

Vitamin K2 in Bone Metabolism and Osteoporosis

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Abstract

This article covers *in vitro*, *in vivo*, and human data on the positive effect of vitamin K2 on osteoporosis. Data is available on vitamin K2 for osteoporosis caused by a number of conditions, including postmenopausal osteoporosis, Parkinson's disease, biliary cirrhosis, stroke, and drug-induced osteoporosis. The activity of vitamin K2 involves both an increase in the bone-building process and a separate decrease in the bone-loss process. Vitamin K2 exerts a more powerful influence on bone than vitamin K1, and should be considered for prevention or treatment in those conditions known to contribute to osteoporosis. (*Altern Med Rev* 2005;10(1):24-35)

Introduction

Vitamin K2 exerts a powerful influence on bone building, especially in osteoporosis, and has been cited as one of the most frequently prescribed treatments for osteoporosis in Japan.¹

The ability to better facilitate bone growth, especially in osteoporosis and fracture, has long been of interest. Repair of non-pathogenic fracture is a normal process, generally engaged in without difficulty. Osteoporosis, a pathogenic process, is increasingly occurring in developed countries, and pathologic fracture due to osteoporosis in the elderly can be a life-shortening event. A five-year prospective study on fracture and mortality rate in men and women age 60 and older found all major fractures were associated with increased mortality, especially in men.²

Osteoporosis, a multifactorial pathology, has been reviewed extensively in recent years.³⁻⁷ A review by Gaby of nutritional and hormonal management of osteoporosis is an excellent and well-referenced source for further edification.⁸

Evaluation of the etiology of osteoporosis in a particular individual can involve examination of hormonal aspects, exercise patterns, nutrient intake, digestion, and nutrient absorption. This article addresses the aspects of vitamin K2 in bone formation. The subject of nutrient absorption is pertinent because the vitamin Ks are lipid soluble; therefore, fat malabsorption may create a deficiency. Recent reviews revealing celiac disease is common (1 in 266)⁹⁻¹¹ underscore its involvement in the etiology of osteoporosis due to malabsorption of necessary bone factors, including vitamin K.¹² Documentation is plentiful illustrating the importance of vitamin K in bone maintenance. Its importance is easily evidenced by the osteoporosis and fractures resulting from long-term use of the anticoagulant drug warfarin, which inhibits the bone-building effect of vitamin K.¹³⁻¹⁸

The Vitamin Ks

Vitamin K is a family of structurally similar, fat-soluble, 2-methyl-1,4-naphthoquinones, including phyloquinone (K1), menaquinones (K2), and menadione (K3). The structural difference is in the substituent R group (Figure 1).

The best-known member of the vitamin K family is phyloquinone (K1), also known as phytonadione because of its relationship with photosynthesis. Phyloquinone is found in higher plants and algae, with the highest concentrations found in green leafy vegetables.¹⁹

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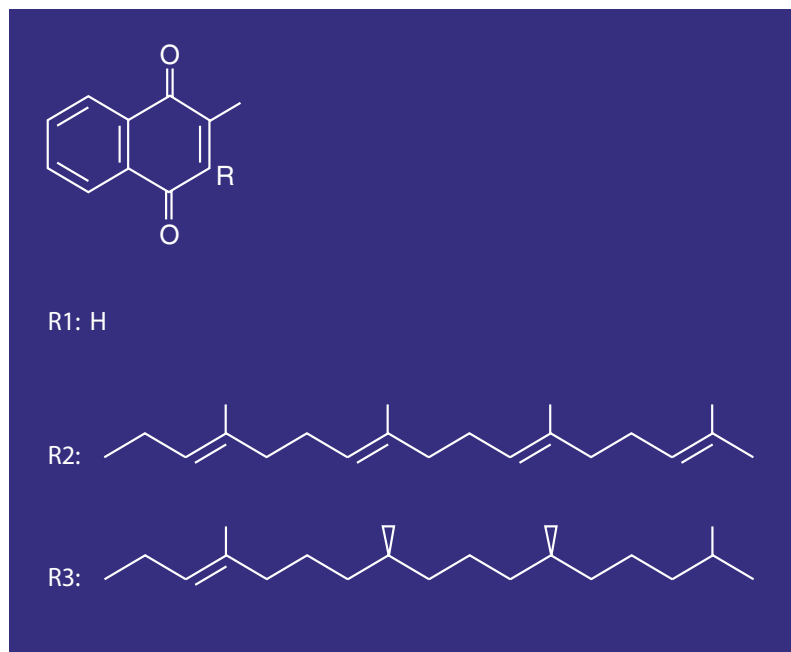
Menaquinones (K2) also occur naturally, but are produced by an array of bacteria, not by higher plants. Recent studies have determined menaquinones can be produced in limited quantities by animals, and probably by humans, from the conversion of other forms of vitamin K.^{20,21} The most common form of vitamin K2 in animals is menaquinone 4 (menatetrenone; MK-4), produced by the processing of exogenous and bacterial naphthoquinones.²² Vitamins K1 and K2 differ only in the substituent R group (Figure 1). Vitamin K1 possesses a phytyl R group (partially saturated polyisoprenoid group), while K2 possesses a repeating, unsaturated trans-polyisoprenyl group. Vitamin K2 as referred to in this article means MK-4 as pictured in Figure 1. Further discussion of vitamin K structures and nomenclature is contained in a previous article.²³

Menadione (K3) is not considered a natural vitamin K, but a synthetic analogue that acts as a provitamin. It possesses a much simpler structure, with no aliphatic R group chain (Figure 1). Although menadione is considered a synthetic analogue, Billeter et al found that phylo-quinone can be cleaved by bacteria in the intestine to form a minor amount of menadione.^{20,24} After absorption, menadione is thought to become alkylated into biologically active isoprenylated menaquinones. However, vitamin K3 cannot exert all the functions of natural vitamin K because of limited transformation into the fat-soluble vitamin K forms.^{25,26}

Mechanism of Action: Gamma-carboxylation

Vitamin K is a cofactor in a number of biochemical pathways. Those most commonly associated with vitamin K are the vitamin K-dependent carboxylation reactions. In these reactions the reduced form of vitamin K (hydroquinone) de-protonates glutamate via the gamma-glutamylcarboxylase enzyme. The epoxide formed is recycled via vitamin K epoxide reductase and quinone reductase, and glutamic acid-containing proteins, such as coagulation factors II (prothrombin), VII, IX, and X, protein C, and

Figure 1. Various Forms of Vitamin K: R1, Menadione (K3); R2, Menaquinone 4 (MK-4, K2); R3, Phylloquinone (K1)



protein S, are carboxylated. Compared to the other vitamin K analogues, vitamin K2 has the most potent gamma-carboxylation activity.²⁷

Vitamin K functions in the posttranslational modification of a number of vitamin-K dependent proteins such as osteocalcin, a bone protein containing gamma-carboxyglutamic acid, discovered in 1975.²⁸ Gamma-carboxylation of the glutamic acid in osteocalcin is vitamin K dependent and involves the conversion of glutamic acid residues (Glu) to gamma-carboxyglutamic acid residues (Gla). A number of calcium-binding proteins, such as calbindin and osteocalcin, contain gamma-carboxyglutamate. These proteins are involved with calcium uptake and bone mineralization. Osteocalcin is synthesized only in osteoblasts.²⁹ Because osteocalcin that is not carboxylated cannot bind to hydroxyapatite, serum levels of osteocalcin are a good biochemical marker of the metabolic turnover of bone.³⁰

Unlike blood coagulation proteins, which need much lower levels of vitamin K for complete gamma-carboxylation, higher levels of vitamin K are essential for the total gamma-carboxylation of osteocalcin.³¹ Dietary intake of vitamin K in 219 healthy adults eating an average American diet was found to

be insufficient for gamma-carboxylation of osteocalcin, while maintaining normal prothrombin time.³² An elevated level of serum glutamic acid- γ -carboxylated osteocalcin is indicative of vitamin K deficiency and is associated with reduced hip bone mineral density (BMD) and increased fracture risk in healthy elderly women.³³ Rats with hypoprothrombinemia were given menadione (K3) or K2 orally (0.1 mg/kg) and the absorption and concentration in the liver were compared. The most potent form was found to be vitamin K2.³⁴

Safety of Vitamin K2 with Respect to Hypercoagulation in Humans

From a large number of clinical trials using dosages in excess of 40 mg/day, there were no reports of side effects associated with any type of hypercoagulable state.^{1,27,35,36} Both animal and clinical studies support the conclusion that vitamin K2 has no abnormal hemostatic activity. In one study, vitamin K2 given to rats at a dose of 250 mg/kg body weight per day for 10 days resulted in no appreciable change in blood coagulation characteristics or platelet aggregation.³⁷

In a clinical study, 29 elderly, osteoporotic patients were given vitamin K2 (15 mg three times daily, 30 minutes post meals) for 12 weeks and monitored for any change in hemostatic balance. After 12 weeks of administration, all hemostatic markers remained within normal range.¹ In another study examining the effect of vitamins K2 (45 mg/day) and D3 (1 mcg/day) on BMD in postmenopausal women, hemostatic measures were also examined. Increases in both coagulation and fibrinolysis were noted, but remained within normal range and in balance, with no adverse reactions observed.²⁷

It should be noted that the anticoagulant effect of warfarin, functioning by its interference with the clotting effect of vitamin K, can be offset with as little as 1 mg of vitamin K.³⁸ Therefore, use of vitamin K is contraindicated in people on anticoagulant therapy.

In Vitro Studies of Vitamin K2: Osteoblastic and Osteoclastic Modulation

Various forms of vitamin K have been transformed into K2 in the femur. Rats fed MK-7 (containing three more isoprene units in the MK-4 side-chain) were found to transform this longer chain analogue into MK-4 in the femur. Vitamin K2 has been shown to be the most important inducer of bone mineralization in human osteoblasts.³⁹ Vitamin K2, in combination with 1- α -25-dihydroxyvitamin D3 has also been shown to increase osteocalcin production.⁴⁰ *In vitro* studies have shown that application of K2 results in gamma-carboxylation of 1- α -25-dihydroxyvitamin D3-induced osteocalcin, which in turn is able to deposit gamma-carboxyglutamic acid-containing osteocalcin to the extracellular matrix on human osteoblasts.⁴¹

In vitro studies using assays from various species demonstrate vitamin K2 inhibits osteoclastogenesis of bone.⁴² Akiyama et al found that a dose-dependent inhibition of mouse 1,25-dihydroxyvitamin D3 stimulated multinucleate osteoclast-like cell formation. The mechanism of osteoclastic inhibition by vitamin K2 is not due to cell toxicity and did not affect cell proliferation.^{29,43} The osteoclastic inhibitory action by K2 is unique to its structure. Vitamin K1 does not affect bone resorption and multinucleate osteoclast-like cell formation.²⁹ *In vitro* studies with mouse cell cultures found a dose-dependent inhibition by K2 of prostaglandin E2 (PGE2) synthesis, which in turn was shown to inhibit bone resorption.⁴³ The inhibition of 1,25-dihydroxyvitamin D3-induced PGE2 production by K2 was found dependent on the inhibition of cyclooxygenase-2 expression.⁴⁴ Further research with human bone marrow cell culture found evidence that the inhibition of osteoclast formation was not due to an increase in cell death, but rather to a decrease in the production of the receptor activator of nuclear factor kappaB ligand (RANKL) and associated osteoclast differentiation factor, which are critical to osteoclastogenesis.⁴⁵ The prevention of bone loss due to the inhibition of bone resorption found for *in vitro* studies has been verified by *in vivo* studies with ovariectomized rats fed vitamin K2 (50 mg/kg) for two weeks.⁴⁶

Animal Studies with Vitamin K2

Rat Model of Disuse Osteopenia

Studies of rats fed a vitamin K-deficient diet determined that larger amounts of vitamin K are needed for femur bone metabolism compared to the liver.⁴⁷ A number of studies have examined orchidectomized or sciatic-neurectomized rats. The sciatic-neurectomized rat is used as a model of immobilization osteopenia in humans and is used to study prevention of disuse osteopenia. The procedure reduces the normal maturation-related increase in cortical and cancellous bone, inducing cortical and cancellous osteopenia. Orchidectomy results in a testosterone deficiency, which in turn reduces periosteal bone formation, while also increasing cancellous bone turnover. The ultimate result is an inhibition of cortical and cancellous bone gain without net bone loss.⁴⁸ Cancellous bone loss is attributable to decreased bone formation and increased bone resorption; whereas, cortical bone loss results from decreased periosteal bone formation and increased endocortical bone resorption.

In neurectomized rats, oral administration of vitamin K2 (10 or 30 mg/kg) for seven to 42 days increased bone mass and maintained spongia microstructure in the immobilized tibiae. In the K2 30-mg/kg group, trabecular number and thickness increased and osteoblast-induced mineralization was enhanced. By day 42, the osteoclast surface per bone perimeter, the number of osteoclasts per bone perimeter, and the mineral apposition rate (MAR) were reduced in the controls, suggesting bone turnover was suppressed. Low-dose vitamin K2 increased MAR and bone formation rate, without increasing bone resorption. In this study, oral administration of vitamin K2 was found to reduce loss of trabecular bone, prevent osteoblast dysfunction, increase bone formation rate, and preserve trabecular microstructure in an immobilization model.⁴⁹

Vitamin K2 (30 mg/kg) administered twice weekly for 10 weeks to orchidectomized rats resulted in suppressed endocortical bone resorption and trabecular bone turnover. Vitamin K2 in sciatic-neurectomized and orchidectomized rats suppressed bone resorption and stimulated bone formation. The evidence indicates K2 has potential to enhance bone formation and inhibit bone resorption in orchidectomized or neurectomized rats.⁴⁸

Rat Model of Postmenopausal Osteoporosis

Estrogen deficiency results in increased bone turnover leading to an increase in osteoclasts and trabecular bone loss. Postmenopausal osteoporosis, characterized by increased fracture risk, can be accurately modeled using ovariectomized animals. Because ovariectomy in rats results in significant decrease of BMD and cancellous bone remodeling, it has been used as a model for estrogen-deficient, postmenopausal bone loss.

The administration of vitamin K2 has been shown to prevent bone loss induced by ovariectomy in rats.^{46,50-52} Vitamin K2 at 50 mg/kg inhibited the expected decreases in trabecular number and BMD of the femur, and improved other bone parameters caused by ovariectomy in only a two-week period.⁴⁶ In contrast, Binkley et al found no benefit on bone turnover or distal femur BMD density in ovariectomized rats.⁵³ This study used an approximately equivalent dose of K2 (50 mg/kg) for three months. The authors suggest these disparate results might be explained by three factors. First, the slight differences in vitamin D3- (2.4 IU/g in previous studies versus 2.2 IU/g by Binkley et al) and calcium- (0.02-0.5% in previous studies versus 1% by Binkley et al) deficient diets are proposed as a causative factor, with the researchers speculating vitamin K may work best in calcium- and/or vitamin D-deprived rats. Second, the use of a different strain of rat might cause the discrepancy, although earlier positive studies used the same strain of rat as the negative study.⁵⁴ Third, the length of the study, Binkley's being one month compared to Akiyama's two-week study, might contribute to the disparity. However, earlier studies found effect after six months, which has been supported by later studies that have shown a minimum of six months for effectiveness at a dosage of 30 mg/kg.^{52,54} Despite the negative results of Binkley et al, recent studies support earlier work that clearly demonstrates vitamin K2 (30 mg/kg) for six months prevented bone loss and fragility of spine and femur in ovariectomized rats.⁵²

Ovariectomy is also a good model to demonstrate degeneration of the microarchitecture of bone associated with osteoporosis. Studies of the three-dimensional trabecular microarchitecture in ovariectomized and calcium-deficient rats fed vitamin K2 (30

mg/kg) for eight weeks demonstrated a significant preservation (approximately 55% that of sham) of trabecular bone volume, connectivity, and trabecular complexity.⁵¹ The protective effect of vitamin K2 on femoral strength and prevention of mechanical-strength decrease has also been supported by recent studies of ovariectomized rats.⁵² Ovariectomized rats given K2 (30 mg/kg) in combination with 1-25-dihydroxyvitamin D3 (0.3 mcg/kg three times weekly) orally for eight weeks demonstrated a significantly higher BMD, cortical thickness, and bone strength than rats given either vitamin alone.⁵⁵

Other Animal Studies of Vitamin K2 and Bone Preservation

Orchidectomized rats given vitamin K2 (30 mg/kg twice weekly, subcutaneously) for eight weeks exhibited a significant increase in cancellous bone volume but not cortical area compared to orchidectomized rats not given vitamin K. The researchers concluded vitamin K2 was more effective at preserving cancellous than cortical bone.⁵⁶ In aged male rats, a calcium-deficient diet resulted in a 12-percent decrease in BMD, which was reversed by the administration of vitamin K2 (30 mg/kg daily) within eight weeks.⁵⁷

Vitamin K2 in Bone Loss from Prednisolone

Bone loss is one of the side effects of corticosteroid use in clinical practice. The damage stems from a reduction in osteoblastic activity and bone formation.^{58,59} Application of prednisolone (3 or 30 mg/kg) and vitamin K2 (15 mg/kg) for eight weeks completely inhibited loss of BMD in trabecular bone, but the data appears to indicate no effect of vitamin K2 on loss of subcortical bone.⁶⁰ These results compare favorably with earlier work on rats given prednisolone (7 mg/kg/day) for nine weeks along with vitamin K2 (17 mg/kg/day). This combination significantly inhibited the decrease in length, dry weight, and bone density of femurs and tibiae, and completely inhibited decrease in urinary gamma-carboxyglutamic acid (Gla). Vitamin K2 (0.4, 10, and 50 mg/kg/day) significantly inhibited the reduction of calcium content in the femur.⁵⁰

Osteopenia Due to Over-expression of GCSF

Transgenic mice (over-expressing granulocyte colony-stimulating factor [GCSF], which causes osteopenia and increased osteoclast number with acceleration of bone resorption) were given vitamin K2 at a dose of 0.05 mg/100 g feed (control group) or 20.0 mg/100 g feed (experimental group) for 12 weeks. The decreased bone mineralization was partially offset in the high vitamin-K group. Microcomputed tomography demonstrated both cortical and trabecular bone increase.⁶¹

Bone Loss due to Phenytoin

The anti-epileptic drug phenytoin has been shown to induce bone loss,⁶² previously ascribed to phenytoin's interference with vitamin D metabolism. In rats, decreased BMD in both diaphysis and metaphysis of femoral bones was thought to be due to decreased levels of vitamin K2 from administration of phenytoin. Administration of vitamin K2 (30 mg/kg daily) prevented BMD reduction from phenytoin (20 mg/kg subcutaneously) over five weeks.⁶³

Human Studies with Vitamin K2

A number of human trials have found vitamin K2 effective in the treatment of osteoporosis (Table 1).^{1,27,35,36,64,65} In a randomized, open-label study, 241 osteoporotic women were given either 45 mg/day vitamin K2 and 150 mg elemental calcium (treatment group; n=120) or 150 mg elemental calcium (control group; n=121). After two years, vitamin K2 was shown to maintain lumbar BMD. Patients receiving K2 also experienced significantly lower fracture incidence (10% versus 30%, in the treatment and control groups, respectively).³⁵ In a double-blind, placebo-controlled, 24-week study, 80 patients with osteoporosis received either 90 mg/day vitamin K2 or placebo. Second metacarpal BMD was increased by 2.20 ± 2.48 percent compared to placebo, which decreased by 7.31 ± 3.65 percent.³⁶

Vitamin K2 in Osteoporosis of Postmenopausal Women

The incidence of osteoporosis is high in postmenopausal women. A number of trials have demonstrated vitamin K2 can induce significant reductions in bone loss in postmenopausal osteoporotic women. In a controlled clinical trial, 172 osteoporotic/osteopenic women (BMD < 0.98 g/cm²) were randomly assigned to receive vitamin K2 (45 mg/day), 1-alpha-hydroxycholecalciferol vitamin D3 (1 mcg/day), both, or placebo for 24 months. Combination therapy resulted in a significant 4.92 ± 7.89 percent increase in BMD, while vitamin K2 alone resulted in only a 0.135 ± 5.44 percent increase in BMD – higher, but not statistically significantly higher, than baseline values. However, at 18- and 24-month evaluations, BMD was significantly higher in the K2 group compared to the control group. In this study, a combination of vitamins K2 and D3 proved more protective than either supplement alone.²⁷

A longitudinal study of 17 postmenopausal women given vitamin K2 (45 mg/day) for one year found that K2 was able to suppress the decrease in spinal BMD, with a slight increase (0.23 ± 0.47%) compared to the control group of 19 postmenopausal women who experienced a decrease (-2.87 ± 0.51%) in BMD.⁶⁶

Ninety-two postmenopausal women, ages 55-81 years, were randomly assigned to one of four groups: vitamin K2 (45 mg/day), 1-alpha-hydroxyvitamin D3 (0.75 mcg/day), a combination of vitamins K and D (same dosage as above), or calcium lactate (2 g/day). The vitamin-K and -D groups both experienced significant increases in BMD compared to the calcium group over a two-year period, while combined treatment was synergistic, significantly increasing lumbar BMD by 1.35 percent.^{65,67}

Vitamin K2 and Bisphosphonates

A number of bisphosphonates (e.g., etidronate, alendronate, and risedronate) are used in the treatment of osteoporosis. These drugs, although generally considered more effective than vitamin K in increasing BMD, seem to work synergistically with it. A recent randomized, open-label study of 98 postmenopausal, osteoporotic women found significantly decreased fracture rates in 23 subjects (2/23) taking

vitamin K2 (45 mg/day) and 25 subjects (2/25) taking etidronate (200 mg/day for two weeks every three months), compared to 24 subjects (6/24) taking calcium lactate (2 g/day). The fracture rate was decreased further in 26 subjects (1/26) taking a combination of vitamin K2 and etidronate.⁶⁸

Alendronate (Fosamax®) encourages cortical bone growth by inducing apoptosis of osteoclasts. The influence of vitamin K2 trabecular and cortical bone formation has been shown not to interfere with bisphosphonates and the apoptosis of osteoclasts. In fact, the authors conclude the combination of vitamin K2 and bisphosphonates could produce an additive effect in osteoporosis prevention.⁴⁴

Vitamin K2 in Osteoporosis of Parkinson's Disease

Although as a general population the elderly are at high risk for osteoporosis, Parkinson's disease compounds the risk. Research of elderly populations has found a high incidence of hip fractures and osteoporosis in Parkinson's patients,^{69,70} in part related to vitamin D deficiency⁷¹ and immobilization⁷² in this population. The deficiency does not seem to be related to lack of 25-hydroxyvitamin D3, but rather to suppression of 1,25-dihydroxyvitamin D3 (the active form of vitamin D) by high serum calcium. The application of vitamin K2 significantly increased 1,25-dihydroxyvitamin D3 and decreased serum calcium.⁷² Vitamin K2 (45 mg/day for 12 months) to 54 female osteoporotic Parkinson's patients 65 years or older resulted in one hip fracture, compared to 10 fractures (eight hip, one radius, one ankle) in 54 matched, untreated, osteoporotic Parkinson's patients. All hip fractures were caused by falls and no significant differences were noted in number of falls between groups. The average bone loss in the untreated group was 4.3 ± 2.5 percent compared to 1.3 ± 0.4 percent in age-matched controls. Vitamin K2-treated patients experienced a 0.9 ± 1.2 percent gain in BMD.⁷²

Vitamin K2 in Bone Loss from Leuprolide

A moderate reduction in BMD is one of the frequent side effects of the gonadotropin-releasing hormone antagonist leuprolide for endometriosis, leiomyomas, and prostate cancer.^{73,74} Administration

of vitamin K2 (45 mg/day; n=28) or the combination of K2 and 1,25-dihydroxyvitamin D3 (45 mg/day and 0.5 mcg/day, respectively; n=28) resulted in partial prevention of bone loss compared to the leuprolide-only group (n=28) or the vitamin D-only group (n=26). Bone loss after six months as measured by lumbar spine BMD was 5.25 percent in the leuprolide-only group, 4.13 percent in the vitamin D group, 3.72 percent in the vitamin K group, and 3.59 in the group taking vitamins K and D.⁷⁵

Vitamin K2 in Bone Loss from Prednisolone

Use of glucocorticoids is the most common cause of drug-induced secondary osteoporosis.⁷⁶ Administration of glucocorticoids for long periods of time can lead to a decrease in bone mineral density of almost four percent.⁷⁷ Several studies found vitamin K2 has a marked effect on the loss of BMD in prednisolone-treated patients. Sixty patients with chronic glomerulonephritis were randomized to four groups: control, 1-alpha-hydroxyvitamin D3 (0.5 mcg/day), vitamin K2 (45 mg/day), or vitamins K2 with D3. Patients concomitantly received prednisolone at a daily dose of 0.7 mg/kg up to a maximum of 40 mg for four weeks, then tapered to 25 mg daily for another four weeks prior to assessment. The control group experienced a significant decrease from baseline in BMD over the eight-week study: -3.19 ± 1.11 percent, compared to the vitamins D, K, and D+K groups that maintained baseline levels (0.28 ± 1.30 , 0.50 ± 1.17 , and 0.44 ± 1.36 percent, respectively).⁷⁸

In a prospective pilot study 20 children being treated with prednisolone and vitamin D3 (0.03 mcg/kg/day) were continued on D3 plus prednisolone or given that combination plus vitamin K2 (approximately 2 mg/kg/day) for 12 weeks. Vitamins K2 and D3 combined had an additive effect, with a significant increase in lumbar BMD and osteocalcin compared to vitamin D3 alone.⁷⁹

Similar results were obtained in a randomized, prospective, controlled study of 20 patients with glomerulonephritis given 0.8 mg/kg/day prednisolone up to a maximum of 40 mg/day for four weeks, then tapered to 20 mg/day over a six-week period. One group received only prednisolone, while a second group also received vitamin K2 (15 mg three times

daily). After 10 weeks, a reduction in lumbar spine BMD (from 1.14 ± 0.12 to 1.10 ± 0.11 g/cm²) was noted in the prednisolone-only group. The vitamin K2 group demonstrated a somewhat slower rate of bone loss (from 1.09 ± 0.09 to 1.07 ± 0.07 g/cm²).⁷⁷

Vitamin K2 in the Treatment of Bone Loss in Biliary Cirrhosis

Patients with primary biliary cirrhosis experience osteodystrophy and increased fracture rate and fat malabsorption that results in deficiencies of vitamins D and K. Serum levels of vitamin K have been found to be low in this population. In a randomized, controlled trial of 27 patients with primary biliary cirrhosis, the treatment group (n=14) received vitamin K2 (45 mg/day) for two years. After one year the control group (n=13) experienced a 3.5 ± 1.2 percent decrease in BMD, while the vitamin K2 group demonstrated a 0.3 ± 2.3 percent increase in BMD. After two years, the control group demonstrated a 6.9 ± 2.1 percent decrease in BMD, compared to only a 0.8 ± 3.4 percent decrease in the K2 group. BMD was significantly higher in the vitamin K2 group during the two-year period compared to controls.⁸⁰

Vitamin K2 in the Treatment of Osteopenia of Stroke Patients and Skeletal Unloading

Victims of stroke are often immobilized, leading to significant loss of BMD. The most pronounced loss of bone occurs on the hemiplegic side compared to the unaffected side. This loss has been attributed to increased bone resorption, immobilization-induced hypercalcemia, and hypovitaminosis D.⁸¹ A recent randomized, controlled trial of 108 hemiplegic stroke victims, 54 subjects treated with 45 mg vitamin K2 daily for 12 months and 54 subjects serving as controls, found K2 effective for preventing disuse bone loss. Second metacarpal BMD on the hemiplegic side increased an average of 4.3 percent with vitamin K2 and decreased an average of 4.7 percent with no treatment. The unaffected side had a 0.9-percent decrease with K2 treatment compared to 2.7-percent decrease with no treatment.⁸²

Table 1. Clinical Studies of Vitamin K for Osteoporosis

Condition	Intervention	Outcome	Reference
Postmenopausal Osteoporosis	45 mg/day K2	Inhibited decrease in BMD	66
	45 mg/day K2; 1 mcg/day D3	Increased BMD	27
	45 mg/day K2; 0.75 mcg/day D3	Increased BMD	65
Postmenopausal Osteoporosis with Bisphosphonates	45 mg/day K2	Increased effectiveness of bisphosphonates	68
Parkinson's Disease	45 mg/day K2	Decreased fracture rate; increased BMD	72
Bone Loss from Leuprolide	45 mg/day K2	Slowed decrease in BMD	75
Bone loss from Prednisolone	15 mg K2 three times/day	Slowed rate of bone loss	77
	45 mg/day K2; 0.5 mcg/day D3	Inhibited decrease in BMD	78
	2 mg/kg/day K2; 0.03 mcg/kg/day D3 (Child Dose)	Increased lumbar BMD	79
Bone Loss in Biliary Cirrhosis	45 mg/day K2	Maintained BMD	80
Osteopenia from Stroke	45 mg/day K2	Increased BMD	82
Skeletal Unloading in A Bedridden Child	2 mg/kg/day K2; 0.05 mcg/kg D3	Increased BMD and Osteocalcin	83
Osteoporosis of Anorexia	45 mg/day K2	Slowed rate of bone loss	88

Skeletal unloading is a serious consequence of prolonged bedridden states leading to pathologic fractures. In a case of a bed-ridden, eight-year-old girl with low BMD, vitamin K2 at a dose of 2 mg/kg/day and vitamin D3 at a dose of 0.05 mcg/kg/day for 12 months resulted in an increase in osteocalcin levels (from 8.2 to 27.9 ng/mL) and cortical BMD of the radius from 0.370 g/cm² to 0.420 g/cm².⁸³

Symptoms of skeletal unloading are also observed in astronauts, due to a microgravity environment.⁸⁴ Vitamin K2 (22 mg/kg) for four weeks to rats subjected to tail suspension mimicking a microgravity environment effectively prevented significant loss of BMD. Analysis revealed that volume and structure of trabecular bone were maintained.⁸⁵ An astronaut on the EUROMIR-95 mission was tested during the first

part of a six-month space flight and found to have increased markers of bone loss. The astronaut was given vitamin K (in this case, vitamin K1) at a dose of 10 mg/day for six weeks, resulting in increased markers of bone formation – osteocalcin (14%) and bone alkaline phosphatase (23%).⁸⁶

Vitamin K2 in the Treatment of Osteoporosis of Anorexia

Anorexia is an eating disorder associated with pronounced weight loss, osteopenia, and osteoporosis that affects approximately one percent of U.S. females.⁸⁷ Twenty-one patients diagnosed with anorexia completed an 11-month study, during which 10 patients were given vitamin K2 (45 mg/day) and 11 chose not to and served as controls. The treatment group experienced significantly slower decrease in BMD compared to controls (-2.8% versus -6.9%, respectively). Levels of gamma-carboxyglutamic acid osteocalcin also significantly increased in the treatment group compared to controls (128.6% versus 28.3%, respectively).⁸⁸

Conclusion

Bone formation and bone loss involves a complex array of nutrients and molecular signals. This article covers the influence of vitamin K (most specifically K2) on these processes as a separate and distinct requirement from other nutrients. *In vitro* studies show vitamin K2 is far more active than K1 in both bone formation and reduction of bone loss.²⁹ Human studies demonstrate the potential of vitamin K2 as a strategic intervention for osteoporosis. This treatment is already in general use outside the United States,¹ at a typical dose of 45 mg daily.

Studies confirm the effectiveness of vitamin K2 for decreased BMD from a variety of causes, including postmenopausal osteoporosis, Parkinson's disease, use of leuprolide or prednisolone, biliary cirrhosis, stroke inactivity, and anorexia. Few, if any, multiple vitamin and mineral supplements contain vitamin K2. The authors recommend it be more widely supplemented as it has beneficial activity far beyond osteoporosis. Supplementation becomes even more important for those with a tendency to lipid malabsorption. A common cause of malabsorption is celiac disease, which affects one in 266 persons.

A normal prothrombin time is not an indication that enough vitamin K activity is present to maintain bone osteocalcin activity. Moderately high doses of vitamin K2 do not produce hypercoagulable or toxic states in humans, although the use of K2, like any vitamin K, is contraindicated in people taking warfarin (Coumadin®).

Considering the extensive application of vitamin K beyond blood coagulation – osteoporosis, anticancer therapy,²³ pain reduction,⁸⁹ mitochondrial aspects,⁹⁰ hepatitis C,⁹¹ and protection of sphingolipids⁹² – the vitamin Ks have been therapeutically underutilized.

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