

Dietary intake of vitamin K in relation to bone mineral density in Korea adults: The Korea National Health and Nutrition Examination Survey (2010–2011)

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(Received 11 August, 2014; Accepted 2 April, 2015; Published online 17 October, 2015)

Low vitamin K nutritional status has been associated with increased risk of fracture, however inconsistent results exist to support the role of vitamin K on bone mineral density depending on ethnic difference and gender. Our objective was to determine vitamin K intake in Korean adults, examine correlation between vitamin K intake and bone mineral density. This study analyzed raw data from the fifth Korea National Health and Nutrition Examination Survey for adults (2,785 men, 4,307 women) aged over 19 years. Cross-sectional analyses showed only positive association between vitamin K intake and femur bone mineral density in men after adjusting bone-related factors. However, women in high tertiles of vitamin K intake had a significantly higher bone mineral density both in femur and lumbar as compared to women in lowest tertiles ($p < 0.05$). The risk for osteoporosis was decreased as vitamin K intake increased in women, but this effect was not persisted after adjusting factors. The findings of this study indicate that low dietary vitamin K intake was associated with low bone mineral density in subjects. From these results we may suggest an increase in dietary vitamin K intakes for maintaining bone mineral density. (2010-02CON-21-C, 2011-02CON-06-C)

Key Words: phylloquinone, bone mineral density, osteoporosis, Korean

Vitamin K is known to promote blood coagulation and is found in large quantities in leafy, green vegetables including kale, broccoli, and spinach.⁽¹⁾ There are increasing number of studies were reported the beneficial effects of vitamin K for a bone health, cardiovascular disease and a cancer beyond blood coagulation activity.⁽²⁾ With regard to bone metabolism, vitamin K is known to play an essential role as a coenzyme in the carboxylation of the γ -glutamic acid protein.⁽³⁾ Dietary reference ranges are decided after considering to minimize a probability of deficiency and risk of excess and to fulfill an optimal body store and status.⁽⁴⁾ Selecting the critical biomarkers to establish proper dietary requirement is an important step in determining dietary references. The present recommended dietary references for vitamin K are set by exclusively based on the action of blood coagulation efficacy by phylloquinone in the liver. For healthy adults, dietary reference range of vitamin K are from 50 to 120 $\mu\text{g}/\text{day}$ in several countries as an Adequate Intakes (AI).⁽⁵⁾ Even though there are lots of findings regarding the several beneficial effects of vitamin K for human health, more evidence are needed regarding the proper dietary reference range about these functions.

Over the past few years, vitamin K has been studied in regarding to regulating effect on bone formation by gamma glutamyl carboxylating of osteocalcin. Cohort studies on vitamin

K and bone health have been carried out in various age and ethnic groups. The Nurses' Health Study of the U.S.A., a prospective study on vitamin K intake in adult women, reported that a low intake of vitamin K increases the prevalence rate of hip fractures.⁽⁶⁾ In a study by Booth *et al.*,⁽⁷⁾ it was revealed that the BMD of women increased with vitamin K intake; however, this trend was not observed in men. The Framingham Heart Study also reported that low vitamin K intake contributes to the increase in the prevalence of hip fractures in elderly men and women.⁽⁸⁾ In the meta-analysis to determine the role of vitamin K on BMD, increased BMD at the lumbar spine but not at the femoral neck was observed by supplementation.⁽⁹⁾ On the other hand, the study by Rejmark *et al.*,⁽¹⁰⁾ which analyzed the Danish Osteoporosis Prevention Study of Denmark, revealed that there was no correlation between vitamin K intake and BMD in adult women. Similarly, a prospective study conducted on elderly Chinese subjects by Chan *et al.*⁽¹¹⁾ revealed that there was no correlation between vitamin K intake and fractures. A number of trials examining the role of vitamin K on bone health have yielded inconsistent results with some studies showing a positive effect on bone and others with no effect depending on the type of vitamin K, its amount, and study populations.

In previous study conducted with 75 Korean young women in their 20s, it was revealed that subjects with low BMD had low vitamin K intake.⁽¹²⁾ In Korea, only small-scale studies have been conducted on the effects of vitamin K intake on bone health. No nationwide cohort study has been conducted to analyze this association in a Korean population. It is necessary to conduct a cohort study on the influence of vitamin K intake on BMD that targets the Korean population.

The purpose of this study is to analyze vitamin K intake in adult men and women aged over 19 years using raw data from the fifth Korea National Health and Nutrition Examination Survey (KNHANES) (2010–2011) and to subsequently determine the correlation between vitamin K intake and BMD. And then it might be further used for reconsidering vitamin K recommendation levels in Korean adults.

Materials and Methods

Study population. The KNHANES was a community-based cross-sectional nation survey conducted nationwide from 2010 to 2011 to assess the health and nutritional status by the Korea Center for Disease Control and Prevention (KCDC). The subjects of this

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study were Korean adults aged over 19 years who had undergone BMD analysis during the 2010–2011 KNHANES. Data from 7,092 subjects (2,785 men, 4,307 women) were used in the final analysis after excluding subjects who did not complete the dietary examination using the 24-h recall method and had calorie intake less than 500.0 kcal/day and over 4,000.0 kcal/day. KNHANES was approved by the KCDC Institutional Review Board. And all the participants in this survey signed an informed consent form.

We investigated the research subjects' primary characteristics and analyze their nutritional intake and lifestyle. KNHANES is composed of 3 parts: a survey of health, physical examination and a survey of nutrition. This research used data of the health survey; gender, age, alcohol intake, smoking status, day of muscular strength exercise, postmenopausal state and hormonal replacement therapy and anthropometric data of the physical examination. We calculated body mass index (BMI) using their height and weight to analyze subjects' obesity. We also used data of dietary survey regarding the usage of dietary supplementation.

In order to examine the results derived using weighted values for the data provided by the complex sample design, weighted values of clustering variables and stratification variables, and weighted values of the 2010–2011 KNHANES data calculated during the preparation of analysis was used.

Dietary assessment, BMD measurement, vitamin D analyses. Trained dietitians collected dietary intake data in person by using 24-h recall method. Each subject's vitamin K (phylloquinone) intake was calculated by Computer Aided Nutritional analysis Program ver. 4.0 (The Korean Nutrition Society, Seoul, Korea) in which the food composition table was supplied by the Korea National Academy of Agricultural Science⁽¹³⁾ and the United States Department of Agriculture database.⁽¹⁴⁾

The BMD measurement were performed in total femur, trochanteric, intertrochanteric, femoral neck, ward and lumbar spine (first, second and third) by using Dual-energy X-ray absorptiometry; DEXA (DISCOVERY-W fan-beam densitometer, Hologic Inc., Bedford, MA) in KNHANES. T-score values of these bone sites were used for analysis. The Osteoporosis status was determined by Asian population criteria; less than –2.5 for osteoporosis and between –2.5 and –1.0 for osteopenia by T-score.⁽¹⁵⁾

Serum vitamin D was analyzed using radioimmunoassay (1470 WIZARD gamma-Counter, PerkinElmer, Finland).

Statistical Analysis. Continuous values were expressed as means with SEM, and categorical values were represented by the frequency and percentage. We compared characteristics between men and women using an analysis of Student's *t* test. Both men and women were classified into 3 groups depending on vitamin K intake and the complex sample general linear model analysis was carried out to investigate the relationship between BMD and vitamin K intake. Proportion or mean of each variable was tested by using an analysis of covariance (ANCOVA). The trend of the relationship between vitamin K intake and BMD with men and women were examined using *p* for trend. The association among the risk for osteoporosis and osteopenia in total femur and vitamin K intake level were identified using the multiple logistic regression analysis and expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Potential confounders were included in a multiple logistic regression as covariates (in case of men, age, calcium intake, dietary supplementation, drinking and smoking habits, serum vitamin D levels, BMI, and day of muscular strength exercise and in case of women, age, calcium intake, dietary supplementation, drinking and smoking habits, serum vitamin D levels, hormonal replacement therapy, postmenopausal status, BMI, and day of muscular strength exercise). For statistical analysis, SPSS ver. 21.0 (IBM SPSS, Armonk, NY) was used, and the level of significance was set at *p*<0.05.

Results

Characteristics of the subjects and vitamin K intake and BMD. The characteristics of the men and women subjects analyzed in this study are shown in Table 1. Total 7,092 subjects were analyzed in this study, the average age of men was investigated to be 44.64 ± 0.48 years old and that of women to be 46.47 ± 0.45 years old. In case of vitamin K, men took as much as 242.73 ± 4.91 $\mu\text{g}/\text{day}$ and women 200.07 ± 3.78 $\mu\text{g}/\text{day}$ (*p*<0.001). The BMD of total femur of men was 0.96 ± 0.00 g/cm^2 and that of women to be 0.84 ± 0.00 g/cm^2 and BMD of the lumbar of men was 0.97 ± 0.00 g/cm^2 and that of women to be 0.92 ± 0.00 g/cm^2 (*p*<0.001). Additionally, The T-score of total femur of men was investigated to be 0.16 ± 0.03 and that of women to be -0.01 ± 0.02 and the femoral neck of men was investigated to be -0.22 ± 0.03 and that of women to be -0.77 ± 0.03 (*p*<0.001). The T-score of lumbar spine of men was investigated to be -0.45 ± 0.03 and that of women to be -0.91 ± 0.03 (*p*<0.05).

Relationship between vitamin K intake and BMD. The comparison of the bone mineral density in men depending on vitamin K intake is shown in Table 2. In men, it turned out that the more intake of vitamin K, the higher BMD of total femur, trochanter and intertrochanter (*p* for trend<0.05). The comparison of the BMD in women depending on vitamin K intake is shown in Table 3. In women, as the intake of vitamin K is higher, BMD of total femur, trochanter, intertrochanter, femoral neck, ward and lumbar spine were turned out to be higher after adjusting bone formation related factors (*p* for trend<0.05). The odds ratios for osteopenia and osteoporosis prevalence in the 3 tertiles divided according to vitamin K intake are listed in Table 4. Osteopenia and osteoporosis prevalence in the total femur was associated with odds ratios of 0.844, and 0.758 (in ascending order of vitamin K intake tertiles), indicating that the risk of osteopenia and osteoporosis significantly decreased as vitamin K intake increased in women (*p*<0.05). However, this trend was not persisted after adjusting for bone-related factors (*p* = 0.167)

Discussion

In this cross-sectional study, vitamin K intake of Korean adults are much higher than AI references, and increased vitamin K intake was associated with BMD both in femur and lumbar bone in the women and only in femur in the men. The previous research reported that osteoporosis prevalence in lumbar spine and femur site were 40.1% and 12.4%, respectively in Koreans women aged 50 to 79. However osteoporosis prevalence in men with same ages were low as 6.5% in lumbar spine, 5.9% in femur.⁽¹⁶⁾ We showed that the difference of BMD in lumbar spine according to vitamin K intakes was only in women, not in men. Therefore, it may speculate that bones of relatively high risk of osteoporosis were more sensitively respond to dietary vitamin K intakes. Vitamin K intakes are different according to the ethnicity and genders in diverse populations. According to the results of the North/South Ireland Food Consumption Survey database, it was reported that vitamin K intake was 84 $\mu\text{g}/\text{day}$ in men and 75 $\mu\text{g}/\text{day}$ in women.⁽¹⁷⁾ Vermeer *et al.*⁽¹⁸⁾ reported that a vitamin K intake in elderly women was 210 $\mu\text{g}/\text{day}$. An analysis of 11 studies carried out by Booth *et al.* revealed that vitamin K intake ranges from 61 $\mu\text{g}/\text{day}$ to 210 $\mu\text{g}/\text{day}$.⁽¹⁾ The vitamin K intake in this study was 243 $\mu\text{g}/\text{day}$ and 200 $\mu\text{g}/\text{day}$ for adult men and women, respectively and was higher than previously reported other cohort studies. The difference in intake compared to other countries is supposed to the dietary habits of Koreans, who consume large amounts of vegetables that contain high vitamin K contents and traditional rice based meal pattern. This can be confirmed from the 2011 KNHANES data that indicate relatively high consumption of grains (316.7 g/day), vegetables (295.4 g/day), and fruits (161.5 g/day).⁽¹⁹⁾ And our previous research regarding contrib-

Table 1. Characteristics of the subjects

Variables	Men (n = 2,785)	Women (n = 4,307)	p
Age (years)	44.64 ± 0.48 ^a	46.47 ± 0.45	<0.001
Weight (kg)	70.07 ± 0.29	57.38 ± 0.18	<0.001
Height (cm)	170.62 ± 0.17	157.14 ± 0.16	<0.001
Body mass index (kg/m ²)	24.02 ± 0.08	23.27 ± 0.78	<0.001
Serum vitamin D (ng/ml)	18.13 ± 0.27	16.17 ± 0.23	<0.001
Muscular strength exercise (day/week)			
0	1,766 (62.2) ^b	3,589 (84.0)	
1	217 (9.1)	168 (4.4)	
2	214 (8.7)	161 (3.8)	
3	210 (8.0)	146 (3.0)	<0.001
4	104 (3.5)	70 (1.7)	
5	249 (8.4)	125 (2.8)	
unknown	4 (0.1)	14 (0.4)	
Current alcohol drinker	1,999 (75.7)	1,535 (39.9)	<0.001
Current smoker	1,072 (45.0)	210 (6.1)	<0.001
Postmenopausal	—	2,209 (40.9)	
Hormonal replacement therapy	—	549 (9.8)	
Nutrient Intake			
Energy (kcal/day)	2,306.0 ± 18.4	1,692.7 ± 13.9	<0.001
Ca (mg/day)	569.2 ± 8.1	452.9 ± 6.6	<0.001
Vitamin K (µg/day)	242.7 ± 4.9	200.1 ± 3.8	<0.001
Bone Mineral Density (g/cm ²)			
Total femur	0.96 ± 0.00	0.84 ± 0.00	<0.001
Trochanter	0.69 ± 0.00	0.61 ± 0.00	<0.001
Intertrochanter	1.16 ± 0.00	1.01 ± 0.00	<0.001
Femoral neck	0.82 ± 0.00	0.71 ± 0.00	<0.001
Ward	0.64 ± 0.01	0.57 ± 0.00	<0.001
Lumbar spine	0.97 ± 0.00	0.92 ± 0.00	<0.001
T-score			
Total femur	0.16 ± 0.03	-0.01 ± 0.02	<0.001
Femoral neck	-0.22 ± 0.03	-0.77 ± 0.03	<0.001
Lumbar spine	-0.45 ± 0.03	-0.91 ± 0.03	<0.05

^aMean ± SEM, ^bN (%).

Table 2. Bone mineral density according to vitamin K intake in men over 19 years

Variables	Tertile of total vitamin K intake (µg/day)/1,000 kcal			p for trend ^b
	Tertile 1: ≤58.07 (n = 928)	Tertile 2: 58.09–121.91 (n = 929)	Tertile 3: ≥121.93 (n = 928)	
Bone Mineral Density (g/cm ²) ^a				
Total femur	0.95 ± 0.01	0.96 ± 0.01	0.97 ± 0.01	0.048
Trochanter	0.66 ± 0.01	0.67 ± 0.01	0.67 ± 0.01	0.033
Intertrochanter	1.15 ± 0.01	1.15 ± 0.01	1.17 ± 0.01	0.037
Femoral neck	0.84 ± 0.01	0.83 ± 0.01	0.84 ± 0.01	0.464
Ward	0.63 ± 0.02	0.63 ± 0.01	0.65 ± 0.01	0.113
Lumbar spine	0.92 ± 0.01	0.91 ± 0.01	0.92 ± 0.01	0.829

^aMean ± SEM. ^bAdjusted for age, serum vitamin D, calcium intake, body mass index, day of muscular strength exercise, alcohol intake, smoking status, dietary supplement.

uting foods of Korean for vitamin K showed that cereals and cereal products were highly ranked.⁽²⁰⁾ As for the high intakes of vitamin K in Korean compared with other countries,^(21,22) it seem that main food source were not only vegetables and fruits but also cereals.

During about half a century, the effect of vitamin K in human was focused only on blood coagulation, and dietary reference intake (DRI) was set based on the degree of hemostasis. The hepatic vitamin K dependent coagulation factors are 100% carboxylated in the normal adults and vitamin-insufficiency in healthy adults has never been reported.⁽²³⁾ However, it was demonstrated

that up to 40–50% of osteocalcin was uncarboxylated in person not in vitamin K deficiency by coagulation activity analysis.⁽²⁴⁾

Osteoporosis is a chronic disease that is attributable to a variety of factors. Recent studies examining the association between macro and micro nutrients and bone health, emphasize that osteoporosis is not just an individual problem but causes national economic loss.^(25,26) Therefore, sufficient dietary intake to prevent osteoporosis is a keen current issue nation widely. Vitamin K is a fat-soluble vitamin and low vitamin K intakes are associated with increased risk of osteoporosis, fracture and osteoarthritis.⁽⁵⁾ In a prospective study investigating the effects of vitamin K intake and

Table 3. Bone mineral density according to vitamin K intake in women over 19 years

Variables	Tertile of total vitamin K intake ($\mu\text{g/day}$)/1,000 kcal			<i>p</i> for trend ^b
	Tertile 1: ≤ 58.23 (<i>n</i> = 1,435)	Tertile 2: 58.32–129.42 (<i>n</i> = 1,437)	Tertile 3: ≥ 129.45 (<i>n</i> = 1,435)	
Bone Mineral Density (g/cm^2) ^a				
Total femur	0.85 \pm 0.01	0.86 \pm 0.01	0.87 \pm 0.01	0.005
Trochanter	0.62 \pm 0.01	0.62 \pm 0.01	0.63 \pm 0.01	0.001
Intertrochanter	1.03 \pm 0.01	1.04 \pm 0.01	1.05 \pm 0.01	0.004
Femoral neck	0.72 \pm 0.01	0.73 \pm 0.01	0.73 \pm 0.01	0.043
Ward	0.58 \pm 0.01	0.59 \pm 0.01	0.60 \pm 0.01	0.026
Lumbar spine	0.92 \pm 0.01	0.93 \pm 0.01	0.93 \pm 0.01	0.020

^aMean \pm SEM. ^bAdjusted for age, serum vitamin D, calcium intake, body mass index, day of muscular strength exercise, postmenopausal state, hormonal replacement therapy, alcohol intake, smoking status, dietary supplement.

Table 4. Odd ratios (ORs) for osteoporosis in femur according to vitamin K intake levels

Variables	Tertile of total vitamin K intake ($\mu\text{g/day}$)/1,000 kcal			<i>p</i> for trend
	Tertile 1	Tertile 2	Tertile 3	
Men				
ORs ^a				
Crude	1	0.824 (0.594–1.145)	0.537 (0.384–0.751)	0.001
Multivariate adjusted ^b	1	0.972 (0.669–1.412)	0.577 (0.384–0.868)	0.013
Women				
ORs				
Crude	1	0.844 (0.686–1.039)	0.758 (0.609–0.943)	0.042
Multivariate adjusted ^c	1	0.980 (0.743–1.302)	0.790 (0.593–1.053)	0.167

Odd ratio (95% confidence interval). ^aT-score ≤ -2.5 and $-2.5 < \text{T-score} < -1$. ^bAdjusted for age, serum vitamin D, calcium intake, body mass index, day of muscular strength exercise, alcohol intake, smoking status, dietary supplement. ^cAdjusted for age, serum vitamin D, calcium intake, body mass index, day of muscular strength exercise, postmenopausal state, hormonal replacement therapy, alcohol intake, smoking status, dietary supplement.

fracture incidence in adult women, it was revealed that a decrease in vitamin K intake causes an increase in fracture risk.⁽⁶⁾ In a study conducted on vitamin K intake and the occurrence of hip joint fractures in 12 regions of Japan, it was reported that vitamin K intake reduces the occurrence of fractures even after controlling for factors that influence bone strength such as calcium, magnesium, and vitamin D; the author therefore recommended consuming vegetables that contain vitamin K to prevent bone mass loss.⁽²⁷⁾ This present study revealed that femur and lumbar BMD increased with an increase in vitamin K intake in women and femur BMD in men. We also found that the higher vitamin K intake were the lower risks of osteoporosis and osteopenia. These positive results are support the relationship between vitamin K intakes and musculoskeletal health in prior studies. However, the risks of osteoporosis according to vitamin K intakes were significantly different only in men after controlling various factors affecting bone density not in women. As for the different results by gender, it may speculate that physiological difference between men and women such as hormone and body composition affected the bone metabolism.^(28,29)

The association with vitamin K insufficiency and bone health cannot be implied causal effect, however, it is reasonable that vitamin K would be involved in carboxylation of vitamin K dependent Gla proteins in bone formations and is a modifiable factor that can prevent bone loss.⁽³⁰⁾ Therefore consideration more than hemostatic effect of vitamin K must be needed to set the dietary requirement analysis process.

The Institute of Medicine, U.S.A. has set the AI levels of vitamin K at 90 μg for women and 120 μg for men;⁽³¹⁾ and the UK recommends an intake of 1 μg per kg of body weight.⁽³²⁾ The AI

levels for Korean adults has been set at 65 $\mu\text{g/day}$ for women and 75 $\mu\text{g/day}$ for men;⁽³³⁾ however, the recommended nutrient intake and tolerable upper intake level standards have not been completely established because of the lack of a large-scale survey on vitamin K intakes. AI was determined on the median intake of Korean by small-scale studies. There were insufficient data to establish dietary recommendation for vitamin K, due to a lack of strong endpoints that reflected adequacy of intake for a defined health outcome. In our study, there are positive effects of vitamin K on BMD much over the current AI levels. Therefore, in recognition of the function of vitamin K effect on bone health, this study results can be used as baseline data when reconsidering the recommended intake level of vitamin K intake in Korean adults in the future.

A study conducted on elderly Chinese subjects presented that potent dietary vitamin K intake was not enough to prevent the occurrence of fractures.⁽¹¹⁾ Several studies were reported the efficacy of vitamin K supplements beyond dietary vitamin K for the prevention of bone loss.^(2,23) There was no immediate change in BMD in postmenopausal women who were supplemented with 5 mg of vitamin K for 2–4 years.⁽³⁴⁾ However, there is limited randomized controlled trial evidence supporting the protective effect of vitamin K supplementation on BMD until now. Therefore it cannot be recommended vitamin K supplementation beyond consuming dietary vitamin K rich diet to prevent musculoskeletal diseases.

This study has several limitations. First we only analyzed the dietary data based on 24-h dietary recall; it may not represent the general dietary intake. Second, only phylloquinone type of vitamin K intake was examined due to lack of food database

about menaquinones. Nonetheless, this study determined the dietary intake of vitamin K in Korean adults and confirmed that vitamin K is indeed a factor that influences bone density. Therefore, the results of this study could be used as the foundation to set vitamin K requirements to maintain bone health other than hemostatic effect.

Acknowledgments

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and Future Planning (project no.: NRF-2012R1A1A3012499).

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Abbreviation

AI	adequate intakes
BMD	bone mineral density
CI	confidence intervals
DEXA	dual-energy X-ray absorptiometry
DRI	dietary reference intake
KCDC	Korea Center for Disease Control and Prevention
KNHANES	Korea National Health and Nutrition Examination Survey
ORs	odds ratios
SEM	standard error of mean

Conflict of Interest

No potential conflicts of interest were disclosed.

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