Alfacalcidol Versus Plain Vitamin D in Inflammation Induced Bone Loss

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ABSTRACT. Inflammatory diseases lead to systemic osteoporosis. Causal factors include increased circulating concentrations of inflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α), glucocorticoid medication, and reduced physical activity. In addition, disturbances of vitamin D metabolism play an important role for the development of inflammation induced osteoporosis. Therefore, D-hormone analogs offer an important treatment option. 1,25-dihydroxyvitamin D (D-hormone) prevented bone loss in the rat model of inflammation mediated osteopenia and in an arthritis model. One explanation is that animals and humans with inflammatory diseases exhibit markedly reduced circulating concentrations of D-hormone, partly the result of inhibition of renal 1-alpha-hydroxylase by TNF-α. In addition, the number of vitamin D receptors is reduced by glucocorticoids. Moreover, D-hormone has pleiotropic effects not only on calcium homoeostasis but also on muscle (improving power), the nervous system, and the immune system. D-hormone inhibits the release of cytokines (IL-1, IL-6, TNF-α) from macrophages and stimulates osteoprotegerin secretion *in vitro* and improves arthritis in animal models. This article reviews the interaction between inflammatory disease and vitamin D metabolism, summarizes the rationale for the therapeutic use of alfacalcidol, and provides recent data from controlled clinical trials comparing the effect of alfacalcidol versus plain vitamin D in secondary osteoporosis. Alfacalcidol, but not plain vitamin D, has pleiotropic effects improving bone and muscle metabolism and clinical symptoms in patients with rheumatoid arthritis. (J Rheumatol 2005;32 Suppl 76:26-32)

Key Indexing Terms:

ALFACALCIDOL | RHEUMATOID ARTHRITIS | INFLAMMATION
BONE DENSITY | INTERLEUKIN | TUMOR NECROSIS FACTOR

INTRODUCTION

Chronic inflammatory diseases are associated with a significant risk for secondary osteoporosis and fractures. For patients with rheumatoid arthritis (RA), the 5-year probability of having a fracture was reported to be up to 34%, depending on sex and glucocorticoid dose[1,2]. Patients with inflammatory bowel disease, especially Crohn's disease, have a high frequency of decreased bone mass[3,4]. The pathogenesis of osteoporosis in inflammatory disease is very complex and involves inflammatory cytokines, glucocorticoid treatment, and decreased muscular function, resulting in decreased bone formation, increased bone resorption, and increased risk for falls. All these factors contribute to the high risk for fracture in these patients. Therefore, the prevention and treatment of inflammation induced bone loss should reflect the complex pathogenesis and influence the different metabolic and functional abnormalities.

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The hormonal form of vitamin D, 1,25-dihydroxyvitamin D (calcitriol) and the prohormone 1α-hydroxyvitamin D (alfacalcidol) appear promising as treatment options because they have pleiotropic actions on calcium homeostasis, bone, muscle, and the immune system. This article reviews the interaction between inflammatory disease and vitamin D metabolism, summarizes the rationale for the therapeutic use of alfacalcidol, and provides recent data from controlled clinical trials comparing the effect of alfacalcidol versus plain vitamin D in secondary osteoporosis.

PATHOGENESIS OF INFLAMMATION INDUCED BONE LOSS AND THE ROLE OF VITAMIN D METABOLISM

Patients with chronic inflammatory diseases such as RA or Crohn's disease exhibit increased circulating concentrations of cytokines such as tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6), as well as other cytokines. TNF-α is involved in the pathogenesis of inflammatory arthritis[5]. Both TNF-α and IL-6 lead to increased bone resorption. TNF-α interacts with RANK signaling in the formation of mature osteoclasts[5]. TNF-α hinders bone-formative action of osteoblasts, suppresses recruitment of osteoblasts from progenitor cells, inhibits expression of matrix protein genes, and stimulates expression of genes that amplify osteoclastogenesis[6-8].

Oelzner and coworkers studied cytokines in postmenopausal women with RA[9]. They found a positive correlation between IL-6 and urinary bone resorption mark-

ers, suggesting that IL-6 is a critical determinant of increased bone resorption in postmenopausal women with RA and high disease activity.

TNF-α inhibits the renal 1α-hydroxylation of 25-hydroxyvitamin D[10], which explains the decreased serum concentration of 1,25-dihydroxyvitamin D observed in chronic inflammatory disease. Patients with RA and high inflammatory activity, as indicated by increased C-reactive protein (CRP) levels, have lower circulating 1,25-dihydroxyvitamin D levels compared to patients with normal CRP. The normal levels of 25-hydroxyvitamin D in these patients suggest that the activity of the 1α-hydroxylase in these patients is decreased due to inflammation[11]. Reduced serum concentrations of 1,25-dihydroxyvitamin D are also found in patients with Crohn's disease[3] and in patients with HIV infection[12], where the 1,25-dihydroxyvitamin D levels were negatively correlated with the TNF-α serum concentration. Moreover, TNF-α induces resistance to 1,25-dihydroxyvitamin D by a mechanism that extends to other members of the steroid hormone nuclear receptor family[6]. These effects of TNF-α on vitamin D metabolism contribute to the negative calcium balance, the secondary increase of parathyroid hormone, and decreased bone formation.

Patients with inflammatory disease are often treated with glucocorticoids, which represent an additional risk for the development of osteoporosis. Glucocorticoids decrease intestinal calcium absorption, inhibit osteoblast activity, induce osteocyte apoptosis, and decrease osteoprotegerin secretion[13-16]. Both inhibition of bone formation and stimulation of bone resorption are the result of glucocorticoid treatment.

In addition to bone metabolism, muscle function is also affected by inflammation and glucocorticoid treatment. TNF-α and IL-1 promote muscle catabolism[17,18], and glucocorticoids interfere with muscle function. Glucocorticoids upregulate myostatin, a negative regulator of muscle mass[19], and high doses result in decreased insulin-like growth factor-I (IGF-1 and IGF-2) expression[20]. Glucocorticoids and cytokines interfere directly with the IGF-1 signaling pathway[21]. Diminished muscular power will facilitate further bone loss and increase the risk for falls and consecutive fractures.

Glucocorticoids may also interfere with the action of vitamin D as suggested by the observation of reduced vitamin D receptor (VDR) numbers in osteoblastic cells[22,23].

RATIONALE FOR ALFACALCIDOL TO PREVENT AND TREAT INFLAMMATION INDUCED BONE LOSS

In vitamin D-deficient patients the supplementation of vitamin D might be useful, because vitamin D deficiency causes secondary hyperparathyroidism and appears to aggravate autoimmune diseases[24]. However, in vitamin D-replete patients the supplementation of vitamin D will not result in increased formation of 1,25-dihydroxyvitamin D, especially in patients with inflammatory disease, where the 1α-hydroxylase activity is reduced. In order to achieve pharmacological effects of the hormonal form of vitamin D, one has to apply 1α-hydroxylated vitamin D metabolites (D-hormone analogs), which do not require 1α-hydroxylase activity. Two compounds are used as drugs, 1,25-dihydroxyvitamin D (calcitriol) and the prohormone 1α-hydroxyvitamin D (alfacalcidol). Alfacalcidol undergoes 25-hydroxylation in the liver and in bone (which is not regulated) and has therefore a favorable pharmacokinetic profile compared to calcitriol. The use of 1α-hydroxylated vitamin D metabolites in inflammatory disease appears indicated for several reasons. Experimental and clinical data prove that the hormonal form of vitamin D increases intestinal calcium absorption, inhibits parathyroid hormone formation, facilitates osteoblast differentiation[25], stimulates osteoprotegerin secretion by human osteoblasts[26], modulates the immune system in a positive manner (such as decreasing IL-6 and TNF-α formation)[27-29], and improves muscle function[30,31].

In an animal model for inflammation induced bone loss 1,25-dihydroxyvitamin D was able to prevent the inhibition of bone formation and to maintain bone mass. To induce inflammation mediated osteopenia in the rat, animals are injected subcutaneously with a sterile suspension of magnesium silicate (talc powder) in saline solution[32]. The resulting sterile granuloma induced an inflammatory reaction accompanied by systemic bone loss, which is mainly due to inhibition of bone formation[33]. Rats with inflammation induced osteopenia exhibit reduced serum concentrations of 1,25-dihydroxyvitamin D[34], similar to patients with chronic inflammatory disease. 1,25-dihydroxyvitamin D treatment was able to prevent reduction of bone formation and to maintain bone mass in this animal model of inflammation mediated osteopenia[35].

CLINICAL EVIDENCE THAT ALFACALCIDOL PREVENTS AND TREATS SECONDARY OSTEOPOROSIS IN PATIENTS WITH INFLAMMATORY DISEASES

Previous studies have demonstrated that alfacalcidol prevents bone loss in patients with inflammatory disease such as RA and glucocorticoid treatment[36]. Alfacalcidol was significantly more effective than native vitamin D[37]. We recently published a controlled clinical study on the pleiotropic effects of alfacalcidol on bone metabolism, cytokines, muscle function, and pain score in elderly patients with RA[38]. In the study 71 inpatients with RA and osteopenia undergoing rehabilitation were included consecutively. Patients with previous osteoporosis treatment and with other diseases influencing bone metabolism were excluded. The presence of osteopenia (T score <–1) either at the spine or at the proximal femur was con-

firmed by dual energy x-ray absorptiometry (Hologic).

Patients were randomly assigned to the 2 treatment groups: Group 1 was treated with 1000 IU plain vitamin D + 500 mg calcium daily, and Group 2 was treated with 1 µg of alfacalcidol + 500 mg calcium daily. The groups did not differ in age, height, weight, disease activity, baseline laboratory findings, or glucocorticoid dosage. The mean age of the patients was 65.1 ± 1.1 years (range 40-80).

Treatment lasted for 4 weeks during the hospital stay. Glucocorticoids and disease modifying drugs were continued in both groups and adapted to activity of joint inflammation, when necessary. All patients received physical therapy including exercise, muscle training, hydro-therapy, thermotherapy, and ergotherapy. Laboratory tests were performed before treatment, after 2 weeks of treatment, and after 4 weeks of treatment. Muscle function was measured as leg extension power, by means of an isokinetic training device (Biodex Medical Systems). The seat position was adjusted for individual leg length. The tests were performed before and after 4 weeks of treatment at both legs at 2 different velocities (6°/s and 12°/s), employing 5 repetitions. Results were expressed as the increase in mechanical work (%) performed during the test cycle. Subjective pain was evaluated using a pain score (summarizing pain scores for different joints) before treatment and after 4 weeks.

Regarding side effects, during alfacalcidol treatment, no hypercalcemia was observed; however, patients with alfacalcidol treatment showed an increased urinary calcium excretion (not exceeding the normal range), suggesting that alfacalcidol improved intestinal calcium absorption. In contrast, treatment with plain vitamin D induced no significant changes in urinary calcium excretion.

In both groups, 25-hydroxyvitamin D levels were normal at baseline, proving normal vitamin D status, and did not change significantly during treatment. Serum parathyroid hormone decreased significantly in the alfacalcidol treated patients, but not in the vitamin D group (Figure 1). Accordingly, only the alfacalcidol treated group exhibited a decrease in the bone resorption marker urinary N-terminal telopeptides of collagen type 1 (Figure 2).

Regarding circulating cytokines, alfacalcidol treatment resulted in a significant decrease of circulating TNF-α (Figure 3), whereas no significant change in the serum concentration of IL-6, IL-12, or osteoprotegerin was found. The decrease in TNF-α confirms preliminary data published by Hein and Oelzner, who observed a decrease in TNF-α and IL-6 and an increase in IL-4 in patients with RA[39].

Regarding muscular function, the alfacalcidol treated patients had a much greater increase in muscle power compared to the patients treated with plain vitamin D (Figure 4). During rehabilitation, most patients experienced improvement in joint pain. However, this improvement was significantly greater in the alfacalcidol treated patients (Figure 5). The improvement of joint pain in these patients may be explained by the decrease in TNF-α (which correlates to pain in patients with RA), but may also be related to the improvement in physical function (muscular function), which allows patients to take more advantage from physical therapy.

In summary, the study of Scharla and co-workers demonstrated that, in patients with RA, alfacalcidol, but not plain vitamin D, improved calcium and bone metabolism, modulated inflammation, improved muscular function, and decreased pain symptoms. As a drawback

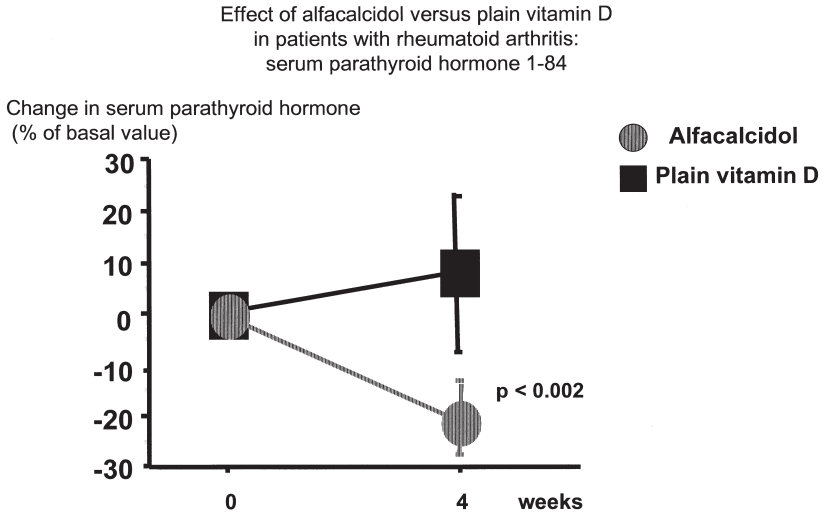

Figure 1. Significant decrease of serum parathyroid hormone in the alfacalcidol treated group after 4 weeks, significantly different compared to the group treated with plain vitamin D. Modified from Scharla, *et al.* arthritis+rheuma 2003;23:268-74, with permission.

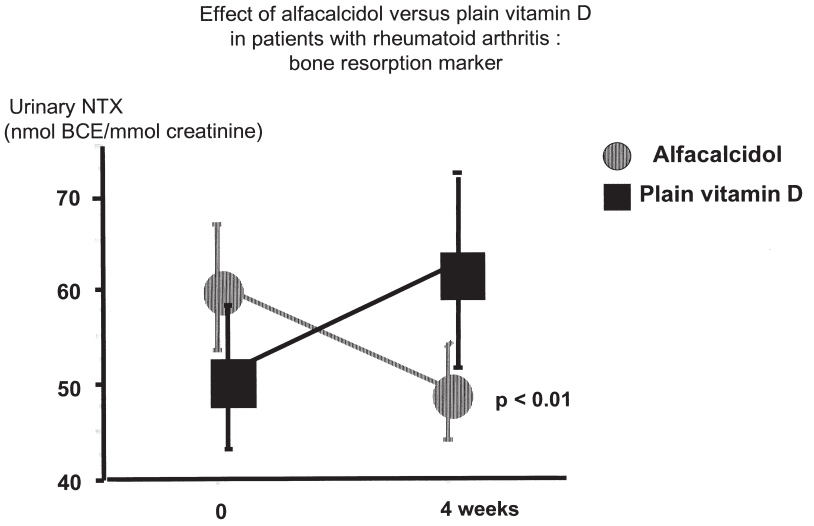

Figure 2. Significant decrease of the bone resorption marker N-terminal telopeptides of collagen type 1 (NTX) in the alfacalcidol treated group after 4 weeks. In contrast, there was a nonsignificant trend to higher values in the group treated with plain vitamin D. BCE: bovine collagen equivalent. From Scharla, *et al.* arthritis+rheuma 2003;23:268-74, with permission.

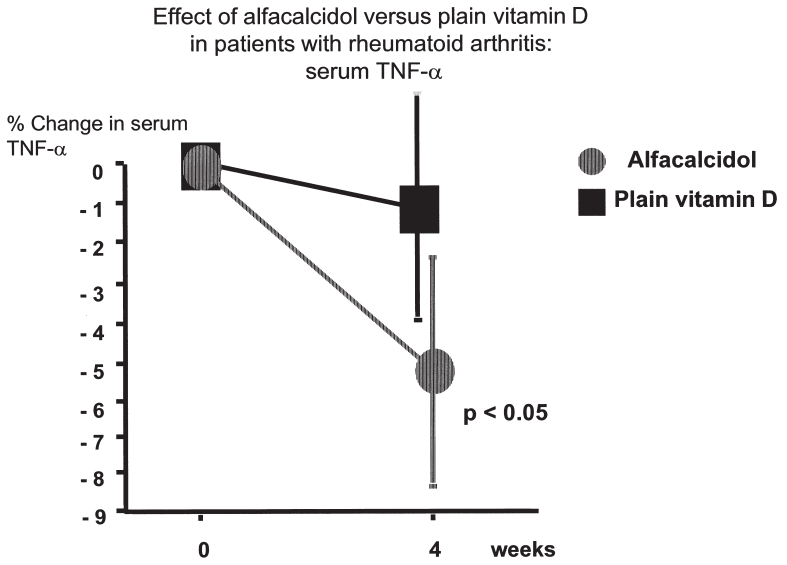

Figure 3. Significant decrease of serum TNF-α in the alfacalcidol treated group after 4 weeks. There was no change in the group treated with plain vitamin D. Modified from Scharla, *et al.* arthritis+rheuma 2003;23:268-74, with permission.

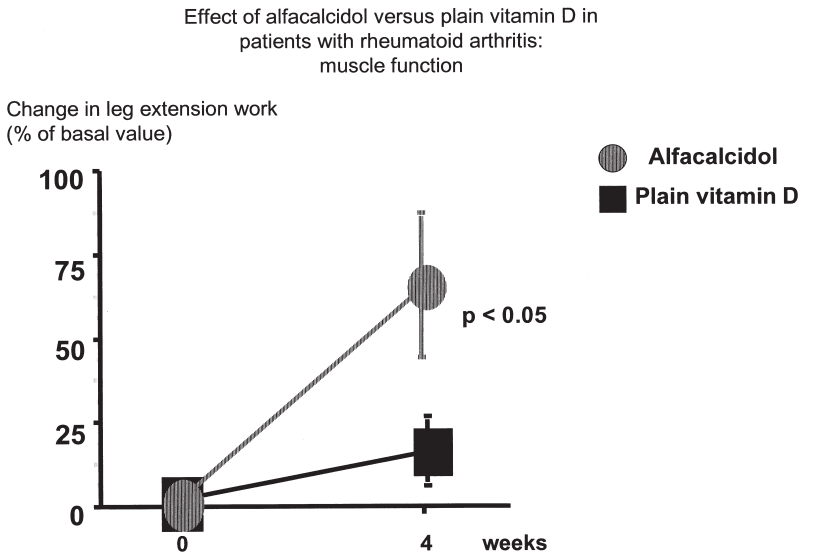

Figure 4. Significant increase of muscular workload (isokinetic leg extension work) after 4 weeks of alfacalcidol treatment (combined with physical therapy). In contrast, the increase in the group treated with plain vitamin D was smaller and not significant compared to baseline. From Scharla, *et al.* arthritis+rheuma 2003;23:268-74, with permission.

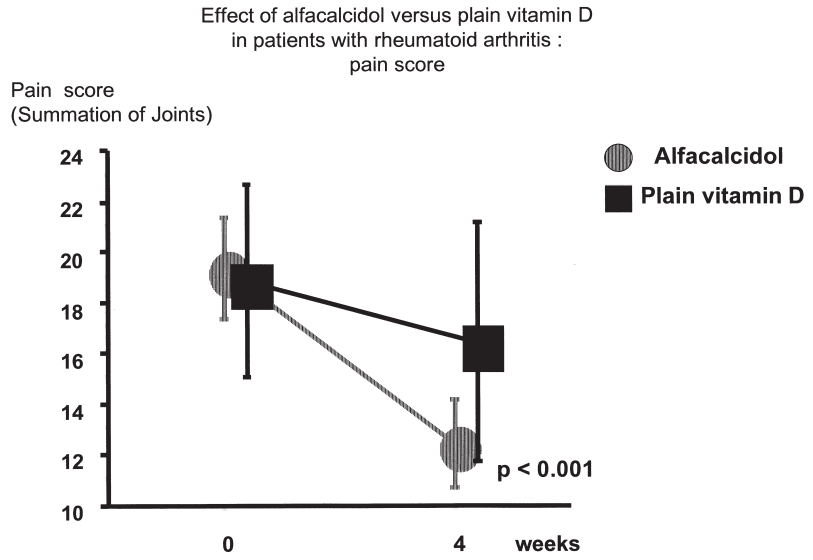

Figure 5. Significant decrease in joint pain (pain score) in the alfacalcidol treated group after 4 weeks (without changing symptomatic and disease modifying therapy). In contrast, the decrease in the group treated with plain vitamin D was smaller and not significant compared to baseline. From Scharla, *et al.* arthritis+rheuma 2003;23:268-74, with permission.

of this study, only short-term effects of alfacalcidol were investigated (4 weeks); for this reason no data on bone mineral density or fracture rate are available. However, these rapid effects of alfacalcidol on improving muscular function and pain intensity are of special value in patients with RA. Patients receiving alfacalcidol treatment are better able to participate in physical therapy and to perform strength training, which in turn has been shown to improve symptoms and quality of life in patients with RA[40].

A recent publication by Ringe and co-workers confirms that in glucocorticoid treated patients the positive effect of alfacalcidol on secondary osteoporosis is maintained during a longer treatment period, and that the fracture rate is lower in alfacalcidol treated patients compared to plain vitamin D treated patients[41].

CONCLUSIONS

Secondary osteoporosis represents a serious problem for patients with chronic inflammatory diseases, such as RA. Disturbances in vitamin D metabolism, resulting in decreased circulating levels of hormonal 1,25-dihydroxyvitamin D and lesser effectiveness at the receptor level, play an important role in the pathogenesis of bone loss. Moreover, diminished effects of the hormonal form of vitamin D contribute to other symptoms such as altered immune reaction and muscle weakness. Experimental *in vitro* evidence and animal experiments provide the basis for the conclusion that D-hormone analogs (such as calcitriol and alfacalcidol) may be able to prevent inflammation-induced bone loss and also to modulate disease activity. Recently published controlled clinical trials provide evidence that treatment with alfacalcidol prevents bone loss and fractures, modulates the immune system, and improves muscular function and pain symptoms in patients with inflammatory disease. In this respect, alfacalcidol was significantly more effective compared to plain vitamin D.

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