Effect of Alendronate on Bone Mineral Density in Male Idiopathic Osteoporosis

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Idiopathic osteoporosis in men is an increasingly recognized disorder accounting for up to 200,000 hip fractures worldwide each year. Although there is no widely accepted or proven efficacious treatment for men with idiopathic osteoporosis, we attempted to examine the effectiveness of alendronate in this disorder. We retrospectively compared the clinical records of male patients with osteopenia (hip or spine T scores less than -1.0, with or without low-trauma fractures) treated either with alendronate 10 mg orally/day and calcium and vitamin D replacement versus conservative treatment with calcium and vitamin D alone. Review included analysis of laboratory studies and bone turnover markers in a subset of patients. We documented bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA) and repeated BMD after an average follow-up of 1.9 and 2.7 years in the alendronate-treated and conservative treatment groups, respectively. At baseline, conservatively-treated and alendronate-treated patients had similar BMD at the lumbar spine and hip. Over the period of observation, the conservatively-treated patients exhibited insignificant changes in BMD at all measured sites. In contrast, alendronate treatment resulted in a significant increase in BMD of the spine (+4.6%, $P = .002$), trochanter (+6.4%, $P = .002$), and total hip (+4.7%, $P = .002$). Indeed, compared with conservative treatment, alendronate-treated patients sustained a significant annualized percent increment of the BMD in the spine (2.7 ± 0.6 *v* 1.1 ± 0.3, $P = .025$), trochanter (4.7 ± 1.7 *v* 0.7 ± 0.6, $P = .025$), and total hip BMD (3.3 ± 0.9 *v* 0.1 ± 0.4, $P = .0009$). These data are among the first that illustrate the potential efficacy of alendronate in the management of idiopathic osteoporosis in men.

OSTEOPOROSIS IN MEN is increasingly recognized as an important public health issue. While men achieve a greater peak bone mass than women, bone loss ensues at the spine and proximal femur at similar rates in individuals over 30 years of age regardless of gender.[1-5] This age-related decline in bone density is associated with an increase in fracture prevalence. Fully, 30% of all hip fractures occur in men,[6] and the lifetime risk of fragility fractures for an average 60-year-old man is approximately 25%.[7] In addition, men are over 3 times more likely to die following a hip fracture than women.[8] These observations predict that osteoporosis in men will indeed have an increasing health and economic impact on an aging worldwide population.

Aside from "natural" declines in bone density due to aging, male osteoporosis is due to underlying factors that reduce bone mass and structural integrity through direct and indirect mechanisms. These factors, which occur in women as well, include hypogonadism, hyperparathyroidism, hyperthyroidism, medications (including glucocorticoids), hypercalciuria, intestinal calcium malabsorption, smoking, and excessive alcohol use. While this "secondary osteoporosis" is more common in men than in women, as many as 45% of men still have no identifiable cause for their osteoporosis.[9] The underlying pathogenesis of idiopathic or primary osteoporosis in men is poorly understood, although there is no evidence to date that suggests that bone remodeling is accelerated in these patients. Indeed, histomorphometric studies suggest a relatively high rate of osteoblast dysfunction in these patients.[10] Possible explanations for osteoblast function in this disorder include deficiency of insulin growth factor-1 (IGF-1),[11] as well as the presence of cytokines and other factors, which influence osteoblast survival and apoptosis.[12] The possible uncoupling of bone formation and resorption may therefore help to explain the reduced bone density that is seen in these men.

Bisphosphonates have been extensively studied in the treatment of postmenopausal osteoporosis, a condition that also represents a relative uncoupling of the bone remodeling processes. Treatment with alendronate significantly increased bone mineral density (BMD) in the hip and spine and decreased the rate of new fractures by approximately half.[13] Despite this proven efficacy in postmenopausal women, few studies to date have addressed the potential efficacy of alendronate or other bisphosphonates in men with osteoporosis. In this retrospective study, we attempted to examine the effectiveness of alendronate in men with idiopathic osteoporosis.

MATERIALS AND METHODS

The medical records of all male patients referred for evaluation of osteopenia with or without low-trauma fractures to the Bone and Metabolic Diseases Clinic at Duke University Medical Center between 1987 to 1998 were reviewed. The current database includes approximately 100 male patients with osteoporosis. Patients were seen by 1 of 3 endocrinologists at our center. All patients without obvious secondary causes for osteoporosis underwent extensive biochemical testing, including evaluation of gonadal, thyroid, corticosteroid, and calciotropic hormone status. Bone remodeling was assessed with serum osteocalcin, fasting second void morning urine for calcium-creatinine ratio, and deoxypyridinolines. Twenty-one Caucasian male patients were identified who did not have obvious causes for low-bone mass, 13 of whom received therapy with 10 mg of oral alendronate daily. No patients were treated concurrently with any other antiresorptive therapies or with any medications known to affect bone metabolism. All patients were treated with daily calcium (1,000 to 1,500 mg) and vitamin D (200 to 400 IU).

BMD testing of the lumbar spine and proximal femur was measured by dual-energy x-ray absorptiometry (DXA) in all patients at baseline and follow-up using the same Hologic QDR 2000 (Hologic, Waltham, MA). Scans were performed by 1 operator at baseline and after a mean of 1.7 and 2.9 years in the alendronate and untreated groups, respectively. Pre-existing vertebral and nonvertebral fractures were identified by review of radiographic reports.

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Statistical Analysis

Pretreatment characteristics were compared using Student's 2-tailed *t* tests, except for fracture prevalence that was compared using Fisher's exact test. BMD results are expressed as mean ± SEM. Within group differences in BMD were compared by using Wilcoxon signed rank testing, and between group differences in BMD over time were analyzed by using Kruskal-Wallis analysis of variance (ANOVA). Statistical significance is defined by P values less than .05.

RESULTS

Clinical characteristics of the treated patients are shown in Table 1. Although men treated with alendronate were significantly older and more likely to have fragility fracture at presentation, the decision to treat was made by the individual clinician and not based on any specific protocol. No patients had active malignant disease or other conditions known to adversely affect bone metabolism. Six of the alendronate-treated patients had received prior treatment for osteoporosis, including 3 who had received cyclic etidronate, 1 who had received cyclic etidronate and low-dose calcitriol, 1 who had received cyclic etidronate, sodium flouride, and calcitonin, and 1 who had received sodium flouride alone. These therapies were stopped at least 3 months before beginning alendronate therapy and were not restarted.

A summary of pretreatment laboratory values, bone turnover studies, and bone density studies is shown in Table 1. The number of patients with available values in each group is shown in parentheses. One patient in the untreated group had an elevated serum alkaline phosphatase of undetermined etiology, which normalized without treatment, and 1 patient in the treated group had a borderline suppressed thyroid-stimulating hormone (TSH), which was subsequently confirmed as normal. One patient in the treated group had a borderline low serum 25-hydroxyvitamin D level at baseline that normalized with replacement. One patient in each group had borderline elevated urinary cortisol, which was deemed clinically insignificant after normal subsequent dexamethasone suppression testing. No patient had significant hypercalciuria (> 4 mg/kg). There were no significant differences in the levels of bone formation or resorption markers between groups in those men tested. Both groups of men had a significant decrement in BMD at all tested skeletal sites, represented by T scores. There were no significant differences in BMD at any site between groups.

Table 1. Pretreatment Characteristics

	Alendronate + Calcium/D (N)	Calcium/D (N)	*P* Value
Age (±SE)	59 ± 3.2 (13)	42 ± 3.6 (8)	.003
Weight (kg)	79.0 ± 4.5	72.4 ± 5.3	NS
% With fractures	85 (13)	38 (8)	.055
Calcium (mg/dL)	9.4 ± 0.5 (13)	9.3 ± 0.2 (8)	NS
Phosphorus (mg/dL)	3.6 ± 0.4 (13)	3.2 ± 0.4 (8)	NS
Creatinine (mg/dL)	1.0 ± 0.1 (13)	1.0 ± 0.1 (8)	NS
Alkaline phosphatase (IU/L)	86 ± 21 (13)	99 ± 34 (8)	NS
TSH (mIU/mL)	1.5 ± 1.2 (10)	1.8 ± 1.7 (5)	NS
25 Hydroxy vitamin D (ng/mL)	30 ± 10 (7)	25 ± 4 (5)	
Parathyroid hormone (pg/mL)	25 ± 9 (7)	40 ± 18 (2)	NS
Free testosterone (ng/mL)	14.6 ± 5.4 (9)	19.3 ± 5.3 (7)	NS
Osteocalcin (ng/mL)*	9.6 ± 4.2 (12)	9.6 ± 3.5 (8)	NS
Urine Deoxypyridinolines (nmol/L/mmol/L creatinine)*	16.4 ± 7.1 (5)	12.9 ± 6.6 (6)	NS
Urine calcium (mg)	209.6 ± 70.8 (13)	206.6 ± 79.6 (7)	NS
Baseline T score			
AP Spine	−2.66 ± 1.1	−2.61 ± 1.2	NS
Femoral neck	−3.19 ± 1.1	−3.17 ± 0.7	NS
Trochanter	−2.04 ± 1.0	−1.84 ± 0.5	NS
Total Hip	−2.49 ± 1.0	−2.30 ± 0.5	NS

NOTE. Standard normal range: osteocalcin 4.6 to 10.2 ng/mL, urine deoxypyridinolines 6 to 23 μmol/L/mmol/L creatinine.

Abbreviation: NS, not significant.

*Normalized result since reference range for assay was not the same for all samples.

The baseline and follow-up absolute BMD values for each group are shown in Table 2. Although some conservatively-treated patients did exhibit increases in BMD at specific skeletal sites (data not shown), there was no significant change in BMD at any site between baseline and follow-up scans for the entire group. In contrast, most of the alendronate-treated patients gained BMD (data not shown). In fact, the observed increase in BMD for the group was statistically significant at the lumbar spine (+0.04 g/cm^2, P = .002), femoral trochanter (+0.04 g/cm^2, P = .002), and total hip (+0.03 g/cm^2, P = .002). More importantly, the annualized percent increase in BMD was significantly greater in alendronate-treated patients at the lumbar spine (2.7 ± 0.6 *v*. 1.1 ± 0.3, P = .025), femoral trochanter (4.7 ± 1.7 *v* 0.7 ± 0.6, P = .025), and total hip (3.3 ± 0.9 *v* 0.1 ± 0.4, P = .0009) than in conservatively-treated patients (Fig 1). Neither group exhibited a significant change in femoral neck BMD.

DISCUSSION

Very few studies to date have examined the effectiveness of treatment for idiopathic osteoporosis in men. Even fewer have addressed the potential efficacy of bisphosphonates, which are established as an effective treatment for postmenopausal osteoporosis. Previous studies have retrospectively evaluated the effectiveness of cyclic etidronate and alendronate. Orme et al[14] found a 9.0% increase in lumbar spine BMD in 10 males (7 of whom had idiopathic osteoporosis) treated with 400 mg of etidronate given for 2 weeks cyclically every 13 weeks for 1 year. No significant effect on BMD was seen in the femoral neck. Anderson et al[15] showed a more modest increase in lumbar spine BMD (3.2%/year) in 40 of 42 men with idiopathic osteoporosis treated with a similar regimen of etidronate for a median of 31 months, again without a significant effect on femoral neck BMD. More recently, Drake et al[16] observed significant gains in lumbar spine (+6.4%) and femoral neck (+4.5%) BMD in 9 patients treated with 10 mg of alendronate for a mean of 14 months, 6 of whom had idiopathic osteoporosis. None of these studies included a comparison group of men who were treated conservatively with calcium and vitamin D replacement.

Table 2. Changes in BMD (g/cm^2) in Alendronate + Calcium/D-Treated Versus Calcium/D-Treated Patients

	Alendronate-Treated Patients			Untreated Patients		
	Pre	Post	*P* Value	Pre	Post	*P* Value
AP spine	0.80 ± 0.03	0.83 ± 0.03	.002	0.81 ± 0.04	0.83 ± 0.04	.058
Neck	0.62 ± 0.03	0.63 ± 0.03	.23	0.61 ± 0.02	0.61 ± 0.03	.888
Trochanter	0.56 ± 0.03	0.60 ± 0.03	.002	0.60 ± 0.02	0.60 ± 0.02	.362
Total hip	0.74 ± 0.03	0.77 ± 0.03	.002	0.76 ± 0.03	0.76 ± 0.04	.40

We also observed a significant increase in lumbar spine BMD (2.7%/year) in men with idiopathic osteoporosis treated with alendronate 10 mg for a mean of 17 months. More importantly, alendronate-treated men increased BMD more than men treated with standard calcium and vitamin D replacement. The observed increases in lumbar spine BMD are also important because the prevalence of vertebral fractures in men with idiopathic osteoporosis can be as high as 50%,[10] which is similar to the rate observed in our patients. Given that the risk for subsequent vertebral fractures is likely significant, one might expect that alendronate would significantly attenuate that risk, based on its proven efficacy in postmenopausal women with preexisting vertebral fractures.[13]

We also observed a significant increase in trochanteric and total hip BMD in alendronate-treated men compared with calcium and vitamin D treatment. This observed effect is potentially important because almost 1.7 million hip fractures occur each year worldwide in men.[6] However, we do acknowledge the fact that the vast majority of hip fractures do occur in elderly men with osteoporosis, which is not well represented by our cohort of younger men with osteoporosis. The reason why alendronate did not increase femoral neck BMD in our study is unclear, although this has been seen in studies with other bisphosphonates.[14,15] It may also have been due to technical effects such as femoral neck rotation. We did not observe significant hypercalciuria in these patients, which is somewhat contrary to the high rate (44%) previously observed by Peris et al.[17] The absence of hypercalciuria suggests that thiazide diuretics would have a limited role in these patients, although thiazides may prevent bone loss in older men.[18]

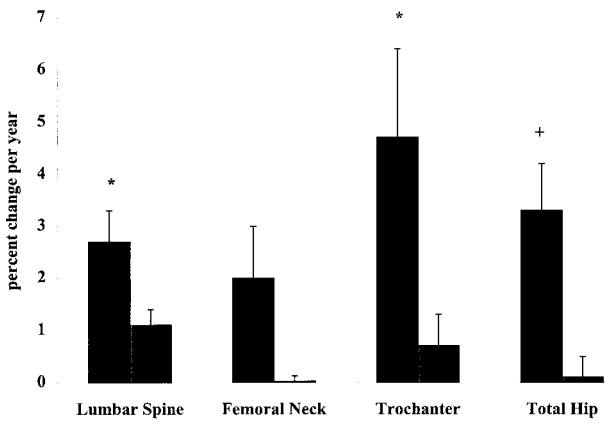

Fig 1. Annualized percent change in BMD at specific skeletal sites in alendronate plus calcium/D-treated (black bars) *v* calcium/D-treated men (gray bars). * *P* = .025; + *P* = .0009.

Bisphosphonates are also effective in men with secondary osteoporosis. Etidronate given cyclically prevented bone loss from the spine in men and women treated with glucocorticoids for at least 12 months, without differences in regards to gender.[19] Adachi et al[20] also demonstrated that cyclic etidronate prevented loss of spine BMD in glucocorticoid-treated men, although the effect was not statistically significant. More recently, studies with the newer bisphosphonates, alendronate and risedronate, suggest that bisphosphonates can increase lumbar spine BMD in glucocorticoid-treated men.[21,22] Neither of these studies, however, demonstrated a significant reduction in the rate of vertebral fractures, although Cohen et al[22] did observe a trend favoring fracture risk reduction that was similar in men and postmenopausal women.

The results of our retrospective study are also consistent with those recently reported by Ho et al,[23] who observed similar increases in lumbar spine and trochanteric BMD in men with primary and secondary osteoporosis who were treated in an open label fashion with alendronate. More importantly, Orwoll et al[24] recently confirmed the efficacy of alendronate in the treatment of men with both primary and secondary osteoporosis in a randomized, controlled, prospective fashion. In addition to demonstrating similar increases in lumbar spine and hip BMD, Orwoll also demonstrated a significant reduction in height loss and morphometric vertebral fractures in men treated with alendronate. These studies in total would seem to suggest that the skeletal response to bisphosphonates is not gender-specific.

Our study results are obviously limited by the fact that it is observational and retrospective, thus necessarily introducing treatment bias. Some men who were treated with alendronate had also received previous therapy with the etidronate. Therefore, some of the observed increase in bone density could have been a lag effect of the previous bisphosphonate therapy. In addition, biochemical assessment of remodeling status with resorption markers was incomplete. Thus, individuals with "high turnover" may have been preferentially treated with alendronate, thus accounting for some of the treatment differences between groups. Finally, the likely inherent heterogeneity of male idiopathic osteoporosis inherently limits our ability to generalize these results, especially given the relatively young age of our cohort.

Nevertheless, we observed a significant effect of alendronate on BMD of the lumbar spine and hip in a group of unselected men with idiopathic osteoporosis compared with conservative treatment. Thus, larger randomized controlled trials are clearly needed to confirm that the observed improvement in BMD does indeed reduce the risk of fracture in men with idiopathic osteoporosis.

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