ORIGINAL RESEARCH ARTICLE

Clin Drug Invest 2009; 29 (7): 471-479
1173-2563/09/0007-0471/$49.95/0

Efficacy of Menatetrenone (Vitamin K_2) against Non-Vertebral and Hip Fractures in Patients with Neurological Diseases

Meta-Analysis of Three Randomized, Controlled Trials

Jun Iwamoto, Hideo Matsumoto and *Tsuyoshi Takeda*

Institute for Integrated Sports Medicine, Keio University School of Medicine, Tokyo, Japan

Abstract

Background and objective: Patients with neurological diseases such as Alzheimer's disease, stroke and Parkinson's disease have been reported to have vitamin K deficiency secondary to malnutrition, which increases the risk of non-vertebral and hip fractures. The purpose of the present study was to clarify the efficacy of menatetrenone (vitamin K_2) against non-vertebral and hip fractures in patients with neurological diseases.

Methods: A literature search was conducted on PubMed from January 1995 to July 2008 to identify randomized controlled trials (RCTs) of use of menatetrenone against non-vertebral and hip fractures in patients with neurological diseases. A meta-analysis of all RCTs meeting these criteria was then performed.

Results: Three RCTs of patients with Alzheimer's disease (n = 178, mean age 78 years), stroke (n = 99, mean age 66 years) and Parkinson's disease (n = 110, mean age 72 years) met the criteria for meta-analysis. These RCTs did not include placebo controls but did have non-treatment controls. According to the meta-analysis, the overall relative risks (95% confidence intervals) for non-vertebral and hip fractures with menatetrenone treatment compared with non-treatment were 0.13 (0.05, 0.35) and 0.14 (0.05, 0.43), respectively, in patients with neurological diseases. No severe adverse events were reported with menatetrenone treatment.

Conclusion: The present meta-analysis of three RCTs suggests that there is efficacy for menatetrenone treatment against non-vertebral and hip fractures among patients with neurological diseases. Further larger placebo-controlled trials are needed to confirm the results of the present study.

Background

In a report by the WHO Scientific Group that evaluated evidence for the efficacy of the various therapies for osteoporosis (table I),[1] the evidence level for the efficacy of menatetrenone (vitamin K_2) in reducing the incidence of vertebral fractures was listed as 'B', which corresponds to positive

Table I. Evidence[a] for the efficacy of therapies in osteoporosis[1]

Intervention	BMD	Vertebral fractures	Non-vertebral fractures	Hip fractures
Calcium	A	B	B	D
Calcium + vitamin D	A	–	A	A
Estrogens	A	A	A	A
Tibolone	A	–	–	–
Alendronic acid	A	A	A	A
Etidronic acid	A	B	D	D
Risedronic acid	A	A	A	A
Ibandronic acid	A	–	–	–
Calcitonin	A	C	C	D
Fluoride	A	C	–	–
Anabolic steroids	A	–	–	D
Calcitriol	C	C	C	–
Alfacalcidol	C	C	–	D
Raloxifene	A	A	–	–
Ipriflavone	B	–	–	–
Menatetrenone (vitamin K_2)	B	B	–	–

a **Evidence level: A** = positive evidence from one or more, adequately powered, randomized controlled trials; **B** = positive evidence from smaller non-definitive randomized controlled trials; **C** = inconsistent results from randomized controlled trials; **D** = positive results from observational studies; – = efficacy not established or not tested.

BMD = bone mineral density.

evidence from smaller non-definitive, randomized, controlled trials (RCTs). An RCT conducted in Japan suggests that menatetrenone maintains lumbar bone mineral density (BMD) and effectively prevents fractures (mainly vertebral fractures) in postmenopausal women with osteoporosis.[2] This and other trials have established the efficacy of menatetrenone against vertebral fractures in postmenopausal women with osteoporosis.[2-4]

It has been well documented that the risk of non-vertebral and hip fractures is high in elderly patients with neurological diseases such as Alzheimer's disease, stroke and Parkinson's disease, because of these patients' greater susceptibility to falls.[5-13] Therefore, a strategy for preventing fall-related fractures should be established in elderly patients with neurological diseases.

Several RCTs have demonstrated the efficacy of menatetrenone against non-vertebral and hip fractures in patients with neurological diseases such as Alzheimer's disease, stroke and Parkinson's disease.[11-13] Furthermore, a systematic review and meta-analysis of RCTs of vitamin K (phytomenadione and menatetrenone) for the prevention of fractures in postmenopausal women with osteoporosis, patients taking oral corticosteroids for kidney disease and patients with neurological disease, has recently been published.[14] However, there has been no systematic review or meta-analysis of RCTs evaluating the efficacy of menatetrenone alone against non-vertebral and hip fractures in patients with neurological diseases. Thus, the present study was conducted to review the literature and perform a meta-analysis to determine the efficacy of menatetrenone against non-vertebral and hip fractures in patients with neurological diseases.

Methods

RCTs of menatetrenone to prevent non-vertebral and hip fractures in patients with neurological diseases were identified through PubMed, using the following search terms: 'menatetrenone', 'fracture', 'Alzheimer's disease', 'stroke' and 'Parkinson's disease'. The literature search was conducted for English publications on RCTs from January 1995 to July 2008. After identification

Table II. Identified randomized controlled trials (RCTs) of efficacy of menatetrenone (vitamin K_2) against non-vertebral and hip fractures in patients with neurological diseases

Study population	Intervention	No. of subjects			Age (y)	Duration of illness (y)	Calcium supplementation	Vitamin D supplementation	Study duration (y)	Reference
		randomized	dropped out	completed						
Alzheimer's disease (women)	Menatetrenone	100	10	90	78.1	6.0	600 mg (elemental calcium)	1000 IU (ergocalciferol)	2	11
	Non-treatment	100	12	88	78.1	6.0				
Parkinson's disease (women)	Menatetrenone	60	6	56	72.3	4.8	No supplementation	No supplementation	1	12
	Non-treatment	60	4	54	71.6	4.9				
Stroke (men and women)	Menatetrenone	54	3	51	66.3	13.9	No supplementation	No supplementation	1	13
	Non-treatment	54	6	48	65.6	13.2				

of these trials, the relative risks and 95% confidence intervals (CIs) for non-vertebral and hip fractures were calculated for each individual RCT. The statistical significance was evaluated by calculating integration relative risk (95% CI) using the fixed effect model. The consistency of the results of RCTs, which is a key to the results of a meta-analysis, was evaluated by study heterogeneity. Study heterogeneity was defined as a significant Cochrane's χ^2 test of heterogeneity (significance level was set at $p < 0.1$). A lower-than-conventional threshold of significance was used because tests of heterogeneity are typically underpowered. Since the event rates for non-vertebral and hip fractures were low and there were zero event rates in studies, we added 0.5 to numbers of whole patients and those with fractures consistent with best practice according to the Cochrane Handbook for Systematic Reviews of Interventions.[15] Publication bias was assessed using the funnel plot and Macaskill (the sample size) and Egger (the inverse of the standard error) tests.[16] The statistical analyses were performed using PC SAS version 8.2 (SAS, Cary, NC, USA).

Results

Identified Randomized Controlled Trials

Three studies met the criteria for RCTs evaluating the efficacy of menatetrenone against non-vertebral and hip fractures in patients with neurological diseases such as Alzheimer's disease, stroke and Parkinson's disease.[11-13] Table II shows the details of the three RCTs, which included patients with Alzheimer's disease (n = 178 women; mean age 78 years), Parkinson's disease (n = 110 women; mean age 72 years) and stroke (n = 99 men and women; mean age 66 years). The durations of illnesses in these RCTs were 6.0 years, 4.8–4.9 years and 13.2–13.9 years, respectively. The respective periods of the studies were 2 years, 1 year and 1 year. Patients with Alzheimer's disease, stroke and Parkinson's disease had vitamin K deficiency secondary to malnutrition as directly determined by the low circulating levels of vitamin K_1. They also had hypovitaminosis D secondary to malnutrition

and sunlight deprivation as determined by the low serum levels of 25 hydroxyvitamin D. All of the RCTs were performed in Japan and utilized a daily dosing regimen of menatetrenone 45 mg/day (a dose-finding study of menatetrenone 15, 45, 90 and 135 mg/day conducted in Japan found that this was the most effective minimum daily dose for the treatment of postmenopausal osteoporosis[17]). Because menatetrenone is a drug rather than a simple dietary supplement, its optimal dose in the treatment of osteoporosis is about 400 times greater than the dietary recommendation of vitamin K. Calcium and vitamin D (ergocalciferol) supplementation were administered in one RCT of patients with Alzheimer's disease,[11] but not in the other two RCTs of patients with stroke and Parkinson's disease because of the presence of hypercalcaemia caused by an immobilization-induced increase in bone resorption.

In the RCT of patients with Alzheimer's disease, 200 patients were randomly divided into two groups (n = 100 in each group) by means of computer-assisted random numbering. Ten patients (10.0%) in the menatetrenone group and 12 patients (12.0%) in the non-treatment group dropped out because of noncompliance, loss to follow-up, intercurrent illness or death. In the RCT of patients with Parkinson's disease, 120 patients were randomly divided into two groups (60 patients in each group) by means of computer-assisted random numbering. Six patients (10.0%) in the menatetrenone group and four patients (6.7%) in the non-treatment group dropped out because of noncompliance, loss to follow-up or intercurrent illness. In the RCT of patients with stroke, 108 patients were randomly divided into two groups (n = 54 in each group). Three patients (5.6%) in the menatetrenone group and six patients (11.1%) in the non-treatment group dropped out because of noncompliance, loss to follow-up or intercurrent illness. No information was provided on the randomization procedure in the RCT of patients with stroke or on compliance with treatment and unexpected co-interventions in any of the three RCTs. Furthermore, it is unclear whether the investigators were blinded to treatment in any of the three RCTs.

Meta-Analysis

A meta-analysis was performed on the three RCTs. Figures 1 and 2 show the results of the meta-analysis for non-vertebral and hip fractures,

Study	Incidence of non-vertebral fractures		Relative risk (95% CI)	Reference
	menatetrenone	non-treatment		
Alzheimer's disease	3/90	22/88	0.13 (0.04, 0.43)	11
Parkinson's disease	1/56	10/54	0.10 (0.01, 0.73)	12
Stroke	0/51	1/48	0.31 (0.01, 7.53)	13
Pooled data	4/197	33/190	0.13 (0.05, 0.35)	

Test for heterogeneity: $\chi^2 = 0.38$ ($p = 0.8277$)
Test for overall effect: $\chi^2 = 16.67$ ($p < 0.0001$)

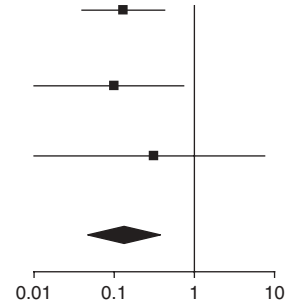

Fig. 1. Effect of menatetrenone on the incidence of non-vertebral fractures in patients with neurological diseases. The relative risks (95% CIs) for the three randomized controlled trials (RCTs) are shown. Since the event rates for non-vertebral fractures were low and there was a zero event rate in some studies, we added 0.5 to numbers of whole patients and those with fractures consistent with best practice according to the Cochrane Handbook for Systematic Reviews of Interventions.[15] Overall, the relative risk (95% CI) of non-vertebral fractures was 0.13 (0.05, 0.35), suggesting an 87% risk reduction with menatetrenone treatment in patients with neurological diseases (heterogeneity $\chi^2 = 0.38$, $p = 0.8277$; overall effect $\chi^2 = 16.67$, $p < 0.0001$).

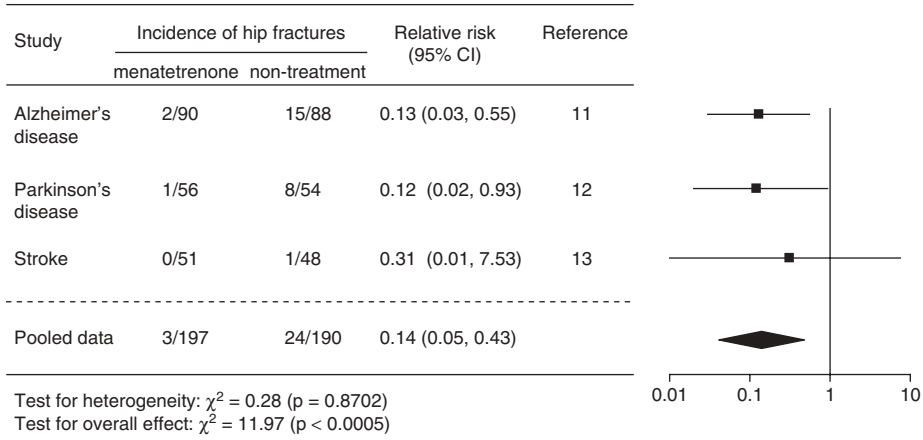

Fig. 2. Effect of menatetrenone on the incidence of hip fractures in patients with neurological diseases. The relative risks (95% CIs) of the three randomized controlled trials (RCTs) are shown. Since the event rates for hip fractures were low and there was a zero event rate in some studies, we added 0.5 to numbers of whole patients and those with fractures consistent with best practice according to the Cochrane Handbook for Systematic Reviews of Interventions.[15] Overall, the relative risk (95% CI) of hip fractures with menatetrenone treatment was 0.14 (0.05, 0.43), suggesting an 86% risk reduction rate with menatetrenone treatment in patients with neurological diseases (heterogeneity $\chi^2 = 0.28$, $p = 0.8702$; overall effect $\chi^2 = 11.97$, $p < 0.0005$)

respectively. According to the results of the RCTs, the relative risks (95% CIs) for non-vertebral fractures with menatetrenone treatment compared with non-treatment were 0.13 (0.04, 0.43) for Alzheimer's disease, 0.10 (0.01, 0.73) for Parkinson's disease and 0.31 (0.01, 7.53) for stroke (figure 1). The respective relative risks (95% CIs) for hip fractures with menatetrenone treatment compared with non-treatment were 0.13 (0.03, 0.55), 0.12 (0.02, 0.93) and 0.31 (0.01, 7.53) [figure 2]. There was no statistical evidence of heterogeneity among the studies ($\chi^2 = 0.38$ and $p = 0.8277$ for non-vertebral fractures; $\chi^2 = 0.28$ and $p = 0.8702$ for hip fractures). Overall, the respective relative risks (95% CIs) for non-vertebral and hip fractures with menatetrenone treatment were 0.13 (0.05, 0.35) and 0.14 (0.05, 0.43) [figures 1 and 2], suggesting 87% and 86% risk reductions for non-vertebral and hip fractures, respectively ($\chi^2 = 16.67$ and $p < 0.0001$ for non-vertebral fractures; $\chi^2 = 11.97$ and $p < 0.0005$ for hip fractures).

The funnel plot was not necessarily asymmetrical (figures not shown) and publication bias was not identified for non-vertebral and hip fractures by the Macaskill ($p = 0.9395$ for non-vertebral fractures; $p = 0.7347$ for hip fractures) and Egger ($p = 0.6709$ for non-vertebral fractures; $p = 0.3843$ for hip fractures) tests.

Adverse Effects

Some adverse effects of menatetrenone treatment were described in patients with Alzheimer's and Parkinson's diseases.[11,12] Among all the subjects in the menatetrenone group in these two studies ($n = 146$), three (2.1%) patients experienced gastrointestinal symptoms such as epigastric pain and nausea, but these subsided within 1 week without discontinuation of menatetrenone treatment. No patients in the menatetrenone group experienced liver or renal dysfunction. Although a possible risk of secondary ischaemic stroke with menatetrenone treatment in patients with stroke ($n = 51$) was discussed in the third trial,[13] no instances of secondary stroke or myocardial infarction were identified in this study. No severe adverse events were reported with menatetrenone treatment in any of the three RCTs.

Discussion

A meta-analysis was conducted to attempt to establish the efficacy of menatetrenone against

non-vertebral and hip fractures in patients with neurological diseases such as Alzheimer's disease, stroke and Parkinson's disease. The results suggest that there is efficacy of menatetrenone against non-vertebral and hip fractures and the treatment was well tolerated in vitamin K-deficient Japanese patients with neurological diseases. However, the quality of this meta-analysis might be limited because the RCTs lacked placebo controls and had small sample sizes with insufficient power to assess fracture risk. Thus, further larger, placebo-controlled trials in other populations are needed to confirm our results.

Vitamin K_2 is known to be a co-factor of γ-carboxylase, which converts the glutamic acid residue in osteocalcin molecules to γ-carboxyglutamic acid and is, therefore, essential for γ-carboxylation of osteocalcin.[18-21] Recent evidence suggests that vitamin K_2 is a transcriptional regulator of bone-specific genes that acts through steroid and xenobiotic receptors to increase the expression of osteoblastic markers.[22] Clinically, menatetrenone increases serum levels of osteocalcin and bone-specific alkaline phosphatase and decreases serum levels of undercarboxylated osteocalcin without affecting the urinary levels of bone resorption markers in postmenopausal women.[23] Thus, the effects of menatetrenone on mineralization and bone formation may play an important role in the treatment of osteoporosis.

Associations among vitamin K deficiency, the risk of hip fracture and BMD in elderly people have been reported.[24-30] Vitamin K deficiency, as indicated by a low serum undercarboxylated osteocalcin level or possibly a low ratio of serum carboxylated osteocalcin to serum total osteocalcin, may contribute to the risk of hip fractures in the elderly, and possibly to BMD loss in selected cohorts of elderly people. Indeed, the serum marker undercarboxylated osteocalcin could be an index of bone quality independent of BMD. Thus, menatetrenone could be useful in the prevention of hip fractures and perhaps non-vertebral fractures (i.e. fractures at sites primarily composed of cortical bone) in elderly people with vitamin K deficiency. This association is supported by a recent report showing that menatetrenone maintains femoral neck bone strength by improving femoral neck width and maintaining the indices of compression, bending and impact strength compared with placebo treatment in healthy postmenopausal women.[23]

In the present study, patients with Alzheimer's disease, stroke and Parkinson's disease had vitamin K deficiency secondary to malnutrition as directly determined by the low circulating levels of vitamin K_1. Vitamin K_1 is essentially supplied by the diet, particularly in green leafy vegetables, while vitamin K_2 is synthesized by bacteria in the gut. This meta-analysis identified 87% and 86% risk reductions in non-vertebral and hip fractures, respectively, with menatetrenone treatment in vitamin K-deficient patients with neurological diseases. There was no statistical evidence of heterogeneity among the studies, and publication bias was not identified for non-vertebral and hip fractures by the funnel plot and Macaskill and Egger tests, although these tests might not have been sufficiently powered to detect a bias given the small number of RCTs identified. However, there may be a criticism that the anti-fracture efficacy of menatetrenone could be chance effects in the present meta-analysis because all RCTs were performed at single centres in selected populations. Thus, further studies may be needed to support the results of the present meta-analysis.

The density, thickness, porosity and mean mineralization of bone in cortical bone may be important factors in determining the fracture risk at sites primarily composed of cortical bone.[31] In a phase III study, menatetrenone only maintained BMD in the metacarpus in patients with age-related osteoporosis.[32] However, in patients with neurological diseases in the three RCTs included in the current meta-analysis, the BMD of the metacarpus, which is composed of cortical bone, increased markedly by 7.5% (+2.3% vs −5.2%) for Alzheimer's disease, 9.0% (+4.3% vs −4.7%) for stroke and 5.2% (+0.9% vs −4.3%) for Parkinson's disease with menatetrenone compared with no treatment.[11-13] Thus, greater increases in BMD and possibly improvements in bone thickness[23] at sites primarily composed of cortical bone in the three RCTs might have contributed to the greater efficacy of menatetrenone

against non-vertebral and hip fractures in patients with neurological diseases. However, further studies may be needed to clarify the mechanism for the greater anti-fracture efficacy of menatetrenone in patients with neurological diseases, because in addition to BMD, several factors such as cortical porosity and mean mineralization of bone might play roles in determining the quality of cortical bone.[31]

Hypovitaminosis D in elderly disabled patients increases the risk for falls and thus the risk for possible subsequent fractures.[33-35] It also induces compensatory hyperparathyroidism, further contributing to a reduction in BMD.[6,11] Consequently, vitamin D and calcium supplementation is required in patients with malnutrition and sunlight deprivation. In the present study, all the RCTs showed the existence of hypovitaminosis D in patients with the three neurological diseases.[11-13] The RCT of patients with Alzheimer's disease included supplementation of calcium and vitamin D because patients had hypovitaminosis D and compensatory hyperparathyroidism.[11] However, the two RCTs of patients with stroke and Parkinson's disease avoided supplementation of either calcium or vitamin D because the patients had hypercalcaemia caused by an immobilization-induced increase in bone resorption.[12,13] Hypercalcaemia, in turn, may inhibit the compensatory hyperparathyroidism that otherwise could occur in response to hypovitaminosis D.[12,13] Theoretically, however, menatetrenone with calcium and vitamin D supplementation could be a suitable treatment in such patients with low circulating levels of vitamin K and hypovitaminosis D. Thus, further studies are required to determine whether calcium and vitamin D supplementation are effective or harmful in preventing fractures and improving calcium and vitamin D metabolism in patients with stroke and Parkinson's disease.

In the RCT of patients with Alzheimer's disease,[11] menatetrenone with calcium and vitamin D supplementation increased serum levels of vitamin K_2 and 25-hydroxyvitamin D, and decreased serum levels of undercarboxylated osteocalcin level and parathyroid hormone (PTH) in association with an increase in the serum level of calcium. A reduction in the serum level of PTH probably induced by calcium and vitamin D supplementation might have contributed to a decrease in bone resorption. On the other hand, in the two RCTs of patients with stroke or Parkinson's disease,[12,13] menatetrenone increased serum levels of vitamin K_2 and either decreased the serum level of undercarboxylated osteocalcin level or increased the serum level of osteocalcin and improved hypercalcaemia probably by suppressing bone resorption. Indeed, menatetrenone inhibits bone resorption partially through inhibition of prostaglandin E_2 synthesis, and its side chain may play an important role in inhibition of bone resorption.[36,37] The reduction in the serum level of calcium induced by menatetrenone treatment increased serum levels of PTH and 1,25-dihydroxyvitamin D. These dramatic changes in biochemical markers might have contributed to a marked increase in BMD and improvements in bone quality.

In the two RCTs of patients with Alzheimer's and Parkinson's diseases, gastrointestinal symptoms such as epigastric pain and nausea were observed in 2.1% of patients, but these subsided within 1 week without discontinuation of menatetrenone treatment.[11,12] No patient experienced liver or renal dysfunction. In the RCT of patients with stroke, no secondary stroke or myocardial infarction occurred in any patient.[13] Finally, no severe adverse events were reported in patients receiving menatetrenone in any of the studies. These results confirm the short-term safety of menatetrenone in patients with neurological diseases such as Alzheimer's disease, stroke and Parkinson's disease. However, because long-term treatment is needed to reduce the life-time risk of non-vertebral and hip fractures, the long-term anti-fracture safety of menatetrenone needs to be established in elderly patients with neurological diseases.

There are notable limitations in the present study. No placebo capsules were administered to the control (non-treatment) groups, resulting in a low quality of meta-analysis. There was no information on the randomization procedure in the RCT of patients with stroke. There was also no information on compliance with treatment

in any the three RCTs. Furthermore, it is uncertain whether the investigators were blinded to treatment in the three RCTs, and the results could therefore have been biased. Other limitations were that the number of subjects evaluated might not have been sufficient to investigate the incidence of hip fractures (particularly in the RCT of patients with stroke with a large 95% CI), and all of the RCTs were performed only in Japanese patients. Thus, it remains uncertain whether the evidence derived from the present study could be translated into Western patients with an increased risk for hip fractures due to neurological diseases and vitamin K deficiency. Further studies are needed to resolve these issues.

Conclusion

The present meta-analysis of three RCTs suggests that there is efficacy against non-vertebral and hip fractures with menatetrenone treatment among vitamin K-deficient Japanese patients with neurological diseases such as Alzheimer's disease, stroke and Parkinson's disease. However, the quality of this meta-analysis might be low because the RCTs had no placebo-controlled design and the small sample sizes may have had insufficient power to assess fracture risk. Thus, further larger placebo-controlled trials in other populations are needed to confirm the results of the present meta-analysis.

Acknowledgements

No sources of funding were used to assist in the preparation of this study. The authors have no conflicts of interest that are directly relevant to the content of this study.

References

1. The WHO Scientific Group. Prevention and management of osteoporosis. World Health Organ Tech Rep Ser 2003; 921: 86-109
2. Shiraki M, Shiraki Y, Aoki C, et al. Vitamin K_2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis. J Bone Miner Res 2000; 15: 515-21
3. Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, alfacalcidol, and vitamin K in postmenopausal women with osteoporosis: The Yamaguchi Osteoporosis Prevention Study. Am J Med 2004; 117: 549-55
4. Iwamoto J, Takeda T, Ichimura S. Effect of menatetrenone on bone mineral density and incidence of vertebral fractures in postmenopausal women with osteoporosis: a comparison with the effect of etidronate. J Orthop Sci 2001; 6: 487-92
5. Iwamoto J, Matsumoto H, Takeda T. Efficacy of risedronate against hip fracture in patients with neurological diseases: a meta-analysis of randomized controlled trials. Curr Med Res Opin 2008; 24: 1379-84
6. Sato Y, Kanoko T, Satoh K, et al. The prevention of hip fracture with risedronate and ergocalciferol plus calcium supplementation in elderly women with Alzheimer disease: a randomized controlled trial. Arch Intern Med 2005; 165: 1737-42
7. Sato Y, Iwamoto J, Kanoko T, et al. Risedronate sodium therapy for prevention of hip fracture in men 65 years or older after stroke. Arch Intern Med 2005; 165: 1743-8
8. Sato Y, Iwamoto J, Kanoko T, et al. Risedronate therapy for prevention of hip fracture after stroke in elderly women. Neurology 2005; 64: 811-6
9. Sato Y, Honda Y, Iwamoto J. Risedronate and ergocalciferol prevent hip fracture in elderly men with Parkinson disease. Neurology 2007; 68: 911-5
10. Sato Y, Iwamoto J, Kanoko T, et al. Alendronate and vitamin D2 for prevention of hip fracture in Parkinson's disease: a randomized controlled trial. Mov Disord 2006; 21: 924-9
11. Sato Y, Kanoko T, Satoh K, et al. Menatetrenone and vitamin D2 with calcium supplements prevent nonvertebral fracture in elderly women with Alzheimer's disease. Bone 2005; 36: 61-8
12. Sato Y, Honda Y, Kaji M, et al. Amelioration of osteoporosis by menatetrenone in elderly female Parkinson's disease patients with vitamin D deficiency. Bone 2002; 31: 114-8
13. Sato Y, Honda Y, Kuno H, et al. Menatetrenone ameliorates osteopenia in disuse-affected limbs of vitamin D- and K-deficient stroke patients. Bone 1998; 23: 291-6
14. Cockayne S, Adamson J, Lanham-New S, et al. Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials. Arch Intern Med 2006; 166: 1256-61
15. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions 4.2.4. [updated March 2005]. Chichester: John Wiley & Sons Ltd, 2005
16. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. Clin Epidemiol 2005; 58: 882-93
17. Orimo H, Fujita T, Onomura T, et al. Clinical evaluation of soft capsule menatetrenone (Ea-0167) in the treatment of osteoporosis: late phase II dose study [in Japanese]. J New Remedies Clinics 1992; 41: 1249-79

18. Hauschka PV, Lian JB, Cole DEC, et al. Osteocalcin and matrix Gla protein: vitamin K-dependent proteins in bone. Physiol Rev 1989; 69: 990-1047
19. Koshihara Y, Hoshi K. Vitamin K_2 enhances osteocalcin accumulation in the extracellular matrix of human osteoblasts in vitro. J Bone Miner Res 1997; 12: 431-8
20. Shearer MJ. Vitamin K. Lancet 1995; 345: 229-34
21. Vermeer C, Jie KSG, Knapen MHJ. Role of vitamin K in bone metabolism. Annu Rev Nutr 1995; 15: 1-22
22. Tabb MM, Sun A, Zhou C, et al. Vitamin K_2 regulation of bone homeostasis is mediated by the steroid and xenobiotic receptor SXR. J Biol Chem 2003; 278: 43919-27
23. Knapen MH, Schurgers LJ, Vermeer C. Vitamin K_2 supplementation improves hip bone geometry and bone strength indices in postmenopausal women. Osteoporos Int 2007; 18: 963-72
24. Booth SL, Tucker KL, Chen H, et al. Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women. Am J Clin Nutr 2000; 71: 1201-8
25. Kaneki M, Hedges SJ, Hosoi T, et al. Japanese fermented soybean food as the major determinant of the large geographic difference in circulating levels of vitamin K_2: possible implications for hip-fracture risk. Nutrition 2001; 17: 315-21
26. Szulc P, Chapuy MC, Meunier PJ, et al. Serum undercarboxylated osteocalcin is a marker of the risk of hip fracture in elderly women. J Clin Invest 1993; 91: 1769-74
27. Szulc P, Chapuy MC, Meunier PJ, et al. Serum undercarboxylated osteocalcin is a marker of the risk of hip fracture: a three year follow-up study. Bone 1996; 18: 487-8
28. Vergnaud P, Garnero P, Meunier PJ, et al. Undercarboxylated osteocalcin measured with a specific immunoassay predicts hip fracture in elderly women: the EPIDOS Study. J Clin Endocrinol Metab 1997; 82: 719-24
29. Luukinen H, Käkönen SM, Pettersson K, et al. Strong prediction of fractures among older adults by the ratio of carboxylated to total serum osteocalcin. J Bone Miner Res 2000; 15: 2473-8
30. Feskanich D, Weber P, Willett WC, et al. Vitamin K intake and hip fractures in women: a prospective study. Am J Clin Nutr 1999; 69: 74-9
31. Epstein S. Is cortical bone hip? What determines cortical bone properties? Bone 2007; 41 Suppl. 1: S3-8
32. Orimo H, Fujita T, Onomura T, et al. Clinical evaluation of Ea-0167 (menatetrenone) in the treatment of osteoporosis: phase III double-blind multicenter comparative study with alfacalcidol [in Japanese]. Clin Eval 1992; 20: 45-100
33. Sato Y, Inose M, Higuchi I, et al. Changes in the supporting muscles of the fractured hip in elderly women. Bone 2002; 30: 325-30
34. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of vitamin D on falls: a meta-analysis. JAMA 2004; 291: 1999-2006
35. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA 2005; 293: 2257-64
36. Hara K, Akiyama Y, Nakamura T, et al. The inhibitory effect of vitamin K_2 (menatetrenone) on bone resorption may be related to its side chain. Bone 1995; 16: 179-84
37. Hara K, Akiyama Y, Tajima T, et al. Menatetrenone inhibits bone resorption partly through inhibition of PGE2 synthesis in vitro. J Bone Miner Res 1993; 8: 535-42

Correspondence: Dr *Jun Iwamoto*, Institute for Integrated Sports Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.
E-mail: jiwamoto@sc.itc.keio.ac.jp