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An Investigation of the Predictors of Bone Mineral Density and Response to Therapy with Alendronate in Osteoporotic Men

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Male osteoporosis is an important disease, with 25–30% of all hip fractures occurring in men. In a recent randomized, placebo-controlled study of osteoporotic males, alendronate 10 mg daily for 2 yr led to significant increments in bone mineral density (BMD), of a similar magnitude to those observed in postmenopausal women. In this study, specimens collected at intervals during the recent trial of alendronate in male osteoporosis, from 197 of the original 241 participants, were assayed for testosterone, estradiol, IGF-I, IGF binding protein 3 (IGFBP-3), bone-specific alkaline phosphatase [BSAP (serum)], and N-telopeptide of type I collagen corrected for creatinine [NTx (urine)]. Together with fracture and densitometry data from the original study, relationships were examined between BMD and serum IGF-I, IGFBP-3, testosterone, estradiol, BSAP, and urine NTx, both at baseline and during treatment with alendronate, to gain possible insights into the pathogenesis of male osteoporosis. Statistically significant ($P \leq 0.05$) associations were documented, at baseline, between the presence of vertebral fracture and each of serum IGF-I, serum IGFBP-3, serum free testosterone, total spine BMD, and total body BMD. No statistically significant correlations were observed between any of the baseline variables (IGF-I, IGFBP-3, estradiol, testosterone, and presence of vertebral fracture) and the BMD response to alendronate at any site. In a multivariate analysis, used to identify possible combinations of factors capable of predicting baseline BMD or response to alendronate, statistically significant ($P \leq 0.01$) relationships were seen, at baseline, between BMD and body mass index, age, and prior fracture. However, no statistically significant relationships were seen between any of the baseline variables (age, body mass index, testosterone, estradiol, IGF-I, IGFBP-3, and prior fracture) and change in BMD at any site. These data suggest that among men with osteoporosis it is not possible to identify patients who would be particularly good candidates for therapy with alendronate on the basis of biochemical or hormonal markers. Alendronate therapy appears to benefit osteoporotic males equally, irrespective of baseline serum testosterone, estradiol, IGF-I, or markers of bone turnover. (*J Clin Endocrinol Metab* 88: 5759–5765, 2003)

OSTEOPOROSIS IS A common medical problem, with over 1.3 million fractures occurring annually in the United States (1). Although the majority of these fractures occur in postmenopausal women, the social and economic burden of osteoporosis-related fracture in men is considerable, with 25–30% of all hip fractures occurring in males (2). Despite this, there is a lack of understanding of the etiology and epidemiology of male osteoporosis. In many cases, a secondary cause is evident, such as alcohol abuse, glucocorticoid excess (either therapy with glucocorticoids or endogenous Cushing's syndrome), hypogonadism, or hyperparathyroidism. In a large number, however, no cause can be identified (so-called idiopathic osteoporosis) (2). A greater understanding of the pathogenesis of idiopathic male osteoporosis and fracture is likely to lead to the development of specific agents aimed at the prevention and treatment of this disease.

Alendronate is a nitrogen-containing bisphosphonate that inhibits the mevalonate pathway and protein prenylation, thereby reducing osteoclast-mediated bone resorption (3). Treatment with alendronate improves bone mineral density (BMD) in women with postmenopausal osteoporosis (PMO) and significantly reduces fracture risk at various sites, including hip, wrist, and vertebrae (4, 5). In men with low bone mass, treatment with alendronate, 10 mg daily for 2 yr, also leads to significant increases in BMD and a reduction of vertebral fracture risk compared with placebo (6). In the latter study, serum and urine samples were obtained at regular intervals throughout the course of the trial. Here, we report the results of assays on those samples for testosterone, estradiol, IGF-I, IGF binding protein 3 (IGFBP-3), and markers of bone turnover. Together with baseline and follow-up measurements of BMD, these data have been used for a more detailed subanalysis of the previously reported cohort of male patients with osteoporosis treated with alendronate (6), with a view to gaining a greater understanding of the pathogenesis of male osteoporosis and the response to therapy with a bisphosphonate.

Abbreviations: BMD, Bone mineral density; BMI, body mass index; BSAP, bone-specific alkaline phosphatase; IGFBP-3, IGF binding protein 3; NTx, N-telopeptide of type I collagen corrected for creatinine; PMO, postmenopausal osteoporosis.

Subjects and Methods

Subjects

The details of the study population have previously been documented (6). Of the 241 otherwise healthy, osteoporotic males, sufficient serum was available for assay in 197, and these 197 are included in these analyses (Table 1). The characteristics of those individuals were not different from the 241 participants in the clinical trial. Entry criteria into the study included BMD at the femoral neck at least 2 SD below mean

TABLE 1. Characteristics of men participating in alendronate study

Variable	Placebo		Alendronate	
	n	Value	n	Value
Age (yr)	77	65 (36–83)	120	66 (31–87)
Race, n (%)	77		120	
Black		0 (0)		1 (1)
Caucasian		77 (100)		116 (97)
Hispanic		0 (0)		3 (3)
Weight (kg)	77	75 (47–111)	120	70 (49–106)
BMI	77	25 (18–34)	120	24 (18–36)
Serum BSAP at baseline (ng/ml)	77	13 (5–26)	120	12 (2–36)
Urinary NTx, of bone collagen at baseline (pmol equivalents/μmol of creatinine)	77	34 (6–187)	119	34 (9–129)
Serum free testosterone at baseline (nmol/liter)	66	0.316 (0.014–0.596)	108	0.324 (0.087–0.704)
Serum estradiol at baseline (pmol/liter)	71	73 (15–184)	118	70 (15–176)
IGF-I at baseline (ng/ml)	77	106 (17–226)	118	124 (13–269)
IGFBP-3 at baseline (ng/ml)	77	2833 (1062–4669)	119	2989 (1402–4890)
Femoral neck BMD (g/cm^2)	76	0.67 (0.43–0.93)	113	0.70 (0.38–0.93)
Total spine BMD (g/cm^2)	77	0.87 (0.47–1.46)	118	0.90 (0.44–1.25)
Total body BMD (g/cm^2)	68	1.04 (0.81–1.21)	110	1.056 (0.71–1.33)
Vertebral fractures at baseline, n (%)	76	40 (53)	116	59 (51)

A total of 77 men were in the placebo group, and 120 men were in the alendronate group. All values except for race and vertebral fractures are given as medians with the range in *parentheses*.

in young normal men and a BMD at the lumbar spine at least 1 SD below the mean in young normal men or a femoral neck BMD at least 1 SD below the young male adult mean in association with a prevalent vertebral deformity or a history of an osteoporotic fracture. Exclusion criteria included any history of metabolic bone disease or therapy with any drug associated with bone loss; significant cardiac, hepatic or renal dysfunction; any cancer other than basal cell carcinoma of the skin; or a history of recent peptic ulcer or abnormal esophageal emptying. Approximately 1/3 of subjects were found to be hypogonadal at baseline (defined as an early morning serum free testosterone $<$ 9ng/dl) and declined testosterone replacement therapy. Hypogonadal men receiving testosterone replacement (n = 2) were analyzed as eugonadal, but must have been on a stable dose for at least 12 months before, and during, the study. All subjects gave written, informed consent.

Study protocol

Subjects were randomized, in a double-blind fashion, to receive alendronate (10 mg daily; n = 146) or placebo (n = 95) for 2 yr. Of the patients included in this analysis, 77 received placebo and 120 received alendronate. All subjects received 500 mg daily of elemental calcium as calcium carbonate and 400–450 IU of vitamin D. For this analysis, frozen (–20 C) serum and urine samples taken at baseline and at 3, 6, 12, 18, and 24 months and were assayed for IGF-I, IGFBP-3, testosterone, estradiol, bone-specific alkaline phosphatase [BSAP (serum)], and N-telopeptide of type I collagen corrected for creatinine [NTx (urine)].

Hormonal measurements

Serum free testosterone measurements were performed on 0800 h fasting blood samples using an equilibrium dialysis technique. Serum total estradiol was measured by an ultrasensitive RIA after extraction and LH20 column chromatography. Serum IGF-I and IGFBP-3 were measured by RIA after formic acid-acetone extraction. Reference data for the laboratory in which IGF-I was measured are given in Table 2.

Measurements of markers of bone turnover

Fasting 0800 h serum and second-morning void urine samples were obtained at baseline and again at 3, 6, 12, 18, and 24 months for measurement of BSAP and urinary NTx. All samples were assayed at a central reference laboratory (Mayo Medical Laboratories, Rochester, MN).

BMD

Lumbar spine (L1–L4), femoral neck, and total body BMD were measured by dual-energy x-ray absorptiometery (DXA) using Hologic (Hologic Corp., Waltham, MA) or Lunar (Lunar Corp., Madison, WI) instruments at baseline and at 6, 12, 18, and 24 months.

TABLE 2. Serum IGF-I concentrations in males from the reference laboratory in which the samples in this study were assayed

Age (yr)	Mean serum IGF-I (ng/ml)	SD
20–29	2158	14
30–39	190	63
40–49	202	62
50–59	163	53
60–69	146	50
70–79	134	48
80–89	107	36
90–99	91	55

The reference population were healthy males between 20 and 80 yr without coexistent disease.

Radiography

Lateral thoracic and lumbar spine radiographs were performed at baseline and at the conclusion of the study. A quantitative morphometric assessment method was used to detect prevalent vertebral fractures at baseline (6, 7). In addition, vertebral height was measured using computer-aided analysis.

Statistical analysis

Descriptive statistics. Men were divided into those receiving placebo (n = 77) and alendronate (n = 120). For continuous variables, the median and range (minimum and maximum values) were used. For categorical variables (*e.g.* fracture) the number of men with fracture and percentage of total were used.

Baseline and follow-up variables. The results of baseline measures performed in duplicate (femoral neck, total spine, and total body BMD; serum BSAP; and urinary NTx) were averaged for the analyses. For the various follow-up measures, the rate of change during the study was estimated in each subject as the slope calculated using the values collected at baseline and at each follow-up visit. Men with a slope greater than four SD from the mean were removed from individual analyses (three men from the collagen NTx analyses and two from the BSAP analyses). Pearson correlation coefficients and probability values were generated for each pair of continuous variables. The relationship between categorical and continuous variables was examined using the

Wilcoxon two-sample test. Median values for each group are provided. In addition, baseline IGF-I and IGFBP-3 levels were compared by decade to the reference population.

Multivariate analyses. Two separate analyses were conducted. First, the relationships between baseline BMD measurements (femoral neck, total spine, and total body BMD; dependent variables) and baseline characteristics [age, body mass index (BMI), testosterone, estradiol, IGF1, IGFBP-3, and prior fracture; independent variables] were examined in three separate models. In the second set of analyses, the relationships between the change in BMD measurements during the treatment period (using the slopes calculated as above) and baseline patient characteristics were explored (again in three separate models for femoral neck, total spine, and total body BMD). For both sets of analyses, each of the independent variables was examined separately in univariate analyses. Those variables associated with a specific BMD measure ($P \leq 0.05$) were then selected for inclusion in the multiple linear regression model. These variables were manually introduced into the model in a forward stepwise manner, beginning with the most significant variable. Variables still significant at the $P \leq 0.01$ level were included in the final model. Two-way interaction terms were examined for all key variables and included when statistically significant. All multivariate analyses were done using SAS software, version 8.01 (SAS, Cary, NC).

Results

Baseline characteristics of the 197 men included in these analyses are shown in Table 1. There were no differences between the placebo- and alendronate-treated groups.

Correlates of baseline BMD

In these men with idiopathic osteoporosis, univariate analyses revealed few associations between baseline variables and BMD. Subjects with prevalent vertebral fractures had lower spinal and total bone BMD (Table 3). Serum free testosterone was negatively associated with spinal BMD, with a similar trend at the femoral neck. Serum free testosterone was not related to biochemical markers of bone remodeling. Serum total estradiol concentrations were not related to BMD, urinary NTx excretion, or serum BSAP levels (Table 4). Baseline serum IGF-I levels (adjusted by decade of age) in the men with idiopathic osteoporosis were lower than in the reference population. However, neither serum IGF-I nor IGFBP-3 levels was correlated with BMD (Table 4). Total spine was positively correlated with age (Table 5), but femoral neck did not correlate with age. Femoral neck, total spine, and total body were all positively correlated with BMI (Table 5).

In the multivariate analysis, BMD was associated with BMI (spine, femoral neck, and total body BMD) previous fracture (spine and total body BMD), and age (spine BMD) (Table 5).

Correlates of change in BMD

Changes in BMD during the 2-yr clinical trial and their correlation with sex steroid levels and biochemical markers of bone remodeling at baseline are shown in Tables 6 and 7. In the placebo-treated subjects, testosterone was weakly correlated with the change in total body BMD, and IGFBP-3 was weakly associated with change in femoral neck and total body BMD. Other variables were not associated with changes in BMD or biochemical markers in the univariate analysis (Table 7). In the multivariate analysis, IGFBP-3 was related to change (positively) in femoral neck BMD, whereas total body BMD increased more in those with higher free testosterone levels (Table 6).

Changes in BMD and biochemical markers in the alendronate-treated groups are also shown in Table 8. No baseline variable was associated with BMD or biochemical marker change in univariate analysis.

Discussion

The characteristics of men with idiopathic osteoporosis have not been well described, and the determinants of change in bone mass with treatment have not been reported. A recent clinical trial of the effectiveness of alendronate in the treatment of idiopathic osteoporosis in men (6) has provided the opportunity to explore these issues in a larger group of men with low bone mass. Recognizing the limitations of *post hoc* analyses, this study was undertaken to gain possible insights into the pathogenesis of male osteoporosis, the determinants of change in BMD and biochemical markers of remodeling in the placebo-treated (calcium and vitamin D) participants, and the variables that might affect the response to therapy with a potent antiresorptive agent.

In the absence of a nonosteoporotic control population it is not possible to contrast the patients with low bone mass reported here to men without osteoporosis. Nevertheless, within this group of men with idiopathic osteoporosis it is useful to identify variables that may be associated with bone mass. For instance, we found that BMD was higher in osteoporotic men who were younger and heavier and had no vertebral fractures. Hence, as in PMO the influence of those

TABLE 3. Relationship between continuous baseline characteristics and presence of vertebral fracture at baseline in men participating in alendronate study

Variable	n	Median value if no fracture	Median value if prior fracture	*P*
Femoral neck BMD	186	0.69	0.68	0.48
Total spine BMD	192	0.94	0.85	<0.01
Total body BMD	188	1.06	1.03	<0.01
IGF-I (ng/ml)	190	124.0	110.0	0.05
IGFBP-3 (ng/ml)	191	2996	2867	0.11
Serum BSAP (ng/ml)	191	12.5	12.0	0.65
Urinary NTx (pmol of bone collagen equivalents/μmol of creatinine)	189	33.00	34.50	0.53
Serum estradiol (pmol/liter)	184	69.75	71.58	0.35
Serum free testosterone (nmol/liter)	171	0.31	0.34	0.14

[a] Wilcoxon rank sum test.

TABLE 4. Relationship between continuous baseline characteristics for men participating in alendronate study

Variable 1	Variable 2	n	Coefficient[a]	*P*
Femoral neck BMD	IGF-I (ng/ml)	189	0.06	0.43
	IGFBP-3 (ng/ml)	190	0.04	0.61
	Serum estradiol (pmol/liter)	183	−0.05	0.50
	Serum free testosterone (nmol/liter)	168	−0.17	0.03
	Serum BSAP (ng/ml)	190	0.10	0.18
	Urinary NTx (pmol of bone collagen equivalents/μmol of creatinine)	187	0.03	0.66
Total spine BMD	IGF-I (ng/ml)	195	−0.06	0.42
	IGFBP-3 (ng/ml)	196	−0.12	0.10
	Serum estradiol (pmol/liter)	189	−0.04	0.51
	Serum free testosterone (nmol/liter)	174	−0.24	<0.01
	Serum BSAP (ng/ml)	196	<0.01	1.0
	Urinary NTx (pmol of bone collagen equivalents/μmol of creatinine)	193	−0.06	0.41
Total body BMD	IGF-I (ng/ml)	191	0.0512	0.48
	IGFBP-3 (ng/ml)	192	−0.04	0.56
	Serum estradiol (pmol/liter)	186	−0.06	0.42
	Serum free testosterone (nmol/liter)	170	−0.10	0.19
	Serum BSAP (ng/ml)	192	−0.1	0.19
	Urinary NTx (pmol of bone collagen equivalents/μmol of creatinine)	189	−0.10	0.16
IGF-I (ng/ml)	Serum estradiol (pmol/liter)	187	−0.19	0.01
	Serum free testosterone (nmol/liter)	172	0.12	0.12
	Serum BSAP (ng/ml)	194	−0.05	0.51
	Urinary NTx (pmol of bone collagen equivalents/μmol of creatinine)	191	−0.01	0.89
	IGFBP-3 (ng/ml)	195	0.73	<0.01
IGFBP-3 (ng/ml)	Serum estradiol (pmol/liter)	188	−0.12	0.1
	Serum free testosterone (nmol/liter)	173	0.16	0.04
	Serum BSAP (ng/ml)	195	−0.07	0.34
	Urinary NTx (pmol of bone collagen equivalents/μmol of creatinine)	192	−0.03	0.71
Serum BSAP (ng/ml)	Serum estradiol (pmol/liter)	188	−0.09	0.21
	Serum free testosterone (nmol/liter)	173	−0.14	0.06
	Urinary NTx (pmol of bone collagen equivalents/μmol of creatinine)	193	0.39	<0.01
Urinary NTx (pmol of bone collagen equivalents/μmol of creatinine)	Serum estradiol (pmol/liter)	185	−0.06	0.42
	Serum free testosterone (nmol/liter)	171	−0.15	0.06
Serum estradiol (pmol/liter)	Serum free testosterone (nmol/liter)	168	0.39	<0.01

[a] Pearson correlation coefficient.

TABLE 5. Multivariate analyses: relationship between baseline BMD measurements and baseline patient characteristics

Outcome (initial BMD measurement)	Significant independent variables	*P*
Femoral neck	BMI	<0.0001
	Low testosterone[a]	0.0276
Total spine	BMI	0.0003
	Younger age[b]	0.0179
	Prior fracture	0.0182
	Low testosterone[a]	0.2033
	Low testosterone, younger age	0.0422
Total body	BMI	0.0004
	Prior fracture	0.0096

Baseline patient characteristics considered for model included age, BMI, testosterone, estradiol, IGF-I, IGFBP-3, and prior fracture.
[a] Low testosterone is defined as <0.312 nmol/liter.
[b] Younger age is defined as men ≤55 yr.

TABLE 6. Multivariate analyses: relationship between change in BMD measurements during the treatment period and baseline patient characteristics

Outcome (change in BMD measurement)	Significant independent variables	*P*
Femoral neck	Treated with alendronate	<0.0001
	Low IGFBP-3 at baseline[a]	0.1162
	Treated, low IGFBP-3	0.0305
Total spine	No significant variables	
Total body	Treated with alendronate	0.0076
	Low testosterone at baseline[b]	0.0461

Baseline patient characteristics considered for model include age, BMI, testosterone, estradiol, IGF-I, IGFBP-3, and prior fracture.
[a] Low IGFBP-3 is defined as less than 2917 ng/ml.
[b] Low testosterone is defined as <0.312 nmol/liter.

factors appears to be preserved in this disorder. On the other hand, variables that have been associated with BMD in non-osteoporotic men did not seem to be related to bone mass in these osteoporotic patients. Biochemical markers of bone remodeling were not associated with bone mass, and although a weak negative association between free testosterone and BMD was noted in univariate models, multivariate analyses did not reveal a significant relationship. Similarly, sex steroid levels were not related to markers of remodeling. Interestingly, serum IGF-I levels in these men with idiopathic osteoporosis were found to be less than in an age-matched reference population of healthy males aged 20–80 yr without coexistent disease, supporting previous reports (8). How-

TABLE 7. Relationship between various baseline characteristics and measurements collected during the treatment period for men participating in alendronate study

Baseline variable	Change in follow-up variable	Placebo			Alendronate		
		n	Coefficient[a]	*P*	n	Coefficient[a]	*P*
IGF-I (ng/ml)	Femoral neck BMD	53	0.18	0.21	90	−0.15	0.1555
	Total spine BMD	56	−0.17	0.22	92	−0.09	0.3793
	Total body BMD	59	0.07	0.60	97	0.01	0.9169
	Urinary excretion of NTx (pmol of bone collagen equivalents/μmol of creatinine)	65	−0.11	0.39	102	−0.03	0.7838
	Serum BSAP (ng/ml)	66	0.20	0.10	102	−0.04	0.7124
IGFBP-3 (ng/ml)	Femoral neck BMD	53	0.29	0.04	91	−0.05	0.6430
	Total spine BMD	56	<0.01	0.99	93	−0.10	0.3375
	Total body BMD	59	0.03	0.03	98	0.05	0.5945
	Urinary excretion of NTx (pmol of bone collagen equivalents/μmol of creatinine)	65	−0.11	0.39	103	−0.10	0.2976
	Serum BSAP (ng/ml)	66	0.14	0.27	103	−0.07	0.4681
Serum estradiol (pmol/liter)	Femoral neck BMD	49	−0.11	0.44	91	−0.17	0.1163
	Total spine BMD	52	−0.10	0.49	93	−0.11	0.2957
	Total body BMD	55	0	0.98	97	−0.02	0.8252
	Urinary excretion of NTx (pmol of bone collagen equivalents/μmol of creatinine)	59	−0.19	0.16	102	0.05	0.6046
	Serum BSAP (ng/ml)	60	−0.23	0.08	102	0.11	0.2594
Serum free testosterone (nmol/liter)	Femoral neck BMD	42	−0.19	0.23	81	<0.01	0.9985
	Total spine BMD	45	0.06	0.68	83	−0.05	0.6219
	Total body BMD	48	0.35	0.01	88	0.12	0.2681
	Urinary excretion of NTx (pmol of bone collagen equivalents/μmol of creatinine)	54	−0.20	0.14	93	−0.08	0.4543
	Serum BSAP (ng/ml)	55	0.02	0.88	93	0.05	0.6535

[a] Pearson correlation coefficient.

TABLE 8. Relationship between measurements collected during the treatment period and presence of vertebral fracture at baseline for men participating in alendronate study

Change in follow-up variable	Placebo				Alendronate			
	n	Median value, no fracture	Median value, prior fracture	*P*	n	Median value, no fracture	Median value, prior fracture	*P*
Femoral neck BMD × 10^4		0.678	−0.04	0.61		2.35	3.10	0.58
Total spine BMD × 10^4		2.31	2.82	0.92		8.63	8.88	0.71
Total body BMD × 10^4		1.33	−0.06	0.38		3.09	3.36	0.21
Urinary excretion of NTx (pmol of bone collagen equivalents/μmol of creatinine × 10^4)		−131.8	−67.1	0.40		−1299.9	−1577.6	0.27
Serum BSAP (ng/ml × 10^4)		−123.9	−45.5	0.18		−462.2	−440.3	0.76

ever, neither IGF-I nor IGFBP-3 was related to bone mass within the cohort. Thus, whereas the influences of major determinants of bone mass in other populations (BMI and age) were observable in men with idiopathic osteoporosis, other factors did not seem to have a major impact. This disruption of expected relationships may reflect the effect of an underlying skeletal disturbance in these men.

The effectiveness of alendronate in raising BMD in males (6) is strikingly similar to that previously documented in large studies of women with PMO (4, 5). Furthermore, the high risk of vertebral fracture over 2 yr in men with low BMD is similar in males (6) and females (5), suggesting that BMD may serve as an equivalent marker of fracture risk in men and women. Given this evidence in support of alendronate as an effective therapy for male osteoporosis, it is of some clinical importance to understand better the factors that might influence change in bone mass in men with low bone mass. However, we were unable to identify determinants of change in BMD, either in those men treated with calcium and vitamin D supplements or in those treated with alendronate. Men with higher rates of bone remodeling, higher serum sex steroid levels, or higher serum IGF-I concentrations did not respond to either therapeutic approach any better than did other men. Multivariate analyses revealed no combination of factors that allowed a prediction of which men would most benefit from therapy.

Although it cannot be assumed that knowledge of the pathogenesis of PMO can be extrapolated directly to the male skeleton, it is likely that the risk of men developing osteoporosis is related to the peak bone mass attained in early adult life and subsequent bone loss in later life. In PMO, estrogen deficiency leads to a progressive decline in BMD in association with elevated markers of bone resorption. Elevated NTx levels (a breakdown product of bone collagen and a robust marker of bone resorption) are seen in many untreated postmenopausal women and decrease with antiresorptive therapy in association with improvements in BMD. Testosterone replacement in hypogonadal males increases BMD, although there are separate data to suggest that this effect is probably mediated via its aromatization to estrogen (9, 10). Hence, if increased bone resorption consequent upon low levels of testosterone and/or estradiol is important in the

pathogenesis of male osteoporosis, baseline correlations between testosterone and/or estradiol and urinary NTx would be predicted. However, no correlation between urinary NTx and either gonadal steroid was observed (Table 2). Furthermore, baseline gonadal steroid concentrations do not appear to predict subsequent changes in NTx in patients treated with alendronate. If gonadal steroid concentrations play a role in dictating the overall level of bone resorption then, by analogy with data from women with PMO, it might be expected that those with the lowest concentrations of testosterone and estradiol (and therefore the highest levels of bone resorption) would exhibit the greatest change in NTx (ΔNTx) with antiresorptive therapy. However, no correlation was observed between baseline concentrations of either estradiol or testosterone and ΔNTx during the course of the study in the treatment arm. Hence, although hypogonadism is a well-documented cause of osteoporosis in men, data from this analysis do not support the hypothesis that variation of serum concentrations of gonadal steroids is an important factor determining the degree of bone resorption in men with idiopathic osteoporosis. Recently, it has been pointed out that estimates of free estradiol and testosterone concentrations are more closely related to bone density and markers of bone remodeling in older men not selected for osteoporosis (11). Free testosterone measures in this study were done with an analog RIA method that has less accuracy than assessments of bioavailable testosterone. Measures of bioavailable estradiol were not available for these analyses but may have provided additional insights into the relationship between estradiol levels and skeletal status in these men.

Reduced IGF-I levels have been postulated to be associated with idiopathic osteoporosis (12, 13). IGF-I knockout mice exhibit delayed bone development, retarded growth, and growth deficiency (14), and serum IGF-I concentration is postulated to account for more than 35% of the variance in femoral BMD in a cross between two inbred strains of mice (15). IGF-I-deficient patients, either due to a mutation in the growth hormone receptor (*e.g.* Laron syndrome) (16) or to an IGF-I gene deletion (17), have low bone mass that improves with IGF-I therapy. Intriguingly, one prospective study has suggested an association between serum IGF-I and postmenopausal fracture, independent of BMD and nutritional status (18). The present study is in keeping with other reports of an association between low serum IGF-I levels and reduced BMD of the spine and forearm in osteoporotic men (8). Baseline serum IGF-I concentrations in this cohort of male patients with osteoporosis were lower than the age- and sex-matched reference ranges. The significance of this difference is muted by the fact that the control samples were not studied in concert with these men with idiopathic osteoporosis. In addition, in this group of osteoporotic men, there was no correlation between serum IGF-I and BMD (Tables 3 and 4), suggesting that in idiopathic male osteoporosis, low serum IGF-I concentrations do not correlate with the severity of bone deficit. This is in contrast to the situation in adult hypopituitarism, in which there are data to suggest that the extent of bone loss correlates with the degree and duration of GH deficiency (19).

It is well documented that osteopenia in adult-onset GH deficiency is associated with reduced activity of the bone remodeling unit and that after an initial decrease due to an expansion of the bone remodeling space, GH therapy leads to long-term increases in BMD (20). If relative IGF-I deficiency plays a role in reducing bone remodeling in idiopathic male osteoporosis, correlations between serum IGF-I and BSAP and NTx would be predicted. However, no statistically significant correlation was observed in this study between IGF-I and markers of bone turnover at baseline. Furthermore, there was no correlation between baseline bone markers and subsequent change in BMD in the calcium/vitamin D-treated group. Finally, baseline IGF-I levels were not related to change in BMD in response to alendronate, suggesting that circulating IGF-I is not a determinant of bisphosphonate activity.

In summary, this study did not find strong predictors of BMD, or change in BMD, in a group of men with idiopathic osteoporosis. In agreement with previous reports, serum IGF-I concentrations were lower than age- and sex-matched reference ranges in men with idiopathic osteoporosis. However, within this group, no statistically significant correlation exists between serum IGF-I and BMD. Moreover, we found no relationship between sex steroid levels and baseline indices of bone remodeling in men with primary osteoporosis. It appears, from this study, that alendronate therapy benefits osteoporotic males equally, irrespective of the degree of bone remodeling or baseline concentrations of serum free testosterone, estradiol, or IGF-I. Hence, these measurements do not appear to be useful for the selection of men who may most benefit from bisphosphonate therapy. Our study highlights the complexities of hormonal interactions with skeletal metabolism and the inadequacy of currently available hormonal or biochemical measures to predict response to alendronate treatment in men. Much remains to be understood about the male skeleton, the pathogenesis of male osteoporosis, and the factors that determine the response to therapy.

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