

# Importance of Alfacalcidol in Clinical Conditions Characterized by High Rate of Bone Loss

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**ABSTRACT.** In postmenopausal osteoporosis, the administration of alfacalcidol to women resulted in an increase in trabecular bone mineral density (BMD), prevention of cortical bone loss, and a significant reduction in the incidence of further vertebral fractures. There is now robust evidence that alfacalcidol may be particularly active in conditions characterized by an increased rate of bone loss. Alfacalcidol 1 µg/day fully prevented vertebral bone loss over 3 years in women after the first year of menopause. In a large cohort of individuals starting treatment with high dose corticosteroid (CS, 46.6 mg equivalent prednisolone per day), the spinal bone loss observed in untreated patients was fully prevented by administration of 1 µg/day alfacalcidol. In patients with established CS-induced osteoporosis, with or without prevalent vertebral fractures, 1 µg/day of alfacalcidol, given for 3 years, increased lumbar spine density, reduced back pain, and showed a significant reduction in the rate of new vertebral fractures, compared to native vitamin D. In cardiac transplant recipients, alfacalcidol and calcium reduced spinal and femoral bone loss, compared to a control group treated with etidronate and calcium. Alfacalcidol-treated patients experienced fewer new vertebral fractures over the 2-year followup. When alfacalcidol and vitamin D<sub>3</sub> were compared in elderly women with radiologic evidence of vertebral fracture, fractional calcium absorption was increased after 3 months with alfacalcidol but was unchanged with vitamin D<sub>3</sub>. In a recent metaanalysis of 14 studies of native vitamin D and 19 studies of D-hormone analogs (alfacalcidol and calcitriol), the D-analogs exerted a higher preventive effect on bone loss and fracture rates in patients with no exposure to CS. In head-to-head studies comparing D-analogs and native vitamin D in patients receiving CS, this metaanalysis identified significant effects favoring D-analogs for femoral neck BMD and spinal fractures. In conclusion, improvement in bone turnover, increase in BMD, and reduction in fracture rates have been described during alfacalcidol treatment in situations characterized by a high rate of bone loss, including CS-induced osteoporosis, early postmenopausal bone loss, and organ transplant. Compared to plain vitamin D, alfacalcidol exerts higher bone-protective effects, thus allowing the doses to be minimized and lowering the risk of adverse effects, including hypercalcemia. (J Rheumatol 2005;32 Suppl 76:21-25)

*Key Indexing Terms:*

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ORGAN TRANSPLANT

## INTRODUCTION

It is well established that the metabolic activation of vitamin D is essential to its biological expression in both animals and humans. Indeed, the term “vitamin D” is inappropriate, since the endogenous production of vitamin D<sub>3</sub> by the skin, its hydroxylation to 25 OH D<sub>3</sub> and 1,25(OH)<sub>2</sub> D<sub>3</sub>, and the induction of specific gene transcription by the latter compound resemble hormonal rather than dietary vitamin activity<sup>1</sup>. Therefore alfacalcidol and calcitriol are often called D-hormone analogs. Vitamin D deficiency, because of poor sunlight exposure or decreased intake, is the most common cause of calci-

um malabsorption, yielding defective skeletal homeostasis in the elderly and subtle but progressive increments in circulating parathyroid hormone (PTH), which contributes to the loss of cortical bone<sup>2</sup>. Other factors that contribute to the so-called “age-related vitamin D deficiency” are defective renal hydroxylation and a progressive decrease in the number of the 1,25 (OH)<sub>2</sub> vitamin D<sub>3</sub> receptors (VDR), which traduce the biological effects of the final metabolite to the intestine and bone<sup>1</sup>. Alfacalcidol was initially synthesized to treat bone diseases in patients with chronic renal failure, since the renal 1-alpha hydroxylation of 25 (OH) D<sub>3</sub> to produce 1,25(OH)<sub>2</sub> D<sub>3</sub> was compromised in these individuals<sup>3</sup>. Further observations showed that osteoblasts contained 25-hydroxylase enzyme, which converts 1-alpha OH D<sub>3</sub> into 1,25 (OH)<sub>2</sub> D<sub>3</sub>, and that there were higher skeletal concentrations of 1,25 (OH)<sub>2</sub> D<sub>3</sub> after 1-alpha OH D<sub>3</sub> administration than after 1,25 (OH)<sub>2</sub> D<sub>3</sub>, despite the fact that serum levels of 1,25 (OH)<sub>2</sub> D<sub>3</sub> were lower after 1-alpha OH D<sub>3</sub> than after 1,25 (OH)<sub>2</sub> D<sub>3</sub> administration<sup>1,4</sup>. In postmenopausal osteoporosis, the administration of alfacalcidol (0.75-1 µg/day) to women resulted in an increase in trabecular bone mineral density (BMD), prevention of cortical bone loss, and a significant reduction in the incidence of further vertebral fracture, without inducing serious adverse effects<sup>5-7</sup>. In a retro-

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spective cohort of 11,377 Japanese women aged over 65 years, those who received vitamin D metabolites for more than 6 months (94.4% receiving alfacalcidol) had a significantly lower rate of hip fracture compared to untreated women, an effect that vanished at the cessation of treatment<sup>8</sup>. While vitamin D and its metabolites are now recognized as effective treatment of osteoporosis<sup>9,10</sup>, there is robust evidence that alfacalcidol may be particularly active in conditions characterized by increased rates of bone loss<sup>11</sup>, and compared to vitamin D, in reduction of vertebral fractures in postmenopausal osteoporosis<sup>9</sup>.

### EARLY POSTMENOPAUSAL BONE LOSS

The goals of prevention programs for postmenopausal osteoporosis are to optimize skeletal development and maximize peak bone mass at skeletal maturity, prevent age-related and secondary causes of bone loss, preserve the structural integrity of the skeleton, and prevent fractures<sup>12</sup>. The sudden cessation of estrogen secretion that follows ovarian failure or removal, in natural or surgical menopause, has been consistently linked to an increase in bone turnover and a high rate of bone loss. Since a high rate of bone loss may be a major determinant of further fracture risk, particularly in women with prevalent low BMD, regulatory authorities and expert forums emphasize the critical importance of preventing bone loss during the early stages of menopause<sup>13,14</sup>. Early animal experiments reported that alfacalcidol given to young rats after ovariectomy (OVX) prevented bone loss at the diaphysis and distal end of the femur. When initiated 3 months after OVX, alfacalcidol partially restored bone mass in OVX animals<sup>15</sup>. These effects of alfacalcidol on bone mass were associated with an improvement of bone biomechanical competence (bone strength, stiffness, maximum angulation displacement, and energy absorbing capacity), compared to untreated OVX animals<sup>16</sup>. Most recently, intestinal absorption of calcium from various sources was upregulated by alfacalcidol in OVX rats. BMD (spine and tibia) was significantly increased in the alfacalcidol supplemented rats receiving either calcium carbonate or egg shell, compared to control animals<sup>17</sup>.

While low dose (0.25 µg/day) of alfacalcidol failed to prevent radial bone loss in early postmenopausal women<sup>18</sup>, 1 µg of alfacalcidol and 500 mg calcium fully prevented vertebral bone loss, over 3 years, in women after the first year of menopause<sup>19</sup>. In a subgroup of patients in which alfacalcidol was interrupted after 2 years of administration, the rate of bone loss observed during the third year was similar to the control group without any medication<sup>19</sup>.

### GLUCOCORTICOID-INDUCED BONE LOSS AND OSTEOPOROSIS (GIOP)

GIOP is the most frequent form of secondary osteoporosis in both sexes. For more than 5 decades, osteoporotic

fractures have been recognized as one of the most devastating complications of chronic treatment with parenteral or oral corticosteroids (CS)<sup>20</sup>. More recently, deleterious effects of inhaled CS on bone turnover, BMD, and fracture rates were also documented by quantitative systematic review performed in patients with asthma and chronic obstructive pulmonary diseases<sup>21</sup>. It is now well accepted that a strong correlation exists between daily dose of CS and risk of fracture. The risk of fracture increases rapidly, within 3 to 6 months, after start of CS therapy<sup>22</sup>. Therefore, there is a consensus to consider the pharmacological management to prevent and treat GIOP<sup>22,23</sup>. In GIOP, there is both a reduction in bone formation and an increase in bone resorption. The former is related to the direct inhibitory effect of CS on osteoblasts. Increase in resorption is a more complex phenomenon. CS directly affect osteoclast function, decrease levels of sex steroids, may decrease intestinal calcium absorption, and increase urinary calcium excretion, resulting in the compensatory increase in PTH release. Eventually, CS directly enhance PTH release and increase responsiveness to PTH<sup>24</sup>. The rationale for using vitamin D or its metabolites to prevent GIOP is mainly to reverse the intestinal calcium malabsorption by antagonizing the effects of CS on gut cells and possibly to exert a direct stimulatory effect on osteoblasts<sup>25</sup>.

In rats treated with low dose prednisolone, treatment with alfacalcidol resulted in a consistent increase in mechanical competence of bone, accompanied by a significant decrease in insulin-like growth factor-1 concentration in the bone matrix<sup>26</sup>. In patients recently diagnosed with rheumatic or pulmonary disorders and receiving 5 to 25 mg prednisone daily, alfacalcidol (0.5-1.0 µg/daily) reduced secondary hyperparathyroidism, prevented decrease in biochemical markers of bone formation (osteocalcin and carboxy-terminal-propeptide of type I collagen), and maintained lumbar or femoral neck BMD, throughout 2 years of administration<sup>27</sup>. We reported that, in a large cohort of individuals starting treatment with high dose CS (46.6 mg equivalent prednisolone per day), the spinal bone loss observed in untreated patients was prevented by the administration of 1 µg/day alfacalcidol (intergroup difference after 12 mo: 6.06%; 95% CI 0.88 to 11.24). The use of alfacalcidol was not associated with significant adverse effects<sup>28</sup>. Alfacalcidol was also investigated in patients taking longterm CS treatment. In CS patients with chronic obstructive lung disease, 2 µg daily alfacalcidol, given for 6 months, raised calcium intestinal absorption and 24-hour urinary calcium excretion while serum PTH concentration and 24-hour urinary hydroxyproline excretion fell significantly. In bone biopsies performed at the end of the 6-month treatment course, active resorption, i.e., interface of osteoclasts and mineralized bone surface as a percentage of total trabecular perimeter, was significantly

reduced compared to baseline biopsies, without changes in osteoid seams or osteoblast seams<sup>29</sup>.

In patients with established GIOP, with or without prevalent vertebral fractures, 1 µg/day of alfacalcidol, given for 3 years, increased lumbar spine density, reduced back pain, and showed a trend toward reduction in the rate of new vertebral fractures, compared to native vitamin D<sup>30</sup>. These results were further confirmed in a larger cohort, showing a significant ( $p < 0.01$ ) benefit of alfacalcidol in terms of spinal BMD (3.2% difference), femoral neck BMD (0.4% difference), and vertebral fracture rates (9.7% vs 24.8%;  $p = 0.005$ ). The rates of patients with nonvertebral fracture were 15% in the alfacalcidol group and 25% in the vitamin D group ( $p = 0.080$ )<sup>31</sup>.

### OSTEOPOROSIS AFTER ORGAN TRANSPLANT

Since the mid-1970s, organ transplant (OT) has become established as effective therapy for endstage renal, hepatic, cardiac, and pulmonary diseases<sup>32</sup>. Several studies have demonstrated that bone loss occurs after OT and that transplant recipients develop symptomatic osteoporosis and fractures, which reduces their quality of life<sup>33</sup>. Besides factors related to the underlying diseases and the pretransplant situation, OT osteoporosis is influenced by the agents used to lower the incidence of organ rejection. The use of calcineurin-calmodulin phosphatase inhibitors (cyclosporine and tacrolimus) or other immunosuppressive agents has permitted reduction in CS use. However, while not yet fully elucidated in humans, the mechanism underlying the deleterious effect of these drugs on bone has been extensively investigated in animals and includes increase in bone turnover or bone resorption, decrease in gonadal steroid synthesis, and inhibition of longitudinal skeletal growth<sup>33</sup>. The mechanism of action of alfacalcidol in preventing OT osteoporosis could be due to the cyclosporine-associated decrease in creatinine clearance, concomitant to a defect in 1,25 (OH)<sub>2</sub> vitamin D production responsible for decreased calcium absorption and subsequent increase in PTH secretion<sup>34</sup>.

Two micrograms of alfacalcidol, given daily for 28 days in 10 men after cardiac transplant, resulted in a 42% reduction in serum PTH levels and 40% reduction in urinary NTX levels<sup>35</sup>. In cardiac transplant recipients, alfacalcidol (0.25–1 µg/day) and calcium reduced spinal and femoral bone loss compared to a control group treated with etidronate and calcium.

Alfacalcidol-treated patients experienced fewer (2 vs 8) new vertebral fractures over the 2-year followup<sup>36</sup>. More recently, alfacalcidol (0.25–2 µg/day) suppressed hyperparathyroidism more rapidly and strongly than calcium carbonate after kidney transplant. However, longterm BMD results did not show a clear superiority of alfacalcidol<sup>37</sup>.

### COMPARISON OF ALFACALCIDOL AND PLAIN VITAMIN D

Few doubts remain concerning the therapeutic benefits that can be obtained from the use of alfacalcidol in clinical conditions characterized by impaired intestinal calcium absorption and the consequent risk of osteoporosis. However, the advantage of using active vitamin D metabolites over the much less expensive vitamin D, which can also enhance calcium balance, should be carefully assessed in the perspective of a rational utilization of health resources. When alfacalcidol (0.50 µg/day) or vitamin D<sub>2</sub> (500-1000 units daily) was compared in elderly women with radiologic evidence of vertebral fractures, fractional calcium absorption was increased after 3 months with alfacalcidol, but was unchanged with vitamin D<sub>2</sub>. There was also a reduction in plasma PTH and alkaline phosphatase levels after 6 months with alfacalcidol, which was not seen in the group receiving vitamin D<sub>2</sub><sup>38</sup>. The authors inferred that alfacalcidol was more effective than vitamin D<sub>2</sub> in stimulating calcium absorption in elderly women with osteoporosis. These clinical results support evidence obtained from studies performed in ovariectomized rats. In these animals, alfacalcidol increased femoral BMD and strength more effectively than vitamin D<sub>3</sub> at given urinary serum calcium levels. Larger doses of vitamin D<sub>3</sub> were required to produce a similar BMD increase, in the face of hypercalcemia and compromised bone quality. Interestingly, alfacalcidol is also capable of increase in bone mass in parathyroidectomized rats, with continuous infusion of PTH, and therefore acts independently of PTH levels. These results suggest that alfacalcidol exerts bone-protective effects independently of its calcium-related effects and that the skeletal action of alfacalcidol takes place, at least in part, independently of suppression of PTH, all elements that strongly suggest superiority of alfacalcidol compared to plain vitamin D<sub>3</sub><sup>39</sup>.

We also<sup>30,31</sup> reported the outcomes of the head-to-head comparison of alfacalcidol and plain vitamin D<sub>3</sub> in GIOP, where superiority of alfacalcidol was observed for changes in spinal BMD, back pain, and vertebral fracture rates. In a recent metaanalysis of 14 studies of native vitamin D and 19 studies of D-analogs (alfacalcidol and calcitriol), the D-analogs exerted a higher preventive effect on bone loss and fracture rates in patients with no exposure to CS. Regarding BMD, studies using D-analogs provided an effect size twice higher than observed in studies using native vitamin D. In head-to-head metaanalysis studies comparing D-analogs and native vitamin D in patients receiving CS, significant effects were identified favoring D-analogs for femoral neck BMD and spinal fracture<sup>40</sup>.

## CONCLUSION

Alfacalcidol, the 1-alpha hydroxylated metabolite of vitamin D, has been repeatedly shown to exert positive effects on BMD and fracture rates in postmenopausal osteoporosis. There is now a convergent body of evidence to consider that this compound is particularly active in clinical conditions characterized by an increased degree of bone resorption and a subsequent high rate of bone loss. Preclinical results obtained in animal models are now supported by clinical studies showing that alfacalcidol may be used in women early post-menopause, in patients starting high dose CS or presenting with GIOP, and in patients after organ transplant. Improvement in bone turnover, increases in BMD, and reduction in fracture rates during alfacalcidol treatment have all been substantiated by well designed randomized controlled trials and quantitative systematic reviews in postmenopausal osteoporosis. Compared to plain vitamin D, alfacalcidol exerted greater effects in reducing vertebral fracture and protecting bone, allowing reduced risk of adverse effects, including hypercalcemia.

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