

Vitamin K Supplement Along with Vitamin D and Calcium Reduced Serum Concentration of Undercarboxylated Osteocalcin While Increasing Bone Mineral Density in Korean Postmenopausal Women over Sixty-Years-Old

Sang Hyeon Je¹, Nam-Seok Joo¹,
Beom-hee Choi², Kwang-Min Kim¹,
Bom-Taek Kim¹, Sat-Byul Park¹,
Doo-yeoun Cho¹, Kyu-Nam Kim¹
and Duck-Joo Lee¹

¹Department of Family Practice and Community Health, Ajou University School of Medicine, Suwon;
²Department of Family Medicine, CHA Biomedical Center, College of Medicine, CHA University, Seoul, Korea

Received: 16 January 2011
Accepted: 12 May 2011

Address for Correspondence:
Duck-Joo Lee, MD
Department of Family Practice and Community Health, Ajou University School of Medicine, 164 Worldcup-ro, Youngtong-gu, Suwon 443-721, Korea
Tel: +82.31-219-5309, Fax: +82.31-219-5218
E-mail: djleemd@msn.com

There are inconsistent findings on the effects of vitamin K on bone mineral density (BMD) and undercarboxylated osteocalcin (UcOC). The present intervention study evaluated the effect in subjects over 60-yr-old. The vitamin K group (vitamin K + vitamin D + calcium supplement; 15 mg of vitamin K2 [menatetrenone] three times daily, 400 IU of vitamin D once a day, and 315 mg of calcium twice daily) and the control group (vitamin D + calcium supplement) were randomly assigned. During the six months of treatment, seventy eight women participated (38 in the vitamin K group and 40 in the control group) and 45 women completed the study. The baseline characteristics of study participants did not differ between the vitamin K and the control groups. In a per protocol analysis after 6 months, L3 bone mineral density has increased statistically significantly in the vitamin K group compared to the control group (0.01 ± 0.03 g/cm² vs -0.008 ± 0.04 g/cm², $P = 0.049$). UcOC concentration was also significantly decreased in the vitamin K group (-1.6 ± 1.6 ng/dL vs -0.4 ± 1.1 ng/dL, $P = 0.008$). In conclusion, addition of vitamin K to vitamin D and calcium supplements in the postmenopausal Korean women increase the L3 BMD and reduce the UcOC concentration.

Key Words: Vitamin K; Undercarboxylated osteocalcin; Bone Mineral Density; Korean Women

INTRODUCTION

Health risk of osteoporosis is increasing in Korean women and there were many trials to reduce and prevent osteoporotic fracture risk (1, 2). Vitamin K plays a role in bone metabolism and may decrease the risk of fracture (3, 4). Vitamin K also acts synergistically with Vitamin D on bone mineral density (BMD) and positively influences the balance of calcium, a key mineral in bone metabolism. As a cofactor for carboxylase activity, vitamin K facilitates the gamma-carboxylation of osteocalcin to increase the formation of bone (5). If the process of gamma-carboxylation is hindered by lack of vitamin K, the concentration of undercarboxylated osteocalcin (UcOC), which has low affinity to hydroxyapatite in bone, increases. An inverse relation between UcOC and BMD, and high serum UcOC levels in women in their 20 sec and 50 sec was recently reported (6). Since high UcOC level may make women in their 50 sec vulnerable to bone fracture, vitamin K supplementation may be worthwhile for women of this age group to improve BMD.

However, the effects of vitamin K supplementation are contro-

versial. Vitamin K supplementation provided protection against fractures, age related BMD decline, and osteoporosis in some studies (7-9), while other studies do not support a BMD benefit of vitamin K supplementation (10-14). Although studies examining the effects of vitamin K supplementation on BMD or osteoporosis have been conducted in many Asian countries (15-18), the role of vitamin K in bone health in Korean postmenopausal women remains unclear.

The present intervention study was designed to test the effects of vitamin K supplementation with vitamin D and calcium for 6 months on BMD and UcOC among the advanced postmenopausal Korean women over sixty years old.

MATERIALS AND METHODS

Subjects and study design

We enrolled the advanced postmenopausal women over 60-yr-old, who did not want to take anti-resorptive agent such as bisphosphonate. Therefore, postmenopausal women over sixty years old living in Seoul, Korea, who visited the Out Patients Clin-

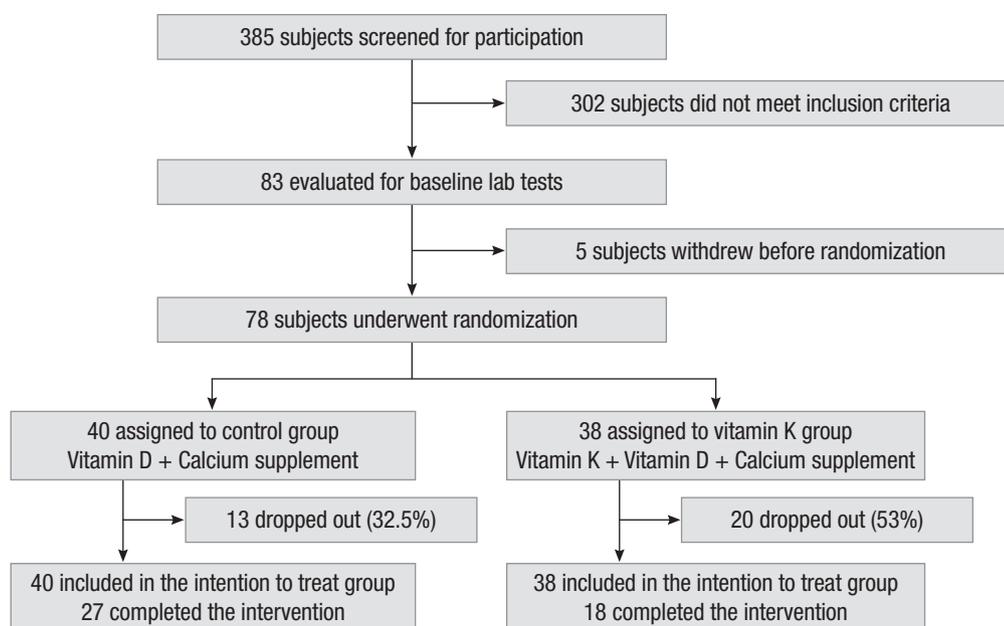


Fig. 1. Screening, randomization and follow up for study subjects.

ic at Cha Hospital in Seoul from January-May 2010 were recruited ($n = 385$) (Fig. 1). Of those screened, 103 women were excluded for taking vitamin K, anti-lipid medications, hormone replacement therapy, or medications influencing bone metabolism aspects such as bisphosphonate, calcitonin, steroids, phenytoin, carbamazepine, rifampicin, heparin, and warfarin. As well, 199 women with diabetes, hypertension, body mass index (BMI) > 30 kg/m², or metabolic bone diseases were excluded. Five other subjects withdrew before randomization for personal reasons. The remaining 78 women were randomly assigned to either the treatment group (vitamin K, $n = 40$) or a control group ($n = 38$). For 6 months, the treatment group received 15 mg of vitamin K₂ (menatetrenone) three times a day after every meal, combination form containing 400 IU of active vitamin D₃ once a day, and 315 mg of calcium carbonate twice daily. During the same period, the control group received 400 IU of vitamin D and 315 mg of calcium twice daily. During the course of the study, 33 women dropped out due to relocation or loss to follow-up. Forty five women completed the study.

Fasting blood (10 hr of fasting in the morning) was collected at baseline and at months 3 and 6. Total cholesterol, triglyceride and high density lipoprotein (HDL) cholesterol were measured by an enzymatic colorimetric assay using a model 7600 apparatus (Hitachi, Tokyo, Japan). The BMD in the lumbar spine (L1-L4) and femur neck, and ward measurements were performed using a QDR 4500 apparatus (Hologic, Waltham, MA, USA) at baseline and 6 months. The serum UcOC was assayed by an enzyme-linked immunosorbent assay using two monoclonal antibodies. Anti-osteocalcin (OC) antibody and a solid-phase anti-Glu 21, 24-OC antibody with recombinant human UcOC (Taka-ra Shuzo, Shiga, Japan) were used. The coefficients of variation (CVs) in the intra- and inter-assay were 7.3% and 9.7%, respec-

tively. CV was measured twice and the average was determined. The study participants reported their medications to the principal investigators at screening, and at months 3 and 6, and were interviewed about side effects at every visit. For assess study compliance, the remaining pill count was checked at all visits, and blood samples were collected at baseline and months 3 and 6.

Statistical analysis

An independent t test was used to compare the baseline demographics and any changes that occurred after 6 months of intervention between the vitamin K group and the control group. To compare any changes in each group after 6 months, the paired t test was used. An intention to treat (ITT) analysis was conducted to obtain standardized outcome variables. In addition, per-protocol (PP) analysis of the 45 subjects was also conducted. A P value < 0.05 was statistically significant. These analyses were done using SPSS version 18.0 (SPSS, Chicago, IL, USA).

Ethics statements

All participants provided written informed consent and this study was reviewed and approved by the institutional review board of Cha Hospital (EKI-GLA-06-32).

RESULTS

A total of 385 postmenopausal women over sixty were screened and 78 women were enrolled in the study (Fig. 1). The main reasons for ineligibility were the used of restricted medications and occurrence of diseases that could affect bone metabolism. In the ITT analysis comparing the characteristics of the vitamin K group with the control group (Table 1), the age at menopause in the vitamin K group (49.6 ± 2.7 yr) was significantly different

Table 1. Characteristics of study participants at baseline by treatment group: ITT analysis

Variables	Vitamin K + D + Ca (n = 38)	Vitamin D + Ca (n = 40)	P value
Age (yr)	68.1 ± 6.3	67.6 ± 6.2	0.750
Height (cm)	153.1 ± 4.9	153.2 ± 5.5	0.956
Weight (kg)	56.0 ± 6.3	57.7 ± 7.6	0.292
Age at menopause (yr)	49.6 ± 2.7	50.8 ± 1.7	0.028
Duration of menopause (yr)	18.4 ± 7.2	16.8 ± 6.8	0.312
SBP (mm/Hg)	128.8 ± 27.0	119.2 ± 17.8	0.317
DBP (mm/Hg)	75.0 ± 19.5	70.2 ± 10.5	0.453
Body mass index (kg/m ²)	23.8 ± 2.5	24.5 ± 2.9	0.278
Total cholesterol (mg/dL)	198.4 ± 36.1	204.0 ± 36.6	0.501
BUN (mg/dL)	15.3 ± 4.0	15.3 ± 3.9	0.993
Creatinine (mg/dL)	0.8 ± 0.1	0.8 ± 0.1	0.639
HDL (mg/dL)	50.8 ± 10.3	52.9 ± 12.7	0.442
Calcium (mg/dL)	9.0 ± 0.4	9.1 ± 0.2	0.449
BMD (g/cm ²)			
Lumbar 1	0.63 ± 0.10	0.62 ± 0.07	0.994
Lumbar 2	0.70 ± 0.10	0.72 ± 0.10	0.333
Lumbar 3	0.76 ± 0.11	0.77 ± 0.10	0.897
Lumbar 4	0.82 ± 0.13	0.78 ± 0.10	0.190
BMD femur neck (g/cm ²)	0.57 ± 0.07	0.58 ± 0.07	0.473
BMD femur ward (g/cm ²)	0.39 ± 0.12	0.39 ± 0.09	0.810
UcOC (ng/dL)	2.2 ± 1.8	1.6 ± 1.0	0.094
Osteocalcin (ng/dL)	10.9 ± 5.4	12.0 ± 6.3	0.484
BSALP (µg/liter)	197.2 ± 54.4	184.2 ± 47.6	0.269

All values are mean ± standard deviation. P values are from independent t test. D, vitamin D; Ca, calcium supplement; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; HDL, high-density lipoprotein; BMD, bone mineral density; UcOC, undercarboxylated osteocalcin; BSALP, serum bone-specific alkaline phosphatase.

from the age at menopause in the control group (50.8 ± 1.7 yr, P = 0.03). Other characteristics did not differ in the treatment group in both ITT and PP analyses. In the PP analysis (Table 2), characteristics of women in the vitamin K group were not different from those in the control group. The mean (± SD) age, age at menopause, and duration of menopause were 67.3 ± 6.3, 50.6 ± 1.9, and 16.6 ± 6.8 yr, respectively, in the vitamin K group and 67.8 ± 6.4, 51.0 ± 1.9, and 16.8 ± 7.0 yr, respectively, in the control group. BMDs in lumbar and femur were similar in both the vitamin K and the control groups. In addition, the UcOC concentration in the vitamin K group (2.1 ± 1.7 ng/dL) was not significantly different from that in the control group (1.5 ± 1.0 ng/dL, P = 0.214). The mean (± SD) osteocalcin level was 9.6 ± 6.4 ng/dL in the vitamin K group and 11.7 ± 6.4 ng/dL in the control group. There were no significant differences in blood urea nitrogen, creatinine, calcium and serum bone-specific alkaline phosphatase (BSALP) between the vitamin K and the control groups. The BMD in L1-L4 and femur neck, and in the ward in the vitamin K group were not different from those in the control group. The serum UcOC level in the vitamin K group (2.1 ± 1.7 ng/dL) was higher than that in the control group (1.5 ± 1.0 ng/dL), but showed no significant difference (P = 0.21). Osteocalcin level was nonsignificantly lower in the vitamin K group (9.6 ±

Table 2. Characteristics of study participants at baseline by treatment group: PP analysis

Variables	Vitamin K + D + Ca (n = 18)	Vitamin D + Ca (n = 27)	P value
Age (yr)	67.3 ± 6.3*	67.8 ± 6.4	0.792
Height (cm)	153.7 ± 5.5	153.4 ± 5.9	0.900
Weight (kg)	57.5 ± 4.9	57.5 ± 8.2	0.991
Age at menopause (yr)	50.6 ± 1.9	51.0 ± 1.9	0.569
Duration of menopause (yr)	16.6 ± 6.8	16.8 ± 7.0	0.931
SBP (mm/Hg)	128.7 ± 7.5	122.8 ± 14.4	0.457
DBP (mm/Hg)	70.2 ± 13.6	72.6 ± 8.5	0.776
Body mass index (kg/m ²)	24.3 ± 2.0	24.3 ± 2.8	0.989
Total cholesterol (mg/dL)	200.1 ± 39.8	192.9 ± 32.8	0.847
Triglyceride (mg/dL)	142.4 ± 46.5	136.5 ± 59.7	0.722
BUN (mg/dL)	16.0 ± 4.2	14.9 ± 4.1	0.421
Creatinine (mg/dL)	0.7 ± 0.1	0.8 ± 0.1	0.627
HDL (mg/dL)	49.6 ± 10.8	53.0 ± 13.8	0.394
Calcium (mg/dL)	9.0 ± 0.4	9.1 ± 0.3	0.330
BMD (g/cm ²)			
Lumbar 1	0.61 ± 0.11	0.63 ± 0.08	0.539
Lumbar 2	0.69 ± 0.11	0.72 ± 0.10	0.394
Lumbar 3	0.75 ± 0.13	0.76 ± 0.09	0.798
Lumbar 4	0.79 ± 0.14	0.77 ± 0.09	0.599
BMD femur neck (g/cm ²)	0.56 ± 0.07	0.58 ± 0.06	0.431
BMD femur ward (g/cm ²)	0.38 ± 0.08	0.39 ± 0.09	0.804
UcOC (ng/dL)	2.1 ± 1.7	1.5 ± 1.0	0.214
Osteocalcin (ng/dL)	9.6 ± 6.4	11.7 ± 6.4	0.301
BSALP (µg/liter)	189.5 ± 64.5	185.6 ± 46.0	0.827

All values are mean ± standard deviation. P values were from independent t test. D, vitamin D; Ca, calcium supplement; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; HDL, high-density lipoprotein; BMD, bone mineral density; UcOC, undercarboxylated osteocalcin; BSALP, serum bone-specific alkaline phosphatase.

6.4 ng/dL) than in the control group (11.7 ± 6.4 ng/dL, P = 0.29). The BSALP level was 189.5 ± 64.5 µg/L in the vitamin K group and 185.6 ± 46.0 µg/L in the control group (P = 0.827). No significant differences in BMD and biomarker values between the vitamin K and the control groups indicated that the randomization worked well. The ITT analysis showed similar results.

After 6 months of treatment, the L3 BMD in the vitamin K group compared to the control group increased statistically significantly (0.01 ± 0.03 g/cm² vs -0.008 ± 0.04 g/cm², P = 0.049). Compared to BMD at baseline, BMD in femur at month 6 was significantly increased in both the vitamin K and the control groups. However, after 6 months of treatment, BMD in the vitamin K group was not statistically different from BMD in the control group. In addition, compared to the baseline, the vitamin K group significantly decreased UcOC concentration (-1.6 ± 1.6 ng/dL, P < 0.01), whereas the UcOC level in the control group did not change (-0.4 ± 1.1 ng/dL). The change in UcOC concentration in the vitamin K group, but not in the control group, confirmed the compliance of the participants in the vitamin K group with the study protocol. Osteocalcin was also non-significantly increased in the vitamin K group (1.6 ± 5.8 ng/dL), but not in the control group (-1.1 ± 6.0 ng/dL). Triglyceride level decreased in the vitamin K group (-10.0 ± 59.1 ng/dL) (Table 3). Three people

Table 3. Changes in BMD and biochemical markers from the baseline to 6 months

Variables	Vitamin K + D + Ca (n = 18)	Vitamin D + Ca (n = 27)	P value
SBP (mm/Hg)	0.5 ± 3.1	1.2 ± 6.1	0.832
DBP (mm/Hg)	11.0 ± 13.1	5.6 ± 4.6	0.480
BMD (g/cm ²)			
Lumbar 1	-0.0009 ± 0.04	0.009 ± 0.04	0.377
Lumbar 2	-0.01 ± 0.04	-0.0048 ± 0.03	0.618
Lumbar 3	0.01 ± 0.03	-0.008 ± 0.04	0.049
Lumbar 4	0.007 ± 0.05	0.005 ± 0.04	0.888
BMD femur neck (g/cm ²)	0.01 ± 0.031	0.01 ± 0.027	0.890
BMD femur ward (g/cm ²)	0.06 ± 0.10	0.03 ± 0.07	0.269
Total cholesterol (mg/dL)	-6.1 ± 42.8	10.6 ± 29.2	0.169
Triglyceride (mg/dL)	-10.0 ± 59.1	10.5 ± 78.7	0.335
UcOC (ng/dL)	-1.6 ± 1.6	-0.4 ± 1.1	0.008
Osteocalcin (ng/dL)	1.6 ± 5.8	-1.1 ± 6.0	0.136
BSALP (μg/liter)	-2.1 ± 34.3	7.6 ± 41.0	0.390
BUN (mg/dL)	-0.5 ± 3.6	0.0 ± 4.1	0.618
Creatinine (mg/dL)	0.02 ± 0.09	0.007 ± 0.08	0.566
HDL (mg/dL)	2.0 ± 9.4	3.0 ± 8.1	0.713
Calcium (mg/dL)	0.2 ± 0.3	0.1 ± 0.3	0.232

All values are mean ± standard deviation. P values from independent t test. D, vitamin D; Ca, calcium supplement; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMD, bone mineral density; UcOC, undercarboxylated osteocalcin; BSALP, serum bone-specific alkaline phosphatase; BUN, blood urea nitrogen; HDL, high-density lipoprotein.

complained of nausea sensation twice after taking vitamin K. No other participants including people in the control group reported adverse events during the study period.

In summary, after 6 months treatment of vitamin K to the postmenopausal women over sixty, the L3 BMD increased significantly compared to the control group. In addition, the changes in some biochemical markers differed by treatment. Compared to the control group, the vitamin K group significantly decreased serum UcOC concentration ($P = 0.008$). Osteocalcin level was higher in the vitamin K group than in the control group, but the difference was not significant ($P = 0.14$).

DISCUSSION

In this study, supplementation with vitamins K and D, and with calcium for 6 months of treatment significantly improved the L3 BMD compared to supplementation with vitamin D and calcium in postmenopausal Korean women over sixty years old. In addition, femur BMD was increased in the vitamin K group (vitamin K + vitamin D + calcium), but a similar increase was observed in the control group (vitamin D + calcium supplementation). The UcOC concentration significantly decreased in the vitamin K group compared to the control group ($P < 0.01$), and the osteocalcin level increased nonsignificantly in the vitamin K group ($P = 0.14$). The triglyceride level decreased in the vitamin K group, but was not statistically different from the control group. Similar results were observed in the ITT analysis.

When vitamin K concentration in the body is low, insufficient amount of osteocalcin completes γ -carboxylation; consequent-

ly, UcOC concentration increases and the affinity to calcium to bone matrix decreases. Gla-residues of osteocalcin combine with calcium and require vitamin K to activate the reaction site. Therefore, measuring UcOC concentration is a more accurate method of monitoring vitamin K than prothrombin in the liver (19).

In a previous cross-sectional study in postmenopausal women, elevated serum UcOC and low spinal BMD were observed in the low plasma phylloquinone (vitamin K₁) group (20). In another study, healthy elderly Scottish women who took vitamin K₁ with vitamin D and calcium showed a sustained increase in BMD at the site of the ultradistal radius in comparison with women taking calcium and vitamin D (21). A combined vitamin K₂ therapy with vitamin D₃ for postmenopausal Japanese women produced low serum UcOC and improved BMD values (22). In an examination of the effects of vitamin K₂ (45 mg/day) supplementation with calcium (1,500 mg/day) on lumbar BMD in postmenopausal women in Indonesia, a meaningful increase in BMD and a decrease in UcOC level were reported (18). On the other hand, a study reported no vitamin K effect on BMD in North American women, prompting the suggestion that women receiving calcium and vitamin D supplements do not need additional vitamin K supplementation to prevent osteoporosis (23). Another recent study of vitamin K₁ supplementation for 2-4 yr in Canadian women also reported no benefits on age-related decline in BMD (12). Our study showed that compared to the control group that took vitamin D and calcium, additional vitamin K supplementation to vitamin D and calcium improved L3 BMD in Korean postmenopausal women over sixty. Our previous cross-sectional study involving Korean women reported an inverse association between UcOC and BMD (6). This dichotomy may partially be due to an ethnic difference and subjects' age in the bone metabolism or response to vitamin K or UcOC. A study of inflammatory bowel disease patients in Japanese women reported a decrease in the concentrations of vitamin K and D, and a resulting decrease in BMD (24). The foregoing results imply that ethnic-related diversity in gastrointestinal absorption may explain the different response to vitamin K supplement and its subsequent effects on BMD (25).

Several studies reported that obesity has been related to the level of vitamin K in adipose tissue, reflecting its fat-soluble nature. In one study, obese patients displayed a lower UcOC concentration and their UcOC/osteocalcin ratio was negatively related with body mass index (26). Another study reported that people with a high serum triglyceride level had high BMD in skeletal muscles (27). On the other hand, adult obesity has been inversely related to circulating indicators of serum vitamin K (28).

Limitations of the study were the small number of participants, relatively high dropout rate, and lack of a placebo group (i.e., no supplementation). The dosages of vitamin K, vitamin D and calcium and the duration of treatment may have been insufficient

to induce responses in related biochemical markers and total BMD. Moreover, we did not measure and compare the dietary vitamin K intake. Also, bone quality was not measured, which might be only a minor limitation. A previous study (6) suggested that UcOC concentration is inversely associated with age, with higher UcOC concentrations in younger women. This suggests that the effect of the vitamin K on osteocalcin may also be age-related. Given the advanced age of our study subjects (mean age 68 yr) and relatively short treatment period, the study may have not been able to discern an increase all part of BMD. However, it is noteworthy that changes in UcOC concentration among older women have been reported, with UcOC concentration in women in their 50 sec being higher than that in women in their 60 sec and 70 sec (6). Therefore, vitamin K may be more effective in preventing bone loss or improving BMD in women aged 50-59 yr, especially in perimenopausal women or women with few years of menopause. A study testing the influence of vitamin K supplementation to perimenopausal women or women with few years of menopause for more than 6 months is needed. In addition, inconsistent findings from different countries suggest that a comparison of Korean data with data from other countries is warranted. A study design involving a longer duration of vitamin K supplementation and with postmenopausal women having a short duration of menopause may prove valuable. Finally, physical activity was not measured.

In conclusion, in this randomized study, supplementation with vitamin K, D and calcium for 6 months improves L3 BMD and reduces UcOC concentration in Korean postmenopausal women over sixty.

REFERENCES

1. Rowe SM, Song EK, Kim JS, Lee JY, Park YB, Bae BH, Hur CI. *Rising incidence of hip fracture in Gwangju City and Chonnam Province, Korea. J Korean Med Sci* 2005; 20: 655-8.
2. Lee DY, Lim SJ, Moon YW, Min YK, Choi D, Yoon BK, Park YS. *Determination of an applicable FRAX model in Korean women. J Korean Med Sci* 2010; 25: 1657-60.
3. Forli L, Bollerslev J, Simonsen S, Isaksen GA, Kvamsdal KE, Godang K, Gadeholt G, Pripp AH, Bjortuft O. *Dietary vitamin K2 supplement improves bone status after lung and heart transplantation. Transplantation* 2010; 89: 458-64.
4. Reid DM, Macdonald HM. *Nutrition and bone: is there more to it than just calcium and vitamin D? QJM* 2001; 94: 53-6.
5. Furie B, Bouchard BA, Furie BC. *Vitamin K-dependent biosynthesis of gamma-carboxylglutamic acid. Blood* 1999; 93: 1798-808.
6. Kim SM, Kim KM, Kim BT, Joo NS, Kim KN, Lee DJ. *Correlation of undercarboxylated osteocalcin (ucOC) concentration and bone density with age in healthy Korean women. J Korean Med Sci* 2010; 25: 1171-5.
7. Booth SL, Broe KE, Peterson JW, Cheng DM, Dawson-Hughes B, Gundberg CM, Cupples LA, Wilson PW, Kiel DP. *Associations between vitamin K biochemical measures and bone mineral density in men and women. J Clin Endocrinol Metab* 2004; 89: 4904-9.
8. Stevenson M, Lloyd-Jones M, Papaioannou D. *Vitamin K to prevent fractures in older women: systematic review and economic evaluation. Health Technol Assess* 2009; 13: iii-xi, 1-134.
9. Troy LM, Jacques PF, Hannan MT, Kiel DP, Lichtenstein AH, Kennedy ET, Booth SL. *Dihydrophyllolquinone intake is associated with low bone mineral density in men and women. Am J Clin Nutr* 2007; 86: 504-8.
10. Emaus N, Gjesdal CG, Almås B, Christensen M, Grimsgaard AS, Bernsten GK, Salomonsen L, Fønnebo V. *Vitamin K2 supplementation does not influence bone loss in early menopausal women: a randomised double-blind placebo-controlled trial. Osteoporos Int* 2010; 21: 1731-40.
11. Volpe SL, Leung MM, Giordano H. *Vitamin K supplementation does not significantly impact bone mineral density and biochemical markers of bone in pre-and perimenopausal women. Nutr Res* 2008; 28: 577-82.
12. Cheung AM, Tile L, Lee Y, Tomlinson G, Hawker G, Scher J, Hu H, Vieth R, Thompson L, Jamal S, Josse R. *Vitamin K supplementation in postmenopausal women with osteopenia (ECKO trial): a randomized controlled trial. PLoS Med* 2008; 5: e196.
13. Booth SL, Dallal G, Shea MK, Gundberg C, Peterson JW, Dawson-Hughes B. *Effect of vitamin K supplementation on bone loss in elderly men and women. J Clin Endocrinol Metab* 2008; 93: 1217-23.
14. Knapen MH, Schurgers LJ, Vermeer C. *Vitamin K2 supplementation improves hip bone geometry and bone strength indices in postmenopausal women. Osteoporos Int* 2007; 18: 963-72.
15. Arunakul M, Niempoog S, Arunakul P, Bunyaratavej N. *Level of undercarboxylated osteocalcin in hip fracture Thai female patients. J Med Assoc Thai* 2009; 92(Suppl 5): S7-11.
16. Booth SL, Lichtenstein AH, O'Brien-Morse M, McKeown NM, Wood RJ, Saltzman E, Gundberg CM. *Effects of a hydrogenated form of vitamin K on bone formation and resorption. Am J Clin Nutr* 2001; 74: 783-90.
17. Tsugawa N, Shiraki M, Suhara Y, Kamao M, Ozaki R, Tanaka K, Okano T. *Low plasma phylloquinone concentration is associated with high incidence of vertebral fracture in Japanese women. J Bone Miner Metab* 2008; 26: 79-85.
18. Purwosunu Y, Muharram, Rachman IA, Reksoprodjo S, Sekizawa A. *Vitamin K2 treatment for postmenopausal osteoporosis in Indonesia. J Obstet Gynaecol Res* 2006; 32: 230-4.
19. Furie B, Furie BC. *Molecular basis of vitamin K-dependent gamma-carboxylation. Blood* 1990; 75: 1753-62.
20. Hodges SJ, Akesson K, Vergnaud P, Obrant K, Delmas PD. *Circulating levels of vitamins K1 and K2 are decreased in elderly women with hip fracture. J Bone Miner Res* 1993; 8: 1241-5.
21. Bolton-Smith C, McMurdo ME, Paterson CR, Mole PA, Harvey JM, Fenton ST, Prynne CJ, Mishra GD, Shearer MJ. *Two-year randomized controlled trial of vitamin K1 (phylloquinone) and vitamin D3 plus calcium on the bone health of older women. J Bone Miner Res* 2007; 22: 509-19.
22. Yasui T, Miyatani Y, Tomita J, Yamada M, Uemura H, Miura M, Irahara M. *Effect of vitamin K2 treatment on carboxylation of osteocalcin in early postmenopausal women. Gynecol Endocrinol* 2006; 22: 455-9.
23. Binkley N, Harke J, Krueger D, Engelke J, Vallarta-Ast N, Gemar D, Checovich M, Chappell R, Suttie J. *Vitamin K treatment reduces undercarboxylated osteocalcin but does not alter bone turnover, density, or geometry in healthy postmenopausal North American women. J Bone Miner Res* 2009; 24: 983-91.
24. Kuwabara A, Tanaka K, Tsugawa N, Nakase H, Tsuji H, Shide K, Kamao

- M, Chiba T, Inagaki N, Okano T, Kido S. *High prevalence of vitamin K and D deficiency and decreased BMD in inflammatory bowel disease. Osteoporos Int* 2009; 20: 935-42.
25. Menzies IS, Zuckerman MJ, Nukajam WS, Somasundaram SG, Murphy B, Jenkins AP, Crane RS, Gregory GG. *Geography of intestinal permeability and absorption. Gut* 1999; 44: 483-9.
26. Foresta C, Strapazzon G, De Toni L, Gianesello L, Calcagno A, Pilon C, Plebani M, Vettor R. *Evidence for osteocalcin production by adipose tissue and its role in human metabolism. J Clin Endocrinol Metab* 2010; 95: 3502-6.
27. Brownbill RA, Ilich JZ. *Lipid profile and bone paradox: higher serum lipids are associated with higher bone mineral density in postmenopausal women. J Womens Health (Larchmt)* 2006; 15: 261-70.
28. Shea MK, Booth SL, Gundberg CM, Peterson JW, Waddell C, Dawson-Hughes B, Saltzman E. *Adulthood obesity is positively associated with adipose tissue concentrations of vitamin K and inversely associated with circulating indicators of vitamin K status in men and women. J Nutr* 2010; 140: 1029-34.

AUTHOR SUMMARY

Vitamin K Supplement Along with Vitamin D and Calcium Reduced Serum Concentration of Undercarboxylated Osteocalcin While Increasing Bone Mineral Density in Korean Postmenopausal Women over Sixty-Years-Old

Sang Hyeon Je, Nam-Seok Joo, Beom-hee Choi, Kwang-Min Kim, Bom-Taek Kim, Sat-Byul Park, Doo-Yeoun Cho, Kyu-nam-Kim and Duck-Joo Lee

This study is to evaluate effects of vitamin K supplementation on bone mineral density (BMD) in postmenopausal Korean women. 78 postmenopausal women over sixty years old were assigned to either control (Calcium & Vitamin D, n = 40) or vitamin K-supplemented group (Calcium, Vitamin D & Vitamin K, n = 38). After 6 months of treatment, the vitamin K group showed decrease of undercarboxylated osteocalcin and increase of BMD. The Intention to Treat (ITT) analysis showed the same result. Such result is contrary to the previous study in North American postmenopausal women.