Risk Factors for Incident Fracture in Older Adults With Type 2 Diabetes: The Framingham Heart Study

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OBJECTIVE

To identify risk factors for fracture in type 2 diabetes.

RESEARCH DESIGN AND METHODS

This prospective study included members of the Framingham Original and Offspring Cohorts. Type 2 diabetes was defined as fasting plasma glucose >125 mg/dL or use of type 2 diabetes therapy. We used repeated-measures Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% CIs for associations between potential predictors and incidence of fragility fracture.

RESULTS

Participants included 793 individuals with type 2 diabetes. Mean ± SD age was 70 ± 10 years; 45% were women. A total of 106 incident fractures occurred over 1,437 observation follow-up intervals. Fracture incidence increased with age (adjusted HRs 1.00, 1.44 [95% CI 0.65, 3.16], and 2.40 [1.14, 5.04] for <60, 60–70, and >70 years, respectively; P_{trend} = 0.02), female sex (2.23 [1.26, 3.95]), HbA_{1c} (1.00, 2.10 [1.17, 3.75], and 1.29 [0.69, 2.41] for 4.45–6.46% [25–47 mmol/mol], 6.50–7.49% [48–58 mmol/mol], and 7.50–13.86% [58–128 mmol/mol]; P_{trend} =0.03), falls in past year (1.00, 1.87 [0.82, 4.28], and 3.29 [1.34, 8.09] for no falls, one fall, and two or more falls; P_{trend} =0.03), fracture history (2.05 [1.34, 3.12]), and lower grip strength (0.82 [0.69, 0.99] per 5-kg increase). Femoral neck bone mineral density, BMI, smoking, physical function, chronic diseases, medications, and physical function were not associated with fracture incidence.

CONCLUSIONS

Prior falls, fractures, low grip strength, and elevated HbA_{1c} are risk factors for fractures in older adults with type 2 diabetes. Evaluation of these factors may improve opportunities for early intervention and reduce fractures in this high-risk group.

Skeletal fragility is a complication of type 2 diabetes in older adults that is often underappreciated, although hip fractures—the fractures with the highest morbidity and mortality—occur two to three times more often in those with type 2 diabetes than in those without type 2 diabetes (1). Further, older adults with type 2 diabetes who sustain fractures are more likely to experience postoperative complications, longer hospitalization, greater health care costs, and loss of physical function and

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independence than individuals without type 2 diabetes who sustain fractures (2,3). Risk factors for fragility fracture in the general population are well established and include older age, female sex, low bone density, low body weight, history of falls and fracture, family history of hip fracture, glucocorticoid use, comorbidities, cigarette smoking, and heavy alcohol use (4). Despite the significant impact of osteoporotic-related fractures on morbidity and quality of life and despite the availability and efficacy of pharmacologic treatment in this population, older adults with type 2 diabetes remain undertreated (5,6). The mechanisms underlying increased fracture risk in type 2 diabetes are complex, involving bone material properties (via advanced glycation end products) (7), bone turnover (8), impairments in bone microarchitecture (9), and nonskeletal factors such as increased falls due to microvascular complications (10), functional impairments, and hypoglycemia (11). Moreover, older adults with type 2 diabetes do not fit the current clinical paradigm of low bone density and low body weight that characterize skeletal fragility, making risk stratification challenging. Prior studies of risk factors for fracture in those with type 2 diabetes have largely been based on clinical samples (12–15) or cohorts with relatively small numbers of individuals with type 2 diabetes (16,17). Thus, the purpose of this study was to identify the clinical characteristics contributing to fragility fractures in a large, population-based study of older adults with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Participants

This analysis is a prospective study of risk factors for incident fractures in 793 individuals with type 2 diabetes. Participants are members of the Framingham Study Original Cohort and Offspring Cohort. The Original Cohort is a population-based cohort established in 1948 in Framingham, MA. The Offspring Cohort was enrolled in 1971 and includes the adult children and spouses of participants in the Original Cohort. Methods of recruitment and data collection have previously been described (18,19). Briefly, cohort members attend study visits every 2–4 years and undergo the same assessments, including comprehensive physical examinations, laboratory testing, and questionnaires. A panel of physicians reviews and adjudicates all major health events and causes of death. For the current study, we selected all participants diagnosed with type 2 diabetes starting in 1990 for the Original Cohort (Fig. 1*A*) and 1998 for the Offspring Cohort (Fig. 1*B*). We selected this sampling frame based on the initiation of incident fracture surveillance at this time.

Study Design

We used a repeated-measures prospective study design—considering each clinic exam as one observation for each individual—and treated the interval of time to incident fracture, death, or the next exam as the follow-up period for that observation. The clinic exam at which type 2 diabetes was first diagnosed was the first (baseline) observation for that individual. The total follow-up time for the study extended through the end of 2009 for the Original Cohort and 2018 for the Offspring Cohort. Thus, each participant could have up to seven separate observations for the Original Cohort (Fig. 1*A*) and three separate observations for the Offspring Cohort (Fig. 1*B*). Data collected at each clinic visit provided baseline measures for each risk set, accounting for changes in measures over time. For each observation, a fracture event was defined as the first fracture occurring in the follow-up interval. Subsequent fractures occurring in the same follow-up period are not included; however, we do include multiple fractures for individuals who experienced a first fracture event in more than one follow-up period.

Incident Fracture

Fractures are actively ascertained in the Framingham Study through a combination of sources including fracture registries, medical records, and standardized questionnaires administered to participants at study visits. Information is obtained on the date of fracture, the skeletal site of the fracture, circumstances as to how the fracture occurred, the role of trauma, and treatment. Physician adjudicators confirm incident fractures by comprehensive review of several overlapping sources including hospitalizations, operative reports, radiographic procedures, discharge summaries, and death records. We excluded fractures of the fingers, toes, skull, and face, as well as pathologic fractures and fractures due to severe trauma. Because

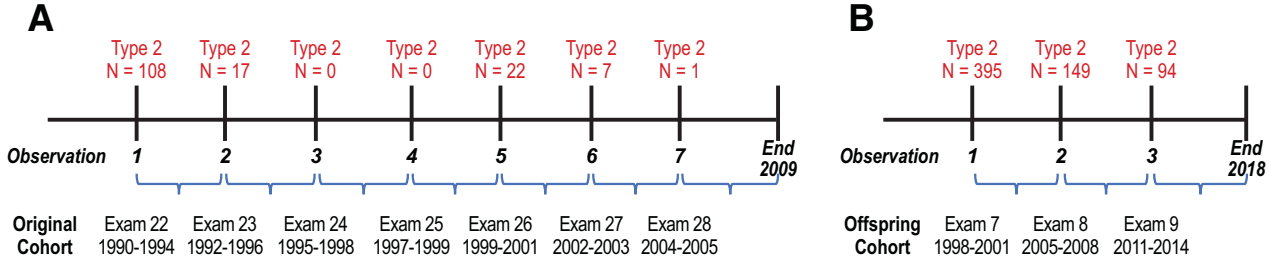

Figure 1—Study design and participants. This analysis is a prospective study of risk factors for incident fracture in 793 individuals with type 2 diabetes. Participants included all individuals classified as having type 2 diabetes from 1990 through 2005 for the Original Cohort (*A*) and 1998 through 2014 for the Offspring Cohort (*B*). The top row shows the number of cohort members diagnosed with type 2 diabetes at each clinic exam (indicated in red). We used a repeated-measures approach, considering each clinic exam as one observation for each individual and treating the interval of time to incident fracture, death, or the next exam as the follow-up period for that observation. Data collected at each exam provided baseline measures for each risk set, allowing for changes in risk factor status and covariates over time. The unique observations, or risk sets, are indicated by blue brackets.

serial radiographs were not obtained and most vertebral fractures go undiagnosed, all vertebral fractures were also excluded.

Type 2 Diabetes

Hemoglobin A_{1c} (HbA_{1c}) (%) and glucose levels (mg/dL) were measured from blood samples drawn after an 8-h fast with standard methods (Roche Diagnostics, Mannheim, Germany). Type 2 diabetes was defined as fasting plasma glucose levels >125 mg/dL (7.0 mmol/dL) or on treatment with insulin or oral antidiabetes agents. Medical histories were reviewed to rule out individuals with type 1 diabetes. HbA_{1c} values used in analyses were available at exam 22 (1990–1994) in the Original Cohort and at exam 7 (1998–2001) and exam 8 (2005–2008) for the Offspring Cohort.

Clinical Characteristics

We evaluated clinical characteristics previously shown to be associated with fracture as potential risk factors. Height (inches) and weight (pounds) were measured with a stadiometer and balance beam scale, respectively, and BMI (weight in kilograms divided by the square of height in meters) was calculated. Standardized questionnaires were used to obtain information on demographic characteristics, smoking, falls in the past year, and history of fractures. DXA scans of the hip were performed with a Lunar DPX-L densitometer (GE Lunar Corp, Madison, WI) (20). DXA was available at exam 22 (1990–1994) for the Original Cohort and all three time points (exam 7 [1998–2001], exam 8 [2005–2008], and exam 9 [2011–2014]) for the Offspring Cohort.

Self-rated health was evaluated as excellent, good, fair, or poor. Impairments in physical ability to perform six activities of daily living (ADL) (eating, dressing, bathing, transferring, toileting, and incontinence) were categorized as severe (unable to perform five or six activities), moderate (unable to perform three or four activities), or mild/none (unable to perform one activity/able to perform all activities).

Trained technicians measured isometric grip strength to the nearest kilogram using a handheld dynamometer; the greatest value from either hand was used. Grip strength was measured at exam 22 (1990–1994) and exam 26 (1999–2001) in the Original Cohort and all three time points (exam 7 [1998–2001], exam 8 [2005–2008], and exam 9 [2011–2014]) for the Offspring Cohort. Physicians performed physical examinations including gathering information on medical history (renal disease, emphysema, degenerative joint disease, dementia, hyperthyroid disease, Parkinson disease, and nonskin cancer) and current medication use. Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or antihypertensive treatment.

Ascertainment of cardiovascular disease (CVD) was conducted through active surveillance, and diagnoses were adjudicated by a three-member panel of physicians who conducted comprehensive, standardized reviews of medical records available from study examinations, physician visits, and hospitalizations. CVD included coronary heart disease (recognized or unrecognized myocardial infarction, identified by electrocardiogram or enzymes), angina pectoris (or coronary insufficiency), stroke, transient ischemic attack, intermittent claudication, and heart failure.

Statistical Analysis

We used a repeated-measures approach to model the association between potential risk factors and fracture incidence in this cohort of individuals with type 2 diabetes. The time between each clinic visit was considered as one period of observation for each participant, and the interval of time to incident fracture, death, or the next clinic visit encompassed each follow-up period. With this approach we treat each observation interval (approximately equal in length) as a mini–follow-up study and pool the multiple observations into a single sample to predict fracture risk.

We used Cox proportional hazards regression models with model-based estimation of covariance and robust variance to calculate unadjusted and multivariable-adjusted hazard ratios (HRs) and 95% CIs for associations between clinical characteristics and incidence of fracture in participants with type 2 diabetes. To test for trend, we entered into the model an ordinal variable, with each level representing the categories of the predictor. We adjusted for age, sex, Framingham cohort (Original/Offspring), height, weight, and current smoking. We further adjusted for type 2 diabetes duration when examining the association between insulin use and fracture. We evaluated concordance with the proportional hazards assumption by evaluating interactions between independent variables and time.

RESULTS

The study included 793 participants with type 2 diabetes (359 women and 434 men), contributing to a total of 1,437 observations. The mean ± SD follow-up time for each observation was 4.5 ± 2.7 years (range 1 month–16 years). The mean number of observations was 2 ± 1 observations per person; 351 individuals contributed one observation, 268 individuals contributed two observations, and 174 individuals contributed three or more observations.

At the first baseline observation, mean ± SD age was 70 ± 10 years (Table 1). Mean duration of type 2 diabetes was 5 ± 7 years, 36% used oral antidiabetes medication, and 11% used insulin. Mean HbA_{1c} was 7.2 ± 1.6% (55 ± 17.5 mmol/mol). More than one-quarter of participants had fallen in the past year (26%) or had a prior fracture (28%). Frequency of moderate-severe ADL impairment was 5%, and more than one-half had bone mineral density (BMD) T scores greater than or equal to −1.0. The most common chronic diseases included hypertension (42%), CVD (34%), and degenerative joint disease (27%). One-third of participants were taking anticholesterol medications and 20% were taking β-blockers, and 13% of women were taking estrogen.

A total of 106 first incident fracture events occurred over a total of 1,437 observation follow-up intervals, such that 84 participants had one incident fracture event and 11 had two incident fracture events (Table 2). The most common fracture sites were hip (27%), upper arm/shoulder (18%), foot/ankle/leg (17%), wrist/forearm (15%), and ribs (14%). The remaining fracture sites (pelvis, elbow, and patella) together comprised 9% of total fractures.

In unadjusted analyses, demographic and anthropometric factors associated

Table 1—Baseline* clinical characteristics of participants with type 2 diabetes—the Framingham Study

N	793
Women, *n* (%)	359 (45)
Age, years	70 ± 10
Weight, lb	193 ± 41
Height, in	66 ± 4
BMI, kg/m^2	31 ± 6
Current smoker, *n* (%)	77 (10)
Type 2 diabetes duration, years	5 ± 7
≤5, *n* (%)	498 (63)
6–10, *n* (%)	114 (14)
>10, *n* (%)	181 (23)
Oral antidiabetes medication use, *n* (%)	283 (36)
Insulin use, *n* (%)	91 (11)
HbA_{1c}†	7.2 ± 1.6
4.45–6.46% (25–47 mmol/mol), *n* (%)	209 (38)
6.50–7.49% (48–58 mmol/mol), *n* (%)	167 (30)
7.50–13.86% (58–128 mmol/mol), *n* (%)	179 (32)
Falls in last year, *n* (%)	
0	378 (74)
1	132 (26)
2+	2 (<1)
History of fracture, *n* (%)	221 (28)
Femoral neck BMD, g/cm^2	0.929 ± 0.163
Femoral neck T score, *n* (%)	
Greater than or equal to −1.0	308 (57)
−2.5 to less than −1.0	193 (36)
Less than or equal to −2.5	38 (7)
Self-rated health, *n* (%)	
Excellent	120 (25)
Good	281 (57)
Fair	74 (15)
Poor	14 (3)
ADL impairment, *n* (%)‡	
Severe	19 (3)
Moderate	14 (2)
None/mild	632 (95)
Grip strength, kg	28 ± 11
Medical conditions, *n* (%)	
Hypertension	337 (42)
Renal disease	37 (5)
Emphysema	20 (3)
Degenerative joint disease	211 (27)
Dementia	28 (4)
Hyperthyroid	35 (4)
Parkinson disease	5 (1)
CVD	267 (34)
Cancer	109 (14)
Medications, *n* (%)	
Estrogen§	39 (13)
Nitroglycerine	39 (5)
Nitrates	44 (6)
β-Blockers	161 (20)
Calcium channel blockers	132 (17)
Diuretics	75 (9)
Anticholesterol	263 (33)
Thyroid	52 (7)
Glucocorticoids	13 (2)
Antianxiety	28 (4)

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with incident fractures in participants with type 2 diabetes included increased age, female sex, and lower height and weight (Table 3). After adjustment for covariates, age and sex remained associated with fracture incidence, whereas height and weight were no longer significant predictors. BMI and smoking were unrelated to fracture risk.

Individuals with >10 years' duration of type 2 diabetes had unadjusted HR 1.64 (95% CI 1.05–2.55) for risk of fracture, relative to those with ≤5 years' duration of type 2 diabetes, although the association did not persist after multivariable adjustment (HR 1.49; 95% CI 0.91–2.44). Use of oral antidiabetes drugs was unrelated to fracture risk (adjusted HR 0.80; 0.50–1.28). The adjusted HR for the association between insulin use and fracture was 1.85 (0.98–3.49). After further adjustment for type 2 diabetes duration (not shown), the HR was attenuated to 1.40 (0.69–2.84). Incidence of fracture increased with higher levels of HbA_{1c}, and P_{trend} remained significant in multivariable models (P_{trend} =0.03).

Two or more falls in the past year (HR 4.35; 95% CI 2.02–9.35 [versus no falls]) and history of fracture (2.41; 1.67–3.48) were strongly associated with higher incidence of fracture in unadjusted analyses in participants with type 2 diabetes. After adjustment for covariates, HRs were attenuated but remained strong (two or more falls HR 3.29; 1.34–8.09; prior fractures HR 2.05; 1.34–3.12).

Unadjusted analyses showed femoral neck BMD (HR 0.59; 95% CI 0.42–0.83 [per 1 g/cm^2 increase]) and grip strength (0.73; 0.65–0.83 [per 5-kg increase]) were inversely related to fracture incidence in participants with type 2 diabetes, whereas no associations were observed for self-reported health or ADL impairment. In multivariable models, grip strength remained a predictor of fracture (0.82; 0.62–0.99 [per 5-kg increase]), whereas BMD was no longer significant.

Current estrogen use in women was not related to fracture risk (adjusted HR 0.36; 95% CI 0.12–1.12); however, numbers were low in this group (three fractures of 44 observations). No other medications were associated with incident fracture, and no differences in

Table 1—Continued

Sleeping	15 (2)
Antidepressants	54 (7)

Data are means ± SD unless otherwise indicated. *Measured at the first observation. †*N* = 555 due to missing data for HbA_{1c}. ‡ADL impairment: severe, unable to perform five or six activities; moderate, unable to perform three or four activities; mild/none, unable to perform one activity/able to perform all activities. §*N* = 306 women.

fracture risk were observed for any chronic diseases.

In sensitivity analyses, we repeated all models with additional adjustment for HbA_{1c} and type 2 diabetes duration. These additional adjustments did not change the results (not shown).

CONCLUSIONS

We found that several well-established risk factors for fracture in the general population also increased fracture risk in older adults with type 2 diabetes. These include older age, female sex, history of fracture, and previous falls (21–24). Although these risk factors are not reversible, they can still be helpful in stratifying risk for individuals with type 2 diabetes. In addition, we found that lower grip strength increased fracture risk in older adults with type 2 diabetes, also similar to the general population (25).

Several risk factors for fracture in the general population were not strong predictors of fracture in our study of older adults with diabetes, including greater height, lower BMI, lower BMD, smoking, poor self-reported health, ADL impairment, dementia and other chronic diseases, and use of antidepressants and other medications. However, point estimates and trends in associations in our study were generally in the same direction as those reported for the general population (4), indicating that our sample size may have been too small for detection of weak-to-moderate associations.

To our knowledge, few studies have investigated the specific association between fracture and grip strength in people with type 2 diabetes (26); however, lower grip strength and accelerated loss of grip strength have been observed in those with type 2 diabetes in comparison with those without type 2 diabetes (27). In contrast, in two prospective cohort studies—the Study of Osteoporotic Fractures (16) and Health ABC (28)—declines in muscle strength largely affected the lower extremities rather than the upper extremities in older women with type 2 diabetes. However, selection bias (28) in participants with type 2 diabetes may have obscured true declines in grip strength.

We found increased risk of fracture in older adults with type 2 diabetes with an HbA_{1c} of 6.50–7.49% (48–58 mmol/mol) and slightly increased risks of fracture in those with type 2 diabetes with an HbA_{1c} of ≥7.5% (58 mmol/mol) in comparison with <6.5%. Our results are consistent with large medical record–based studies of older adults with type 2 diabetes in the U.S. (12). The reasons for increased fracture among individuals with type 2 diabetes are not yet fully understood, but multiple mechanisms have been proposed including poor longitudinal glucose control resulting in reduced bone quality (29), falls associated with hypoglycemia (30,31), and potentially some antihyperglycemic medications (32). Other studies have shown that lower levels of HbA_{1c} are associated with increased risk of fracture. For example, Lee et al. (14) found that HbA_{1c} <6.5% (48 mmol/mol) was associated with increased risk of fracture and Puar et al. (33) found that tighter glycemic control (HbA_{1c} <7.0% [53 mmol/mol]) was associated with increased risk of hip fracture in comparison with HbA_{1c} >8.0% (64 mmol/mol). Findings from the U.K. general practice electronic database demonstrated that individuals with type 2 diabetes with documented hypoglycemic events had 1.24 times greater incidence of fracture in comparison with those with type 2 diabetes without documentation of hypoglycemic events (15).

A common result of treatment, hypoglycemia may increase fracture risk through increasing falls (34), as hypoglycemic episodes can cause confusion, gait abnormalities, and blurred vision. Current HbA_{1c} reflects control for the immediate past 3 months, but longitudinal measurements of HbA_{1c} are more valuable for assessment of long-term control. Individuals with worsening control over time are more likely to develop complications associated with type 2 diabetes such as peripheral neuropathy. Three components of diabetic neuropathy include peripheral sensory, peripheral motor, and autonomic neuropathy. These can be associated with decreased strength, loss of coordination, orthostatic hypotension, and hypoglycemic unawareness, all of which can increase risk of falls (35).

Microvascular complications of diabetes have also been associated with an increased risk of falls, which provides a partial explanation for fractures. Specifically, diabetes-related complications of decreased peripheral nerve function, poor vision, and decreased renal function were all associated with an increased risk of falls (36). Even a mild decrease in renal

Table 2—Skeletal sites of incident fractures in participants with type 2 diabetes—the Framingham Study

Skeletal site	*n*	%
Hip	29	27
Upper arm/shoulder	19	18
Foot/ankle/leg	18	17
Wrist/forearm	16	15
Ribs	15	14
Pelvis	4	4
Elbow	3	3
Patella	2	2
Total	106*	100

*A total of 106 first incident fracture events occurred over a total of 1,437 follow-up observation intervals; 84 individuals sustained 1 incident fracture event, and 11 individuals sustained 2 incident fracture events (total participants *N* = 793).

Table 3—Association between clinical characteristics and incidence of fracture in participants with type 2 diabetes—the Framingham Study

	Incident fractures (*n* = 106)	Observations (*N* = 1,437)	Incidence (*n/N*), %	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*
Age, years					
<60	9	172	5	1.00	1.00
60–69	25	386	6	1.58 (0.76, 3.29)	1.44 (0.65, 3.16)
70+	72	879	8	3.42 (1.74, 6.71)	2.40 (1.14, 5.04)
P_{trend}				<0.01	0.02
Sex					
Men	33	781	4	1.00	1.00
Women	73	656	11	2.53 (1.66, 3.87)	2.23 (1.26, 3.95)
Weight in quartiles					
1 (93–160 lb)	34	343	10	1.00	1.00
2 (161–186 lb)	30	350	9	0.50 (0.30, 0.83)	0.78 (0.45, 1.35)
3 (187–215 lb)	20	347	6	0.39 (0.23, 0.69)	0.69 (0.37, 1.31)
4 (216–350 lb)	16	348	5	0.29 (0.16, 0.53)	0.64 (0.33, 1.26)
P_{trend}				<0.01	0.57
Height in quartiles					
1 (55.50–62.75 in)	37	326	11	1.00	1.00
2 (63.00–65.75 in)	24	318	8	0.69 (0.42, 1.16)	1.05 (0.61, 1.80)
3 (66.00–68.50 in)	14	322	4	0.36 (0.20, 0.65)	0.82 (0.40, 1.69)
4 (68.75–77.00 in)	17	312	5	0.41 (0.23, 0.73)	1.20 (0.52, 2.69)
P_{trend}				<0.01	0.78
BMI in quartiles					
1 (17.31–27.17 kg/m^2)	26	319	8	1.00	1.00
2 (27.22–30.39 kg/m^2)	22	320	7	0.74 (0.43, 1.28)	0.90 (0.52, 1.57)
3 (30.39–34.64 kg/m^2)	25	320	8	0.82 (0.48, 1.40)	0.87 (0.50, 1.51)
4 (34.67–58.29 kg/m^2)	19	319	6	0.65 (0.37, 1.16)	0.81 (0.45, 1.46)
P_{trend}				0.49	0.91
Current smoker					
No	98	1,323	7	1.00	1.00
Yes	8	114	7	0.76 (0.39, 1.51)	0.87 (0.42, 1.77)
Type 2 diabetes duration, years**					
≤5	34	548	6	1.00	1.00
6–10	23	351	7	1.04 (0.61, 1.78)	0.99 (0.55, 1.79)
>10	49	538	9	1.64 (1.05, 2.55)	1.49 (0.91, 2.44)
P_{trend}				0.07	0.19
Oral antidiabetes medication use	25	331	8	0.68 (0.42, 1.09)	0.80 (0.50, 1.28)
Insulin use	13	113	12	1.66 (0.86, 3.18)	1.85 (0.98, 3.49)
HbA_{1c}					
4.45–6.46% (25–47 mmol/mol)	19	301	6	1.00	1.00
6.50–7.49% (48–58 mmol/mol)	30	255	12	2.10 (1.19, 3.72)	2.10 (1.17, 3.75)
7.50–13.86% (58–128 mmol/mol)	19	233	8	1.17 (0.61, 2.22)	1.29 (0.69, 2.41)
P_{trend}				0.02	0.03
Falls in last year					
0	27	422	6	1.00	1.00
1	10	93	11	1.84 (0.89, 3.82)	1.87 (0.82, 4.28)
2+	10	62	16	4.35 (2.02, 9.35)	3.29 (1.34, 8.09)
P_{trend}				<0.01	0.03
History of fracture	54	434	12	2.41 (1.67, 3.48)	2.05 (1.34, 3.12)
Femoral neck BMD (g/cm^2 increase)				0.59 (0.42, 0.83)	0.79 (0.49, 1.26)
Femoral neck T score					
Greater than or equal to −1.0	21	434	5	1.00	1.00
−2.5 to less than −1.0	30	300	10	2.19 (1.25, 3.83)	1.24 (0.67, 2.31)
Less than or equal to −2.5	6	44	14	2.92 (1.15, 7.42)	1.55 (0.56, 4.34)
P_{trend}				<0.01	0.67
Self-rated health (fair/poor vs. good/ excellent)	7	88	8	2.08 (0.85, 5.12)	1.85 (0.61, 5.60)

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Table 3—Continued

	Incident fractures (*n* = 106)	Observations (*N* = 1,437)	Incidence (*n/N*), %	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*
ADL impairment (moderate/severe vs. none/mild)†	3	58	5	1.99 (0.78, 5.09)	0.82 (0.22, 3.03)
Grip strength (5-kg increase)				0.73 (0.65, 0.83)	0.82 (0.69, 0.99)
Medical conditions					
Hypertension	36	382	9	0.87 (0.56, 1.36)	0.95 (0.61, 1.48)
Renal disease	5	70	7	0.86 (0.34, 2.17)	1.15 (0.45, 2.93)
Emphysema	1	35	3	0.58 (0.08, 4.34)	0.72 (0.09, 5.83)
Degenerative joint disease	28	313	9	0.98 (0.64, 1.53)	0.74 (0.45, 1.21)
Dementia	3	45	7	3.72 (0.83, 16.54)	—
Hyperthyroid	8	76	11	1.27 (0.65, 2.51)	1.06 (0.52, 2.16)
Parkinson disease	0	8	0	—	—
CVD	38	526	7	1.39 (0.91, 2.14)	1.05 (0.65, 1.69)
Cancer	16	232	7	1.14 (0.63, 2.06)	1.05 (0.55, 2.03)
Medications					
Estrogen‡	3	44	7	0.36 (0.12, 1.12)	0.49 (0.15, 1.58)
Nitroglycerine	4	46	9	1.34 (0.49, 3.72)	1.33 (0.49, 3.60)
Nitrates	4	54	7	1.43 (0.40, 5.08)	1.90 (0.58, 6.27)
β-Blockers	16	180	9	0.83 (0.45, 1.52)	0.93 (0.50, 1.76)
Calcium channel blockers	12	154	8	0.89 (0.47, 1.69)	1.07 (0.55, 2.08)
Diuretics	8	83	10	0.92 (0.46, 1.82)	1.16 (0.60, 2.24)
Anticholesterol	41	456	9	0.77 (0.53, 1.13)	0.84 (0.52, 1.34)
Thyroid	8	61	13	1.39 (0.66, 2.94)	1.59 (0.79, 3.22)
Glucocorticoids	2	16	13	2.07 (0.67, 6.34)	1.98 (0.67, 5.86)
Antianxiety	3	36	8	0.92 (0.30, 2.82)	0.55 (0.14, 2.24)
Sleeping	4	17	24	2.26 (0.78, 6.53)	1.34 (0.37, 4.83)
Antidepressants	1	58	2	0.16 (0.02, 1.15)	—

Data are *n* unless otherwise indicated. *Adjustment for age, sex, cohort, weight, height, smoking (except when these characteristics are the independent variable of interest). —Too few observations to provide stable estimate. **Duration of diabetes treated as a continuous variable and expressed per year; unadjusted HR 1.04 (95% CI 1.01, 1.06) and adjusted HR 1.03 (95% CI 1.01, 1.05). †ADL impairment: moderate/severe, unable to perform three or more activities; none/mild, able to perform all activities or unable to perform. ‡*N* = 306 women.

function could account for an increased fall risk related to loss of lower muscle strength (31). Additionally, autonomic neuropathy leads to loss of symptoms associated with hypoglycemia, and this loss of awareness and lower glucose levels can lead to falls (37). The Study of Osteoporotic Fractures demonstrated an increased fall risk in women with diabetes, especially in those receiving insulin as treatment, who had more than double the risk of multiple falls in comparison with women without diabetes. Poor balance and peripheral neuropathy were the key risk factors for falls (30). Finally, intensive glycemic control did not increase the risk of fractures or falls in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (38) compared with standard glycemic control—findings consistent with those of other investigations (13,39,40). Vavanikunnel et al. (40) proposed that the lack of association between glycemic control and fracture risk may be due to the beneficial effects of insulin resistance on the skeleton in the early stages of type 2 diabetes. Taken together, the results of our study surrounding glucose control support the importance of carefully considering HbA_{1c} levels in older adults with type 2 diabetes to avoid hypoglycemic events and identify opportunities for fracture prevention (5).

The current study has several strengths. First, ascertainment of type 2 diabetes, fractures, and clinical risk factors is robust. Second, the long duration of follow-up, nearly 100% retention, and community-based sampling allow for generalizability of results. However, the largely Caucasian sample limits applicability to other race groups. Third, comprehensive ascertainment of clinical risk factors and laboratory assessments ensure high validity and ability to adjust for important confounders. A limitation of this study is the low incidence of fractures in certain strata. This could explain the lack of associations observed between fracture and several characteristics in participants with type 2 diabetes, including femoral neck BMD, BMI, smoking, self-rated health, chronic diseases, medications, and physical function. However, examining multiple risk sets allowed us to maximize the use of our data collected over several decades in nearly 800 cohort members with type 2 diabetes of advanced age.

In conclusion, most older adults with type 2 diabetes have normal or elevated BMD, so determination of appropriate thresholds for drug treatment is challenging. This study demonstrates additional risk factors for fracture in type 2 diabetes that should inform clinicians deciding who to treat with anti-fracture therapies. Consideration of other factors beyond the current screening tool of BMD, including fracture and fall history, low grip strength, and poor glucose control, may allow for

better disease management and health outcomes in older adults with type 2 diabetes.

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