

PAMIDRONATE TO PREVENT BONE LOSS DURING ANDROGEN-DEPRIVATION THERAPY FOR PROSTATE CANCER

MATTHEW R. SMITH, M.D., PH.D., FRANCIS J. MCGOVERN, M.D., ANTHONY L. ZIETMAN, M.D., MARY ANNE FALLON, L.P.N., DOUGLAS L. HAYDEN, M.A., DAVID A. SCHOENFELD, PH.D., PHILIP W. KANTOFF, M.D., AND JOEL S. FINKELSTEIN, M.D.

ABSTRACT

Background Treatment with a gonadotropin-releasing hormone agonist decreases bone mineral density and increases the risk of fracture in men with prostate cancer. We conducted a controlled study of the prevention of osteoporosis in men undergoing treatment with a gonadotropin-releasing hormone agonist.

Methods In a 48-week, open-label study, we randomly assigned 47 men with advanced or recurrent prostate cancer and no bone metastases to receive either leuprolide alone or leuprolide and pamidronate (60 mg intravenously every 12 weeks). Bone mineral density of the lumbar spine and the proximal femur was measured by dual-energy x-ray absorptiometry. Trabecular bone mineral density of the lumbar spine was measured by quantitative computed tomography. Forty-one men completed the study.

Results In men treated with leuprolide alone, the mean (\pm SE) bone mineral density decreased by 3.3 ± 0.7 percent in the lumbar spine, 2.1 ± 0.6 percent in the trochanter, and 1.8 ± 0.4 percent in the total hip, and the mean trabecular bone mineral density of the lumbar spine decreased by 8.5 ± 1.8 percent ($P < 0.001$ for each comparison with the base-line value). In contrast, the mean bone mineral density did not change significantly at any skeletal site in men treated with both leuprolide and pamidronate. There were significant differences between the two groups in the mean changes in bone mineral density at 48 weeks in the lumbar spine ($P < 0.001$), trochanter ($P = 0.003$), total hip ($P = 0.005$), and trabecular bone of the lumbar spine ($P = 0.02$).

Conclusions Pamidronate prevents bone loss in the hip and lumbar spine in men receiving treatment for prostate cancer with a gonadotropin-releasing hormone agonist. (N Engl J Med 2001;345:948-55.)

Copyright © 2001 Massachusetts Medical Society.

PROSTATE cancer is the most common cancer and the second leading cause of death from cancer among U.S. men. In 2001, there will be approximately 198,100 new cases of prostate cancer and 31,500 deaths from prostate cancer in the United States.¹

Androgen-deprivation therapy with a gonadotropin-releasing hormone agonist is the mainstay of treatment for metastatic prostate cancer. Evidence that early androgen-deprivation therapy improves outcomes has led to increased use of gonadotropin-releasing hormone agonists in men without distant metastases. Early primary androgen-deprivation therapy improves survival for men with locally advanced, nonmetastatic

prostate cancer.² Adjuvant androgen-deprivation therapy improves survival for men with locally advanced prostate cancer treated with radiation therapy³ and for men with lymph-node-positive prostate cancer treated with radical prostatectomy and pelvic lymphadenectomy.⁴ After surgery or radiation therapy for early-stage prostate cancer, gonadotropin-releasing hormone agonists are commonly administered to men in whom a rising serum concentration of prostate-specific antigen is the only indication of recurrent disease, although the effects of early androgen-deprivation therapy on the outcomes for these men are unknown.

Osteoporosis is an important complication of androgen-deprivation therapy. Such therapy decreases bone mineral density⁵⁻⁸ and increases the risk of fracture.⁹⁻¹¹ There have been no controlled studies of the prevention or treatment of osteoporosis in men receiving a gonadotropin-releasing hormone agonist.

Pamidronate is a second-generation bisphosphonate that potently inhibits osteoclast-mediated bone resorption. Pamidronate is indicated for the treatment of Paget's disease of bone, hypercalcemia associated with cancer, and osteolytic bone metastases from breast cancer and multiple myeloma. In addition, intravenous pamidronate increases bone mineral density in women with postmenopausal osteoporosis¹² and in patients with glucocorticoid-induced osteoporosis.¹³ In this study, we evaluated whether intravenous pamidronate prevents bone loss in men receiving a gonadotropin-releasing hormone agonist for prostate cancer.

METHODS

Study Subjects

The subjects were recruited from the medical oncology, radiation oncology, and urology clinics at the participating institutions. They had locally advanced, lymph node-positive, or recurrent prostate cancer and no bone metastases according to radionuclide bone scans. Men with Paget's disease, hyperthyroidism, Cushing's disease, hyperprolactinemia, chronic liver disease, or chronic renal insufficiency (serum creatinine concentration, > 2.0 mg per deciliter [$177 \mu\text{mol}$ per liter]) were excluded. Men were also excluded if they had received androgen-deprivation therapy, glucocorticoids, bisphosphonates, calcitonin, or suppressive doses of thyroxine within the previous year.

Study Design

The men were randomly assigned to 48 weeks of treatment with either 3-month depot leuprolide (Lupron Depot, TAP Pharma-

From Massachusetts General Hospital (M.R.S., F.J.M., A.L.Z., M.A.F., D.L.H., D.A.S., J.S.F.) and the Dana-Farber Cancer Institute (P.W.K.) — both in Boston. Address reprint requests to Dr. Smith at Massachusetts General Hospital, Cox 640, 100 Blossom St., Boston, MA 02114, or at smith.matthew@mgh.harvard.edu.

ceuticals, Deerfield, Ill.; 22.5 mg given intramuscularly every 12 weeks) or 3-month depot leuprolide and pamidronate disodium (Aredia, Novartis Oncology, East Hanover, N.J.; 60 mg given intravenously for two hours every 12 weeks). All of the men also received bicalutamide (Casodex, AstraZeneca, London; 50 mg orally daily) for four weeks to prevent the potential flare associated with initial leuprolide administration, calcium carbonate (500 mg daily), and a daily multivitamin containing 400 IU of vitamin D.

The subjects were evaluated at base line and at 2, 4, 8, 12, 24, and 48 weeks. Serum and urine samples were obtained between 8 a.m. and 10 a.m. at each visit and stored at -80°C. Serum concentrations of bone-specific alkaline phosphatase and osteocalcin and urinary excretion of deoxypyridinoline and N-telopeptide were measured at the end of the study in stored samples. Serum concentrations of testosterone, estradiol, parathyroid hormone, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D were measured at base line, 24 weeks, and 48 weeks. Bone mineral density was measured by dual-energy x-ray absorptiometry at base line, 24 weeks, and 48 weeks. Trabecular bone mineral density of the lumbar spine was measured by quantitative computed tomography (CT) at base line and at 48 weeks.

The study was reviewed and approved by the institutional review board of Dana-Farber Partners Cancer Care, and all subjects gave written informed consent. The study sponsor had no role in the

study design; in the collection, analysis, or interpretation of the data; or in the writing of this report.

Measurements of Bone Mineral Density

Posteroanterior measurements of the bone mineral density of the lumbar spine and measurements of the bone mineral density of the proximal femur were made by dual-energy x-ray absorptiometry with a densitometer (QDR 4500A, Hologic, Waltham, Mass.). Trabecular bone mineral density of the lumbar spine was determined by quantitative CT (GE Model i, General Electric Medical Systems, Milwaukee). Axial scans were obtained through the midbody of the first four lumbar vertebrae. The density of the trabecular bone was determined by comparison with an internal hydroxyapatite standard, and the values for the vertebrae that could be evaluated were then averaged. Measurements of bone mineral density were not performed on bones with fractures, deformities, or focal sclerosis.

Measurements of Biochemical Values

Serum concentrations of testosterone, estradiol, and 25-hydroxyvitamin D were measured by radioimmunoassays. Serum concentrations of parathyroid hormone and osteocalcin were measured by immunoradiometric assays. Serum 1,25-dihydroxyvitamin D was measured by a radioreceptor assay. Serum bone-specific alkaline

TABLE 1. BASE-LINE CHARACTERISTICS OF MEN WITH PROSTATE CANCER TREATED WITH LEUPROLIDE ALONE OR LEUPROLIDE AND PAMIDRONATE.*

CHARACTERISTIC	LEUPROLIDE (N=22)	LEUPROLIDE AND PAMIDRONATE (N=21)	NORMAL RANGE
Age (yr)	65±10	69±9	
Body-mass index†	27±3	27±3	
Dietary calcium (mg/day)	925±324	781±346	
Race (%)			
White	91	95	
Black	9	5	
Prior androgen-deprivation therapy (%)	5	10	
Prior pelvic-radiation therapy (%)	41	48	
Cigarette use >10 pack-yr (%)	45	33	
Alcohol intake >1 drink/day (%)	32	24	
Prostate-specific antigen (ng/ml)	15±15	14±26	
Testosterone (ng/dl)‡	355±119	402±131	270-1070
Estradiol (pg/ml)§	26±8	26±7	10-50
25-Hydroxyvitamin D (ng/ml)¶	24±6	22±8	15-43
1,25-Dihydroxyvitamin D (pg/ml)	37±14	34±14	18-62
Parathyroid hormone (pg/ml)	46±41	43±18	10-60
Bone mineral density (g/cm ²)			
Lumbar spine	1.046±0.132	1.111±0.137	
Femoral neck	0.796±0.117	0.822±0.119	
Total hip	0.983±0.145	0.987±0.144	
Trochanter	0.786±0.140	0.776±0.143	
Trabecular bone mineral density of the lumbar spine (mg/cm ³)	102±32	93±29	

*Plus-minus values are means ±SD. P>0.05 for each comparison between groups.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡To convert values to nanomoles per liter, multiply by 0.0347.

§To convert values to picomoles per liter, multiply by 3.671.

¶To convert values to nanomoles per liter, multiply by 2.496.

||To convert values to picomoles per liter, multiply by 2.6.

TABLE 2. LABORATORY VALUES IN MEN WITH PROSTATE CANCER TREATED WITH LEUPROLIDE ALONE OR LEUPROLIDE AND PAMIDRONATE.*

VARIABLE	BASE LINE	24 Wk	48 Wk	P VALUE
Testosterone (ng/dl)†				
Leuprolide	355±25	14±2	51±39	<0.001
Leuprolide and pamidronate	402±29	19±7	30±16	<0.001
Estradiol (pg/ml)‡				
Leuprolide	26±2	7±1	7±2	<0.001
Leuprolide and pamidronate	26±2	5±1	7±2	<0.001
25-Hydroxyvitamin D (ng/ml)§				
Leuprolide	24±1	26±2	26±1	0.051
Leuprolide and pamidronate	22±2	26±2	24±2	0.084
1,25-Dihydroxyvitamin D (pg/ml)¶				
Leuprolide	37±3	38±3	38±3	0.47
Leuprolide and pamidronate	34±3	39±3	32±3	0.81
Parathyroid hormone (pg/ml)				
Leuprolide	46±9	33±3	35±4	<0.001
Leuprolide and pamidronate	43±4	31±3	35±4	<0.001
Prostate-specific antigen (ng/ml)				
Leuprolide	14.7±3.1	0.7±0.2	0.8±0.4	<0.001
Leuprolide and pamidronate	13.9±5.8	0.5±0.1	1.4±1.1	<0.001

*Plus-minus values are means ±SE. P values were determined for mean changes from base line at 24 and 48 weeks by repeated-measures analysis of covariance. P>0.05 for each comparison between groups.

†To convert values to nanomoles per liter, multiply by 0.0347.

‡To convert values to picomoles per liter, multiply by 3.671.

§To convert values to nanomoles per liter, multiply by 2.496.

¶To convert values to picomoles per liter, multiply by 2.6.

phosphatase, urinary *N*-telopeptide, and urinary deoxy pyridinoline were measured by enzyme immunoassays.

Statistical Analysis

The primary end point of the study was the percentage change in the posteroanterior measurement of bone mineral density in the lumbar spine at 48 weeks. Primary analysis of efficacy data was performed according to the intention-to-treat principle. All men with bone-density measurements at base line and 48 weeks were included in the evaluation.

The percentage change in bone mineral density from base line to 48 weeks was compared between groups by analysis of covariance with control for base-line values.¹⁴ Interval estimates for the differences between groups in the percentage change from base line to 48 weeks were calculated by *t*-tests without control for base-line values.¹⁴ Changes in serum concentrations of gonadal steroids, calcium regulatory hormones, and prostate-specific antigen at 24 and 48 weeks were compared between groups by repeated-measures analysis of covariance with control for base-line values and week.¹⁵ Changes in biochemical markers of bone turnover were compared between groups as planned secondary analyses by repeated-measures analysis of covariance with control for base-line values.¹⁵ The model included a time effect, a treatment effect, and a time-by-treatment interaction. Base-line characteristics were compared between groups by using Fisher's exact test for categorical variables and *t*-tests for continuous variables.¹⁴

Statistical analyses were performed with SAS software (version 8.1, SAS Institute, Cary, N.C.). Values are reported as means ±SE unless otherwise indicated. All P values are two-sided, and values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Characteristics of the Subjects

Forty-seven men were randomly assigned to treatment, and 43 completed the base-line evaluation. The base-line characteristics of the men assigned to treat-

ment with leuprolide alone and the men assigned to treatment with both leuprolide and pamidronate were similar (Table 1). Two men assigned to treatment with leuprolide and pamidronate withdrew before the first follow-up measurement of bone mineral density at 24 weeks. Forty-one men completed the study. Three of these 41 men discontinued leuprolide early because of bothersome vasomotor flushing: 2 men receiving leuprolide alone discontinued the drug after 36 weeks, and 1 man receiving leuprolide and pamidronate discontinued leuprolide after 24 weeks. The remaining men received all of their assigned treatment.

Gonadal Steroids, Calcium Regulatory Hormones, and Prostate-Specific Antigen

The serum concentrations of testosterone, estradiol, parathyroid hormone, and prostate-specific antigen decreased significantly in both groups ($P<0.001$ for each comparison with the base-line value) (Table 2). The nadir serum concentrations of testosterone were in the range of that in castrated men (<50 ng per deciliter [1.7 nmol per liter]) for all subjects. The changes in serum testosterone, estradiol, parathyroid hormone, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and prostate-specific antigen concentrations did not differ significantly between the two groups.

Bone Mineral Density

There were significant differences between the two groups in the mean changes in bone mineral density at 48 weeks in the lumbar spine ($P<0.001$), trochan-

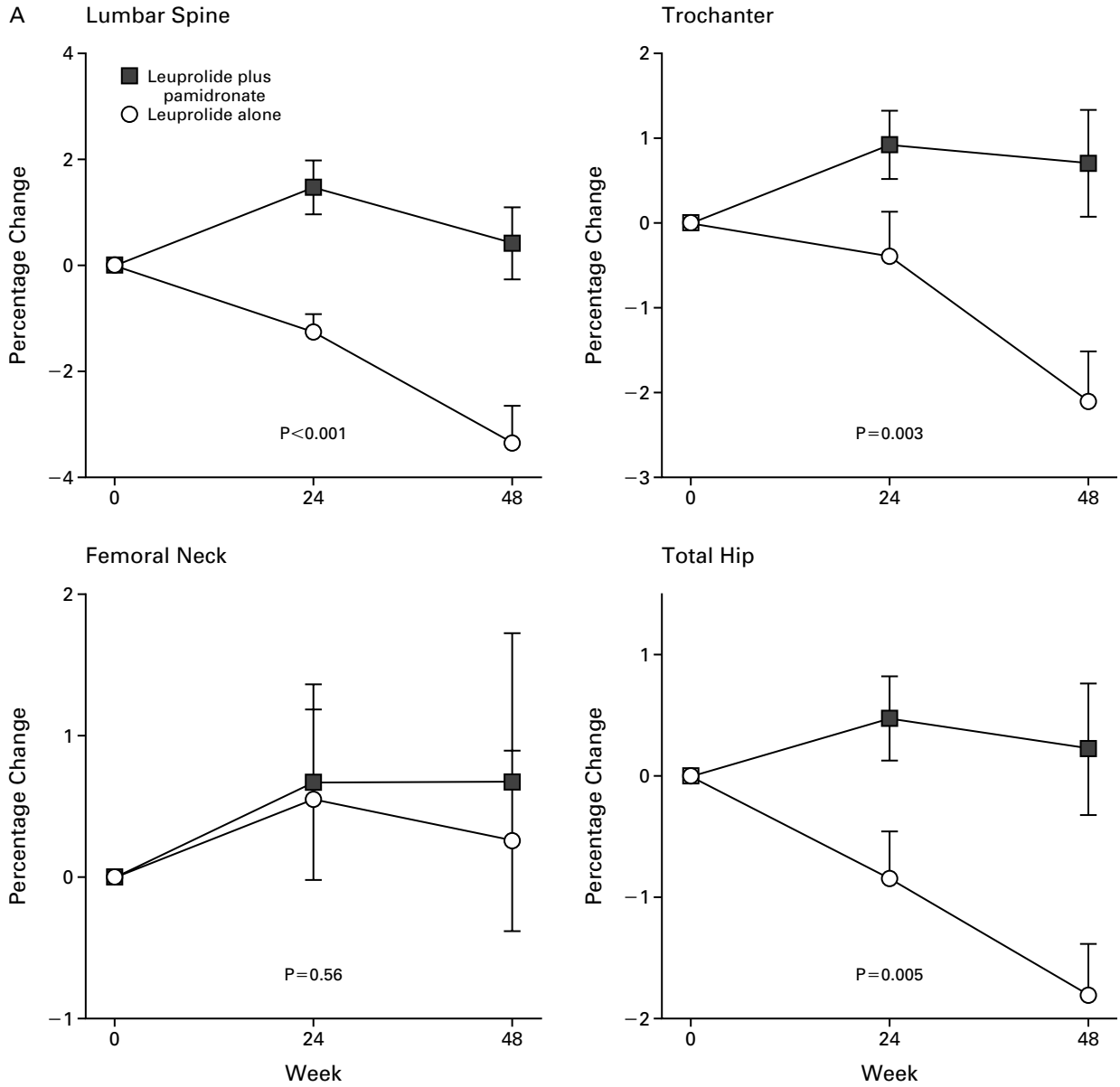
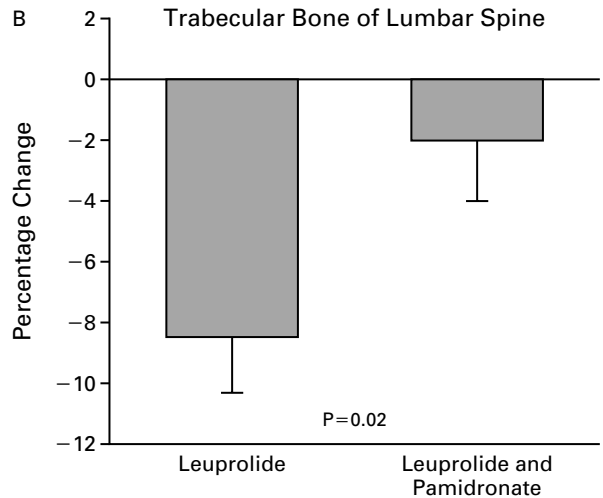


Figure 1. Mean (\pm SE) Changes from Base Line in Bone Mineral Density in Men with Prostate Cancer Treated with Leuprolide Alone or Leuprolide and Pamidronate. P values are for between-group comparisons of the percentage change from base line to 48 weeks.



ter ($P=0.003$), and total hip ($P=0.005$) (Fig. 1A). In the men treated with leuprolide alone, the mean bone mineral density decreased by 3.3 ± 0.7 percent in the lumbar spine, 2.1 ± 0.6 percent in the trochanter, and 1.8 ± 0.4 percent in the total hip at 48 weeks ($P<0.001$ for each comparison with the base-line value), but the mean bone mineral density in the femoral neck did not change significantly ($P=0.87$ for the comparison with the base-line value). In contrast, the mean bone mineral density did not change significantly at any skeletal site in the men treated with both leuprolide and pamidronate. At 48 weeks, the absolute differences between the groups in the percentage change from the base-line value were 3.8 percent (95 percent confidence interval, 1.8 to 5.7 percent) for the lumbar spine, 2.8 percent (95 percent confidence interval, 1.1 to 4.6 percent) for the trochanter, and 2.0 percent (95 percent confidence interval, 0.7 to 3.4 percent) for the total hip.

The mean changes in trabecular bone mineral density of the lumbar spine also differed significantly between the two groups ($P=0.02$) (Fig. 1B). This measurement decreased by 8.5 ± 1.8 percent in the men treated with leuprolide alone ($P<0.001$ for the comparison with the base-line value) and by 2.0 ± 2.0 percent in the men treated with both leuprolide and pamidronate ($P=0.32$ for the comparison with the base-line value) (Fig. 1B). The absolute difference between the groups from base line to 48 weeks was 6.5 percent (95 percent confidence interval, 1.0 to 11.9 percent).

Biochemical Markers of Bone Turnover

The mean changes in the serum concentrations of bone-specific alkaline phosphatase and osteocalcin and in the urinary excretion of deoxypyridinoline and *N*-telopeptide differed significantly between the two groups ($P<0.001$ for the treatment effect for each marker) (Fig. 2). In men treated with leuprolide alone, the concentrations of each marker increased progressively over the study period. Marker changes were more complex in men treated with both leuprolide and pamidronate. Serum bone-specific alkaline phosphatase and osteocalcin concentrations initially decreased and then approached or returned to base-line levels by 48 weeks. Urinary excretion of deoxypyridinoline and *N*-telopeptide initially decreased and then increased and exceeded the base-line value after 12 weeks.

Adverse Events

Serious adverse events occurred in eight men (Table 3). These adverse events were not necessarily related to the therapy. Two men treated with pamidronate withdrew because of adverse events (angiosarcoma and memory disorder). Adverse events related to treatment with a gonadotropin-releasing hormone agonist, including anemia, fatigue, and vasomotor flushing, were

common in both groups (Table 3). Three men treated with pamidronate had transient arthralgias and fevers that were consistent with the acute-phase reaction associated with intravenous bisphosphonates.

DISCUSSION

This study demonstrates that intravenous pamidronate prevents bone loss in the hip and spine in men undergoing treatment for prostate cancer with a gonadotropin-releasing hormone agonist. Trabecular bone mineral density decreased by 8.5 percent in men receiving leuprolide alone but did not change significantly in men receiving both leuprolide and pamidronate. Because low bone mineral density is an important determinant of the risk of fracture,¹⁶ these findings suggest that pamidronate may reduce that risk in men receiving a gonadotropin-releasing hormone agonist for the treatment of prostate cancer. In women with postmenopausal osteoporosis treated with bisphosphonates, beneficial effects of a similar magnitude on bone mineral density are associated with large reductions in the risk of fracture.^{17,18}

In men over 65 years of age who had low-normal serum testosterone concentrations, testosterone treatment as compared with placebo did not increase bone mineral density in the lumbar spine.¹⁹ In men with primary osteoporosis and normal or near-normal serum free testosterone concentrations, daily oral administration of alendronate increased bone mineral density and helped prevent vertebral fractures.²⁰ Additional studies are required to determine whether oral bisphosphonates prevent bone loss in men with serum testosterone concentrations in the castrated range.

Bone mineral density is decreased in men with hyperprolactinemic hypogonadism, men with idiopathic hypogonadotropic hypogonadism, young castrated men, and older men receiving a gonadotropin-releasing hormone agonist for benign prostatic hyperplasia.²¹ In uncontrolled studies of men with congenital or acquired primary or secondary hypogonadism, testosterone-replacement therapy increased bone mineral density.²²⁻²⁴ Many hypogonadal men, however, have contraindications to testosterone-replacement therapy. Our study demonstrates that pamidronate prevents bone loss in men with severe hypogonadism and suggests that pamidronate represents a valuable alternative to testosterone-replacement therapy for the prevention of hypogonadal bone loss in men with contraindications to testosterone treatment.

In our study, changes in bone mineral density of the lumbar spine were greater when measured by quantitative CT than when measured by dual-energy x-ray absorptiometry, probably because of limitations of dual-energy x-ray absorptiometry in older men. In normal men, lumbar-spine bone mineral density increases after the age of 55 years when measured by dual-energy x-ray absorptiometry,^{19,25} because of the formation of spinal osteophytes and calcification of

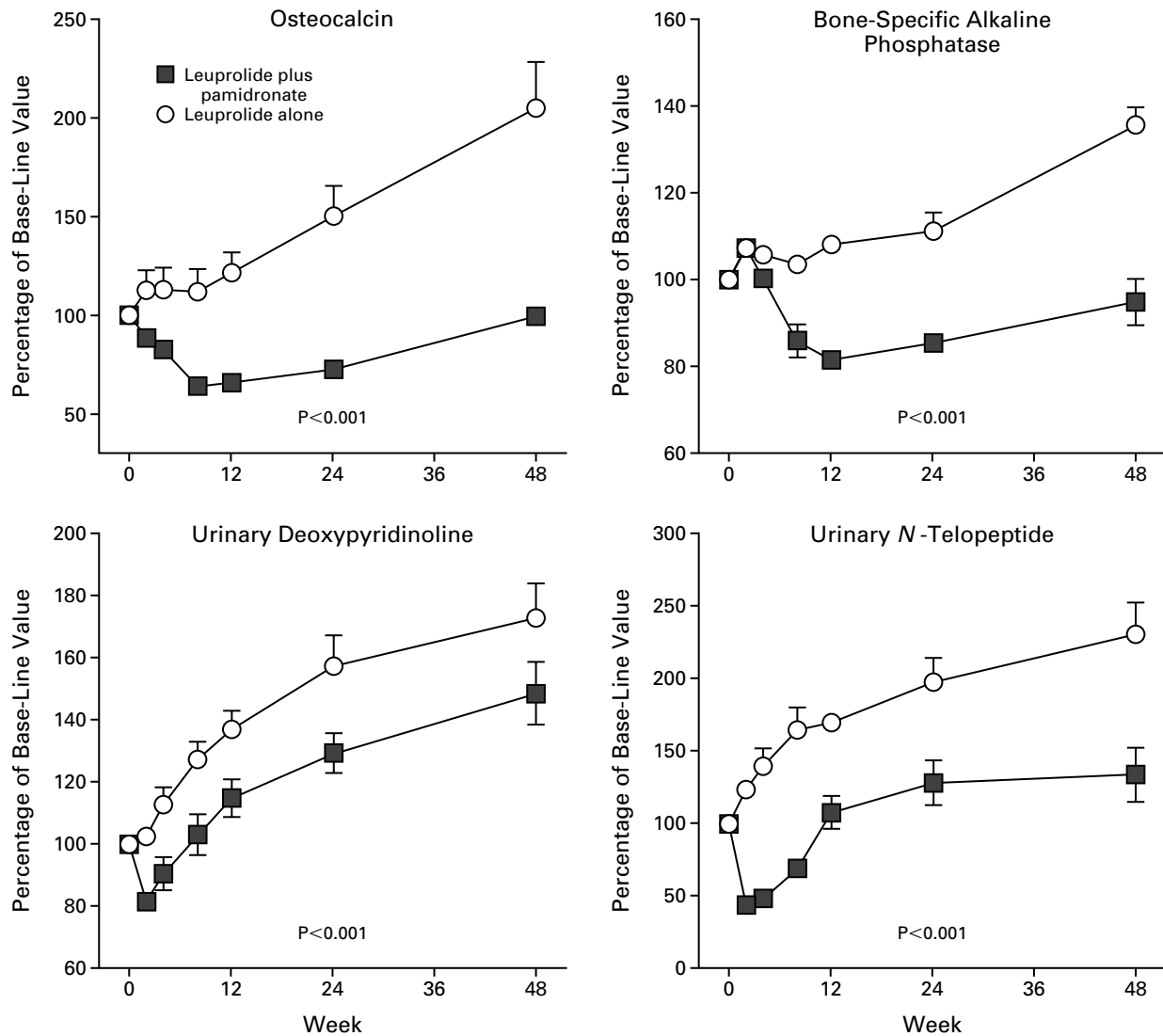


Figure 2. Changes in Serum Concentrations of Bone-Specific Alkaline Phosphatase and Osteocalcin and Urinary Excretion of Deoxyypyridinoline and *N*-telopeptide in Men with Prostate Cancer Treated with Leuprolide Alone or Leuprolide and Pamidronate. Values are expressed as the mean (\pm SE) percentage of the base-line value. P values are for the treatment effect according to repeated-measures analysis of covariance controlled for the base-line value. Standard-error bars that are not visible are covered by the symbol.

paravertebral structures.²⁶ Because measurement by quantitative CT is restricted to the central region of the vertebral bodies, it allows for selective assessment of trabecular bone mineral density without the confounding effects of overlying calcification or spinal osteophytes.²⁷

Our study showed that there were complex changes in biochemical markers of bone turnover. After the first treatment with leuprolide and pamidronate, markers of bone resorption decreased sharply and then returned to near base-line concentrations before the next treatment. Because markers of bone resorption were

not evaluated between subsequent treatment cycles, we cannot determine whether each pamidronate treatment resulted in similar sharp, transient decreases in these markers. Beneficial effects on bone mineral density with transient suppression of bone-resorption markers have been reported in patients with glucocorticoid-induced osteoporosis treated with intravenous pamidronate¹³ and in women with postmenopausal osteoporosis treated with intravenous ibandronate.²⁸ In a one-year prospective, randomized study of glucocorticoid-induced osteoporosis, a single treatment with 90 mg of pamidronate was as effective at pre-

TABLE 3. ADVERSE EVENTS IN MEN WITH PROSTATE CANCER TREATED WITH LEUPROLIDE ALONE OR LEUPROLIDE AND PAMIDRONATE.

EVENT	LEUPROLIDE (N=22)	LEUPROLIDE AND PAMIDRONATE (N=21)
	no. (%)	
Serious events*	3 (14)	5 (24)
Acute-phase reaction†	0	3 (14)
Anemia	20 (91)	19 (90)
Fatigue	8 (36)	7 (33)
Weight gain \geq 5 kg	3 (14)	2 (10)
Vasomotor flushing	17 (77)	12 (57)

*Serious events were delirium, gastric cancer, and hematuria among men receiving leuprolide alone and colon cancer, cystitis, hepatic angiosarcoma, lymphoma, and memory disorder among men receiving leuprolide and pamidronate.

†The acute-phase reaction consisted of transient arthralgias and fevers.

venting bone loss as a regimen of 30 mg of pamidronate given every three months, although sustained decreases in bone-resorption markers were observed only with the three-month treatment schedule.²⁹ Additional studies are required to determine the best dose and schedule of administration for pamidronate therapy in hypogonadal men.

Our study has limitations. It was designed to determine whether pamidronate prevents bone loss, and larger studies are required to determine whether treatment decreases the incidence of fracture. Most of the men were white, and the benefits of pamidronate might not occur in other racial groups. Finally, the open-label design may have affected subjective end points, such as reported adverse events.

In summary, intravenous pamidronate prevents bone loss in the hip and lumbar spine in men receiving a gonadotropin-releasing hormone agonist for prostate cancer.

Supported by grants from the National Institutes of Health (K24 DK02759 [to Dr. Finkelstein] and RR-1066), a National Institutes of Health Clinical Associate Physician Award (to Dr. Smith), awards from CaP CURE and Novartis Oncology, and a Doris Duke Charitable Foundation Clinical Scientist Development Award (to Dr. Smith).

We are indebted to Drs. Alexander Althausen, Daniel George, Joseph Grocela, Niall Heney, and William Shipley for referring subjects; to the dedicated nursing and nutrition staffs of the Mallinckrodt General Clinical Research Center, Massachusetts General Hospital; to Ms. Ellen Anderson for performing dietary assessments; to Ms. Denise Keefe for supervising performance of the study protocol in the General Clinical Research Center; to Ms. Robbin Cleary, Ms. Irene Lerman, and Ms. Sarah Zhang for performing bone-density tests; and to Mr. Gregory Neubauer for performing biochemical measurements.

REFERENCES

- Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. *CA Cancer J Clin* 2001;51:15-36.
- The Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. *Br J Urol* 1997;79:235-46.
- Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;337:295-300.
- Messing EM, Manola J, Sarosdy M, Wilding G, Crawford ED, Trump D. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *N Engl J Med* 1999;341:1781-8.
- Daniell HW, Dunn SR, Ferguson DW, Lomas G, Niazi Z, Stratte PT. Progressive osteoporosis during androgen deprivation therapy for prostate cancer. *J Urol* 2000;163:181-6.
- Diamond T, Campbell J, Bryant C, Lynch W. The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma: longitudinal evaluation and response to intermittent cyclic etidronate therapy. *Cancer* 1998;83:1561-6.
- Maillefert JE, Sibilia J, Michel F, Saussine C, Javier RM, Tavernier C. Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. *J Urol* 1999;161:1219-22.
- Eriksson S, Eriksson A, Stege R, Carlstrom K. Bone mineral density in patients with prostatic cancer treated with orchidectomy and with estrogens. *Calcif Tissue Int* 1995;57:97-9.
- Daniell HW. Osteoporosis after orchidectomy for prostate cancer. *J Urol* 1997;157:439-44.
- Townsend MF, Sanders WH, Northway RO, Graham SD Jr. Bone fractures associated with luteinizing hormone-releasing agonists used in the treatment of prostate carcinoma. *Cancer* 1997;79:545-50.
- Hatano T, Oishi Y, Furuta A, Iwamuro S, Tashiro K. Incidence of bone fracture in patients receiving luteinizing hormone-releasing hormone agonists for prostate cancer. *BJU Int* 2000;86:449-52.
- Thiebaud D, Burckhardt P, Melchior J, et al. Two years' effectiveness of intravenous pamidronate (APD) versus oral fluoride for osteoporosis occurring in the postmenopause. *Osteoporos Int* 1994;4:76-83.
- Boutsens Y, Jamart J, Esselincx W, Stoffel M, Devogelaer JP. Primary prevention of glucocorticoid-induced osteoporosis with intermittent intravenous pamidronate: a randomized trial. *Calcif Tissue Int* 1997;61:266-71.
- Rosner B. *Fundamentals of biostatistics*. 3rd ed. Boston: PWS-Kent Publishing, 1990.
- Littell RC, Milliken GA, Stroup WW, Wolfinger RD. *SAS systems for mixed models*. Cary, N.C.: SAS Institute, 1996.
- Cummings SR, Black DM, Nevitt MC, et al. Appendicular bone density and age predict hip fracture in women. *JAMA* 1990;263:665-8.
- Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998;280:2077-82.
- Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 1999;282:1344-52.
- Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. *J Clin Endocrinol Metab* 1999;84:1966-72.
- Orwoll E, Ettinger M, Weiss S, et al. Alendronate for the treatment of osteoporosis in men. *N Engl J Med* 2000;343:604-10.
- Finkelstein JS. Androgens and bone metabolism. In: Neischlag E, Behre HM, eds. *Testosterone: action, deficiency, substitution*. Berlin, Germany: Springer-Verlag, 1998:187-207.
- Katznelson L, Finkelstein JS, Schoenfeld DA, Rosenthal DI, Anderson EJ, Klibanski A. Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. *J Clin Endocrinol Metab* 1996;81:4358-65.
- Wang C, Eyre DR, Clark R, et al. Sublingual testosterone replacement improves muscle mass and strength, decreases bone resorption, and increases bone formation markers in hypogonadal men: a clinical research center study. *J Clin Endocrinol Metab* 1996;81:3654-62.
- Finkelstein JS, Klibanski A, Neer RM, et al. Increases in bone density during treatment of men with idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab* 1989;69:776-83.
- Zmuda JM, Cauley JA, Glynn NW, Finkelstein JS. Posterior-anterior and lateral dual-energy x-ray absorptiometry for the assessment of vertebral

osteoporosis and bone loss among older men. *J Bone Miner Res* 2000;15:1417-24.

26. Orwoll ES, Oviatt SK, Mann T. The impact of osteophytic and vascular calcifications on vertebral mineral density measurements in men. *J Clin Endocrinol Metab* 1990;70:1202-7.

27. Grampp S, Jergas M, Gluer CC, Lang P, Brastow P, Genant HK. Radiologic diagnosis of osteoporosis: current methods and perspectives. *Radiol Clin North Am* 1993;31:1133-45.

28. Thiebaud D, Burckhardt P, Kriegbaum H, et al. Three monthly intra-

venous injections of ibandronate in the treatment of postmenopausal osteoporosis. *Am J Med* 1997;103:298-307.

29. Boutsen Y, Jamart J, Esselinckx W, Devogelaer JP. Primary prevention of glucocorticoid-induced osteoporosis with intravenous pamidronate and calcium: a prospective controlled 1-year study comparing a single infusion, an infusion given once every 3 months, and calcium alone. *J Bone Miner Res* 2001;16:104-12.

Copyright © 2001 Massachusetts Medical Society.