Treatment with vitamin D₃ and/or vitamin K₂ for postmenopausal osteoporosis

Jun Iwamoto, Tsuyoshi Takeda and Shoichi Ichimura

Department of Sports Medicine, School of Medicine, Keio University, ¹Department of Orthopaedic Surgery
Kyorin University School of Medicine, Tokyo, Japan

(Received for publication on January 29, 2003)

Abstract. It is established in Japan that treatment with 1α-hydroxyvitamin D₃ (alfacalcidol) slightly reduces bone turnover, sustains lumbar bone mineral density (BMD), and prevents osteoporotic vertebral fractures in postmenopausal women with osteoporosis, while vitamin K₂ (menatetrenone) enhances γ-carboxylation of bone glutamic acid residues and secretion of osteocalcin, sustains lumbar BMD, and prevents osteoporotic fractures in patients with osteoporosis. Available evidence suggests that the effect of vitamin K₂ on mineralization by human periosteal osteoblasts is enhanced in the presence of 1,25 dihydroxyvitamin D₃ in vitro. The effect of vitamin K₂ on BMD in ovariectomized rats is affected by the plasma 25-hydroxyvitamin D₃ level in vivo, and is significant only when rats are fed a diet containing vitamin D₃. Based on this line of evidence, combined treatment with alfacalcidol and menatetrenone for osteoporosis is surmised to be more effective than treatment with menatetrenone alone, and may have anabolic effects on osteoporotic bone. This combined treatment may increase bone formation as well as bone resorption over the mild anti-resorptive effect of alfacalcidol itself, and shows the greatest effect on lumbar BMD or the incidence of vertebral fractures in studies in which the mean age and years since menopause of subjects were low and the degree of osteoporosis was mild. It may be effective for mild postmenopausal osteoporosis in which age-related deterioration of trabecular bone properties remains below the threshold for vertebral fractures, even if bone resorption is increased and trabecular bone has deteriorated. (Keio J Med 52 (3): 147-150, September 2003)

Key words: vitamin D₃, vitamin K₂, postmenopausal osteoporosis, bone formation, bone resorption

Introduction

One α-hydroxyvitamin D₃ (alfacalcidol) and vitamin K₂ (menatetrenone) are widely used for the treatment of osteoporosis in Japan. It is established that treatment with alfacalcidol slightly reduces bone turnover, sustains lumbar bone mineral density (BMD), and prevents osteoporotic vertebral fractures in postmenopausal women with osteoporosis.¹ It is also reported that treatment with active vitamin D metabolites including alfacalcidol or calcitriol with or without calcium supplementation is effective in preventing hip fractures in elderly women.²³ On the other hand, menatetrenone enhances γ-carboxylation of bone glutamic acid (Glu) residues and secretion of osteocalcin, sustains lumbar BMD, and prevents osteoporotic fractures in patients with osteoporosis.⁴ It has been suggested that vitamin K insufficiency might contribute to osteoporotic fractures.⁵⁶ The effect of vitamin K₂ on bone formation and resorption is not yet established. Vitamin K₂ is a cofactor of γ-carboxylase, which converts the Glu residue to a γ-carboxyglutamic acid (Gla) residue in osteocalcin molecules, and is essential for γ-carboxylation of osteocalcin.⁷⁸ Available evidence suggests that vitamin K₂ 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 In regard to the interaction between vitamin K₂ and vitamin D₃, the effect of menatetrenone on mineral-
ization by human periosteal osteoblasts is enhanced in the presence of 1,25 dihydroxyvitamin D3 in vitro.12 The effect of menatetrenone on femoral BMD in ovariectomized rats is affected by the plasma 25-hydroxyvitamin D3 level in vivo, and is significant only when rats are fed a diet containing vitamin D3.13 The effect of menatetrenone on lumbar BMD is greater in osteoporotic patients with higher serum levels of 1,25- and 24,25-dihydroxyvitamin D3 and 25-hydroxyvitamin D3.14 This line of evidence allows us to surmise that the efficacy of combined treatment with alfalcacidol and menatetrenone for osteoporosis may be greater than that of treatment with menatetrenone alone, and may have beneficial anabolic effects on osteoporotic bone. However, the results of this combined treatment for postmenopausal osteoporosis have not always been consistent. This paper discusses the effect of treatment with alfalcacidol and/or menatetrenone for postmenopausal osteoporosis.

Treatment with Alfalcacidol or Menatetrenone for Postmenopausal Osteoporosis

Preclinical studies

Alfalcacidol causes dose-dependent suppression of bone resorption, and yet maintains or even stimulates bone formation, as reflected in increases in the serum osteocalcin level and the bone formation rate at both trabecular and cortical sites in ovariectomized rats.15 Alfalcacidol can also prevent ovariectomy-induced deterioration of trabecular bone microarchitecture.16 On the other hand, the effect of menatetrenone on bone loss induced by ovariectomy in rats remains controversial. Some studies show that menatetrenone prevents early bone loss through the inhibition of bone resorption,17 and protects against the loss of trabecular bone volume and its connectivity in ovariectomized rats.18 Another study shows that menatetrenone does not reduce the ovariectomy-associated increase in bone turnover or decline in distal femoral BMD.19 Thus, the effect of menatetrenone on bone loss and bone formation and resorption in ovariectomized rats is not established. However, there is some evidence indicating that menatetrenone retards the increase in bone turnover in orchidectomized rats and ameliorates the increase in bone resorption and decrease in bone formation in sciatic neurectomized rats.20 Because the doses of alfalcacidol and menatetrenone used in these studies are pharmacologic, not physiologic, it is not known whether these results are applicable to humans.

Clinical studies

It is established that treatment with alfalcacidol slightly reduces bone turnover, sustains lumbar BMD, and prevents osteoprotic vertebral fractures in postmenopausal women with osteoporosis.1 Calcitriol also reduces bone turnover in postmenopausal women, which is partly a consequence of the enhanced intestinal absorption of calcium and suppressed serum parathyroid hormone level.21 The increase in serum 25-hydroxyvitamin D level and decrease in serum parathyroid hormone level by treatment with active vitamin D3 may be greater in patients with a lower baseline serum 25-hydroxyvitamin D level.22 Calcitriol with calcium supplementation is effective in preventing hip fractures in elderly women.2 On the other hand, treatment with menatetrenone enhances γ-carboxylation of bone Glu residues and secretion of osteocalcin, sustains lumbar BMD, and prevents osteoporotic fractures in patients with osteoporosis.4 The effect of menatetrenone on lumbar BMD may be greater in early postmenopausal (≤5 years after menopause) women than in late (>5 years after menopause) postmenopausal women.23 Serum undercarboxylated osteocalcin may reflect the low activity of vitamin K, and a higher incidence of femoral neck fractures is observed in patients with higher levels of undercarboxylated osteocalcin.5,24,25 The reason that despite no significant increase in BMD, both drugs individually prevent osteoporotic fractures including vertebral fractures remains uncertain. Bone strength is primarily determined not only by BMD, but also by bone microarchitecture, skeletal mineralization, microdamage, etc. Thus, both drugs may individually have the potential at least to improve deterioration of bone architecture as shown in preclinical studies using animals, resulting in improvement of the deterioration of bone strength and subsequent osteoporotic fractures.

Combined Treatment with Alfalcacidol and Menatetrenone for Postmenopausal Osteoporosis

Preclinical studies

No evidence has been reported concerning the therapeutic effect of combined administration of vitamin D3 and vitamin K2 on bone mass in animals with established osteoporosis induced by ovariectomy. However, a few studies have demonstrated a preventative effect of this combined treatment on bone mass in ovariectomized rats. Matsunaga et al.26 and Hara et al.27 demonstrated that combined treatment of alfalcacidol and menatetrenone was more effective for loss of bone mass and/or bone properties in ovariectomized rats. Although these two studies did not clarify the mechanism of the positive effect of this combined treatment on ovariectomy-induced osteoporosis, these results may support the synergistic effect of combined treatment with alfalcacidol and menatetrenone on bone loss in the early phase of estrogen deficiency after the menopause.
Clinical studies

A few well-controlled studies have demonstrated the effect of combined treatment with alfacalcidol and menatetrenone on postmenopausal osteoporosis.28-30 Ushiroyma et al.28 reported that in early postmenopausal women with osteopenia/osteoporosis31,32 (mean age: 52.8-54.1 years), treatment with alfacalcidol or menatetrenone sustained lumbar BMD over 2 years, while this combined treatment increased serum cmenatetrenone on postmenopausal osteoporosis. Combined treatment with alfacalcidol and menatetrenone had the greatest effect on lumbar BMD, and prevents osteoporotic fractures in patients with osteoporosis.13 In early postmenopausal women with osteopenia/osteoporosis, on the other hand, even though increased bone resorption caused by this combined treatment erodes thick trabeculae, trabecular bone volume and trabecular bone properties may remain below the threshold for vertebral fractures. Thus, combined treatment with alfacalcidol and menatetrenone may be effective for mild postmenopausal osteoporosis in which the age-related deterioration of bone properties remains below the threshold for the occurrence of vertebral fractures, even if bone resorption is increased and trabecular bone has deteriorated.

Conclusions

Treatment with 1α-hydroxyvitamin D₃ (alfacalcidol) slightly reduces bone turnover, sustains lumbar BMD, and prevents osteoporotic vertebral fractures in postmenopausal women with osteoporosis, while vitamin K₂ (menatetrenone) enhances γ-carboxylation of bone Glu residues and secretion of osteocalcin, sustains lumbar BMD, and prevents osteoporotic fractures in patients with osteoporosis. Combined treatment with alfacalcidol and menatetrenone may increase bone formation as well as bone resorption over the mild anti-resorptive effect of alfacalcidol itself, and shows the greatest effect on lumbar BMD in studies in which the mean age and years since menopause of subjects were low and the degree of osteoporosis was mild. It may be effective for mild postmenopausal osteoporosis in which age-related deterioration of trabecular bone properties remains below the threshold for vertebral fractures, even if bone resorption is increased and trabecular bone has deteriorated.
References


