J Orthop Sci (2001) 6:487–492

Journal of
Orthopaedic Science

Effect of menatetrenone on bone mineral density and incidence of vertebral fractures in postmenopausal women with osteoporosis: a comparison with the effect of etidronate

Jun Iwamoto[1], Tsuyoshi Takeda[1], and Shoichi Ichimura[2]

[1] Department of Sports Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
[2] Department of Orthopaedic Surgery, National Defense Medical College, Saitama, Japan

Abstract The purpose of the present study was to compare the effects of etidronate and menatetrenone on bone mineral density (BMD) and the incidence of vertebral fractures in postmenopausal women with osteoporosis. Seventy-two osteoporotic women, more than 5 years after menopause, 53–78 years of age, were randomly divided into three administration groups: E group; intermittent cyclical etidronate (200 mg/day, 14 days per 3 months; $n = 25$); M group; menatetrenone (45 mg/day, daily; $n = 23$); and C group (control); calcium lactate (2 g/day, daily; $n = 24$). Forearm BMD was measured by dual-energy X-ray absorptiometry at 0, 6, 12, 18, and 24 months after the treatment started. There were no significant differences in age, body mass index, years since menopause, and initial BMD among the three groups. One-way analysis of variance (ANOVA) with repeated measurements showed a significant decrease in BMD in the C group ($P < 0.0001$). Two-way ANOVA with repeated measurements showed a significant increase in BMD in the M group compared with that in the C group ($P < 0.0001$), and a significant increase in BMD in the E group compared with that in the C and M groups ($P < 0.0001$ and $P < 0.01$, respectively). The indices of new vertebral fractures/1000 patient-years in the E and M groups were significantly higher than that in the C group ($\chi^2 = 47.7$; $P < 0.0001$ and $\chi^2 = 42.4$; $P < 0.0001$, respectively), and did not differ significantly between the E and M groups. The present preliminary study provides evidence to suggest that, despite the lower increase in BMD produced by menatetrenone, this agent, as well as etidronate, may have the potential to reduce osteoporotic vertebral fractures in postmenopausal women with osteoporosis.

Key words Menatetrenone · Etidronate · Osteoporosis · Bone mineral density (BMD) · Vertebral fracture

Introduction

Osteoporosis, which is characterized by low bone mass and increased risk of fractures, is a major public health problem. While age-related bone loss in men is modest, women usually experience marked bone loss after menopause, with accelerated bone remodeling.[17,18,22] Because of physiological changes associated with menopause, osteoporosis primarily affects untreated late postmenopausal women.

To date, in Japan, the administration of etidronate (bisphosphonate) has been one of the most useful forms of treatment for osteoporosis in postmenopausal women. Intermittent cyclical administration of etidronate has been shown to increase bone mineral density (BMD) in the lumbar spine, the femoral neck, and the forearm, and to reduce the incidence of fractures in postmenopausal women with osteoporosis.[9,10,14,21,23,25,32,34,38] On the other hand, because menatetrenone (vitamin K_2) has been suggested to play a role in bone mineralization,[12,13,28] it has been recognized as suitable for the treatment of osteoporosis. Actually, two studies have shown that menatetrenone may just sustain lumbar BMD, but reduce the incidence of fractures in postmenopausal women with osteoporosis.[16,30] Although etidronate may be more effective than menatetrenone for increasing BMD in postmenopausal women with osteoporosis, the efficacy of etidronate and menatetrenone in reducing the incidence of fractures has not been comparatively assessed. The purpose of the present open, prospective, randomized study was to compare the effects of etidronate and menatetrenone on BMD and the incidence of vertebral fractures in postmenopausal women with osteoporosis.

Offprint requests to: J. Iwamoto
Received: January 9, 2001 / Accepted: June 8, 2001

Subjects and methods

Subjects

Seventy-two osteoporotic women, more than 5 years after menopause, 53–78 years of age, were recruited in autumn 1998 at a hospital. All of them were diagnosed as having osteoporosis, based on the Japanese criteria.[26] They were randomly divided into three administration groups: intermittent cyclical etidronate (200 mg/day, 14 days per 3 months) (E group; $n = 25$); menatetrenone (45 mg/day, daily) (M group; $n = 23$); and calcium lactate (2 g/day, daily) (C group [controls]; $n = 24$). Preliminary screening included the taking of a medical history, a physical examination, blood biochemical tests, plain X-ray examination of the thoracic and lumbar spines, and the measurement of BMD. Biochemical tests were performed by standard automated laboratory techniques. BMD was measured as described below. None of the subjects had a history of hormone (estrogen) replacement therapy or had ever taken medication that affects bone metabolism prior to the present trial. None of the subjects had participated in sporting activity for at least the previous 5 years and none of them participated in such activity during the present trial. The serum calcium, phosphorus, and alkaline phosphatase levels were within normal limits in all subjects. Informed consent was obtained from each of the participants.

Diet evaluation, and calcium and vitamin D supplementation

All subjects completed 7-day food records during the initial screening, according to the instructions provided by a registered dietitian. After the initial dietary assessment, all subjects were strictly encouraged to consume 800 mg of calcium and 400 IU of vitamin D daily in their meals, as outlined by the dietitian.[2,5,6,19,24]

Measurement of BMD

Forearm (distal radius) BMD on the nondominant side was measured by dual-energy X-ray absorptiometry (DXA), using a DTX-200 (Osteometer; MediTech, CA, USA). The site of measurement in the distal radius was the region between the point where the radius and the ulna are separated by 8 mm and a point 24 mm in the proximal direction from that point. The mean coefficient of variation (100 × SD/mean) of five measurements, each time repositioned within 72 h, was 0.9% in ten persons. BMD was assessed at baseline and 6, 12, 18, and 24 months after the treatment started.

Assessment of vertebral fractures

At the beginning of the study, plain X-ray examination of the thoracic and lumbar spines was performed to find evidence of vertebral fractures. At the end of the study, plain X-ray examination of the thoracic and lumbar spines was also performed to assess the incidence of new vertebral fractures during the treatment. Vertebral fracture was defined according to vertebral height obtained from lateral X-ray films, based on the Japanese criteria.[26] Briefly, vertebral height was measured at the anterior (A), center (C), and posterior (P); when (1) more than 20% reduction of vertebral height (A, C, and P) compared with the neighboring vertebrae was observed; (2) C/A or C/P was less than 0.8; or (3) A/P was less than 0.75, the presence of vertebral fracture was confirmed.

Statistical analysis

Data values are expressed as means ± standard error (SE). Analysis of variance (ANOVA) with Fisher's protected least significant difference (PLSD) test was used to compare differences in baseline characteristics among the three groups. One-way ANOVA with repeated measurements was used to examine the significance of longitudinal changes in BMD in each group. Two-way ANOVA with repeated measurements was used to compare the longitudinal changes in BMD among the three groups. The χ^2-test was used to compare the indices of new vertebral fractures/1000 patient-years, as the fracture incidence. A significance level of $P < 0.05$ was used for all comparisons.

Results

Characteristics of subjects

Table 1 shows the baseline characteristics of the study subjects. The mean age of the subjects in the E, M, and C groups was 64.3, 65.4, and 66.0 years, respectively. There were no significant differences in mean age; height; body weight; body mass index; years since menopause; serum calcium, phosphorus, and alkaline phosphatase levels; and daily calcium intake among the three groups. The mean initial forearm BMD of the subjects in the E, M, and C groups was 0.245, 0.246, and 0.254 g/cm^2, respectively. There were no significant differences in initial forearm BMD among the three groups.

Changes in BMD

Figure 1 shows the longitudinal percent changes in forearm BMD. In the C group, the mean percent changes in BMD were −1.4% at 6 months, −2.4% at 12 months, −1.7% at 18 months, and −1.7% at 24 months compared with baseline, and these longitudinal changes

Table 1. Characteristics of study subjects

	E ($n = 25$)	M ($n = 23$)	C ($n = 24$)
Age (years)	64.3 ± 1.3	65.4 ± 1.2	66.0 ± 1.1
Height (m)	1.48 ± 0.01	1.47 ± 0.01	1.47 ± 0.01
Body weight (kg)	46.3 ± 1.7	44.7 ± 1.9	45.3 ± 1.7
Body mass index (kg/m^2)	21.2 ± 0.7	20.6 ± 0.7	20.9 ± 0.6
Years since menopause	17.0 ± 1.3	18.3 ± 1.5	16.0 ± 1.2
Serum calcium (mg/dl)	9.2 ± 0.1	9.2 ± 0.1	9.3 ± 0.1
Serum phosphorus (mg/dl)	3.3 ± 0.1	3.3 ± 0.1	3.2 ± 0.1
Serum ALP (IU/l)	232.3 ± 9.6	232.8 ± 9.6	223.8 ± 9.8
Calcium intake (mg/day)	498.3 ± 25.6	487.5 ± 29.8	512.2 ± 35.2
Forearm BMD (g/cm^2)	0.245 ± 0.017	0.246 ± 0.017	0.254 ± 0.013

Data values are expressed as means ± SE. There were no significant differences in any characteristics at baseline among the three groups (by analysis of variance [ANOVA] with Fisher's protected least significant difference [PLSD] test). E, Etidronate administration; M, menatetrenone administration; C, calcium lactate administration (control); BMD, bone mineral density; ALP, alkaline phosphatase

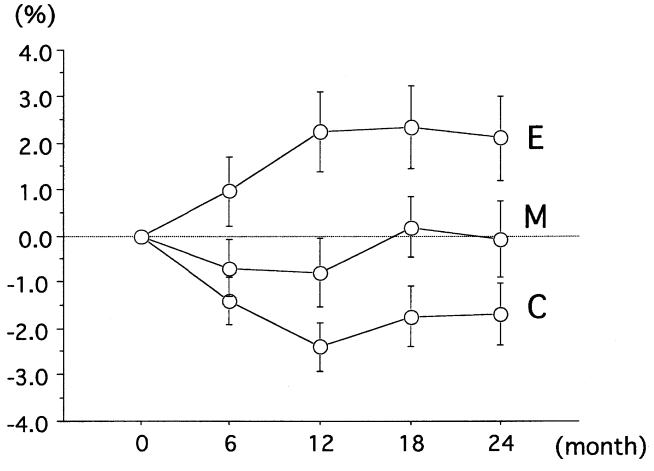

Fig. 1. Longitudinal percent changes in forearm bone mineral density (BMD). Data values are expressed as means ± SE. One-way analysis of variance (ANOVA) with repeated measurements showed a significant decrease in BMD in the C group ($P < 0.0001$), no significant changes in BMD in the M group, and a significant increase in BMD in the E group ($P < 0.01$). Two-way ANOVA with repeated measurements showed a significant increase in BMD in the M group compared with the C group ($P < 0.0001$), and a significant increase in BMD in the E group compared with the C and M groups ($P < 0.0001$ and $P < 0.01$, respectively). *E*, Etidronate administration; *M*, menatetrenone administration; *C*, calcium lactate administration (control)

were significant ($P < 0.0001$, one-way ANOVA). The corresponding changes in the E group were +1.0%, +2.2%, +2.3%, and +2.1%, and these longitudinal changes were significant ($P < 0.01$, one-way ANOVA). The corresponding changes in the M group were −0.7%, −0.8%, +0.2%, and −0.1%, and these longitudinal changes were not significant (one-way ANOVA). Two-way ANOVA with repeated measurements showed a significant increase in BMD in the M group compared with the C group ($P < 0.0001$), and a significant increase in the E group compared with the C and M groups ($P < 0.0001$ and $P < 0.01$, respectively).

Incidence of vertebral fractures

At the beginning of the study, plain X-ray examination of the thoracic and lumbar spines revealed evidence of vertebral fractures in eight patients in the E group, in seven patients in the M group, and in seven patients in the C group. In the E group, 1 vertebral fracture was observed in four patients, 2 vertebral fractures in three patients, and 3 vertebral fractures in one patient; in total, 13 vertebral fractures (9 thoracic and 4 lumbar vertebral fractures) were observed. In the M group, 1 vertebral fracture was observed in four patients and 2 vertebral fractures in three patients; in total, 10 vertebral fractures (7 thoracic and 3 lumbar vertebral fractures) were observed. In the C group, 1 vertebral fracture was observed in three patients, 2 vertebral fractures in three patients, and 3 vertebral fractures in one patient; in total, 12 vertebral fractures (7 thoracic and 5 lumbar vertebral fractures) were observed.

A vertebral fracture occurred during the 24-month period of treatment in two patients in the E group, in two patients in the M group, and in six patients in the C group. In each of the E and M groups, a thoracic vertebral fractures occurred in two patients who had not revealed any vertebral fractures at baseline. In the C group, a thoracic vertebral fracture occurred in each of two patients who had not revealed any vertebral fractures at baseline. A thoracic vertebral fracture also occurred in each of two had patients who had revealed one or two vertebral fractures at baseline, and a lumbar vertebral fracture occurred in each of two patients who

had revealed two or three vertebral fractures at baseline.

The indices of new vertebral fractures/1000 patient-years in the E, M, and C groups were 40.0, 43.5, and 125.0, respectively. The indices of new vertebral fractures/1000 patient-years in the E and M groups were significantly higher than that in the C group ($\chi^2 = 47.7$; $P < 0.0001$ and $\chi^2 = 42.4$; $P < 0.0001$, respectively), and did not differ significantly between the E and M groups ($\chi^2 = 0.2$; $P = 0.6557$). The rate of reduction of occurrence of a new vertebral fracture in the E and M groups compared with the C group was 68.0% and 65.2%, respectively. During the treatment, none of the subjects suffered from any other fractures, in the hip, wrist, or shoulder joints.

Adverse effects

Adverse effects, such as gastrointestinal symptoms, occurred primarily during the first 4 weeks of treatment, in five patients in the E group and in two patients in the C group. However, other adverse effects, such as skin, nervous system, musculoskeletal, or urinary tract-related symptoms were not observed in patients in the E and C groups. In patients in the M group, adverse effects, such as gastrointestinal, skin, nervous system, musculoskeletal or urinary tract-related symptoms were not observed.

Discussion

Inadequate intake of calcium and vitamin D and inadequate exposure to sunlight seem to be some of the major reasons for the increase in the population with osteoporosis.[5,7,8] Inadequate exposure to sunlight, in particular, results in decreased production of vitamin D_3, and induces vitamin D_3 deficiency with inadequate vitamin D intake. Therefore, calcium and vitamin D_3 supplementation may be one of the reasonable therapeutic approaches to the treatment of osteoporosis. In the present study, because inconsistent intake of calcium and vitamin D among the subjects could affect BMD, daily intake of calcium and vitamin D was unified through nutritional treatment. The daily nutritional intake of calcium and vitamin D in the present study was determined based on the previous reports,[2,5,6,19,24] and it was expected to be of value in maintaining bone health in postmenopausal or elderly women.

Although the effects of calcium supplementation on BMD in postmenopausal women with osteoporosis have not always been consistent, it is possible that calcium supplementation may have little effect in preventing bone loss in women early after menopause, but may have the potential to bring about a positive effect on bone mass in women late after menopause, who are elderly, have a low-calcium diet, and/or have apparent evidence of osteoporosis.[3,4] The patients in our control group were given supplemental calcium, 2 g of calcium lactate (267 mg of elemental calcium) daily, as a treatment for osteoporosis, which was expected to bring about beneficial effects on BMD. However, calcium supplementation could not maintain forearm BMD. This is probably because the factors of age, calcium intake at baseline, and/or evidence of osteoporosis in the subjects in the present study did not have enough power to result in a positive effect on forearm BMD. Further study with a large number of subjects and a long duration of observation may be needed to clarify whether calcium supplementation results in a positive effect on forearm BMD in such postmenopausal osteoporotic women as the subjects in the present study.

Etidronate a bisphosphonate, is an antiresorptive agent. Intermittent cyclical administration of etidronate has been shown to increase BMD in postmenopausal women with osteoporosis.[9,10,14,21,23,25,32,34,38] With regard to its mechanism of action, bisphosphonate has been shown to suppress bone remodeling (decreased bone resorption followed by decreased bone formation) in postmenopausal women.[1,15] Available evidence suggests that the administration of bisphosphonate to postmenopausal women suppresses osteoclastic activity and decreases the depth of erosion in trabecular bone, resulting in an increase in cancellous bone mass.[31,33,36] Recently, the rate of increase in bone mineral content or density from baseline as a result of etidronate treatment with vitamin D supplementation for 1–4 years has been reported to be 3.2%–15.9% (mean, 6.3%) in the lumbar spine,[9,10,14,21,23,25,32,34,38] 0.9%–5.5% (mean 2.6%) in the femoral neck,[14,21,23,28] and 1.5% in the forearm.[32] These results suggest that bone response to etidronate administration in postmenopausal women may be greater in the lumbar spine than in the femoral neck and the forearm. In the present study, a similar increase in forearm BMD (2.1%) was observed through the 24-month period of intermittent cyclical administration of etidronate. Intermittent cyclical administration of etidronate significantly increased BMD, probably by suppressing bone resorption.

Vitamin K_2, menatetrenone, is known to be essential for the carboxylation of osteocalcin.[12,28] Because noncarboxylated osteocalcin cannot bind to hydroxyapatite in mineralized tissues until the γ-carboxylation of osteocalcin occurs,[13,28] vitamin K_2 may play a role in mineralization in bone. In addition, an inhibitory effect of vitamin K_2 on bone resorption in vitro has also been reported.[11] Based on these results of experimental studies, administration of menatetrenone to postmenopausal women with osteoporosis was expected to not only increase bone formation but also to decrease bone

resorption. A few well controlled prospective clinical studies have been reported concerning the effect of menatetrenone administration on lumbar BMD in postmenopausal women.[16,30] Available evidence suggests that the administration of menatetrenone to postmenopausal women with osteoporosis increased bone formation without any significant alterations in bone resorption, resulting in sustained lumbar BMD.[30] Thus, clinically, menatetrenone administration seems to just sustain lumbar BMD in postmenopausal women with osteoporosis, probably not by decreasing bone resorption but by increasing bone formation (mineralization of bone). It is possible that, in the present study, because the administration of menatetrenone did not significantly suppress bone resorption in a state of increased bone resorption (remodeling), there were no significant changes in BMD from baseline, and there was only a small increase in BMD compared with that in the controls with administered calcium, in contrast to etidronate administration, which significantly increased BMD by suppressing bone resorption.

The correlation between lumbar BMD and the incidence of vertebral fractures should be examined. However, because elderly patients often have degenerative disc diseases and/or osteoporotic vertebral fractures in the lumbar spine, it is often not possible to evaluate lumbar BMD. Based on a recent report suggesting that forearm BMD could identify patients with osteoporosis in the spine or femoral neck,[20] we measured BMD in the skeletal site of the forearm, rather than the lumbar spine. Both etidronate and menatetrenone administration reduced the incidence of vertebral fractures compared with the incidence in controls with administered calcium. While etidronate administration increased forearm BMD and reduced the incidence of vertebral fractures, the effect of menatetrenone administration was apparent as a reduction in the incidence of vertebral fractures (an increase in bone quality), rather than as an increase in forearm BMD (an increase in bone quantity). The percent reduction in the occurrence of new vertebral fractures has been reported to be 30.0%–88.9% (mean, 59.7%) with etidronate treatment and vitamin D supplementation for 2.5–4 years,[21,32,34] and 64.0% with menatetrenone treatment for 24 months.[30] The reduction in the incidence of new vertebral fractures seems to be similar for etidronate and menatetrenone administration. This supports the concept that a stronger effect on BMD does not guarantee more efficient prevention of new fractures.[29]

The mechanism by which menatetrenone significantly reduced the incidence of new vertebral fractures, despite inducing no significant increase in BMD, remains unclear. Because the effects of menatetrenone on bone turnover may be quite different from those seen with potent inhibitors of bone resorption, such as the bisphosphonate, etidronate, the mechanism of the prevention of bone fractures by menatetrenone may be different from that of etidronate. Shiraki et al.[30] suggested that menatetrenone possibly enhanced both the γ-carboxylation of glutamic residues and the secretion of the osteocalcin molecule, resulting in the prevention of new vertebral fractures, based on reports that undercarboxylated osteocalcin could be associated with bone fracture in osteoporosis.[27,35,37] Thus, menatetrenone may reduce bone fracture in osteoporosis by enhancing bone mineralization, in contrast to etidronate, which suppresses bone resorption and prevents bone fracture. We speculate that, while strong suppression of bone resorption in postmenopausal women with osteoporosis results in an increase in BMD and bone mechanical strength, increased bone formation (mineralization of bone) may play an important role in an increase in bone mechanical strength, rather than BMD. Our results demonstrate evidence for the efficacy of menatetrenone administration in increasing bone mechanical strength.

In the present study, menatetrenone did not cause adverse effects, such as gastrointestinal, skin, nervous system, musculoskeletal, or urinary tract-related symptoms, while etidronate caused gastrointestinal symptoms in 20% of the subjects. Menatetrenone is contraindicatied in infants, pregnant or lactating women, and patients who are taking warfarin; however, none of the postmenopausal women in the present study had a history of taking warfarin. Menatetrenone may have some advantages over etidronate in terms of the incidence of adverse effects.

The cost of a menatetrenone prescription (45 mg/day, daily) for 24 months was greater (by about twofold) than that of an etidronate prescription (200 mg/day, 14 days per 3 months). However, because the incidence of new vertebral fractures was similar with the menatetrenone and etidronate treatments, the cost of treatment for fractures, including pain relief, may also be similar. If both treatments are continued in all patients, with no patients dropping out, the cost of osteoporosis treatment, including the cost of medication and treatment for relief of pain caused by vertebral fractures, may be greater for menatetrenone treatment than for etidronate treatment. However, if we consider that compliance is better for menatetrenone treatment than for intermittent cyclical etidronate treatment, menatetrenone may have some advantages over etidronate in terms of the total cost of the treatment for vertebral fractures in osteoporotic patients, because of a lower number of dropout patients and, subsequently, fewer patients who experience new vertebral fractures.

In conclusion, the present preliminary study provides evidence suggesting that menatetrenone, despite inducing a lower increase in BMD than etidronate, may have

the potential to reduce osteoporotic vertebral fractures in postmenopausal women with osteoporosis as well as etidronate. In postmenopausal women with osteoporosis, menatetrenone seems to be effective for the prevention of osteoporotic vertebral fractures, rather than for increasing BMD. Further study with a large number of subjects and a long duration of observation may be needed to confirm the efficacy of menatetrenone for the treatment of osteoporosis.

References

1. Bettica P, Bevilacqua M, Vago T, et al. Short-term variations in bone remodeling biochemical markers: cyclical etidronate and alendronate effects compared. J Clin Endocrinol Metab 1997;82: 3034–9.
2. Chesnut CH III. Osteoporosis and its treatment. N Engl J Med 1992;326:406–8.
3. Cumming RG. Calcium intake and bone mass: a quantitative review of the evidence. Calcif Tissue Int 1990;47:194–201.
4. Dawson-Hughes B. Calcium supplementation and bone loss: a review of controlled clinical trials. Am J Clin Nutr 1991;54(Suppl 1):274S–80S.
5. Fujita T. Studies of osteoporosis in Japan. Metabolism 1990; 39(Suppl 1):39–42.
6. Fujita T. Clinical guidelines for the treatment of osteoporosis in Japan. Calcif Tissue Int 1996;59(Suppl 1):S34–7.
7. Fujita T, Fujii Y, Goto B, et al. A 3-year comparative trial in osteoporosis treatment: effect of combined alfacalcidol and elcatonin. J Bone Miner Metab 1997;15:223–6.
8. Gannage-Yared M-H, Chemali R, Yaacoub N, et al. Hypovitaminosis D in a sunny country: relation to lifestyle and bone markers. J Bone Miner Res 2000;15:1856–62.
9. Guanabens N, Farrerons J, Perez-edo L, et al. Cyclical etidronate versus sodium fluoride in established postmenopausal osteoporosis: a randomized 3-year trial. Bone 2000;27:123–8.
10. Gürlek A, Bayraktar M, Gedik O. Comparison of calcitriol treatment with etidronate-calcitriol and calcitonin-calcitriol combinations in Turkish women with postmenopausal osteoporosis: a prospective study. Calcif Tissue Int 1997;61:39–43.
11. Hara K, Akiyama Y, Tajima T, et al. Menatetrenone inhibits bone resorption partly through inhibition of PG E_2 synthesis in vitro. J Bone Miner Res 1993;8:535–42.
12. Hauschka PV, Lian JB, Gallop PM. Direct identification of the calcium-binding amino acid, γ-carboxyglutamate, in mineralized tissue. Proc Natl Acad Sci USA 1975;72:3925–9.
13. Hauschka PV, Carr SA. Calcium-dependent α-helical structure in osteocalcin. Biochemistry 1982;21:2538–47.
14. Heaney A, Stelle I, Taggart H. Long-term efficacy of cyclical etidronate therapy in postmenopausal osteoporosis. Ir J Med Sci 1997;166:257–9.
15. Herd RJM, Balena R, Blake GM, et al. The prevention of early postmenopausal bone loss by cyclical etidronate therapy: a 2-year double-blind, placebo-controlled study. Am J Med 1997;103:92–9.
16. Iwamoto I, Kosha S, Noguchi S, et al. A longitudinal study of the effect of vitamin K_2 on bone mineral density in postmenopausal women: a comparative study with vitamin D_3 and estrogen-progestin therapy. Maturitas 1999;31:161–4.
17. Iwamoto J, Takeda T, Otani T, et al. Age-related changes in cortical bone mass in women: metacarpal bone mass measurement study. J Orthop Sci 1998;3:90–4.
18. Iwamoto J, Takeda T, Ichimura S, et al. Age-related changes in cortical bone mass in men: metacarpal bone mass measurement study. J Orthop Sci 2000;5:4–9.
19. Johnston CC Jr. Development of clinical practice guidelines for prevention and treatment of osteoporosis. Calcif Tissue Int 1996;59(Suppl 1):S30–3.
20. Jones T, Davie MWJ. Bone mineral density at distal forearm can identify patients with osteoporosis at spine or femoral neck. Br J Rheumatol 1998;37:539–43.
21. Lyritis GP, Tsakalakos N, Paspati I, et al. The effect of a modified etidronate cyclical regimen on postmenopausal osteoporosis: a 4-year study. Clin Rheumatol 1997;16:354–60.
22. Maggio D, Pacifici R, Cherubini A, et al. Age-related cortical bone loss at the metacarpal. Calcif Tissue Int 1997;60:94–7.
23. Masud T, Mulcahy B, Thompson AV, et al. Effects of cyclical etidronate combined with calcitriol versus cyclical etidronate alone on spine and femoral neck bone mineral density in postmenopausal women. Ann Rheum Dis 1998;57:346–9.
24. Meunier PJ, Chapuy MC, Arlot ME, et al. Effect of a calcium and vitamin D3 supplementation on non-vertebral fracture rate, femoral bone density and parathyroid function in elderly women. A prospective placebo-controlled study. J Bone Miner Res 1991;6:S135.
25. Miller PD, Neal BJ, McIntyre DO, et al. Effect of cyclical therapy with phosphorus and etidronate on axial bone mineral density in postmenopausal osteoporotic women. Osteoporos Int 1991;1: 171–6.
26. Orimo H, Sugioka Y, Fukunaga M, et al. Diagnostic criteria of primary osteoporosis. J Bone Miner Metab 1998;16:139–50.
27. Plantalech L, Guillaumont M, Vergnaud P, et al. Impairment of gamma carboxylation of circulating osteocalcin (bone gla protein) in elderly women. J Bone Miner Res 1991;6:1211–6.
28. Price PA. Vitamin K-dependent formation of bone gla protein (osteocalcin) and its function. Vitam Horm 1985;42:65–108.
29. Rosen CJ. Pre-emptive bone strikes in prevention of osteoporosis. Lancet 1998;351:927–8.
30. 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.
31. Steiniche T, Hasling C, Charles P, et al. The effects of etidronate on trabecular bone remodeling in postmenopausal spinal osteoporosis: a randomized study comparing intermittent treatment and an ADFR regime. Bone 1991;12:155–63.
32. Storm T, Thamsborg G, Steiniche T, et al. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990; 322:1265–71.
33. Storm T, Steiniche T, Thamsborg G, et al. Changes in bone histomophometry after long-term treatment with intermittent, cyclic etidronate for postmenopausal osteoporosis. J Bone Miner Res 1993;8:199–208.
34. Storm T, Kollerup G, Thamsborg G, et al. Five years of clinical experience with intermittent cyclical etidronate for postmenopausal osteoporosis. J Rheumatol 1996;23:1560–4.
35. 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.
36. Thomas T, Barou O, Vico L, et al. Recurrence of vertebral fracture with cyclical etidronate therapy in osteoporosis: histomorphometry and X-ray microanalysis evaluation. J Bone Miner Res 1999;14:198–205.
37. 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.
38. Wimalawansa SJ. A 4-year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with postmenopausal osteoporosis. Am J Med 1998;104:219–26.