Prostate Cancer and Prostatic Diseases (2002) 5, 304–310
 1365–7852/02 $25.00
www.nature.com/pcan

Androgen deprivation in men with prostate cancer is associated with an increased rate of bone loss

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The objective of this work was to determine the effect of androgen deprivation therapy (ADT) on rates of bone mineral density (BMD) loss in men with prostate cancer. It was a prospective study comparing men receiving ADT to age matched controls for 2 y. Subjects received a history, physical exam, bone mineral density measurement, and laboratory evaluation every 6 months. Thirty-nine subjects receiving continuous ADT for prostate cancer (subjects) were compared to 39 age-matched controls not receiving ADT (controls). Twenty-three subjects and 30 controls completed the study through 24 months. Men in the ADT group demonstrated greater rates of bone mineral density loss than men in the control group at every site except the lumbar spine. Twenty-four month per cent of bone mineral density loss is presented as mean ± standard error (s.e.). At the distal forearm, the ADT group value was $-9.4\% \pm 1.0\%$ and $-4.4\% \pm 0.3\%$ for controls ($P < 0.0005$). The ADT group femoral neck values were $-1.9\% \pm 0.7\%$ and $0.6\% \pm 0.5\%$ in the control group ($P = 0.0016$). The ADT group total hip value was $-1.5\% \pm 1.0\%$ and $0.8\% \pm 0.5\%$ in the control group ($P = 0.0018$). The ADT group trochanter value was $-2.0\% \pm 1.3\%$ and $-0.1\% \pm 0.5\%$ in the control group ($P = 0.0019$). The ADT group lumbar spine value was $-0.2\% \pm 0.8$ % and $1.1\% \pm 0.6\%$ in the control group ($P = 0.079$). Our data demonstrate greater rates of bone mineral density loss in men receiving androgen deprivation therapy for prostate cancer.
Prostate Cancer and Prostatic Diseases (2002) **5,** 304–310. doi:10.1038/sj.pcan.4500599

Keywords: androgen deprivation; prostate cancer; bone loss

Introduction

Hormonal manipulation with androgen deprivation therapy (ADT) is currently the preferred treatment in the management of advanced or recurrent prostate cancer.[1,2] This therapy has significant side effects that include decreased libido, hot flashes, anemia, muscle weakness, and possibly osteoporosis.[3–6]

The use of prostate specific antigen (PSA) in the diagnosis, treatment, and follow-up of prostate cancer patients has significantly changed the definition of disease recurrence. In the PSA era, ADT is frequently initiated based on a rising PSA after primary treatment for prostate cancer.[7,8] Consequently, these practices lead to longer periods of ADT exposure than in the pre-PSA era since disease recurrence is now identified and treated at earlier stages based solely on serum PSA levels.

There has been increasing concern over osteoporosis as a potential complication of ADT. It is known that hypogonadism accounts for 5–33% of the cases of osteoporosis in men.[9] Recent data suggest a relationship between ADT, osteoporosis, and bone fractures.[5,10–19,23–25]

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The opinions and assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the US Army or the Department of Defense.
Received 30 January 2002; revised 21 April 2002; accepted 25 April 2002

We performed a longitudinal study to assess the effects of ADT on bone mineral density and urinary markers of bone turnover in men with advanced or recurrent prostate cancer.

Material and methods

Study design

A 2-y, prospective study design was utilized to assess the effect of ADT on bone mineral density and biochemical markers of bone turnover. Male patients over the age of 50 were recruited from the Urology clinic at Walter Reed Army Medical Center. Subjects were enrolled between November 1996 and July 1997 and followed for 2 y. ADT study subjects consisted of patients identified through records screening who had received continuous androgen deprivation for a minimum of 6 months for either advanced prostate cancer on presentation or for recurrent disease following primary, local therapy (radical prostatectomy or radiation therapy). Recurrence of prostate cancer after primary therapy (radical prostatectomy or radiation therapy) was defined as two or more prostate specific antigen (PSA) levels ≥ 0.2 ng/ml after radical prostatectomy or three consecutive rises in PSA after a nadir value following radiation therapy. Initiation of ADT was at the discretion of each subject's attending urologist. ADT consisted of luteinizing hormone releasing hormone (LHRH) analog injections (leuprolide or goserelin) bi lateral orchiectomy. Concomitant antiandrogen therapy (flutamide or bicalutamide) was administered to treatment subjects who tolerated these medications. Radionuclide bone scans were not consistently obtained in all ADT subjects prior to initiation of ADT or during ADT, therefore, bone scan data are not included in this report. Subjects could be enrolled in the ADT group with or without a radionucleide bone scan.

Control subjects consisted of individuals with other urologic conditions such as erectile dysfunction or benign prostatic hyperplasia recruited from the Urology clinic at Walter Reed Army Medical Center. Prostate cancer patients who had completed primary therapy (radical prostatectomy or radiation therapy) with no evidence of disease (NED) at follow-up visits were also recruited as control subjects. NED status was defined as undetectable PSA (< 0.1 ng/ml) following radical prostatectomy or stable PSA (non-rising PSA) following radiation therapy.

Subjects in either group were excluded from the study if they had a prior or present history renal failure, active alcoholism, hyperthyroidism, hyperparathyroidism or hypoparathyroidism, rheumatoid arthritis, active non-cutaneous malignancies, liver disease, sarcoidosis, tuberculosis, malabsorption syndromes, rickets, Paget's disease, gastric or small bowel surgery, Klinefelter's syndrome or pituitary tumors. Subjects were also excluded if they were taking estrogens, androgens, glucocorticoids, phosphates, diuretics, calcium supplements greater than 1500 mg per day, vitamin D doses exceeding 5000 IU per day, calcitonin, therapeutic doses of fluoride, thyroid hormone suppression, diphenylhydantoin, phenobarbital, or bisphosphonates. Control subjects with prostate cancer who had received any previous form of ADT (neoadjuvant, adjuvant, or intermittent hormonal therapy) were not allowed on the study. During the study period, ADT study subjects who had three or more consecutive rises in PSA or any single increase in PSA ≥ 5.0 ng/ml were dropped from the study due to the high probability of hormone refractory prostate cancer. A stable or undetectable PSA was required to be enrolled and remain enrolled in the ADT study group.

After obtaining informed consent, potential study subjects underwent an initial screening interview consisting of a review of their medications, medical history, and a physical examination. Following screening, these individuals underwent measurements of the following in the serum: blood urea nitrogen (BUN), creatinine, 25-hydroxyvitamin D, free T4, thyroid stimulating hormone (TSH), parathyroid hormone (PTH), albumin, and alkaline phosphatase. Serum testosterone and PSA levels were measured in all subjects. PSA measurements were used to assess disease stability in all individuals with prostate cancer (controls with prostate cancer in remission and ADT subjects). Prostate biopsy was recommended to control subjects with abnormal PSA values or abnormal digital rectal examination. New prostate cancer diagnosis (three cases) identified in control subjects during the 24-month study is addressed later in the results section.

Following this initial evaluation, subjects were enrolled in the study and bone mineral density measurements, urine markers of bone turnover, dietary calcium intake, exercise frequency and type were assessed. Height and weight measurements were obtained to calculate body mass index (BMI). Bone mineral density measurements of the distal forearm, femoral neck, total hip, trochanter, and lumbar spine (L1 to L4) were performed by dual energy X-ray absorptiometry (DEXA) using a Hologic QDR-2000 densitometer (Hologic Inc., Waltham, MA, USA) at study entry and every 6 months for a total of 24 months. All bone mineral density studies were done by the same technician (DS — see Acknowledgements), on the same machine (QDR-2000 densitometer), in the same facility (Endocrinology clinic, Walter Reed Army Medical Center) and interpreted by the same physician (WED, co-author). The physician interpreting the bone mineral density studies and the technician performing the studies were blinded as to whether patients were receiving ADT or not. A reference bone mineral density measurement was performed daily with the QDR-2000 using a phantom spine (known standard) to ensure consistent, accurate measurements. Bone mineral density data were recorded as grams/centimeter^2. The per cent change in bone mineral density was calculated and compared in each group. Twenty-four hour urine collections for pyridinoline cross-links, deoxypyridinoline cross-links, and milligrams calcium/gram creatinine were measured at study entry and 24 months. Dietary questionnaires were administered at each visit and daily calcium intake was calculated according to the method described by Angus.[20] In addition, exercise frequency and type was recorded for each subject. Each ADT subject was age matched (± 5 y) to a control subject for data analysis once enrolment in the study was completed (see Results).

The Walter Reed Army Medical Center Human Use Committee and the Department of Clinical Investigation approved this study.

Statistical analysis

Baseline demographic and laboratory data are presented as the mean ± standard deviation (± s.d.) and compared between groups using the two-sample *t*-test. Data not normally distributed are presented as the median and range and compared by the Wilcoxon rank sum test. Changes in urinary deoxypyridinoline, urinary pyridinoline, and milligrams of calcium/gram of creatinine in urine within each group were examined using the Wilcoxon signed ranks test (SPSS for Windows, version 9). Comparison of exercise type between groups was examined using Fisher's exact test (StatXact-Turbo, Cytel Software, Cambridge, MA, USA). Bone mineral density data are presented as mean ± standard error (± s.e.), and measurements at multiple time points were compared within groups and between groups using repeated measures analysis of variance (BMDP release 7.0, program 5V). The association of BMI with baseline bone mineral density was examined using Spearman's rank correlation coefficient.

Results

Sample characteristics

One hundred and ninety-one subjects were screened for study enrolment, 94 were excluded based on strigent enrollment criteria. After initial laboratory evaluation and physical examination, eight additional individuals were excluded because of abnormal laboratory studies (four had low 25 hydroxy vitamin D, two had an elevated TSH, one had an elevated PTH, one ADT patient had recurrence of prostate cancer after 4 y of ADT; his PSA was 23). In addition, one ADT subject voluntarily withdrew from the study after initial screening. Of the remaining 88 subjects, 10 individuals in the control group were excluded due to lack of aged-matched cases (± 5 y) in the ADT group. Seventy-eight subjects remained and were included in this study. There were 39 subjects in each group. The median duration of ADT in the study group at entry was 30 months with a range of 6–66 months. The type of ADT received by the study subjects is as follows: 24 received LHRH analogs with antiandrogens, three received LHRH analogs only, 10 received orchiectomy and antiandrogens, and two received orchiectomy alone.

Clinical, biochemical and bone mineral density measurements at study entry are summarized in Table 1. There were no statistically significant differences in the mean age, BMI, dietary calcium intake, or exercise frequency between the two groups. Exercise duration and type were similar in the two groups (Table 1).

Thirty control subjects and 23 ADT subjects completed the 2-y study. Seven control subjects and three ADT subjects voluntarily withdrew from the study over 2 y Two control patients and five ADT patients began medications in the exclusion criteria during the study and these individuals were dropped from the study at the

Table 1 Demographic, laboratory (with normal range listed) and bone mineral density measurements for subjects at entry

	Study group ADT ($n=39$)	Control group ($n=39$)	*P*-value
Age (years)	73.4 ± 6.6	71.8 ± 6.6	0.30
Body mass index (kg/m^2)	27.1 ± 3.3	27.9 ± 6.1	0.46
Daily calcium intake (mg/day)	907.3 ± 388.4	817.9 ± 340.3	0.32
Exercise frequency (sessions/week)	4.4 ± 2.7	4.2 ± 2.8	0.77
Exercise type			
None	8 (21%)	7 (18%)	0.99
Non-weight bearing	5 (13%)	5 (13%)	
Weight-bearing	25 (64%)	26 (67%)	
Unknown	1 (3%)	1 (3%)	
Blood urea nitrogen (mg/dl) (normal 9–20 mg/dl)	17.2 ± 5.0	17.0 ± 4.7	0.83
Serum creatinine (mg/dl) (normal 0.8–1.5 mg/dl)	1.1 ± 0.2	1.1 ± 0.2	0.37
Serum 25 hydroxyvitamin D (ng/ml) (normal 9.0–52 ng/dl)	26.4 ± 10.1	24.4 ± 8.1	0.34
Serum free T4 (ng/dl) (normal 0.71–1.85 ng/dl)	1.1 ± 0.1	1.1 ± 0.1	0.35
Thyroid stimulating hormone (MIU/ml) (normal 0.27–4.20 MIU/ml)	1.9 ± 0.7	2.2 ± 1.3	0.26
Parathyroid hormone (pg/ml) (normal 12–72 pg/ml)	29.5 ± 12.7	33.2 ± 14.9	0.24
Albumin (g/dl) (normal 0.39–0.50 g/dl)	0.42 ± 0.03	0.41 ± 0.03	0.72
Alkaline phosphatase (U/l) (normal 38–126 U/l)	88.1 ± 41.6	71.0 ± 18.7	0.022
24-h urine pyridinoline (nM/mM) (normal 20–61 nM/mM)	54.3 ± 17.0	40.6 ± 17.1	0.001
24-h urine deoxypyridinoline (nM/mM) (normal 4–19 nM/mM)	14.7 ± 5.8	10.0 ± 3.2	< 0.0005
Urine Ca/urine Cr (mg/g)	161.8 ± 86.8	91.9 ± 74.0	< 0.0005
Total testosterone (ng/dl) (normal 241–827 ng/dl)	5 (0–25)	413 (163–1497)	< 0.0005
PSA (ng/ml)	0 (0–1.9)	1.0 (0–19.3)	< 0.0005

Data presented as mean ± s.d. or median (range).

time that use of the prohibited medications was identified. Two ADT subjects died during the study; one from prostate cancer and one from a non-prostate cancer cause. Development of hormone refractory prostate cancer (rising PSA on ADT) caused exclusion of four ADT subjects during the study. These were the only four patients in the ADT group who developed hormone refractory prostate cancer during the study. These patients were all referred to the Hematology Oncology service where they were started on corticosteroids that were part of the exclusion criteria. Two ADT subjects developed diseases during the study that were in the exclusion criteria which caused elimination from the study. Three new cases of prostate cancer were diagnosed during the study in the control group. These men were treated for their prostate cancer and remained in the control group as their PSA values were undetectable (radical prostatectomy) or stable (radiation) after definitive therapy (two underwent radical prostatectomy and one received radiation therapy). Ten control subjects had known prostate cancer that had either been treated with radical prostatectomy or radiation therapy prior to study enrolment. These individuals demonstrated undetectable or stable PSA values (for prostatectomy or radiation therapy, respectively) prior to study enrolment and during the study. No bone fractures were identified in either control or ADT subjects during the follow-up period. All data collected on subjects dropped during the study was used in the analysis up until the time the individual was dropped from the study.

Laboratory, demographic, and bone mineral density data comparison

Laboratory, demographic, and BMD comparison is summarized in Table 1.

Differences in baseline BMD at study entry (mean $\pm$s.e.) were noted only in the distal forearm (Table 2). In the ADT group, the mean entry value was $0.70\,g/cm^2 \pm 0.01$ *vs* $0.75\,g/cm^2 \pm 0.01$ for the control group ($P = 0.003$). BMD changed significantly during the study period between the two groups at all sites except the lumbar spine. Twenty-four month values are presented as mean per cent change BMD $\pm$ s.e. In the distal forearm, the BMD decreased by $-9.4\% \pm 1.0\%$ ($P < 0.0005$, repeated measures ANOVA) in the ADT group and $-4.4\% \pm 0.3\%$ ($P < 0.0005$) in the control group (Figure 1). The difference in the rate of change in BMD between the two groups at the distal forearm was statistically significant ($P < 0.0005$, repeated measures ANOVA). The femoral neck BMD decreased by $-1.9\% \pm 0.7\%$ ($P = 0.027$) in the ADT group and increased by $+0.6\% \pm 0.5\%$ ($P = 0.0056$) in the control group (Figure 2). This difference in rate of change in BMD at the femoral neck between groups was statistically significant ($P = 0.0016$). The total hip BMD decreased in the ADT group by $-1.5\% \pm 1.0\%$ ($P = 0.0004$) and increased in the control group by $+0.8\% \pm 0.5\%$ ($P = 0.001$; Figure 3). The difference in the rates of BMD change between ADT and control groups at the total hip was statistically significant ($P = 0.0018$). The BMD change at the trochanter was $-2.0\% \pm 1.3\%$ ($P = 0.025$) in the ADT group and $-0.1\% \pm 0.5\%$ ($P = 0.81$) in the control group (Figure 4). The differences in rates of BMD change at the trochanter were statistically significant between groups ($P = 0.0019$). Finally, the lumbar spine BMD change was $-0.2\% \pm 0.8\%$ ($P = 0.71$) in the ADT group and $+1.1\% \pm 0.6\%$ ($P = 0.079$) in the control group (Figure 5). The differences in rates of BMD change at the lumbar spine were not statistically significant between the two groups ($P = 0.25$). Osteoporosis (*t*-score defined as

Table 2 Baseline bone mineral density[a]

	ADT	Control	*P*-value
Forearm	0.70 ± 0.01	0.75 ± 0.01	0.003
Femoral neck	0.78 ± 0.02	0.77 ± 0.02	0.80
Total hip	0.94 ± 0.02	0.96 ± 0.02	0.74
Trochanter	0.75 ± 0.02	0.75 ± 0.02	0.84
Lumbar spine	1.05 ± 0.04	1.06 ± 0.03	0.87

[a]Data are presented as mean $\pm$ s.e. in g/cm^2.

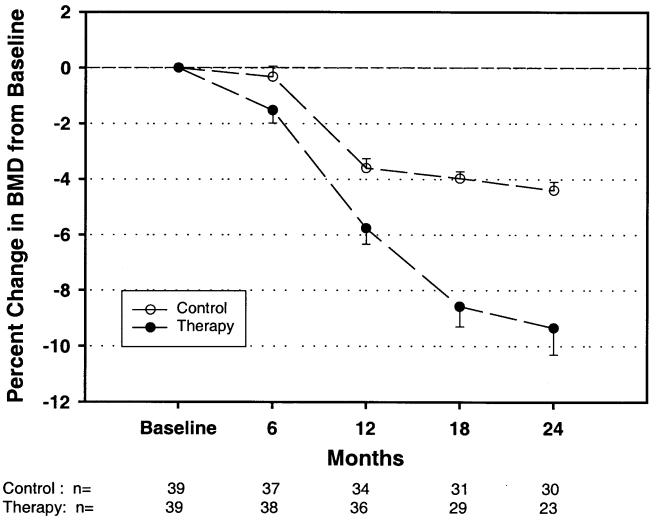

Figure 1 *Per cent change (mean $\pm$ s.e.) in BMD at the distal forearm between ADT and control subjects.*

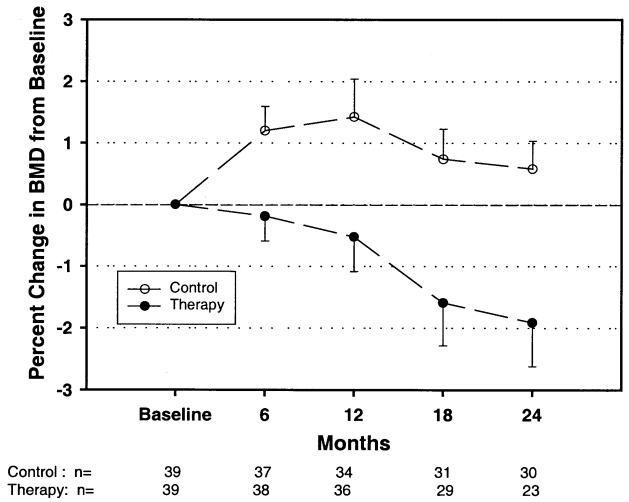

Figure 2 *Per cent change (mean $\pm$ s.e.) in BMD at the femoral neck between ADT and control subject.*

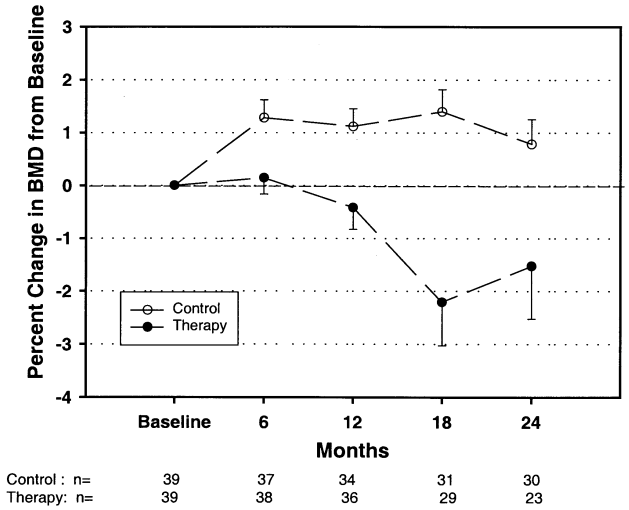

Figure 3 *Per cent change (mean ± s.e.) in BMD at the total hip between ADT and control subject.*

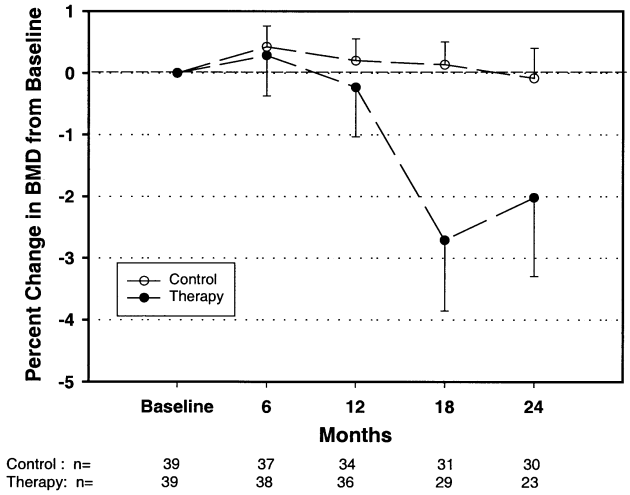

Figure 4 *Per cent change (mean ± s.e.) in BMD at the trochanter between ADT and control subject.*

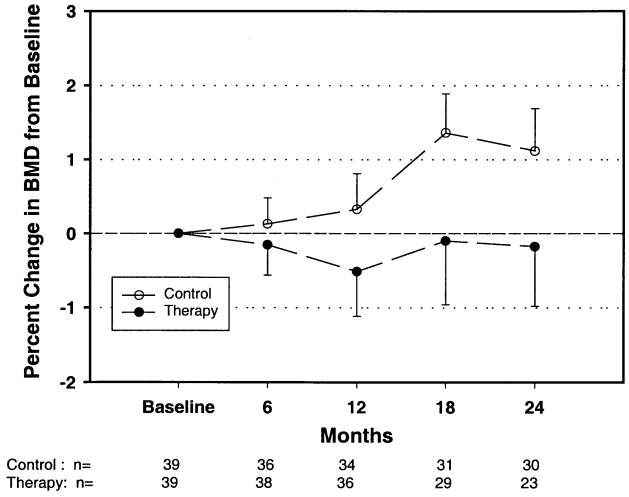

Figure 5 *Per cent change in (mean ± s.e.) BMD at the lumbar spine between ADT and control subject.*

BMD ≤ -2.5 standard deviations below young normal peak bone mass) was seen in significantly more numbers of ADT subjects than control subjects in the study. Data from all subjects was used until the patient was dropped from the study. The percentage of subjects with osteoporosis at the last data point available for the subject is reported in Table 3. BMI was weakly correlated with baseline total hip bone mineral density ($r = 0.33$, $P = 0.003$). There were no other significant associations between BMI and any other baseline BMD or change in BMD parameters. Urinary markers of bone turnover were significantly different between the ADT and control groups (pyridinoline, deoxypyridinoline) as were comparisons of testosterone and serum alkaline phosphatase (Table 1). There were no significant differences in demographics between the ADT and control group.

Discussion

Several studies have suggested a relationship between androgen deprivation therapy in men with prostate cancer and osteoporosis.[5,10–19,23–25] Our longitudinal study demonstrates that ADT in men with prostate cancer is associated with an accelerated rate of BMD loss. In addition, increased levels of urine deoxypyridinoline, pyridinoline, and milligrams calcium/gram of creatinine indicate increased bone turnover in men receiving ADT for prostate cancer.

Studies of osteoporosis in men are limited, and many investigators have suggested that ADT is associated with both osteoporosis and fractures. Collinson *et al* reported the development of osteoporotic fractures in two men undergoing treatment with LHRH analogues,[12] and LHRH analogues have been shown to decrease BMD over time in the lumbar spine of men with benign prostatic hypertrophy.[13] Stepan *et al* showed a progressive loss of BMD in the lumbar spine of 12 subjects who had undergone surgical castration.[14] In addition, castrated subjects in the Stepan study showed elevated urine levels of biochemical markers indicating accelerated bone turnover. In a retrospective chart review of 224 patients receiving LHRH analog therapy, Townsend *et al* reported the incidence of osteoporotic hip fractures to be three times greater than the expected incidence for the same age population.[10] Daniell retrospectively examined the records of 235 patients with non-stage A prostate carcinoma and compared the cumulative incidence of osteoporotic fractures in the 59 subjects who had undergone therapeutic orchiectomy to the 176 patients who did not have an orchiectomy.[5] Cumulative, non-pathologic

Table 3 Percentage of subjects in control and ADT groups with osteoporosis at last data point available[a]

	Control	ADT
Osteoporosis distal forearm	25.6% ($n = 10$)	64.1% ($n = 24$)
Osteoporosis femoral neck	12.8% ($n = 5$)	41.0% ($n = 16$)
Osteoporosis total hip	5.1% ($n = 2$)	7.7% ($n = 3$)
Osteoporosis trochanter	0% ($n = 0$)	0% ($n = 0$)
Osteoporosis lumbar spine	10.5% ($n = 4$)	12.8% ($n = 5$)

[a]Percentage expressed as $n/39$.

fractures were more frequent (8 *vs* 2 respectively, $P < 0.001$) in the orchiectomy group and occurred earlier in this group than in controls. Daniell's group recently completed a prospective study comparing BMD changes at the femoral neck in 42 men treated with ADT for prostate cancer and 12 control subjects.[15] This study demonstrated progressive bone loss associated with ADT. Oefelein *et al* found ADT is associated with an increased risk of skeletal fracture, but found that African-American race and increased BMI seem to exert protective effects against bone fracture in men receiving ADT for prostate cancer.[23] Our study failed to show differences in BMD loss due to African-American race, or increased BMI.

A prospective study from a group of French researchers demonstrated accelerated bone loss in a small group of men with prostate cancer (9 of 12 subjects followed for 18 months) treated with gonadotropin-releasing hormone agonists.[17] Serum osteocalcin was elevated in this study group indicating increased bone turnover. A group from Australia found accelerated bone loss in a group of 12 prostate cancer patients treated with goserelin and flutamide that was reversed by etidronate therapy.[18] Kiratli *et al* recently demonstrated that BMD tends to decrease in association with longer periods of ADT. The greatest bone loss in their cross-sectional study was in patients on ADT up to 10 y.[19]

Diamond *et al* and Smith *et al* both recently demonstrated the efficacy of pamidronate in preventing bone loss in men receiving ADT for prostate cancer.[24,25] Both studies were similar in design and duration, with the major difference being the number of patients studied (Diamond *et al*—18 subjects, Smith *et al*—41 subjects,) and the frequency of pamidronate administration (Diamond *et al*—90 mg i.v. single dose, Smith *et al*—60 mg i.v. every 12 weeks for 48 weeks). Both studies suggest that pamidronate compared to placebo inhibits bone loss associated with androgen deprivation used to treat men with prostate cancer.

Osteoporosis in men is a heterogeneous condition encompassing a wide variety of etiologies and it is common to identify several potential explanations for bone loss and fractures in a single patient.[9] Hypogonadism alone accounts for 16–23% of osteoporosis associated with fractures.[21,22] We meticulously screened our patient population and eliminated over half of our screened subjects for enrollment in this study due to factors discovered that could affect bone metabolism. Increased rates of bone loss were associated with ADT, even when confounding variables were accounted for in our study.

The distal forearm was the only bone site that demonstrated significant differences in BMD between groups at the beginning of the study. This was an unexpected finding. One would expect that a group of men deprived of androgens for a median time period of 30 months would have significant differences in BMD at all measured sites compared to controls. Perhaps the size of our study groups was too small to demonstrate differences at 30 months of ADT. There were no differences in rates of bone loss in the lumbar spine. The lumbar spine is a frequent site of degenerative arthritic changes in aging populations. Diamond *et al* stated that lumbar spine measurements with DEXA were pseudoelevated in their study due to spondyloarthropathy in 85% of their study subjects, but CT scan did demonstrate significant lumbar spine BMD loss in men receiving ADT for prostate cancer.[24] Degenerative arthritis changes in the lumbar spine may be the reason no differences in rates of bone loss were seen between these groups at the lumbar spine by DEXA measurement. Longer follow-up (beyond 2 y) would possibly show greater differences between these groups. In addition, our study examined rates of late bone loss as the median time on ADT was 30 months. Men receiving ADT to treat prostate cancer may show a similar pattern to post-menopausal women who show high initial rates of bone loss at initiation of menopause followed by a subsequent slower rate of bone loss.[26] Our study design did not capture the same effect in men, probably because of its 2-y duration. Our study did demonstrate a higher incidence of osteoporosis at the distal forearm and femoral neck when control and ADT subjects' BMD were compared at the last available data point available for each subject. No significant differences in osteoporosis incidence were seen at the total hip, trochanter, and lumbar spine by this comparison method. A follow-up study would be best performed as a multi-center setting to accumulate larger numbers of subjects to be followed over a longer period of time (> 2 y). Nevertheless, we believe the differences demonstrated are clinically significant and warrant further prospective study in a larger group of subjects.

Conclusion

This study indicates that men who are receiving ADT to treat advanced or recurrent prostate cancer lose BMD at a faster rate than a group of age-matched controls. Urinary markers of bone turnover were also significantly elevated in ADT patients, further supporting the different rates of change seen in the BMD. Based on these findings, we believe ADT patients are at increased risk for osteoporosis. Surveillance for bone loss should be considered in these patients.

Acknowledgements

The authors wish to acknowledge LTC Karen Wish, RD, PhD for her calculations of dietary calcium data and Mr David Stott, BS for his technical support in performing all bone mineral density measurements for this study. This research was funded by the U.S. Army Medical Research and Development Command, and the Department of Clinical Investigation Work Unit #2819 from Walter Reed Army Medical Center.

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