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Bone Loss following Hypogonadism in Men with Prostate Cancer Treated with GnRH Analogs

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It is known that bone mineral density (BMD) is low in men who are hypogonadal. However, the rate and sites of bone loss following testosterone deficiency are not known. The resulting hypogonadism after GnRH analog therapy for the treatment of prostate cancer allows us to examine bone loss and bone resorption immediately after testosterone withdrawal. Therefore, we examined the effects of GnRH analog treatment on bone loss and bone resorption in men with prostate cancer. BMD and serum and urine concentrations of markers of bone turnover were determined in men with prostate cancer and in age-matched controls. Measurements were taken before GnRH therapy and 6 and 12 months after instituting therapy. After 12 months of GnRH therapy, the BMD of the total hip and ultra distal radius decreased significantly ($P < 0.001$) in men with prostate cancer compared with the controls. The mean bone loss was 3.3% and 5.3%, respectively. The observed reduction in BMD in the spine (2.8%) and the femoral neck (2.3%) did not reach statistical significance. No significant bone loss was observed in the control subjects. The concentration of the urine marker of bone resorption, N-telopeptide, was significantly increased from baseline and from controls at both 6 and 12 months in patients treated with GnRH analog therapy compared with control subjects ($P < 0.05$). The concentration of a serum marker of bone formation, bone-specific alkaline phosphatase, was not significantly different from baseline or from controls at 6 and 12 months. Thus, the decreased total hip and ultra distal radius BMD and increased urinary N-telopeptide concentration after testosterone withdrawal demonstrate an increase in trabecular bone loss and enhanced bone resorption. These findings demonstrate a significant loss of bone in men with prostate cancer after receiving GnRH therapy and suggest that the total hip and radius are the preferred sites for monitoring bone loss in older men. In addition, markers of bone resorption may be helpful. (*J Clin Endocrinol Metab* 87: 3656–3661, 2002)

OSTEOPOROSIS IS NO longer recognized as a problem confined only to women. Although bone loss averages 2% per year immediately after estrogen deficiency in women, it can vary from less than 1% to more than 5% per year (1). In the early postmenopausal years, the rate of bone loss in the spine is greater than in the hip (2, 3) and the forearm (4). It is known that men who are hypogonadal have lower bone density than age-matched controls (5), but the rate and sites of bone loss after testosterone withdrawal are not known.

Androgen deprivation therapy (ADT) using GnRH analogs is the standard of care for the treatment of advanced prostate cancer. GnRH analogs result in hypogonadism that can lead to increased rates of bone resorption, bone loss, and osteoporosis. There are many cross-sectional case-control and cohort studies documenting low bone mineral density (BMD) in men with prostate cancer (6–13). We prospectively examined the effects of GnRH analogs on the rate and sites of bone loss and bone turnover in men with prostate cancer after testosterone withdrawal and compared the findings to age- and sex-matched controls.

Subjects and Methods

Subjects

Fifteen patients with prostate cancer (age, 75 ± 8 yr) who were scheduled to receive Zoladex, a GnRH analog, as a sc pellet every 3 months were enrolled. All men with prostate cancer had a prostatic biopsy and tissue diagnosis of adenocarcinoma. The stage of their prostate cancer included pT3aN0MX (n = 1), pT3bN0MX (n = 1), cT1cN0MX (n = 6), cT2bN0MX (n = 3), cT3aN0MX (n = 2), and cT3bN0MX (n = 2), where p represents pathological diagnosis; c, clinical diagnosis; T, primary tumor; N, nodes; M, metastasis; 1c, tumor identified by needle biopsy; 2b, tumor involves more than half of a lobe; 3a, unilateral extracapsular extension; and 3b, bilateral capsular invasion. Two men with prostate cancer underwent radical prostatectomies. None of the men with prostate cancer received prior chemotherapy. Bone scans were negative for bone metastasis. Thirteen aged-matched control subjects (age, 70 ± 8 yr) with normal serum concentrations of prostate specific antigen (PSA) were enrolled from the Veterans Affairs Medical Center endocrine clinic and urology clinic. None of the subjects had a disease or treatment that affected bone metabolism. Subjects were excluded if they had a history of abnormal thyroid function, abnormal liver function tests, glucocorticoid use, renal insufficiency, hypogonadism, hyperprolactinemia, hyperparathyroidism, major vascular medical event within 6 months of screening, alcohol consumption greater than four drinks per day, or illicit drug use.

All subjects who were studied signed Institutional Review Board-approved informed consent documents. Each subject received a history and physical. Blood samples were obtained in a nonfasting state, and 24-h urine samples were collected on ice. BMDs were measured, blood was obtained from the men with prostate cancer before receiving their first dose of GnRH analog, and urine was obtained within 1 wk. Flutamide, an antiandrogen, was also administered with GnRH analog therapy for 2 wk.

Bone mineral densitometry

BMDs were determined at baseline, 6, and 12 months. Dual energy x-ray absorptiometry (DEXA) was performed on Hologic DPX 2000 (Hologic, Inc., Bedford, MA) located at the General Clinical Research Center at the University of Texas Health Science Center (San Antonio,

Abbreviations: ADT, Androgen deprivation therapy; BMD, bone mineral density; CV, coefficient(s) of variation; DEXA, dual energy x-ray absorptiometry; PSA, prostate specific antigen.

TX). The L1-L4 lumbar spine, total hip, femoral neck, and radius (ultra distal, mid, one third, and total) were measured. The nondominant hip and forearm were measured. All measurements were obtained and analyzed using standard protocols provided by the manufacturer. The short-term *in vivo* precision of the BMD was determined on 27 subjects performed in duplicate on the same day. The precision of the lumbar spine was 0.009 g/cm^2 [coefficient of variation (CV)% = 1.0%]. The precision of the total hip was 0.007 g/cm^2 (CV% = 0.87%). The precision of the manufacturer's spine phantom was 0.0017 g/cm^2 (CV% = 0.17%).

Biochemical measurements

Markers of bone turnover were determined at baseline, 6, and 12 months. Urinary N-telopeptide concentrations were assayed from a 24-h urine collection using an enzyme-linked immunoabsorbent assay (Ostex, Seattle, WA). Serum bone-specific alkaline phosphatase and serum osteocalcin concentrations were measured by RIA (Metra Biosystem, Mountain View, CA).

Statistical methods

Baseline characteristics of the men with prostate cancer and control group and differences in the percentage change over time between the men with prostate cancer and control group and within each group were compared using the mixed linear model with repeated measures All analyses were computed with Statistical Analysis Systems. The power analysis and sample size were calculated by PASS 2000 (NCSS Statistical Software, Kaysville, UT) and were performed on the basis of empirical data of BMD, the primary objective. We calculated the number needed to treat on the basis of the rate of bone loss documented in postmenopausal women with estrogen deficiency (2–5%) and the bone loss seen in young hypogonadal men (5%), along with the mean BMD in men between the ages of 60 and 80 yr based on the National Health and Nutrition Examination Study (NHANES) and Hologic data. We expected approximately 5% of BMD loss per year; a 3% loss of BMD is considered to be clinically significant. A conservative estimate of noncentrality parameter (magnitude of mean differences) was used to calculate power and sample size. The power analysis for the design was based on the 2 (treatment) $\times$ 3 (assessment time) split-plot factorial design with a significant level of $\alpha = 0.05$ and 80% power. A sample size of 10 in each treatment was determined to be sufficient to detect 5% difference of BMD loss for treatment and assessment time interaction. We did not estimate power and sample size on markers of bone turnover *a priori* but did *post hoc* calculation as suggested by the reviewer with the data available today. A sample size of 15, 12, and 8 in each group is sufficient to detect a significant difference in the percentage changes over time between groups with 80% of power and a significant level of 0.05 for osteocalcin, bone-specific alkaline phosphatase, and urinary N-telopeptide, respectively.

Results

Table 1 gives the clinical characteristics of the men recruited. Men with prostate cancer had a significantly lower baseline BMD in the total hip than controls. According to the World Health Organization classification criteria (BMD of 2.5 SD or more below young adult peak bone mass or T-score), none of the subjects fulfilled the criteria for osteoporosis. The criterion of osteopenia (BMD between 1 and 2.5 SD below young adult peak bone mass or T-score) was fulfilled by 20% (n = 3) in the men with prostate cancer and 23% (n = 3) in the controls. Except for the PSA levels and total hip BMD, there were no significant differences in other baseline characteristics in the men with prostate cancer compared with the control subjects. The age, serum osteocalcin, and testosterone concentrations were higher in the men with prostate cancer than the controls, but the differences were not statistically significant.

Subjects

All men treated with GnRH analogs became hypogonadal as defined by undetectable testosterone concentrations. The mean $\pm$ SD serum testosterone concentration decreased in the men with prostate cancer from 467 $\pm$ 276 mg/dl at baseline to 28 $\pm$ 20 mg/dl at 12 months. The testosterone concentrations in the control subjects were unchanged (409 $\pm$ 189 mg/dl at baseline *vs.* 412 $\pm$ 183 mg/dl at 12 months). The concentration of PSA 12 months after GnRH administration was less than one in all but four patients.

Rate and site of bone loss

The total hip (Fig. 1C) and ultra distal radius (Fig. 2C) BMD at 12 months decreased significantly ($P < 0.001$) in the men with prostate cancer receiving GnRH analog therapy compared with the controls. The mean bone loss was 3.3% and

TABLE 1. Baseline characteristics of patients with prostate cancer and control subjects

Baseline characteristics	Controls (n = 13)	Patients (n = 15)	*P* value	Factor for SI conversion
Age (yr)	70 $\pm$ 8	75 $\pm$ 8	0.10	
Weight (kg)	87 $\pm$ 17	82 $\pm$ 14	0.37	
Height (cm)	172 $\pm$ 5	172 $\pm$ 7	0.82	
S calcium (mg/dl)	9.04 $\pm$ 0.22	8.99 $\pm$ 0.48	0.96	0.25 (mmol/liter)
S PTH (pg/ml)	43 $\pm$ 15	36 $\pm$ 22	0.71	0.95 (pmol/liter)
S 25 (OH) vit D (ng/ml)	25 $\pm$ 10	24 $\pm$ 10	0.99	2.496 (nmol/liter)
S osteocalcin (ng/ml)	6.35 $\pm$ 2.72	12.1 $\pm$ 21.01	0.40	1 (μg/liter)
S bone ALP (ng/ml)	15.42 $\pm$ 4	13.21 $\pm$ 3.5	0.17	
Estradiol (pg/ml)	29.8 $\pm$ 16.8	35.7 $\pm$ 17.6	0.49	3.671 (pmol/liter)
S testosterone (ng/dl)	409 $\pm$ 189	467 $\pm$ 276	0.78	0.0347 (nmol/liter)
U N-telopeptide (nmol BCE/mmol Cr)	35 $\pm$ 29	30 $\pm$ 15	0.89	
PSA (ng/ml)	1.7 $\pm$ 2.4	42.3 $\pm$ 44.9	0.004	1 (μg/liter)
Lumbar spine BMD (g/cm^2)	1.10 $\pm$ 0.19	1.06 $\pm$ 0.11	0.59	
Femoral neck BMD (g/cm^2)	0.87 $\pm$ 0.20	0.74 $\pm$ 0.13	0.06	
Total hip BMD (g/cm^2)	1.12 $\pm$ 0.16	0.99 $\pm$ 0.11	0.03	
Radius ultra distal BMD (g/cm^2)	0.53 $\pm$ 0.05	0.49 $\pm$ 0.05	0.10	
Radius 1/3 BMD (g/cm^2)	0.79 $\pm$ 0.06	0.79 $\pm$ 0.04	0.89	
Radius mid BMD (g/cm^2)	0.68 $\pm$ 0.06	0.67 $\pm$ 0.05	0.52	

S, Serum; U, urine; PTH, intact parathyroid hormone; vit D, vitamin D; ALP, alkaline phosphatase; BCE, bone collagen equivalents; Cr, creatinine.

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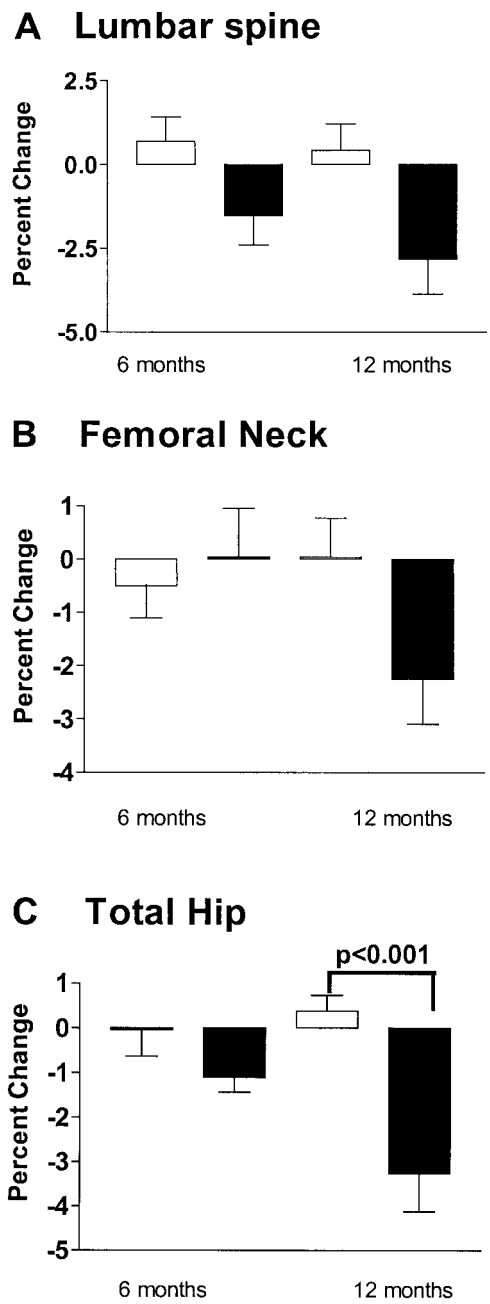

FIG. 1. Central BMD. Percentage change ± SE BMD from baseline of AP lumbar spine (A), femoral neck (B), and total hip (C) in normal controls (white bars) and patients with prostate cancer 6 and 12 months after beginning GnRH analog therapy (*black bars*).

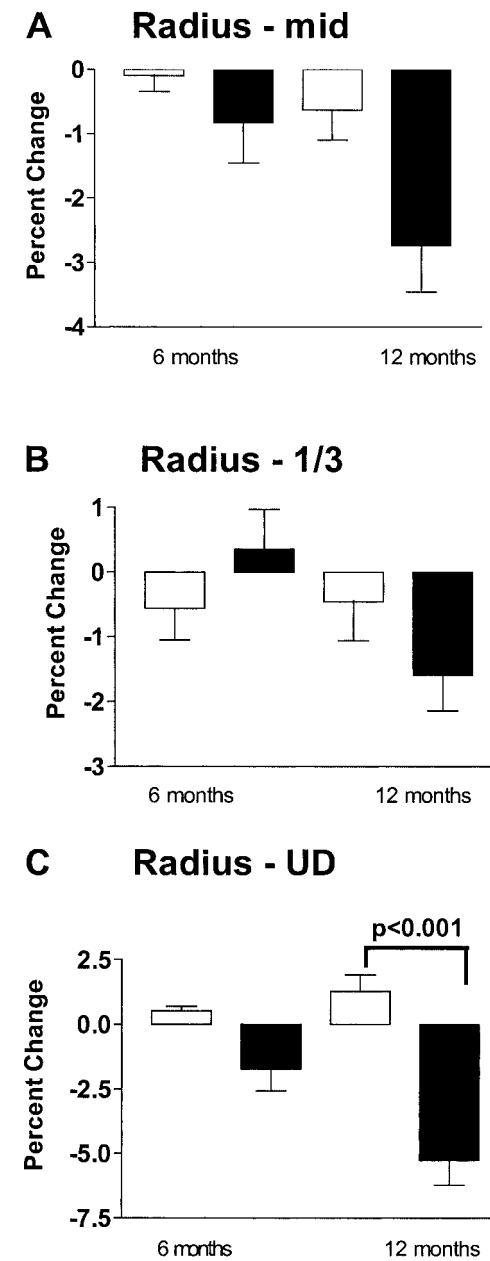

FIG. 2. Peripheral BMD. Percentage change ± SE BMD from baseline of mid radius (A), distal one third radius (B), and ultra distal (UD) radius (C) in normal controls (*white bars*) and patients with prostate cancer 6 and 12 months after beginning GnRH analog therapy (*black bars*).

5.3%, respectively. The decrease in BMD in the spine (2.8%), femoral neck (2.3%), mid radius (2.7%), and one third radius (1.6%) was not statistically significant (Figs. 1, A and B, and 2, A and B). There was also a significant decrease in the BMD of the total radius from baseline to 12 months (data not shown). No significant bone loss was observed in the control subjects. This suggests that bone loss is evident at 12 months after androgen deprivation and occurs in all sites. BMD measurements of the total hip and ultra distal radius sites are the most sensitive in demonstrating the loss.

Markers of bone turnover

The concentration of the urine marker of bone resorption, N-telopeptide (Fig. 3A), was significantly increased from baseline at both 6 and 12 months in the men with prostate cancer treated with GnRH analog ($P < 0.05$). The concentration of a serum marker of bone formation, bone-specific alkaline phosphatase, did not show a significant change at 6 or 12 months in both men with prostate cancer and control subjects. The concentration of another serum marker of bone formation, osteocalcin, also did not change, but the sample

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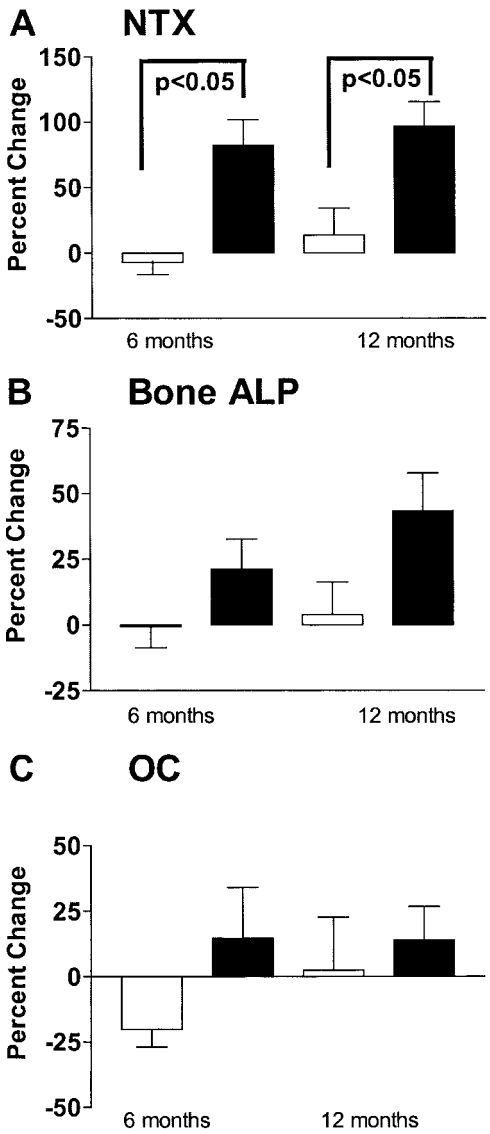

FIG. 3. Markers of bone turnover. Percentage change ± SE from baseline of urine N-telopeptide (*NTX*) levels (A), serum bone-specific alkaline phosphatase (*Bone ALP*) levels (B), and osteocalcin (*OC*; C) in normal controls (*white bars*) and patients with prostate cancer 6 and 12 months after beginning GnRH analog therapy (*black bars*).

size was not large enough. This suggests that markers of bone resorption may be useful in this setting.

Discussion

The results reported here demonstrate three major findings. First, significant bone loss occurs in the year immediately after androgen withdrawal in men with prostate cancer. Second, the total hip and ultra distal radius are the skeletal sites most affected. Third, the marker of bone resorption, N-telopeptide, increases after androgen withdrawal.

It is well appreciated that the diminution of BMD immediately after the menopause is most pronounced in the sites of the skeleton composed of trabecular or cancellous bone. Bone loss immediately following estrogen deficiency after menopause predominately occurs in the spine, which is composed of 66% trabecular bone and 34% cortical bone. The rate of loss is reported to be between 1.46 and 1.82% per year (2, 3, 14) but can be as high as 5%. The rate of early postmenopausal changes of bone loss as measured in the femoral neck, composed of 25% trabecular and 75% cortical, is less than the spine (2, 3). In addition, the bone loss seen in the spine is greater than the loss seen in the forearm (4). Therefore, the spine is the acceptable site in measuring the rate of bone loss in postmenopausal women and the site for determining response to therapy. There also exists a strong relationship between bone density and fracture risk in women. The strongest predictor of fracture risk in women is the BMD of the total hip (15). In addition, the concentrations of the markers of turnover, including both the markers of resorption such as collagen cross-links (N-telopeptide and C-telopeptide) and markers of bone formation such as osteocalcin and bone-specific alkaline phosphatase, increase significantly following estrogen deficiency after surgical menopause (16). These markers are increased 6 months after GnRH analog therapy in women with endometriosis (17). The increase can be seen as early as 3 months after estrogen deficiency (16).

In contrast to the extensive studies in women, it is not clear how BMD defines osteoporosis in men or how well it predicts fractures. Aging men tend to loose cancellous bone at a rate of 12% per decade and cortical bone at a rate of 0.5–1% per year (18). In contrast to women, bone density of the forearm is the strongest predictor of fractures in men (15). Because men do not experience a menopausal equivalence of testosterone deficiency, it is not clear whether the bone loss seen immediately after testosterone withdrawal mimics what is seen with estrogen deficiency. It is well recognized that osteoarthritis involving the spine or aortic calcifications may overestimate BMD as measured by DEXA. This may mask age-related bone loss, especially in men who have a higher incidence of osteoarthritis in the spine and aortic calcifications. Not surprisingly, the use of the spine as a site for determining osteoporosis in men has been in question, although measuring the spine density by computerized tomography or lateral spine by DEXA may overcome this obstacle. As in this study, the BMD of the posterior-anterior spine as determined by DEXA did not show the expected bone loss after testosterone withdrawal. This was probably due to the presence of osteoarthritis and/or aortic calcifications. Lumbar spine x-rays were not performed to confirm this. The bone density of the ultra distal radius, however, which is predominately composed of cancellous bone similar to the spine, significantly decreased. Likewise, the total hip composed of approximately 50% cancellous and 50% cortical bone also decreased significantly. In contrast, skeletal sites composed predominately of cortical bone, such as the femoral neck and mid and one third radius, decreased, but the decrease did not reach statistical significance. Taken together, these findings support the rapid loss of cancellous bone over cortical bone in aging men after testosterone withdrawal that appears to be greater than the loss seen in women after estrogen deficiency. With men, in contrast to women, the total hip and ultra distal radius sites are preferred for monitoring bone loss when the BMD is assessed by conventional DEXA.

The loss of BMD documented after 1 yr of GnRH analog

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therapy could be confounded by the lower baseline BMD in the total hip in the men with prostate cancer compared with the controls. Factors contributing to this finding are unclear. A few reports have documented lower BMD in men with prostate cancer before receiving ADT. Three factors have been identified and include low testosterone levels before ADT, slender stature, and cigarette smoking (19). The baseline testosterone level and height and weight were the same in both groups. The numbers of current (n = 1) or past use of cigarettes (n = 2) were also similar in both groups. Lower vitamin D and estradiol concentrations or higher PTH concentrations could help explain a lower baseline total hip BMD. However, there were no differences in these concentrations between the two groups. A correlation was noted between lower vitamin D levels and lower BMD at baseline (data not shown). This was evident in both groups. Older individuals tend to have lower BMD in the hip. The subjects with prostate cancer were slightly older than the control group, although this difference did not reach statistical significance. Another possibility for this lower total hip BMD at baseline in men with prostate cancer is the release of cytokines from prostate cancer tumor cells. It is known that prostate cancer tumor cells produce cytokines such as IL-6, which is known to modulate cancer cell growth and increase bone resorption. In clinically localized prostate cancer, the preoperative plasma IL-6 predicted biochemical progression after surgery (20). If the subjects with lower total hip BMD were actively losing BMD before therapy, the loss seen after GnRH analog would likely be exaggerated. Perhaps men with the diagnosis of prostate cancer begin to lose bone in the hip before GnRH therapy. Subjects with prostate cancer not treated with ADT may be a more appropriate control group to sort out this finding.

In contrast to other studies of bone loss documented in hypogonadal men, this is the first case-controlled prospective study demonstrating the rate of bone loss immediately after testosterone withdrawal in older men. In a unique one-time study of young men with testosterone deficiency, Stepan *et al.* (21) studied 12 males (mean age, 28 ± 6 yr) who had undergone bilateral orchiectomy because of sexual delinquency. A progressive loss of lumbar bone density as a function of time after orchiectomy occurred as determined by dual photon absorptiometry. The mean bone loss in the first 2 yr was 7% per year. The large loss of bone was documented in the spine of younger men who presumably did not have osteoarthritis or aortic calcifications. The hip and forearm were not measured. It is also known that men with long-standing hypogonadism have lower BMD compared with aged-matched controls. Finkelstein *et al.* (5) demonstrated that men with long-standing hypogonadism due to idiopathic hypogonadotropic hypogonadism had marked decreases in both cortical and trabecular bone density compared with age-matched controls.

The present study is in agreement with other reports (6–13) documenting bone loss in men with prostate cancer receiving ADT. This is the first prospective study of bone loss at different skeletal sites after ADT. In a recent cross-sectional case-controlled study, Stoch *et al.* (6) reported a significantly lower BMD at the lateral spine *vs.* total hip *vs.* distal one third radius in men with prostate cancer receiving GnRH analog compared with eugonadal men with prostate cancer. In another cross-sectional study of the longitudinal effects of ADT on bone density, Kiratli *et al.* (10) reported lower total hip BMD in men treated with ADT compared with age- and sex-matched control subjects from the NHANES. There was a trend for a decreased hip BMD with increasing years of ADT, and this decrease was more dramatic in patients who had undergone surgical castration than those receiving medical ADT. In a study of elderly men (mean age, 72 yr) with benign prostatic hypertrophy, BMD of the spine and markers of formation were determined before and after 6 and 12 months of GnRH therapy (22). Data from 17 men at 6 months and 10 men at 12 months were analyzed. Ten of 17 men demonstrated individual loss of bone in the lumbar spine. Other skeletal sites were not measured. Unlike the present study in which the increase in the concentration of the marker of bone formation, serum osteocalcin, was not statistically significant, their study demonstrated a significant increase in the serum concentration of osteocalcin. Urine markers of bone resorption were not measured. BMD in another study (23) was determined prospectively in the hip as determined by dual photon absorptiometry and distal radius, determined by single photon absorptiometry before and 1 yr after orchiectomy. A significant decrease in the BMDs of the distal radius and the femoral neck was noted. The lumbar spine, total hip, ultra distal, and mid radius were not measured. Daniell *et al.* (7) measured the BMD of the femoral neck at baseline and up to 42 months after orchiectomy or chemical castration. After orchiectomy, the average bone loss was 2.4% in the first year in both groups. This is comparable to the decrease in the BMD of the femoral neck in the present study. The total hip was not measured. Taken together, loss of bone mass after ADT in the treatment of prostate cancer can occur in all sites of the skeleton as determined by DEXA. Our results demonstrate that bone loss can be detected as early as 1 yr post-ADT and is best documented in the total hip and ultra distal radius. No significant bone loss at any site was found in age-matched controls. The small size of the study may have prevented the decrease seen in the other sites from reaching significance.

Although the clinical use of markers of bone turnover in individual patients is limited, it is well reported that both markers of bone formation and resorption are increased immediately after estrogen deficiency (16, 17). In the present study, concentrations of the marker of bone resorption, urinary N-telopeptide, significantly increased at 6 and 12 months, which is comparable to the increase seen in estrogen deficiency. The serum concentrations of the markers of bone formation, bone-specific alkaline phosphatase and osteocalcin, did not change. The reason for this is unclear. The small sample size had inadequate power to detect the differences in osteocalcin. Many studies of men with prostate cancer have reported increases in markers of turnover in men with bone metastasis (23–28). One study by Clarke *et al.* (23) demonstrated a disassociation in the levels of the markers of bone formation 4 wk after orchiectomy. Levels of serum bone-specific alkaline phosphatase decreased immediately after orchiectomy, but osteocalcin increased. The urine concentrations of hydroxyproline creatinine and calcium, measured as markers of bone resorption, also increased. This diver-

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gence in activity of bone turnover is not understood but would be better addressed in future studies with a larger sample size.

Smith *et al.* (29) recently reported the prevention of bone loss with concurrent administration of pamidronate and GnRH analog in men with prostate cancer. The BMD, as measured by DEXA, in men treated with GnRH analog (n = 22) alone decreased by 3.3% in the spine and 1.8% in the total hip at 48 wk. The femoral neck BMD did not change significantly. A 8.5% decrease in the spine trabecular BMD as measured by computerized tomography was also noted, but forearm BMD was not measured. Serum concentration of bone-specific alkaline phosphatase and osteocalcin and urinary excretion of N-telopeptide increased in men treated with GnRH analog alone. The findings of this study are consistent with the pattern of bone loss seen in women after the menopause. In contrast to the present study, the subjects treated with GnRH analog alone were 10 yr younger, which could explain the difference in the rate and sites of bone loss. Taken together, both studies demonstrate significant bone loss in the first year after GnRH analog therapy in men with prostate cancer.

In conclusion, bone loss undoubtedly occurs in men with prostate cancer treated with ADT. This study supports the use of DEXA to measure the BMD of the total hip and ultra distal radius sites in detecting the bone loss. In addition, assessing urinary N-telopeptide may be helpful. Because prostate cancer is the most frequent visceral neoplasm affecting men and treatment of prostate cancer with ADT is the mainstay of therapy, studies are needed to address the risk of fractures in these men and the avenues to prevent bone loss.

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