Peripheral or Axial Bone Density Measurements to Identify Osteoporosis in Prostate Cancer Patients Undergoing Androgen Deprivation Therapy?

Vivek K. Wadhwa and Nigel J. Parr

OBJECTIVES
To compare aDEXA and pDEXA in patients with advanced prostate cancer (PCa) undergoing androgen deprivation therapy (ADT). A significant proportion of patients presenting with advanced PCa are osteoporotic, and many will become so because of ADT. Guidelines have recommended bone densitometry assessment before beginning ADT, with subsequent monitoring. However, axial dual energy x-ray absorptiometry (aDEXA) scanners, being large, expensive, and hospital-based, are not always widely available. Peripheral DEXA (pDEXA), with portable, office-based machines can be used, but the results have mostly been compared with aDEXA in women without cancer.

METHODS
A total of 73 men (mean age 76 years) with advanced PCa, who were receiving ADT and found to be osteoporotic (T score ≤ −2.5) on pDEXA (Osteometer-DTX200) were also scanned by aDEXA (Hologic-QDR 4500 DEXA). Comparisons were made between the bone mineral density measurements of the ultradistal forearm and axial sites.

RESULTS
The mean ± SD T score of the forearm, femoral neck, total hip, and lumbar spine was 3.4 ± 0.8, −2.6 ± 1.0, −1.8 ± 0.9, and −0.8 ± 1.3, respectively. Of the 73 men, 67, 61, and 39 were found to be osteoporotic or osteopenic at the femoral neck, total hip, and lumbar spine, respectively. The correlation coefficients between the forearm and axial T scores were all significant (P < .05): femoral neck, r = 0.32, total hip, r = 0.34, lumbar spine, r = 0.24.

CONCLUSIONS
When osteoporosis is diagnosed on pDEXA, most patients with PCa will be either osteoporotic or osteopenic at the hip, but a large proportion will be normal at the lumbar spine. In this setting, lumbar DEXA might be less reliable at predicting the fracture risk probably owing to calcification and degenerative changes.

Prostate cancer (PCa) is the most common male cancer and second leading cause of cancer death. Androgen deprivation therapy (ADT) is the mainstay of treatment for advanced disease and is increasingly being used in nonmetastatic PCa, for both locally advanced disease and biochemical failure. This has led to more men receiving ADT and for a longer duration. ADT reduces testosterone to castrate levels within 2 weeks and is associated with accelerated bone loss and increased fracture risk. Furthermore, significant bone loss might have occurred even before ADT. We have previously reported that approximately 40% of men presenting with advanced PCa are already osteoporotic, with a mean bone mineral density (BMD) 6.6% less than that in age-matched controls. Fractures significantly decrease the quality of life and independently correlate negatively with PCa survival.

It has been recommended that men undergo routine bone densitometry measurements before beginning ADT, with additional monitoring once or twice yearly. Conventionally, the spine and hip are regarded as the most important measurement sites using axial dual energy x-ray absorptiometry (aDEXA). However, axial scanners are expensive, with significant maintenance costs, are large, and tend to be limited to specialist centers. As a result, conventional DEXA is not always widely available to all patients. This has led to an increasingly need to make bone densitometry measurements more widely available to allow for the identification of those at high risk of fragility fractures, for whom preventive treatment, such as bisphosphonates, can be considered. Peripheral devices, measuring the forearm BMD, are portable, are less costly, and can be used in the office/clinic setting, with the potential for a rapid throughput of patients. With the
ability to deliver immediate results, they provide a “point of care” test. Moreover, forearm BMD has been shown to be the strongest predictor of fracture risk in men and is not affected by the calcification and degenerative changes that can corrupt the lumbar spine BMD measurement in older men. In addition, the distal radius is rarely involved by osteoblastic metastases, which can corrupt aDEXA measurements at the lumbar spine.

Previous studies comparing bone densitometry measurements at different sites have predominantly been in postmenopausal women without cancer. The aim of our study was to compare aDEXA and peripheral DEXA (pDEXA) in men with advanced PCa undergoing ADT.

**MATERIAL AND METHODS**

**Patients**

We studied 73 men (mean age ± SD 76 ± 7.3 years, range 53-89) with locally advanced nonmetastatic prostate PCa, undergoing ADT, who were osteoporotic at the forearm. All men had a tissue diagnosis of PCa. Patients with any illness or taking medication that would affect bone and mineral metabolism, including bisphosphonates, were excluded.

**Study Design**

The height, weight, and body mass index were recorded for all men. The patients underwent a radionuclide bone scan to assess their metastatic status. Posteroanterior and lateral radiographs of the thoracolumbar spine were obtained. A fracture was defined by altered morphology and a decrease in vertebral height of ≥20% at any aspect of the vertebral body (anterior, central, or posterior). The peripheral BMD of the nondominant forearm (ultradistal region) was measured using an Osteometer DTX-200 scanner (Osteometer Meditech, Hawthorne, CA). Within 4 weeks, the patients subsequently underwent axial BMD measurements of the femoral neck, total hip, and lumbar spine (L1-L4), using a Hologic QDR-4500 (Hologic, Waltham, MA). Quality control was performed daily, by scanning a phantom provided by the manufacturer, to ensure the long-term stability of the machines. All patients were evaluated at a single center, using the same bone densitometers to provide greater precision in monitoring the BMD.

The values obtained included the T scores (difference between a patient’s BMD and the mean BMD in healthy young adults, matched for sex and ethnic origin), Z scores (difference between a patient’s BMD and the mean BMD expected for the patient’s peers, matched for age, sex, and ethnic origin), and BMD measurements (g/cm²). The T and Z scores for the patients were calculated using the manufacturer’s reference data for the spine and forearm sites and the Third National Health and Nutrition Examination Survey reference data for the femoral neck site. The men were classified according to the World Health Organization criteria, defining osteoporosis as a T score of ≤−2.5 at the spine, hip, or forearm, osteopenia as a T score of −1.0 to −2.5, and normal as a T score of ≥−1.0.8

The Local Ethics Research Committee approved the protocol.

**Statistical Analysis**

The results are presented as the mean ± SD. Linear regression analyses were performed between the pDEXA and aDEXA measurements, and Pearson correlation coefficients were determined. Scatter plots were constructed to demonstrate the comparison between the variables. Statistical analysis was performed using the Statistical Package for the Social Sciences, version 15.0 (SPSS, Chicago, IL). All P values are two-sided, and P < .05 was considered statistically significant.

**RESULTS**

The median duration of ADT was 24 months. The mean height was 171.5 ± 6.6 cm, weight 70.3 ± 11.7 kg, and body mass index 23.8 ± 3.3 kg/m². Bone scans showed no evidence of metastases. Radiographs of the thoracolumbar spine revealed wedge fractures in 11 patients (15%), degenerative changes, including osteophytosis and disc space narrowing, in 59 patients (81%), and normal vertebrae in 3 patients (4%). Patients with a vertebral wedge fracture had a significantly greater mean lumbar spine T score of −0.1 ± 1.1 compared with −1.0 ± 1.3 in those without fracture (P < .001).

The precision, assessed by the coefficient of variation, of the DTX-200 scanner was 1.6% for the forearm. For the Hologic QDR-4500, the coefficient of variation was 1.5% for the femoral neck, 1.4% for the total hip, and 1.2% for the lumbar spine. The mean BMD measurements at the peripheral and axial sites are listed in Table 1. Of the 73 patients identified as osteoporotic at the forearm, 67, 61, and 39 had a reduced BMD (osteoporosis or osteopenia) at the femoral neck, total hip, and lumbar spine, respectively. The proportion of patients who were osteoporotic, osteopenic, and normal at different sites is shown in Figure 1.

The correlation coefficients between the forearm and axial sites for T scores, Z scores, and BMD (g/cm²) are listed in Table 2. The strongest correlation between the pDEXA and aDEXA T scores was between the forearm and total hip (r = 0.34). The weakest was between the...
forearm and lumbar spine \((r = 0.24)\). All correlations between the forearm and axial sites were statistically significant \((P < .05)\). Figure 2 shows scatterplots of T score measurements of the forearm against axial sites.

**COMMENT**

Osteoporosis is increasingly being recognized as a common condition in older men. Osteoporotic fractures are associated with significant morbidity and mortality in elderly men, with a 30% mortality rate from hip fracture at 1 year.\(^9\) One third of all hip fractures occur in men, and more than one half of those who survive require long-term care.\(^9\) Advanced PCa itself can result in increased bone turnover, probably owing to mild parathyroid overactivity.\(^10\) Furthermore, ADT for PCa causes rapid and severe bone loss, with BMD decreases of 4%-13% yearly.\(^11\) BMD has been shown to predict for fractures as well as the blood pressure predicts for stroke and better than the serum cholesterol predicts for cardiovascular disease.\(^12\) A reduction in BMD by 1 SD can increase the risk of fractures by up to threefold.\(^13\) DEXA scans measure the BMD and can identify those at risk of fracture and target preventative treatment. Compared with aDEXA scanners, those for pDEXA are smaller, cheaper, simpler to operate, and have an exceptionally low radiation dose (0.001 \(\mu\)Sv compared with 12 \(\mu\)Sv for the hip or spine). A meta-analysis of prospective studies, by Marshall et al.,\(^12\) to determine how well BMD measurements at different skeletal sites predict for different fracture types found most sites had virtually the same predictive ability. A single BMD measurement at the forearm was able to predict the fracture risk, including hip fractures, during a 25-year period in a cohort of 410 women, with a mean age 54 years.\(^14\) In contrast to extensive studies in women, limited studies are available of BMD prediction for fractures in men. A population-based sample of 348 men (aged 22-90 years) found forearm BMD to be the strongest predictor of fracture risk.\(^6\) Furthermore, osteoporotic fracture risk was associated with BMD measurements at all sites (ie, neck, trochanter, total hip, lumbar spine, and wrist) in both sexes \((P < .001)\), except for spinal BMD in men. In a Swedish study of 242 men prospectively followed up for 7 years, the forearm BMD predicted forthcoming fractures at all sites, including the forearm, hip, and spine.\(^15\) Furthermore, in a prospective study of 15 men with PCa undergoing 12

**Table 2.** Correlation between T scores, Z scores, and BMD for 73 patients measured by peripheral and axial dual-energy x-ray absorptiometry

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<tr>
<td>Forearm and spine L1-L4</td>
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BMD, bone mineral density.
months of ADT, bone loss was most marked at the forearm. Testosterone has been shown to be an independent positive predictor of BMD at the forearm and hip, but not at the lumbar spine, in 2908 Swedish men (mean age 75 years), with low testosterone an independent predictor of osteoporosis–related fracture. In our study, the correlation was better between the forearm and total hip T scores ($r = 0.34$) than between the forearm and lumbar spine ($r = 0.24$). Many have advocated the use of Z scores, which compare individual patients to others of the same age. We found similar correlation coefficients between the peripheral and axial Z scores (Table 2).

We assessed the ultradistal forearm, composed predominantly of trabecular bone (65%), similar to the spine (66%) and total hip (50%), which is more sensitive to causes of bone loss than cortical bone. In contrast, the femoral neck is composed of 25% trabecular and 75% cortical bone. Other forearm sites such as the mid-distal and one-third radius are composed predominantly of cortical bone.

The trabecular-rich lumbar spine is generally considered the most relevant measure of BMD for the evaluation of longitudinal changes, because of its rapid response to aging, disease, and treatment. However, in a population-based study of 113 men and 187 women aged $\geq 60$ years (mean age 69 years), Jones et al. demonstrated that the lumbar spine BMD might be erroneous owing to spinal degenerative disease. Men with osteophytes had 21% greater BMD than those without. The spinal BMD in these patients might not accurately predict the underlying fracture risk. As in our study, most older men (96%) were found to have evidence of degenerative changes or fractures on spinal radiography. In elderly men (mean age 75 years) receiving 12 months of ADT, Mitter et al. found the BMD in the spine did not decrease significantly, in contrast to that in the total hip and forearm. In older men, osteoarthritis in the spine with osteophyte formation and aortic calcifications can falsely elevate the BMD, masking bone loss due to increased age and ADT. When correlating the lumbar spine BMD with that in other sites, Mole et al. excluded patients $>70$ years. However, men presenting with advanced PCa requiring hormonal manipulation are often elderly. The mean age in our study of men taking ADT for a median of 2 years was 76 years. Furthermore, in patients with PCa, sclerotic metastases in the lumbar spine can corrupt the BMD measurements.

Vertebral fractures are the most common and yet least well-investigated fractures, especially in men. Only about one third are clinically recognized. However, missed silent fractures contribute to increased morbidity and mortality, including back pain, kyphosis, and functional impairment affecting daily living. The presence of a prevalent vertebral fracture increases the risk of future vertebral fractures and treatment can prevent this. A study by Shahinian et al. of 50613 men in the Surveillance, Epidemiology, and End Results-Medicare database revealed that men undergoing ADT and surviving $\geq 5$ years from diagnosis, had a fracture rate of 19.4% compared with 12.6% for those not receiving ADT. The fracture rate increased with the number of doses of luteinizing hormone-releasing hormone analog received. The rate of spinal fractures was 3.2% in those receiving ADT compared with 1.6% for those without ADT. We believe retrospective database studies have underestimated the true incidence of vertebral fractures. Our study revealed a 15% prevalence of vertebral fractures in a group of elderly men with a disease associated with reduced BMD and taking ADT for a median of 2 years. This compares to a prevalence of 6.9% in the Rotterdam population-based study of 1498 men aged $\geq 55$ years. In patients with PCa, who have been taking ADT for prolonged periods and who present with back pain, after excluding metastatic disease, it seems clear that radiography of the thoracolumbar spine should be performed to detect vertebral compression fractures.

Other studies correlating axial and pDEXA have predominantly been in women. Lu et al. reported the correlation between different BMD sites in 7671 women ($\geq 65$ years, mean 71) from the Study of Osteoporotic Fractures. The correlation coefficients between BMD measurements (g/cm$^2$) of the forearm and axial sites were highly significant ($P < .0001$) at the femoral neck ($r = 0.53$), total hip ($r = 0.60$), and lumbar spine ($r = 0.57$). Mole et al. evaluated 88 patients (13 men and 75 women) aged 23-89 years. The correlation between Z scores of the ultradistal forearm and femoral neck ($r = 0.72$, n = 33) was better than between the forearm and lumbar spine ($r = 0.63$, n = 33), but patients $>70$ years or with vertebral fractures/deformity were excluded from the study.

Data comparing peripheral and axial scanning in patients with PCa are limited. Bae et al. recently compared accuDEXA of the middle phalanx of the middle finger with hip DEXA in patients with PCa undergoing ADT. The T scores between the 2 sites had a weak linear correlation ($r = 0.04$, $P = .1$). This was probably because the phalangeal bones have a greater ratio of cortical-to-trabecular bone than even the femoral neck.

After a chart review study, Bruder et al. suggested forearm BMD measurement should be used in place of, or in addition to, lumbar spine BMD measurement in elderly men with PCa undergoing ADT. Bruder et al. determined the prevalence of osteopenia and osteoporosis by aDEXA and pDEXA measurements in 89 patients with PCa (mean age 77 years) undergoing ADT for a mean duration of 2.7 years. BMD measurements revealed osteoporosis of the hip or spine in 27% and osteopenia in 51% of patients. In a subset of 53 patients, who also underwent BMD measurement of the forearm, the prevalence of osteoporosis increased from 25% to 53%. However, data regarding correlation coefficients were not included, and no fracture assessment was performed with...
plain radiographs. Nevertheless, we agree with their conclusion that forearm DEXA is a useful investigation in the assessment of osteoporosis in patients with PCa undergoing ADT. One limitation of our study was a lack of information on incident fractures. We advocate large-scale prospective studies, with fracture incidence, to evaluate the use of forearm BMD measurement in fracture risk in men with PCa undergoing ADT.

CONCLUSIONS
Our findings support the use of forearm pDEXA in patients with PCa undergoing ADT. The correlations with the hip were better than those for the lumbar spine, which is often affected by degenerative changes in this older age group of patients. The use of pDEXA, which can be used in the setting of a clinic, will make BMD investigations more accessible to patients. However, clinicians must bear in mind that BMD measurements only provide an estimate of a patient’s fracture risk. Other risk factors, such as age, previous fragility fracture, medication, and low BMD, must be considered when determining the optimal treatment for individual patients.

Acknowledgment. To Helen Wong, Statistician, Clatterbridge Centre for Oncology, UK for statistical advice.

References