REVIEW

Treatment with vitamin D_3 and/or vitamin K_2 for postmenopausal osteoporosis

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Abstract. It is established in Japan that treatment with 1α-hydroxyvitamin D_3 (alfacalcidol) slightly reduces bone turnover, sustains lumbar bone mineral density (BMD), and prevents osteoporotic vertebral fractures in postmenopausal women with osteoporosis, while vitamin K_2 (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 K_2 on mineralization by human periosteal osteoblasts is enhanced in the presence of 1,25 dihydroxyvitamin D_3 *in vitro*. The effect of vitamin K_2 on BMD in ovariectomized rats is affected by the plasma 25-hydroxyvitamin D_3 level *in vivo*, and is significant only when rats are fed a diet containing vitamin D_3. 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 D_3, vitamin K_2, postmenopausal osteoporosis, bone formation, bone resorption

Introduction

One α-hydroxyvitamin D_3 (alfacalcidol) and vitamin K_2 (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.[2,3] 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.[5,6]

The effect of vitamin K_2 on bone formation and resorption is not yet established. Vitamin K_2 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.[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]

In regard to the interaction between vitamin K_2 and vitamin D_3, the effect of menatetrenone on mineral-

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ization by human periosteal osteoblasts is enhanced in the presence of 1,25 dihydroxyvitamin D_3 *in vitro*.[12] The effect of menatetrenone on femoral BMD in ovariectomized rats is affected by the plasma 25-hydroxyvitamin D_3 level *in vivo*, and is significant only when rats are fed a diet containing vitamin D_3.[13] The effect of menatetrenone on lumbar BMD is greater in osteoporotic patients with higher serum levels of 1,25- and 24,25-dihydroxyvitamin D_3 and 25-hydroxyvitamin D_3.[14] This line of evidence allows us to surmise that the efficacy of combined treatment with alfacalcidol 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 alfacalcidol and/or menatetrenone for postmenopausal osteoporosis.

Treatment with Alfacalcidol or Menatetrenone for Postmenopausal Osteoporosis

Preclinical studies

Alfacalcidol 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] Alfacalcidol 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 alfacalcidol 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 alfacalcidol slightly reduces bone turnover, sustains lumbar BMD, and prevents osteoporotic 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 D_3 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 ($\leqq$ 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 Alfacalcidol and Menatetrenone for Postmenopausal Osteoporosis

Preclinical studies

No evidence has been reported concerning the therapeutic effect of combined administration of vitamin D_3 and vitamin K_2 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 alfacalcidol 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 alfacalcidol 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] Ushiroyama *et al.*[28] reported that in early postmenopausal women with osteopenia/osteoporosis[31,32] (mean age: 52.8–54.1 years), treatment with alfacalcidol or menatetrenone sustained lumbar BMD over 2 years, while this combined treatment increased serum c-terminal peptide of type I procollagen (PICP) level as well as urinary pyridinoline level and tended to increase osteocalcin level from baseline, resulting in a significant increase in lumbar BMD by 4.92%. We also reported that in late postmenopausal women (mean age: 64.0 years), treatment with alfacalcidol or menatetrenone sustained lumbar BMD over 2 years, while this combined treatment significantly increased lumbar BMD by 1.35% with a significantly greater increase than either treatment with alfacalcidol or menatetrenone alone.[29] On the other hand, Kobayashi *et al.*[30] reported that in elderly patients with osteoporosis, combined treatment with alfacalcidol and menatetrenone over 2 years increased urinary deoxypyridinoline level, resulting in a decrease in lumbar BMD and an increase in the incidence of vertebral fractures, while treatment with alfacalcidol increased lumbar BMD with a significantly greater increase than combined treatment, and treatment with menatetrenone decreased it by a similar degree to combined treatment.

Thus, the results of combined treatment with alfacalcidol and menatetrenone for postmenopausal osteoporosis are not always consistent. However, it appears that this combined treatment had 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. The effects of combined treatment with alfacalcidol and menatetrenone on bone mass appear to be greater than those of either treatment with alfacalcidol or menatetrenone alone in early postmenopausal women with mild osteoporosis rather than in late postmenopausal women with established osteoporosis. Curiously, the effect of this combined treatment in postmenopausal women with osteoporosis seems to be anabolic despite the mild anti-resorptive effect of alfacalcidol itself. The effect of menatetrenone on bone formation may become significant in the presence of alfacalcidol.

The reason why combined treatment with alfacalcidol and menatetrenone had the greatest effect on lumbar BMD or the incidence of vertebral fractures in the studies in which the mean age and years since menopause of subjects were low and the degree of osteoporosis subjects had was mild, remains uncertain. The difference between early postmenopausal women with mild osteoporosis and late postmenopausal women with established osteoporosis lies in deterioration of trabecular bone architecture and properties, because as trabecular thickness and trabecular number decrease, trabecular spacing increases, and trabecular bone volume and network deteriorate with age in postmenopausal women, and these factors play an important role in the determination of trabecular bone properties.[33] Therefore, age and severity of osteoporosis may influence the effect of anabolic agents on postmenopausal osteoporosis because they also increase bone resorption. Thin trabeculae due to aging and/or severe osteoporosis are easily perforated by increased bone resorption caused by combined treatment with alfacalcidol and menatetrenone despite increased bone formation, resulting in deterioration of the trabecular bone volume and trabecular network and an increased risk of vertebral fractures. 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. Then, increased bone formation can increase trabecular bone volume without the occurrence of 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.

Conclusion

Treatment with 1α-hydroxyvitamin D_3 (alfacalcidol) slightly reduces bone turnover, sustains lumbar BMD, and prevents osteoporotic vertebral fractures in postmenopausal women with osteoporosis, while vitamin K_2 (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.

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