THE CLINICAL AND METABOLIC EFFECTS OF CALCITRIOL IN THE TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

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SUMMARY

Osteoporosis is the most common metabolic disease of bone whose management is controversial. To evaluate the efficacy and safety of calcitriol (1,25-dihydroxyvitamin DJ in postmenopausal osteoporosis, this prospective, randomized, one-year clinical trial was planned. Seventy patients aged between 45-69 years were randomly assigned to receive either calcitriol (0.25gr twice daily) or supplemental calcium (1gr/day) for one year. Lumbar spine and femoral neck bone mineral density (BMD) values, pain intensity and disability measure scores and bone turnover markers J$erum osteocalcin and urinary hydoxyproline levels) were used as outcome parameters of treatment.

The groups were similar with regard to age, body mass index, years since menopause, baseline bone mineral measurements, pain intensity and disability measure scores initially. In calcitriol group, lumbar spine BMD values, pain intensity and urinary hydroxyproline levels were significantly improved at the end of the trial whereas no change was observed in femoral neck BMD values, disability measures and serum osteocalcin levels. No significant changes of outcome parameters were found in calcium group. The compliance to treatment protocols was high and no clinical or laboratory side effect of drugs was observed.

As a conclusion calcitriol treatment was found to be effective and safe in the treatment of postmenopausal osteoporosis.

Key words: *Osteoporosis, calcitriol, calcium, treatment*

ÖZET

POSTMENOPOZAL OSTEOPOROZDA KALSİTRİOL TEDAVİSİNİN KLİNİK VE METABOLİK ETKİLERİ

Tedavisi halen tartışmalı olan osteoporoz, kemiğin en sık görülen metabolik kemik hastalığıdır. Bu prospektif, randomize, bir yıllık klinik çalışma, postmenopozal osteoporozda kalsitriolün (1,25-dihidroksivitamin 03) etkinliği ve güvenliğini araştırmak için planlandı. Yaşları 45-69 arasında değişen 70 hasta, bir yıl boyunca kalsitriol (Günde iki kez 0.25gr) veya ilave kalsiyum (1gr/gün) alacak şekilde randomize olarak iki gruba ayrıldılar. Tedavi sonuçlarının izlenmesi için lomber omurga ve femur boynu kemik mineral dansiteleri (KMD), ağrı şiddeti, özürlülük skorları, ve kemik dönüşüm göstergeleri (serum osteokalsin ve idrar hidroksiprolin düzeyleri) kullanıldı.

Başlangıçta gruplar yaş, vücut kitle indeksi, menopoz sonrası geçen süre, başlangıç KMD'leri, ağrı şiddeti, ve özürlülük skorları açısından özdeşti. Çalışmanın sonunda kalsitriol grubunda lomber omurga KMD değerleri, ağrı şiddeti ve idrar hidroksiprolin düzeyleri belirgin olarak düzeldi ancak femur boynu KMD değeri, özürlülük skorları ve serum osteokalsin düzeylerinde değişiklik gözlenmedi. Kalsiyum grubunda incelenen değişkenlerden hiçbirinde fark bulunmadı. Tedavi protokollerine uyum yüksekti ve ilaçların klinik veya laboratuvar yan etkileri gözlenmedi.

Sonuç olarak postmenopozal osteoporozda kalsitriol tedavisi etkin ve güvenli bulundu.

Anahtar Kelimeler: *Osteoporoz, kalsitriol, kalsiyum, tedavi*

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures (1). Increased fracture risk makes it a major cause of morbidity, mortality and disability (2). Main clinical features as bone pain and dorsal kyphosis by limiting mobility, are the main causes

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of disability (3). Prevention programs for an early age, identification of risk factors, careful diagnosis through bone mass measurement and treatment which includes medication and rehabilitation, all combine to reduce bone loss and associated risk of fracture and its sequela (4). Reduced calcium absorption, due primarily to a deficiency in activation of vitamin D and a vitamin D reseptor deficiency caused by estrogens is a cardinal feature in postmenopausal osteoporosis (5). Decreased circulating levels of calcitriol, malabsorbtion of calcium from gastrointestinal tract and increased bone resorption rate are also important factors in the pathogenesis of postmenopausal osteoporosis (3,6,7). It was shown that negative calcium balance in postmenopausal osteoporosis is due to impairment of intestinal calcium transport resulting from reduced $1,25(OH)_2$ D synthesis associated with impaired activity of renal 250HD-1 -a hydroxylase no longer stimulated by estrogens (3). Calcitriol which is a synthetic compound that is identical with the most active metabolite of vitamin D, 1,25-dihydroxycholecalciferol, formed in the kidney as the end product of vitamin D metabolism (8). Among the agents that have been used to treat postmenopausal osteoporosis, calcitriol has attracted considerable interest during the past decade because of its ability to increase gastrointestinal absorption of calcium and also to stimulate osteoblastic and osteoclastic activity in the skeleton (7). Metabolic studies have shown that calcium absorption can be normalized and calcium balance improved after administration of calcitriol (9). Despite some of the unsatisfactory results (10), in most of the previous studies, calcitriol was found to be effective in not only restoring a normal calcium absorption (6) but also resulting in relief from pain, improvement of ambulancy, reduction in fracture occurrence (3,6,9,11) and increase in bone mineral content (12). As it has a narrow therapeutic window adequately supervised periodic monitoring of serum calcium and creatinine levels were also advised (13).

The aim of this study was to investigate the efficacy of calcitriol in the treatment of postmenopausal osteoporosis. OMERACT III identified some clinical and non-clinical outcome parameters for osteoporosis trials. The mainly suggested parameters were fractures, bone mineral densities - measured at two sites, the lumbar spine and proximal femur, biochemical markers- including at least one resorption and one formation maker, disability and pain assessments, and change in height (14). Comparative studies of responsiveness represented bone mineral density measures, biochemichal markers, disability and pain assessments as feasible outcome parameters for osteoporosis clinical trials (15). Lack of agreement on best method for defining fractures limited their use as an outcome parameter (16). Moreover the responsiveness of fracture rates was found to be poor (15). Considering these previous data, bone mineral density measures (lumbar spine and femoral neck with DEXA), changes in biochemical markers (osteocalcin for bone formation and urinary hydroxyproline for resorption), pain intensity (Visual Analogue Scale-VAS) and disability (Health Assessment Questionnaire-HAQ) assessments were used as outcome parameters in evaluating the efficacy of calcitriol treatment in postmenopausal osteoporosis. The safety of the drug was also determined by patient interviews about possible side effects and screening biochemical parameters of bone metabolism (serum calcium, phosphorus, parathyroid hormone, alkaline phosphates, creatinine, and urinary calcium levels) every three months.

MATERIAL AND METHOD

In this prospective, randomized clinical trial among the attended patients of our osteoporosis clinic, 70 fully ambulatory postmenopausal women between 45-69 years old who met the World Health Organization osteoporosis criteria (17) were asked to participate into the study. The patients who had evidence of any disease associated with osteoporosis and history of using any drug known to affect bone metabolism, specifically taking estrogens were excluded. The patients were randomly assigned according to even or odd protocol numbers to rece-

ive treatment with calcitriol (0.25 ug. twice a day) or supplemental calcium (1gr. of elemental calcium daily) for one year. No other drug was given including analgesics. The patients were given no specific instructions regarding dietary calcium intake and were encouraged to walk for an hour daily. Besides sociodemographic and clinical parameters, screening consisted of baseline history, physical examination, and routine laboratory chemistry evaluation. The lumbar spine and femoral neck bone mineral densities were measured by Dual Energy X-ray Absorbsiometry (Lunar-DEXA) initially and at the end of the year. Pain intensity was assessed twice by 100mm. horizontal VAS (0=none, 100=severe pain) (18). Patients placed "X" on the scale to indicate the severity of pain intensity and the score was determined by measuring from the "none" marker to the "X" using a metric ruler. Physical disability was assessed by Health Assessment Questionnaire (HAQ) initially and at the end of the year in which patients are asked to rate their degree of difficulty on 4 point scales in 8 areas of daily life (19). Scores from the 8 subscales are averaged to obtain the HAQ score with a possible range of 0 to 3 and increments of 0.125 units. A higher score is taken to indicate a greater degree of disability. The use of HAQ as an outcome measure in antirheumatic drug research was highly recommended (20). It was used to evaluate low extremity mobility (21) and suggested as a physical disability scale (22) for patients with osteoporosis before. Prior to initiation and at the end of the therapy, each patient also had the following performed: assessment of hydroxyproline in a 24-hour urine collection obtained after three days of ingesting a low hydroxyproline diet, determination of creatinine clearance and measurements of serum levels of osteocalcin. Patients were interviewed about the signs and symptoms of possible side effects. Safety profile of calcitriol was also followed by biochemical parameters of bone metabolism (serum calcium, phosphorus, parathormon, alkaline phosphates, and 24-hour urinary calcium levels) and renal and hepatic functional tests for every three month.

Statistical Analysis

Data were entered into a computerized data base and analyzed using the SPSS package. Descriptive statistics of the patients' age, duration of menopause, body mass index was calculated initially. According to normality assumption Student's *t* Test was applied in order to compare the baseline values of age, duration of menopause, body mass index, lumbar spine and femoral neck BMD values, pain intensity and disability scores. Paired-Sample t Test was used to compare the initial and final score of outcome parameters such as lumbar spine and femoral neck BMD values, pain intensity, disability scores and bone turnover markers (serum osteocalcin and urinary hydoxyproline levels). The alpha criterion for significance was set at $p<0.05$ for all tests.

RESULTS

All of the patients enrolled into the study completed the trial. The clinical and biochemical characteristics of the groups at baseline are shown in Table 1. The groups were similar with regard to age, body mass index, years since menopause, baseline bone mineral measurements, pain intensity and disability measure scores. The differences

Table 1. Comparison of baseline mean (SD) values of patients treated with calcitriol (n=35) or calcium (n=35)

Variable	Calcitriol Group	Calcium Group	P value
Age, years	60.0 (5.2)	58.6 (7.6)	0.625
Duration of menopause, years	16.3 (7.05)	14.2(4.5)	0.703
Body mass index, kg/m^2	27.4 (4.7)	26.9 (3.8)	0.507
Lumbar spine BMD, gr/cm^2	0.72 (0.13)	0.74(0.15)	0.799
Femoral neck BMD, gr/cm^2	0.70 (0.12)	0.69 (0.13)	0.857
Pain intensity-VAS	57 (17)	60 (13)	0.645
Disability score-HAQ	9.8(2.1)	10.02 (0.8)	0.880

Table 2. Change in lumbar spinal and femoral neck BMD values, pain intensity and disability measure scores, and bone turnover markers

Variable	Group	Baseline	Final
Lumbar spine BMD, gr/cm^2	Calcitriol	0.72(0.13)	0.79(0.11)*
	Calcium	0.74(0.15)	0.72 (0.14)
Femoral neck BMD, gr/cm^2	Calcitriol	0.70(0.12)	0.71 (0.13)
	Calcium	0.69(0.13)	0.68 (0.10)
Pain intensity-VAS	Calcitriol	57(17)	39(12)**
	Calcium	60 (13)	59 (17)
Disability score-HAQ	Calcitriol	9.8(2.1)	8.9(1.1)
	Calcium	10.02 (0.8)	10.00(1.1)
Hydroxyproline / creatinine	Calcitriol	18.2(0.8)	14.1 (0.6)**
	Calcium	15.5(0.9)	14.9(1.0)
Osteocalcin ng/ml	Calcitriol	10.1 (1.4)	10.8 (0.8)
	Calcium	9.6 (0.4)	10.0(1.0)
		* **p < 0.05**	** p < **0.01**

between initial and final assessments of two groups were shown in Table 2. Improvement in lumbar spine BMD values, pain intensity and hydroxyproline / creatinine ratio of calcitriol group was found to be statistically significant. The differences of these parameters for calcium group were not significant. No statistically significant change was observed in femoral neck BMD values, disability measure scores or serum levels of osteocalcin at the end of the year for both of the groups.

The compliance of our patients with calcitriol therapy was tested by the fact that they diligently came to our outpatient clinic for follow-up analysis. None of the patients experienced any elevation of plasma or urinary calcium levels. Hepatic and renal functions were not impaired and no renal-stone formation was observed.

DISCUSSION

In this study calcitriol was found to be effective in the prevention of bone loss at lumbar spine of women with postmenopausal osteoporosis. The results of studies concerning the management of osteoporosis with calcitriol were conflicting, some showing a beneficial effect and others no benefit (3). Significant increases in fractional calcium absorption, in total body calcium and bone density of spine together with decreases in urinary hydroxyproline excretion were reported during the therapy with calcitriol (3).

Significant decrease was observed in urinary hydroxyproline levels of calcitriol group. Urinary hydroxyproline levels reflects the resorption of bone matrix and its reduced levels in the urine may show the decreased rate of bone resorption (23). It was reported that by raising calcium absorption, calcitriol could decrease bone resorption (6,11). In this study, possibly due to short treatment duration, no significant changes were observed at serum osteocalcin levels of groups. However, in previous long-term studies increases in serum osteocalcin concentrations despite some fluctuations during therapies with calcitriol were reported. The increases in osteocalcin levels observed under calcitriol treatment were evaluated as a consequence of osteoblast stimulation (12). In this study it was observed that treatment with 0,5u.g/day calcitriol therapy without supplemental calcium during one year reduced bone resorption in postmenopausal osteoporosis but bone formation was not seem to be stimulated. Aloia also presented similar results about calcitriol and explained its positive effect on BMD by decreased bone resorption but not by incresed bone formation (6). Gallagher et al suggested calcitriol dosage to stimulate bone formation as 2ng/day (23).

Osteoporosis represents more than bone loss; it is a clinical syndrome with functional sequela consisting of vertebral deformities resulting in chronic

back pain and disability (22). Besides BMD values and bone turnover markers, treatment efficacy was also evaluated by changes in pain intensity and functional ability measure scores in this study. Caniggia et al reported that calcitriol treatment resulted in a consistent and often dramatic relief from pain and improvement of mobility (3). In contrast with the enhancement in pain intensity, no significant change was observed in functional ability measure scores in this study. Not only the pain intensity but dorsal kyphosis and limited mobility were also accused in functional disability development (3). All of the patients were ambulatory women with a 38% incidence of kyphosis in this trial and their disability measure scores were low initially and treatment of one year could be relatively short to observe any significant improvement in functional status.

No significant change in urinary calcium excretion was observed throughout the study. In some of the previous clinical studies, hypercalcemia and hypercalciuria was reported during calcitriol therapies (24). Dechant et al reported hypercalcemia and hypercalciuria during calcitriol therapy as infrequent and mild at recommended dosages and generally responding to reductions in calcium intake and/or calcitriol dosage (25). Cannigia et al suggested calcitriol treatment without calcium supplementation and allowing patients their usual diet during the treatment (3). This way of application also prevents hypercalcemia formation. In most of the studies reporting hypercalciuria, the daily calcitriol dosage was higher than our trial. Besides, in a previous study from our osteoporosis clinic, we documented the mean dietary intake as 500mg/day for Turkish women after menopause (unpublished data). This amount is considerably lower than the results reported from Western countries and might explain the lack of hypercalciuria in our study.

As a conclusion calcitriol was found to be effective and safe in the treatment of postmenopausal osteoporosis. It has a positive effect on pain intensity and spinal bone mineral density, possibly by decreasing bone resorption that shows its value in long term therapy goals.

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