Research Development Timeline

1929

Henrik Dam discovered the role of a lipid-soluble substance needed for normal coagulation -later named vitamin K.

1975-1985

Esmon et al. (1975) published the mechanism of action of vitamin K.

Price et al. (1976) discovered the gamma-carboxylated protein osteocalcin from bone.

Price et al. (1983) published the isolation and characteri-zation of the vitamin K-dependent Matrix Gla-protein.

Hart et al. (1985) published the first description of modern vitamin K analysis and that osteoporotic patients with fractures have low serum vitamin K1 concen- trations.

2001-2003

Kaneki et al. (2001) suggested that higher MK-7 levels from natto consump-tion may contribute to the relatively lower fracture riskin Japanese women.

Schurgers et al. (2002) published that differences in fat solubility between various K vitamins may result in substantial differences in their plasma transport and deliveries to target tissues.

Braam et al. (2003) published that a food supplement containing minerals, vitamin D, and vitamin K1 may contribute to reducing post-menopausal bone loss.

2004

Geleijnse et al. published that dietary intake of vitamin K2 – but not vitamin K1 – is associated with a reduced risk of coronary heart disease (The Rotterdam Study).

Schurgers et al. concluded that food supplements providing 100 µg/day of vitamin K1 did not significantly interfere with oral anticoagu-lant therapy.

2007

Schurgers et al. published that natural natto-derived MK-7 has a higher absorption and efficacy compared to synthetic vitamin K1 in healthy adults.

Schurgers et al. used rats in demonstrating that arterial calcification and the resulting decreased arterial distensibil ity are reversible through high intake of vitamin K.

Knapen et al. published that vitamin K2 supplementation helps maintaining bone strength in post-menopausal women.

Cranenburg et al. (review article) discussed potential new application areas of vitamin K for healthy individuals to prevent bone and vascular disease, as well as for patients on oral anticoagulant treatment to offer them protection against coumarin-induced side effects.

2008

Tsugawa et al. found that Japanese women with vitamin K1 insufficiency in bone have increased suscep-tibility for vertebral fracture independently from BMD.

Nimptsch et al. published a large population study suggesting an inverse association between the intake of vitamin K2 – but not that of vitamin K1 -and prostate cancer.

Cranenburg et al. concluded that circulating ucMGP may be used as a biomarker to identify those at risk for developing cardiovascular calcification.

van Summeren et showed that a better vitamin K status was associated with more pronounced increase in bone mass in healthy children.

2009

Beulens et al. found that high dietary vitamin K2 intake – but probably not vitamin K1 – was associated with reduced coronary calcification in post-menopausal women. Adequate vitamin K2 intake could therefore be important for prevention of cardiovascular disease.

Gast et al. found that a high intake of menaquinones, especially MK-7, MK-8, and MK-9 reduced the incidence of coronary heart disease.

Koos et al. suggested that oral anticoagulation may be associated with decreased circulating ucMGP levels in patients with aortic valve disease.

van Summeren et al. demonstrated that modest MK-7 supplementation increases circulating concentrations of MK-7 and increases osteocalcin carboxylation in healthy children.

2010

Førli et al. demonstrated positive correlation between vitamin K2 supplementation and bone mass in patients recovering from lung and heart transplantations.

Schurgers et al. suggested that the circulating inactive form of Matrix Gla-protein is a surrogate marker for vascular calcification in chronic kidney disease.

Nimptsch et al. indicated that dietary intake of menaqui-nones is associated with a reduced risk of incident and fatal cancer.

Rees et al. found that vitamin K2 intake is associated with fewer CHD events.

2011

Moschonis G. et al. suggested site-specific effect of combining nutrition and lifestyle counseling with consumption of fortified dairy products enriched with calcium, vitamin D, and K on bone mass.

Fujita Y. et al. showed that habitual intake of natto was associated with a beneficial effect on bone health in elderly men, and this association is primarily due to vitamin K content of natto.

Pucaj K et al. performed safety and toxicological evaluation of synthetic vitamin K2 (menaquinone-7). All generated data, including clinical observations, ophthalmology, clinical pathology, gross necropsy, and histopathology, revealed no compound-related toxicity in rats.

2012

Westenfeld R et al. The study showed evidence of a functional vitamin K deficiency in hemodialysis patients, which can be treated effectively by vitamin K2 (MK-7) supplementation.

Theuwissen E et al. Vitamin K2 in is safe with respect to the haemostatic system, and should be beneficial for bone and cardiovascular system health.

Kanellakis S et al. evaluated the changes in parameters of bone metabolism in postmenaopausal women following a 12-month intervention period using dairy products enrichted with calcium, vitamin D and Vitamin K1 o K2 (MK7). The study revealed more favorable changes in bone metabolism and bone mass indices for Vitamin K-supplemented groups.

2013

Knapen et al. showed for the first time clinically statistically significant protection of the vertebrae and the hip (femoral neck) against osteoporosis. After three years of supplementation of 180mcg Vitamin K2/MK-7 (MenaQ7) daily, improvements in both bone-mineral content and bone-mineral density were statistically significant in the MenaQ7 group. Moreover bone strength was statistically improved, demonstrating therapeutic benefits for the MK-7 group as compared to the placebo group. This data indicates that MK-7 supplementa-tion helps postmeno-pausal women to prevent bone loss.

Theuwissen E et al. The study classified healthy children and adults above 40 years as groups with prominent vitamin K deficiency.

Rogier Caluwé et al. Menaquinone supplementation may be a novel approach to prevent vascular calcifications in chronic haemodialysis patients.

International Science and Health Foundation
www.ishf.eu office@ishf.eu

INTERNATIONAL SCIENCE AND HEALTH FOUNDATION

Research Development Timeline

MenaQ7® Natural Vitamin K2

1936
Dam and Schønheyder described the occurrence and chemical nature of vitamin K.

1936
Dam et al. published the mode of action of vitamin K.

1936
Schønheyder described the quantitative determination of vitamin K.

1936
Almquist published the purification of the anti-hemorrhagic vitamin.

1939
Binkley et al. published the isolation of vitamin K1.

1939
McKee et al. published the isolation of both vitamin K1 and K2.

1943
Dam and Doisy received the Nobel Price in medicine for the discovery of vitamin K.

1975
Esmon et al. published the mechanism of action of vitamin K and identified the vitamin K cycle as vital for the activity of carboxylase enzyme.

1976
Price et al. published the discovery of the γ-carboxylated protein from bone.

1983
Price et al. published the isolation and characterization of the vitamin K-dependent Matrix Gla-protein.

1985
Hart et al. published the first description of modern vitamin K analysis and that osteoporotic patients with fractures have low serum vitamin K1 concentrations.

1987
Price et al. published that the skeleton is sensitive to vitamin K deficiency due to abnormalities in osteocalcin function.

1989
Vermeer et al. published that vitamin K deficiency influences the ratio of serum uncarboxylated to carboxylated osteocalcin.

1991
Hodges et al. published that women with osteoporotic fractures are low in vitamin K2 levels.

1993
Szulc et al. published that an increase in uncarboxylated osteocalcin is predictive for hip fractures.

1994
Shanahan et al. published that calcification-regulating proteins are found in atherosclerotic plaques in humans.

1995
Douglas et al. published that vitamin K reduces the level of uncarboxylated osteocalcin.

1995
Hara et al. published that the inhibitory effect of vitamin K2 on bone resorption may be due to its side-chain.

1996
Vermeer et al. published that vitamin K improves the bone turnover profile.

1997
Sokoll et al. published that the US dietary vitamin K intake is not sufficient to fully carboxylate osteocalcin.

1997
Luo et al. published that MGP knock-out mice experience massive and fatal arterial calcification.

1998
Knapen et al. published the correlation of serum osteocalcin with BMD in women during the first 10 years after menopause.

1999
Feskanich et al. published that low dietary vitamin K1 correlates with hip fractures.

2000
Schurgers et al. published measurements of vitamin K1 and K2 in various food products from Dutch supermarkets.

2000
Braam et al. published an assay for Matrix Gla-protein in serum for applications in the cardiovascular field.

2001
Schurgers et al. published that inhibition of vitamin K-dependent carboxylation of MGP promotes vascular calcification.

2001
Kaneki et al. published that the only significant factor that correlated with lower hip fracture risk in a large population-based study was vitamin K2 (MK-7).

2002
Schurgers et al published that the various forms of vitamin K have differential lipoprotein transport pathways in humans.

2002
Katsuyama et al. published that the intake of natto with high amounts of MK-7 is associated with improved BMD.

2003
Booth et al. published that the recommended adequate intake levels of vitamin K1 in women do not support maximal osteocalcin -carboxylation in older women.

2003
Braam et al. published that vitamin K1 supplementation retards bone loss in post-menopausal women between 50 and 60 years of age.

2003
Vermeer et al. published that the intake of vitamin K2 is a simple way to improve bone and vascular health.

2004
Braam et al. published the beneficial effects of vitamin K on elastic properties of the vessel walls in post-menopausal women.

2004
Geleijnse et al. published that high intake of vitamin K2 – but not K1 – reduces the risk for cardiovascular diseases with 50% (The Rotterdam Study).

2004
Schurgers et al. published that food supplements providing 100 µg/day of vitamin K1 do not significantly interfere with oral anticoagulant therapy.

2005
Schurgers et al. found novel conformation-specific antibodies against the vascular protein MGP.

2005
Villines et al. published that dietary intake of vitamin K1 appeared to be unrelated to premature coronary calcification in a screening population.

2006
Tsugawa et al. published that MK-7 is the vitamin K form found in serum of women with reduced risk of bone fractures.

2006
Ikeda et al. published that intake of MK-7 is associated with reduced bone loss in post-menopausal women in a population-based study (JPOS study).

2006
Ketteler et al. reviewed calcification and cardio vascular health especially in relation to chronic kidney disease patients.

2007
Schurgers et al. used rats in demonstrating that that arterial calcification and the resulting decreased arterial distensibility are reversible by high intake of vitamin K.

2007
Cranenburg et al. published an up-to-date review on the function of vitamin K.

2007
Knapen et al. published that vitamin K2 supplementation improves hip bone geometry and bone strength indices in post-menopausal women.

2007
Schurgers et al. published that natural natto-derived MK-7 has a higher absorption and efficacy compared to synthetic vitamin K1 in humans.

2008
Cranenburg et al. published that circulating inactive MGP is a biomarker for cardiovascular calcification in patients with cardiovascular diseases.

2008
Tsugawa et al. found that low plasma vitamin K in healthy women resulted in increased susceptibility for vertebral fractures independently from BMD.

2008
Nimptsch et al. published a large population-based study showing that consuming dairy products containing higher menaquinones, like MK-7 reduces the risk of prostate cancer substantially. No such reduction was observed with vitamin K1-containing food.

2008
Yaegashi et al. published an association of hip fracture incidence and intake of calcium, magnesium, vitamin D and vitamin K.

2008
Krueger et al. published the importance of vitamin K in dialysis patients. The possibility of vitamin K as a therapeutic vitamin is discussed as well.

2008
van Summeren et al. showed that a better vitamin K status was associated with more pronounced increase in bone mass in healthy children.

2009
Beulens et al. found among 564 post-menopausal women that intake of vitamin K2 – but not vitamin K1 – was associated with reduced coronary calcification, and that adequate vitamin K2 intake could be important for prevention of cardiovascular disease.

2009
van Summeren et al. demonstrated that modest MK-7 supplementation increases circulating concentrations of MK-7 and increases osteocalcin carboxylation in healthy children.

2009
Gast et al. found that a high menaquinone intake reduces the incidence of coronary heart disease.

2009
Koos et al. suggested a relation of circulation Matrix Gla-protein and anticoagulation status in patients with aortic valve calcification.

2010
Førli et al. demonstrated a positive correlation between vitamin K2 and an improvement in bone health in patients recovering from lung and heart transplantations.

2010
Schurgers et al. suggested that the circulating inactive form of Matrix Gla-protein is a surrogate marker for vascular calcification in chronic kidney disease.

2010
Nimptsch et al. indicated that a daily intake of vitamin K2 significantly reduces the risk of cancer or cancer mortality.

2010
Rees et al. found that vitamin K2 intake is associated with fewer CHD events.

2011
Moschonis G. et al. suggested site-specific effect of combining nutrition and lifestyle counseling with consumption of fortified dairy products enriched with calcium, vitamin D, and K on bone mass.

2011
Fujita Y. et al. showed that habitual intake of natto was associated with a beneficial effect on bone health in elderly men, and this association is primarily due to vitamin K content of natto.

2011
Pucaj K et al. performed safety and toxicological evaluation of synthetic vitamin K2 (menaquinone-7). All generated data, including clinical observations, ophthalmology, clinical pathology, gross necropsy, and histopathology, revealed no compound-related toxicity in rats.

2012
Westenfeld R et al. confirmed that most hemodialysis patients have a functional vitamin K deficiency. More importantly, they found that inactive MGP levels can be decreased markedly by daily vitamin K(2) supplementation.

2012
Theuwissen E et al. found that low-dose menaquinone-7 supplementation improved extra-hepatic vitamin K status, but had no effect on thrombin generation in healthy subjects.

2012
Kanellakis S et al.evaluated the changes in parameters of bone metabolism in postmenaopausal women following a 12-month intervention period using dairy products enrichted with calcium, vitamin D and Vitamin K1 o K2 (MK7). The study revealed more favorable changes in bone metabolism and bone mass indices for Vitamin K-supplemented groups.

2013
Knapen et al. showed for the first time clinically statistically significant protection of the vertebrae and the hip (femoral neck) against osteoporosis. After three years of supplementation of 180mcg Vitamin K2/MK-7 (MenaQ7) daily, improvements in both bone-mineral content and bone-mineral density were statistically significant in the MenaQ7 group. Moreover bone strength was statistically improved, demonstrating therapeutic benefits for the MK-7 group as compared to the placebo group.

2013
Theuwissen E et al. The study established the vitamin K status across age groups based on circulating levels of ucOC and dp-ucMGP, i.e. markers for the vitamin K status of bone and the vasculature, respectively. Accordingly, the study classified healthy children and adults above 40 years as groups with prominent vitamin K deficiency and thus appropriate groups for vitamin K supplementation.

2013
Rogier Caluwé et al. Chronic haemodialysis patients have high levels of inactive MGP, possibly related to a low dietary vitamin K intake. Pharmacological doses of MK-7 dose-dependently reduce dp-uc-MGP.

International Science and Health Foundation
www.ishf.eu office@ishf.eu

INTERNATIONAL SCIENCE AND HEALTH FOUNDATION