

The D-Hormone Analog Alfacalcidol: The Pioneer Beyond the Horizon of Osteoporosis Treatment

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ABSTRACT. Over the last 30 years, several clinical trials have reported the efficacy of D-hormone analogs to treat primary and secondary osteoporosis, and their genomic and nongenomic mode of action have been demonstrated with the progress of biochemical research technologies. Recent metaanalyses reviewed the preventive effect on falls and fractures of “vitamin D₃” in the elderly population, mainly based on studies with alfalcidol and calcitriol. In future a clear differentiation must be made between calcium and plain vitamin D supplementation in very old, vitamin D-deficient women and men (> 75 years) and the pharmacological treatment of patients with established osteoporosis using D-hormone analogs, independent of a patient's vitamin D status. The dual action of D-hormone analogs on bone and muscle is unique, and differentiates them from all other, bone-specific antiosteoporotic drugs. Based on its efficacy in preventing falls, alfalcidol is an excellent partner for combination therapy to improve the antifracture efficacy, especially in elderly patients. Further research is required to elucidate the mechanism of new actions of D-hormone analogs on muscle, nerves, brain, and on the immune system, to determine their application in different diseases. (J Rheumatol 2005;32 Suppl 76:4-10)

Key Indexing Terms:

D-HORMONE ANALOGS

OSTEOPOROSIS

TREATMENT

AGED

INTRODUCTION

Vitamin D₃ is a well known substance that regulates calcium metabolism and cell proliferation. It has been 30 years since 1,25-dihydroxy vitamin D₃, the final active product of vitamin D₃, was discovered and its chemical structure identified. Recently, Bischoff, *et al*¹ reported the reduction of falls by vitamin D₃ in the elderly population with vitamin D deficiency, while Gallagher, *et al* demonstrated a reduction in falls and nonvertebral fractures using D-hormone (calcitriol) in elderly women with normal vitamin D serum levels². Pfeifer, *et al* demonstrated that low muscle function in the elderly population is attributed to low vitamin D₃ status³. Verhaar, *et al* found that alfalcidol plays a significant role in improving decreased muscle strength and function⁴. Active vitamin D analogs are called D-hormones, because their potent pharmacological action is independent of vitamin D status. We conducted several clinical trials on the treatment of osteoporosis with alfalcidol⁵⁻⁷. This article summarizes the history of a D-hormone analog, alfalcidol.

DISCOVERY OF VITAMIN D ANALOGS

McCollum, *et al* discovered vitamin D in 1922 as an anti-rachitic substance in cod-liver oil⁸; then in the 1930s Windaus, *et al* purified vitamin D₂ and vitamin D₃ and identified their chemical structures^{9,10}. About 30 years after the discovery of vitamin D₃, DeLuca, *et al* separated 25-OH-D₃ and identified its chemical structure¹¹, and then Kodicek, DeLuca, and Norman demonstrated that 25-OH-D₃ was converted to 1,25-dihydroxy vitamin D₃ [1,25(OH)₂D₃] in the kidney and that this metabolite is the most active one¹²⁻¹⁴.

Although vitamin D was known as anti-rachitic substance, its mode of action was unclear. The discovery of 1,25 (OH)₂D₃ revealed that 1,25(OH)₂D₃ is produced in the kidney and has an important role in regulating calcium metabolism. The discovery of 1,25(OH)₂D₃ was the advent of vitamin D₃ research, and several medical companies focused on researching its analogs for treatment of renal osteodystrophy or secondary hyperparathyroidism caused by renal dysfunction.

During the same decade, osteoporosis was not recognized as a syndrome but as physiological aging of bone, and there was no effective treatment available. As many reports on Ca metabolism, vitamin D₃, and D-hormone were published, osteoporosis was recognized as a metabolic bone disease and was included in the list of diseases treated with vitamin D₃ analogs.

ALFACALCIDOL, PRODRUG OF 1,25(OH)₂D₃ (D-HORMONE)

Alfalcidol is a vitamin D₃ analog that is converted to the final active form of vitamin D₃, [1,25(OH)₂D₃], by 25-hydroxylation in the liver (Figure 1). This compound shows the same potency as 1,25(OH)₂D₃ in the laborato-

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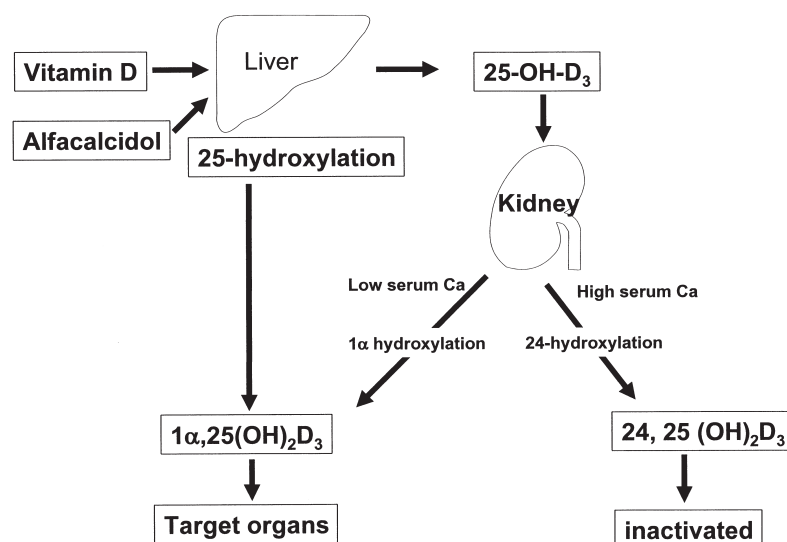


Figure 1. Metabolic pathways of vitamin D and alfacalcidol.

ry animal model¹⁵, and alfacalcidol is easier to chemically synthesize than $1,25(\text{OH})_2\text{D}_3$ and has a wider therapeutic window. Four companies, Chugai Pharmaceuticals (Japan), Leo (Denmark), Teijin Limited (Japan), and Teva Pharmaceuticals (Israel), separately initiated and developed a pharmaceutical product containing alfacalcidol. These developments were conducted under license to various patents, including those held by the Wisconsin Alumni Research Foundation and the Research Institute for Medicine and Chemistry, Cambridge.

First approvals were obtained from ministries of health for various indications at the end of the 1970s and at the beginning of the 1980s. Product launches followed soon after under the brand names of Onealfa, Alfarol, and Alpha D_3 . Alfacalcidol was the first vitamin D_3 analog to be indicated for the treatment of osteoporosis.

CLINICAL TRIALS IN OSTEOPOROSIS IN JAPAN

Inoue, *et al* contributed by developing a radiographic qualitative system to measure bone mineral density (BMD) of the second metacarpal bone, which made BMD assessment easier¹⁶. Several clinical trials were conducted in Japan to demonstrate that alfacalcidol maintains BMD in both postmenopausal osteoporosis and senile osteoporosis. In 1992, Hayashi, *et al* demonstrated that alfacalcidol reduced the incidence of vertebral fractures in both postmenopausal women who already had vertebral fractures and those who had not had fractures, in a multicenter trial¹⁷. Orimo, *et al* also reported the reduction of fractures with the treatment of alfacalcidol in comparison to those treated with only calcium⁷. Tanizawa, *et al* showed a reduction of hip fractures with alfacalcidol or calcitriol in his retrospective study in Sado Island¹⁸. Shiraki, *et al* reported that alfacalcidol main-

tained BMD in patients; they also reported that radius BMD density increased by treatment with alfacalcidol for several years¹⁹. A postmarketing survey of alfacalcidol was conducted in 13,550 osteoporotic patients. Dose of alfacalcidol given to the patients ranged from 0.5 $\mu\text{g}/\text{day}$ (14.4%) to 1 $\mu\text{g}/\text{day}$ (58.9%), and most patients treated were above the age of 60 years (93%). Adverse effects of alfacalcidol were found in 1.1%. Hypercalcemia ($\text{Ca} > 11 \text{ mg/dl}$) was found in 0.22% and increase of blood urea nitrogen was found in 0.15%, but no kidney stone was found²⁰. An observation study on alfacalcidol of 8093 patients for 6 years revealed only one case of kidney stone formation²¹. No other serious side effects have been described in the literature concerning treatment with alfacalcidol.

These data suggest that alfacalcidol is a safe drug for the treatment of involutional osteoporosis. Alfacalcidol became a major treatment in Japan, especially in the fields of internal medicine, orthopedics, and geriatric medicine, based on this clinical evidence.

RAISING THE STATUS OF ALFACALCIDOL IN THE INTERNATIONAL MEDICAL COMMUNITY

In 1984, Christiansen held the First International Symposium on Osteoporosis, where a consensus development conference was also held. The conference published a consensus report on epidemiology, prevention, diagnosis, and treatment of osteoporosis every 3 years. The second symposium focused on estrogen and calcitonin as a treatment of osteoporosis, but there was no apparent discussion of vitamin D.

In 1989, Chugai Pharmaceuticals held a satellite symposium on alfacalcidol at the first joint meeting of the American Society of Bone and Mineral Research and the

Table 1. Sponsored symposia on alfacalcidol at international conferences on osteoporosis.

Year/International Meeting	Place	Chair	Symposium Title
ASBMR-ICCRH, 1989	Montreal	E. Ogata, <i>et al</i>	Vitamin D and Metabolic Bone Disease
International Symposium on Osteoporosis, 1993	Hong Kong	L Avioli, <i>et al</i>	Osteoporosis: Therapy with Vitamin D Metabolites and Analogs
WCO, 1996	Amsterdam	D.J. Baylink, and E. Ogata	New Aspects in Therapy with Active Vitamin D Derivatives
WCO, 1998	Berlin	J.-Y. Reginster and J. C. Gallagher	Alfacalcidol – New Aspects of a Physiological Anti-Osteoporotic Therapy
WCO, 2000	Chicago	D. J. Baylink and E. Ogata	New Aspects of Alfacalcidol and D-Hormone Analogs
WCO, 2002	Lisbon	J.-Y. Reginster and J. D. Ringe	New Findings on the Effects of Alfacalcidol and D-Hormone Analogs on Fractures
WCO, 2004	Rio de Janeiro	J.-Y. Reginster and J. D. Ringe	Glucocorticoid/Inflammation-induced Osteoporosis – Pleiotropic Effects of D-Hormone Analogs

ASBMR: American Society for Bone and Mineral Research – International Conferences on Calcium regulating Hormones;
WCO: World Congress on Osteoporosis.

International Conference on Calcium Regulating Hormone in Montreal²². At this symposium, Raisz, Pettifor, Ogata, and Gallagher presented evidence on active vitamin D analogs in basic research, in pediatrics, as well as in relation to the treatment of hypoparathyroidism and osteoporosis, and Orimo described the situation of osteoporosis and its treatment in Japan.

In 1990, the Third International Symposium on Osteoporosis was held in Copenhagen. Tilyard reported on the antifracture efficacy of calcitriol at the poster session of the symposium. These data have been published in detail²³.

Chugai Pharmaceuticals and Teijin Limited collaborated to raise the status of alfacalcidol in the treatment of osteoporosis. Planned and organized with the help of Christiansen, Ogata, and Avioli, and with presentations by DeLuca, Hruska, Suda, Tilyard, Chesnut, and Orimo, the first joint satellite symposium, “Osteoporosis: Therapy with Vitamin D₃ Metabolites and Analogs” was held in March 1993 in Hong Kong²⁴. DeLuca, Hruska, and Suda presented basic data including genomic and nongenomic action, as well as the mechanism of intestinal Ca absorption; Tilyard, Chesnut, and Orimo discussed clinical data including reduction of fractures and efficacy for BMD of calcitriol, comparative data on pharmacokinetics between calcitriol and alfacalcidol, and a postmarketing survey review of alfacalcidol showing its low side effects²⁰. The report included a first description of osteoporosis as a disease in the elderly population and described the efficacy of D-hormone analogs²⁴.

In 1996, the European pharmaceutical company Teva, producer of alfacalcidol, and Tosse, the distributor of Teva's alfacalcidol in Germany, held a satellite symposium with Chugai and Teijin on alfacalcidol at the World Congress on Osteoporosis in Amsterdam. In 1998 Teva and Tosse held a satellite symposium on alfacalcidol at the

IOF World Congress on Osteoporosis in Berlin. The proceedings of these symposia were published^{25,26}. Similar satellite symposia were held in Chicago in 2000²⁷, in Lisbon in 2002²⁸, and in Rio de Janeiro in 2004²⁹ (Table 1).

CLINICAL EVIDENCE UPDATE FOR THE TREATMENT OF OSTEOPOROSIS

In their metaanalysis, Papadimitropoulos, *et al* reported on the efficacy of vitamin D₃ and D-hormone treatment in preventing osteoporosis in postmenopausal women. Using the Cochrane systematic review method, their report showed the advantageous efficacy of “hydroxylated vitamin D” (alfacalcidol, calcitriol) versus plain vitamin D³⁰. D-hormone analogs had a consistently greater influence on BMD than did plain vitamin D. The difference between groups was statistically significant for total body ($p < 0.03$) and for combined forearm ($p < 0.01$) after the final year of treatment. D-hormone analog therapy statistically significantly reduced the prospective risk of vertebral fractures (relative risk = 0.64; 95% confidence interval 0.44-0.92). Treatment with plain vitamin D failed to reach statistical significance³⁰. The decrease in risk of vertebral fractures using D-hormone analogs was found to be in the range of bisphosphonates or raloxifene. The number needed to treat (NNT), i.e., number of patients that have to be treated for 2 years to prevent one vertebral fracture, is not different using D-hormone analogs (NNT = 94) in comparison to other antiosteoporotics, e.g., risedronate (NNT = 96), alendronate (NNT = 72), or raloxifene (NNT = 99), as shown in a summary of metaanalyses³¹.

A second metaanalysis confirmed the effects on bone mass and, very importantly, the decrease in the vertebral fracture risk using D-hormone analogs (RR = 0.53; 95% CI 0.47-0.60)³² (Figure 2). In this metaanalysis, a reduc-

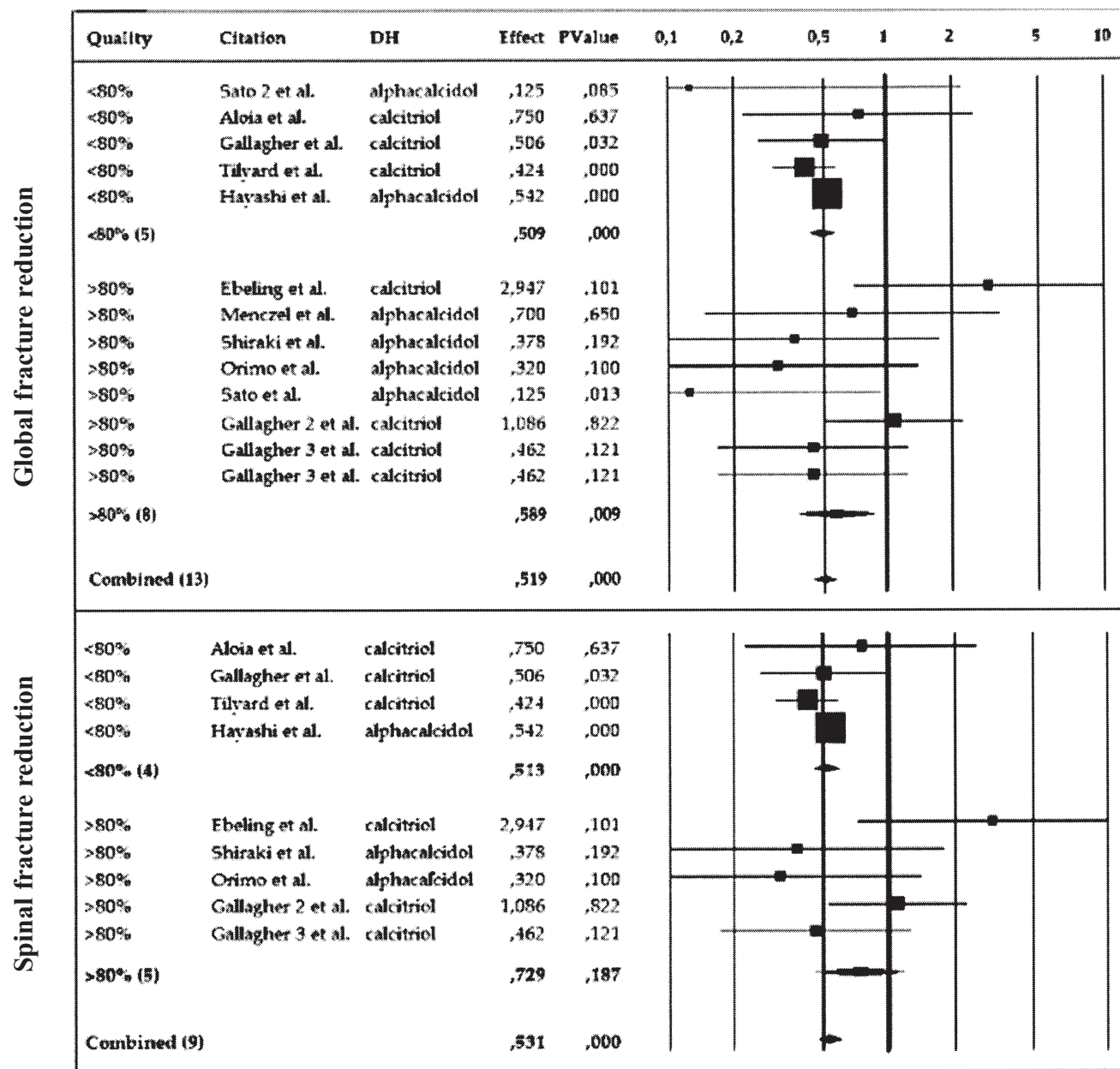


Figure 2. Efficacy of alfacalcidol and calcitriol in fracture reductions. Adapted with permission from Richy, et al. *Osteoporos Int* 2004;15:301-10³².

tion of nonvertebral fractures (RR = 0.34; 95% CI 0.16-0.71) was proven. That 2 independent metaanalyses show corresponding results is a very strong additional proof of the efficacy of D-hormone analogs in the reduction of vertebral fractures.

On the other hand, several recent "mega" trials on osteoporosis treatment, such as the Fracture Intervention Trial³³, Vertebral Efficacy with Risedronate Therapy³⁴, and Multiple Outcomes of Raloxifene Evaluation³⁵, which showed a significant reduction in fractures, included vitamin D in both intervention and control groups, indicating that vitamin D is recognized as a com-

plement to new medical treatment. In some subgroups with reduced renal activation of vitamin D, e.g., age-related decreased creatinine clearance (< 65 ml/min), chronic inflammatory diseases, or with reduced vitamin D efficacy based on D-hormone receptor (VDR) deficits, e.g., in corticosteroid-induced osteoporosis, alfacalcidol should be prescribed instead of plain vitamin D in a combination strategy with bone-specific antiosteoporotics like alendronate³⁶.

Glucocorticoid/inflammation-induced osteoporosis (GIOP) as the main secondary form is an underestimated disease. Alfacalcidol and calcitriol, based on the patho-

genesis of GIOP/inflammation-induced bone loss and fracture, have demonstrated their usefulness in the therapy of GIOP³⁷. Some studies that examined prevention of GIOP by using alfacalcidol in patients with different underlying diseases demonstrated the inhibition of bone loss, even in cases of very high doses of GC of 2046 mg prednisolone daily^{38,39}. Another study on GIOP has shown no therapeutic efficacy with plain vitamin D using high doses of 7000 IU and 1 g calcium per day⁴⁰. The prevention of bone loss after cardiac transplant was recently shown in a one year, prospective, randomized, double-blind, clinical trial comparing 0.5 µg calcitriol and 10 mg alendronate daily with a nonrandomized untreated control group. Bone loss was minimal and did not differentiate between the calcitriol and alendronate group versus vertebral and femoral bone loss in controls⁴¹. New vertebral fractures occurred in 6.8% of alendronate subjects, 3.6% of subjects treated with calcitriol, and 13.6% of controls⁴¹. Additionally, in 2 new metaanalyses, treatment with D-hormone analogs has been shown to maintain statistically significant bone mass in 6 and 11 clinical trials, respectively, with patients using glucocorticoids (GC)^{32,42}. The recently published analysis also showed significant reduction of the vertebral fracture rate using D-hormone analogs in GIOP compared with no treatment, placebo, plain vitamin D, and/or calcium⁴².

The aim of a recent study was to compare the therapeutic efficacy of alfacalcidol versus plain vitamin D in patients with established GC-induced osteoporosis⁴³. Patients taking longterm GC therapy were included as matched pairs to receive randomly either 1 µg alfacalcidol plus 500 mg calcium per day (group A, n = 103) or 1000 IU vitamin D plus 500 mg calcium (group B, n = 101). The 2 groups were well matched in terms of age, sex ratio, mean height and weight, daily dosage and duration of GC therapy, and the percentages of the 3 included underlying diseases: chronic obstructive pulmonary disease, rheumatoid arthritis, and polymyalgia rheumatica. During the 3-year study a median increase of BMD at the lumbar spine of 2.4% in group A versus a loss of 0.8 % in group B was observed ($p < 0.0001$). The 3-year rate of patients with at least one new vertebral fracture was 9.7% among those assigned to the alfacalcidol group, as compared to 24.8% among those assigned to the vitamin D group (risk reduction: 0.61; 95% CI 0.24 to 0.81; $p = 0.005$). In accord with the observed fracture rate, the alfacalcidol group showed a substantially larger decrease in back pain than the plain vitamin D group ($p < 0.0001$). Generally, side effects in both groups were mild, and only 3 patients in the alfacalcidol group and 2 patients in the vitamin D group had moderate hypercalcemia.

Vitamin D-hormone receptors (VDR) have been found in skeletal muscle and nerve⁴⁴; muscle contraction and relaxation in skeletal muscle and nerve is controlled by VDR and D-hormone via the influx and efflux of calci-

um, and via muscle protein synthesis⁴⁵. It has been recently confirmed in VDR-gene-deleted mice that absence of VDR causes a reduction of skeletal muscle fiber size based on increased expression of myogenic regulation factors (Myf5, Myogenin, E2A), through which the strictly regulated differentiation and maturation of muscle cells is disturbed⁴⁶. Muscular abnormalities are independent of secondary, metabolic changes, e.g., hypocalcemia or hyperparathyroidism. This confirms the direct efficacy of VDR. That a treatment with D-hormone of VDR-positive myoblasts *in vitro* downregulates the mentioned myoregulating transcription factors also points to the important role of D-hormone and VDR in muscle development⁴⁶. Older age is significantly associated with decreased VDR expression in human skeletal muscle tissue⁴⁷. A positive correlation was found between femoral muscle strength and function and D-hormone serum levels in the elderly^{48,49}. Muscle strength measured by leg extension power declined with age and showed significant positive correlation with D-hormone serum levels⁴⁸. Higher D-hormone status and a calcium intake of 500 mg/day in older persons are significant determinants of better functional mobility measured by Timed Up and Go Test⁴⁹. These results suggest that age-related and corticosteroid/inflammation-induced decline in muscle strength and function and increase in falls could be in part explained by decreased VDR and decreased D-hormone in serum and/or at the receptor level (Table 2).

In a prospective study 489 osteopenic women, aged 65-77 years with normal calcidiol serum levels [$25(\text{OH})\text{D} = 77.5 \text{ nmol/l}$], were randomized in a double-blind trial using treatment with a placebo, calcitriol 0.25 µg twice daily, conjugated equine estrogens (CEE) 0.625 mg plus medroxyprogesterone acetate 2.5mg (hormone replacement therapy, HRT) daily, and a combination of HRT or estrogen replacement therapy and calcitriol⁵⁰. Hysterectomized women (n = 290) were not given the progestin, but received estrogen alone (ERT). There was a significant decrease of 38% in the incidence of falls in comparison to placebo

Table 2. Rationale for treatment of sarcopenia in old age with alfacalcidol. From Boland, *Endocr Rev* 1986⁴⁵;7:434-48; Endo, et al, *Endocrinology* 2003;144:5138-44⁴⁶; Bischoff-Ferrari, et al, *J Bone Miner Res* 2004;19:265-9⁴⁷.

- Muscle and nerve cells do have D-hormone receptors (VDR)
- VDR in muscle cells are decreasing with age
- VDR gene-deleted mice develop smaller muscle fibers based on impaired muscle cell differentiation
- D-hormone counterbalances these abnormalities in myoblastic cells
- Treatment with alfacalcidol increases the ratio of fast-twitch type II muscle fibers in elderly
- D-hormone regulates the calcium metabolism in muscles (control of muscle contraction and relaxation).

only in the calcitriol treated group. In addition a reduction in fall-related fractures in the 2 groups treated with calcitriol, compared to the noncalcitriol groups, could be shown⁵⁰.

In a double-blind trial, 378 Swiss community-dwelling women (n = 191) and men (n = 187) averaging 75 years of age were randomized to receive either 1 µg alfalcidol or placebo daily for 9 months. Falls and dietary calcium intake were assessed using questionnaires. Baseline calcitriol and calcitriol serum levels were within the normal ranges. When compared to the group taking placebo, those treated with alfalcidol were found to have a significant reduction in the number of fallers (OR 0.45, 95% CI 0.21-0.97, p = 0.04) and in the number of falls (OR 0.46, 95% CI 0.22-0.99, p = 0.045) of participants with a total calcium intake of more than 500 mg calcium⁵¹.

A recently published metaanalysis on the effect of vitamin D on falls included a subgroup analysis to differentiate between effect sizes of plain vitamin D and D-hormone analogs⁵². For 3 studies involving 613 participants treated with cholecalciferol, the corrected OR of falling was 0.83 (95% CI 0.65-1.06). In contrast, the reduction of fallers was statistically significant based on 2 studies involving 626 patients treated with D-hormone analogs (OR 0.71, 95% CI 0.55-0.92). It is worth mentioning that most participants in the plain vitamin D group were vitamin D-deficient, unlike the participants treated with D-hormones, who had normal serum vitamin D levels.

The rationale for this observation is the recognized knowledge that D-hormone analogs can act without metabolic activation in the kidney, which results in higher concentrations of D-hormone at the receptors of the target organs (Figure 1)⁵³. The difference between plain vitamin D and D-hormone analogs regarding falls can be explained by the fact that there is an expression of its own receptor by D-hormone⁵⁴. Thus, improvement of bone strength, muscle power, and brain function can be hypothesized, e.g., promotion of balance and increased cognitive capabilities, resulting in a reduction of falls and fractures⁵⁵.

Ringe and Schacht described active vitamin D analogs such as alfalcidol and calcitriol as D-hormone preparations that play a physiologically significant role in bone and muscle, and in the immune system; they can be used as pharmacologically active drugs and therefore must be clearly differentiated from plain vitamin D³⁶.

CONCLUSION

Over the last 30 years, several clinical trials have reported the efficacy of D-hormone analogs to treat primary and secondary osteoporosis; and its genomic and nongenomic mode of action have been demonstrated with the progress of biochemical research technologies. Recent metaanalyses reviewed the preventive effect on falls and fractures with "vitamin D₃" in the elderly population mainly based on studies with alfalcidol and calcitriol.

In future a clear differentiation must be made between supplementation using calcium and plain vitamin D in very old, vitamin D-deficient women and men (> 75 years), and in the pharmacological treatment of patients with established osteoporosis using D-hormone analogs, independent of the patient's vitamin D status. The dual action of D-hormone analogs on bone and muscle is unique, and differentiates the product from all other bone-specific antiosteoporotic drugs. Based on its efficacy in reducing falls, alfalcidol is an excellent partner for combination therapy to improve antifracture efficacy, especially in elderly patients. Further research is required to elucidate the mechanism of these new actions of D-hormone analogs on muscle, nerves, brain, and the immune system for application in different diseases.

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