Clinical Fractures Among Older Men With Diabetes Are Mediated by Diabetic Complications

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Introduction: Type 2 diabetes mellitus among older women has been associated with increased bone mineral density, but paradoxically with increased fracture risk. Findings among older men have varied, and potential mechanisms have not been fully elucidated.

Methods: A retrospective study of male veterans 65 to 99 years of age who received primary care in the Veterans Health Administration from 2000 to 2010, using administrative data from all 146 Veterans Health Administration medical centers linked to Centers for Medicare and Medicaid Services Medicare fee-for-service data. Potential mediating factors of the diabetes-associated risk were evaluated using negative binomial regression models with the outcomes of any clinical fracture and hip fracture.

Results: Of 2,798,309 Veterans included in the cohort, 900,402 (32.3%) had a diagnosis of diabetes. After adjusting for age, race, ethnicity, body mass index, alcohol and tobacco use, rheumatoid arthritis, and corticosteroid use, the risk of any clinical fracture associated with diabetes was 1.22 (95% confidence interval, 1.21 to 1.23) and that of hip fracture was 1.21 (95% confidence interval, 1.19 to 1.23). Significant mediating factors included peripheral neuropathy, cardiovascular disease, and congestive heart failure, with 45.5% of the diabetes-associated fracture risk explained by these diagnoses.

Conclusions: Older male Veterans with diabetes have a 22% increased risk of incident clinical fracture compared with those without. A significant portion of this risk is explained by diabetes-related comorbidities, specifically peripheral neuropathy and congestive heart failure. Identification of these mediating factors suggests possible mechanisms, as well as potential interventions. (***J Clin Endocrinol Metab*** **103: 281–287, 2018)**

Diabetes mellitus affects >29 million persons in the United States, with the highest rates among adults >65 years of age (1). At an annual cost of $245 million, a significant proportion of the burden results from complications of diabetes, including renal and cardiovascular disease. Among its complications, diabetes mellitus has been associated with a significant increased risk for fracture (2–5). However, type 2 diabetes mellitus among older adults has also been associated with increased bone mineral density (BMD); thus, the increased fracture rate presents a clinical paradox (6–8).

The underlying mechanisms for this paradoxical increased fracture risk remain controversial. A number of

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Abbreviations: BMD, bone mineral density; BMI, body mass index; CI, confidence interval; CMS, Centers for Medicare and Medicaid Services; MrOS, Osteoporotic Fractures in Men; OR, odds ratio; RR, relative risk; VHA, Veterans Health Administration.

complex interactions between bone and diabetes have been previously reviewed (9, 10). Although older adults with diabetes have an increased risk of falls (11–13), several studies have shown that the higher fracture risk persists even after adjusting for fall risk (14, 15). Others have suggested that diabetes-related changes in bone quality also contribute to the increased fracture risk (16, 17). These bone changes could be mediated in part by other diabetes-associated conditions such as impaired renal function or cardiovascular disease, both of which have been associated with lower bone quality and increased fracture risk (18, 19). However, others have postulated that diabetes complications are simply a marker of more severe diabetes and do not indicate a mechanism of action.

Some studies have suggested a differential effect of diabetes on fracture risk by sex, with the increased fracture risk confined to women, whereas others have shown no interaction. Furthermore, there has been substantial variation in the magnitude of the risk estimates (20–24). Therefore, we conducted this study to confirm and precisely quantify the risk of fracture (both clinical and hip) among older men with diabetes, and then to identify potential mediating factors of the fracture risk. We hypothesized that comorbidities, especially those related to complications of diabetes, mediate the observed increase in fracture risk.

Methods

Using administrative data from all 146 Veterans Health Administration (VHA) medical centers, we conducted a retrospective study of a cohort of male veterans aged 65 to 99 years who received primary care in the VHA from 2000 to 2010. Receiving primary care was defined as having two or more visits to a primary care provider in 2 consecutive calendar years. Men with a diagnosis of osteoporosis, osteoporosis medication prescription, or any clinical fracture in the 3 years prior to their start date were excluded. The VHA data sources included the inpatient treatment file, outpatient care file, the fee-basis file, and the Pharmacy Benefits Management Services outpatient treatment file. Because some veterans receive urgent/emergent medical care at non–Veterans Affairs facilities, the cohort was limited to those ≥65 years of age, and VHA data were linked to Centers for Medicare and Medicaid Services (CMS) Medicare fee-for-service data for more complete capture of medical care. The Medicare data sources were derived from fee-for-service Medicare, including part A (inpatient, including skilled nursing, home health, and hospice) and part B (outpatient) claims. Data were analyzed on the Veterans Affairs Informatics and Computing Infrastructure. The study was approved by the Institutional Review Board at the Durham Veterans Administration Medical Center.

Diabetes was defined as presence of diabetes-related ICD9 codes (250.xx) on two or more inpatient or outpatient visits, or the presence of one code in addition to prescription for diabetes medication. Birman-Deych *et al.* (25) validated this definition, showing 75% sensitivity and 99% specificity. Diabetes medications included insulin, metformin, thiazolidinediones, and sulfonylureas/secretagogues. It was not possible to accurately distinguish between type 1 and type 2 diabetes in this administrative dataset; however, >98% of those classified with diabetes had at least one code indicating type 2 diabetes, and prior studies of veterans have documented low rates of true type 1 diabetes because this diagnosis precludes military service (26).

Clinically apparent fractures were ascertained from ICD9 codes in inpatient and outpatient Veterans Affairs and CMS files, utilizing codes 733.93 to 733.95, 767.3, 800 to 829, and V54.13, as well as CPT codes for fracture treatment. ICD9 codes related to fractures of the fingers, toes, and skull/face were excluded.

Demographic variables included age, race, and ethnicity. Physical measurements included body mass index (BMI) at baseline. Comorbidities included a history of cerebrovascular disease, cardiovascular disease, peripheral vascular disease, myocardial infarction, hypertension, chronic obstructive pulmonary disease, chronic liver disease, prostate cancer, mood disorders, seizure disorders, rheumatoid arthritis, and neuropathy. Presence of a comorbid disease was defined as one or more of the respective ICD9 codes in two or more separate inpatient or outpatient visits. For example, peripheral neuropathy was defined as presence of ICD9 codes 356.x, 357.x, 250.6, 353.5, 713.5, and 354.0 to 355.9, and congestive heart failure was defined as ICD9 codes 425.x and 428.x (additional definitions are available from the authors upon request). Chronic kidney disease was defined as the presence of respective ICD9 codes on two or more inpatient or outpatient visits, or creatinine clearance <60 mL/min on at least two laboratory measurements at least 3 months apart. Chronic corticosteroid use was defined as three or more continuous months of use of glucocorticoid medication at an average daily dose ≥10 mg of prednisone equivalents. History of tobacco use was defined as ICD9 codes for tobacco dependence, tobacco use, or presence of a prescription for nicotine replacement.

Natural language processing using a validated extraction process from radiology and consult databases in the Veterans Affairs Informatics and Computing Infrastructure platform was used to extract results from BMD assessments by dual x-ray absorptiometry on individual veterans. The databases were queried for any text fields with keywords such as DEXA, DXA, bone density, BMD, T score, and adjacent text searches that extract site-specific BMD results.

Descriptive statistics were used to characterize the study population, with means and standard deviation values for continuous variables and with frequencies and percentages for categorical variables. The χ^2 test for categorical variables or the Student *t* test for continuous variables was used to examine the difference in distributions of baseline characteristics between those with and without diabetes. The fracture outcomes of interest were any clinical fracture and hip fracture. Association of diabetes with clinical fracture risk was evaluated using negative binomial regression modeling and with hip fracture using logistic regression. The initial model evaluated association of diabetes with the fracture outcome, controlling for fracture-related comorbidities, including age, race/ethnicity, BMI, rheumatoid arthritis, corticosteroid use, tobacco use, and alcohol use, which were then added to the model. Relative risks (RRs) of clinical fracture or odds ratio (OR) of hip fracture

associated with diabetes with 95% confidence intervals (CIs) are presented. To evaluate potential mediating factors, comorbidities associated with both diabetes and metabolic bone disease were added individually to the fracture-related model, specifically cerebrovascular disease, cardiovascular disease, peripheral vascular disease, myocardial infarction, hypertension, chronic obstructive pulmonary disease, chronic liver disease, prostate cancer, mood disorders, seizure disorders, and neuropathy. Mediation factors were identified by comparing CIs for diabetes-associated fracture risk prior to and after inclusion of potential factors in the regression model. Nonoverlapping 95% CIs were deemed to be significant factors. A final model was evaluated that included all significant mediating factors into a single model. The percentage of the mediated effect was calculated as the relative change in the parameter estimate after inclusion of the potential mediator to the model. All analyses were done in the SAS System for Windows (version 9.3; SAS Institute, Cary, NC).

Results

Among the 2,798,309 veterans in the cohort, 900,402 (32.3%) had diabetes. Baseline characteristics of the study population stratified by diabetes status are presented in Table 1. Compared with those without diabetes, men with diabetes were slightly older (71.2 vs 70.8 years), with greater BMI (30.1 vs 28.0 kg/m^2), and more likely to report Black race (10.2% vs 7.6%). Older men with diabetes were also more likely to suffer from chronic kidney disease, cardiovascular disease, and neuropathy. Among those with a BMD assessment ordered in routine clinical care during the cohort period (n = 150,026), those with diabetes had a higher femoral neck BMD, compared with those without diabetes (T score −0.51 vs −0.28, $P < 0.001$).

During the study period, there were 56,905 clinical fractures among older men without diabetes and 25,840 among those with diabetes. Of those, there were 7575 hip fractures among those without diabetes and 3601 among those with diabetes. The overall fracture rate was 0.117 per 1000 days at risk, with 0.130 per 1000 days among older men with diabetes compared with 0.111 per 1000 days among those without diabetes. Common sites of fracture among older men with diabetes included vertebra, rib, hip, and lower extremity (Table 2).

After adjusting for age, race, ethnicity, BMI, alcohol and tobacco use, and corticosteroid use, the risk of any clinical fracture associated with diabetes was 1.22 (95% CI, 1.21 to 1.23). Fracture risk was similar between those with diabetes treated without antihyperglycemic agents [RR, 1.17 (1.16 to 1.18)] and those prescribed oral agents only [RR, 1.18 (1.16 to 1.19)]. The most common oral agent prescriptions were sulfonylureas (73.6%), metformin (54.5%), and thiazolidinediones (10.4%). However, fracture risk was significantly higher for those prescribed both insulin and an oral agent [RR, 1.40 (1.37 to 1.43)] and those prescribed insulin only [RR, 1.54 (1.51-1.58)]. Significant mediating factors for

Table 1. Baseline Characteristics by Diabetes Status

	Without Diabetes Mellitus (N = 1,897,907)	With Diabetes Mellitus (N = 900,402)	*P*
Age, y (mean ± SD)	71.8 ± 6.6	72.1 ± 6.5	<0.001
BMI, kg/m^2 (mean ± SD)	28.0 ± 4.7	30.1 ± 5.4	<0.001
Race, %			
White	71.7	71.2	<0.001
Black	7.6	10.2	
Other	3.4	5.0	
Unknown	17.3	13.6	
Femoral BMD T score[a]	−0.51 ± 1.44	−0.28 ± 1.45	<0.001
Comorbidities, %			
Alcohol abuse	18.1	17.5	<0.001
Tobacco use	22.5	20.1	<0.001
Rheumatoid arthritis	0.7	0.5	<0.001
Corticosteroid use	1.7	1.6	0.19
Chronic kidney disease			
Stage 3	22.7	27.7	<0.001
Stage 4/5	0.9	2.0	
Neuropathy	13.6	23.8	<0.001
Cardiovascular disease	8.4	11.2	<0.001
Cerebrovascular disease	0.65	1.00	<0.001
Congestive heart failure	12.6	21.3	<0.001
Chronic lung disease	25.0	24.5	<0.001
Chronic liver disease	7.7	7.9	<0.001
Seizure disorder	3.9	4.8	<0.001

Abbreviation: SD, standard deviation.

[a]When available (N = 150,026).

Table 2. Fracture Site According to Diabetes Status

Fracture Site, n (%)	Without Diabetes Mellitus (N = 1,897,907)	With Diabetes Mellitus (N = 900,402)
Total	56,905	25,840
Vertebral	15,319 (26.9)	5,745 (22.2)
Rib	10,314 (18.1)	4,677 (18.1)
Hip	7,575 (13.3)	3,601 (13.9)
Other lower limb	6,471 (11.4)	2,983 (11.5)
Tibia/fibula	4,779 (8.4)	2,726 (10.6)
Radius/ulna	4,250 (7.5)	2,024 (7.8)
Humerus	2,421 (4.3)	1,468 (5.7)
Scapula/clavicle	1,568 (2.8)	692 (2.7)
Pelvis	1,464 (2.6)	649 (2.5)
Femur	1,391 (2.4)	619 (2.4)
Patella	921 (1.6)	407 (1.6)
Sternum	194 (0.3)	90 (0.3)
Other upper limb	134 (0.2)	73 (0.3)
Other	23 (0.0)	6 (0.0)

diabetes-associated fracture risk included comorbidities associated with diabetes complications (Table 3): peripheral neuropathy explained 21.1% of the fracture risk, congestive heart failure explained 16.6%, and cardiovascular disease explained 6.9%. However, chronic kidney disease and cerebrovascular disease did not significantly mediate the fracture risk. As expected, comorbidities that are not associated with diabetic complications (*e.g.*, chronic liver disease, chronic pulmonary disease) were not significant mediation factors and were not included in the final model. In the final model, inclusion of peripheral neuropathy, cardiovascular disease, and congestive heart failure resulted in mediation of 45.5% of the total fracture risk.

For hip fracture, the OR associated with diabetes, after adjusting for demographic factors and fracture-related comorbidities, was 1.21 (95% CI, 1.19 to 1.23). As observed with risk of any clinical fracture, peripheral neuropathy was a significant mediator of the diabetes-associated hip fracture risk (20% of fracture risk explained) (Table 4). Both cardiovascular disease and congestive heart failure trended toward a significant mediation effect; however, the CIs were overlapping with the baseline model. Forty-one percent of the hip fracture risk associated with diabetes was explained with inclusion of peripheral neuropathy, cardiovascular disease, and congestive heart failure.

Discussion

In this large retrospective cohort study of men >65 years of age, after controlling for multiple fracture-related risk factors, diabetes mellitus remained independently associated with a significant 20% increase in any clinical fracture and hip fracture. Our estimate of the magnitude of the fracture risk associated with diabetes in men is largely consistent with, but more precise than, prior prospective studies. The Osteoporotic Fractures in Men (MrOS) cohort had a 22% increased risk associated with diabetes; however, there was not a significant difference in rate of hip fracture associated with diabetes mellitus in the MrOS study [3.3 per 1000-person-years (non-diabetes) vs 3.1 per 1000-person-years (diabetes)] (24). In the Health ABC study, the unadjusted RR was 1.61; the risk was lower in our study compared with that observed in the Health ABC study, but study participants in Health ABC were slightly older than those in MrOS and in the present study (8). A prior population-based study in Ontario, Canada, showed a significant increase in hip fracture risk associated with diabetes, after adjusting for multiple confounders, including age, medical comorbidities, and medication use (hazard ratio, 1.18; 95% CI, 1.12 to 1.24) (5). Interestingly, there was a statistically

Table 3. RR of Any Clinical Fracture Associated With Diabetes and Mediating Effect of Comorbidities on Diabetes-Associated Risk

	RR (95% CI)	% of Diabetes Effect Mediated
Diabetes[a]	1.22 (1.21–1.23)	—
+ Chronic kidney disease	1.21 (1.20–1.22)	NS
+ Neuropathy	1.17 (1.16–1.18)	21.1
+ Cardiovascular disease	1.19 (1.18–1.20)	6.9
+ Cerebrovascular disease	1.21 (1.20–1.22)	NS
+ Congestive heart failure	1.18 (1.17–1.19)	16.6
+ Chronic obstructive lung disease	1.22 (1.21–1.23)	NS
+ Chronic liver disease	1.22 (1.21–1.23)	NS

Abbreviation: NS, not significant.

[a] All models were adjusted for age, race/ethnicity, tobacco use, alcohol use, glucocorticoid use, rheumatoid arthritis, and BMI.

Table 4. OR for Hip Fracture Associated With Diabetes and Mediating Effect of Comorbidities on Diabetes-Associated Risk

	OR (95% CI)	% of Diabetes Effect Mediated
Diabetes[a]	1.21 (1.19–1.23)	—
+ Chronic kidney disease	1.20 (1.18–1.21)	NS
+ Neuropathy	1.16 (1.15–1.18)	20.0
+ Cardiovascular disease	1.18 (1.17–1.20)	NS
+ Cerebrovascular disease	1.21 (1.19–1.22)	NS
+ Congestive heart failure	1.18 (1.16–1.19)	NS
+ Chronic obstructive lung disease	1.21 (1.19–1.23)	NS
+ Chronic liver disease	1.21 (1.19–1.22)	NS

Abbreviation: NS, not significant.

[a] All models were adjusted for age, race/ethnicity, tobacco use, alcohol use, glucocorticoid use, rheumatoid arthritis, and BMI.

significant sex interaction, with men having lower risk than women. Compared with prior studies among older women, our study suggests that the magnitude of both any clinical fracture and hip fracture risk, associated with diabetes, among older men is comparable to that reported in older women.

Nearly half of the increased risk in clinical fracture was mediated by diabetes-related comorbidities, including neuropathy and cardiovascular disease, but not by unrelated comorbidities such as chronic liver or pulmonary disease. There was no mediation observed by chronic kidney disease or cerebrovascular disease. In contrast to our results, diabetes-related comorbidities were not associated with increased fracture risk in the Health ABC study; however, those authors acknowledge that they may not have had sufficient power to observe such an effect. Although some have hypothesized that diabetes is simply a marker of poor health status, our study had ample power to suggest a direct effect of diabetes on incident fracture risk by specific mechanisms.

Peripheral neuropathy was the most important mediator of fracture risk observed in our cohort. Prior studies have shown a significant risk of falls associated with both peripheral neuropathy and type 2 diabetes, as well as a contribution of such falls with regard to fracture risk (11, 12, 27, 28). For example, in the Women's Health Initiative–Observational Study, Bonds *et al.* (14) found that older women with diabetes reported more falls at baseline and during follow-up, compared with those without diabetes (44% vs 32%). Thus, our data reinforce the importance of fall risk reduction interventions for both female and male patients with diabetes, particularly those with peripheral neuropathy.

We also found significant mediation by congestive heart failure, suggesting a direct effect of diabetes on bone and calcium metabolism. Congestive heart failure has been associated with lower serum 25-hydroxyvitamin D levels, increased parathyroid hormone levels, increased magnesium and calcium excretion, and fracture risk (29–32). In animal studies, increased aldosterone (as found in heart failure) stimulated increased calcium excretion and increased parathyroid hormone levels (33, 34). In a case-control study of male veterans, Carbone *et al.* (35) showed fewer fractures in patients prescribed spironolactone, an aldosterone antagonist. Also, studies have shown increased levels of inflammatory cytokines (*e.g.*, interleukin-6 and tumor necrosis factor-α) associated with congestive heart failure (36, 37), which have also been associated with increased fracture risk, as well as frailty and physical performance (38–41). Although this suggests that congestive heart failure may also lead to increased falls risk, the mediation seen in the present study appears to be independent of that seen with peripheral neuropathy. Our findings suggest that bone density screening and fracture prevention strategies should be emphasized for patients with comorbid diabetes and heart failure.

Our results should be interpreted in light of the study strengths and weaknesses. To our knowledge, this is the largest cohort study among older men of diabetes and fracture risk, allowing for precise estimates of fracture risk within this population. Because of the linkage with the CMS database, there was high ascertainment for clinical fracture, as prior studies have demonstrated good sensitivity and specificity for ICD9 fracture codes (42–44). However, potential weaknesses should be acknowledged. In contrast to prior prospective studies, covariates in this study were limited to those that were available in administrative datasets, and some laboratory (*e.g.*, 25-hydroxyvitamin D, parathyroid hormone levels) and fracture-related risk factors (*e.g.*, falls not resulting in health care utilization, parental hip fracture history) were not measured. We were unable to quantify duration of diabetes, or accurately assess diabetes control in our dataset. Finally, prior studies have shown that veterans have higher risk of fracture compared with nonveterans (45–48). Therefore, the generalizability of the results in this study may be limited. However, the comparison group in this study was also veterans, thus reducing variability between groups and selection bias.

In conclusion, this large cohort study confirmed a 22% increased risk of incident clinical fracture associated with diabetes among older men. This risk was independent of other known risk factors for fracture. A significant portion of this risk was explained by diabetes-related comorbidities, specifically peripheral neuropathy and congestive heart failure. Identification of these mediating factors suggests possible mechanisms for the diabetes effect, as well as potential interventions.

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