S-7-2 **Role of the Active Vitamin D Metabolite and 1 α -Hydroxylated Analogs in the Treatment of Postmenopausal Osteoporosis**

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INTRODUCTION

Age-related osteoporosis is a common disorder of the skeleton, characterized by progressive bone loss and increased risk of fractures. It occurs most frequently in postmenopausal women and in the elderly, where it is responsible for a high incidence of bone fractures and, consequently, for relevant social costs.

The pathogenesis of osteoporosis has long been a matter of debate and various theories have been put forward in order to explain the pathophysiology of this condition in detail.

However, a series of well documented findings are almost unanimously recognized. Patients with osteoporosis show reduced calcium absorption when compared with age-matched control subjects [1] and this abnormality is particularly relevant in those patients who have a low calcium diet, which is a clear indication of a failure of the adaptation mechanism physiologically mediated by the active vitamin D metabolite, 1,25-dihydroxyvitamin D [$1,25(\text{OH})_2\text{D}$], that is known to be the single most important, if not exclusive, regulator of intestinal calcium transport [2].

Actually, the serum levels of $1,25(\text{OH})_2\text{D}$ have been shown to be reduced in these patients as compared with normal peers [3-5] and a positive correlation has been found between serum $1,25(\text{OH})_2\text{D}$ and calcium absorption [3].

It appears that the decrease in $1,25(\text{OH})_2\text{D}$ levels cannot be accounted for by a lack of precursor 25-hydroxyvitamin D (25OHD), since the serum levels of the latter compound have been generally found to be normal [3] or even increased [6], but rather by an impaired synthesis of $1,25(\text{OH})_2\text{D}$. In fact, the administration of 25OHD_3 to osteoporotic patients is virtually useless, whereas physiological doses of synthetic $1,25(\text{OH})_2\text{D}_3$ (calcitriol) or of 1α -hydroxylated synthetic analogs, such as 1α -hydroxyvitamin D_3 (alphacalcidol), restore normal calcium absorption in osteoporotic patients [7].

The above remarks point to the impairment of calcium absorption as an important factor in the occurrence of the negative calcium balance ultimately leading to bone loss in osteoporosis; therefore, the improvement of intestinal calcium absorption should be regarded as a fundamental step in the treatment of osteoporosis. Calcitriol and its synthetic analogs are the only substances which have been demonstrated to be capable of exerting such an effect.

During the last decade we have gathered a very large experience with calcitriol therapy of postmenopausal osteoporosis, in terms of both the number of patients treated and the duration of treatment. Another large group of osteoporotic patients were given alphacalcidol instead of calcitriol.

STUDY DESIGN

Entered into the study were 422 women with symptomatic postmenopausal osteoporosis, aged 49-78 yrs. Criteria for admission were listed elsewhere [8].

A group of 301 patients were administered calcitriol at an oral dose of $0.5 \mu\text{g}$ twice a day without Ca supplementation; the numbers of patients treated for 1-10 years was 301, 228, 162, 96, 71, 46, 26, 15, 7 and 2, respectively.

A group of 121 patients received oral alphacalcidol at the dose of 1.0 μg per day; all of them were treated for at least 1 year and 50 for at least 2 years.

Several parameters of calcium and phosphate metabolism and renal function were determined in baseline conditions and at various intervals during treatment, as reported elsewhere [8].

Serum $1,25(\text{OH})_2\text{D}$ levels were measured by radioreceptor assay, using a thymus receptor, after lipid extraction of samples, column chromatography and HPLC [9]; the results were transformed logarithmically. Serum osteocalcin was evaluated using an assay kit (ImmunoNuclear, Stillwater, Minn, USA).

Total body bone density (TBBD), expressed as g/cm^2 , was measured by computer-aided total-body dual-energy X-ray absorptiometry (Lunar DPX, Madison, Wis, USA) with a precision of 0.75 %. Single regions of interest, such as trunk, pelvis, etc., were also considered. Variations not exceeding the precision range were referred to as no change [10]. A control group of 25 untreated osteoporotic women was also studied.

Statistical analyses were performed as reported elsewhere [8].

CALCITRIOL TREATED GROUP

Before the start of treatment, intestinal radiocalcium absorption, expressed as the circulating fraction of the dose (fx), was significantly lower than the normal range ($\text{fx} = 0.128 \pm 0.02$; mean $\pm$ SD). Calcitriol promoted a significant increase ($P < .01$), that persisted throughout the treatment (the average of 1307 determinations was 0.213 ± 0.05).

Fasting plasma calcium did not change significantly; only rare and transient elevations above the upper normal limit were observed (31 out of 1490 determinations). In no patient did treatment need to be discontinued. Hypercalciuria was observed continuously ($P < .01$) (average of 1490 determinations: $325 \pm 139 \text{ mg}/24 \text{ h}$) (Fig. 1); however, no changes occurred in renal function, as demonstrated by urinalysis, blood urea nitrogen (BUN), serum creatinine and creatinine clearance and no renal stones developed.

The 24 h urinary hydroxyproline (HOP) excretion did not change significantly during the treatment, while the ratio of calcium/HOP in urine increased ($P < .01$) (Fig. 1). No correlation was found between 24 h urinary calcium and HOP during therapy.

Fig. 1. Changes in urinary calcium (A), HOP (B) and calcium/HOP ratio (C) during calcitriol treatment.

Plasma phosphate did not change significantly, whereas 24 h urinary phosphate excretion increased significantly ($P < .01$) (baseline value: $669 \pm 234 \text{ mg}/24 \text{ h}$; mean value on treatment: $814 \pm 264 \text{ mg}/24 \text{ h}$).

Before the initiation of treatment serum osteocalcin, measured in 72 patients of this group, averaged lower than in 32 age-matched control women (3.8 ± 1.1 and $6.8 \pm 2.0 \text{ ng}/\text{mL}$, respectively, $P < .01$). One year of calcitriol therapy promoted a significant increase ($4.5 \pm 1.4 \text{ ng}/\text{mL}$, $P < .01$).

Total-body density was determined before and after 12 and 24 months of treatment in 90 patients of this group. Mean increases of 1.07 and 0.78 % were observed after 1 and 2 years of treatment, respectively, as compared with a corresponding decrease of 2.05 and 5.00 % in the control group. Even better

results were obtained in the region of the trunk, which is mainly representative of spongy bone. Altogether, about 85 % of calcitriol treated women improved or did not lose bone.

From a clinical point of view, calcitriol treatment resulted in a consistent and often dramatic relief from pain and improvement of mobility.

ALPHACALCIDOL TREATED GROUP

Among these patients 13 failed to respond to alphacalcidol treatment in terms of intestinal calcium absorption. These cases are herewith referred to as "non responders"; their results are reported separately.

Before the start of treatment, intestinal radiocalcium absorption was significantly lower than normal ($fx = 0.133 \pm 0.02$). Not including the group of non responders, 108 patients showed a significant increase in calcium absorption ($P < .01$) (the average of 240 measurements on treatment was 0.204 ± 0.04). Non responders showed a brisk increase in calcium absorption when a dose of 2 μ g of alphacalcidol was administered. No significant changes in plasma calcium and phosphate were observed.

Alphacalcidol promoted a significant increase ($P < .01$) in urinary calcium excretion, except non responders: the baseline level was 172 ± 80 mg/24 h, while the average of 290 determinations during treatment was 306 ± 138 mg/24; however, no changes in renal function occurred, as demonstrated by urinalysis, BUN, serum creatinine and creatinine clearance and no renal stones developed. Urinary phosphate excretion increased noticeably. Urinary HOP did not change significantly during the treatment.

Total-body density was determined before and after 12 and 24 months of treatment in 90 patients of this group. It remained unchanged after 1 year and showed a mean decrease of 1.01 % after 2 years, as compared with a corresponding decrease of 2.05 and 5.00 % in the control group. Once again the trunk did better than the whole skeleton. Altogether, about 60 % of calcitriol treated women improved or did not lose bone.

The serum levels of $1,25(\text{OH})_2\text{D}$ were measured before and after 6, 12 and 24 months of treatment in 39, 21, 34 and 6 patients, respectively (Table I). Baseline values were lower than in normal peers ($P < .01$).

Table I. Serum $1,25(\text{OH})_2\text{D}$ in patients on alphacalcidol therapy.

Months of therapy	0	6	12	24
$1,25(\text{OH})_2\text{D}$ (pg/ml)	28.8 ± 12.4	43.6 ± 16.0	46.3 ± 26.6	48.6 ± 24.3
P		<.01	<.01	<.01

The patients who responded in terms of calcium absorption showed a significant positive correlation between fx and serum $1,25(\text{OH})_2\text{D}$ after 6, 12 and 24 months of therapy. This was not the case among non responders (Fig. 2).

Fig. 2. Correlations between fx and $1,25(\text{OH})_2\text{D}$ levels after 6 (A), 12 (B) and 24 (C) months of alphacalcidol therapy. * $P < .05$, ** $P < .01$. ■ Before; □ after: ■ responders, □ non responders.

THERAPEUTIC CONSIDERATIONS

The results of the present study confirm the key role of the active vitamin D metabolite in the pathogenesis and treatment of age-related osteoporosis. Actually, $1,25(\text{OH})_2\text{D}$ levels lower than normal were found in our osteoporotic patients and physiological doses of calcitriol were shown to be effective in restoring a normal intestinal transport of calcium.

Concerning alphacalcidol our results confirm that this compound can only act after conversion by the liver to calcitriol [11] and that it is not equipotent in comparison with the latter, since in several patients higher doses are needed in order to obtain similar effects.

Treatment with 1α -hydroxylated vitamin D related compounds is capable of blocking the progressive bone loss which has been demonstrated to occur in osteoporotic subjects in the absence of any treatment; in most cases an increase in bone density has been observed.

This effect is of particular relevance, not only from a clinical standpoint, but also in terms of the mechanism of action of calcitriol on bone.

Stimulation by calcitriol of osteoclast-mediated resorption of bone was described several years ago [12]; this one has long been considered the only direct effect of calcitriol on bone, in accordance with the general opinion that the main action of $1,25(\text{OH})_2\text{D}_3$ was to increase calcium and phosphate levels in extracellular fluids, even at the expense of bone. This view did not take into account that resorption is actually the first stage of bone remodeling. However, our results indicate that the predominant in vivo effect on bone is maintenance of bone density, or even its increase. On the other hand, the hypercalciuria we observed during therapy was certainly not of resorptive origin, since urinary HOP excretion did not change and no significant correlation was observed between urinary calcium and HOP during treatment, so that hypercalciuria was mainly due to the effect of calcitriol on intestinal calcium transport. Moreover, we were able to demonstrate that calcitriol stimulates the synthesis of osteocalcin by osteoblasts in osteoporotic patients.

The conclusion can be drawn that calcitriol and alphacalcidol not only stimulate intestinal calcium absorption in postmenopausal osteoporotic patients; but also promote bone remodeling and the synthesis of bone proteins. Both calcitriol and alphacalcidol represent safe, effective and unexpensive treatments for osteoporosis.

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