⁴⁴

Vitamin K2 as MK-7 is unique because it impacts arterial calcification, and no other compound (drug or vitamin) has been shown to do this. It turned out that this nutrient also lends a vital cardiovascular support to patients with chronic kidney disease who are on dialysis and renal transplant recipients. As compared to the general population, subclinical vitamin K deficiency is highly prevalent among these two groups of patients and is associated with an increased risk of cardiovascular disease (CVD). Nutritional management, such as a very-low-protein diet, may be necessary to delay the progression of renal disease, however, deficiencies in essential nutrients, such as vitamins K2 and D, must be overcome to prevent vascular calcification (VC) in the kidney category of patients.⁴⁵

A study published by Kurnatowska et al. was the first that assessed the effect of vitamin K2 substitution on atherosclerosis and calcification progression in the chronic kidney disease (CKD) group of patients. The results showed that the supplementation with vitamin K2 slowed significantly the progression of common carotid intima-media thickness (CCA-IMT), which is a good indicator of atherosclerosis and a well-established predictor of cardiovascular episodes and death in general and in CKD population. The progression of coronary artery calcification (CAC) in these patients who received vitamin K2 with D was less than in patients treated only with vitamin D.⁴⁶

A single-arm study conducted as part of the KING trial (vitamin K2 In reNal Graft) among 60 renal transplant recipients with stable graft function evaluated the association between the change in vitamin K status and indices of arterial stiffness following 8 weeks of menaquinone-7 (vitamin K2) supplementation (360 µg once daily). While previous cardiovascular study in healthy postmenopausal women showed an improvement in arterial elasticity after 3 years

of supplementation, the results collected in this trial were especially impressive as the statistically significant effect was seen very quickly. After just 8 weeks of MK-7 supplementation, low vitamin K status represented by dp-ucMGP level was significantly reduced by 55.1%. When controlled for age, durations of hemodialysis and transplantation, and the change in 24-hour mean arterial pressure, the improvement in arterial stiffness was independently associated with the reduction in dp-ucMGP concentration. Moreover, supplementation was associated with a 14.2% reduction in mean cfPWV. The previously observed 80% prevalence of subclinical vitamin K deficiency in the renal transplant population has reduced by 40%. One can assume that longer MK-7 supplementation may lead to even better results, and secure improvement in cardiovascular outcomes in CKD and renal transplant patients.⁴⁷

Rheumatoid arthritis and joints

In the recent years the researchers tried to address the therapeutic benefits of MK-7 in the management of patients with rheumatoid arthritis (RA). A study in 2015 was designed to clarify the therapeutic role of MK-7 added to normal therapeutic regimen of RA in patients with different stages of the disease with a clinical follow up through a randomized clinical trial. 84 RA patients (24 male, 60 female with an average age of 47.2 years) were enrolled in this cross sectional study and divided into MK-7 treated group (n=42) and MK-7 naïve group (n=42). MK-7 capsules were administered in a dose of 100µg/day for three months in the first group without changing in other medications. In MK-7 treated group, a significant decrease for the levels of undercarboxylated osteocalcin (ucOC), erythrocyte sedimentation rate (ESR), disease activity score assessing 28 joints with ESR (DAS28-ESR), C-reactive protein (CRP) and matrix metalloproteinase (MMP-3) was found, and a marked decrease in RA clinical and biochemical markers for moderate and good response compared to non-responders was observed in ucOC, ESR and DAS28-ESR. The results suggest that MK-7 improves disease activity in RA patients. Therefore, MK-7 represents a

new promising agent for RA in combination therapy with other disease modifying antirheumatic drugs.⁴⁸ A similar cross-sectional study was already conducted in 2013 and gave comparable results, namely the vitamin K2-treated group showed lower serum CRP, MMP-3, and DAS28-CRP. In the longitudinal study, patients who were additionally treated with vitamin K2 without changing their other medications for three months demonstrated significant decreases in serum CRP, MMP-3, and DAS28-CRP. For this reason vitamin K2 may be used to improve disease activity besides osteoporosis in RA.⁴⁹

Also in 2013 clinical efficacy of alendronate monotherapy and combined therapy with menatetrenone (vitamin K2) in postmenopausal RA patients with osteoporosis or osteopenia was evaluated by Japanese researchers. The results that were published clearly showed that combined therapy with alendronate and vitamin K2 decreases bone metabolism marker levels and serum ucOC levels, and increases lumbar spine and femoral neck bone density in postmenopausal RA patients with abnormal ucOC levels and osteoporosis or osteopenia.⁵⁰

An eight-week registry study that was conducted in 2019 aimed to use Jumpstart Nutrition® bone supplementing combination with vitamin K2 and coenzyme-Q10 characterized by an innovative delivery system that improves bioavailability of calcium-to-phosphorus ratio (CPR) and parathyroid hormone (PTH) in the management of osteoarthritis (OA). Upon completion of this registry study its author indicated that Jumpstart Nutrition® can be used safely for effective management of OA patients for the amelioration of CPR, PTH and functional activities confirmed with biomarkers and radiological images correlated with the Kellgren-Lawrance scale.⁵¹

The purpose of another study was to evaluate the distribution of vitamin K2 in subchondral bone in osteoarthritic knee joints. This study suggested that vitamin K2 might affect bone turnover since medial condyles showing advanced OA had lower vitamin K2 levels, while lateral condyles showing less advanced

OA contained more vitamin K2. Gender and age were not correlated with vitamin K2 localization. All cases had Grade IV OA, and this study suggested that OA grade might be important in controlling the vitamin K2 levels in human bones.⁵²

Diabetes

Since metabolic health lies in space between the hormone insulin and your glucose sensitivity, it is crucial to know the biological mechanisms behind the association between vitamin K2 and glucose metabolism. Type 2 diabetes mellitus (T2DM) that frequently co-occurs with microvascular and macrovascular complications continues to be a major public health problem around the world. Individuals with T2DM are not only suffering from significant emotional and physical misery, but are also compromised to an increased risk of dying from severe complications. In recent years, evidence from prospective observational studies and clinical trials has shown T2DM risk reduction with vitamin K2 supplementation: with each 10- μ g increment of vitamin K2 intake, T2DM risk has been reduced by 7%. It has also been established that vitamin K2 has a more significant effect on T2DM than vitamin K1. This is due to the following facts: vitamin K2 increases insulin sensitivity through involvement of vitamin K-dependent-protein osteocalcin, vitamin K2 may reduce progression of insulin resistance (IR) via anti-inflammatory properties and lipid-lowering effects, and finally vitamin K2 suppresses inflammation via inactivating NF- κ B signalling pathway.⁵³

Recently Chinese authors have systematically reviewed research on the association between vitamin K and type 2 diabetes and diabetes-related biomarkers in humans. They arrived at the conclusion that vitamin K plays an important role in the prevention and control of type 2 diabetes, which may be related to the improvement of insulin metabolism and blood glucose level.⁵⁴

For the purpose of addressing the therapeutic potential of vitamin K in the regulation of glucose homeostasis in patients with diabetes, animal model research was conducted in 2018. The researchers noticed that vitamin K2 administration could improve glycemic status in type 2 diabetic rats by induction of OC gene expression. Furthermore, osteocalcin could increase β -cell proliferation, energy expenditure, and adiponectin expression.⁵⁵

Authors of a 2015 animal model study noticed that combined vitamins K2 plus 1,25(OH)₂D₃ treatment significantly enhanced migration and the re-appearance of surface microvilli and ruffles of osteoblasts of db/db mice, and they thus assumed that vitamins K2 plus D₃ combination could be a novel therapeutic strategy in treating diabetes-associated osteoporosis.⁵⁶

Results of a 2011 placebo-controlled trial were consistent with previous studies and demonstrated that vitamin K2 supplementation for 4 weeks increased insulin sensitivity in healthy young men, which according to the authors seemed to be related to elevated cOC rather than modulation of inflammation.⁵⁷

Findings of a review of the available preclinical and clinical evidence conducted in 2011 suggested a possible beneficial effect of vitamin K2 supplementation on bone quality in type 2 diabetic patients. These persons are at high risk of bone fractures even if their bone mineral density is normal or high. This is likely explained by poor bone quality and extraskeletal factors. Vitamin K2 stimulates γ -carboxylation of osteocalcin and can increase bone formation through steroid and xenobiotic receptors. Clinical studies of type 2 diabetic patients have shown detrimental collagen cross-links in bone; low serum insulin-like growth factor-I and osteocalcin concentration are associated with an increased risk of fractures. A therapeutic strategy for preventing fractures in type 2 diabetic patients remains to be established. A preclinical study showed that vitamin K2 administration in a type 2 diabetic rat model had

the following skeletal benefits: increased serum osteocalcin, improved collagen cross-link profiles, and increased bone strength.⁵⁸

Results of an epidemiological study published in 2010 showed that both phylloquinone and menaquinones intakes may be associated with a reduced risk of type 2 diabetes.⁵⁹

Brain health

Vitamin K, a fat-soluble nutrient was historically discovered in 1935 for its role in blood coagulation, and as such has been thoroughly explored. In recent years, studies conducted *in vitro* and on animals highlighted vitamin K involvement in brain cells development and survival. In the brain vitamin K occurs predominantly as MK-4. It was established that MK-4 represents >98% of total vitamin K in brain in both 6-month and 21-month-old rats. Highest concentrations of MK-4 were found in midbrain and pons medulla, and lowest concentrations were observed in cerebellum, olfactory bulb, thalamus, hippocampus, and striatum. In particular, vitamin K seems to have an antiapoptotic and anti-inflammatory effect mediated by the activation of Growth Arrest Specific Gene 6 (Gas6) and protein S. These two vitamin K-dependent proteins (VKDP), namely Gas6 and protein S, although not being directly associated with cognition or cognitive impairment, are closely linked to the brain and have the potential to influence the underlying cognitive process through their cell signaling actions in neurons (both Gas6 and protein S), the glia (Gas6) as well as antithrombotic activity (protein S). As a unique cofactor to the γ -glutamyl carboxylase enzyme, vitamin K contributes to the biological activation of proteins Gas6 and protein S, ligands for the receptor tyrosine kinases of the TAM family (Tyro3, Axl, and Mer). In the nervous system, Gas6 has been involved in functions such as cell survival, chemotaxis, mitogenesis, cell growth, and myelination. Specifically, Gas6 has been shown to prevent apoptosis of gonadotropin-releasing hormone (GnRH) neurons via the recruitment of the phosphatidylinositol 3-kinase (PI3-K) signaling pathway and subsequent

stimulation of the extracellular signal-regulated (ERK) and the serine-threonine (Akt) kinases. In addition to its signaling actions in neurons, Gas6 modulates survival and functions of the glia and microglia. It has been shown to promote the survival of human oligodendrocytes *in vitro* and to protect them from tumor necrosis factor alpha (TNF α)-induced apoptosis through activation of the Axl receptor and the PI3-K/Akt signaling pathway. Gas6 was found to suppress the microglial phenotype following a lipopolysaccharide (LPS) challenge, suggesting an anti-inflammatory role for Gas6. Importantly, two independent reports recently provided evidence for a modulatory role of Gas6 in remyelination. Protein S has been shown to offer neuronal protection during ischemic/hypoxic injury, through its antithrombotic functions and TAM-related signaling actions. In a murine *in vivo* model of stroke, protein S was found to significantly reduce brain infarction and edema volumes and to improve post-ischemic cerebral blood flow in treated animals. Protein S treatment was also associated with less fibrin deposition and infiltration with neutrophils, and fewer apoptotic neurons, an effect also observed in cultured neurons. These effects of protein S at the cellular level resulted in improved motor performance of the protein S-treated animals. Recently, the researchers further showed that protein S protected neurons from NMDA-induced toxicity and apoptosis through the Tyro3-PI3-K-Akt pathway.

Moreover, vitamin K is also involved in the synthesis of sphingolipids, an important class of lipids present in high concentrations in brain cell membranes. They are present in particularly high concentrations in cells of the central nervous systems with the major sphingolipids consisting in ceramide, sphingomyelin, cerebroside, sulfatide, and ganglioside. Studies with animals support a role for vitamin K in the biosynthesis of sphingolipids. Initially appreciated for their role as essential structural components of cell membranes, sphingolipids are now known to participate in important cellular events such as signaling, proliferation, differentiation, senescence, transformation and survival of brain cells. In recent years, studies have linked alterations in sphingolipid metabolism to age-related cognitive decline and

neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.^{60, 61, 62}

Alzheimer's disease (AD) and other forms of dementia

Human studies on the impact of vitamin K deficiency in brain function are limited, therefore it is still a matter of debate today whether vitamin K deficiency is associated to cognitive decline. Vitamin K antagonists (VKAs such as warfarin, acenocoumarol, and fluindion), used worldwide as oral anticoagulants, according to recent studies may have a negative influence on cognitive domains such as visual memory, verbal fluency and brain volume. The two most common types of dementia in Western countries are Alzheimer's disease (up to 60% of cases) and vascular dementia (up to 20% of cases). They are easily mistaken one for another due to their similarities in symptomatology, pathophysiology, and risk factors. The mechanism underlying Alzheimer's disease is the deposition of β -amyloid peptide ($A\beta$) and the neurofibrillary tangles of the microtubule binding protein tau. In particular, $A\beta$ peptides are responsible for the massive neuronal death that defines the disease.^{63, 64}

One study found that patients with early-stage Alzheimer's disease consumed less vitamin K than did cognitively intact control subjects. In 2001, Allison hypothesized that vitamin K deficiency could contribute to the pathogenesis of Alzheimer's disease, based on the potential actions of vitamin K in the brain and through a link to the apolipoprotein E genotype. The apolipoprotein E₄ allele, an established risk factor for Alzheimer's disease, is also associated with lower plasma vitamin K levels.⁶⁵ Six studies demonstrated, in a population of 65 years and older, a direct correlation between low vitamin K dietary intake or serum concentration and deteriorated cognitive and behavioral performances.^{66, 67, 68, 69, 70, 71} A few studies concluded that Vitamin K seems to prevent $A\beta$ -induced apoptosis through the activation of Gas6, showing a pro-survival effect on brain cells.⁷²

As for vascular dementia, the main causes are represented by several vascular pathologies that result in cerebral ischemia. Studies published in the last years have attributed to protein S (activated by vitamin K) a role in improving post-ischemic cerebral blood flow and potentially leading to a more favorable cognitive outcome.⁷³

Moreover the use of VKAs was shown to influence brain metabolism. The few papers published until now point out, to a limited extent, a potential correlation between the use of VKAs and both cognitive decline and brain focal atrophies.^{74, 75, 76, 77}

Considering the growing social and economic burden linked to the increasing number of patients suffering from cognitive impairment and dementia, further researches on this topic can prove to be beneficial and applicable results can be expected.

Parkinson's disease (PD)

Mitochondria are called the power plants of the cell that are responsible for supplying the energy for its operation. They generate this energy by transporting electrons. Most of a cell's ATP is produced there in the process of oxidative phosphorylation. This activity is disrupted in Parkinson's patients resulting in no energy production, causing brain cells to die and lose neural communication, which leads to lack of movement (akinesia), tremors, and muscle stiffness. Mitochondrial dysfunction was proposed to be an integral player in the development of Parkinson's disease (PD) nearly 40 years ago, and since those initial discoveries, evidence of the role it may play in this neurodegeneration continues to increase. There is now evidence to suggest a role not only for a loss of mitochondrial function in terms of ATP provision and calcium buffering capacity, but also the degradation of these organelles through mitophagy and the interaction of mitochondria with other organelles and proteins in this disease.⁷⁸

Parkinson's patients have several genetic defects, including PINK 1 and Parkin mutations, that lead to reduced mitochondrial activity. In one study, researchers found that fruit flies (*Drosophila*) with a PINK1 or Parkin mutation lost their ability to fly. They discovered that the mitochondria in these flies were defective, just as in Parkinson's patients. Because of this they generated less intracellular energy – energy the insects needed to fly. When the flies were given vitamin K2, the energy production in their mitochondria was restored and the insects' ability to fly improved. The researchers were also able to determine that the energy production was restored because the vitamin K2 had improved electron transport in the mitochondria. This in turn led to more efficient adenosine triphosphate (ATP) production. Vitamin K2 plays a role in the energy production of defective mitochondria. Because defective mitochondria are also found in Parkinson's patients with a PINK1 or Parkin mutation, vitamin K2 potentially offers hope for a new treatment for PD.⁷⁹

Recently, a case-control study was conducted that involved 93 PD patients and 95 healthy controls. Overall, the serum vitamin K2 level of PD patients (3.49 ± 1.68 ng/ml) was significantly lower than that of healthy controls (5.77 ± 2.71 ng/ml). When the PD patients were stratified by disease progression, the authors observed that the serum vitamin K2 level of late stage patients was further decreased to 3.15 ± 1.18 ng/ml while the serum vitamin K2 level of early stage patients was 3.92 ± 2.09 ng/ml. In summary, the researchers found the serum vitamin K2 level in PD patients is lower than that in healthy controls. The decrease of vitamin K2 level may be related to the occurrence and progression of PD by loosening the regulation of inflammatory responses and coagulation cascades signal.⁸⁰

Multiple sclerosis (MS)

Multiple sclerosis (MS) is a devastating neurological disease, which is characterized by multifocal demyelinating lesions in the central nervous

system. Although vitamin K participation in the brain pathology has not been fully explained, it is well known that oxidative stress has a critical role in neurodegenerative diseases. Further, vitamin K2 was found to have beneficial effects on the nervous system – it seems to protect neurons and oligodendrocytes from oxidative injury and in fruit flies it was shown to protect against mitochondrial damage, a pathology associated with Parkinson's disease. Moreover, vitamin K2 can reduce inflammation and the consequences of autoimmune diseases, such as multiple sclerosis (MS). Because of the potential role of vitamin K2 in MS and the possibility that it may be associated with its clinical features, Austrian researchers decided to assess vitamin K2 serum levels in MS patients in comparison to healthy controls and correlate these levels with clinical appearance, medication, and disability status in a new paper published in *Wiener klinische Wochenschrift* (The Central European Journal of Medicine). A cross-sectional study was performed in the area of Tehran, Iran. Overall, 45 MS patients (31 females and 14 of the relapsing-remitting type) and 29 healthy controls (19 females) were included in the analysis. Researchers measured K2 serum levels by the double antibody sandwich Enzyme-linked Immunosorbent Assay (ELISA) technique in MS patients and age and sex matched controls, both under vitamin D supplementation, and related it to disease characteristics and treatment. The vitamin K2 serum levels were more than three-fold higher in healthy controls as compared to MS patients ($p < 0.001$): healthy controls had a median level of 866ng/ml compared to a median level of 196ng/ml in MS cases. Female patients had significantly lower vitamin K2 levels than males and a decrease with age by approximately 10% per decade was found. Vitamin K2 levels were lower with increasing numbers of attacks per year and were higher in patients with optic nerve lesions. This study showed that the substantially lower levels of vitamin K2 in MS patients could be due to depletion, lower production in the gut, diminished absorption or, less likely, reduced intake of precursor vitamin K1. The role of K2 in MS development and progress deserves further study.⁸¹

In another study the role of vitamin K in remyelination was investigated by using an animal model for MS. Demyelination was induced in mice by feeding them a special 0.3% cuprizone-containing diet for 6 weeks. And after that period, cuprizone was removed from the diet and mice were allowed to remyelinate for either 1 or 3 weeks, in the absence or presence of vitamin K (i.p. phylloquinone, 2mg, three times per week). When compared with the control group, it was shown that vitamin K enhanced the production of total brain sulfatides after both remyelination cycles.⁸²

Migraine

A better understanding of disease pathophysiology to help guide future research on migraine management is needed, since according to the WHO migraine is estimated as the fifth highest cause of years lost due to disability. In a case-control single-center observational study Lebanese researchers compared arterial stiffness and markers of vitamin K2 status between a cohort of patients with untreated migraine vs. their age- and sex-matched non-migraine controls. The outcome of their project that was published in *Headache* constitutes an important message for migraineurs who are more prone to an increased risk of major cardiovascular events. Individuals with migraine have worse indices of arterial stiffness as compared with their age- and sex-matched control subjects. This increase in arterial stiffness is correlated with an increase in markers of vitamin K2 deficiency in the migraine with aura (MWA) group. It seems that people who suffer from migraine might benefit from MK-7 supplementation, however there is a need to direct the focus of research in this domain toward examining the effect of vitamin K2 supplementation on migraine frequency, arterial stiffness and cardiovascular outcome in patients with migraine.⁸³

Peripheral neuropathy (PN)

Diabetic peripheral neuropathy is a frequent and severe complication of diabetes. A recent study aimed to evaluate factors associated with sensitive diabetic neuropathy in Type 2 Diabetes, and, in particular, dephospho-uncarboxylated Matrix-gla-protein (dp-ucMGP), the inactive form of MGP. Since MGP is expressed in several components of the nervous system and is involved in some neurological disease, it is likely to play a role in peripheral nervous system homeostasis. The association between diabetic neuropathy and the inactive form of MGP suggests the existence of new pathophysiological pathways to explore. Further studies are needed to determine if dp-ucMGP may be used as a biomarker of sensitive neuropathy. Since dp-ucMGP is a marker of poor vitamin K status, clinical studies are warranted to explore the potential protective effect of high vitamin K intake on diabetic peripheral neuropathy.⁸⁴

Another study with the objective to assess the efficacy, tolerability and safety of vitamin K2-MK7 in patients with peripheral neuropathy was conducted in 100 participants presenting with PN and suffering from either Vitamin B12 Deficiency (VBD, megaloblastic anaemia) or Type 2 Diabetes Mellitus (T2DM). For the first time, in larger sample size, it has been shown that vitamin K2-MK7 at a dose of 100 mcg twice a day for 8 weeks has a therapeutic activity for the symptoms of PN in VBD and T2DM. It also helps in relieving the associated symptoms of PN such as cramps, burning pain, weakness, and fatigue. The reduction in symptoms was persistent even after the discontinuation of vitamin K2-MK7. Vitamin K2-MK7 was also well tolerated by all patients. Thus, it proves that vitamin K2-MK7 offers a confirming therapeutic effect in PN due to VBD or T2DM. Further, a multicentric placebo-controlled randomized double-blind trial can clearly establish the effect of vitamin K2-MK7, also in case of residual neuropathy.⁸⁵

Depression and anxiety

Late life depression significantly decreases the quality of life and it is often accompanied by significant medical burden and disability. Although major depression is a very common disease, the pathogenesis is still presently unknown. Depression in the elderly is complex and it may occur for various reasons and under different conditions. It has already been pointed out that diet and nutrition, particularly vitamins, may influence this medical condition. One cross-sectional study aimed to investigate the association between dietary vitamin K and depressive symptoms in a large cohort of older adults from North America. The authors reported that depressive symptoms were significantly lower in people with higher dietary vitamin K intake. People in the highest quartile of vitamin K intake (i.e., >232 ug/day) had significantly lower odds of having depressive symptoms at baseline and each per 100 ug/day increment was associated with a significant lower odds of this condition of 12%. These findings remained unaltered after adjustment for potential confounders. A role for vitamin K in the prevention and treatment of depressed mood may be suggested based on this research results. However, future longitudinal and intervention studies are still needed in this domain.⁸⁶

Moreover, in an animal study researchers examined the effects of vitamin K2 on the behavior of rats with metabolic syndrome and looked for relationships with the effects on blood sugar. This study demonstrated that vitamin K2 prevented the development of anxiety and depression, but did not improve the memory deficit caused by the dietary manipulation in an experimental model of metabolic syndrome. It might be that the anxiolytic effect of vitamin K2 is at least partly due to its effects on blood glucose, while the antidepressant effect is glucose-independent.⁸⁷

Eye health

Vitamin K2 found in microgram concentrations in the diet has a profound effect as a calcium manager and can also be helpful in managing ocular microvascular diseases such as glaucoma and age-related macular degeneration (AMD). Matrix Gla Protein (MGP) is a vitamin K-dependent protein, described primarily in the vascular system, and inactive form of MGP colocalizes with sites of arterial calcification and atherosclerotic lesions. The MGP gene has been found to be among the 10 most highly expressed genes in the human trabecular meshwork (TM), and its expression is affected by conditions associated with glaucoma. Glaucoma, an optic neuropathy characterized by the death of the retinal ganglion cells, is the second most frequent cause of irreversible blindness worldwide. The prevalence of glaucoma, particularly primary open-angle glaucoma (POAG), increases with age, affecting approximately 1% of people at age 40 and reaching approximately 4% of people by the age of 80. The outflow pathway tissue, composed of the TM and Schlemm's canal, is responsible for the maintenance of physiological pressure inside the eye. This tissue performs its function by regulating the resistance to aqueous humor outflow. Failing to regulate aqueous humor resistance properly can result in an elevation of intraocular pressure (IOP), the major risk factor for the development of glaucoma. MGP is abundantly expressed in the eye, where it takes part in preserving the structural integrity of the TM, the sclera and the retinal ganglion cells. The human TM may undergo a calcification process with age. Inhibition of the calcification mechanism mediated by MGP could be used to regulate resistance and elevated IOP.⁸⁸

Researchers from the University of Leuven studied a randomly recruited Flemish population and found that low vitamin K2 status represented by raised plasma level of dp-ucMGP is a long-term predictor of smaller retinal arteriolar diameter in the general population. Recent observations highlight the possibility that vitamin K2 supplementation might promote ocular

health, therefore this fat-soluble nutrient can no longer be ignored by the eyecare community.⁸⁹

Schnyder corneal dystrophy (SCD) is a rare autosomal dominant disorder characterized by bilateral abnormal accumulation of cholesterol and other lipid deposits in the corneal stroma leading to progressive vision loss. So far no pharmacological treatment is available to inhibit its development or progression. It is caused by UBIAD1 pathogenic variants. In vitro and animal in vivo studies on SCD pathogenesis revealed a deficiency in vitamin K synthesis due to impaired structure and enzymatic function of the UBIAD1 protein. In a recent study, the authors aimed to assess for the first time the corneal and vascular vitamin K status in SCD patients and resolve the presence of different MGP forms in human corneal tissue. MGP was reported to prevent calcification by adsorbing to growing HA crystals in cardiovascular system, and one may assume that a similar mechanism could occur in the cornea. No calcium deposits have been reported in corneas of SCD patients. Substantial amounts of MGP were identified in human cornea and most of it in its fully matured and active form. The level of mature MGP did not differ between SCD and control corneas. In primary keratocytes from SCD patients, a highly increased MGP expression and presence of immature MGP forms were detected. Significantly elevated plasma concentration of inactive MGP was found in SCD patients. The authors arrived at a conclusion that high amount of MGP and the predominance of mature MGP forms in human cornea indicate that vitamin K metabolism is active in the visual system. Availability of MGP seems of vital importance for a healthy cornea and may be related to protection against corneal calcification. Systemic MGP findings reveal a poor vascular vitamin K status in SCD patients and indicate that SCD may lead to cardiovascular consequences. The link between low vitamin K status, high dp-ucMGP and increased risk of CVD is widely recognized, and lately it was also associated with smaller retinal arteriolar diameter. No longitudinal studies of cardiovascular health were performed in SCD patients. Only two studies reported the prevalence of CVD and arterial

hypertension (major CVD risk factor) in SCD patients. In the study presented here, measurements in SCD patients revealed elevated plasma dp-ucMGP levels indicating a poor systemic vitamin K status and a higher risk of developing CVD. These data emphasize that SCD not only affects the cornea but may also have important systemic consequences, and suggest that SCD patients may require counselling on the elevated risk of CVD and may benefit from vitamin K supplementation.⁹⁰

Dental health

Dental caries has traditionally been viewed as a tooth de-mineralizing process limited to the oral cavity. New understandings of oral/systemic links propose that dental caries is an uncontrolled inflammatory response controlled by the brain and moderated through the hypothalamus/parotid axis of the endocrine system. The role of reactive oxygen species in the hypothalamus is a signaling factor in establishing tooth vulnerability or resistance. Vitamin K2 appears to have a significant antioxidant role in the brain as well as a key nutrient in the management of calcium in the body including bones and cardiovascular tissues. Vitamin K2 works in concert with calcium and vitamin D. This systemic paradigm of dental caries places nutrition on the leading edge of prevention because it is focused on the cause of the disease rather than traditional preventive efforts focused on the symptoms. Vitamin K2 also appears to have a potential salivary buffering role in the exocrine portion of the parotid gland as well as the other salivary glands.⁹¹

Moreover, a 2019 paper demonstrated new associations between the microbiome and dental caries at the strain and functional levels. The study revealed potentially relevant connection between vitamin K2 and caries.⁹² Additional research reports document that vitamin K2 can assist in significantly reducing dental caries by sustaining and improving the salivary buffering capacity via its impact on the secretion/flow of calcium and inorganic phosphates.⁹³

Vitamin K2 and aging

Aging is a convoluted biological phenomenon, which is manifested as an age-related functional decline caused by a progressive dysregulation of certain cellular and organismal processes. Many chronic diseases including cardiovascular diseases, chronic obstructive pulmonary disease, chronic kidney disease, diabetes, osteoarthritis, osteoporosis, sarcopenia, stroke, neurodegenerative diseases (including Parkinson's, Alzheimer's and Huntington's diseases), and many forms of cancer are associated with human aging.⁹⁴

Chronic kidney disease (CKD) is a clinical model of premature ageing characterized by cardiovascular disease, persistent uraemic inflammation, osteoporosis muscle wasting and frailty. The accelerated early vascular ageing (EVA) process mediated by medial vascular calcification (VC) is a hallmark of senescence as well as a strong predictor of cardiovascular morbidity and mortality in the CKD population.

Recently published review by Dai et al. showed that vitamin K plays an important role in accelerated early vascular aging in kidney patients. It has been shown before that the beneficial task of vitamin K in health has far exceeded its function as a γ -glutamyl carboxylase (GGCX)-dependent hepatic clotting factor in coagulation. The acts of conversion and activation of extrahepatic vitamin K-dependent proteins play an important role in multiple physiopathological processes of energy metabolism, inflammation, bone mineralization and ectopic VC. More importantly, emerging evidence

has revealed the multifunctional capacity of vitamin K with its antioxidant and anti-inflammatory effects. It is not surprising that vitamin K might be beneficial to cardiovascular health and ageing. Indeed, the clinical role of vitamin K in several age-related chronic diseases has been well illustrated so far. Although the underlying mechanism behind the association between vitamin K and an ageing phenotype has not been clearly illustrated, such epidemiological evidence at least highlights the beneficial effect of vitamin K over and above its role as a nutritional remedy or supplement.⁹⁵

It is tempting to speculate that vitamin K exerts significant influence in cellular senescence given its antioxidant and anti-inflammatory results, even though no direct effect of vitamin K in cellular aging processes has been identified yet. Apart from being an antioxidant and immune-modulator, it has been shown that vitamin K2 acts as a mitochondrial carrier, where mitochondrial dysfunction was rescued by vitamin K2 addition. Growing evidence suggests vitamin K is a crucial player in counteracting oxidative stress, DNA damage, cellular senescence and inflammaging – a chronic low-grade inflammation that develops with advanced age, whereby vitamin K supplementation may provide novel therapeutic strategy targeting EVA in patients with CKD. More solid perspectives and results are to be expected from ongoing randomized clinical trials (e.g. VitaK-CAC trial, the Aortic Valve DECalcification trial) evaluating the effect of vitamin K2 in VC progression among CKD population, and from future studies testing the long-term protective effects of vitamin K in EVA and senescence-related endpoints.

CONCLUSION

It is strange that a vitamin with such a substantial – and growing – body of evidence is considered “newly recognized,” but that is indeed the case. The confirmation that vitamin K2 positively impacts bone and cardiovascular health has elucidated the mechanism, giving way to more detailed examinations of how this vital nutrient feeds into other health areas. With more study comes further understanding and an undeniable argument for establishing a K2-specific RDI, which is the first step in helping the global population correct a deficiency that can allow them to age in a healthy way.

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