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# Bone Loss in Men with Prostate Cancer Treated with Gonadotropin-Releasing Hormone Agonists*

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**ABSTRACT**

Prostate cancer is the most common visceral malignancy in men. As the tumor is testosterone dependent, a frequent treatment modality involves therapy with GnRH agonists (GnRH-a) resulting in hypogonadism. Because testosterone is essential for the maintenance of bone mass in men, we postulated that GnRH-a therapy would negatively impact skeletal integrity. We compared bone mineral density (BMD), biochemical markers of bone turnover, and body composition in 60 men with prostate cancer (19 men receiving GnRH-a therapy and 41 eugonadal men) and BMD in 197 community-living healthy controls of similar age. BMD was assessed by dual energy x-ray absorptiometry and ultrasound. Biochemical markers of bone turnover, included markers of bone resorption (urinary N-telopeptide) and bone formation markers (bone-specific alkaline phosphatase and osteocalcin). Body composition (total body fat and lean body mass) was assessed by dual energy x-ray absorptiometry.

Significantly lower BMD was found at the lateral spine ($0.69 \pm 0.17$ *vs.* $0.83 \pm 0.20$ g/cm$^2$; $P < 0.01$), total hip ($0.94 \pm 0.14$ *vs.* $1.05 \pm 0.16$ g/cm$^2$; $P < 0.05$), and forearm ($0.67 \pm 0.11$ *vs.* $0.78 \pm 0.07$ g/cm$^2$; $P < 0.01$) in men receiving GnRH-a compared with the eugonadal men with prostate cancer. Significant differences were also seen at the total body, finger, and calcaneus (all $P < 0.01$). BMD values in eugonadal men with prostate cancer and healthy controls were similar. Markers of bone resorption (urinary N-telopeptide) and bone formation (bone-specific alkaline phosphatase) were elevated in men receiving GnRH-a therapy compared with those in eugonadal men with prostate cancer. Men receiving GnRH-a also had a higher percent total body fat ($29 \pm 5\%$ *vs.* $25 \pm 5\%$; $P < 0.01$) and lower percent lean body weight ($71 \pm 5\%$ *vs.* $75 \pm 5\%$; $P < 0.01$) compared with eugonadal men with prostate cancer. In conclusion, men with prostate cancer receiving androgen deprivation therapy have a significant decrease in bone mass and increase in bone turnover, thus placing them at increased risk of fracture. (*J Clin Endocrinol Metab* **86:** 2787–2791, 2001)

PROSTATE CANCER IS the most common visceral malignancy and the second leading cause of death from cancer in men (1). The androgen dependence of prostate cancer (2) has resulted in androgen ablation becoming a cornerstone of treatment for advanced prostate cancer. This is readily achieved through the use of GnRH agonists (GnRH-a) in depot form, which provides a reliable means of medical castration (3) and has become the overwhelming preference of patients (4). Testosterone falls to castrate levels within 2 weeks after initiating therapy (3). This therapy is effective in reducing tumor growth in 80–90% of patients.

Androgens are essential in maintaining skeletal integrity in adult men, and hypogonadism constitutes a major risk factor for male osteoporosis (5). Biochemical evidence of hypogonadism is seen in up to 50% of men with hip fractures (6, 7) and accounts for a 5-fold increase in hip fracture risk compared with that in eugonadal men (6, 8). Androgen deprivation by orchidectomy in men with prostate cancer results in a 7-yr cumulative fracture incidence of 13.6% *vs.* 1.1% in those men without androgen deprivation (9). A recent retrospective analysis of men with prostate cancer treated with GnRH-a revealed 3 times the incidence of hip fractures compared with healthy men in the same age group (10). The impact of GnRH-a therapy on bone mass is also significant. In a cross-sectional study, 13 of 13 men exhibited femoral neck osteopenia after at least 18 months of therapy (11). More recently, it has been shown in an 18-month prospective study that 6 of 12 eligible men receiving GnRH agonist therapy had a statistically significant decrease in femoral neck bone mineral density (BMD) of 6.6% compared with the baseline (12).

Few data are available on bone turnover or the mechanism of bone loss in these patients. In healthy males both markers of bone formation and bone resorption remain stable beyond the third decade of life (13). Furthermore, few data are available on potential changes in body composition after androgen deprivation therapy. However, hypogonadism would be expected to decrease lean body mass and increase total body fat (14, 15). We postulated that men with prostate cancer receiving therapy with GnRH-a would have low bone mass coupled with higher markers of bone turnover and alterations in body composition. To examine this question we compared bone mass, biochemical markers of bone turnover, and body composition in men with prostate cancer with and

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without androgen deprivation therapy. To determine whether eugonadal men with prostate cancer have decreased bone mass, we compared our 41 eugonadal men with controls of similar age (16).

## Subjects and Methods

### *Participants*

Sixty men with prostate cancer over the age of 60 yr were recruited from clinics at the Beth Israel Deaconess Medical Center and Harvard Vanguard Medical Associates in Boston, MA, as well as from newspaper advertisements. All prostate cancer subjects had had prior surgery and/or irradiation and were classified as stage $D_0$ or $D_2$ using the Whitmore-Jewitt staging system (17). Subjects were included in the study if 1) they had never used GnRH-a or other treatment producing hypogonadism; or 2) they had been treated with GnRH-a for a minimum of 6 months. We excluded men who had any disease (hyperparathyroidism, chronic renal disease, malabsorption, *etc.*) or were taking any drugs (bisphosphonates, glucocorticoids, anticonvulsants, *etc.*) that impact bone mineral metabolism. Subjects with cancers other than cutaneous malignancies were also excluded. BMD normative data were obtained from 197 ambulatory, community-dwelling men who responded to a series of newspaper advertisements for a prior study (16). The protocol was reviewed and approved by the institutional review board at the Beth Israel Deaconess Medical Center. All subjects were advised of the nature of the study, and written informed consent was obtained before enrollment.

### *BMD and ultrasound*

BMD of the nondominant hip, posterior-anterior and lateral spine (L1–L4), nondominant forearm, and total body were measured by dual energy x-ray absorptiometry (DEXA), using a QDR-4500A bone densitometer (Hologic, Inc., Bedford, MA) at the General Clinical Research Center, Beth Israel Deaconess Medical Center (Boston, MA). As previously reported, the coefficients of variation of BMD in men at our institution are 0.94%, 0.73%, and 1.65% for posterior-anterior spine, total hip, and femoral neck, respectively (16). Fractured vertebrae were eliminated from spinal analysis as in previous studies (18). Measurements of the radius included ultradistal, mid, and one third distal radius. Measurements of the femur included total hip, femoral neck, and trochanter. BMD of the nondominant middle phalanx of the third finger was obtained using accuDEXA (Schick, New York, NY). For the Sahara Clinical Bone Sonometer (Hologic, Inc.), the broadband ultrasound attenuation and speed of sound results are combined to form the quantitative ultrasound index, which is used to obtain an estimate of heel BMD in grams per $cm^2$. Measurements of the nondominant heel were obtained. If a subject had a previous fracture at any site (hip, forearm, finger, or heel), that site was not included in the analysis.

### *Measurements of body habitus*

Measures of body habitus included height (centimeters), weight (kilograms), and body mass index [weight (kilograms)/height $(meters)^2$]. Height was determined with a Harpenden stadiometer, and weight was measured with an ACME Digital In-Bed Scale. The percent body fat and lean muscle mass were determined using QDR-4500A bone densitometer (Hologic, Inc.) software (19).

### *Markers of bone turnover and gonadal status*

Serum specimens were frozen at −70 C after collection. Osteocalcin, bone-specific alkaline phosphatase (BSAP), PTH, and 25-hyrdoxyvitamin D were measured using methodology previously described (20, 21). Serum total and free testosterone were measured using a commercially available RIA diagnostic kit (Diagnostic Products, Los Angeles, CA). Serum estradiol was measured by RIA based on a technique modified by Endocrine Sciences, Inc., and serum sex hormone-binding globulin was measured using an immunoradiometric assay developed at Endocrine Sciences Esoterix (Esoterix, Inc., Calabasas Hills, CA). Serum LH and FSH concentrations were determined using commercially available Delphia two-site fluoroimmunometric assay kits (E.G.&G. Wallac, Inc., Akron, OH). Second morning urine specimens for N-telopeptide cross-links of type 1 collagen (NTx) and creatinine determinations were immediately frozen at −20 C. Urinary NTx assays were performed using methodology previously described (20, 21).

### *Statistical analysis*

Continuous variables are summarized as the mean ± SD. The Kruskal-Wallis test (the extension of the Wilcoxon rank-sum test to more than two groups, a nonparametric test similar to ANOVA) was used to compare the medians among the three groups of men for continuous demographic and BMD measurements [prostate cancer patients receiving GnRH-a for at least 6 months, prostate cancer patients never taking GnRH-a, and controls collected in a previous study (16) to develop normative data in men]. When this overall test was statistically significant, we performed two *post-hoc* Wilcoxon rank-sum tests 1) comparing the two groups of patients with prostate cancer and 2) comparing patients not taking GnRH-a to controls of similar age. The *P* values reported for these *post-hoc* comparisons were Bonferroni-adjusted for the two tests. For continuous data collected only in men with prostate cancer (*e.g.* biochemical data and markers), a Wilcoxon rank-sum test was used to compare the two groups. Fisher's exact test (and extensions) was used to compare binary variables between groups. Correlations were assessed using the Spearman rank correlation. To assess the possibility that age differences accounted for differences between groups, we used multiple linear regression to assess the group effect adjusted for age. $P < 0.05$ was considered statistically significant.

## Results

### *Subject characteristics*

Demographic characteristics of the 60 men with prostate cancer and the 197 similar-age healthy controls who participated in the study are presented in Table 1. Nineteen men with prostate cancer received hormone ablation therapy with GnRH agonists, and 41 men with prostate cancer did not. Controls were significantly younger than the cancer patients, but the difference between the 2 groups of patients was not significantly different. There were no significant differences in weight, height, or body mass index among the three groups. The mean duration of GnRH-a use was 41 months (range, 6–108). The percent total body fat was significantly higher in subjects receiving GnRH-a therapy (29 ± 5% *vs.* 25 ± 5%), whereas percent lean body mass was significantly lower (71 ± 5% *vs.* 75 ± 5%) in these subjects (Table 1). As expected, hormonal levels (free and total testosterone, LH, and FSH) were significantly lower in patients receiving GnRH-a therapy. Furthermore, serum estradiol was also significantly lower in patients receiving GnRH-a therapy, whereas sex hormone-binding globulin was not.

### *BMD and ultrasound data*

The BMDs of the lateral spine, total hip, distal one third radius, midradius, ultradistal radius, and total body were significantly lower in the subjects treated with GnRH-a compared with eugonadal men with prostate cancer (all $P < 0.05$; most $P < 0.01$; Table 2). Heel ultrasound and finger accuDEXA were also significantly lower in the hypogonadal men ($P < 0.01$; Table 2). The average BMD in the hypogonadal men ranged from 6.5–17.3% lower than that in the eugonadal men depending on site. Prostate cancer without GnRH-a treatment was not associated with excess bone loss (Table 2). No statistically significant differences between the 41 men with prostate cancer not treated with GnRH-a therapy and

**TABLE 1.** Clinical characteristics of men with prostate cancer and controls

| Characteristics | Controls | Without GnRH-a | With GnRH-a |
|---|---|---|---|
| No. | 197 | 41 | 19 |
| Age (yr) | 66 ± 10 | 70 ± 9[a] | 72 ± 6 |
| Wt (kg) | 83.7 ± 15.2 | 81.6 ± 12.2 | 84.4 ± 14.7 |
| Ht (cm) | 173.0 ± 7.2 | 175.0 ± 7.0 | 173.4 ± 7.5 |
| Body mass index (kg/m$^2$) | 27.9 ± 4.4 | 26.6 ± 3.3 | 28.0 ± 3.9 |
| % Total fat | NA | 25 ± 5 | 29 ± 5[b] |
| % Total lean BW | NA | 75 ± 5 | 71 ± 5[b] |
| Total testosterone (ng/dL) | NA | 393 ± 112 | 16 ± 9[b] |
| Free testosterone (pg/mL) | NA | 10.20 ± 3.02 | 0.67 ± 0.33[b] |
| Estradiol (ng/dL) | NA | 2.63 ± 0.97 | 0.62 ± 0.19[c] |
| SHBG (nmol/L) | NA | 87.55 ± 99.86 | 88.53 ± 111.22 |
| FSH (U/L) | NA | 9.19 ± 8.69 | 2.89 ± 1.90[b] |
| LH (U/L) | NA | 5.44 ± 3.33 | 1.38 ± 2.53[d] |

NA, Not assessed.
[a] $P < 0.05$, without GnRH-a *vs.* controls.
[b] $P < 0.01$, with GnRH-a *vs.* without GnRH-a.
[c] $P < 0.001$, with GnRH-a *vs.* without GnRH-a.
[d] $P < 0.05$, with GnRH-a *vs.* without GnRH-a.

**TABLE 2.** Bone mineral density in men with prostate cancer compared to healthy controls

| BMD (g/cm$^2$) | Controls | Without GnRH-a | With GnRH-a | % Decrease with GnRH-a |
|---|---|---|---|---|
| PA spine | 1.11 ± 0.19 | 1.12 ± 0.21 | 1.04 ± 0.21 | 6.5 |
| Lateral spine | 0.81 ± 0.15 | 0.83 ± 0.20 | 0.69 ± 0.17[a] | 17.0 |
| Total hip | 1.01 ± 0.13 | 1.05 ± 0.16 | 0.94 ± 0.14[b] | 10.3 |
| Femoral neck | 0.81 ± 0.12 | 0.82 ± 0.15 | 0.75 ± 0.12 | 8.3 |
| Trochanter | 0.79 ± 0.12 | 0.82 ± 0.15 | 0.73 ± 0.14 | 10.9 |
| Distal 1/3 radius | 0.77 ± 0.07 | 0.78 ± 0.07 | 0.67 ± 0.11[a] | 14.1 |
| Midradius | 0.65 ± 0.07 | 0.66 ± 0.07 | 0.55 ± 0.11[c] | 17.3 |
| Ultra distal radius | 0.48 ± 0.07 | 0.49 ± 0.07 | 0.41 ± 0.09[b] | 15.8 |
| Total body | NA | 1.27 ± 0.14 | 1.13 ± 0.13[c] | 10.7 |
| Finger | 0.59 ± 0.07 | 0.61 ± 0.07 | 0.52 ± 0.09[a] | 14.3 |
| Heel ultrasound | 0.56 ± 0.14 | 0.59 ± 0.17 | 0.51 ± 0.27[a] | 13.4 |

NA, Not assessed.
[a] $P < 0.01$, with GnRH-a *vs.* without GnRH-a.
[b] $P < 0.05$, with GnRH-a *vs.* without GnRH-a.
[c] $P < 0.001$, with GnRH-a *vs.* without GnRH-a.

the 197 healthy volunteers were noted in the BMD and ultrasound values (Table 2).

The duration of GnRH agonist therapy was associated with reduction in BMD. Spearman correlations between duration of use of GnRH-a and BMD were negative for all sites, ranging from −0.11 (lumbar spine) to −0.68 (radius one third distal and radius ultradistal). Correlations were significant for all three radius measurements and finger BMD (all $P <$ 0.01) as well as whole body ($P < 0.05$)

Adjustment for age using multiple linear regression did not substantially affect the results. The difference in heel ultrasound between the two groups of patients was no longer statistically significant. In addition, correlations of duration of GnRH-a use were no longer significant for the finger BMD or the whole body BMD when adjusted for age.

*Biochemical markers of bone and mineral metabolism and general laboratory data*

PTH, 25-hydroxyvitamin D, and calcium levels did not differ between those men who were treated with hormonal ablation and those who were not (Table 3). Urinary NTx, a marker of bone resorption, was significantly higher in the men receiving GnRH-a therapy as was serum BSAP, a marker of bone formation (both $P < 0.01$). There was no significant difference in osteocalcin, another marker of bone formation. No correlation was seen between markers of bone turnover and duration of GnRH-a treatment. Hemoglobin and hematocrit levels were also significantly lower in hypogonadal men compared with eugonadal men with prostate cancer (Table 3).

**TABLE 3.** Biochemical data and markers of bone turnover in prostate cancer patients treated with GnRH-a therapy

| Parameter | Without GnRH-a | With GnRH-a |
|---|---|---|
| Hemoglobin (g/dL) | 13.84 ± 1.05 | 12.45 ± 1.07[a] |
| Hematocrit (%) | 42.04 ± 2.99 | 37.72 ± 3.16[a] |
| PSA (μg/L) | 4.33 ± 7.70 | 3.78 ± 5.97 |
| Serum calcium (mg/dL) | 9.16 ± 0.39 | 9.10 ± 0.31 |
| Serum albumin (g/dL) | 4.34 ± 0.30 | 4.25 ± 0.14 |
| 25OHD (ng/mL) | 20.22 ± 6.97 | 22.91 ± 5.81 |
| Intact PTH (pg/mL) | 41.76 ± 18.60 | 33.73 ± 13.14 |
| Markers of bone turnover | | |
| Urinary NTX (nmol/L BCE·mmol/L creatinine) | 35.97 ± 19.95 | 78.21 ± 47.95[a] |
| BSAP (U/L) | 21.99 ± 6.53 | 36.43 ± 28.69[b] |
| Osteocalcin (ng/mL) | 8.83 ± 4.57 | 10.86 ± 5.81 |

[a] $P < 0.001$, with GnRH-a *vs.* without GnRH-a.
[b] $P < 0.01$, with GnRH-a *vs.* without GnRH-a.

## Discussion

Our results suggest that men with prostate cancer who undergo hormonal ablation with GnRH agonist therapy have significantly lower BMD at almost all skeletal sites assessed by various techniques, including the use of newer peripheral testing modalities such as finger accuDEXA and calcaneal ultrasound. Overall, we found a decrease in bone mass that ranged from 6.5–17.3% according to the site chosen for evaluation. Coupled with low bone mass, these men also exhibit high bone turnover with increased markers of bone formation and resorption. Although low testosterone levels may be responsible for the above differences between the two groups (with and without GnRH-a), it is also possible that low estradiol levels may play a pivotal role in regulating bone resorption. Recent data from estrogen receptor-negative and aromatase-deficient men suggest that estrogen plays an important role in the acquisition of peak bone mass (22, 23). Furthermore, estrogen, not testosterone, has been shown to prevent an increase in bone resorption in men with pharmacological suppression of both testosterone and estrogen using a combination of GnRH-a therapy and an aromatase inhibitor (24). We also observed a significantly higher percentage of total body fat and lower hemoglobin in our hypogonadal men compared with the eugonadal men with prostate cancer. These latter findings are consistent with testosterone withdrawal in hypogonadal men (15, 25). In contrast, men with prostate cancer not receiving GnRH-a therapy do not differ from similar-age controls with respect to bone mass evaluation.

Because the rate of loss of cortical bone mass is 0.5–1%/yr in healthy men (26, 27), our results suggest that GnRH-a therapy is associated with more than a decade increase in aging of the male skeleton. This is clinically relevant, because BMD is tightly associated with fracture risk in men, and the wrist is a strong predictor of osteoporotic fractures in men (odds ratio, 1.5; 95% confidence interval, 1.1–2.0) (28). In our study bone mass at the distal radius was 14% lower in men receiving hormonal ablation than in those who were not. These findings would support the 5% incidence of osteoporotic fractures reported in men with prostate cancer treated with GnRH-a (10).

Bone resorption and formation markers remain remarkably stable in healthy men beyond the third decade of life (13, 29). Hypogonadism, by contrast, increases bone resorption, resulting in higher urinary NTx levels. Our study is in agreement with that of Fairney (30), who reported that urinary NTx was higher (77.5 *vs.* 33.9 bone collagen equivalents/mm creatinine) in men with prostate cancer receiving GnRH agonist therapy than in controls. Other studies in men with acquired hypogonadism have reported higher levels of BSAP compared with normal men (15), which we also observed in our subjects. Because higher rates of bone turnover are associated with greater fracture rates in elderly women (31, 32), the finding of a higher rate of bone resorption and formation in these patients may help explain a potential mechanism for the greater fracture rate in men previously described (6, 8)

We compared the bone mass measurements in the eugonadal prostate cancer subjects to those in 197 healthy men to determine whether prostate cancer by itself was associated with low BMD. We found no significant differences in either BMD or heel ultrasound measurements. This suggests that prostate cancer by itself is not an intrinsic risk factor for bone loss, but, rather, that treatment for prostate cancer resulting in hypogonadism puts the patient at increased risk for osteoporosis. We did not evaluate markers of bone turnover in our healthy volunteers. Although it is likely that the markers would not be significantly different from those in the eugonadal patients, this would have further demonstrated that early stage prostate cancer has minimal impact on the skeleton.

Although the greatest degree of bone loss may occur with the initiation of hormone reduction therapy, both the elevated urinary NTx and serum BSAP levels suggest ongoing bone turnover in men who have already received therapy for at least 6 months. Furthermore, we were able to demonstrate a significant correlation between the duration of GnRH-a therapy usage and the reduction in BMD at the one third distal radius and total body. As both of these sites are rich in cortical bone (~80%), this may reflect ongoing cortical bone loss associated with prolonged hypogonadism. This would be consistent with the bone mass findings observed in long-standing hypogonadism seen with hyperprolactinemia, which is associated with a significant reduction in both trabecular and cortical bone density (33, 34). The marked reduction in spinal bone density, rich in trabecular bone and also found in men with acquired hypogonadism (15), was evident in our subjects, who had significantly lower lateral spine BMD than the eugonadal men.

An alternative mechanism for bone loss in androgen-deficient men could be a decrease in body weight associated with a decrease in BMD. Diet- and exercise-induced weight loss is associated with a 2-fold greater rate of loss in hip BMD (35). Women who lose the greatest amount of weight also tend to lose the most bone mass and have the greatest increase in urinary NTx (35). Weight loss of greater than 10% in men is also a risk factor for hip fracture (relative risk, 2.27; 95% confidence interval, 1.13–4.59) (36). However, our results show no difference in body weight or body mass index in those men treated by androgen deprivation, but, rather, an alteration in body composition. Testosterone withdrawal is associated with an increase in total body fat and loss of lean body mass (15, 25); this is consistent with our findings. Our results suggest that the loss of lean body mass or the increase in total body fat is associated with bone loss, rather than loss of total body weight.

The strengths of this study include the use of state of the art bone densitometry technology (DEXA) as well as the use of novel ultrasound technology and the performance of all bone mass measurements by the same technician for BMD comparisons. In addition, we recruited our own group of controls. Furthermore, we simultaneously examined markers of bone turnover and total body composition in the prostate cancer subjects. Limitations of the study include the lack of longitudinal data for individual subjects to ascertain heterogeneity in bone loss or change in markers or total body composition on an individual basis. A potential confounding factor includes the possibility that metastatic prostate cancer itself could alter biochemical markers of bone turnover. Further studies are needed to examine how changes in markers

may be able to target subjects with the greatest propensity to lose bone or alter body composition.

This study highlights the impact of hormone ablation therapy on skeletal health as evidenced by both a marked decrease in bone mass coupled with a significant rise in markers of bone turnover. These data support the observation that androgen deprivation for the treatment of prostate cancer is associated with low bone density and/or fractures. Because these patients are easily identifiable, an early assessment of bone mass and bone turnover may help with their long-term clinical management to ensure maintenance of skeletal integrity during androgen ablation for prostate cancer. Furthermore, we believe that future studies will be conducted to determine the efficacy of antiresorptive agents that ameliorate bone loss in this at-risk male population.

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