

Risk Factors for the Development of Osteoporosis and Osteoporotic Fractures Among Older Men

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ABSTRACT. *Objective.* Osteoporotic fractures are associated with significant morbidity and mortality particularly among older men. However, there is little information regarding risk factors among this population. The aims of our study were to determine risk factors for osteoporosis and fragility fractures and the predictive value of bone mineral density (BMD) measurements for development of fragility fractures in a cohort of elderly Caucasian and African American men.

Methods. We evaluated 257 men aged 70 years or older for risk factors for osteoporosis and fragility fractures using a detailed questionnaire and BMD assessment. Exclusion criteria included conditions known to cause osteoporosis such as hypogonadism and chronic steroid use, current treatment with bisphosphonates, bilateral hip arthroplasties, and inability to ambulate independently.

Results. Age, weight, weight loss, androgen deprivation treatment, duration of use of dairy products, exercise, and fracture within 10 years prior to study entry were associated with osteoporosis ($p \leq 0.05$). Fragility fractures were associated with duration of use of dairy products, androgen deprivation treatment, osteoporosis, and history of fracture within 10 years prior to BMD assessment ($p \leq 0.05$). There were some differences in risk factors between the Caucasian and African American populations, suggesting that risk factors may vary between ethnic groups.

Conclusion. Although men with osteoporosis had a higher rate of fractures, the majority of fractures occurred in men with T-scores > -2.5 standard deviations below the mean, suggesting that factors other than BMD are also important in determining risk. (First Release July 15 2009; J Rheumatol 2009;36:1947–52; doi:10.3899/jrheum.080527)

Key Indexing Terms:
OSTEOPOROSIS

FRACTURES

RISK FACTORS

Osteoporosis has long been considered a disease primarily affecting women, and hence, osteoporosis in men is a relatively under-studied area. However, men sustain approximately 30% of all hip fractures and have a 2-fold excess mortality within the immediate post-fracture period^{1,2}. Up to 50% of men who sustain hip fractures require institutionalized care, with only 41% recovering their pre-fracture level of functioning^{3,4}. Men also suffer greater functional impairment from severe vertebral deformities compared to women⁵. As the population ages there is likely to be a

marked increase in the requirement for care for men with osteoporotic fractures, resulting in higher healthcare costs. Therefore, it is important to identify those men who are at risk in order to institute preventive measures. There are relatively few studies that have evaluated the risk factors for osteoporotic fractures in men and these have primarily been in Caucasians^{6,7}.

The aims of our study were to determine risk factors for osteoporosis and fragility fractures and assess the value of bone mineral density (BMD) measurements in determining risk of fragility fractures among a cohort of elderly Caucasian and African American men.

MATERIALS AND METHODS

Study participants. This was an observational study, the sampling frame for which was outpatient attendees to the general medical clinics at the Cincinnati Veterans Administration Medical Center (VAMC) over the period of November 2002 through April 2003. All male patients attending these clinics aged 70 years or greater were potential recruits to the study. Patients were first assessed by their attending physician or nurse practitioner and then referred to the study team for potential inclusion in the study. Patients with conditions known to cause osteoporosis, such as chronic steroid use (defined as a cumulative dose $>$ prednisone 7.5 mg/day for 3 months or its equivalent), rheumatoid arthritis and hypogonadism, current treatment with bisphosphonates, bilateral hip arthroplasties, and inability to ambulate independently were excluded. Written informed consent to participate in the study was obtained from each patient enrolled. The study was approved by the Institutional Research Board at the University of Cincinnati and the Research and Development committee at the VAMC.

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Supported in part by a grant from Procter and Gamble Pharmaceuticals, Mason, Ohio, USA.

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Accepted for publication April 21, 2009.

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A second component of the study was to determine the occurrence of fragility fractures over the 3-year post-enrollment period among the cohort of men enrolled.

Data collection. Data were ascertained from 2 sources. First, a thorough review of the electronic medical record (EMR) for each patient. From this the following data were recorded: age at study entry, race, weight at study entry, current and prior history of medical conditions and medication use, fracture history, tobacco and alcohol use. Second, a face-to-face interview with each patient was conducted by one member of the study team to ascertain further information likely to be deficient or unavailable from the EMR. Such data included self-reported height; weight; change in height or weight since the age of 25 years; history of immobilization for longer than 2 months; fracture history; use of tobacco, alcohol, calcium supplements, vitamin D, antacids and other medications; consumption of dairy products; amount and type of physical activity; onset of puberty; impotence; medical conditions; and family history of osteoporosis and/or low-trauma fractures.

To determine the presence of osteoporosis, BMD was assessed at the femoral neck using the same dual x-ray absorptiometry (DEXA) scanner, the GE Lunar Prodigy with Encore software version 6.8, which has a precision error of $< 0.01 \text{ g/cm}^2$. The scanner was recalibrated daily. All scans were reviewed by the study team to ensure that they had been performed correctly. T-scores were calculated based on reference values for healthy young Caucasian males. Osteoporosis was defined as BMD (T-score) ≤ -2.5 standard deviations (SD) below the mean for healthy young males.

For the second component of the study, the EMR of all study enrollees were reviewed again in June 2006 to determine the occurrence of low trauma fractures (LT-FX), defined as those caused by a fall from a standing height or less, over the 3 years post-enrollment. In addition, when available, lateral chest and spine radiographs of subjects were also reviewed by 2 researchers using the semiquantitative visual grading method of Genant, *et al* to look for evidence of occult vertebral fractures⁸.

Data for each patient were entered into a specifically designed computerized proforma from which data were exported into an Excel spreadsheet.

Statistical analysis. Statistical analysis was carried out using SAS V.9 software. Associations between osteoporosis and all potential predictor variables were analyzed using parametric and nonparametric statistical analyses as required. Differences in means were analyzed using the 2-sample t-test or Wilcoxon rank-sum test as appropriate. Differences in percentages were analyzed using the chi-squared test or Fisher's exact test as required. Multivariate analysis using logistic regression analysis was conducted with osteoporosis as the dependent variable. The same strategy was applied to analysis of fragility fractures. A p value ≤ 0.05 was considered to be significant. Since patient numbers were relatively small, those variables that were not significant on univariate analysis were not included in the multivariate analysis; for the same reason those variables that did not reach statistical significance on multivariate analysis were deleted from the model.

RESULTS

A total of 297 men aged 70 years or older were recruited, of whom 257 had BMD assessments; those who did not have BMD measurements were not included in the analysis.

Data were available through the EMR on all subjects, since all received their care at the VAMC. No patient was lost to followup. There were 33 deaths (13%) during the course of the study. Forty-five men had prostate cancer; 17 of them were receiving gonadotrophin-releasing hormone (GnRH) agonist therapy. Only 39 patients were taking calcium and 90 were taking vitamin D supplements; 90 were taking a multivitamin and 193 were eating dairy products regularly. Height loss (mean loss of 2.7 inches) was reported by 214 patients. Lateral chest radiographs, obtained for clinical

care purposes, available for 123 men, were evaluated for vertebral fractures.

The results for risk factors for osteoporosis are presented in Tables 1 and 2.

There were 17 (7%) patients with osteoporosis and 238 patients (93%) without osteoporosis. Osteoporosis occurred in 13% of patients with prostate cancer and 29% of those receiving androgen deprivation therapy.

There were no differences between the groups in distribution by race, history of fracture (ever), or height loss. The groups differed significantly on age at entry (those with osteoporosis were older), weight at study entry (those with osteoporosis were lighter), weight loss (higher percentage with osteoporosis had lost weight), exercise (lower percentage with osteoporosis exercised), duration of use of dairy products (those with osteoporosis had taken dairy products for a shorter period of time), fracture within 10 years prior to study entry (higher percentage with osteoporosis had a fracture), and GnRH agonist therapy (higher percentage with osteoporosis had received hormonal therapy). While these differences were found in univariate analysis it is more important to note that age, weight loss, duration of use of dairy products, and GnRH agonist therapy remained significant in multivariate logistic regression analysis and are therefore independent risk factors for osteoporosis in men.

Analysis of risk factors for osteoporosis in the Caucasian population alone revealed similar results (Table 2). The groups differed significantly on age at study entry, weight at entry, weight loss, exercise, duration of use of dairy products, fracture within 10 years prior to study entry, and GnRH agonist therapy. Age, weight loss, duration of use of dairy products, and GnRH agonist therapy remained significant in multivariate logistic regression analysis and are therefore independent risk factors for male osteoporosis among older Caucasian men.

Of the 39 African American patients, only 1 was found to have osteoporosis. The sample was too small to draw any conclusions for this subgroup.

Fragility fractures. Thirty-three clinical low-trauma fractures occurred among 31 men during a mean (\pm SD) followup period of 34 (\pm 3) months; this equated to an incidence of 3.1% per patient/year. In addition, 10 of the 123 patients for whom radiographs were available had occult vertebral fractures, which equated to a total of 43 fractures among 41 men. Nine (23%) of 39 African Americans compared with 32 (17%) of 218 Caucasians had fragility fractures. Clinical fragility fractures occurred in 17 (10%) of 134 patients with T-score > -1.0 SD (normal BMD), 17 (16%) of 106 patients with a T-score between -1.0 and -2.5 SD, and 7 (41%) of 17 patients with T-score ≤ -2.5 SD below the mean for young, healthy males (Figure 1). Although more fragility fractures occurred in patients with normal BMD, a greater percentage of patients with osteoporosis had fragility fractures compared with those with

Table 1. Factors associated with osteoporosis in older men.

Variable	Osteoporosis		p, univariate	p, multivariate	OR (95% CI)
	Yes (n = 17)	No (n = 238)			
Age, yrs: mean (SD)	79.0 (5.5)	76.6 (4.4)	0.03 ^a	0.04	1.2 (1.0–1.4)
Weight, lbs: mean (SD)	168.9 (38.5)	189.6 (31.3)	0.04 ^a	Deleted from MV model	
Dairy products, yrs: median (range)	32.5 (0–65)	60.0 (0–80)	0.003 ^b	0.007	1.02 (1.0–1.04)
	n (%)	n (%)			
Caucasian	16 (94)	200 (84)	NS ^c	Not included in MV model	
African American	1 (6)	38 (16)			
Height loss	16 (94)	198 (83)	NS ^c	Not included in MV model	
Weight loss	10 (59)	56 (24)	0.003 ^c	0.03	5.8 (1.2–28.5)
History of exercise	4 (24)	119 (50)	0.04 ^c	Deleted from MV model	
Combined calcium/vitamin D	4 (24)	27 (11)	NS ^c	Not included in MV model	
GnRH agonist therapy	5 (29)	12 (5)	0.003 ^c	0.003	15.0 (2.5–90.0)
Fracture at any time prior to entry	4 (40)*	52 (35)	NS ^c	Not included in MV model	
Fracture in 10 yrs prior to entry	4 (24)	14 (6)	0.02 ^c	Deleted from MV model	

^a 2-sample T-test; ^b Wilcoxon rank-sum test; ^c Fisher's exact test. * Some values missing. NS: not significant; MV: multivariate; GnRH: gonadotrophin-releasing hormone.

Table 2. Factors associated with osteoporosis in older Caucasian men.

Variable	Osteoporosis		p, univariate	p, multivariate	OR (95% CI)
	Yes (n = 16)	No (n = 200)			
Age, yrs: mean (SD)	79.1 (5.6)	76.6 (4.4)	0.03 ^a	0.02	1.2 (1.0–1.5)
Weight, lbs: mean (SD)	165.6 (37.1)	189.7 (30.9)	0.02 ^a	Deleted from MV model	
Dairy products, yrs: median (range)	45 (0–65)	60.0 (0–80)	0.001 ^b	0.01	1.02 (1.0–1.04)
	n (%)	n (%)			
Height loss	15 (94)	165 (83)	NS ^c	Not included in MV model	
Weight loss	9 (56)	45 (23)	0.006 ^c	0.02	5.9 (1.4–25.3)
History of exercise	4 (25)	102 (51)	0.045 ^d	Deleted from MV model	
Combined calcium/vitamin D	4 (25)	24 (12)	NS ^c	Not included in MV model	
GnRH agonist therapy	5 (31)	8 (4)	0.001 ^c	0.001	25.3 (3.4–164.9)
Fracture at any time prior to entry	4 (40)*	46 (36)	NS ^c	Not included in MV model	
Fracture in 10 yrs prior to entry	4 (25)	14 (7)	0.03 ^c	Deleted from MV model	

^a 2-sample T-test; ^b Wilcoxon rank-sum test; ^c Fisher's exact test; ^d chi-square test. * Some values missing. NS: not significant; MV: multivariate; GnRH: gonadotrophin-releasing hormone.

normal BMD (Figure 1). Eight (47%) patients receiving androgen deprivation for prostate cancer had fragility fractures.

The results for risk factors for osteoporotic fractures are presented in Tables 3 and 4. The groups differed significantly on history of fracture within 10 years prior to study entry, androgen deprivation treatment, and osteoporosis (Table 3). There were no differences between the groups in distribution by age, race, height loss, weight loss, weight at study entry, exercise, or calcium and/or vitamin D usage.

In Caucasians only, weight loss and use of dairy products were also significant on univariate analysis but were not significant on multivariate analysis (data not shown). Therefore the conclusions for the Caucasians are the same as for the whole group; the reason for this is that the whole group is heavily weighted by Caucasians.

In contrast, analysis of African Americans revealed a statistical association only with age (Table 4). However, a valid assessment of osteoporosis and androgen deprivation therapy is not possible in this group because of the small numbers.

DISCUSSION

Few studies have evaluated the risk factors for osteoporosis and fragility fractures in men. The prevalence of osteoporosis in our study of elderly men was 7%, which is similar to the estimated prevalence of 3%–6% in men aged > 50 years as reported in the Third National Health and Nutrition Survey (NHANES III), which also used the mean for young, healthy males as the reference⁹. Occult vertebral fractures were present in 8.1% of men in our study, which is similar to findings by O'Neill, *et al*¹⁰. In their cross-sectional pop-

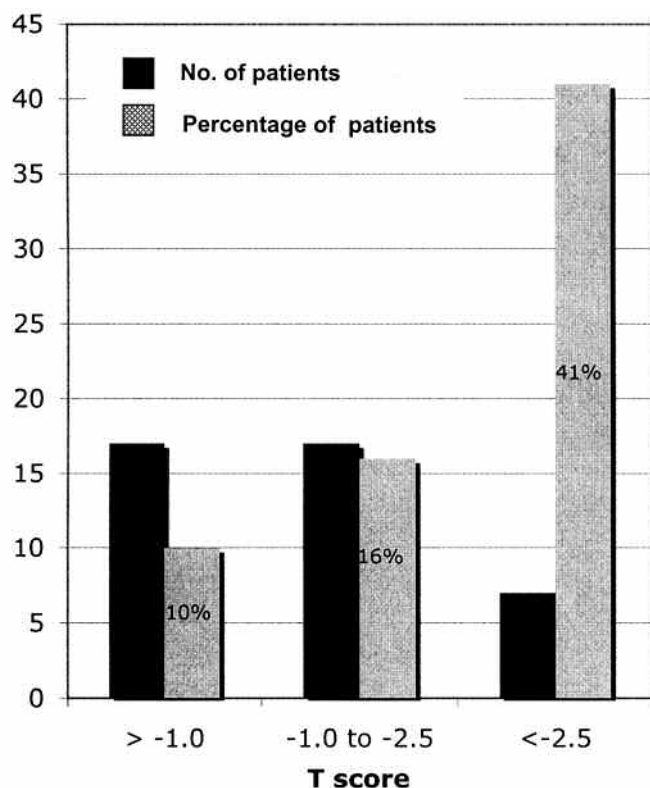


Figure 1. Number of patients (black bars) and percentage of patients (gray bars) with fragility fractures within 3 different groups stratified according to baseline bone mineral density determined by dual-energy X-ray absorptiometry.

ulation-based survey of European men aged 50–79 years, the prevalence of vertebral deformities varied from 8% to 20% depending on the country.

As in women, BMD has been demonstrated to predict fragility fractures in men^{11–15}. However, there is considerable overlap in BMD measurements between men who develop and do not develop fractures¹⁶. Our study demonstrates that although men with osteoporosis had a higher rate of fragility fractures, the majority of fractures occurred in the group of men with T-scores > -2.5 SD below the mean, suggesting that other factors are also important in determining risk. Similar to our findings, a longitudinal study of 759 French men found nearly 40% of those who developed fractures had normal BMD and less than 20% of the fractures occurred in men with T-score < -2.0 SD below the mean¹³. In another large population-based longitudinal study of elderly men and women, only 21% of nonvertebral fractures occurred in men with a T-score < -2.5 below the mean¹⁷. For the same type of fracture, men have been found to have higher BMD measurements relative to women¹⁸. This, in conjunction with our observations, suggests that factors other than BMD may be more important in determining risk for osteoporotic fractures in men compared to women.

In our analysis, history of fracture within 10 years prior to study entry, androgen deprivation treatment for prostate cancer, and osteoporosis were significant risk factors for fragility fractures. Prostate cancer is one of the most frequently diagnosed cancers in men, with more than 500,000 new cases diagnosed per year worldwide¹⁹. The prevalence of osteoporosis in men with prostate cancer has been reported in other studies to be 25%–63%^{20–22}. In concordance with other studies, we found that androgen deprivation therapy for prostate cancer was a risk factor for fractures and osteoporosis^{21,23–26}. Osteoporosis was present in 13% of our patients with prostate cancer and 29% of those receiving androgen deprivation therapy; 28% of patients with prostate

Table 3. Factors associated with fragility fractures in older men.

Variable	Fragility Fractures		p, univariate	p, multivariate	OR (95% CI)
	Yes (n = 41)	No (n = 214)			
Age, yrs: mean (SD)	77.5 (4.7)	76.6 (4.5)	NS ^a	Not included in MV model	
Weight, lbs: mean (SD)	190.1 (29.6)	187.9 (32.6)	NS ^a	Not included in MV model	
Dairy products, yrs: median (range)	50.0 (1–80)	60.0 (0–80)	NS ^b	Not included in MV model	
	n (%)	n (%)			
Caucasian	32 (78)	184 (86)	NS ^d	Not included in MV model	
African American	9 (22)	30 (14)			
Osteoporosis (DEXA scan)	7 (17)	10 (5)	0.01 ^c	0.05	3.0 (1.0–9.1)
Height loss	38 (93)	176 (82)	NS ^d	Not included in MV model	
Weight loss	15 (37)	51 (24)	NS ^d	Not included in MV model	
History of exercise	15 (37)	108 (50)	NS ^d	Not included in MV model	
Combined calcium/vitamin D	7 (17)	24 (11)	NS ^c	Not included in MV model	
GnRH agonist therapy	8 (20)	9 (4)	0.002 ^c	0.007	4.3 (1.5–12.6)
Fracture at any time prior to entry	6 (24)*	50 (37)	NS ^d	Not included in MV model	
Fracture in 10 yrs prior to entry	7 (17)	11 (5)	0.01 ^c	Deleted from MV model	

^a 2-sample T-test; ^b Wilcoxon rank-sum test; ^c Fisher's exact test; ^d chi-square test. * Some values missing. NS: not significant; MV: multivariate; DEXA: dual-energy X-ray absorptiometry; GnRH: gonadotrophin-releasing hormone.

Table 4. Factors associated with fragility fractures in older African American men.

Variable	Fragility Fractures		p
	Yes (n = 9)	No (n = 30)	
Age, yrs: mean (SD)	79.3 (2.8)	75.8 (4.6)	0.03 ^a
Weight, lbs: mean (SD)	191.2 (24.8)	189.7 (36.1)	NS ^a
Dairy products, yrs: median (range)	70.0 (2–80)	27.5 (0–80)	NS ^b
	n (%)	n (%)	
Osteoporosis (DEXA scan)	0 (0)	1 (3)	NS ^c
Height loss	9 (100)	25 (83)	NS ^c
Weight loss	2 (22)	10 (33)	NS ^c
History of exercise	3 (33)	14 (47)	NS ^c
GnRH agonist therapy	2 (22)	2 (7)	NS ^c

^a 2-sample T-test; ^b Wilcoxon rank-sum test; ^c Fisher's exact test. * Some values missing. NS: not significant; DEXA: dual-energy X-ray absorptiometry; GnRH: gonadotrophin-releasing hormone.

cancer and 47% of those receiving androgen deprivation therapy had fragility fractures. These numbers are higher than those reported in a recent study in which 19.4% of men who received androgen deprivation therapy had fractures compared to 12.6% of those who did not²⁶. In that study, the risk of fracture increased with the number of doses of hormonal therapy administered in the first year after diagnosis. With androgen deprivation treatment being increasingly used in the treatment of prostate cancer, larger numbers of men are at risk for both osteoporosis and fractures. Therefore, BMD assessments and institution of preventive measures such as supplementation with calcium and vitamin D may be useful in these patients. Of note, in 1 study evaluating the prevalence of osteoporosis in men with prostate cancer, 55% of the patients had a daily calcium intake < 800 mg and 17% had hypovitaminosis D²⁰. Bisphosphonates have also been reported to be beneficial in the prevention and treatment of osteoporosis in these patients²⁷.

In contrast to previous studies in which Caucasian race has been reported to be a risk factor for osteoporotic fractures, the incidence of fragility fractures was higher among the African Americans in our study. This was despite the fact that osteoporosis occurred more frequently in the Caucasian (7.4%) compared with the African American patients (2.6%). African American men have been reported to have higher BMD in the lumbar spine, femoral neck, trochanter, and radius compared to Caucasian and Hispanic men, which may be the result of higher peak bone mass and/or a slower decline in bone mass^{28–31}. The GE Lunar Prodigy DEXA scanner uses a Caucasian normative database to calculate T-score; the prevalence of osteoporosis among the African American patients in our study may have been higher if an African American normative database was used instead. However, in our study 9 African American patients had fractures, while only 1 had osteoporosis based on DEXA assessment, suggesting that factors other than BMD are important

in determining fracture risk for African American men; this is consistent with previous studies in which the majority of men who sustain fragility fractures have T-scores > –2.5 SD^{13,17}. We found fracture within 10 years, androgen deprivation therapy, and osteoporosis to be risk factors for fragility fractures for Caucasians, in contrast to African Americans, where age appears to be an important factor; this suggests that risk factors may differ between Caucasians and African Americans.

One of the limitations of the study was the use of lateral chest radiographs rather than dedicated radiographs of the lumbar and thoracic spine to determine fragility fractures; this would most likely underestimate the number of fractures. We measured BMD at the femoral neck, which is consistent with the WHO FRAX tool assessment (<http://www.shef.ac.uk/FRAX/index.htm>). However, some patients may have had osteoporosis at other sites, such as the forearm, which was previously reported to be a predictor for osteoporotic fractures among men³². Another limitation is the possibility of selection bias, since all of the patients were drawn from a single clinic site.

Although men with osteoporosis had a higher rate of fractures, the majority of fractures occurred in men with T-scores > –2.5 SD below the mean, suggesting that factors other than BMD are also important in determining risk.

ACKNOWLEDGMENT

We thank the patients and staff at the Veterans Administration Medical Center, Cincinnati.

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