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Vertebral Fracture Risk in Diabetic Elderly Men: The MrOS Study

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Abstract

Type 2 diabetes (T2DM) is associated with a significant increase in risk of nonvertebral fractures, but information on risk of vertebral fractures (VFs) in subjects with T2DM, particularly among men, is lacking. Furthermore, it is not known whether spine bone mineral density (BMD) can predict the risk of VF in T2DM. We sought to examine the effect of diabetes status on prevalent and incident vertebral fracture, and to estimate the effect of lumbar spine BMD (areal and volumetric) as a risk factor for prevalent and incident morphometric vertebral fracture in T2DM (n = 875) and nondiabetic men (n = 4679). We used data from the Osteoporotic Fractures in Men (MrOS) Study, which enrolled men aged ≥ 65 years. Lumbar spine areal BMD (aBMD) was measured with dual-energy X-ray absorptiometry (DXA), and volumetric BMD (vBMD) by quantitative computed tomography (QCT). Prevalence (7.0% versus 7.7%) and incidence (4.4%

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Disclosures

All authors state that they have no conflicts of interest.

versus 4.5%) of VFs were not higher in T2DM versus nondiabetic men. The risk of prevalent (OR, 1.05; 95% CI, 0.78 to 1.40) or incident vertebral-fracture (OR, 1.28; 95% CI, 0.81 to 2.00) was not higher in T2DM versus nondiabetic men in models adjusted for age, clinic site, race, BMI, and aBMD. Higher spine aBMD was associated with lower risk of prevalent VF in T2DM (OR, 0.55; 95% CI, 0.48 to 0.63) and nondiabetic men (OR, 0.66; 95% CI, 0.5 to 0.88) (p for interaction = 0.24) and of incident VF in T2DM (OR, 0.50; 95% CI, 0.41 to 0.60) and nondiabetic men (OR, 0.54; 95% CI, 0.33 to 0.88) (p for interaction = 0.77). Results were similar for vBMD. In conclusion, T2DM was not associated with higher prevalent or incident VF in older men, even after adjustment for BMI and BMD. Higher spine aBMD and vBMD are associated with lower prevalence and incidence of VF in T2DM as well as nondiabetic men.

Keywords

VERTEBRAL FRACTURES; DIABETES; BONE QCT; VOLUMETRIC BMD; FRACTURE RISK ASSESSMENT

Introduction

Type 2 diabetes (T2DM) affects nearly 390 million people worldwide[1] and causes a wide range of potential complications, including an increased risk of fractures.[2,3] T2DM is associated with an increased risk of hip fractures,[3] including atypical femur fractures,[4,5] as well as with a 30% to 70% greater risk of fracture of the proximal humerus and foot in older women.[6] This observation has been confirmed by other large prospective studies including individuals of both genders,[7–10] as well as by meta-analyses.[11,12] Less information is available on vertebral fracture (VF) risk in subjects with T2DM. This is likely due to difficulty in identifying VFs, as most are clinically silent.[13] Furthermore, most studies that assessed VF risk in T2DM included only women. The Iowa Women's Health Study reported increased risk of clinical vertebral fracture in subjects with T2DM (adjusted relative risk [RR], 1.43; 95% CI, 1.05 to 1.97).[14] The Women's Health Initiative Observational Study showed an increased risk of clinical spine/tailbone fractures (adjusted RR, 1.2; 95% CI, 1.1 to 1.3).[7] However, these studies relied on clinical VFs (eg, self-reported or registry-based); studies in which spine radiographs were used to identify VFs found no significant increase in the risk of prevalent or incident VFs in women with T2DM compared to their nondiabetic counterparts.[6,15,16] To date, information on VF risk in T2DM men is very limited and conflicting, and mostly based on prevalent VFs.[16–20] Thus, it is still not clear whether VF risk is increased in men with T2DM.

Although fracture risk prediction plays a key role in the clinical management of patients, it is challenging in T2DM.[21] Dual-energy X-ray absorptiometry (DXA) is the clinical standard for bone mineral density (BMD) assessment and fracture prediction. However, it has been argued that DXA for predicting fractures may not perform adequately in patients with T2DM because several studies have shown that individuals with T2DM have normal or higher BMD as compared with subjects without diabetes mellitus (DM).[22] Schwartz and colleagues[23] have shown that femoral neck BMD T-score by DXA is associated with hip and nonspine fracture risk in T2DM older adults, but fracture risk in these subjects is higher

for a given *T* score when compared to nondiabetic older adults. Another study conducted in Japanese subjects reported that the absolute DXA spinal BMD values for detecting VFs were higher and sensitivity and specificity were lower in T2DM participants than in healthy controls, suggesting that spine BMD by DXA is not sensitive enough to assess the risk of VFs in this group.[24] These observations highlight the need to evaluate whether an established method to predict fractures, such as lumbar spine BMD, performs adequately also in patients with T2DM. To clarify these issues, we used data from the Osteoporotic Fractures in Men (MrOS) study, a large multicenter prospective observational study examining incidence and predictors of fractures in older men. We sought to determine whether (i) prevalence and incidence of VFs in T2DM men are higher than in non-DM men, and (ii) lumbar spine BMD measured by DXA is associated with VFs in T2DM men compared to men without DM. As an exploratory aim, we also tested the hypothesis that BMD measured by quantitative computed tomography (QCT)—which can determine in three dimensions the volumetric BMD (vBMD) and which can facilitate analysis of trabecular and cortical bone separately—predicts prevalent and incident VFs in men with diabetes better than DXA in the lumbar spine areal BMD (aBMD).

Materials and Methods

We used data from the MrOS study, which enrolled 5994 men aged 65 years or older from March 2000 through April 2002.[25] Men were recruited from population-based listings in six areas of the United States: Birmingham, AL; Minneapolis, MN; Palo Alto, CA; the Monongahela Valley near Pittsburgh, PA; Portland, OR; and San Diego, CA.[25,26] The institutional review boards of each center approved the study protocol, and written informed consent was obtained from all participants. For the present analysis, men without fasting glucose ($n = 406$) or evaluable baseline spine X-ray ($n = 34$) were excluded. Diabetes status was determined by self-report, use of diabetes medication, or fasting plasma glucose ≥ 126 mg/dL. History of clinical fractures, falls, stroke, heart attack, and chronic obstructive pulmonary disease (COPD) were collected by self report. Participants with a clinical fracture before baseline were asked for age at fracture occurrence. Weight, height, and body mass index (BMI) were measured using standard methods. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI (CKD Epidemiology Collaboration) formula.[27]

Morphometric VFs

Morphometric VFs were identified on spine X-rays at baseline and at the secnd visit, which occurred on average 4.6 years later, as described.[28,29] In brief, lateral thoracic and lumbar spine radiographs were acquired according to study protocol. The general process for review of spine images was as follows. First, all spine images were assessed for quality and using a "triage" process by trained technicians, the purpose of which was to eliminate grossly normal images from semiquantitative (SQ) scoring, thereby reducing the number of images that needed to be read by the physician reader. Once triage was complete, all films from participants with a possible fracture or other abnormality were evaluated by another physician reader using the SQ method of Genant and colleagues[30]; triage-negative films were assumed to be fracture free and the SQ score was set to zero for all levels. The triage process had few false negatives (ie, a high sensitivity: 96.8%), and the SQ scoring had

excellent reproducibility kappa scores ranged from 0.79 to 0.92 on a series of quality assurance readings. Prevalent VF was defined as SQ 2; incident VF was defined as an increase of ≥ 1 SQ from baseline.

aBMD

Lumbar spine (L_1 to L_4), the total hip, and its subregions (femoral neck; trochanter) aBMD, were measured at baseline. The same scanner model was used at all six sites (QDR 4500 W; Hologic, Inc., New Bedford, MA, USA). Standardized procedures for participant positioning and scan analysis were followed for all scans. All DXA operators were centrally certified based on an evaluation of scanning and analysis techniques. Cross-calibration studies performed before the baseline MrOS visit showed no linear differences across scanners, and the maximum percentage difference in mean total spine BMD between scanners was 1.4%.[31] Participant scans were not corrected for cross-machine differences, but statistical models were adjusted for clinic site. DXA participant results were corrected when needed for longitudinal changes in machine performance, based on regular scans of Hologic spine phantoms at each site. Femoral neck BMD *T*-score was calculated using a young white female reference population.[32]

vBMD

The first 650 men and all nonwhite men enrolled at each site were referred for QCT scans of the hip and lumbar spine, which were obtained at the baseline visit on 3786 men.[33] After excluding those without baseline diabetes status or vertebral X-rays, there were 3342 men available for these analyses.

As previously described,[34] vBMD (g/cm^3) of the lumbar spine was measured using QCT and images were acquired using a GE Prospeed (Birmingham), GE Hispeed Advantage (Minneapolis), Philips MX-8000 (Palo Alto), Siemans Somatom + 4 (Pittsburgh), Philips CT-Twin (Portland), Toshiba Acquilion (Portland) site, or Picker PQ-5000 (San Diego). All QCT scans were centrally processed and analyzed at the University of California at San Francisco. Image processing was performed using published methods.[34] Each participant's scan included a calibration standard of three hydroxyapatite concentrations (150, 75, and 0 mg/cm^3). Images were converted from the native scanner Hounsfield Units (HU) to equivalent concentration (g/cm^3) of calcium hydroxyapatite contained in the calibrations standard. Lumbar spine images were acquired using settings of 120 kVp, 150 mA, 1 mm slice thickness, 512 × 512 matrices, and measurement using an anatomical region 5 mm above the L_1 superior endplate to 5 mm below the L_2 inferior endplate. The region of interest (ROI) was defined as the 10-mm slice in the mid-vertebra section for each vertebra. Integral volume of the ROI was computed as the total volume within the periosteal boundary. vBMD for trabecular compartment was computed over all voxels within this region.

Statistical analysis

Characteristics of the cohort are presented separately by baseline diabetes status. χ^2 Tests were used for categorical variables, and *t* tests were used for continuous variables to assess the statistical significance of differences between groups. Values are presented as mean

(standard deviation [SD]) unless otherwise indicated. Logistic regression analysis was used to examine the effect of diabetes status on vertebral fractures. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for prevalent and incident vertebral fractures in T2DM men versus non-DM men. All models included adjustment for age, race and clinic site. COPD was not associated with diabetes; stroke and heart attack were not associated with fracture risk and, therefore, were not included in the models.

Logistic regression models were used to estimate the effect of aBMD and vBMD on the prevalence of VFs in men with and without T2DM, adjusted for age, race/ethnicity, clinic site, BMI, eGFR, history of falls, and prior fracture history. ORs (95% CI) were calculated for prevalent and incident VFs per SD unit increase in BMD. The association was tested for interaction between BMD measure and diabetes status.

To calculate the average difference in *T* scores between T2DM and non-DM men with the same risk of VF, we used logistic models to estimate the associations of DXA BMD *T*-score and T2DM with the outcomes of prevalent and incident VFs, adjusted for age, BMI, race/ethnicity, and clinic. The difference in *T*-score for those with and without T2DM but the same VF risk was calculated as the ratio of the regression coefficient for T2DM to the coefficient for *T*-score as published,[23] with a 95% CI obtained by the delta method.

All analyses were conducted using SAS (version 9.4; SAS Institute, Inc., Cary, NC, USA) and Stata (version 14.2; Stata Corporation, Inc., College Station, TX, USA).

Results

Baseline characteristics of MrOS participants according to diabetes status are shown in Table 1. Diabetes was reported in 875 men. The mean age of the participants was 73.6 ± 5.6 years, with an average baseline BMI in the overweight range in both groups. The majority of participants were white. Two percent (2.0%) of the nondiabetic subjects and 2.2% of those with T2DM were on an antiosteoporosis treatment.

Prevalent VFs were identified in 61 (7.0%) men with T2DM and in 359 (7.7%) men without T2DM. A total of 80 subjects were treated with insulin and five (6.2%) had prevalent vertebral fractures. Incident VFs occurred in 25 (4.4%) of T2DM and 159 (4.5%) of non-DM men. Among men with QCT available (3342), 527 had diabetes including 40 with prevalent fractures and 15 with incident VFs. In models adjusted for age, race, clinic site, and BMI, the risk of prevalent VFs in T2DM men was not increased compared with men without DM (Table 2). Further adjustment for aBMD (OR, 1.05; 95% CI, 0.78 to 1.40) or vBMD (OR, 1.30; 95% CI, 0.89 to 1.88) increased the estimated association between DM and VFs, but without reaching statistical significance. Similarly, risk of incident VFs was not significantly higher in T2DM men versus non-DM men in all analyzed models (Table 2). For example, in models adjusted for spine aBMD as well as age, race/ethnicity, clinic site, and BMI, the OR for T2DM and incident fracture was 1.28 (95% CI, 0.81 to 2.00). However, CIs for these estimates were wide and power to detect modest associations was limited.

Higher spine aBMD was similarly and negatively associated with prevalent VFs in men with T2DM (OR per SD increase 0.55 [95% CI, 0.48 to 0.63]) and without diabetes (OR, 0.66 [95% CI, 0.50 to 0.88], p for interaction = 0.24). Results were similar for vBMD (Table 3).

Higher spine aBMD and integral vBMD were similarly and negatively associated with incident VFs in T2DM and without diabetes (Table 4). However, higher trabecular vBMD was more strongly associated with incident VFs in non-DM men (OR, 0.33; 95% CI, 0.24 to 0.45), compared to men with diabetes (OR, 0.64; 95% CI, 0.36 to 1.13) (p for interaction = 0.04).

Considering the challenge of interpreting BMD T-scores in diabetic patients,[23] we have analyzed mean differences in T-scores, comparing men with and without diabetes at a similar fracture risk. The difference in BMD T-score comparing DM and non-DM men with similar VF risk was 0.64 (95% CI, −0.43 to 1.71), 0.51 (95% CI, −0.38 to 1.41), and 0.51 (95% CI, −0.62 to 1.61) units for lumbar spine, total hip, and femoral neck BMD T-score, respectively. BMD T-score underestimated risk of VF in T2DM, but the results were not statistically significant.

Discussion

In this analysis from the MrOS study, we sought to determine whether prevalence and incidence of VFs in men with T2DM are higher than in men without diabetes, and whether lumbar spine aBMD is similarly associated with VFs in T2DM men as it is in men without DM. Our findings suggest that the risk of prevalent or incident VFs in elderly men with T2DM is not substantially increased compared with men without DM, even after the higher BMD in T2DM was taken into account.

The finding that T2DM was not significantly associated with increased VFs is in agreement with some, but not all, reports in the literature. A registry-based case-control study by Vestergaard and colleagues[19] reported a higher risk of spine fractures in women and men with T2DM (adjusted OR, 1.34; 95% CI, 0.97 to 1.86), but the results were borderline significant.. The Malmo Preventive Project found an increased risk of incident VFs in women (RR, 3.56; 95% CI, 1.75 to 7.23), but not in men (RR, 0.85; 95% CI, 0.27 to 2.65).[17] However, these studies used clinical fracture, not morphometric VFs, as the outcome. Previous studies from MrOS have shown that only a minority of morphological VFs were previously diagnosed as clinical VFs.[35] Available studies based on spine radiographs have yielded conflicting results.[16,18,20] Our data are in agreement with those from the Canadian Multicentre Osteoporosis Study, which found no evidence of an increase in the prevalence of vertebral fractures in T2DM men aged 50 years and older (adjusted OR, 0.77; 95% CI, 0.49 to 1.22).[16] Another group reported that the presence of T2DM was an independent risk factor for prevalent VFs in Japanese men aged 50 years and older (OR, 4.73; 95% CI, 2.19 to 10.2) after adjusting for age, BMI, and lumbar spine BMD.[20]

Because VFs are a major cause of pain and disability,[36,37] it is important to identify subjects at increased risk of VFs. In the present analysis, having diabetes was not statistically significantly associated with increased odds of prevalent or incident VFs.

Adjustment for BMD increased the estimate of the association between DM and VFs. This suggests that BMD— either areal or volumetric—may underestimate the risk of VFs in men with diabetes, which would be consistent with the observation that the risk of nonvertebral fracture at a given BMD level is higher in individuals with T2DM as compared with those without diabetes.[23] In order to address how well the BMD *T*-score predicts VF in DM and non-DM men, we estimated the reduction in BMD *T*-score equivalent to having DM. For incident VFs, we found a nonsignificant trend suggesting that having DM equates to having a femoral neck and a total hip BMD *T*-score approximately 0.5 units lower, and a lumbar spine BMD *T*-score approximately 0.6 units lower as compared with not having DM. Although not significant, it is worth noting that this finding is consistent with results for hip and nonvertebral fractures. In an analysis of three large prospective observational studies (the Study of Osteoporotic Fractures[38] [SOF], MrOS, and the Health ABC study), the *T*-score in a man with DM was found to be associated with hip fracture risk equivalent to a man without DM with a *T*-score of approximately 0.4 units lower; ie, for a given risk men with DM have a higher *T*-score as compared with men without DM.[23]

To further characterize the relationship between diabetes and BMD, we examined the associations between aBMD, vBMD, and VF in DM and non-DM men. In a previous analysis of men participating in the MrOS study, spine aBMD and vBMD both predicted clinical VFs,[39] but the association with morphometric VFs has not been investigated in MrOS. Data available from other cohorts have shown that aBMD and vBMD are associated with prevalent morphometric vertebral fractures,[40,41] whereas aBMD and trabecular vBMD predict incident VFs[42,43] in older men. Our results indicate that in general lower BMD (either areal or volumetric) is associated with prevalent and incident morphometric VFs in T2DM as well as non-DM men. Thus, as reported for nonvertebral fractures,[23] lower BMD is a risk factor for VF in T2DM men. We also found that higher trabecular vBMD was more protective against incident VFs in non-DM men than in men with T2DM. This weaker relationship with VF in T2DM men for trabecular but not integral vBMD suggests that changes in cortical bone may be more important for bone strength in DM, but this may also be a chance finding. Our results differ from a previous report of no significant association of aBMD at any site with the presence of VFs in Japanese T2DM male and female patients.[44]

The observation that the risk of prevalent or incident VFs in elderly men with T2DM is not increased compared with men without DM is in contrast with the increased risk of hip fractures in patients with T2DM.[6–12] Our results show a trend for an increased risk of incident VF by 30% in aBMD-adjusted models, and the 95% CI extends to a doubling of risk. Thus, the limited number of incident fractures among diabetics in our cohort make it difficult to rule out a modest increased risk. It is also possible that differences in the cortical to trabecular bone ratio between the spine and the hip might account for this discrepancy.[45] Increased cortical porosity is likely to contribute to the elevated risk of nonvertebral fractures in patients with T2DM.[46–48] A previous analysis of the MrOS population using peripheral QCT showed that T2DM men had low bone strength for body weight at predominantly cortical sites (distal tibia and radius).[49] Thus, it is tempting to speculate that the hip and other nonvertebral sites—which have a higher proportion of cortical bone—are more susceptible to the effects of diabetes. Furthermore, if there is no actual increase in the

risk of VF with diabetes, the rate and mechanisms of falls in diabetic individuals may be particularly important in determining the increased risk of hip and other nonvertebral fractures.

The assessment of vBMD is a strength of our study. Furthermore, we analyzed a large and well-characterized cohort of older men with a long follow-up, for whom morphometric assessment of VFs was available. Fasting glucose (FG) was available in all study subjects; therefore, it is unlikely to have included men with undiagnosed diabetes. An important limitation of this study was the lack of information on diabetes duration and glycated hemoglobin (HbA1c) levels; therefore, data on VFs could not be assessed in relation to diabetes duration or glycemic control in this analysis. It is possible that some diabetic participants had type 1 diabetes although given the age of our cohort, the great majority of diabetic participants would likely have T2DM. Finally, when data were adjusted for use of antidiabetic medications there were no differences in both prevalent or incident VFs

In conclusion, in this analysis of MrOS T2DM was not significantly associated with higher prevalent or incident VFs in elderly men, even after adjustment for BMI and BMD. Lower aBMD or vBMD was associated with higher odds of prevalent and incident VFs in DM as well as non-DM men.

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Table 1.

Subjects' Baseline Characteristics

	No diabetes (*n* = 4679)	Diabetes (*n* = 875)	Overall (*n* = 5554)	*p*
Age (years), mean±SD	73.6 ± 5.9	73.7 ± 5.6	73.6 ± 5.9	0.45
Non-white, *n* (%)	398 (8.5)	143 (16.3)	541 (9.7)	<0.001
History of fracture, *n* (%)[a]				
No fracture before baseline	2063 (44.2)	402 (45.9)	2465 (44.5)	0.13
Fracture after age 50 years, before baseline	1090 (23.3)	177 (20.2)	1267 (22.9)	
Fracture before age 50 years	1517 (32.5)	296 (33.8)	1813 (32.7)	
History of falls, *n* (%)	949 (20.3)	218 (24.9)	1167 (21.0)	<0.01
History of stroke, *n* (%)	239 (5.1)	71(8.1)	310 (5.6)	<0.001
History of heart attack, *n* (%)	599 (12.8)	183 (20.9)	782 (14.1)	<0.001
History of COPD, *n* (%)	485 (10.4)	108 (12.3)	593 (10.7)	0.08
eGFR (CKD-EPI) (mL/min/1.73 m^2), mean±SD	75.4 ± 14.8	72.9 ± 17.7	75.0 ± 15.3	<0.01
Total spine aBMD (g/cm^2), mean±SD	1.06 ± 0.19	1.12 ± 0.18	1.07 ± 0.19	<0.001
Spine integral vBMD (g/cm^2), mean±SD	0.22 ± 0.04	0.24 ± 0.04	0.23 ± 0.04	<0.001
Diabetes medications, *n*				
Any hypoglycemic drug	-	475		
Insulin	-	80		
Sulfonylurea	-	312		
Metformin	-	216		
Thiazolidinedione	-	67		
Other	-	2		

COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.

[a]History of fracture before baseline was missing for 9 men without diabetes.

Table 2.

Diabetes and Risk of Morphometric Vertebral Fracture in Older Men

	Prevalent vertebral fractures		Incident vertebral fractures	
Model	***n***	**OR (95%CI)**	***n***	**OR (95%CI)**
Model 1: age, race, clinic site	5554	0.91 (0.74–1.18)	4102	1.05 (0.68–1.62)
Model 2: Model 1, BMI	5554	0.93 (0.70–1.25)	4102	1.10 (0.71–1.71)
Model 3: Model 2, spine aBMD	5545	1.05 (0.78–1.40)	4097	1.28 (0.81–2.00)
Model 4: Model 2, spine vBMD	3342	1.30 (0.89–1.88)	2475	1.40 (0.78–2.53)

Model 1: adjusted for age, race, clinic site; Model 2: Model 1, BMI; Model 3: Model 2, spine aBMD; Model 4: Model 2, spine vBMD.

Table 3.

Association of BMD From DXA and Spine QCT at Baseline With Prevalent Vertebral Fractures in Men With or Without T2DM

	No diabetes OR (95% CI)	Diabetes OR (95% CI)	*p*
Femoral neck BMD	0.54 (0.47–0.62)	0.64 (0.49–0.85)	0.26
Total spine aBMD	0.55 (0.48–0.63)	0.66 (0.5–0.88)	0.24
Integral vBMD (spine)	0.40 (0.33–0.48)	0.5 (0.35–0.71)	0.26
Trabecular vBMD (spine)	0.42 (0.35–0.52)	0.52 (0.36–0.75)	0.33

Models adjusted for age, race, clinic site, BMI, eGFR, falls, and prior fracture history. Values of *p* are for interaction between diabetes status and BMD. OR is per 1 SD increase in BMD.

Table 4.

Association of BMD From DXA and Spine QCT at Baseline With Incident Vertebral Fractures in Men With or Without T2DM

	No diabetes OR (95% CI)	Diabetes OR (95% CI)	*p*
Femoral neck BMD	0.62 (0.51–0.75)	0.71 (0.46–1.1)	0.58
Total spine aBMD	0.50 (0.41–0.60)	0.54 (0.33–0.88)	0.77
Integral vBMD (spine)	0.34 (0.26–0.46)	0.42 (0.22–0.78)	0.58
Trabecular vBMD (spine)	0.33 (0.24–0.45)	0.64 (0.36–1.13)	0.04

Models adjusted for age, race, clinic site, BMI, eGFR, falls, and prior fracture history. Values of *p* are for interaction between diabetes status and BMD per SD increase in BMD. OR is per 1 SD increase in BMD.