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Effect of Vitamin K Supplementation on Bone Loss in Elderly Men and Women

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Abstract

Context: Vitamin K has been implicated in bone health, primarily in observational studies. However, little is known about the role of phylloquinone supplementation on prevention of bone loss in men and women.

Objective: The objective of this study was to determine the effect of 3-yr phylloquinone supplementation on change in bone mineral density (BMD) of the femoral neck bone in older men and women who were calcium and vitamin D replete.

Design, Participants, and Intervention: In this 3-yr, double-blind, controlled trial, 452 men and women (60–80 yr) were randomized equally to receive a multivitamin that contained either 500 μg/d or no phylloquinone plus a daily calcium (600 mg elemental calcium) and vitamin D (400 IU) supplement.

Main Outcome Measures: Measurements of the femoral neck, spine (L2–L4), and total-body BMD, bone turnover, and vitamins K and D status were measured every 6–12 months. Intent-to-treat analysis was used to compare change in measures in 401 participants who completed the trial.

Results: There were no differences in changes in BMD measurements at any of the anatomical sites measured between the two groups. The group that received the phylloquinone supplement had significantly higher phylloquinone and significantly lower percent undercarboxylated osteocalcin concentrations compared with the group that did not receive phylloquinone. No other biochemical measures differed between the two groups.

Conclusions: Phylloquinone supplementation in a dose attainable in the diet does not confer any additional benefit for bone health at the spine or hip when taken with recommended amounts of calcium and vitamin D.

Epidemiological evidence has shown associations between poor vitamin K nutrition and age-related bone loss in elderly men and women (1,2). Vitamin K is a cofactor for the posttranslational γ-carboxylation of glutamic acid in certain proteins, including osteocalcin, which has been thought to act as a regulator of bone mineralization. The mineral-binding capacity of osteocalcin is dependent on the γ-carboxylation of its three glutamate residues, such that partially carboxylated osteocalcin may have reduced binding to the mineral in bone. The proportion of osteocalcin that is not carboxylated [percent

undercarboxylated osteocalcin (%ucOC)] is used as a sensitive marker of vitamin K status (3). Usual dietary intakes of vitamin K do not support complete carboxylation of osteocalcin (4), and short-term dietary vitamin K deficiency may increase bone turnover in older adults (5).

In a recent metaanalysis of 13 randomized controlled trials with data on bone loss, the authors concluded that supplementation with either of two forms of vitamin K, menaquinone-4 (MK-4) and phylloquinone, reduces bone loss because all but one study reported a benefit in bone mineral density (BMD) in response to vitamin K supplementation (6). However, the optimal dose and form of vitamin K for this putative protective effect on bone loss is currently unknown, with the majority of studies using doses of MK-4 that are approximately 400-fold higher than current dietary recommendations of 90–120 μg phylloquinone/d for women and men, respectively (7). Furthermore, the studies had been conducted almost exclusively in Japanese postmenopausal women, and there is little information about the role of vitamin K supplementation in reducing bone loss in older men or women of other ethnicities. The authors of the metaanalysis concluded that although vitamin K-rich diets should be encouraged, larger clinical trials were required before conclusions could be drawn regarding the use of vitamin K supplements to reduce fracture risk (6).

The primary objective of this study was to determine whether 3 yr of supplementation with phylloquinone, in an amount that is expected to be both nutritionally optimal and safe, would reduce bone loss in older men and women when taken with recommended amounts of calcium and vitamin D. Phylloquinone, which is present in leafy green vegetables and certain plant oils, is the predominant dietary form of vitamin K (8). A secondary objective of this study was to determine the effect of supplemental phylloquinone on measures of bone turnover, as defined by serum osteocalcin and collagen type-I-cross-link N-telopeptides (NTx).

Subjects and Methods

Study participants

Healthy, ambulatory men and postmenopausal women, aged 60–80 yr, were recruited though direct mailings, newspaper advertisements, and notices in community centers. Exclusion criteria included a kidney stone in the past 5 yr; hyperthyroidism; bilateral hip surgery; therapy with a bisphosphonate, calcitonin, estrogen, tamoxifen, testosterone, or warfarin in the previous 6 months; known coronary disease; prior open heart surgery; atrial fibrillation; pacemaker; femoral neck BMD more than 1.8 SD below the mean for subjects of the same age and sex; laboratory evidence of kidney or liver disease; and inability to provide informed consent. We assessed 599 individuals for eligibility through a physical examination and assessment of the individuals' medical history and diet, analysis of blood and urine, and measurement of femoral neck BMD. Of these, 125 were found to be ineligible. Of those eligible, equal numbers were randomly assigned to either treatment (n = 238) or nontreatment (n = 236). Of those randomized, 22 (nine in the treatment group and 13 in the nontreatment group) chose not to enroll (Fig. 1).

Study design

In this 3-yr, double-blind, controlled trial, study participants came to the research site every 6–12 months for measurements of BMD, biochemical assays, and other measurements. Participants were randomized to either the treatment or nontreatment group, with stratification according to sex. Of the 421 whites, 14 Blacks, four Hispanics, 11 Asians, and two Native Americans who enrolled, 51 discontinued taking one or both of the daily supplements, five died, 13 withdrew for medical reasons, 11 were no longer able to come to the study site, and 22 either lost interest or were lost to contact (Fig. 1). All participants signed a written informed consent, and this study was approved by the Institutional Review Board at Tufts University. This study was also registered with ClinicalTrials.gov (NCT00183001).

The majority of the 51 participants who discontinued taking the supplements did so in the first 6 months. These participants were encouraged to return for all subsequent follow-up study visits. At the last visit, 401 study participants (88.7% of the 452 enrolled) were evaluated and were included in the main intention-to-treat analyses. The 358 participants who took the supplements throughout the study period were included in the secondary analysis.

Supplements

The subjects were advised to maintain their usual diets and to avoid taking dietary supplements, including calcium, vitamin D, or vitamin K, throughout the study. The treatment group received 500 μg phylloquinone as part of a daily effervescent multivitamin formulation (one tablet), whereas the nontreatment group received the multivitamin formulation without phylloquinone (one tablet). The basic effervescent multivitamin tablet contained vitamin B_1 (1.6 mg), vitamin B_2 (1.8 mg), vitamin B_6 (2.1 mg), vitamin B_{12} (3 μg), vitamin C (75 mg), vitamin E (12 mg), pantothenic acid (6 mg), niacin (20 mg), folate (160 μg), and biotin (30 μg). Each study participant was instructed to take the multivitamin tablet each morning dissolved in a 5- to 6-ounce glass of water. All study participants also received a second daily effervescent tablet that contained 600 mg elemental calcium in the form of calcium carbonate, and 10 μg (400 IU) vitamin D in the form of cholecalciferol. Subjects were instructed to take the calcium and vitamin D supplement at the same time as the multivitamin tablet. The mean rate of adherence with treatment, assessed on the basis of pill counts over 3 yr, was 89.1% for the multivitamin supplemented with phylloquinone and 88.5% for the group who received the multivitamin without phylloquinone. Adherence to the calcium and vitamin D supplements was 92.0% in the phylloquinone group and 91.0% in the nonphylloquinone group. For those who continued taking the supplements throughout the study, mean adherence was 93.7% for the multivitamin supplemented with phylloquinone and 93.8% for those taking the multivitamin without phylloquinone.

The supplement manufacturer (Hermes Arzeneimittel GMBH, Munich, Germany) produced a 12-month supply on an annual basis. The multivitamins containing phylloquinone were packaged in unmarked plastic tubes (20 supplements per tube), identical to those multivitamins not containing phylloquinone, and stored at room temperature. Only the pharmacy (Birds Hill Pharmacy, Needham, MA) and the study statistician were unblinded to the randomization scheme. To verify stability of the phylloquinone, a tablet from 10% of the tubes containing phylloquinone were analyzed upon receipt and every 4–5 months. Each tablet containing phylloquinone contained a mean ± SD of 564 ± 77 μg phylloquinone upon receipt; at 19 months, the final content was 428 ± 32 μg phylloquinone.

Measurements

BMD of the spine (L2–L4), femoral neck, and whole body was determined at baseline and 6, 12, 24, and 36 months of follow-up by dual-energy x-ray absorptiometry (GE Lunar Prodigy, Madison, WI). Scanner software version 5.0 was used for acquisition and analysis. The group root mean square average coefficients of variations for the dual-energy x-ray absorptiometry measurements were 1.66% (femoral neck), 1.04% (L2–L4), and 0.67% (total body) (9). A phantom was scanned every other week as a control; the BMD of the phantom was stable throughout the study. Three-year change in BMD was calculated by subtracting baseline from the yr 3 measure at each anatomical site.

All blood samples were drawn between 0700 and 1000 h after a minimum of a 10-h fast, and dedicated aliquots of plasma and serum were stored at −80 C and protected from light until the time of analysis. Urine measurements were made in 24-h collections. Analyses were performed as the samples were collected. Plasma concentrations of phylloquinone (done as singlet determinations) were determined by reversed-phase HPLC using post-column chemical reduction of phylloquinone to hydroquinone, followed by fluorometric detection (10). The total coefficients of variation (CV) for the two control sera with an average phylloquinone result of 1.2 and 4.5 nmol/liter were 7.4 and 8.0%, respectively. Plasma 25-hydroxyvitamin D was measured by RIA (DiaSorin, Stillwater, MN). The total CV for the in-house

control value with a mean value of 20.6 ng/ml was 16.0%. This control was run from July 2002 to January 2007. Plasma 1,25-dihydroxyvitamin D was measured by RIA (DiaSorin). An in-house control pool was run on all assays. The total CV for this control was 15.9%. The mean value of the control was 45.8 pg/ml. This control was run from October 2002 to March 2007. Serum total and undercarboxylated osteocalcin was measured by RIA, using the method of Gundberg *et al.* (3). The antibody recognizes both carboxylated and undercarboxylated osteocalcin. Carboxylated osteocalcin was separated from undercarboxylated osteocalcin by adsorption on hydroxyapatite. Total osteocalcin was determined in the serum before adsorption and undercarboxylated osteocalcin was measured in the adsorbed serum. The total CV for the three control sera with an average total OC result of 6.4, 14.7, and 23.8 μg/liter were 8.8, 8.9, and 7.6%, respectively. Urinary NTx was measured by ELISA (Osteomark International, Seattle, WA). The total CV for a control with a mean NTx concentration of 14.4 nM bone collagen equivalents was 18.8%.

Leisure, household, and occupational activity was estimated with use of the Physical Activity Scale for the Elderly questionnaire (11). Tobacco and alcohol use was determined by questionnaire. Height was measured with a stadiometer and weight with a digital scale. Usual dietary intakes over the year before entry in the study were assessed using the Willett Food Frequency Questionnaire, which has been validated for the assessment of vitamin K intake (12).

Statistical analysis

The two study groups were compared at baseline by using Student's *t* tests for independent samples. The effect of treatment on bone density was assessed by fitting analysis of covariance models with final BMD (or, equivalently, change in BMD) as the response, treatment as a study factor, and baseline BMD and sex as covariates. There were no significant interactions of sex and study group in the ANOVA models of change in BMD. All analyses were carried out using SAS version 9.1, and were considered to be statistically significant at $P < 0.05$. Selected secondary analyses were restricted to the study participants who completed the study and took the supplements throughout the study period. There were five outliers (one had a double hip replacement, and four had invalid final scans, possibly due to poor positioning) that were removed from the analysis because there were no statistically significant effects regardless of their inclusion or exclusion.

Results

As summarized in Table 1, baseline characteristics of the participants were similar in the two treatment groups, with the exception of a lower body weight and lower lumbar spine BMD among the women in the non-vitamin-K-supplemented group.

The vitamin K-supplemented group had a significant 3-yr increase in plasma phylloquinone concentrations ($P < 0.0001$) and a significant 3-yr decrease in %ucOC ($P < 0.0001$), whereas there were no changes over the same time period in the non-vitamin-K-supplemented group (Table 2). With the exception of women in the non-vitamin-K-supplemented group ($P = 0.27$), there was an overall increase in mean plasma 25-hydroxyvitamin D concentrations ($P < 0.001$) and a decrease in mean 1,25-dihydroxyvitamin D concentrations ($P < 0.001$) in response to a daily supplement of 400 IU vitamin D (Table 2). However, the magnitude of change did not differ between the vitamin K-supplemented group and the non-vitamin-K-supplemented group. There were no other significant changes in measures over the 3-yr period, including measures of bone turnover (serum NTx and total osteocalcin) (Table 2).

There was no difference in 3-yr change in femoral neck BMD between the vitamin K- and non-vitamin-K-supplemented groups ($P = 0.94$) (Fig. 2A). Likewise, there were no differences in 3-yr change in lumbar spine or whole-body BMD between the two groups ($P = 0.98$ and 0.81, respectively) (Fig. 2, B and C). There were also no effects of vitamin K on any of the outcomes when stratified within each

group by baseline %ucOC (data not shown).

When the statistical analyses were restricted to those study participants who completed the study and took the supplements throughout the study period, the results were similar to those reported in the intent-to-treat analysis (data not shown). Similarly, when statistical analyses were conducted separately for men and women, the results were similar to those reported for men and women combined (data not shown).

Discussion

In this 3-yr, randomized, double-blind, controlled trial, daily supplemental vitamin K, in amounts that are achievable by dietary intake, did not have an effect on bone health, as measured by change in BMD or bone turnover in older men and women who were calcium and vitamin D replete.

Poor vitamin K nutrition has been linked to osteoporosis in observational studies. Dietary surveys indicate that different subgroups of the population, including the elderly, are at risk of vitamin K intakes below the adequate intake, which is defined as 90–120 μg/d for women and men, respectively (7,13). The associations between phylloquinone intakes and low BMD or increased risk of hip fractures may be suggestive of causality or simply consistent with an overall healthy diet. By nature of their study design, observational studies usually are unable to isolate the effects of a single nutrient from those of the dietary patterns associated with high intakes of foods rich in that nutrient. Phylloquinone intake may be a marker for an overall healthy diet because green leafy vegetables are consistently the primary dietary form of vitamin K (14). In addition, high intakes of alkaline-producing foods, specifically the fruits and vegetables, and their associated minerals, have also been associated with higher BMD (15). Food sources rich in vitamin K contain other nutrients and phytochemicals that are associated with bone health, thus clinical trials are required to isolate the effects of vitamin K supplementation on bone.

Results of only two long-term clinical trials investigating phylloquinone supplementation on bone loss are currently available. In the study by Braam *et al.* (16), 3-yr intake of 1 mg/d phylloquinone plus calcium and vitamin D in supplement form reduced bone loss at the femoral neck in postmenopausal women, aged 50–60 yr, compared with a placebo or a supplement containing calcium and vitamin D (16). There was no beneficial effect of phylloquinone observed in the spine BMD. These results are confounded by the fact that the calcium- and vitamin D-supplemented group had similar bone loss to the placebo group at the 3-yr measures. In a second, 2-yr study of healthy, nonosteoporotic women at least 60 yr of age, 200 μg phylloquinone plus calcium and vitamin D daily resulted in a modest increase in bone mineral content of the radius but not at the femoral neck or trochanter (17). In contrast, our results indicate no beneficial effect of phylloquinone supplementation at doses that fall between these two published trials. Because we did not measure the ultradistal radius in our study, it is not known whether we would have observed a similar positive finding at this anatomical site to those of Bolton-Smith *et al.* (17). In addition, our control group, who received supplemental calcium and vitamin D in amounts that have been demonstrated to reduce age-related bone loss in elderly men and women (18), did not lose bone over the 3-yr period of measurement. Therefore, we conclude that phylloquinone supplementation in doses attainable in the diet does not confer any additional benefit for bone health at the spine or hip when taken concurrently with recommended amounts of calcium and vitamin D. Likewise, phylloquinone supplementation did not confer any additional benefits on measures of bone turnover above that achieved by calcium and vitamin D supplementation alone.

There has been much emphasis on the use of %ucOC as a marker of vitamin K in bone. However, it is still not known what the physiological implications are for a high %ucOC (*i.e.* poor vitamin K status). It has been reported that supplementation with about 1000 μg/d phylloquinone is necessary to achieve maximal carboxylation of osteocalcin (19). However, this conclusion can be influenced by the methodology used to determine %ucOC. In the current study, there was a significant increase in mean plasma phylloquinone concentrations and a significant decrease in mean %ucOC, which confirms an

improvement in vitamin K status in the treatment group. However there was no concomitant improvement in bone measures in the treatment group when compared with the control group, regardless of baseline %ucOC. In the context of our findings, it is still not known what the physiological implications are for a maximally carboxylated osteocalcin measure.

The authors of the first metaanalysis to assess whether oral vitamin K supplementation can reduce bone loss and prevent fractures concluded that although vitamin K-rich diets should be encouraged, the burden of proof to justify vitamin K supplementation in the elderly needed to be established in larger clinical trials (6). All the studies used in the metaanalysis for hip fracture risk were limited to Japan, which may reflect unique dietary, environmental, and/or genetic factors that favor the positive effects of MK-4 supplementation. The majority of clinical trials evaluated used daily doses of 45 mg MK-4, which are about 500-fold higher than current adequate intakes for women (7). A recent editorial identified unpublished data from a trial involving about 3000 patients that were not included in the metaanalysis (20). The unpublished data indicated a lack of effect of 36-month MK-4 supplementation of 45 mg MK-4/d on fracture risk, which may have changed the outcome of the metaanalysis had these data been available for inclusion. MK-4 can also be the product of tissue-specific conversion directly from dietary phylloquinone (21), a conversion that can occur in bone, albeit in much lower concentrations compared with those attained through supplementation at 45 mg/d. The mechanism by which MK-4 confers a potential protective effect on bone is not well understood, and it is plausible that the effects of these doses are conferred by a different mechanism to any putative effects using nutritional doses of dietary forms of vitamin K.

Supplemental calcium and vitamin D has been demonstrated to reduce age-related bone loss in elderly men and women (18), so we designed this study to address the question of whether vitamin K supplementation conferred an effect in addition to calcium and vitamin D. Although the biological mechanisms are unknown, there is some evidence from observational (22) and intervention (23,24) studies to suggest that there is either an additive or synergistic effect of vitamin D and vitamin K on bone health. However, in our study, vitamin K did not confer any additional benefit on bone loss. Although their mean baseline phylloquinone concentrations were lower that those reported in a community-based sample from the same geographical region (25), the men and women who participated in our study had self-reported phylloquinone intakes well above the current adequate intakes (7) and were, in general, a healthy population for this age group. It is plausible that given their healthy status and generous intakes of vitamin K in their usual diets, the additional vitamin K did not confer any additional benefit. We also did not assess fracture risk or the impact of vitamin K on bone geometry.

In conclusion, vitamin K supplementation in amounts that are achievable in the diet do not confer any additional benefit on bone health in healthy older men and women when taken with recommended amounts of calcium and vitamin D.

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Footnotes

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This study is registered with ClinicalTrials.gov (NCT00183001). This manuscript has not been submitted to Clinical Trials.gov.

Disclosure Statement: S.L.B., M.K.S., C.G., J.W.P., and B.D.-H. have nothing to declare; G.D. consulted for a legal matter unrelated to this study.

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Abbreviations: BMD, Bone mineral density; CV, coefficients of variation; MK-4, menaquinone-4; NTx, collagen type-I-cross-link N-telopeptides; %ucOC, percent undercarboxylated osteocalcin.

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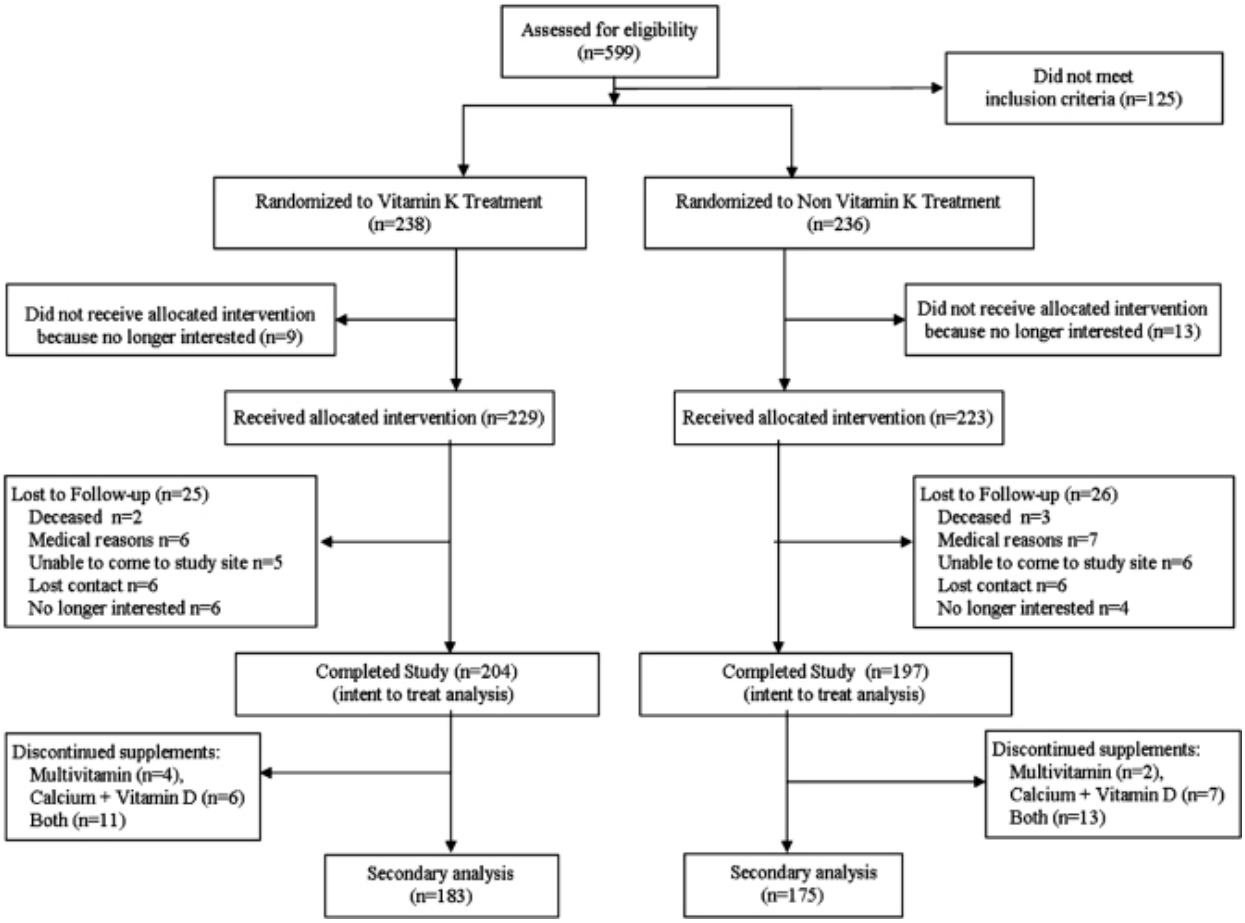
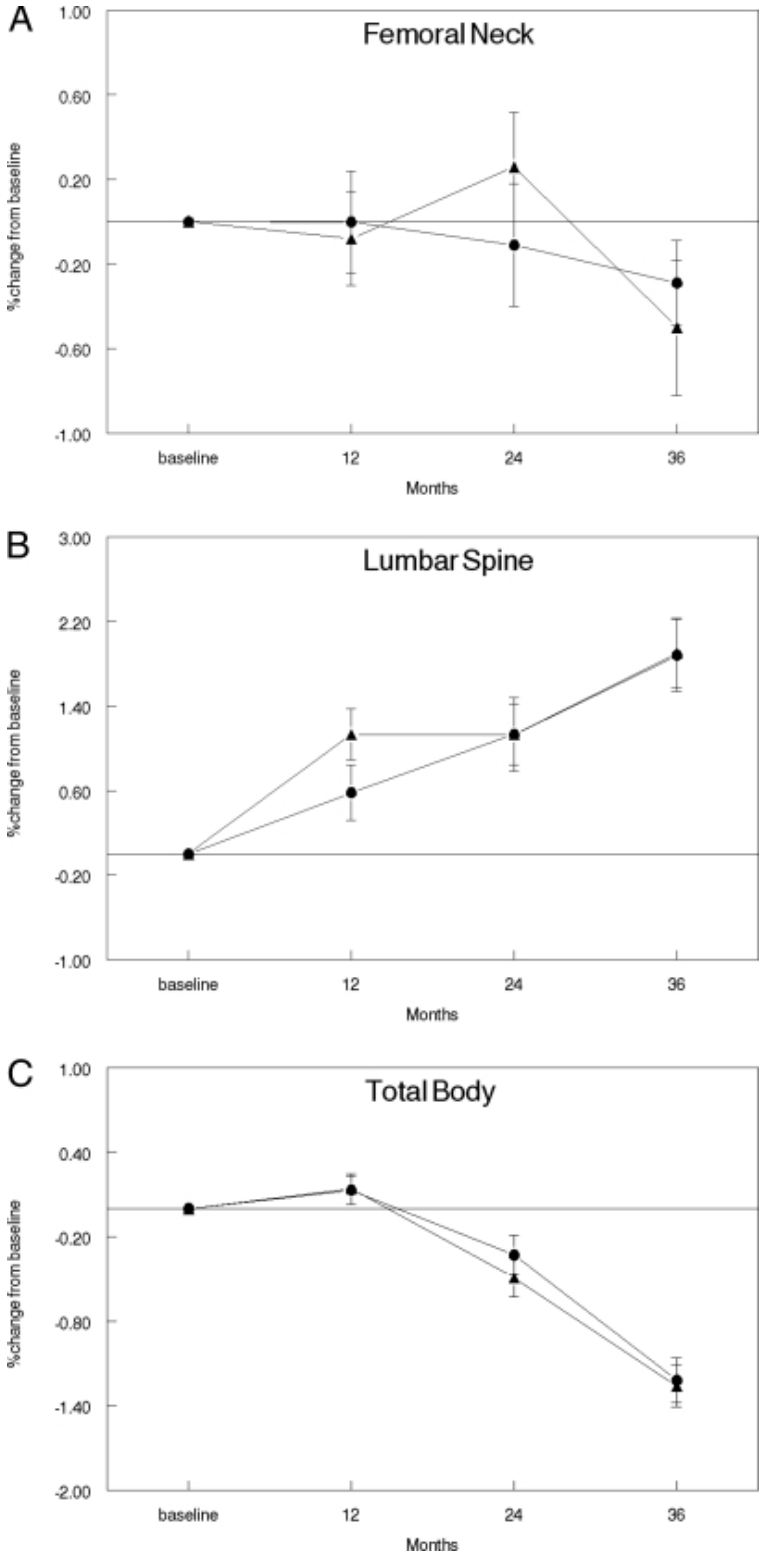
Figures and Tables

Figure 1



Study profile.

Figure 2



Mean (SEM) percent 3-yr change in BMD relative to baseline in the vitamin K (▲) and non-vitamin K (•) supplementation groups. A, Femoral neck; B, lumbar spine; C, total body.

Table 1

Baseline characteristics of vitamin K and non-vitamin K supplementation groups

Parameters	Men		Women	
	Vitamin K	No Vitamin K	Vitamin K	No Vitamin K

	supplementation (n = 95)	supplementation (n = 90)	supplementation (n = 134)	supplementation (n = 133)
Age (yr)	69 (5)	69 (6)	68 (6)	68 (5)
Height (cm)	174 (7)	174 (7)	161 (7)	160 (6)
Weight (kg)	85 (15)	84 (15)	74 (15)[a]	70 (14)[a]
Smoker, n (%)	3 (3.2)	9 (10.0)	10 (7.5)	3 (2.3)
Physical activity score	130 (66.0)	140 (62)	123 (54)	127 (62)
Phylloquinone intake (μg/d)	180 (121)	166 (118)	173 (92	179 (104)
BMD (g/cm^2)				
Femoral neck	0.946 (0.139)	0.954 (0.126)	0.875 (0.118)	0.866 (0.116)
Lumbar spine	1.310 (0.229)	1.318 (0.232)	1.167 (0.205)[a]	1.113 (0.184)[a]
Total body	1.274 (0.109)	1.271 (0.109)	1.141 (0.104)	1.122 (0.092)

Results are mean (SD) unless otherwise indicated.

[a]Significant difference between treatment groups at baseline ($P < 0.05$).

Table 2

Mean (SD) initial biochemical and BMD measures and 3-yr change for vitamin K and non-vitamin K supplementation groups

	Men (n = 164)		Women (n = 237)	
	Baseline	3-yr change	Baseline	3-yr change
Plasma phylloquinone (nmol/liter)				
Vitamin K supplemented	1.4 (2.2)	+1.5 (2.4)	1.1 (1.4)	+2.3 (2.7)
Non-vitamin K supplemented	1.1 (1.9)	−0.3 (1.8)[a]	1.2 (1.1)	+0.1 (1.3)[a]
%ucOC				
Vitamin K supplemented	35.9 (15.7)	−18.5 (22.9)	42.8 (16.9)	−18.7 (20.1)
Non-vitamin K supplemented	39.1 (14.9)	+0.8 (18.1)[a]	41.6 (17.3)	+3.1 (21.0)[a]
Plasma 25-hydroxyvitamin D (ng/ml)				
Vitamin K supplemented	22.8 (9.2)	+3.7 (10.2)	22.7 (8.5)	+2.3 (9.1)
Non-vitamin K supplemented	20.8 (8.0)	+4.3 (7.9)	24.3 (8.5)	+0.9 (8.7)
Plasma 1,25-dihydroxyvitamin D (pg/ml)				
Vitamin K supplemented	46.0 (23.3)	−7.4 (25.0)	46.8 (20.7)	−7.3 (21.5)
Non-vitamin K supplemented	44.7 (18.1)	−7.2 (19.4)	49.1 (20.0)	−8.2 (23.0)
Serum total osteocalcin (ng/ml)				
Vitamin K supplemented	7.7 (2.6)	−0.8 (2.0)	8.7 (3.2)	−1.0 (3.0)
Non-vitamin K supplemented	7.7 (2.4)	−0.8 (1.8)	9.0 (3.1)	−0.9 (3.1)
NTx (nM BCE)				
Vitamin K supplemented	14.1 (3.3)	+1.1 (4.6)	15.3 (4.0)	+0.03 (6.1)

Non-vitamin K supplemented	14.4 (4.3)	+1.3 (5.0)	16.5 (4.8)	−1.0 (6.1)
Ca:creatinine ratio, 24-h urine (mg/g)				
Vitamin K supplemented	93 (62)	+8 (51)	131 (69)	+5 (60)
Non-vitamin K supplemented	95 (56)	+13 (50)	143 (76)	+6 (73)
Femoral neck BMD (g/cm^2)				
Vitamin K supplemented	0.946 (0.139)	−0.001 (0.038)	0.875 (0.118)	−0.009 (0.041)
Non-vitamin K supplemented	0.954 (0.126)	+0.005 (0.036)	0.866 (0.116)	−0.008 (0.035)
Lumbar spine BMD (g/cm^2)				
Vitamin K supplemented	1.310 (0.229)	+0.044 (0.053)	1.167 (0.205)	+0.009 (0.057)
Non-vitamin K supplemented	1.318 (0.232)	+0.043 (0.048)	1.113 (0.184)	+0.009 (0.054)
Total-body BMD (g/cm^2)				
Vitamin K supplemented	1.274 (0.109)	−0.009 (0.025)	1.141 (0.104)	−0.018 (0.025)
Non-vitamin K supplemented	1.271 (0.109)	−0.008 (0.033)	1.122 (0.092)	−0.018 (0.023)

[a]Significant difference in 3-yr change between treatment groups ($P < 0.001$).