Vitamin K intake and bone mineral density in women and men[1–4]

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ABSTRACT

Background: Low dietary vitamin K intake has been associated with an increased risk of hip fracture in men and women. Few data exist on the association between dietary vitamin K intake and bone mineral density (BMD).

Objective: We studied cross-sectional associations between self-reported dietary vitamin K intake and BMD of the hip and spine in men and women aged 29–86 y.

Design: BMD was measured at the hip and spine in 1112 men and 1479 women ($\bar{x} \pm$ SD age: 59 ± 9 y) who participated in the Framingham Heart Study (1996–2000). Dietary and supplemental intakes of vitamin K were assessed with the use of a food-frequency questionnaire. Additional covariates included age, body mass index, smoking status, alcohol use, physical activity score, and menopause status and current estrogen use among the women.

Results: Women in the lowest quartile of vitamin K intake ($\bar{x}$: 70.2 μg/d) had significantly ($P \leq 0.005$) lower mean (±SEM) BMD at the femoral neck (0.854 ± 0.006 g/cm^2) and spine (1.140 ± 0.010 g/cm^2) than did those in the highest quartile of vitamin K intake ($\bar{x}$: 309 μg/d): 0.888 ± 0.006 and 1.190 ± 0.010 g/cm^2, respectively. These associations remained after potential confounders were controlled for and after stratification by age or supplement use. No significant association was found between dietary vitamin K intake and BMD in men.

Conclusions: Low dietary vitamin K intake was associated with low BMD in women, consistent with previous reports that low dietary vitamin K intake is associated with an increased risk of hip fracture. In contrast, there was no association between dietary vitamin K intake and BMD in men. *Am J Clin Nutr* 2003;77:512–6.

KEY WORDS Vitamin K intake, bone mineral density, hip, spine, Framingham Heart Study

INTRODUCTION

There is emerging evidence that vitamin K may have a protective role against age-related bone loss that is mediated through the vitamin K-dependent γ-carboxylation of certain proteins in bone, including osteocalcin (1, 2). The primary dietary form of vitamin K is phylloquinone (vitamin K_1), which is concentrated in green vegetables and certain plant oils (3).

Several epidemiologic studies reported associations between biological markers of vitamin K status, such as plasma phylloquinone and the percentage of osteocalcin that is not carboxylated, and the risk of low bone mineral density (BMD) (4, 5) and hip fracture (6–8). Although suggestive, these studies were criticized for the potential confounding effect of overall poor nutrition (1, 2). In the Nurses' Health Study, low dietary phylloquinone intake was associated with an increased risk of hip fracture in women, even after calcium and vitamin D intakes were controlled for in the analysis (9). In the original Framingham Heart Study cohort, low dietary phylloquinone intake was also associated with an increased risk of hip fracture in elderly men and women (10). However, there was no association between BMD (either cross-sectionally or in 4-y changes) and dietary phylloquinone intake (10). Potential explanations for the lack of association between dietary phylloquinone intake and BMD in the original Framingham Heart Study cohort include the older age of the cohort (mean age: 75 y), who may not have had current dietary patterns that were consistent with those throughout adulthood; the small sample size (n = 888), which may have attenuated the ability to detect statistically significant differences in BMD; and the possibility that any putative role of vitamin K in the risk of hip fracture was independent of BMD (10). In the present study, our objective was to examine cross-sectional associations between dietary phylloquinone intake and BMD at the hip and spine in a group of men and women with a wide age span who participated in the Offspring cohort of the Framingham Heart Study.

SUBJECTS AND METHODS

Subjects

The Framingham Offspring Study is a longitudinal, community-based study of cardiovascular disease among the children and

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spouses of the participants in the original Framingham Heart Study cohort (11). In 1971, 5124 participants were enrolled in the Offspring Study and have returned every 3–4 y for an extensive physical examination, comprehensive questionnaires, anthropometric measurements, blood chemistries, and assessment of cardiovascular and other risk factors by trained clinical personnel. Between 1996 and 2000, there were 3532 participants in the sixth examination cycle of the Framingham Offspring Study. Valid data from a food-frequency questionnaire (FFQ) and BMD measurements were available for 3223 and 2952 participants, respectively. Of those with both valid FFQ data and BMD measurements, 56 participants were excluded from the analysis because they were taking anticoagulants, including the vitamin K antagonist, warfarin, thereby reducing the final sample to 2591 (1112 men and 1479 women). The Institutional Review Boards for Human Research at Boston University and Tufts-New England Medical Center approved the protocol.

Dietary assessment

Usual dietary intakes for the previous 12 mo were assessed by using a 126-item semiquantitative FFQ as described elsewhere (12). This FFQ was validated for numerous nutrients (12), including phylloquinone (9). Questionnaires were mailed to the subjects before the exam and, once completed, were returned to the examination site. Questionnaires in which subjects reported energy intakes < 2.51 and > 16.74 MJ/d (600 and 4000 kcal/d, respectively) or in which questions for > 12 food items were left blank were considered invalid and were excluded from further analysis (n = 112). Vitamin and mineral supplement use and the specific type of breakfast cereal that was most commonly consumed were used in the estimation of total micronutrient intakes. Phylloquinone intakes included intakes from multivitamin and mineral preparations and other nutrient supplements. Of the entire study group, 59 men and 108 women reported phylloquinone supplement use, with a mean (± SD) daily intake of 1.2 ± 5.2 μg phylloquinone from supplements (men: 1.0 ± 4.8; women: 1.4 ± 5.5). The mean dietary phylloquinone intakes reported by these supplement users were 143 ± 80 and 173 ± 96 μg/d for men and women, respectively, which were not significantly different from the mean phylloquinone intake reported for the entire study group.

Bone mineral density

BMD was measured in the hip and spine by using dual-energy X-ray absorptiometry (DPX-L; Lunar, Madison, WI). CVs for the dual-energy X-ray absorptiometry measurements of the hip were 1.7% for the femoral neck, 2.5% for the trochanter, 4.1% for Ward's area, and 0.9% for the lumbar spine (13).

Covariate information

The risk factors that were identified for age-related bone loss in the original Framingham cohort (13) were adjusted for in the statistical analysis. Height and weight were measured at the sixth examination while the subjects stood. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Current smokers were defined as subjects who reported smoking cigarettes on a regular basis during the previous year. Physical activity was assessed by using a validated questionnaire of self-reported activity in the past 7 d (14–16). Menopause status was defined as having no menstrual periods for ≥ 1 y or currently taking postmenopausal estrogens. Estrogen use was classified as either current use or no use at the time of the examination.

Statistical analysis

SAS statistical software (release 8.1; SAS institute, Cary, NC) was used for all statistical analysis. Analysis was conducted separately for men and women because factors affecting age-related bone loss are not identical for men and women, and average BMD measures for men are higher than those for women (13). Measures of BMD at the femoral neck, trochanter, Ward's area, and lumbar spine (L2–L4) were regressed on total phylloquinone intake separately for the men and the women, and adjustment for potential confounders (age, BMI, dietary and supplemental intakes of calcium and vitamin D, alcohol intake, energy intake, caffeine intake, physical activity, smoking status, and estrogen use and menopause status among the women) was performed by using multiple regression. Because high phylloquinone intakes are also associated with high green-vegetable intakes (17), an additional adjustment for dietary intakes of potassium, which is present in fruit and vegetables (18), was done in a separate analysis. To avoid an assumption of linearity, we calculated quartiles separately for the men and the women before the regression analyses. For each BMD measure, we used 2 models to evaluate the association between phylloquinone intake quartile and BMD. First, we regressed the BMD measures on a grouping variable, defined by 4 groups for the quartiles. This model is essentially an analysis of covariance in which the mean BMD values across the 4 quartiles are examined for differences. Second, we considered the grouping variable, defined by the quartiles, as a semiquantitative measure that ordinally defines phylloquinone intakes according to magnitude. This model tests for a linear trend in mean values across the 4 quartiles. In both models, we adjusted for the potential confounders to obtain the association between phylloquinone intake and BMD, with adjustment for age, BMI, smoking status, and other covariates. Because the mean BMD values increased with each quartile in the women, we report the latter results.

To determine whether any associations between phylloquinone and BMD changed with age within the Offspring cohort, we stratified the subjects by age (< 59 and ≥ 59 y) and repeated the multivariate analysis by using sex-specific general linear models. The cutoff of 59 y corresponded to the mean age of both the men and the women in the Offspring cohort.

To assess a potential interaction between vitamin K intake and calcium or vitamin D supplement use, the men and the women were stratified according to current calcium or vitamin D supplement use (yes or no), and the analyses were repeated by using sex-specific general linear models. Most of the men and women taking calcium supplements were also taking vitamin D supplements, so the data for the 2 nutrients were combined.

RESULTS

The mean (± SD) dietary phylloquinone intakes of the men and the women were 153 ± 115 and 171 ± 103 μg/d, respectively (**Table 1**), which were consistent with intakes reported from the same FFQ in the Nurses' Health Study (9) and in the original cohort from the Framingham Heart Study (10). Dietary phylloquinone intakes were significantly correlated with dietary intakes of vitamin D (r = 0.24, P = 0.0001) and calcium (r = 0.27, P = 0.0001) in the women. Similar correlations were noted among the men. There was no significant correlation between dietary

TABLE 1
Subject characteristics[1]

	Men (n = 1112)	Women (n = 1479)
Age[2] (y)	59 ± 9[3] (35–86)	58 ± 9 (29–83)
BMI (kg/m^2)	28.7 ± 4.4	27.1 ± 5.5
Dietary intakes		
Phylloquinone (μg/d)	153 ± 115	171 ± 103
Energy (MJ/d)	8.16 ± 2.61	7.31 ± 2.39
Caffeine (mg/d)	273 ± 210	235 ± 194
Calcium (mg/d)	753 ± 365	756 ± 354
Vitamin D (μg/d)	5.8 ± 7.3	5.9 ± 3.3
Supplement use (%)		
Phylloquinone	5.3	7.3
Calcium	19.2	46.0
Vitamin D	32.6	45.2
Alcohol intake		
(mL/wk)	99 ± 126	45 ± 72
(oz/wk)	3.3 ± 4.2	1.5 ± 2.4
Current smoker (%)	12.5	14.3
Former smoker (%)	66.7	52.7
Physical activity score[4]	156 ± 86	136 ± 71
Postmenopausal (%)	NA	80.7
Estrogen use (%)	NA	28.5
BMD (g/cm^2)		
Femoral neck	0.978 ± 0.139	0.876 ± 0.143
Trochanter	0.891 ± 0.141	0.720 ± 0.137
Ward's area	0.786 ± 0.158	0.731 ± 0.172
Spine (L2–L4)	1.329 ± 0.208	1.161 ± 0.203

[1] NA, not applicable; BMD, bone mineral density.
[2] Range in parentheses.
[3] $\bar{x}$ ± SD.
[4] Range of possible values: 0 to ≥400.

phylloquinone intake and calcium or vitamin D supplement use. More women than men reported supplement use, with ≈45% of the women reporting calcium and vitamin D supplement use. In contrast, < 10% of the men or of the women consumed phylloquinone from supplements.

Higher dietary phylloquinone intakes were associated with higher BMD measures at the hip and spine in the women (**Table 2**). These significant associations persisted even after covariates such as age, BMI, alcohol intake, energy intake, caffeine intake, dietary and supplemental intakes of calcium and vitamin D, physical activity, smoking status, current estrogen use, and menopause status were controlled for. When dietary potassium intake was included in the model as an additional covariate, the associations were still significant [P = 0.01, 0.02, 0.009, and 0.007 for femoral neck, trochanter, Ward's area, and spine (L2–L4) BMD, respectively]. In contrast, dietary phylloquinone intake was not significantly associated with any of the BMD sites in the men (**Table 3**).

Among both the younger women (< 59 y) and the older women (≥ 59 y), adjusted mean BMD values at the hip and spine were highest in those in the highest quartile of phylloquinone intake (data not shown). In the men, there were no apparent associations between dietary phylloquinone intake and BMD at any site, regardless of age group (data not shown).

Among both the women who were current supplement users and those who did not use supplements, those in the highest quartile of phylloquinone intake had the highest adjusted mean BMD values at the hip and spine (data not shown). However, some of the comparisons were not significant because of the small sample size within groups (ie, supplement use compared with no supplement use). In the men, there were no apparent associations between dietary phylloquinone intake and BMD at any site, regardless of current supplement use (data not shown).

DISCUSSION

In this study of middle-aged women and men, vitamin K intakes were in the range reported in other cohorts (9, 10). Although higher than the current adequate intakes of 120 and 90 μg/d for men and women, respectively (19), the intakes reported with the use of this FFQ are overestimates compared with those estimated from diet records (9). However, in an analysis of 369 men and 468 women from the sixth examination of the Framingham Offspring Study, plasma phylloquinone concentrations were significantly associated with self-reported total phylloquinone intake, as estimated by the FFQ, after adjustment for potential nondietary confounding factors (17). Therefore, the FFQ appears to be appropriate for ranking subjects by their phylloquinone intake.

Among the women enrolled in this study, low dietary phylloquinone intake was associated with low BMD. These results are consistent with those of other epidemiologic studies that reported an increased risk of hip fracture among persons with a low phyl-

TABLE 2
Bone mineral density (BMD) by quartile of phylloquinone intake in women[1]

	Quartile				
	1 (13–101 μg/d) (n = 369)	2 (102–148 μg/d) (n = 370)	3 (149–216 μg/d) (n = 370)	4 (217–983 μg/d) (n = 370)	P[2]
	g/cm^2				
Femoral neck	0.854 ± 0.006	0.876 ± 0.006	0.882 ± 0.006	0.888 ± 0.006	0.0004
Trochanter	0.705 ± 0.006	0.722 ± 0.006	0.725 ± 0.006	0.730 ± 0.006	0.005
Ward's area	0.705 ± 0.008	0.734 ± 0.008	0.738 ± 0.008	0.746 ± 0.008	0.0005
Spine (L2–L4)	1.140 ± 0.01	1.156 ± 0.009	1.156 ± 0.009	1.190 ± 0.01	0.001

[1] $\bar{x}$ ± SEM. Adjusted for age, BMI, dietary and supplemental intakes of calcium and vitamin D, alcohol intake, energy intake, caffeine intake, physical activity, smoking status, current estrogen use, and menopause status. The mean phylloquinone intakes were 70, 125, 179, and 309 μg/d in quartiles 1, 2, 3, and 4, respectively.
[2] For linear trend across quartiles.

TABLE 3
Bone mineral density (BMD) by quartile of phylloquinone intake in men[1]

	Quartile				
	1 (8–87 μg/d) (n = 278)	2 (88–129 μg/d) (n = 278)	3 (130–189 μg/d) (n = 278)	4 (190–1956 μg/d) (n = 278)	P^2
			g/cm^2		
Femoral neck	0.988 ± 0.008	0.973 ± 0.008	0.971 ± 0.008	0.983 ± 0.008	0.653
Trochanter	0.898 ± 0.008	0.879 ± 0.008	0.891 ± 0.008	0.896 ± 0.008	0.899
Ward's area	0.798 ± 0.009	0.787 ± 0.009	0.775 ± 0.009	0.786 ± 0.009	0.272
Spine (L2–L4)	1.329 ± 0.013	1.337 ± 0.012	1.336 ± 0.012	1.315 ± 0.013	0.469

[1] $\bar{x}$ ± SEM. Adjusted for age, BMI, dietary and supplemental intakes of calcium and vitamin D, alcohol intake, energy intake, caffeine intake, physical activity, and smoking status. The mean phylloquinone intakes were 60, 107, 157, and 288 μg/d in quartiles 1, 2, 3, and 4, respectively.
[2] For linear trend across quartiles.

loquinone intake (9, 10), a low plasma phylloquinone concentration (4), and an elevated percentage of undercarboxylated osteocalcin (7). Collectively, these results provide further support to the hypothesis that dietary vitamin K is a modifiable factor that can attenuate age-related bone loss.

In the original Framingham Heart Study cohort, there was no association between dietary phylloquinone intake and BMD (both cross-sectionally and in 4-y changes) in women (10). The present study does not support our previous hypothesis formulated on the basis of the original Framingham cohort that dietary phylloquinone may protect against hip fracture, independent of BMD. The lack of association in the original Framingham cohort may be explained by the smaller sample size (557 women) and the older age ($\bar{x}$: 75 y) of the women compared with the sample size and the age of the women in the present study (1479 and 59 y, respectively). However, our finding of an association between vitamin K intake and BMD in both the younger women (< 59 y) and the older women (≥ 59 y) in the present study suggests that the age difference was not the reason for the inconsistencies between the 2 cohorts. Unfortunately, there was an insufficient number of women in the present study whose age overlapped that of the women in the original Framingham cohort to examine the BMD-diet associations, which would have been necessary to eliminate the possibility that older subjects had current dietary patterns that were inconsistent with those throughout adulthood. Furthermore, the current literature on the effect of age on biological markers of vitamin K reports contradictory results, although at least one study reported that plasma phylloquinone and the percentage of osteocalcin that is not carboxylated varies little with aging (20).

In this study of 1479 women, although significant, the cross-sectional differences in BMD across quartiles of phylloquinone intake at each skeletal site were modest. However, even these small differences in BMD may be important in the prediction of hip fracture risk. For example, Cummings et al (21) reported that each SD decrease in BMD of the femoral neck is associated with a 2.6-fold increase in the age-adjusted risk of hip fracture and that each SD decrease in BMD is associated with a 2.0-fold increase in spine fracture risk.

Dietary phylloquinone intake was not associated with BMD at any of the femoral or lumbar sites in the men, which is consistent with data from the original Framingham cohort (10). There may be a sex-specific effect of vitamin K on bone, as suggested by the present study. However, metabolic studies do not support the hypothesis that there are sex-specific differences in changes in biological markers of bone turnover and vitamin K status in response to vitamin K depletion, supplementation, and antagonism (22–24). A caveat to metabolic studies is their short-term duration, whereas the FFQ used in the present study captures long-term (1 y) dietary phylloquinone intake. To the best of our knowledge, there are no published epidemiologic studies that examined associations between biological markers of vitamin K status and BMD in men for comparison.

Although these data contribute to an expanding body of literature that supports a putative role of dietary vitamin K in reducing age-related bone loss, the limitations of previous epidemiologic studies (1, 2) are also applicable to the present study. In this population of men and women, high dietary vitamin K intakes are positively associated with high dietary intakes of green, leafy vegetables (17), suggestive of an overall healthy lifestyle. In addition, high intakes of alkaline-producing foods, specifically fruit and vegetables, and their associated minerals, potassium and magnesium, are associated with high BMD (18, 25). However, the positive association between dietary vitamin K and BMD at the hip and spine was significant among the women in the present study, even after adjustment for dietary potassium. Reported dietary intakes of vitamin K in the present study were also correlated with dietary, but not supplemental, intakes of both calcium and vitamin D in both the men and the women. Because these 3 nutrients do not share common food sources, the observed correlations are probably consistent with an overall healthy diet. Therefore, although the analyses in the present study were controlled for potential confounding effects on BMD, it can be argued that there is an overall confounding effect of poor nutrition and certain lifestyle factors that contribute to bone loss. Until the mechanisms by which vitamin K affects bone loss are elucidated, interpretation of these studies will remain difficult. In conclusion, in the Offspring cohort of the Framingham Heart Study, higher dietary phylloquinone intakes were associated with higher BMD in women but not in men.

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