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Fracture Risk in Diabetic Elderly Men: The MrOS Study

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Abstract

Objective—Diabetes mellitus is associated with increased fracture risk in women but few studies are available in men. To evaluate the relationship between diabetes and prospective non-vertebral fractures in elderly men, we used data from the Osteoporotic Fractures in Men (MrOS) study.

Research Design and Methods—MrOS enrolled 5,994 men (≥65 years). Diabetes (ascertained by self-report, use of diabetes medication or elevated fasting glucose) was reported in 881 subjects of whom 80 used insulin. Hip and spine bone mineral density (BMD) were measured with dual x-ray absorptiometry. After recruitment, men were followed for incident nonvertebral fracture with a tri-annual questionnaire for an average of 9.1 (SD 2.7) years. The Cox proportional hazards model was used to assess incident risk of fractures.

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Authors Contributions

NN: concept, concept and data interpretation-Writing the MS-Final approval of the MS. *KEE, ESS:* concept & design, acquisition/ interpretation of data-Critical review for important intellectual content- Final approval of the MS. *ARH, DES, TLD, EB-C, DCB, DMB, SRC*: acquisition and interpretation of data-Revising the article for important intellectual content-Final approval of MS. *LP*: data acquisition and analysis-Revising the article-Final approval of the MS. *AVS*: **Guarantor of the study**. Substantial contributions to conception and design, analysis and interpretation of data- Revising the article critically for important intellectual content-Final approval of the version to be published.

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Results—In models adjusted for age, race, clinic site and total hip BMD, the risk of non-vertebral fracture was higher in men with diabetes, compared with normoglycemic men, [hazard ratio (HR) 1.30 (95% CI: 1.09–1.54)] and was elevated in men using insulin (HR 2.46; 95% CI 1.69–3.59). Men with impaired fasting glucose did not have a higher risk of fracture compared to normoglycemic men (HR 1.04; 95% CI 0.89–1.21). After multivariable adjustment, the risk of non-vertebral fracture remained higher only among men with diabetes who were using insulin (HR 1.74; 95% CI 1.13–2.69).

Conclusions—Men with diabetes who are using insulin have an increased risk of non-vertebral fracture for a given age and BMD.

Keywords

bone; diabetes; fractures; IGT; insulin; osteoporosis

For many years, diabetic patients were not considered at risk for osteoporosis, based on reports of their higher bone mineral density compared with healthy subjects. However, a 2001 analysis from the Study of Osteoporotic Fractures (SOF) revealed that older women with type 2 diabetes had an increased risk of non-vertebral fractures (1), a finding confirmed in later studies (2; 3). Two meta-analyses, which included data on more than one million subjects, reported an odds ratio (OR) of 1.4–1.7 for hip fractures in type 2 diabetes patients (4; 5). Insulin use appears to be associated with increased fracture risk, possibly as a marker of long-standing diabetes (1). The increased risk of fracture in women with diabetes may be partly explained by more frequent falls (1). In addition, diabetic bone may be more fragile at a given bone mineral density (BMD) (6).

However, most of the available data for non-vertebral fracture have been collected in women or in studies that did not report sex-specific results. A meta-analysis of five studies showed an increased risk of hip fracture in men with type 2 diabetes (RR=2.8; 95% CI 1.2–6.6) (4). Results for non-vertebral fractures in men also suggested an increased risk, but this has not been clearly demonstrated (7–10). Previous studies were hampered by the small number of men included; most have not been able to adjust for BMD or falls.

Therefore, utilizing data from the Osteoporotic Fractures in Men (MrOS), a large multicenter prospective observational study examining incidence and predictors of fractures in older men, here, we evaluated 1) the effect of diabetes or impaired fasting glucose on risk of non-vertebral fractures in elderly men, taking into account BMD and falls and 2) risk factors for fracture among older men with diabetes, including the effect of diabetes medications.

Methods

Participants

From March 2000 through April 2002, 5,994 men ≥ 65 years were enrolled in the baseline examination of the prospective Osteoporotic Fractures in Men (MrOS) study (11; 12). Men were recruited from population-based listings in 6 areas of the United States: Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; the Monongahela Valley near

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Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California. Men with a history of bilateral hip replacement and men who were unable to walk without the assistance of another person were excluded. The institutional review boards of each center approved the study protocol, and written consent was obtained from all participants.

Diabetes and impaired fasting glucose status

Participants attended a baseline clinic visit and up to 5 follow up visits. Baseline diabetes status was ascertained using fasting glucose levels, self-reported diagnosis of diabetes, and the medication inventory (described below). In men without self-reported diabetes or use of diabetes medications we used ADA criteria. They were considered to have normoglycemia if their fasting glucose level was 2.58 mmol/l and considered to have impaired fasting glucose (IFG) if their fasting glucose level was between 2.58–3.23 mmol/l (15). Men with a fasting glucose ≥3.26 mmol/l and/or self-reported diabetes, and/or use of medications to treat diabetes were considered to have diabetes. Patients using insulin were analyzed separately. At the follow up visits, men were queried regarding history of diabetes, and a new medication inventory was obtained. Diabetes and insulin use status were updated based on these reports. Fasting glucose was not available at followup visits. Hemoglobin A1c was not measured in MrOS.

Fracture ascertainment

As previously described, after recruitment, men were followed for incident fracture with a tri-annual questionnaire administered by mail or telephone (16). Average followup for fractures was 9.1 (SD 2.7) years. Reports of fracture were followed up by study staff to determine date, description of how the fracture occurred, and any trauma associated with the fracture. Fractures were centrally adjudicated by physician review of medical records and X-ray reports without knowledge of diabetes status. We included only confirmed nonspine fractures. We included fractures regardless of trauma level. High trauma fractures are associated with low bone density in men and women (17), and exclusion of fractures resulting from excess trauma has been reported to underestimate the contribution of osteoporosis to fractures (18)..

Covariates

Questionnaire and Medication Inventory—At baseline, information on demographic, anthropometric, personal and family medical history, lifestyle, functional status, visual, and neuromuscular function, frailty, as well as cognitive data were obtained by self-report, interview, or examination by trained and certified staff (12). Data on age and race/ethnicity (white, black, Asian, Hispanic, Native Hawaiian/Pacific Islander, American Indian/Alaskan Native, and multiracial) were collected. Physical activity was assessed with the Physical Activity Scale for the Elderly (PASE) (13) together with questions on daily sedentary activity (sometimes/often sit >4 hours/day). Additional questions included specific common medical conditions (e.g., diabetes mellitus, hypothyroidism, heart attack, and stroke), personal history of fracture ≥50 years of age, maternal history of hip fracture. Participants were asked about falls in the previous 12 months at baseline and follow-up visits. General health status was self-rated as excellent/good versus fair/poor/very poor. Participants were

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asked about mood during the previous 4 weeks to assess depression. Lifestyle risk factors included smoking (current, past, never), and dietary intake of calcium and vitamin D. Functional status was assessed by summing the amount of difficulty (0–3 scale) with five instrumental activities of daily living (IADLs including difficulty with walking 2–3 blocks outside on level ground, climbing 10 steps without resting, preparing meals, doing heavy housework, and shopping for groceries or clothes (overall score range: 0–15)(13). The Block 98 semiquantitative food frequency questionnaire (FFQ; Block Dietary Data Systems, Berkeley, CA, USA) was specifically modified for MrOS to capture the most important sources of calcium and vitamin D in older men in the United States. The nutrient composition was calculated using the USDA Database for Standard Reference, Version 12, and the 1994–1996 Continuing Survey of Food Intake in Individuals (CSFII) database. For this analysis, we used usual daily intake of calcium (mg) and vitamin D (IU) from diet and supplements. Participants were instructed to bring in all prescription medications taken in the past 30 days to their clinic visit, and specially trained study coordinators recorded these medications. The Iowa Drug Information Service Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA) was used to identify ingredient(s) in the medications (14); these data were stored in an electronic medications inventory database (San Francisco Coordinating Center, San Francisco, CA). Specific classes of medications of interest, including diabetes medications, were centrally coded by trained staff. This medication inventory was also obtained at follow-up visits.

Functional Assessment: Examination measurements included anthropometry, cognitive function, visual function, neuromuscular function, and BMD. Body weight (kg, indoor clothing without shoes) was recorded with a calibrated balance beam or electronic scale. Height (cm) was measured using a wall-mounted Harpenden stadiometer (DyFed). The modified mini-mental state (3MS) examination was conducted to assess cognitive function (scored 0–100) (19). We assessed contrast sensitivity (vision contrast test system; Visitech Consultants, Dayton, OH, USA). Participants were asked to stand from a chair without using their arms; those who were unable to do a single chair stand were classified as “unable” to complete the test. All men who were able to complete the single-chair stand were asked to complete the repeated chair-stand test. The ability and time required to complete 5 stands without using the arms were recorded. If they were unable to do 5 chair stands, used their arms during the test, were unable to complete the test, or refused to do the repeated chair stand test, they were also classified as “unable.” Grip strength (kg) was measured twice by a hand-held dynameter (Jamar) in both right and left arms; the average of right and left was used in analysis. Frailty was evaluated through 5 components, similar to criteria proposed by Fried et al (20): weight loss between baseline and second examination (~3.4 years), weakness (low grip strength), poor energy (based on answer to question: Do you feel full of energy?), slowness (slow walking speed), low physical activity (PASE). Those with 3 or more components were categorized as frail, 2 components as pre-frail or intermediate, and 0 components as robust (21).

Dual energy x-ray absorptiometry—Total body, lumbar spine (L1 to L4), and total femur areal (a) BMD, and body composition (total body lean mass and total body fat mass) were measured at baseline and up to 3 followup visits using dual energy x-ray

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absorptiometry. The same scanner model was used at all six sites and at all visits (QDR 4500 W, Hologic, Inc., 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 found no linear differences across scanners, and the maximum percentage difference in mean total spine BMD between scanners was 1.4% (22). Participant scans were not corrected for cross machine differences, but statistical models are adjusted for clinic site. DXA participants results were corrected as needed for longitudinal changes in machine performance, based on regular scans of Hologic spine and whole body phantoms at each site.

Biochemistry—Baseline fasting morning serum was collected and stored at −70°C. Glucose was measured using a hexokinase method using previously unthawed serum (Northwest Lipid Metabolism and Diabetes Research Laboratories, Seattle, WA). The inter-assay coefficient of variance (CV) for glucose based on blind duplicates was <3%. Serum creatinine was measured on previously thawed specimens with a Roche COBAS Integra 800 automated analyzer (Roche Diagnostics Corp., Indianapolis, IN), using a variation of the Jaffe enzymatic method. The assay was calibrated daily, and inter- and intra-assay CVs were 5.3%. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation (23).

Statistical analysis—Characteristics of the cohort are presented separately by baseline diabetes status. The Cox proportional hazards model was used to assess the association between diabetes and the time to first non-spine fracture after baseline during 9.1 (2.7) years years of follow-up. The primary analysis included diabetes compared with no diabetes as the reference group; a secondary analysis included diabetes with insulin use, diabetes without insulin use, and impaired fasting glucose, compared with normoglycemia as the reference group. Diabetes status was entered into these models as a time-dependent covariate. Total hip BMD and falls in the previous year were also modeled as time-dependent covariates. Other variables were entered as baseline measurements.

All models included adjustment for age, race and clinic site. Total hip BMD and fall history were each added separately to this model to assess their influence on the relationship between diabetes and fracture. In the first analysis (diabetes compared with no diabetes), addition of falls almost completely attenuated the association between diabetes and nonspine fracture, and a larger multivariable model was not developed. In the second analysis, addition of falls to the model did not fully attenuate the relationship between diabetes with insulin use and fracture risk. To develop a multivariable model, additional variables were selected for initial inclusion in the model based on risk factors for fracture previously identified in the MrOS cohort (16). The initial variables, in addition to history of diabetes, age, race, clinic site, total hip BMD, and falls in the previous year were: history of fracture for age ≥50 years; maternal hip fracture; calcium intake; vitamin D intake; current use of oral corticosteroids, loop diuretics, SSRIs, tricyclic antidepressants, or thiazolidinediones (TZDs); current smoker; history of stroke, thyroid dysfunction or heart attack; self-rated health compared with others; difficulty with IADLs; body mass index (BMI); hours per day

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sitting upright; physical activity (PASE score); eGFR; grip strength; unable to stand up from chair without using arms; contrast sensitivity; score on Teng 3MS; frailty status; and felt downhearted most of time. Variables were retained if their removal changed the coefficient for insulin-using diabetes mellitus by ≥10% compared with the minimally-adjusted model. A complete list of variables retained in the analysis is reported as footnote in table 3. A Wald test was used to determine whether the hazard ratio for insulin-using diabetes was statistically different from the hazard ratio for non-insulin-using diabetes in the multivariable model for nonspine fracture.

A Cox proportional hazards model was used to assess risk factors for nonspine fracture among diabetic men only. Variables were identified in advance and included key demographics (age, race/ethnicity), factors associated with fracture risk in other populations (total hip BMD, falls) and diabetes-related factors (diabetes medications, fasting glucose). All variables were retained in the model. All analyses were conducted using SAS Version 9.13 (SAS Institute, Inc., Cary, NC).

Results

Baseline characteristics of MrOS participants according to diabetes status are reported in Table 1. Among a total of 5994 study subjects, 2027 subjects were IGT, 881 were diabetics of whom 80 were on insulin treatment. Ninety percent of participants were white. Median age was approximately 73.5 years, with average baseline BMI in the overweight range in all groups. Total hip BMD was also higher in diabetic men and was progressively lower in men with impaired fasting glucose and in men with normal glucose levels. Men with diabetes had lower physical performance for grip strength and chair stand. Men using insulin reported more falls than other men and were more likely to report a history of fractures

Table 2 presents the incidence of non-vertebral fractures by diabetes status. Among 3,086 men with normal fasting glucose, 459 had at least one non-vertebral fracture during the average followup of 9.1 years. During the same followup 107 diabetic men without insulin use and 20 men using insulin developed at least one non-vertebral fracture. The incidence rate of non-vertebral fracture was similar for normoglycemic men (1.74 per 100 person-years), those with impaired fasting glucose (1.62 per 100 person years), and those with diabetes who were not using insulin (1.69 per 100 person years), but was higher in those using insulin (3.56 per 100 person-years).

Adjusting for age, race and clinic site, diabetic men did not have an increased risk of non--vertebral fractures compared with men without diabetes (HR = 1.12; 95% CI 0.94–1.34). However, with additional adjustment for total hip BMD, diabetes was associated with increased fracture risk (HR=1.30; 95% CI 1.09–1.54). In a model that was additionally adjusted for history of falls, however, the relationship between diabetes and fracture was no longer significant (HR 1.08; 95% CI 0.91–1.29).

When men were categorized by insulin use and by diabetes status, men using insulin had a higher risk of all non-vertebral fractures (HR 2.24; 95% CI 1.53–3.27) despite their higher BMD, compared with normoglycemic men. (Table 3). Diabetic men who were not treated

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with insulin did not have a higher fracture risk (HR 0.98; 95% CI 0.80–1.20) nor did men with impaired fasting glucose (HR 0.95; 95% CI 0.81–1.10). In a model controlling also for total hip BMD, men with diabetes who were not using insulin had a modestly increased risk of non-vertebral fractures compared with men who were normoglycemic, but the increased risk was not statistically significant (HR 1.18; 95% CI 0.96–1.44). The addition of total hip BMD did not appreciably alter the relationship between insulin use and fracture risk (HR 2.46; 95% CI 1.69–3.59). We therefore added an adjustment for fall risk (Table 3, Model 3), and found the association between insulin-using diabetes and fracture risk was attenuated, but still significantly elevated (HR 1.98; 95% CI 1.34–2.15). In other multivariable models (Table 3, Model 4) additionally adjusted for BMI and other covariates associated with bone loss, , and fracture, risk of non-vertebral fracture remained elevated only among insulin treated diabetics (HR 1.74; 95% CI 1.13–2.69). No effect was found in noninsulin users or in men with impaired fasting glucose. The hazard ratios for diabetes with insulin use (HR 1.74; 95% CI 1.13–2.69) and for diabetes without insulin use (HR 1.00; 95% CI 0.85–1.18) were statistically different (Wald test p-value 0.017).In a separate model that included only men with a diagnosis of diabetes at baseline (Table 4), factors that were associated with an increased risk of fractures included lower total hip BMD (HR 1.69; 95% CI 1.38, 2.06)), falls in the last 12 months (HR 1.61; 95% CI 1.06, 2.44), and sulfonylurea use (HR 1.66; 95% CI 1.09, 2.51). Hispanic, but not black or Asian, men had a significantly elevated risk relative to white men. Use of thiazolidinediones (TZD) or metformin did not affect the risk for fractures. In this model a significantly increased risk of fractures was not observed among insulin users. Baseline fasting glucose level was also not longer associated with fracture risk.

Discussion

Our findings suggest that older men with diabetes mellitus have an increased risk of non-vertebral fractures, compared with normoglycemic men, adjusting for age and total hip BMD. However, diabetic men receiving insulin treatment had nearly double the risk of fractures compared to non-diabetics, after adjustment for covariates available in MrOS. In diabetic men who were not using insulin, the fracture rate was not increased during an average 9-year follow-up. Impaired fasting glucose did not affect the fracture rate. Factors associated with an increased risk of fractures included lower total hip BMD, recent falls, and sulfonylurea use.

A few previous studies have estimated relative risk for non-vertebral or all clinical fractures associated with diabetes in men. The Rotterdam study reported that although men with diabetes had higher BMD, they had an increased non-vertebral fracture risk in unadjusted models [crude HR 1.61 (1.05–2.46)], but the relationship was not significant after adjustment for age, BMI, BMD and other factors [HR 1.64 (0.93–2.90)] (24). The Malmo study of middle-aged men (43.7±6.6 years old) found an increased risk of low-energy fractures with diabetes [adjusted RR 2.38 (1.65–3.42)] (9). Melton et al reported that men with diabetes had increased risk of any fractures in models adjusted for age [RR 1.4 (1.3–1.6)] (10). In the TROMSO study, where vit D supplements and physical exercise are common, type 2 diabetes was not significantly associated with risk of non-vertebral fracture in men [adjustedRR 1.21 (0.6–2.47)] (7).

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In our study men with diabetes had a higher risk of fracture at a given age and BMD, consistent with previous findings in this cohort and others (25). These results suggest BMD and FRAX may underestimate fracture risk in diabetic men. In this cohort of older men, the increased risk of fracture with diabetes, considering all diabetic men as a group, was accounted for by worse physical performance and increased falls. Functional limitations and lower limb strength have been reported in diabetic patients which can be a consequence of increased muscle protein breakdown and fat infiltration (26–28). However, in diabetic men who were using insulin, an increased risk of fracture persisted even after taking into account physical performance, falls, and other fracture-related risk factors. Some previous studies have also reported an increased risk of fracture in those using insulin. Most of these studies combined men and women together in their analyses (7; 10; 30) but one Italian study reported increased risk in men separately (31).

Our findings are consistent with several potential mechanisms of increased fracture risk in diabetics. First, patients receiving insulin have a higher propensity for hypoglycemic events which could increase the risk of falls. Those taking insulin may also have more severe disease or longer disease duration and thus likely have microvascular involvement and peripheral neuropathy which increases the prevalence of chronic gait/balance impairments and subsequently falls. Not unexpectedly, we found that diabetic men using insulin reported more falls than healthy men, similar to reports in diabetic women (2). Insulin users are usually more likely to have chronic hyperglycemia, which may impair bone quality in the diabetic skeleton (32). In fact, although areal BMD may be higher in patients with type 2 diabetes compared with healthy subjects, a previous study in the MrOS cohort found that the bone structure of diabetic patients may have an overall decreased strength and lowered resistance to fractures (33). In addition, high glucose levels produce a larger concentration of advanced glycation end products in the bone, which have been associated with low bone strength in post-mortem studies (34) and with fracture in diabetic patients (35). Therefore, with compromised bone quality, low-trauma events may increase fracture risk.

In addition, other factors related to type 2 diabetes such as micro- and macro-vascular complications, oxidative stress, renal dysfunction, elevated renal calcium loss and persistent inflammation present in type 2 diabetes may further impair bone health and increase fracture risk. Interestingly, in the Blue Mountain study in Australia, specifically designed to determine risk factors for eye disease in diabetic patients, the risk of fractures in insulin users was strongly influenced by retinopathy. Their poor vision caused an increased risk of falls. Poor vision may also be a marker for longer duration of diabetes, more severe diabetes, or poorer glycaemic control. In the Blue Mountain Study insulin users had a 2.7 RR of dying (95% CI 1.7– 4.4) during a 5-year followup.

In our effort to identify variables contributing to the higher risk of fracture among MrOS men with insulin-treated diabetes, we considered a range of risk factors for fracture that are also associated with diabetes, including more frequent falls, poorer physical performance and vision, reduced renal function and history of cardiovascular events. However, these risk factors accounted for only a small portion of the association between insulin-treated diabetes and fracture risk in our models.

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Risk factors for fracture in men with diabetes, considered as a separate group, included lower BMD and more frequent falls. In the same subgroup, an increased risk of fractures was observed in those treated with sulfonylureas, medications known to cause hypoglycaemic events and in turn falls (36). Fracture risk appeared to be similarly elevated with insulin use, but the association was not statistically significant and, with limited numbers of participants in this category, the confidence intervals were wide.

Our results suggest that diabetic patients and caregivers should pay more attention to preventive measures to avoid falls, particularly in patients treated with insulin and sulfonylureas. Our study did not find any protective effect of metformin on fractures, a finding confirmed by other authors (7; 10). There was also no increased risk with TZD use. Reports from clinical trials have found increased fracture risk with TZD use in women, but not men (37). As already reported (14), patients with impaired fasting glucose did not have an increased risk of fractures, implying that mild hyperglycaemia does not predict bone health.

In our study we have investigated for the first time risk of fractures in a well-characterized cohort of elderly men with a long follow up, one notable study strength. We lack information on diabetes duration, HBA1c levels, and peripheral nerve function. Without HBA1c or OGTT, diabetes may have been under-diagnosed. Diabetes was determined by fasting glucose levels as well as self-report, but some men with undiagnosed diabetes may have been misclassified as not having diabetes. However, self-report is considered a valid method to detect diabetes (38, 39). Study participants were community dwelling volunteers who were ambulatory and mainly white. Our results may not be applicable to the broader population of older men. Finally, we cannot exclude that diabetes patients on insulin could have been affected by long standing type 1 diabetes. We think that this is very unlikely since in general, type 1 diabetes is a rare condition that dramatically increases the risk of cardiovascular diseases and only 40% of patients survive more than 40 years of disease (40–42). Type 1 diabetes men who do survive to older age are often in poor health. Many are no longer living in the community, and those who are would be unlikely to volunteer for a study like MrOS.

Our findings indicate that the risk of non-vertebral fracture is 30% higher in men with diabetes for a given BMD. Men who take insulin have more than double the risk of fractures. Taken together with previous findings in women, our findings highlight the importance of diabetes as a risk factor for fractures, and underscore the importance of preventive measures for diabetic patients receiving insulin.

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Abbreviations

BMI	Body Mass Index
BMD	Bone Mineral Density
GFR	glomerular filtration rate
MrOS	Osteoporotic Fractures in Men Study
TZDs	thiazolidinediones

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Table 1

Baseline characteristics of MrOS participants by diabetes status

Characteristic	Normal Glucose	Impaired Fasting Glucose	Diabetes no insulin use	Diabetes insulin use	P-value
Total Number	3086	2027	801	80	
Age, (years)	73.7 ± 6.0	73.5 ± 5.8	73.8 ± 5.6	73.3 ± 5.1	0.16
Race,					<0.01
White	2787 (90.3)	1837 (90.6)	676 (84.4)	62 (77.5)	
Black	111 (3.6)	70 (3.5)	50 (6.2)	13 (16.3)	
Asian	90 (2.9)	64 (3.2)	36 (4.5)	1 (1.3)	
Hispanic	63 (2.0)	35 (1.7)	26 (3.2)	2 (2.5)	
Other	35 (1.1)	21 (1.0)	13 (1.6)	2 (2.5)	
BMI (Kg/m^2)	26.5 ± 3.4	28.0 ± 3.9	29.1 ± 4.2	29.5 ± 4.4	<0.01
Total Hip BMD (g/cm^2)	0.94 ± 0.14	0.97 ± 0.14	1.01 ± 0.15	0.99 ± 0.16	<0.01
Falls in previous year					<0.01
0 fall	2446 (79.3)	1618 (79.8)	617 (77.0)	45 (56.3)	
1 fall	361 (11.7)	244 (12.0)	104 (13.0)	13 (16.3)	
2 – 3 falls	234 (7.6)	133 (6.6)	63 (7.9)	18 (22.5)	
4 – 5 falls	32 (1.0)	22 (1.1)	10 (1.2)	3 (3.8)	
6+ falls	13 (0.4)	10 (0.5)	7 (0.9)	1 (1.3)	
Any fractures ≥50 years age	755 (24.5)	521 (25.8)	171 (21.3)	22 (27.5)	0.14
History of stroke,	170 (5.5)	102 (5.0)	62 (7.7)	10 (12.5)	0.02
History of heart attack,	371 (12.0)	278 (13.7)	167 (20.8)	18 (22.5)	<0.01
Estimated GFR (ml/min) (CKD-EPI)	75.2 ± 14.9	75.5 ± 14.6	73.2 ± 17.4	69.0 ± 19.3	<0.01
Felt downhearted ≥ most of time,	82 (2.7)	64 (3.2)	31 (3.9)	1 (1.3)	0.22
Tricyclic antidepressant use,	43 (1.4)	35 (1.8)	21 (2.8)	9 (11.3)	<0.01
Current smoker,	107 (3.5)	73 (3.6)	26 (3.2)	0 (0.0)	0.37
Grip Strength (kg)					<0.01
0 Unable/Refused	60 (1.9)	32 (1.6)	17 (2.1)	4 (5.0)	

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Characteristic	Normal Glucose	Impaired Fasting Glucose	Diabetes no insulin use	Diabetes insulin use	P-value
1 Low: 7.00 ≤ Q1 < 33.0	688 (22.3)	454 (22.4)	252 (31.5)	30 (37.5)	
2 33.0 ≤ Q2 < 38.50	748 (24.2)	491 (24.2)	207 (25.8)	21 (26.3)	
3 38.50 ≤ Q3 < 44.0	772 (25.0)	515 (25.4)	169 (21.1)	15 (18.8)	
4 44.0 < Q4	817 (26.5)	535 (26.4)	156 (19.5)	10 (12.5)	
Unable to complete chair stands,	72 (2.3)	61 (3.0)	38 (4.8)	9 (11.3)	<0.01
During day/hours/sitting upright,	6.2 ± 3.1	6.1 ± 3.0	6.4 ± 3.2	7.0 ± 3.6	<0.01

Results are presented as Number (%), or mean (SD). **BMD**: Bone Mineral Density. **BMI**: Body mass Index. **GFR**: glomerular filtration rate

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Table 2

Incidence rate of non-vertebral fracture by baseline diabetes status in older men

Group	N with any fracture	Total N	Person years (x 1000)	Incidence rate, per 100 person-years
Normal fasting glucose	459	3086	26.4	1.74
Impaired fasting glucose	285	2027	17.5	1.62
Diabetes, no insulin use	107	801	6.3	1.69
Diabetes, insulin use	20	80	0.6	3.56

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Table 3

Adjusted hazard ratio for fracture by diabetes status in older men

Model	Diabetes, all[a]	Impaired fasting glucose[b]	Diabetes, no insulin	Diabetes, insulin use[b]
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Unadjusted model	1.08 (0.91, 1.28)	0.93 (0.79, 1.08)	0.94 (0.77, 1.50)	1.94 (1.35, 2.80)
2. Adjusted for age, race, clinic	1.12 (0.94, 1.34)	0.95 (0.81, 1.10)	0.98 (0.80, 1.20)	2.24(1.53, 3.27)
3. Adjusted for Model 1 plus total hip BMD	1.30 (1.09, 1.54)	1.04 (0.89, 1.21)	1.18 (0.96, 1.44)	2.46 (1.69, 3.59)
4. Adjusted for Model 1 plus falls in the year before baseline	1.08 (0.91, 1.29)	0.95 (0.82, 1.11)	0.94 (0.77, 1.15)	1.98 (1.34, 2.15)
5. Multivariable model [c]	----	1.00 (0.85, 1.18)	1.00 (0.80, 1.25)	1.74 (1.13, 2.69)

[a] Reference group is men without diabetes

[b] Reference group is men with normal fasting glucose

[c] Adjusted for age, race, clinic site, total hip BMD (time varying), number of falls in previous year (time varying), BMI, history of fracture age 50+, history of stroke, history of heart attack, eGFR, depression, tricyclic antidepressant use, current smoker, grip strength, unable to complete chair stands, hours sitting upright during day. 5298 participants included in multivariable model.

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Table 4

Risk factors for non-vertebral fracture in older men with diabetes

Variable	HR[a] (95% CI)
Age (per 5 year increase)	1.07 (0.88, 1.29)
Race/ethnicity	
White	1.00 (reference)
Black	0.90 (0.35, 2.29)
Hispanic	3.57 (1.44, 8.87)
Asian	1.44 (0.56, 3.77)
Total hip BMD (per 1 SD decrease[b])	1.69 (1.38, 2.06)
Fell in year before baseline (Yes/No)	1.61 (1.06, 2.44)
Fasting glucose (per 1 SD increase[c])	1.02 (0.91, 1.11)
Insulin use (Yes/No)	1.62 (0.78, 3.37)
Metformin use (Yes/No)	0.96 (0.60, 1.54)
Sulfonylurea use (Yes/No)	1.66 (1.09, 2.51)
TZD use (Yes/No)	1.18 (0.64, 2.16)

[a] Adjusted for all other variables in table. 779 participants included in model.

[b] 1 SD = 0.1 g/cm^2

[c] 1 SD = 0.63 mmol/l