Bone Mineral Density Changes in Patients With Prostate Cancer During the First 2 Years of Androgen Suppression

Juan Morote,* Anna Orsola, Jose M. Abascal, Jacques Planas, Enrique Trilla, Carles X. Raventos, Lluis Cecchini, Gloria Encabo and Jaume Reventos

From the Department of Urology, Nuclear Medicine (GE) and Basic Research Unit (JR), Vall d'Hebron Hospital, Autónoma University School of Medicine, Barcelona, Spain

Purpose: We characterized bone mineral density changes in patients with prostate cancer on androgen deprivation therapy during the first 2 years of uninterrupted therapy, and identified which location most reflects bone mass loss.

Materials and Methods: Using dual energy x-ray absorptiometry, bone mineral density was prospectively assessed in patients with nonmetastatic prostate cancer at the lumbar spine and femoral neck, Ward's triangle, trochanter and total hip. Measurements were performed at baseline and yearly thereafter in patients on ADT, and at baseline and 1 year in controls (age matched patients with prostate cancer, free of biochemical progression after radical prostatectomy).

Results: A total of 62 patients were included in the study, 31 in each group. Median age (70 and 69 years, respectively), mean Gleason score and mean baseline serum testosterone did not significantly differ. Patients receiving ADT experienced a significant bone mass loss at 12 months in all locations, ranging from 2.29% to 5.55% ($p < 0.001$). In contrast, bone mineral density did not change significantly (0.64% to 1.68%) in patients not receiving ADT. In the 20 patients on ADT after 24 months, the second year decrease was not as severe, nor was it significant compared to first year values. The major bone mass loss occurred in Ward's triangle, with decreases of 5.55% at 12 months and 7.05% at 24 months.

Conclusions: Bone mineral density decreases during the first 24 months of androgen suppression with the most relevant effect occurring in the first year. Ward's triangle is the axial skeletal site that reflects the major bone mass loss. Because the deleterious impact of long-term androgen suppression on bone mineral density is inversely related to fracture risk and indirectly related to survival in patients with prostate cancer, early diagnosis and prevention of bone mass loss are warranted in these patients.

Key Words: prostatic neoplasms, osteoporosis, androgens

Androgen deprivation therapy is increasingly being used in nonmetastatic prostate cancer, either as early mainstream treatment in men with locally advanced tumors or in an adjuvant manner after biochemical failure (prostate specific antigen relapse). Because this treatment is potentially prolonged, associated long-term effects should be taken into consideration by patients and physicians. Chemical castration induced by LH-RH agonists is associated with an increase in bone resorption.[1] This may lead to osteoporosis, a relevant side effect in patients with prostate cancer, because it increases the risk of bone fractures.[2] Moreover, recent data demonstrate a negative correlation between skeletal fractures and overall survival in men with prostate cancer on androgen suppression.[3]

BMD dynamics are well documented in postmenopausal women, with yearly decreases ranging from 1% to 5%.[4] The lumbar spine, with a 70% trabecular bone content, shows a higher rate of bone loss than the hip and forearm during the years following menopause. Therefore, this location is used to evaluate the speed of female osteoporosis, as well as to determine the response to treatment.[5] Conversely measurements at the total hip and at femoral Ward's triangle have been defined as the strongest predictors of overall fracture risk and of hip fracture risk, respectively.[4]

In recent years attention has been drawn toward demineralization in the aging male, in whom rates of annual bone mass loss range between 0.5% and 1%.[4] This rate increases with androgen suppression, however the dynamics of bone loss and potential for osteoporotic bone fractures in patients on ADT have not been clearly characterized. Most studies analyzing loss of BMD in men undergoing androgen suppression are cross-sectional.[1,2,6–11] At present only 4 studies involving few patients have addressed this issue prospectively, and mainly analyze bone density at the lumbar spine or femoral neck.[12–15] We have previously shown that bone loss might be independent of the modality of androgen suppression (maximum androgen blockade or chemical castration).[2] In the current report we better characterize the bone adverse effects of long-term androgen suppression and identify the best site to measure bone loss. Thus, we prospectively evaluated the dynamics of BMD in the lumbar spine and 4 hip sites in patients with nonmetastatic prostate cancer during a 2-year period.

MATERIALS AND METHODS

Study Group

The study group included patients with locally advanced nonmetastatic prostate cancer, selected for uninterrupted

Submitted for publication May 22, 2005.

* Correspondence: Urology Department, Vall d'Hebron University Hospital, Po Vall d'Hebron 119-129, 08035 Barcelona, Spain (e-mail: jmorote@vhebron.net).

DOI:10.1016/S0022-5347(05)00999-7

TABLE 1. *Patient characteristics*

	Control Group	Study Group	p Value
No. pts	31	31	—
Median pt age (range)	69 (65–76)	70 (65–80)	0.059
Mean Gleason score (range)	5.96 (4–9)	7.12 (6–10)	0.032
Mean ng/ml serum prostate specific antigen (range)	0.1 (0.00–0.4)	103.5 (7.2–320.5)	0.001
Mean ng/dl baseline serum testosterone (range)	523.9 (245.1–963.2)	490.9 (239.0–741.2)	0.486

androgen suppression as monotherapy with 3 months of depot LH-RH agonist. All patients had a histological diagnosis of prostate carcinoma and absence of bone metastases as assessed by bone scintigraphy. Patients with bone metabolic diseases, prior hormonal treatment, or prior or concomitant treatment with other drugs known to affect bone metabolism were excluded from study. The control group included age matched patients with prostate cancer free of biochemical progression after radical prostatectomy.

Bone Mineral Density Measurements

Bone mineral density was measured by DEXA using a Lunar® DPX IQ-4977 densitometer. The area of bone mineral density (gm/cm^2) was measured at the lumbar spine (L2-L4) as well as at the femoral neck, Ward's triangle, trochanter and total hip. The Ward's triangle is a region of interest at the femoral neck (between the principal compressive group of the femoral head and the principal tensile group and the secondary compressive group of the femoral neck) measured using the scan analysis software provided by principal commercial manufacturers. Densitometric measurements were performed at baseline and yearly thereafter in patients on ADT, and at baseline and 1 year in controls.

Statistical Methods

The nonparametric Wilcoxon's matched pairs signed-rank test was used to compare paired data of 2 groups. The nonparametric Mann-Whitney U test was used to compare independent data of 2 groups. The nonparametric Friedman test was used to compare paired data of k-groups. Two-tailed tests were used for all comparisons and $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS® v.12 software.

RESULTS

Clinical Characteristics

A total of 62 patients were included in the study, 31 in the study group and 31 in the control group with a median age of 70 and 69 years, respectively. Clinical stage was T3a N0 M0 in 14 patients, T3b-4 N0 M0 in 7 patients and T2-4 N1 M0 in 10 patients, whereas patients in the control group had clinically localized prostate cancer (20 T1c N0 M0 and 11 T2a N0 M0). Mean Gleason score and mean baseline serum testosterone did not differ significantly between groups. Serum testosterone decreased to castrate levels, 48.2 ng/dl (range 20 to 63), with ADT, remaining suppressed throughout the study. Table 1 details baseline patient characteristics.

Bone Densitometry Results

Patients on ADT experienced a significant bone mass loss in all the analyzed locations at 12 months compared to baseline values. The decrease ranged from 2.29% to 5.55% depending on the site as plotted in table 2 ($p < 0.001$ for each comparison with the corresponding baseline level). In contrast, bone mineral density did not change significantly in patients not on androgen suppression in a 1-year period. In this control group, for all locations, only a slight decrease (ranging between 0.64% and 1.68%) in BMD was identified (table 3). When BMD changes were analyzed in the subset of 20 patients on androgen suppression who were followed for 24 months, the decrease persisted throughout followup. Interestingly, rates of bone loss during the second year were not as severe, nor were they significant compared to first year values at all evaluated sites (table 4). At last followup (24 months) maximum cumulative bone mineral density decrease reached 7.05%.

TABLE 2. *Bone mineral density changes after 1 year of androgen deprivation therapy*

BMD Zone	Baseline	12 Mos	% Variation of Mean
Lumbar spine:			
Mean ± SD (range)	1.193 ± 0.235 (0.80–1.66)	1.136 ± 0.236 (0.75–1.60)	−4.80
Median (95% CI)	1.188 (1.106–1.279)	1.132 (1.049–1.222)	
Femoral neck:			
Mean ± SD (range)	0.840 ± 0.133 (0.56–1.15)	0.814 ± 0.129 (0.54–1.08)	−2.99
Median (95% CI)	0.831 (0.791–0.889)	0.812 (0.767–0.862)	
Ward's triangle:			
Mean ± SD (range)	0.718 ± 0.141 (0.40–1.00)	0.679 ± 0.145 (0.43–0.96)	−5.55
Median (95% CI)	0.702 (0.668–0.770)	0.666 (0.625–0.732)	
Trochanter:			
Mean ± SD (range)	0.866 ± 0.173 (0.58–1.18)	0.836 ± 0.180 (0.54–1.16)	−3.63
Median (95% CI)	0.895 (0.811–0.922)	0.838 (0.770–0.903)	
Total hip:			
Mean ± SD (range)	0.987 ± 0.178 (0.62–1.31)	0.951 ± 0.182 (0.59–1.27)	−3.76
Median (95% CI)	1.004 (0.922–1.053)	0.958 (0.884–1.018)	

$p = 0.001$.