

PREVALENCE OF OSTEOPENIA AND OSTEOPOROSIS BY CENTRAL AND PERIPHERAL BONE MINERAL DENSITY IN MEN WITH PROSTATE CANCER DURING ANDROGEN-DEPRIVATION THERAPY

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ABSTRACT

Objectives. To determine the prevalence of osteopenia and osteoporosis by central (spine and hip) and peripheral (radius) bone mineral density (BMD) in men with prostate cancer undergoing androgen-deprivation therapy (ADT). Low BMD and fractures are prevalent in this group of men. Most published studies on ADT-related bone loss have documented the loss of BMD in the spine and hip as measured by dual x-ray absorptiometry. In one study, the loss of BMD was most pronounced at the radius.

Methods. In a chart review of patients receiving ADT, the spine and hip BMD results were recorded in 89 patients. Of these 89 patients, the BMD of the radius was also recorded in 53.

Results. In the 89 patients with BMD measurements of the spine and hip, 24 (26.9%) had osteoporosis of the hip or spine as defined by a T score of -2.5 or less, and 45 patients (50.6%) had osteopenia (T score -1.0 to -2.5). In the subset of 53 patients who also had the BMD of the radius measured, the results of the BMD of the radius changed the category of diagnosis in 18 patients (34%). The prevalence of osteoporosis increased from 25% to 53% when the results of the radius were included.

Conclusions. Men with prostate cancer treated with ADT have a high prevalence of osteopenia and osteoporosis as determined by peripheral and central BMD measurements. The use of the peripheral BMD measurement appears to identify more patients with osteoporosis and suggests its use in the evaluation of osteoporosis in men receiving ADT. UROLOGY 67: 152–155, 2006. © 2006 Elsevier Inc.

Low bone mineral density (BMD) and fractures are prevalent in men with prostate cancer receiving androgen-deprivation therapy (ADT).¹ Recent prospective studies have demonstrated a significant loss of BMD in the spine and hip in the first year after ADT.^{2–4} In the study by Mittan *et al.*,³ the loss of BMD was most pronounced at the radius (5.3%) 12 months after the initiation of ADT. Although measuring the BMD of the spine is recommended in the assessment of osteoporosis in postmenopausal women and for monitoring therapy, it is also well recognized that osteoarthritis involving

the spine or aortic calcifications may overestimate the BMD as measured by dual x-ray absorptiometry (DXA). This may mask the diagnosis and amount of bone loss, especially in older men who have a greater incidence of osteoarthritis in the spine and aortic calcifications. The use of the spine as a site for determining osteoporosis in men has been questioned. For this reason, we began to measure the radius routinely as an additional site in older men at risk of osteoporosis. We, therefore, wished to determine the prevalence of osteopenia and osteoporosis using central (spine and hip) and peripheral (radius) BMD measurement in men with prostate cancer who were receiving ADT.

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MATERIAL AND METHODS

SUBJECTS

The University of Texas Health Science Center Institutional Review Board and Veterans Affairs Research and Development Committee reviewed and approved this chart review. All identifiers were removed from the data, and informed consent was not required.

The medical records of patients at their urology clinic visit at the South Texas Veterans Affairs Health Care System were reviewed. We identified 125 men with prostate cancer who were receiving ADT or who had undergone orchiectomy. BMD results were found for 89 men. No data were collected with regard to previous treatment of prostate cancer (ie, radical prostatectomy or radiotherapy). Data were collected on the length and form of ADT (ie, gonadotrophic-releasing hormone or luteinizing hormone-releasing hormone agonist therapy or orchiectomy). None of the patients had prior bone disease, but bone metastasis was documented by technetium bone scan in 6 patients. Calcium or vitamin D supplementation was not recorded.

BMD MEASUREMENTS

BMD by DXA was performed using a Hologic DPX 2000 located at the General Clinical Research Center at the University of Texas Health Science Center in San Antonio, Texas. The sites measured included the L1–L4 lumbar spine, total hip, femoral neck, and nondominant radius, including the total radius and distal one-third sites. The distal one-third radius is composed of 20% trabecular and 80% cortical bone and is determined automatically by the DXA software to lie between 83 and 103 mm from the distal endplates of the radius. All measurements were obtained and analyzed using the standard protocols provided by the manufacturer. According to the World Health Organization classification criteria,⁵ patients were considered to have osteoporosis if the spine, total hip, or femoral neck or radius had a BMD of 2.5 SD or more below the young adult peak bone mass or T score. Patients were classified as having osteopenia if the BMD was between 1 and 2.5 SD below the young adult peak bone mass or T score. The male reference population was used.⁶

LABORATORY MEASUREMENTS SUBGROUP

Some of the patients who met the criteria for osteopenia or osteoporosis of the spine or hip were referred for additional investigation to identify any secondary causes of bone loss, in addition to the cause known from ADT-induced hypogonadism. Serum intact parathyroid hormone (normal 15 to 65 pg/mL), 25-hydroxyvitamin D (25-OH D, normal 10 to 47 pg/mL), chemistry 20, and 24-hour urine collection for creatinine, calcium, and N-telopeptide were measured in 34 patients. The serum and urine calcium and creatinine concentrations were measured using a multichannel autoanalyzer (LX-20, Beckman-Coulter, Fullerton, Calif). 25-OH D levels were measured using a chemiluminescence immunoassay (ARUP, Salt Lake City, Utah). Intact parathyroid hormone levels were determined by chemiluminescence (Immulite, Diagnostic Products, Los Angeles, Calif).

STATISTICAL ANALYSIS

Data are expressed as the percentage of the total number. The comparison of the radius versus spine/hip results for patients to be classified as having osteoporosis was analyzed by McNemar's test in the matched case-control study. The likelihood of a diagnosis change with radius for age less than 80 years versus 80 years or older was analyzed by the chi-square test. *P* values less than 0.05 were considered statistically significant. The statistical analyses were performed using Stata statistical software for Windows, release 8.0 (Stata, College Station, Tex).

RESULTS

We reviewed the patient charts of 125 men with prostate cancer who were receiving ADT at the

Urology Clinic of the South Texas Veterans Affairs Health Care System. All men diagnosed with prostate cancer were diagnosed by prostate biopsy and tissue diagnosis of adenocarcinoma. None of the men had received prior chemotherapy. Of the 125 patient charts reviewed, 89 patients (71%) had a BMD measurement of the hip and spine, indicating a high referral rate by the urologist for BMD assessment independent of other osteoporosis risk assessments. The mean age was 77 ± 7 years. Of the 125 patients, 30.3% were Mexican American, 58.4% were white, and 9% were African American; for 2.2% the race/ethnicity was unknown. The mean baseline BMD T score at the spine was -0.50 ± 2.3 and at the total hip was -0.95 ± 1.1 . Fifty-three patients also had the BMD of the radius measured. In this group of patients, the mean age was 76 ± 8 years (range 56 to 96, median 78). Of the 53 patients with the radial BMD measured, 24% were Mexican American, 66% were white, and 9% were African American. The mean time of ADT was 2.7 ± 2.5 years (range 6 months to 9 years, median 2 years); 27 patients had received ADT for less than 2 years, 13 for 2 to 4 years, and 13 for more than 4 years. According to the medical records, no patient had received bisphosphonate therapy, although 6 subjects had had bone scans positive for bone metastasis. Calcium or vitamin D supplementation was not recorded.

In those patients with BMD measurements of the spine and hip only (data not shown), 77% were classified as having osteopenia or osteoporosis. The criteria for these designations were made on the basis of the spine, total hip, or femoral neck having a BMD of greater than 1.0 SD below the young adult peak bone mass or a T score of less than -1.0 . Of the 89 patients, 24 (26.9%) had osteoporosis of the hip or spine as defined by a T score of -2.5 or less, 45 (50.6%) had osteopenia (T score -1.0 to -2.5), and 20 (22.5%) were classified as normal (T score -1.0 or more). In the subset of 53 patients who also had the BMD of the radius measured, 44 (83%) were categorized as having either osteopenia or osteoporosis. The mean baseline T score at the total radius was -2.5 ± 1.7 , and the mean baseline T score of the distal one-third radius was -2.26 ± 1.9 (range 1.3 to -7.0). If only the results of the spine were used, about one half of the 24 patients (45%) were considered normal, 21% fulfilled the criteria for osteopenia, and 11% fulfilled the criteria for osteoporosis (Fig. 1). The spine could not be analyzed in 12 patients either because of a history of spine surgery or because the landmarks of the spine were unidentifiable. If only the hip was used (either the total hip or the femoral neck), only 11 (21%) of 53 patients were normal, 60% fulfilled the criteria for osteopenia, and 19% fulfilled the criteria for osteo-

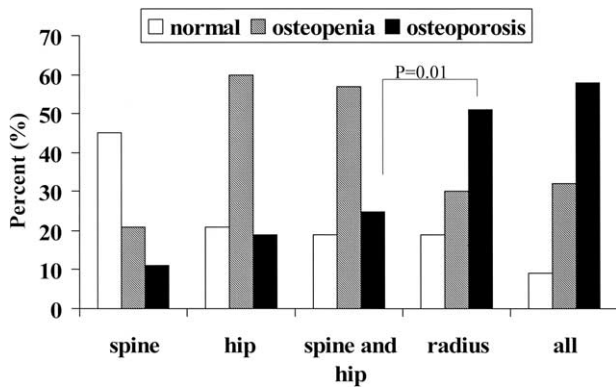


FIGURE 1. Prevalence of osteoporosis in men with prostate cancer treated with ADT by spine BMD alone ($n = 41$), hip BMD alone ($n = 53$), both spine and hip BMD ($n = 53$), radius BMD alone ($n = 53$), and all sites ($n = 53$).

porosis (Fig. 1). Finally, if the total radius or distal one-third radius were used, 19% were normal, 36% fulfilled the criteria for osteopenia, and 45% fulfilled the criteria for osteoporosis (Fig. 1). Thirteen men fulfilled the criteria for osteoporosis using the central (spine or hip) BMD measurement and 28 fulfilled the criteria for osteoporosis if the radius was included. Thus, 15 more men were identified as having osteoporosis, and the prevalence of osteoporosis doubled when the results of the radius were used. The odds ratio for patients to be classified as having osteoporosis using the radius BMD versus the spine or hip combined was 3.75 (95% confidence interval 1.19 to 15.5; exact $P = 0.019$, McNemar's test). Thus, patients were more likely to be identified having osteoporosis using the radius BMD than the spine and hip BMD combined. The results of the BMD of the radius changed the category of diagnosis (either from normal to osteopenia or osteopenia to osteoporosis) in 18 (34%) of the 53 patients who had the radius measured.

The diagnosis was changed in 50% of men 80 years old or older ($n = 22$) and was changed in 23% of men younger than 80 years old ($n = 31$). The odds ratio for the diagnosis change was 3.4 (95% confidence interval 1.06 to 11.09; $P = 0.038$) for patients 80 years or older compared with those younger than 80 years old. Therefore, the radius was more likely to change the category of diagnosis in patients 80 years old or older than in those younger than 80 years of age. This suggests that including the radius would be useful for all ages, and more significant in older patients. The results of the spine BMD was not interpretable in 6 men older than 80 years and in 6 men younger than 80 years. In white men ($n = 35$), the diagnosis was changed in 34% when the radius was used. In African-American men ($n = 5$), the diagnosis was

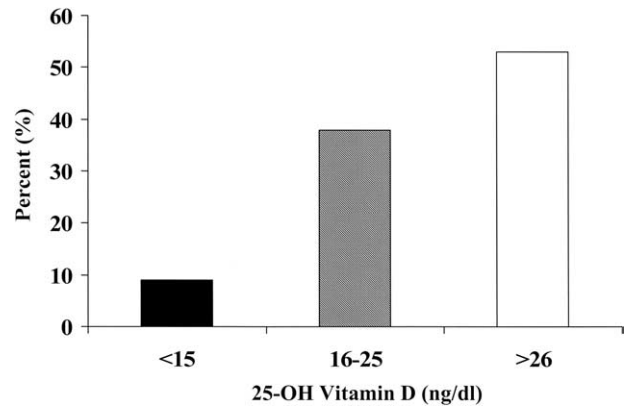


FIGURE 2. 25-OH vitamin D levels in men with prostate cancer treated with ADT diagnosed with osteopenia or osteoporosis ($n = 34$).

not changed in any. In Mexican-American men ($n = 13$), the diagnosis was changed in 38%.

Thirty-four patients with the diagnosis of osteoporosis or osteopenia were referred to a specialist and underwent an evaluation of secondary causes of osteoporosis. Three patients (8.8%) were classified as having vitamin D deficiency, with an absolute 25-OH D concentration of 15 ng/mL or less. Thirteen patients (38%) had an absolute 25-OH D concentration of 16 to 25 ng/mL and were considered to have vitamin D insufficiency (Fig. 2). An intact parathyroid hormone concentration greater than 50 pg/mL was found in 11 patients (31.4%). In addition, urinary concentrations of N-telopeptide, a marker of bone resorption, were elevated (more than 38) in 73.3%. The increase was most prevalent and pronounced in patients with osteoporosis (81.3%) compared with patients with osteopenia (64.3%).

COMMENT

In the current study, we have confirmed the high prevalence of osteoporosis diagnosed by spine and hip BMD measurements in men with prostate cancer who were receiving ADT. The use of the radius as an additional site, especially in men older than 80 years, identified more men with osteoporosis. We also identified a high prevalence of vitamin D deficiency or insufficiency and secondary hyperparathyroidism in men diagnosed with osteoporosis. These results suggest that BMD at the radius should be measured in addition to, or in place of, the spine BMD, as measured by DXA in older men with prostate cancer who are receiving ADT. In addition, these results also suggest that vitamin D deficiency and secondary hyperparathyroidism may be additional risk factors for osteoporosis in men with prostate cancer receiving ADT.

The relationship between bone density and fracture risk is strong in women, with the strongest

predictive site being the BMD of the total hip.⁷ In contrast to women, the BMD of the forearm is the strongest predictor of fractures in men.⁸ Bone loss immediately after estrogen deficiency in women occurs predominately in the spine. Older men, however, tend to have significant degenerative disease involving the spine that renders the spine BMD by DXA difficult to interpret. This may cause underdiagnosis of osteoporosis in this population if only the central (spine and hip) BMD by DXA is measured. In a recent study, bone loss after ADT was most pronounced in the radius.³ Although hypogonadal osteoporosis is associated with a reduction in both cortical and trabecular bone density, it has been noted that low testosterone levels correlated strongly with the BMD of the ultra distal radius.⁹ In addition, in men with restored gonadal function after reversal of hyperprolactinemia, a significant increase in radial bone density was noted compared with a minimal rise in the BMD in the spine.¹⁰ Although one may argue that including the radius adds to the cost, measuring only the radius will save money and time. More data are needed to determine whether the radius truly predicts the risk of fractures in this population, whether therapy with a bisphosphonate improves the BMD at the radius, and whether the radius can be used in monitoring therapy in the prevention of bone loss. In addition, more studies are needed to determine the effect of therapy in osteoporosis prevention on other skeletal-related side effects of prostate cancer.

Vitamin D deficiency is a common disorder of calcium metabolism and osteoporosis, with an incidence that increases with advanced age. The serum 25-OH D level is the most clinically reliable indicator of vitamin D status. Malabanan *et al.*¹¹ and others consider a level of 25-OH D greater than 30 ng/mL to be optimal and below to be vitamin D insufficiency. The clinical consequences of vitamin D deficiency are secondary hyperparathyroidism and an increased risk of osteopenia and bone fractures.¹² Vitamin D levels are also known to vary with seasonal changes, peaking in the summer and reaching a low in the winter.^{13,14} This is especially true at latitudes greater than 40°. Our center is located much lower than 40° latitude, in South Texas, a region of abundant sunshine and temperate climate. Although we did not document the season in which the 25-OH D levels were drawn, we believe seasonal affects were less relevant. In addition, the prevalence of vitamin D deficiency is not known in men of similar age not receiving ADT at our institution. Although our sample size was small, the finding that more than one fourth of our subjects had either vitamin D deficiency or insufficiency was quite surprising. The prevalence of vitamin D deficiency in this population needs to be confirmed by other studies.

CONCLUSIONS

Men with prostate cancer treated with ADT show a high prevalence of osteopenia and osteoporosis by peripheral and central BMD measurements. The use of peripheral BMD appears to identify more patients with osteoporosis and suggests its use in the evaluation of osteoporosis in men with prostate cancer receiving ADT. Additional studies are needed to confirm the use of the radius BMD in fracture risk prediction and the use of this site in monitoring therapy. Vitamin D deficiency should be considered in the evaluation and treatment of osteoporosis in men with prostate cancer.

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REFERENCES

1. Shahinian VB, Kuo YF, Freeman JL, *et al*: Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 352: 152–164, 2005.
2. Smith MR, McGovern FJ, Zeitman AL, *et al*: Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med* 345: 948–955, 2001.
3. Mittan D, Miller E, Basler J, *et al*: Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. *J Clin Endocrinol Metab* 87: 3656–3661, 2002.
4. Smith MR, Eastham J, Gleason DM, *et al*: Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for non metastatic prostate cancer. *J Urol* 169: 2008–2012, 2003.
5. The WHO Study Group: *Assessment of Fracture Risk and Its Application to Screening for Postmenopausal Osteoporosis*. Geneva, World Health Organization, 1994.
6. Faulkner KG, and Orwoll E: Implications in the use of T-scores for the diagnosis of osteoporosis in men. *J Clin Densitom* 5: 87–93, 2002.
7. Marshall D, Johnell O, and Wedel H: Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 312: 1254–1259, 1996.
8. Melton LJ, Atkinson EJ, O'Connor MK, *et al*: Bone density and fracture risk in men. *J Bone Miner Res* 13: 1915–1923, 1998.
9. Kelly PJ, Pocock NA, Sambrook PN, *et al*: Dietary calcium, sex hormones and bone density in men. *BMJ* 300: 1361–1364, 1990.
10. Greenspan SL, Oppenheim DS, and Kilbanski A: Importance of gonadal steroids to bone mass in men with hyperprolactinemic hypogonadism. *Ann Intern Med* 110: 526–531, 1989.
11. Malabanan A, Veronikis IE, and Hollick MF: Redefining vitamin D insufficiency. *Lancet* 351: 805–806, 1998.
12. Lips P: Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocrinol Rev* 22: 477–501, 2001.
13. Thomas MK, Lloyd-Jones DM, Thadhani RI, *et al*: Hypovitaminosis D in medical inpatients. *N Engl J Med* 338: 777–783, 1998.
14. Harris SS, and Dawson-Hughes B: Seasonal changes in plasma 25-hydroxyvitamin D concentrations of young American black and white women. *Am J Clin Nutr* 67: 1232–1236, 1998.