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Vertebral Fractures and the Misclassification of Osteoporosis in Men with Prostate Cancer

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Abstract

Purpose—Androgen deprivation therapy (ADT) has become the cornerstone of treatment for both advanced and non-metastatic prostate cancer. The presence of a non-traumatic vertebral fracture (VF) identifies a patient who has clinical osteoporosis. Vertebral Fracture Analysis (VFA), a dual-energy X-ray absorptiometry (DXA)-based technology identifies VFs in conjunction with a standard bone mineral densitometry (BMD) exam. The objective of this study is to determine if VFA will increase the diagnosis of osteoporosis in men with prostate cancer on ADT.

Materials and Methods—116 men ≥ 60 years of age with non-metastatic prostate cancer receiving androgen-deprivation therapy (ADT) for ≥ 6 months underwent DXA of the spine, hip, and one-third distal radius, VFA), and conventional vertebral x-rays.

Results—Approximately 40% of the men had clinically defined osteoporosis. The use of conventional DXA criteria (spine and hip) alone resulted in the misdiagnosis of approximately 75% of patients. VFA and addition of the one-third distal radius site performed by DXA both increased the rate of diagnosis and reduces the misclassification of osteoporosis in men with prostate cancer, compared to conventional DXA criteria alone. Analysis indicated that VFA assessment of mild, moderate, and severe fractures from all readable vertebrae (T5-L4) had a kappa, sensitivity, and specificity of 0.92, 100% and 95%, respectively, with semi-quantitative radiography.

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Conclusions—Men with prostate cancer on ADT should be screened for osteoporosis at the initiation of therapy, and evaluation should include DXA of the one-third distal radius in addition to the spine and hip, as well as evaluation for VFs.

Keywords

androgen deprivation therapy; vertebral fractures; vertebral fracture assessment; osteoporosis; bone mineral density

Introduction

Prostate cancer is the most common visceral malignancy and the second leading cause of cancer-related death in men.¹ Androgen deprivation therapy (ADT) has become the cornerstone of treatment for both advanced and non-metastatic prostate cancer, nearly quadrupling in use over the past decade.^{2,3} Despite its therapeutic benefits, ADT has been associated with bone loss and increased fracture rates.⁴ Notably, the duration of ADT treatment has been associated with the magnitude of bone loss and fracture risk.⁵ This is especially important given that many patients are on ADT permanently.⁶

Vertebral fractures (VFs) are the most common type of osteoporotic fracture. The presence of a non-traumatic VF identifies a patient who has clinical osteoporosis. VFs have been associated with increased morbidity and mortality and greatly diminished quality of life.^{7,8} Additionally, a VF increases the risk of a new fracture up to 4-fold, thereby changing the patient's therapeutic management.⁹ However, only one quarter to one-third of patients with VF present with symptoms associated with the fracture.¹⁰ Given the significant clinical impact of VFs, their detection is of prime importance to the care of the patient.

Lateral radiographs of the thoracolumbar spine have been the gold standard in identifying VFs. The Genant semi-quantitative approach is most often used in osteoporosis evaluation because of its objectivity and reproducibility.^{11,12} However, standard radiography requires considerable radiation exposure and often is performed at a different hospital or radiology unit. In contrast, Vertebral Fracture Analysis (VFA) is a dual-energy X-ray absorptiometry (DXA)-based technology that identifies VFs in conjunction with a standard bone mineral densitometry (BMD) exam. Thus, VFA has the potential to be a more convenient method of identifying VFs, using radiation levels similar to standard DXA and much lower than a lateral X-ray. Recent studies have indicated that VFA exhibits good agreement with radiography reliably aiding in the identification of VFs.^{13,14}

There are currently no official bone density guidelines to assess skeletal integrity in men with prostate cancer on ADT. Furthermore, there are no guidelines to assess which men with prostate cancer are at greatest risk for bone loss. Therefore, the objectives of this study were to determine if VFA by DXA would improve the diagnosis of osteoporosis in men with prostate cancer on ADT who were being screened by BMD alone; assess the accuracy of VFA identification by DXA relative to the reference standard of vertebral radiography; and determine if the inclusion of the 1/3 distal radius site in conjunction with spine, hip and femoral neck BMD increases the identification of men with clinically-defined osteoporosis.

Methods and Materials

Design and Subjects

This cross-sectional study included men ≥ 60 years of age with non-metastatic prostate cancer receiving androgen-deprivation therapy (ADT) for ≥ 6 months. ADT included orchiectomy or gonadotropin releasing hormone agonists, with or without an anti-androgen.

Patients were recruited from physicians in the Pittsburgh, Pennsylvania area and screened via telephone interviews. Men were excluded if they had metastatic prostate cancer, had non-metastatic prostate cancer with a prostate-specific antigen level > 4 (unless undergoing adjustments to their therapy), or used medications known to alter bone mineral metabolism within the past year (i.e., bisphosphonates, corticosteroids, anti-seizure medications). Patients were advised of the nature of the study and provided written informed consent before enrollment. The University of Pittsburgh Institutional Review Board approved the study.

Outcome Measures

Participants were evaluated at the Clinical and Translational Research Center at the University of Pittsburgh. Bone mineral density (BMD, g/cm^2) of the hip (total hip and femoral neck), lumbar spine, and 1/3 distal radius was assessed by dual-energy x-ray absorptiometry (DXA), using a Hologic Discovery A (Hologic, Inc; Bedford, MA). Measurements were obtained and analyzed using standard manufacturer protocols. BMD was evaluated as T-scores (number of standard deviation units from adult peak bone mass). T-scores were used to classify participants according to the World Health Organization criteria for defining osteoporosis (T-score ≤ -2.5 SD), low bone mass (T-score between -2.5 and -1.0 SD), and normal (T-score ≥ -1.0 SD).¹⁵ The coefficient of variation (CV) for our DXA machine is 1.3% for the spine and 1.4% for the total hip BMD.¹⁶

Vertebral fracture analysis (VFA) was performed during the same initial visit through lateral spine imaging of T5-L4 on the Hologic Discovery A, using the manufacturer's standard protocols. The vertebral bodies from the scan were visually identified by a technician certified by the International Society of Clinical Densitometry (ISCD) and classified using computer-calculated reductions in vertebral height according to the method of Genant.¹¹ Fractures were classified as grade 1 (mild) with a 20–25% loss of vertebral height, grade 2 (moderate) with a 25–40% loss of vertebral height, or grade 3 (severe) with greater than 40% loss of vertebral height. All fractures were confirmed by lateral thoracic and lumbar vertebral x-ray, graded by a single radiologist.

Measures of Clinical Characteristics

Participants completed food frequency questionnaires to evaluate total calcium and vitamin D intake from both diet and vitamin supplements.¹⁷ Each subject completed a standardized questionnaire designed to document putative risk factors of osteoporosis. This questionnaire included questions regarding family, medical, surgical, and fracture history, in addition to information on medication, activity level, tobacco, and alcohol use. Height was obtained with a Harpenden stadiometer (Holtain Ltd., Crymych, Dyfed, United Kingdom), weight was measured with a Health-O-meter balance-beam scale (Sunbeam, Boca Raton, Florida) and body mass index (BMI, kg/m^2) was calculated. Patients were asked to report their tallest height from memory and height loss was calculated as the difference between tallest height and current height.

Statistical Analysis

SAS[®] version 9 (SAS Institute, Inc., Cary, North Carolina) was used for all statistical analyses. We used appropriate descriptive statistics to summarize the participant characteristics, and used independent samples *t*-tests to compare BMD measures between those with and without VFs. We used a two-way contingency table cross-tabulation to summarize and describe identification of those with osteoporosis that should be treated using the standard (lumbar spine, total hip and femoral neck) BMD- and VF-based criteria. The sensitivity of the results to adding 1/3 distal radius site to the standard BMD-based criterion was also examined. We used the kappa (κ) statistic to quantify agreement between

DXA and SQ radiography for VF identification, and computed sensitivity and specificity of VF identification via DXA using SQ radiography as the reference “gold” standard. Finally, we used logistic regression models to examine whether greater duration of ADT and/or height loss increased the risk of a VF.

Results

One hundred and sixteen men with an average age of 75 years were recruited; thirty-eight had one or more vertebral fractures. Of men with vertebral fractures, 42% (n=16) had ≥ 2 fractures. Thirty-two men had mild (grade 1) fractures and 10 men had moderate-to-severe fractures. Of men with mild fractures, 17 men had only a single grade 1 fracture. The remaining 15 men had either multiple grade 1 fractures or a combination of mild and moderate-to-severe fractures.

Across all participants, average total calcium intake was 1269 mg/day and the average total intake of vitamin D was 839 IU/day. Seventy two participants were taking calcium supplements and 76 participants were taking vitamin D supplements. The average value of calcium supplement was 567 mg/day (range = 28–2000 mg/day) and the average value of vitamin D supplements was 838 IU/day (range =112–8400 IU/day).

There was no significant difference in age, BMI, calcium intake, vitamin D intake, or duration ADT between men with and without VFs (Table 1). There was a trend for greater height loss in men with vertebral fracture ($p < 0.06$). There was no difference in BMD measured at the spine, total hip, or 1/3 distal radius between men with and without fractures. However, men with vertebral fractures had significantly lower BMD measured at the femoral neck. There was no significant increased risk of vertebral fracture with either increasing height loss or increasing duration of ADT.

Thirty two percent (37/114) of men in this study were found to have normal BMD (at the spine, total hip, and femoral neck). However, 24% (9/37) of men with normal BMD had at least one VF (Figure 1). Therefore, these men had clinically-defined osteoporosis and would have been misclassified by BMD criteria alone. Fifty nine percent (67/114) of men had low BMD (osteopenia) at either the spine, total hip, or femoral neck. Of the men with low BMD, 34% (23/67) had at least one VF and would have been misclassified by BMD criteria alone (Figure 1). Nine percent (10/114) of men in this study were found to have osteoporosis based upon standard BMD criteria alone, 40% (4/10) of whom had VFs. Of all patients with clinically defined osteoporosis (n=42), 76% (32/42) would have been misclassified by DXA alone.

Of men with moderate-to-severe vertebral fractures (n=10), two men had normal BMD and five men had low BMD measured at either the spine, total hip, or femoral neck. These men had clinically-defined osteoporosis and would have been misclassified by BMD criteria alone. Of all men with either a single moderate-to-severe vertebral fracture or with multiple grade 1 fractures (n=15), nine men had normal BMD and four men had low BMD measured at either the spine, total hip, or femoral neck. The majority of these men also had clinically-defined osteoporosis and would have been misclassified by BMD criteria alone.

The addition of the 1/3 distal radius to standard DXA assessment sites (i.e. spine PA, total hip, and femoral neck) resulted in 28% of men (32/114) being defined as having osteoporosis by bone mineral density criteria alone. This is a 19% increase from the use of standard sites only (n=10). When using the additional 1/3 distal radius site, we found that 23% of men with normal BMD had VFs and 37% with low BMD had VFs (Figure 1). Thus, the addition of the 1/3 distal radius site resulted in the misclassification of only 46% (n=27) of patients with clinically defined osteoporosis.

For each patient whom underwent VFA, confirmatory lateral thoracic and lumbar vertebral x-rays were performed. A kappa statistic, sensitivity, and specificity was determined for each vertebral level and overall (Table 4). Overall, the sensitivity and specificity of VFA vs. SQ radiography was found to be 100% and 95%, respectively. The overall kappa statistic was found to be 0.92.

Discussion

The diagnosis of osteoporosis is common in men undergoing ADT, as approximately 40% of the men in this study had clinically defined osteoporosis by either DXA criteria or presence of a vertebral fracture. However, our results suggest that the use of DXA-based BMD criteria alone has the potential to considerably under-diagnose osteoporosis. Notably, we found that the use of BMD criteria alone resulted in the misdiagnosis of approximately 75% of patients with clinically defined osteoporosis. Furthermore, when used in conjunction with BMD, vertebral fracture analysis (VFA) increases the rate of diagnosis and reduces the misclassification of osteoporosis in men with prostate cancer.

Previous studies have indicated that the rate of fracture in men on ADT ranges between 5–20% depending on the duration of therapy.^{18,19,20} Additional factors may attribute to the higher fracture rate of approximately 33% found in our population. It is possible that the chosen WHO threshold may be less useful in men than in women. There are no current evidence-based guidelines for screening in men and no data regarding the validity of a particular cutoff value. The higher levels of VFs in this cohort might also be related to a lower use of preventative measures in men than in women. Current guidelines recommend that men over the age of 50 take in 1200 mg daily calcium.²¹ The Institute of Medicine has recently recommended 600 IU of Vitamin D for men aged 50–70, and 800 IU of Vitamin D for men over 70 years.²² While no official guidelines exist regarding men with prostate cancer on ADT, authorities recommend that all these men should receive preventative measures with calcium and vitamin D.²³ Though the average daily intake of calcium and vitamin D in men with and without fractures approximated these recommendations, over one-third of men in this study were not taking Ca and vitamin D supplements.

The duration of ADT necessary for fractures to occur is unclear. To be enrolled in this study, patients were required to have received continuous ADT for a minimum of six months. However, VFs may require several years of androgen deprivation to occur. Lopez et al found that in twelve men with prostate cancer on ADT, fractures were found after an average of 25 months.²⁴ Authors noted, however, that findings were limited by the lack of confirmatory x-rays and asymptomatic fractures were possibly missed. A similar study indicated that VFs occurred after a mean of 40 months of ADT in 38 men with prostate cancer.²⁵ Shahinian et al indicate that the risk of VF increases within 12 months of ADT initiation.²⁰ The presence of VFs in men after as few as 6 months of ADT in this study suggests the detrimental impact on bone may appear early.

Our results support other studies documenting the misdiagnosis of osteoporosis using DXA-based BMD criteria, as well as the utility of VFA. In a recent study of healthy men over age 50, El Maghraoui found undiagnosed VFs in nearly 30% of patients using VFA.²⁶ Importantly, in this study 14% of men with low BMD (i.e. osteopenia) and 9% of men with normal BMD were found to have at least one previously undetected VF. Similarly, in a large scale prospective study, Freitas found that approximately 80% of men with incident fractures did not have osteoporosis as defined by BMD criteria.²⁷ Specifically, 41% of men had normal BMDs and 46% had low BMDs. Therefore, the rate of misclassification found in this study corroborates the misclassification rate reported by Freitas.

This study characterized all vertebral fractures utilizing semiquantitative (SQ) radiography according to the method of Genant.¹¹ This methodology has been well-validated in both clinical trials and in clinical practice. We found that VFA and SQ radiography assessment of fractures from all readable vertebrae had a kappa, sensitivity, and specificity of 0.92, 100% and 95%, respectively. Sensitivity and specificity ranged from 83–100% and 98–100%, respectively, at individual vertebral levels, with the lowest sensitivity between thoracic levels T7-T9. In a recent study by Fuerst et al., three radiologists experienced in VFA independently read VFA scans and radiographs using the Genant semiquantitative method on two separate occasions. After analyzing data from all readable vertebrae, the kappa statistic, sensitivity and specificity were found to be 0.64–0.77, 0.65–0.84, and 0.97–0.98 respectively.²⁸ Authors concluded that although VFA image quality is lower resolution than radiographical images, it is feasible to detect and score VFs using this technique. Similarly, Schousboue et al indicate that in a population of elderly women, lateral and AP absorptiometry with selective radiographic follow-up is an effective strategy to detect moderate-to-severe VF. The findings of this study corroborate these results. Unlike other studies, we found that VFA approximates the efficacy of SQ radiography in the identification of mild VFs.^{28, 29} The higher reliability of VFA demonstrated in this study might be attributed to the use of a single technologist trained in VFA and single radiologist for the acquisition of these images.

The decline in BMD at the forearm site may be unique to men. Our group has previously shown that as duration of ADT continues, men experience progressive bone loss at the radius.³⁰ If the use of T-scores from the 1/3 distal radius site were used in conjunction with spine, hip and femoral neck bone mineral density, more men would have been identified as osteoporotic by BMD criteria alone. Additionally, more of the men with VFs would have been identified as also having osteoporosis by BMD criteria and, subsequently, fewer men would have been misclassified. Though further research is needed in this area, these results indicate that measurement of BMD at this site in addition to standard sites might increase the identification of men with clinically-defined osteoporosis.

This study has several strengths. We were able to recruit a reasonable size cohort in a selective population of older men with prostate cancer on ADT. Additionally, the study is one of only a few which is able to compare BMD, vertebral fractures, and height loss in the same population. We used the same dual-energy x-ray absorptiometry instrument for all BMD measurements and DXA and VFA were performed by the same technologist during the same visit to eliminate the potential of a fracture occurring after the DXA was performed. It is unlikely that some of the VFs we detected were non-osteoporotic because men with metastatic disease were excluded (all men had negative bone scans). Most importantly, all fractures were confirmed by x-ray and read systematically by a single radiologist.

Our study also has several limitations. Our population was predominately Caucasian. This factor and the age criteria for inclusion limits the application of our results to people <65 and to minorities. All subjects were questioned systematically about traumatic fracture, the age of occurrence, and whether or not it was an osteoporotic fracture. However, we cannot exclude that some subjects did not recall or did not report remote traumas. Similarly, recall bias may have influenced the peak height recorded for each patient. Because our study required only 6 months of ADT, it included both men on chronic ADT and those just beginning ADT. However, if anything, this would indicate that our results underestimate the number of VFs present in the population of men on ADT, since 6 months is a relatively short duration of therapy in this group. This thereby increases the generalizability of the results.

We conclude that men osteoporosis is a common diagnosis in men with prostate cancer undergoing ADT. DXA-based BMD criteria alone will under diagnosis osteoporosis in this population. VFA increases the rate of diagnosis and reduces the misclassification of osteoporosis in men with prostate cancer, compared to BMD criteria alone. Addition of the one-third distal radius site performed by the DXA also decreased the rate of misclassification. These data suggest that men with prostate cancer on ADT should be screened for osteoporosis at the initiation of therapy, and evaluation should include DXA of the one-third distal radius in addition to the spine and hip, as well as evaluation for vertebral fractures.

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Fig. 1. Percentage of men without vertebral fracture (0 VF), with one vertebral fracture (1 VF), and more than one vertebral fracture (>1 VF) classified as normal, low bone mass (osteopenic), or osteoporotic at conventional sites (the spine PA, total hip or femoral neck) and with the addition of the 1/3 distal radius site.

Table 1

Clinical characteristics of the subjects

Characteristic	Vertebral Fracture + (N = 38) Mean ± SE	Vertebral Fracture – (N = 78) Mean ± SE	P
Age (years)	76.2 ± 1.2	73.7 ± 0.9	0.09
Average Height Loss (inches)	4.8 ± 0.6	3.6 ± 0.3	0.06
Average % Height Loss	0.027 ± 0.003	0.020 ± 0.002	0.06
Body Mass Index (kg/m ²)	29.5 ± 0.88	29.5 ± 0.45	1.00
Duration of ADT (years)	4.6 ± 0.9	3.4 ± 0.4	0.23
# on Combination Therapy	14	31	
# on Single Agent Therapy	24	47	
Total Calcium Intake (mg/day)	1378.3 ± 103.5	1215.6 ± 70.8	0.20
Total Vitamin D Intake (IU/day)	1046.6 ± 226.7	736.2 ± 63.2	0.19
BMD T-score			
Spine PA	–0.2 ± 0.3	0.2 ± 0.2	0.20
Total hip	–0.8 ± 0.2	–0.5 ± 0.1	0.17
Femoral neck	–1.5 ± 0.1	–1.2 ± 0.1	0.03
1/3 Distal radius	–1.5 ± 0.3	–1.5 ± 0.2	0.84