Yonsei Medical Journal
Vol. 44, No. 5, pp. 751 - 756, 2003

Review Article

Combined Treatment with Vitamin K_2 and Bisphosphonate in Postmenopausal Women with Osteoporosis

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Vitamin K_2, as well as bisphosphonates, such as etidronate, alendronate, and risedronate, is widely used in the treatment with osteoporosis in Japan. Etidronate increases the lumbar bone mineral density (BMD), and prevents new vertebral fractures, in patients with osteoporosis, while alendronate and risedronate increase the lumbar and femoral neck BMDs, and prevent new vertebral and femoral neck fractures. Vitamin K_2 enhances γ-carboxylation of bone glutamic acid residues and the secretion of osteocalcin, sustains the lumbar BMD, and prevents osteoporotic fractures in patients with osteoporosis. Bisphosphonates, such as alendronate and risedronate, rather than vitamin K_2, should be initially chosen for the treatment of osteoporosis, because they are more efficacious than vitamin K_2. Available evidence suggest that risedronate prevents deterioration of the connectivity of the trabeculae in ovariectomized rats, whereas vitamin K_2 increase the trabecular thickness, and that a combination of risedronate and vitamin K_2 has a synergistic effect on preventing the deterioration of trabecular bone architecture induced by estrogen deficiency. Some studies have shown that combined treatment with etidronate and vitamin K_2 appears to be more effective than etidronate alone in the prevention of new osteoporotic vertebral fractures. Based on these findings, combined treatment with vitamin K_2 and bisphosphonates may be more efficacious in the prevention new vertebral fractures than a single treatment with bisphosphonate in postmenopausal women with osteoporosis. Thus, this combined treatment should be recommended for the treatment of postmenopausal osteoporosis. It is proposed that the role of vitamin K_2 should be emphasized, when used in combination with bisphosphonates, especially in patients with vitamin K deficiency.

Key Words: Vitamin K_2, bisphosphonate, postmenopausal osteoporosis, bone mineral density (BMD)

Received April 10, 2003
Accepted July 21, 2003

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INTRODUCTION

Vitamin K_2, as well as bisphosphonates, such as etidronate, alendronate, and risedronate, is widely used for the treatment of osteoporosis in Japan. Some studies have shown similarly to etidronate, that vitamin K_2 prevents new vertebral fractures in postmenopausal women with osteoporosis, or patients with steroid-induced osteoporosis, despite smaller increases in the bone mineral density (BMD).[1,2] However, the efficacy of vitamin K_2 for osteoporosis seems to be similar to that of active vitamin D_3, but the effects of active vitamin D_3 on the BMD, and the incidence of osteoporotic fractures, seem to be smaller than those with alendronate and risedronate.[3-6] Thus, it is evident that alendronate and risedronate are more effective than vitamin K_2 in increasing the BMD and preventing osteoporotic fractures, and vitamin K_2 seems to be less efficacious for osteoporosis treatment than those with bisphosphonates. Bisphosphonates, such as alendronate and risedronate, rather than vitamin K_2, should be initially chosen for the osteoporosis treatment. With regard to the raised question, "How could vitamin K_2 be used in the treatment of osteoporosis?" This paper discusses the position of vitamin K_2 in the treatment of postmenopausal osteoporosis.

Effects of vitamin K_2 on bone metabolism

Vitamin K_2 is a cofactor of γ-carboxylase, which converts glutamic acid (Glu) residue to a γ-carbo-

xyglutamic acid (Gla) residue in osteocalcin molecules, and is essential for γ-carboxylation of osteocalcin.[7,8] Available evidence suggests that vitamin K_2 enhances osteocalcin accumulation in the extracellular matrix of osteoblasts, *in vitro*.[9] Osteocalcin knockout mice develop hyperostosis,[10] suggesting that Gla-containing osteocalcin promotes normal bone mineralization. Although the role of osteocalcin in bone mineralization remains obscure, it may regulate the growth of hydroxyapatite crystals.[11] There is some evidence indicating that vitamin K_2 retards the increase in bone turnover in orchidectomized rats, and ameliorates the increase in bone resorption and the decrease in bone formation in sciatic neurectomized rats.[12] These findings suggest that vitamin K_2 regulates bone metabolism.

Treatment with vitamin K_2 for postmenopausal osteoporosis

Several experimental and clinical studies have shown the effect of vitamin K_2 on bone loss with estrogen deficiency. The effect of vitamin K_2 on the bone loss induced by ovariectomy in rats remains controversial. Some studies have shown that vitamin K_2 prevents early bone loss through the inhibition of bone resorption,[13] and protects against the loss of trabecular bone volume and its connectivity in ovariectomized rats.[14] Another study showed that vitamin K_2 did not reduce the ovariectomy-associated increase in bone turnover or decline in the distal femoral BMD.[15] Thus, the effect of vitamin K_2 on bone loss, bone formation and resorption in ovariectomized rats has not been established.

Clinically, vitamin K_2 enhances γ-carboxylation of bone Glu residues and the secretion of osteocalcin, sustains the lumbar BMD, and prevents osteoporotic fractures in patients with osteoporosis.[16] Active vitamin D_3, alfacalcidol, has been established to slightly reduces bone turnover, sustains the lumbar BMD, and prevents osteoporotic vertebral fractures in postmenopausal women with osteoporosis.[17] The efficacy of vitamin K_2 on osteoporosis seems to be similar to that of active vitamin D_3. It has been suggested that vitamin K deficiency may contribute to osteoporotic fractures.[18,19] Serum undercarboxylated osteocalcin may reflect a low vitamin K activity, and a higher incidence of femoral neck fractures is observed in patients with higher levels of undercarboxylated osteocalcin.[18,20,21] Thus, it is surmised that vitamin K_2 might have the potential to prevent osteoporotic femoral neck fractures. The effect of vitamin K_2 on the lumbar BMD may be greater in early postmenopausal ($\leqq$ 5 years after menopause) women than in late postmenopausal women.[22] The reason for this remains uncertain, but it is suggested that treatment with vitamin K_2 should be started early in the postmenopausal period. Despite the fact of no significant increase in the BMD, the reason vitamin K_2 prevents osteoporotic fractures, including vertebral fractures, also remains uncertain. Bone strength is primarily determined, not only by the BMD, but also by the bone microarchitecture, skeletal mineralization, microdamages, and bone turnover, etc. Thus, vitamin K_2 may have the potential to at least prevent deterioration of the bone architecture, as shown in preclinical studies using animals, and result in amelioration of the deterioration of bone strength and subsequent osteoporotic fractures.

Treatment with bisphosphonates for postmenopausal osteoporosis

A number of randomized controlled studies have reported the efficacy of etidronate, alendronate, and risedronate in osteoporosis.[3-6,23-36] Alendronate and risedronate increase the lumbar and femoral neck BMDs, preventing new vertebral and femoral neck fractures in patients with osteoporosis,[3-6,29-36] and etidronate increases the lumbar BMD, preventing new vertebral fractures.[23-28] To date, in Japan, the available evidence indicates that alendronate prevents new osteoporotic fractures in patients with osteoporosis.[4] The percentage increase in the lumbar BMD after 1-year of treatment was reported to be 2.4 - 3.4% for etidronate, 6.21% for alendronate, and 4.9 - 6.4% for risedronate.[3-6,28]

Combined treatment with vitamin K_2 and bisphosphonates for postmenopausal osteoporosis

Only a few studies have examined the effects of

the combination of vitamin K_2 with bisphosphonates on bone loss with estrogen deficiency. Ito[37] clearly demonstrated that risedronate prevents deterioration of the connectivity of the trabeculae in ovariectomized rats, whereas vitamin K_2 increase the trabecular thickness, and that a combination of risedronate and vitamin K_2 has a synergistic effect on preventing the deterioration in the trabecular bone architecture induced by estrogen deficiency. This finding allows us to propose that combined treatment of a bisphosphonate with vitamin K_2 appears to be more effective than a bisphosphonate alone in preventing new osteoporotic fractures.

The effects of the combination of vitamin K_2 and bisphosphonates on osteoporosis in postmenopausal women with osteoporosis was examined [38,39] to establish the benefit of vitamin K_2 in addition to the effects of etidronate on postmenopausal osteoporosis (Fig. 1). Based on a recent report suggesting that the forearm BMD can identify patients with osteoporosis of the spine or femoral neck,[40] and to examine the effect of treatment on the incidence of thoracic and lumbar vertebral fractures, we measured the forearm (the distal radius rich in cancellous bone) BMD. Table 1 shows the characteristics of our study subjects. The forearm (distal radius) BMD was decreased from the baseline over 24 months with calcium treatment, sustained with vitamin K_2 treatment, and increased similarly by treatment with vitamin K_2 plus etidronate or etidronate alone (Fig. 2). After 24 months of treatment, the incidences of vertebral fracture were similarly reduced by treat

Study design
Open-labeled, randomized, controlled study

Subjects
Ninety-eight postmenopausal women with osteoporosis (age 65.5 years, range 53-78 years)
Informed consent was obtained from all subjects

Groups
Vitamin K_2 (menatetrenone 45 mg/day, n=23)
Cyclical etidronate (200 mg/day for 2 weeks every 3 months, n=25)
Vitamin K_2 plus cyclical etidronate (n=26)
Calcium (calcium lactate 2g/day, n=24)

Duration
24 months

End points
Forearm (distal radius) BMD measured by DXA using DTX-200 (Osteometer)
Incidence of vertebral fractures (T4-L4 vertebrae)

Fig. 1. Protocol of our study.

Table 1. Characteristics of Study Subjects

	Vitamin K_2	Etidronate	Etidronate plus vitamin K_2	Calcium
Number of subjects	23	25	26	24
Age (years)	65.4 ± 1.2	64.3 ± 1.3	66.0 ± 1.2	66.0 ± 1.1
Height (m)	1.47 ± 0.01	1.48 ± 0.01	1.47 ± 0.01	1.47 ± 0.01
Body weight (kg)	44.7 ± 1.9	46.3 ± 1.7	47.1 ± 1.5	45.3 ± 1.7
Body mass index (kg/m^2)	20.6 ± 0.7	21.2 ± 0.7	21.6 ± 0.5	20.9 ± 0.6
Years since menopause	18.3 ± 1.5	17.0 ± 1.3	16.4 ± 1.3	16.0 ± 1.2
Serum calcium (mg/dl)	9.2 ± 0.1	9.2 ± 0.1	9.3 ± 0.1	9.3 ± 0.1
Serum phosphorus (mg/dl)	3.3 ± 0.1	3.3 ± 0.1	3.3 ± 0.1	3.2 ± 0.1
Serum ALP (IU/l)	232.8 ± 9.6	232.3 ± 9.6	228.3 ± 9.6	223.8 ± 9.8
Forearm BMD (g/cm^2)	0.246 ± 0.017	0.245 ± 0.017	0.251 ± 0.010	0.254 ± 0.013
Number of prevalent vertebral fractures per patient	0.400 ± 0.141	0.565 ± 0.187	0.429 ± 0.140	0.500 ± 0.181

Data are expressed as the mean ± SE. Analysis of variance (ANOVA), with Fisher's PLSD test, was used to compare the data between the four groups. There were no significant differences in any of the baseline characteristics between the four groups. ALP, alkaline phosphatase; BMD, bone mineral density.

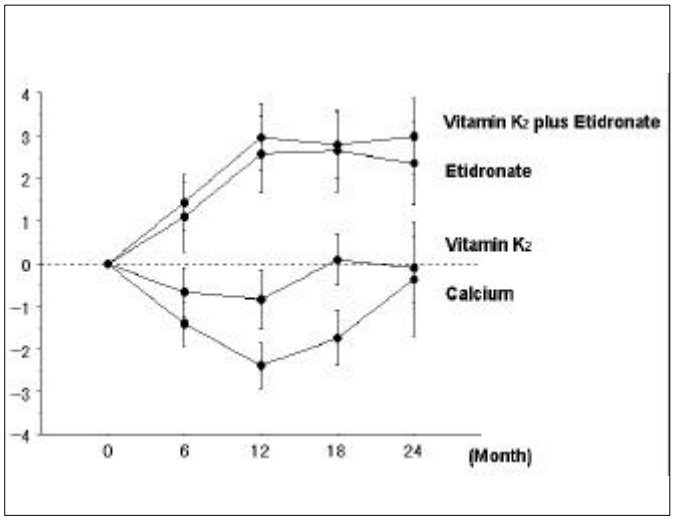

Fig. 2. Changes in forearm (distal radius) BMD. Data are expressed as the mean ± SE. A one-way analysis of variance (ANOVA), with repeated measurements, was used to examine the significance of longitudinal changes of the BMD in each group. A two-way ANOVA, with repeated measurements, was used to compare the longitudinal changes of the BMD between the two groups. BMD was decreased by treatment with calcium ($p<0.05$), sustained by treatment with vitamin K_2 (no significant change) and increased by treatment with etidronate or vitamin K_2 plus etidronate (both $p<0.05$). The longitudinal change of the BMD, by treatment with vitamin K_2 and/or etidronate, differed from that by treatment with calcium (both $p<0.01$). The longitudinal changes of the BMD, by treatment with vitamin K_2 plus etidronate or etidronate, differed from that by treatment with vitamin K_2 ($p<0.05$), but the efficacy of the combination of vitamin K_2 and etidronate, compared to that with etidronate alone, was not observed. BMD: bone mineral density.

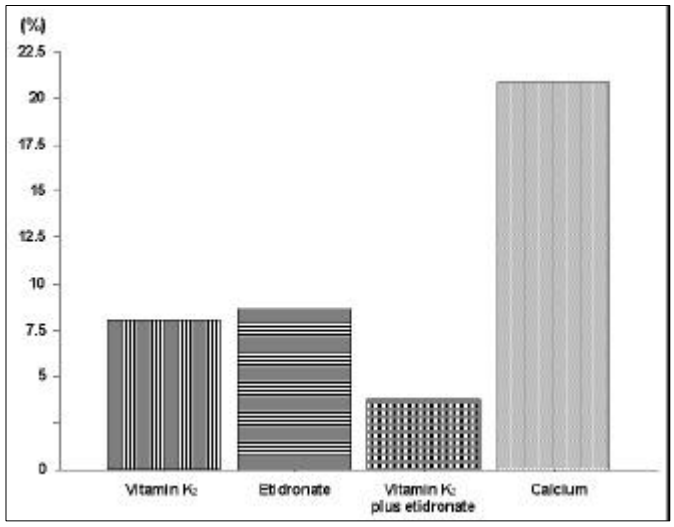

Fig. 3. Incidence of vertebral fractures. A vertebral fracture occurred in two patients treated with vitamin K_2 or etidronate, in one treated with vitamin K_2 plus etidronate, and in six treated with calcium. The incidences of vertebral fractures for treatment with vitamin K_2, etidronate, vitamin K_2 plus etidronate, and calcium were 8.0, 8.7, 3.8, and 20.8%, respectively. When evaluated as the number of vertebral fractures per 1000 patient-years, the incidence of vertebral fractures was significantly lower in vitamin K_2 and/or etidronate treatment groups than in the calcium treatment control group (all $p<0.01$), and in the vitamin K_2 plus etidronate treatment group than in either of the alone groups (both $p<0.01$).

ment with vitamin K_2 or etidronate, compared with that by treatment with calcium, and markedly reduced by treatment with vitamin K_2 plus etidronate (Fig. 3). Although further studies with a large number of subjects may be required, our study suggests that cyclical etidronate, combined with vitamin K_2, appears to be more effective than cyclical etidronate alone in the prevention new vertebral fractures in postmenopausal women with osteoporosis. Taking our results, together with the suggestion that vitamin K deficiency may contribute to osteoporotic fractures, it is proposed that the role of vitamin K_2 should be emphasized, when used in combination with bisphosphonates, especially in patients with vitamin K deficiency. Combined treatment with vitamin K_2 and bisphosphonates seems to have the greatest efficacy in the prevention of new osteoporotic fractures, and this combined treatment should be recommended in the treatment of postmenopausal women with osteoporosis.

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