0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(8):3841–3846

doi: 10.1210/jc.2003-032058

Raloxifene to Prevent Gonadotropin-Releasing Hormone Agonist-Induced Bone Loss in Men with Prostate Cancer: A Randomized Controlled Trial

MATTHEW R. SMITH, MARY ANNE FALLON, HANG LEE, AND JOEL S. FINKELSTEIN

Division of Hematology and Oncology (M.R.S., M.A.F.) and Endocrine Unit (J.S.F.), Department of Medicine, and the Biostatistics Center (H.L.), Massachusetts General Hospital, Boston, Massachusetts 02114

GnRH agonists decrease bone mineral density and increase fracture risk in men with prostate cancer. Raloxifene increases bone mineral density in postmenopausal women, but its efficacy in hypogonadal men is not known. In a 12-month open-label study, men with nonmetastatic prostate cancer (n = 48) who were receiving a GnRH agonist were assigned randomly to raloxifene (60 mg/d) or no raloxifene. Bone mineral densities of the posteroanterior lumbar spine and proximal femur were measured by dual energy x-ray absorptiometry. Mean (±SE) bone mineral density of the posteroanterior lumbar spine increased by 1.0 ± 0.9% in men treated with raloxifene and decreased by 1.0 ± 0.6% in men who did not receive raloxifene ($P = 0.07$). Bone mineral density of the total hip increased by 1.1 ± 0.4% in men treated with raloxifene and decreased by 2.6 ± 0.7% in men who did not receive raloxifene ($P < 0.001$). Similar between-group differences were observed in the femoral neck ($P = 0.06$) and trochanter ($P < 0.001$). In men receiving a GnRH agonist, raloxifene significantly increases bone mineral density of the hip and tends to increase bone mineral density of the spine. (*J Clin Endocrinol Metab* 89: 3841–3846, 2004)

ANDROGEN DEPRIVATION THERAPY by either bilateral orchiectomies or chronic administration of a GnRH agonist is the cornerstone of treatment for metastatic prostate cancer. Additionally, GnRH agonists are often administered to men with recurrent or locally advanced nonmetastatic prostate cancer. In 1994, the total Medicare expenditure for treatment of prostate cancer was $1.4 billion, and greater than one third of that amount was spent for GnRH agonists (http://www.ahrq.gov/clinic/prossumm.htm).

Osteoporosis is an important complication of GnRH agonist treatment in men with prostate cancer. GnRH agonists decrease bone mineral density (1–4) and increase fracture risk (5–8).

Estrogens play an important role in skeletal homeostasis in normal men. Estrogen receptors are expressed in osteoblasts and osteoclasts (9–11). In older men, serum estradiol levels are positively associated with spinal bone mineral density and negatively associated with vertebral fracture risk (12–14). Estrogens contribute to the regulation of both bone formation and bone resorption in men (15, 16).

Raloxifene is a selective estrogen receptor modulator that mimics the effects of estrogens in bone without stimulatory effects in most other tissues (17). Raloxifene prevents early postmenopausal bone loss in women and reduces the rate of vertebral fractures in women with postmenopausal osteoporosis (18, 19). Less is known about the efficacy of raloxifene in men.

In this study, we evaluated the effects of raloxifene on bone mineral density in men receiving a GnRH agonist for nonmetastatic prostate cancer.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

Subjects and Methods

Study subjects

Study participants were recruited at Massachusetts General Hospital (Boston, MA) between February 2000 and February 2002. All subjects were receiving treatment with a GnRH agonist for prostate cancer for 6 months or more at study entry. Subjects had a radionuclide bone scan within 6 months of initiating GnRH agonist treatment or 6 months before study entry. Men with bone metastases or evidence of progressive disease (serum prostate-specific antigen >150% nadir value) were excluded. Men with metabolic bone disease, history of treatment for osteoporosis, history of deep venous thrombosis or pulmonary embolus, serum calcium less than 8.4 or more than 10.6 mg/dl, or serum creatinine concentration more than 2.0 mg/dl (177 μmol/liter) were also excluded.

Study design

After a screening visit, eligible subjects were assigned randomly using computer-generated cards to receive raloxifene (Evista, Eli Lilly and Co., Indianapolis, IN; 60 mg by mouth daily) or no raloxifene for 12 months. Subjects were aware of their treatment assignment. Compliance was assessed with patient diaries. Subjects in both groups continued treatment with a GnRH agonist. All subjects received calcium carbonate (500 mg daily) and a daily multivitamin containing 400 IU vitamin D. There was no required run in period. Study personnel who performed or analyzed the main study outcomes were blinded to the treatment assignments.

After randomization, subjects were evaluated at the Mallinckrodt General Clinical Research Center at Massachusetts General Hospital at baseline, 6, and 12 months. Serum and urine samples were obtained at each visit and stored at −80 C. Bone mineral density and body composition were measured by DXA at baseline, 6, and 12 months. The institutional review board of Dana Farber Partners Cancer Care approved the study. All subjects gave written informed consent.

Study endpoints

The bone mineral density of the posteroanterior lumbar spine and proximal femur was determined by DXA using a Hologic QDR 4500A densitometer (Hologic, Inc., Waltham, MA). Lean and fat mass were also determined by DXA (software version 11.2, Hologic, Inc.).

Serum concentrations of testosterone (Diagnostic Products, Los Angeles, CA), estradiol (Nichols Institute, San Juan Capistrano, CA), 25-hydroxyvitamin D (DiaSorin, Stillwater, MN), PTH (Nichols Institute), and amino-terminal propeptide of type I collagen (DiaSorin) were measured by RIAs or immunoradiometric assays. The lower limits of detection for serum testosterone and estradiol were 6 ng/dl (0.2 nmol/liter) and 3 pg/ml (11 pmol/liter), respectively. Urinary deoxypyridinoline (Metra Biosystems, Mountain View, CA) was measured by enzyme immunoassay. Serum cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations were measured by colorimetric enzymatic assays on an automated clinical chemistry analyzer (Roche Diagnostics/Roche Molecular Biochemicals, Indianapolis, IN).

Statistical analyses

The primary study endpoint was the percent change in the bone mineral density of the posteroanterior lumbar spine from baseline to 12 months. The power calculations for this study assume a 3.0% SD of the change from baseline (2) and dropout rate of 20%. The sample size of 48 subjects (24 subjects/group) provides 80% power to detect a difference of at least 2.8% using a two-sided t test ($\alpha = 0.05$). Percent changes in

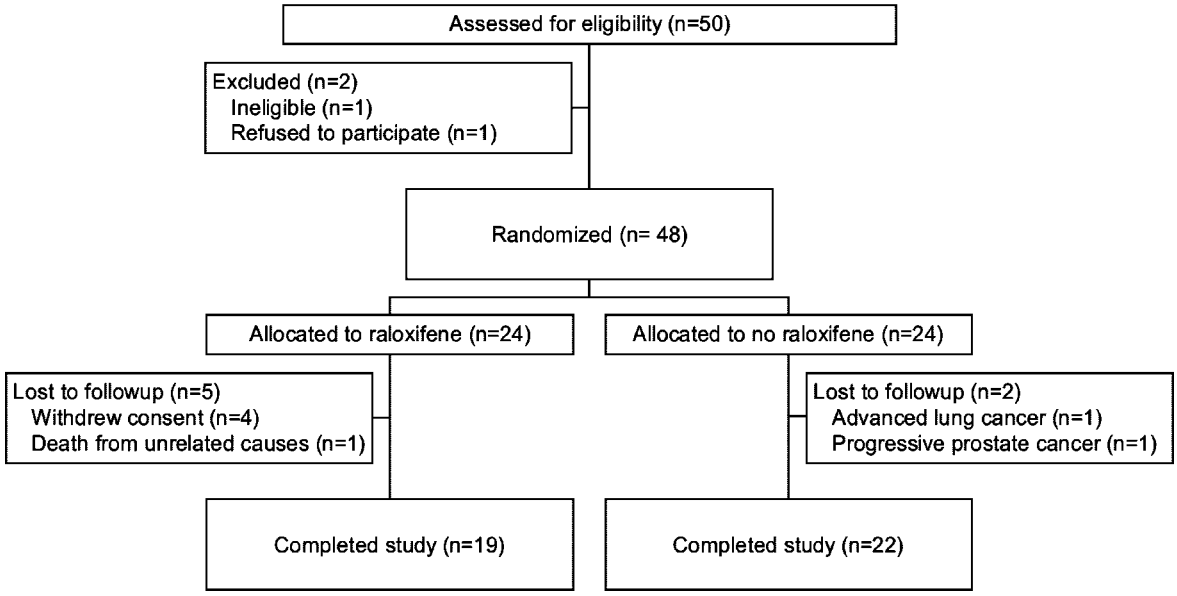

FIG. 1. Flow diagram.

TABLE 1. Baseline characteristics

Characteristic	Raloxifene (n = 20)	No raloxifene (n = 24)	Normal range
Age (yr)	72 ± 10	68 ± 9	
Race (%)			
Non-Hispanic white	95	100	
Non-Hispanic black	5	0	
Duration of GnRH agonist treatment (months)			
Mean	31 ± 24	37 ± 41	
Median (range)	31 (6–111)	19 (6–138)	
Body mass index (kg/m^2)	29.8 ± 3.6	28.1 ± 3.5	
Posteroanterior lumbar spine			
Bone mineral density (g/cm^2)	1.096 ± 0.188	1.060 ± 0.115	
t Score	0.05 ± 1.71	−0.21 ± 1.02	
z Score	0.96 ± 1.82	0.72 ± 0.97	
Total hip			
Bone mineral density (g/cm^2)	0.999 ± 0.161	0.991 ± 0.127	
t Score	−0.30 ± 1.04	−0.34 ± 0.89	
z Score	0.54 ± 1.09	0.41 ± 0.79	
Hemoglobin (g/dl)	13 ± 1	13 ± 1	13.5–17.5
Testosterone (ng/dl)[a]	15 ± 5	18 ± 15	270–1070
Estradiol (pg/ml)[b]	6 ± 4	5 ± 5	10–50
SHBG (nmol/liter)	39 ± 20	42 ± 22	13–71
25-Hydroxyvitamin D (ng/ml)[c]	25 ± 9	31 ± 9	15–43
PTH (pg/ml)	35 ± 14	39 ± 27	10–60
Serum PINP (μg/ml)	46 ± 18	59 ± 24	21–78
Urinary deoxypyridinoline (nmol BCE/mmol creatinine)	7.3 ± 1.7	7.3 ± 2.0	2.3–5.4

Plus-minus values are means ± SD. PINP, Amino-terminal propeptide of type I collagen; BCE, bone collagen equivalents.
[a] To convert testosterone from nanograms per deciliter to nanomoles per liter, multiply by 0.0347.
[b] To convert estradiol from picograms per milliliter to picomoles per liter, multiply by 3.671.
[c] To convert 25-hydroxyvitamin D from nanograms per milliliter to picomoles per liter, multiply by 2.496.

bone mineral density, body composition, gonadal steroids, and biochemical markers of bone turnover from baseline to 12 months were compared between groups using *t* tests (20). All data were included in the efficacy analyses, including data from subjects who discontinued treatment early.

Statistical analyses were performed using SAS version 8.1 (SAS Institute, Inc., Cary, NC). Values are reported as means ± SE unless specified otherwise. All *P* values are two sided, and values less than 0.05 are considered statistically significant.

Results

Characteristics of the subjects

Forty-eight eligible subjects were recruited between February 2000 and February 2002. Forty-four subjects completed the baseline evaluation (Fig. 1). Baseline characteristics of men assigned to raloxifene and men assigned to no raloxifene were similar (Table 1).

Forty-one subjects completed study testing (Fig. 1). One man assigned to raloxifene died from causes unrelated to prostate cancer or study treatment at month 2. Two men in the group that did not receive raloxifene treatment withdrew before completing the study; one man withdrew after he was diagnosed with lung cancer at month 6, and another man withdrew after he developed progressive disease at month 7. No other subject experienced disease progression during the study. All available data were included in the efficacy analyses, including data from a subject who discontinued treatment after 6 months due to an adverse event.

Gonadal steroids

Mean serum testosterone levels at baseline were in the castrate range in both groups (Table 1). Changes in serum total testosterone, estradiol, and SHBG levels did not differ significantly between the groups (Fig. 2).

Bone mineral density

The mean (±SE) bone mineral density of the posteroanterior lumbar spine increased by 1.0 ± 0.9% in the men treated with raloxifene and decreased by 1.0 ± 0.6% in the men who did not receive raloxifene ($P = 0.07$) (Fig. 3A). The between-group differences in percent change from baseline to 12 months was 2.0% (95% confidence interval, −0.2–4.0%).

Mean changes in bone mineral density of the total hip and trochanter differed significantly between groups. Bone mineral density of the total hip increased by 1.1 ± 0.4% in the men treated with raloxifene and decreased by 2.6 ± 0.7% in men who did not receive raloxifene ($P < 0.001$) (Fig. 3B). Bone mineral density of the trochanter increased by 1.6 ± 0.5% in the men treated with raloxifene and decreased by 2.4 ± 0.8% in men who did not receive raloxifene ($P < 0.001$) (Fig. 3C). Bone mineral density of the femoral neck increased by 0.3 ± 0.8% in the men treated with raloxifene and decreased by 1.7 ± 0.6% in men who did not receive raloxifene ($P = 0.06$) (Fig. 3D). The between-group differences in percent change from baseline to 12 months were 3.7% (95% confidence in-

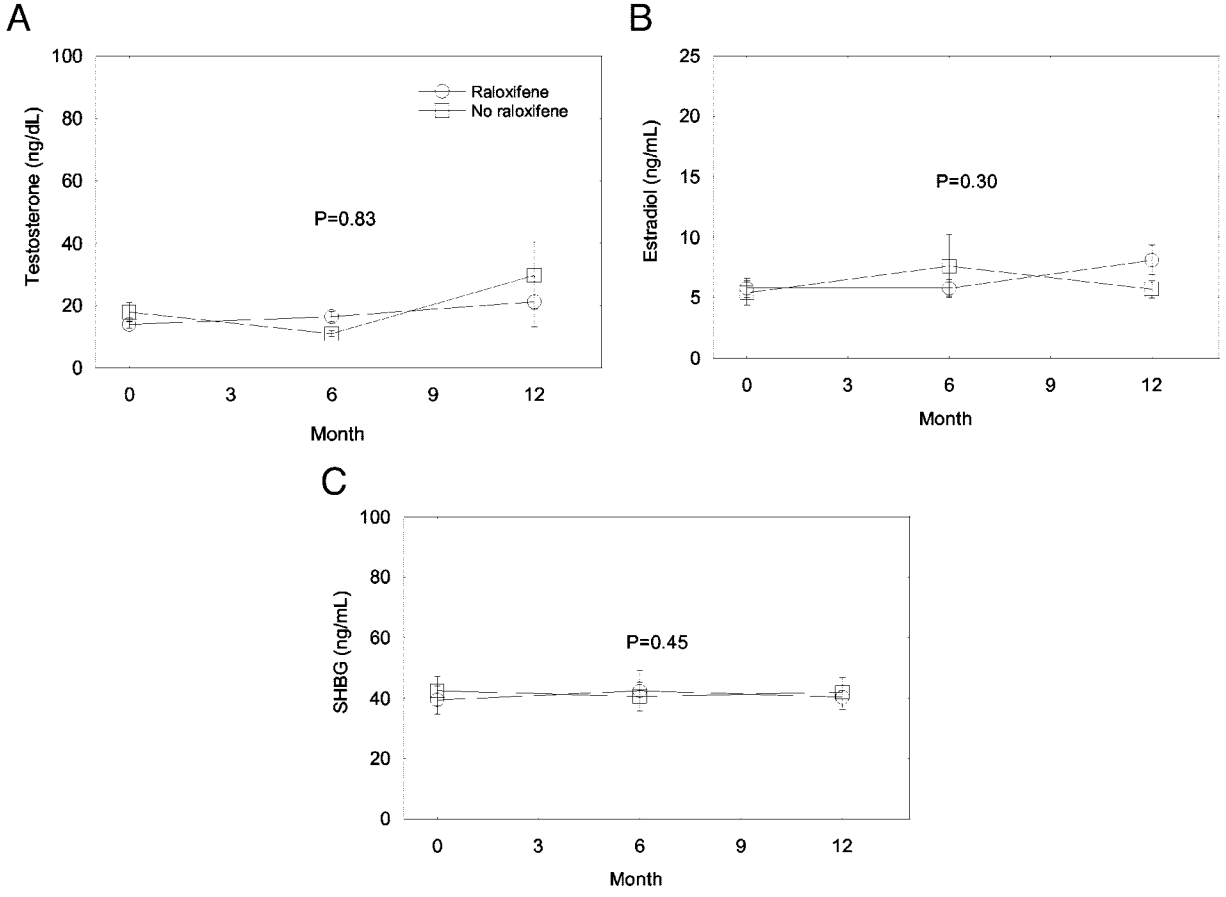

FIG. 2. Changes in mean (±SE) serum concentrations of total testosterone, estradiol, and SHBG. *P* values are for between-group comparisons of the percentage change from baseline to 12 months.

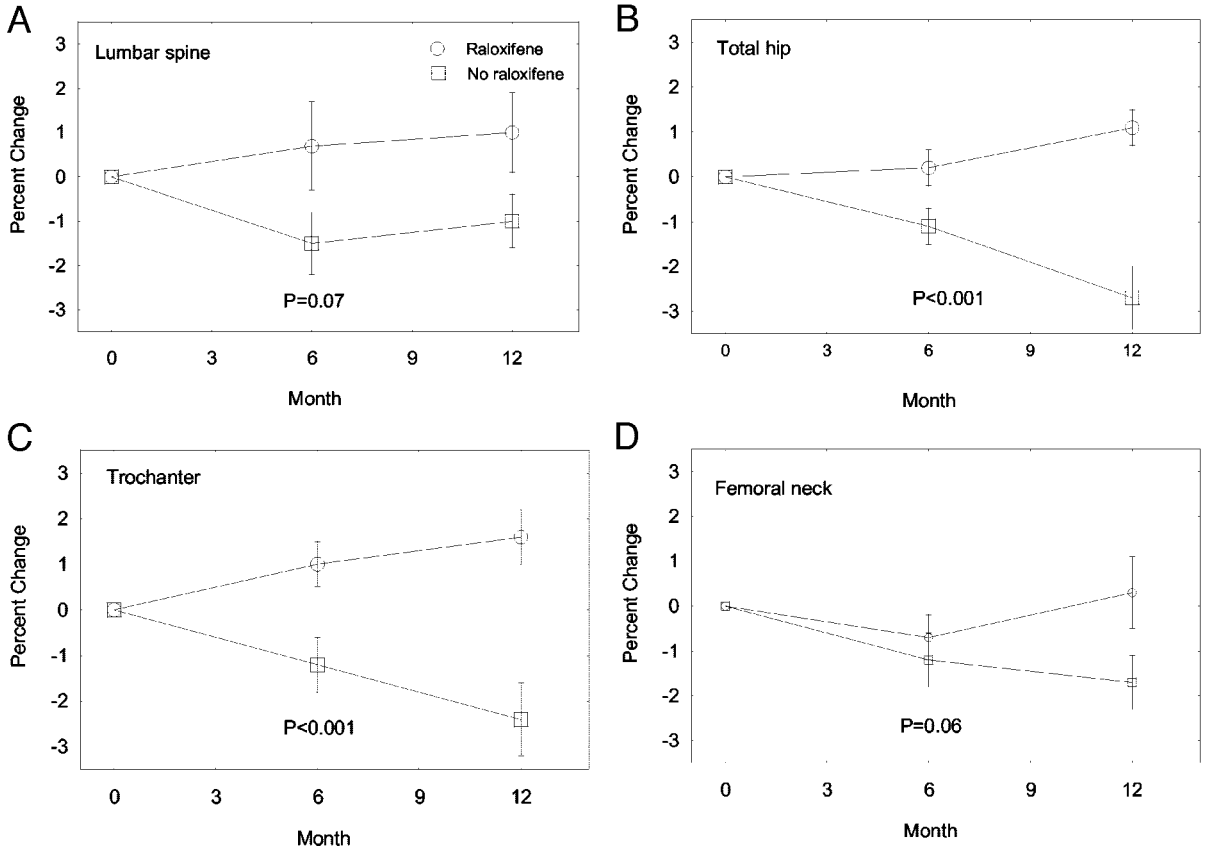

FIG. 3. Mean (±SE) changes from baseline in bone mineral density. *P* values are for between-group comparisons of the percentage change from baseline to 12 months.

terval, 2.0–5.4%) for the total hip, 3.9% (95% confidence interval, 1.9–5.9%) for the trochanter, and 2.0% (95% confidence interval, −0.1–4.0%) for the femoral neck.

In men treated with raloxifene, changes in bone mineral density of posteroanterior lumbar spine and total hip did not correlate with either baseline estradiol levels or baseline free estrogen index (data not shown).

Biochemical markers of bone turnover

Serum concentrations of amino-terminal propeptide of type I collagen and urinary excretion of deoxypyridinoline were elevated at baseline (Table 1). Mean serum concentrations of amino-terminal propeptide of type I collagen decreased by 20.3 ± 9.3% in the men treated with raloxifene and increased by 13.9 ± 11.1% in men who did not receive raloxifene ($P = 0.03$) (Fig. 4A). Urinary excretion of deoxypyridinoline decreased by 6.4 ± 7.8% in the men treated with raloxifene and increased by 10.3 ± 5.4% in men who did not receive raloxifene ($P = 0.10$) (Fig. 4B). The between-group differences in percent change from baseline to 12 months was 34.2% (95% confidence interval, 4.2–64.2%) for amino-terminal propeptide of type I collagen and 16.6% (95% confidence interval, −3.7–37.0%) for urinary excretion of deoxypyridinoline.

In men treated with raloxifene, changes serum concentration of amino-terminal propeptide of type I collagen and urinary excretion of deoxypyridinoline did not correlate with either baseline estradiol levels or baseline free estrogen index (data not shown).

Body composition and serum lipoproteins

Mean changes in body mass index, lean mass, fat mass, and serum lipoproteins did not differ significantly between groups (Table 2).

Adverse events

One man had a pulmonary embolus after 6 months of treatment with raloxifene. Subsequent testing revealed no factors associated with increased thromboembolic risk except for an elevated plasma homocysteine level. There were no other serious treatment-related adverse events.

Discussion

This study demonstrates that raloxifene increases bone mineral density of the hip and tends to increase bone mineral density of the spine in men receiving a GnRH agonist for prostate cancer. To our knowledge, this is the first randomized controlled trial to evaluate the effects of raloxifene on bone mineral density in men. The changes in bone mineral density observed in our subjects are comparable with the increases in bone mineral density in postmenopausal women treated with raloxifene (18). Bone density changes of similar

magnitude reduce vertebral fracture risk in postmenopausal women with osteoporosis (19).

In postmenopausal women, raloxifene decreases markers of both bone formation and bone resorption (18, 21, 22). In our study, raloxifene significantly decreased serum concentration of amino-terminal propeptide of type I collagen, a marker of bone formation. Raloxifene also tended to decrease urinary excretion of deoxypyridinoline, a marker of bone resorption. These preliminary observations suggest that raloxifene increases bone mineral density by similar mechanisms in postmenopausal women and severely hypogonadal men.

Tamoxifen increases bone mineral density in postmenopausal women but decreases bone mineral density in premenopausal women (23, 24). Similarly, the effects of raloxifene on bone mineral density in men may depend on baseline estradiol levels. In our study of severely hypogonadal men (mean serum estradiol, 6 ± 1 pg/ml), raloxifene significantly increased bone mineral density of the hip. In a study of mildly hypogonadal elderly men (mean serum estradiol, 28 ± 2 pg/ml), raloxifene had no significant effect of biochemical markers of bone turnover (25). Changes in bone turnover correlated with baseline estradiol levels, however, suggesting that the efficacy of raloxifene may depend on estradiol levels (25). Baseline estradiol levels did not predict changes in bone mineral density or biochemical markers of bone turnover in our subjects, probably because estradiol levels were uniformly low.

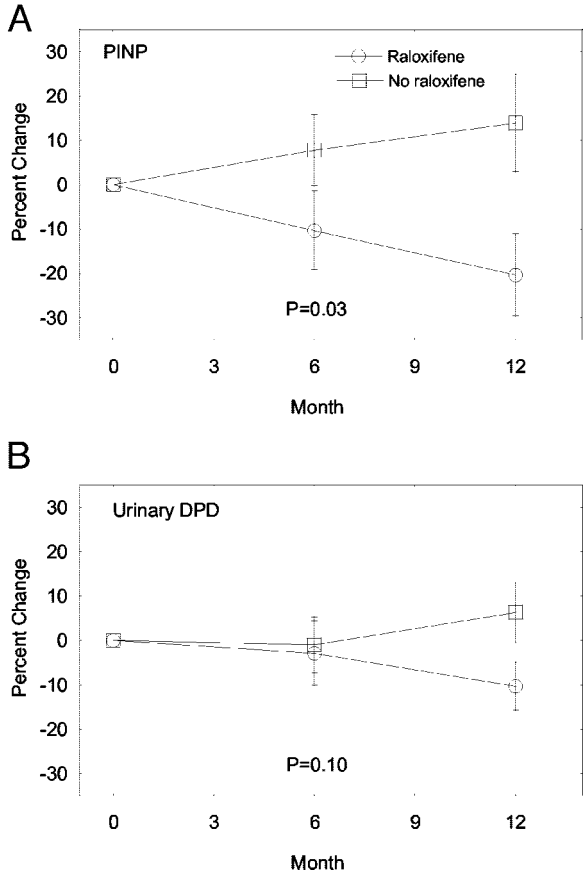

FIG. 4. Mean (±SE) changes from baseline in biochemical markers of bone turnover. *P* values are for between-group comparisons of the percentage change from baseline to 12 months.

Most other studies of men receiving treatment with a GnRH agonist have evaluated the effects of initial therapy. In contrast, the median duration of prior treatment in our subjects was more than 2 yr. Bone mineral density decreased in our control subjects at similar rate to that reported in men receiving initial GnRH agonist treatment (2). In addition, baseline levels of urinary deoxypyridinoline in our subjects were similar to those reported in men during short-term GnRH agonist treatment (2, 26). These observations suggest that long-term treatment with a GnRH agonist is associated with a persistent high bone turnover state and steady decline in bone mineral density.

In postmenopausal women, raloxifene increases the risk for venous thromboembolic events by approximately 3-fold (19). One subject in our study had a pulmonary embolus. In considering raloxifene for the treatment or prevention of osteoporosis in men with prostate cancer, the potential reduction in fracture risk must be weighed against the increased risk for thromboembolic events.

Bisphosphonates also prevent bone loss in men receiving GnRH agonist therapy for prostate cancer. In two randomized controlled trials, intravenous pamidronate prevented bone loss in men treated with a GnRH agonist (2, 27). In another randomized controlled trial, intravenous zoledronic acid increased bone mineral density in men treated with a GnRH agonist or bilateral orchiectomies (28). Additional studies are needed to compare the efficacy and safety of raloxifene with bisphosphonates in hypogonadal men.

In postmenopausal women, raloxifene significantly decreases serum concentrations of total cholesterol and low-density lipoprotein cholesterol (18). In contrast, raloxifene did not significantly change serum total cholesterol and low-density lipoprotein cholesterol concentrations in our severely hypogonadal male subjects. Raloxifene also had no effect on serum concentrations of total lipid profiles in mildly

TABLE 2. Percentage changes in body composition and serum lipoproteins from baseline to 12 months

Outcome	Raloxifene	No raloxifene	Absolute difference between groups (95% confidence interval)	*P* value
Body mass index[a]	0.8 ± 0.8	0.5 ± 0.9	0.2% (−2.2, 2.7)	0.84
Fat mass	0.7 ± 2.1	2.3 ± 2.2	1.6% (−4.7, 7.8)	0.62
Lean mass	0.5 ± 0.7	−0.9 ± 0.6	1.5% (−0.5, 1.3)	0.13
Total cholesterol	−4.8 ± 3.3	−0.9 ± 3.6	3.8% (−6.1, 13.9)	0.44
High-density lipoprotein cholesterol	3.8 ± 2.6	0.2 ± 4.0	4.0% (−5.8, 13.9)	0.41
Low-density lipoprotein cholesterol	−4.8 ± 5.1	3.7 ± 5.5	8.6% (−6.7, 23.9)	0.26
Triglycerides	3.1 ± 8.0	4.7 ± 7.5	1.6% (−20.6, 23.8)	0.88

[a] Calculated as weight in kilograms divided by the square of height in meters.

hypogonadal men (25). Additional studies are needed to determine whether selective estrogen receptor modulators have gender-specific effects on lipoprotein metabolism.

Our study has limitations. Although personnel who performed or analyzed the main outcomes were blinded to treatment assignments to minimize any potential bias, the open-label design may have influenced study outcomes through unintended effects on subject behavior. In addition, the open-label design may have influenced adverse event reporting. The study was designed to compare changes in bone mineral density. Larger studies are required to assess differences in fracture incidence.

In summary, raloxifene significantly increased bone mineral density of the hip and tended to increase bone mineral density of the spine in men receiving a GnRH agonist for prostate cancer. Raloxifene may represent a novel therapy to prevent bone loss in hypogonadal men.

Acknowledgments

We thank the dedicated staffs of Mallinckrodt General Clinical Research Center and Massachusetts General Hospital Bone Density Center.

Received December 4, 2003. Accepted May 7, 2004.

Address all correspondence and requests for reprints to: Dr. Matthew R. Smith, Massachusetts General Hospital, Cox 640, 100 Blossom Street, Boston, Massachusetts 02114. E-mail: smith.matthew@mgh.harvard.edu.

This work was supported by the Prostate Cancer Foundation, by a National Institutes of Health Clinical Associate Physician Award (to M.R.S.), and by grants from the National Institutes of Health (to J.S.F.) (K24 DK02759) and the Mallinckrodt General Clinical Research Center (M01-RR-01066). The study sponsors played no role in the study design, in collection, analysis, and interpretation of data, or in writing of this report.

References

1. **Maillefert JF, Sibilia J, Michel F, Saussine C, Javier RM, Tavernier C** 1999 Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. J Urol 161:1219–1222
2. **Smith MR, McGovern FJ, Zietman AL, Fallon MA, Hayden DL, Schoenfeld DA, Kantoff PW, Finkelstein JS** 2001 Pamidronate to prevent bone loss in men receiving gonadotropin releasing hormone agonist therapy for prostate cancer. N Engl J Med 345:948–955
3. **Eriksson S, Eriksson A, Stege R, Carlstrom K** 1995 Bone mineral density in patients with prostatic cancer treated with orchidectomy and with estrogens. Calcif Tissue Int 57:97–99
4. **Diamond T, Campbell J, Bryant C, Lynch W** 1998 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 83:1561–1566
5. **Daniell HW** 1997 Osteoporosis after orchiectomy for prostate cancer. J Urol 157:439–444
6. **Townsend MF, Sanders WH, Northway RO, Graham Jr SD** 1997 Bone fractures associated with luteinizing hormone-releasing hormone agonists used in the treatment of prostate carcinoma. Cancer 79:545–550
7. **Hatano T, Oishi Y, Furuta A, Iwamuro S, Tashiro K** 2000 Incidence of bone fracture in patients receiving luteinizing hormone-releasing hormone agonists for prostate cancer. BJU Int 86:449–452
8. **Oefelein MG, Ricchuiti V, Conrad W, Seftel A, Bodner D, Goldman H, Resnick M** 2001 Skeletal fracture associated with androgen suppression induced osteoporosis: the clinical incidence and risk factors for patients with prostate cancer. J Urol 166:1724–1728
9. **Need AG, Horowitz M, Stiliano A, Scopacasa F, Morris HA, Chatterton BE** 1996 Vitamin D receptor genotypes are related to bone size and bone density in men. Eur J Clin Invest 26:793–796
10. **Eriksen EF, Colvard DS, Berg NJ, Graham ML, Mann KG, Spelsberg TC, Riggs BL** 1988 Evidence of estrogen receptors in normal human osteoblast-like cells. Science 241:84–86
11. **Oursler MJ, Pederson L, Fitzpatrick L, Riggs BL, Spelsberg T** 1994 Human giant cell tumors of the bone (osteoclastomas) are estrogen target cells. Proc Natl Acad Sci USA 91:5227–5231
12. **Slemenda CW, Longcope C, Zhou L, Hui SL, Peacock M, Johnston CC** 1997 Sex steroids and bone mass in older men. Positive associations with serum estrogens and negative associations with androgens. J Clin Invest 100:1755–1759
13. **Khosla S, Melton 3rd LJ Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL** 1998 Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. J Clin Endocrinol Metab 83:2266–2274
14. **Greendale GA, Edelstein S, Barrett-Connor E** 1997 Endogenous sex steroids and bone mineral density in older women and men: the Rancho Bernardo Study. J Bone Miner Res 12:1833–1843
15. **Falahati-Nini A, Riggs BL, Atkinson EJ, O'Fallon WM, Eastell R, Khosla S** 2000 Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. J Clin Invest 106:1553–1560
16. **Leder BZ, LeBlanc KM, Schoenfeld DA, Eastell R, Finkelstein JS** 2003 Differential effects of androgens and estrogens on bone turnover in normal men. J Clin Endocrinol Metab 88:204–210
17. **Balfour JA, Goa KL** 1998 Raloxifene. Drugs Aging 12:335–341; discussion 342
18. **Delmas PD, Bjarnason NH, Mitlak BH, Ravoux AC, Shah AS, Huster WJ, Draper M, Christiansen C** 1997 Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N Engl J Med 337:1641–1647
19. **Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, Christiansen C, Delmas PD, Zanchetta JR, Stakkestad J, Gluer CC, Krueger K, Cohen FJ, Eckert S, Ensrud KE, Avioli LV, Lips P, Cummings SR** 1999 Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 282:637–645
20. **Rosner B** 1990 Fundamentals of biostatistics. 3rd ed. Boston: PWS-Kent Publishing Company
21. **Draper MW, Flowers DE, Huster WJ, Neild JA, Harper KD, Arnaud C** 1996 A controlled trial of raloxifene (LY139481) HCl: impact on bone turnover and serum lipid profile in healthy postmenopausal women. J Bone Miner Res 11:835–842
22. **Reginster JY, Sarkar S, Zegels B, Henrotin Y, Bruyere O, Agnusdei D, Collette J** 2004 Reduction in PINP, a marker of bone metabolism, with raloxifene treatment and its relationship with vertebral fracture risk. Bone 34:344–351
23. **Love RR, Mazess RB, Barden HS, Epstein S, Newcomb PA, Jordan VC, Carbone PP, DeMets DL** 1992 Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. N Engl J Med 326:852–856
24. **Powles TJ, Hickish T, Kanis JA, Tidy A, Ashley S** 1996 Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. J Clin Oncol 14:78–84
25. **Doran PM, Riggs BL, Atkinson EJ, Khosla S** 2001 Effects of raloxifene, a selective estrogen receptor modulator, on bone turnover markers and serum sex steroid and lipid levels in elderly men. J Bone Miner Res 16:2118–2125
26. **Smith MR, Fallon MA, Goode MJ** 2003 Cross-sectional study of bone turnover during bicalutamide monotherapy for prostate cancer. Urology 61:127–131
27. **Diamond TH, Winters J, Smith A, De Souza P, Kersley JH, Lynch WJ, Bryant C** 2001 The antiosteoporotic efficacy of intravenous pamidronate in men with prostate carcinoma receiving combined androgen blockade: a double blind, randomized, placebo-controlled crossover study. Cancer 92:1444–1450
28. **Smith MR, Eastham J, Gleason D, Shasha D, Tchekmedyian S, Zinner N** 2003 Randomized controlled trial of zoledronic acid to prevent bone loss in men undergoing androgen deprivation therapy for nonmetastatic prostate cancer. J Urol 169:2008–2012

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.