ORIGINAL ARTICLE

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Type 2 Diabetes and Risk of Hip Fractures and Non-Skeletal Fall Injuries in the Elderly: A Study From the Fractures and Fall Injuries in the Elderly Cohort (FRAILCO)

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ABSTRACT

Questions remain about whether the increased risk of fractures in patients with type 2 diabetes (T2DM) is related mainly to increased risk of falling or to bone-specific properties. The primary aim of this study was to investigate the risk of hip fractures and non-skeletal fall injuries in older men and women with and without T2DM. We included 429,313 individuals (aged 80.8 ± 8.2 years [mean ± SD], 58% women) from the Swedish registry "Senior Alert" and linked the data to several nationwide registers. We identified 79,159 individuals with T2DM (45% with insulin [T2DM-I], 41% with oral antidiabetics [T2DM-O], and 14% with no antidiabetic treatment [T2DM-none]) and 343,603 individuals without diabetes. During a follow-up of approximately 670,000 person-years, we identified in total 36,132 fractures (15,572 hip fractures) and 20,019 non-skeletal fall injuries. In multivariable Cox regression models where the reference group was patients without diabetes and the outcome was hip fracture, T2DM-I was associated with increased risk (adjusted hazard ratio (HR) [95% CI] 1.24 [1.16–1.32]), T2DM-O with unaffected risk (1.03 [0.97–1.11]), and T2DM-none with reduced risk (0.88 [0.79–0.98]). Both the diagnosis of T2DM-I (1.22 [1.16–1.29]) and T2DM-O (1.12 [1.06–1.18]) but not T2DM-none (1.07 [0.98–1.16]) predicted non-skeletal fall injury. The same pattern was found regarding other fractures (any, upper arm, ankle, and major osteoporotic fracture) but not for wrist fracture. Subset analyses revealed that in men, the risk of hip fracture was only increased in those with T2DM-I, but in women, both the diagnosis of T2DM-O and T2DM-I were related to increased hip fracture risk. In conclusion, the risk of fractures differs substantially among patients with T2DM and an increased risk of hip fracture was primarily found in insulin-treated patients, whereas the risk of non-skeletal fall injury was consistently increased in T2DM with any diabetes medication. © 2016 American Society for Bone and Mineral Research.

KEY WORDS: GENERAL POPULATION STUDIES; FRACTURE RISK ASSESSMENT; FRACTURE PREVENTION; TYPE 2 DIABETES

Introduction

The United Nations estimates that within the next 30 years, the global life expectancy will increase substantially[1] and as a consequence, age-associated diseases are expected to increase. Diabetes is by far one of the world's largest health challenges of this time, affected not only by age itself but most of all by lifestyle changes such as increased access to high-energy rich food and less expenditures. The International Diabetes Federation estimates that in 2015, approximately 415 million people suffered from diabetes, and this figure is expected to reach 642 million in 2040. Type 2 diabetes (T2DM) accounts for more than 90% of all individuals with diabetes, and more than 94 million people with diabetes are ages 65 to 79 years.[2]

In parallel, there is another age-related epidemic ongoing as osteoporosis is estimated to affect 200 million women worldwide, and approximately 1.6 million hip fractures, the most severe of the osteoporotic fractures, occur annually.[3] Traditionally, T2DM has not been considered as a risk factor for osteoporotic fractures and studies have shown that patients with T2DM have normal or increased bone mineral density (BMD) compared with non-diabetic controls.[4] Nevertheless,

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several studies,[5–9] but not all,[10,11] have reported an increased risk of hip fractures among patients with T2DM. A decade ago, two large meta-analyses presented unanimously that both type 1 diabetes (T1DM) and T2DM were related to increased risk of hip fracture, although the relationship was more profound for T1DM and BMD was indeed higher in patients with T2DM.[12,13] Recently, an updated meta-analysis including 21 studies confirmed the previous results, and patients with T2DM had approximately 30% increased risk of hip fracture compared with non-diabetic individuals.[14] However, many of the studies that were included in these meta-analyses were fairly small with a limited number of fractures and sometimes not well characterized even regarding type 1 or type 2 diabetes. In addition, because T2DM represents a heterogeneous disorder, it seems reasonable not classifying all patients into the same group without taking into consideration disease severity or antidiabetic medications. Furthermore, many previous studies included patients that were aged 60 to 70 years and the incidence peak for hip fractures occurs in much older patients.[15]

To date, the underlying reasons for the association between diabetes and fractures remain unclear. Evidence has been presented regarding alterations in bone microarchitecture, bone turnover, and osteogenic cells, but other extra-skeletal factors such as medications, disturbed vision, impaired muscle strength, intensive glycemic control, and frequent falls may be just as important.[16] Patients with diabetes have indeed an increased risk of falling.[17] However, none of the previous studies exploring the risk of hip fractures have presented data on coincident risk for other non-skeletal fall-related injuries. To be able to improve risk assessment and for better understanding of the complex relationship between T2DM and fractures, further studies in this area are warranted.

The primary aim of this study was to investigate the risk of hip fractures and non-skeletal fall injuries in patients with T2DM, collected from a large cohort of elderly patients with information regarding comorbidities, antidiabetic medications, and assessment of risk of falling. As a secondary aim, we investigated the risks of other non-hip fractures and made subset analyses based on sex.

Materials and Methods

Study population

The Fractures and Fall Injuries in the Elderly Cohort (FRAILCO) is a patient-based cohort study where Swedish national directories are linked in order to study associations regarding fractures, fall injuries, morbidity, mortality, and medications. The cohort consists of 429,313 men and women (aged 80.8 ± 8.2 years (mean $\pm$ SD), range 65–109 years, 58% women) included between 2008 and 2014 in the Swedish national directory "Senior Alert."[18] Patients were followed from the time of registration until death, emigration, or the end of 2014, resulting in approximately 670,000 person-years with a median follow-up time of 1.3 years (interquartile range 0.6–2.3). The directory was originally designed to serve as a quality registry to support improvements in preventive care for older adults and includes more than 20% of the entire Swedish population in this age group. Swedish citizens aged 65 years or older were registered in connection to a visit to a health care facility by a licensed allied health professional, regardless of diagnosis, comorbidities, functioning, and health. In the end of 2014, more than 90% of all municipalities in Sweden were connected to Senior Alert, and all participants were registered with information about age, sex, height, and weight along with a number of parameters related to the risk of falling, pressure ulcers, and nutrition. Information concerning medications, diagnoses, fall injuries, fractures, and deaths, in relation to time of registration, were collected using the Drug Dispensation Register (2005–2014), the Patient Register (2001–2014 for outpatient visits and 1987–2014 for admitted patients), and Cause of Death Register. Information regarding immigration and emigration was included from Statistics Sweden. The study was approved by the regional ethical review board in Gothenburg.

Procedures

We defined "treatment with insulin" as any known prescriptions of insulin and "treatment with oral antidiabetics" as any prescription of non-insulin antidiabetics (including injectable GLP-1 analogues) in the Drug Dispensation Register. Because many patients receive their diagnosis of type 2 diabetes in primary-care units and thus not included in the Patient Register and because of possible misclassifications between ICD E10 to E11, patients were classified as type 1 diabetes if they were diagnosed with E10 and had received prescriptions of insulin but no other non-insulin antidiabetic medications. We subsequently defined type 2 diabetes as all other patients with diabetes, based on either a diagnosis of E10 with oral antidiabetics, E11, or without any diagnosis but with known prescriptions of antidiabetic medications. If patients were diagnosed as E10 (type 1 diabetes) but had no prescriptions of any antidiabetic medications in the register, they were classified as diabetes unknown ($n = 1008$) and excluded from the present study (Fig. 1).

Outcomes

Incident hip fracture was defined as a fractured femoral head, neck, trochanter, or subtrochanteric part of femur, in combination with a code for surgical procedure (ICD codes in Supplemental Tables S1 and S2) that occurred after the registration to Senior Alert. To further ascertain that the defined combination of codes represented a new hip fracture and not a previous hip fracture with a revisit, the second fracture was discarded if the codes were repeated within 5 months. Incident non-skeletal fall injury was classified as any injury (except fractures) occurring after the time of inclusion that was accompanied by a code representing a fall (ICD codes in Supplemental Table S3). As a secondary aim, we investigated relationships to other non-hip fractures (any fracture, wrist, upper arm, major osteoporotic fracture [MOF], and ankle), which were defined in the same procedures as above and as specified in Supplemental Table S1. We did not include vertebral fracture in the study because these fractures are seldom diagnosed and have a low rate of registration in Swedish registers.

Comorbidities

Comorbidities were defined according to ICD codes specified in Supplemental Table S4. From the Senior Alert questionnaire, 99% of the registered individuals provided information regarding previous known falls (yes/no), which was used as a surrogate marker for risk of falling. Previous glucocorticoid treatment was defined as any previous period the patient had retrieved prescriptions for more than 450 mg of prednisolone or equivalents during three months or more (Supplemental Table S5). For the survival analyses, Charlson comorbidity

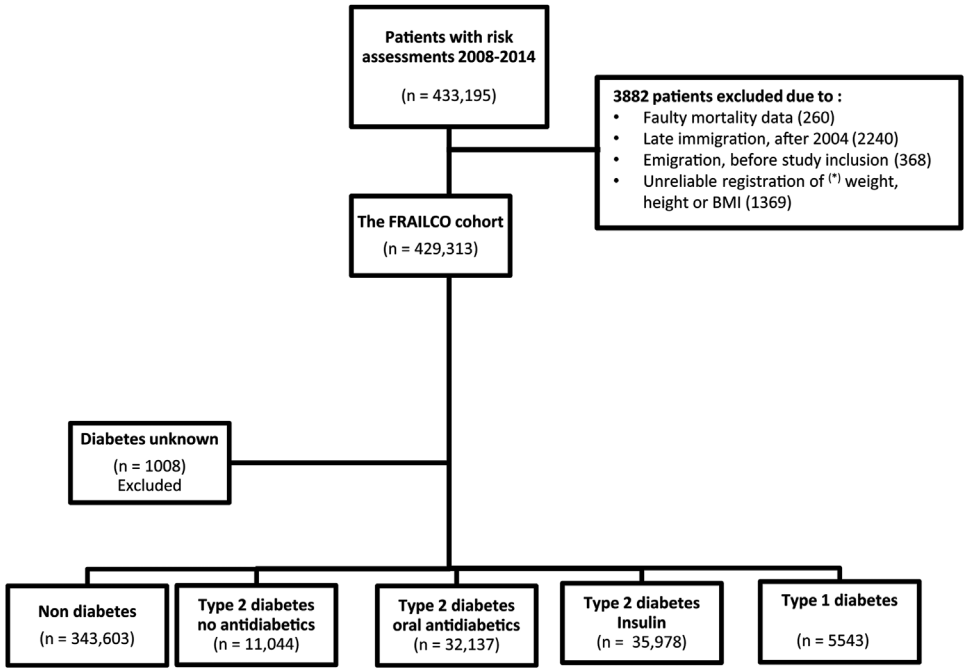

Fig. 1. Flow chart of the entire cohort. *Accepted values after exclusion of top and bottom 1% were weight 30–176 kg, height 114–197 cm, and BMI 12.23–73.05 kg/m^2.

index[19] (excluding diabetes) was used to quantify comorbidity. The index was calculated as a weighted sum of the following diseases (ICD-10 codes in Supplemental Table S6): one point each for dementia, ischemic heart disease, congestive heart failure, cerebrovascular disease, disease of arteries, arterioles, and capillaries, chronic pulmonary disease, chronic liver disease; one point for mild renal failure and an extra point if severe renal failure; two points each for hemiplegia, peptic ulcer disease, tumor without metastasis, lymphoma, or leukemia; and six points for metastatic solid tumor. Characterization of general condition, food, and liquid intake at the time of risk assessment was performed using questions from the validated RAPS or Norton scales[20] used in Senior Alert for risk assessment of decubitus ulcers.

Statistical analysis

Age and body mass index (BMI) are presented as mean ± SD and all comorbidities as proportions. We used Cox proportional time-dependent hazards models to estimate hazards for the different groups of diabetes and the outcomes, and for the survival analyses, the reference group was patients without diabetes. To adjust for comorbidities, all models were adjusted for age, sex, height, and weight (multivariate 1) and as a second step we introduced traditional risk factors into the models (age, sex, height, weight, previous fracture, rheumatoid arthritis, glucocorticoid use, alendronate use), including Charlson comorbidity index (multivariate 2). Ultimately, we added previous self-reported known fall injury as an estimate of risk for falling (multivariate 3). In the analyses where men and women were compared within the same corresponding diabetes group, the models were fully adjusted (multivariate 3). All statistical analyses were performed using IBM SPSS version 23.

Results

We identified 79,159 patients with T2DM (41% with only oral antidiabetics [T2DM-O], 45% with insulin [T2DM-I], and 14% with no antidiabetic medications [T2DM-none]), 5543 patients with T1DM, and 343,603 patients without diabetes. The baseline characteristics of the different groups in the cohort are presented in Table 1. In summary, patients with diabetes were younger, had higher BMI, and had a lower proportion of women compared with patients without diabetes. During the study period, 47% ($n = 2588$) of the patients with T1DM and 36% ($n = 28{,}499$) of the patients with T2DM died compared with 34% ($n = 115{,}264$) among patients without diabetes. There were no major differences in general health (based on the RAPS and Norton scales) between the groups because a majority of all patients were classified as in fairly good condition, eating three-quarters of a portion and drinking more than 700 mL a day. The patients with T2DM had less frequently experienced a previous fracture and those with T1DM had more previous fractures in the history compared with those without diabetes. Patients with diabetes (T1DM or T2DM) had a much higher frequency of all investigated comorbidities except for rheumatoid arthritis and dementia, which were less frequent in patients with T2DM than in patients without diabetes. Among patients with antidiabetic medications, there were more patients with prescriptions of metformin in the group with T2DM-O compared with T2DM-I, but the groups had similar prescriptions of sulphonylurea, pioglitazone, and sitagliptin. Patients with insulin treatment were more frequently diagnosed with retinopathy and the same pattern was found regarding diagnosis of "any diabetes complication" (Table 1).

Baseline characteristics of the cohort subdivided according to sex are presented in Table 2. Women were older and had to a larger extent suffered from a previous fracture (which was

Table 1. Clinical Characteristics of the Cohort

	Non-diabetes ($n = 343,603$)	T2DM-none ($n = 11,044$)	T2DM-O ($n = 32,137$)	T2DM-I ($n = 35,978$)	T1DM ($n = 5543$)
Age, years (mean ± SD)	81.1 (8.3)	80.6 (7.8)	79.4 (7.6)	79.3 (7.7)	78.8 (7.7)
Sex (% females)	203,567 (59%)	6006 (54%)	16,503 (51%)	17,953 (50%)	2660 (48%)
BMI kg/m^2 (mean ± SD)	24.9 (4.8)	26.4 (5.3)	27.1 (5.2)	28.3 (5.7)	26.3 (5.2)
Inclusion site					
Hospital	218,034 (63%)	7876 (71%)	21,893 (68%)	22,020 (61%)	3560 (64%)
Nursing home	84,023 (24%)	1967 (18%)	5966 (19%)	8403 (23%)	1246 (22%)
Primary care center	13,348 (3.9%)	424 (3.8%)	1480 (4.6%)	1487 (4.1%)	213 (3.8%)
Residential home service	18,469 (5.4%)	497 (4.5%)	1904 (5.9%)	2914 (8.1%)	355 (6.4%)
Rehab unit	9630 (2.8%)	276 (2.5%)	883 (2.7%)	1142 (3.2%)	168 (3.0%)
General health description					
General condition (good or fairly good)	308,021 (90%)	9820 (90%)	28,793 (90%)	31,460 (88%)	4829 (88%)
Nutrition (3/4 portion or more)	273,249 (80%)	8939 (82%)	26,220 (82%)	29,472 (83%)	4455 (81%)
Drinking (>700 mL/d)	305,005 (89%)	9959 (91%)	29,083 (91%)	32,797 (92%)	5040 (92%)
Previous events					
Any fracture	112,690 (33%)	3385 (31%)	8702 (27%)	10,449 (29%)	2069 (37%)
Hip fracture	31,689 (9.2%)	892 (8.1%)	2216 (6.9%)	2457 (6.8%)	553 (10%)
Major osteoporotic fracture	73,582 (21%)	2127 (19%)	5199 (16%)	6057 (17%)	1253 (23%)
Diagnosis of fall injury	116,421 (34%)	3609 (33%)	9377 (29%)	11,350 (32%)	2187 (39%)
Self-reported fall injury (yes/no)	136,754 (40%)	4329 (40%)	12,658 (40%)	14,892 (42%)	2383 (44%)
Incident events					
Death	115,264 (34%)	3929 (36%)	10,082 (31%)	14,488 (40%)	2588 (47%)
Fractures					
Any	29,604 (8.6%)	844 (7.6%)	2295 (7.1%)	2771 (7.7%)	530 (9.6%)
Hip	12,926 (3.8%)	331 (3.0%)	944 (2.9%)	1119 (3.1%)	218 (3.9%)
Wrist	1825 (0.5%)	52 (0.5%)	98 (0.3%)	128 (0.4%)	23 (0.4%)
Upper arm (chollum chir.)	2261 (0.7%)	74 (0.7%)	205 (0.6%)	244 (0.7%)	60 (1.1%)
Major osteoporotic fracture	17,718 (5.2%)	505 (4.6%)	1320 (4.1%)	1580 (4.4%)	312 (5.6%)
Ankle	828 (0.2%)	31 (0.3%)	83 (0.3%)	121 (0.3%)	27 (0.5%)
Non-skeletal fall injury	16,193 (4.7%)	568 (5.1%)	1497 (4.9%)	1761 (4.9%)	281 (5.1%)
Comorbidities					
Rheumatoid arthritis	8785 (2.6%)	256 (2.3%)	689 (2.1%)	918 (2.6%)	169 (3.0%)
Dementia	36,255 (11%)	1243 (11%)	2798 (8.7%)	3500 (10%)	706 (13%)
Neurological diseases	96,846 (28%)	4222 (38%)	9438 (29%)	11,073 (31%)	2495 (45%)
Hypertension	139,780 (41%)	8261 (75%)	18,522 (58%)	20,812 (58%)	4287 (77%)
Ischemic heart disease	70,857 (21%)	4484 (41%)	9217 (29%)	11,351 (32%)	2600 (47%)
Heart arrhythmias	80,263 (23%)	4448 (40%)	8530 (27%)	9655 (27%)	1967 (35%)
Congestive heart failure	50,837 (15%)	3362 (30%)	6150 (19%)	8842 (25%)	1929 (35%)
Stroke	47,969 (14%)	2665 (24%)	5347 (17%)	6562 (18%)	1422 (26%)
Chronic obstructive pulmonary disease	25,220 (7.3%)	1287 (12%)	2411 (7.5%)	2906 (8.1%)	523 (9.4%)
Chronic liver disease	3413 (1.0%)	245 (2.2%)	471 (1.5%)	734 (2.0%)	201 (3.6%)
Renal failure	16,587 (5%)	1390 (13%)	2203 (7%)	4865 (14%)	1282 (23%)
Malignant tumor (any)	152,120 (44%)	6517 (59%)	14,768 (46%)	16,948 (47%)	3991 (72%)
Diabetes retinopathy	—	560 (5.1%)	3016 (9.4%)	8521 (24%)	3208 (58%)
Diagnosis of diabetes complication	—	1262 (11%)	5356 (17%)	13,200 (37%)	4329 (78%)
Medications					
Glucocorticoids	42,383 (12%)	1432 (13%)	3675 (11%)	5392 (15%)	770 (14%)
Alendronate	34,079 (9.9%)	924 (8.4%)	2099 (6.5%)	2515 (7.0%)	498 (9.0%)
Metformin	—	—	26,769 (83%)	25,500 (71%)	—
Sulphonylurea	—	—	13,613 (42%)	15,202 (42%)	—
Pioglitazone	—	—	1169 (3.6%)	1486 (4.1%)	—
Sitagliptin	—	—	1465 (4.6%)	1699 (4.7%)	—

Patients divided into those without diabetes, those with T2DM and insulin treatment (T2DM-I), T2DM and oral antidiabetics (T2DM-O), and T2DM without any antidiabetic medicines (T2DM-none) or T1DM.

Table 2. Clinical Characteristics of the Cohort Subdivided into Men and Women

	Men (n = 181,616)					Women (n = 246,689)				
	Non-diabetes (n = 140,036)	T2DM-none (n = 5038)	T2DM-O (n = 15,634)	T2DM-I (n = 18,025)	T1DM (n = 2883)	Non-diabetes (n = 203,567)	T2DM-none (n = 6006)	T2DM-O (n = 16,503)	T2DM-I (n = 17,953)	T1DM (n = 2660)
Age, years (mean ± SD)	79.5 (8.4)	79.0 (7.6)	78.0 (7.3)	77.9 (7.4)	77.3 (7.5)	82.3 (8.2)	82.0 (7.7)	80.7 (7.6)	80.7 (7.7)	80.4 (7.7)
BMI, kg/m^2 (mean ± SD)	25.1 (4.3)	26.4 (4.7)	27.0 (4.7)	28.0 (5.2)	26.0 (4.7)	24.8 (5.2)	26.5 (5.7)	27.2 (5.6)	28.6 (6.2)	26.6 (5.6)
Previous events										
Any fracture	34,952 (23%)	1127 (22%)	3067 (20%)	3880 (22%)	850 (30%)	80,738 (40%)	2258 (38%)	5635 (34%)	6569 (37%)	1219 (46%)
Hip fracture	8339 (6.0%)	268 (5.3%)	645 (4.1%)	792 (4.4%)	211 (7.3%)	23,350 (12%)	624 (10%)	1571 (9.5%)	1665 (9.3%)	342 (13%)
Major osteoporotic fracture	17.370 (12%)	595 (12%)	1502 (10%)	1822 (10%)	454 (16%)	56,212 (28%)	1532 (26%)	3697 (22%)	4235 (24%)	799 (30%)
Diagnosis of fall injury	35.301 (25%)	1263 (25%)	3533 (23%)	4472 (25%)	918 (32%)	81,120 (40%)	2346 (39%)	5844 (35.4%)	6878 (38%)	1269 (48%)
Self-reported fall injury (yes/no)	49.426 (36%)	1775 (36%)	5497 (36%)	6955 (39%)	1168 (41%)	87,328 (43%)	2554 (43%)	7161 (44%)	7937 (45%)	1215 (46%)
Incident events										
Death	48,706 (35%)	1842 (37%)	4937 (32%)	7246 (40%)	1343 (47%)	66,558 (33%)	2087 (35%)	5145 (32%)	7242 (40%)	1245 (47%)
Fractures										
Any	8554 (6.1%)	278 (5.5%)	761 (4.9%)	1013 (5.6%)	226 (7.8%)	20,043 (9.8%)	566 (9.4%)	1477 (8.9%)	1720 (9.6%)	304 (11%)
Hip	4017 (2.9%)	106 (2.1%)	320 (2.0%)	414 (2.3%)	97 (3.4%)	8909 (4.4%)	225 (3.7%)	624 (3.8%)	705 (3.9%)	121 (4.5%)
Wrist	240 (0.2%)	8 (0.2%)	21 (0.1%)	17 (0.1%)	10 (0.3%)	1585 (0.8%)	44 (0.7%)	77 (0.5%)	111 (0.6%)	13 (0.5%)
Upper arm (collum chir.)	449 (0.3%)	17 (0.3%)	48 (0.3%)	63 (0.3%)	19 (0.7%)	1812 (0.9%)	57 (0.9%)	157 (1.0%)	181 (1.0%)	41 (1.5%)
Major osteoporotic fracture	5266 (3.8%)	157 (3.1%)	446 (2.9%)	569 (3.2%)	140 (4.9%)	12,452 (6.1%)	348 (5.8%)	874 (5.3%)	1011 (5.6%)	172 (6.5%)
Ankle	191 (0.1%)	12 (0.2%)	16 (0.1%)	38 (0.2%)	12 (0.4%)	637 (0.3%)	19 (0.3%)	67 (0.4%)	83 (0.5%)	15 (0.6%)
Non-skeletal fall injury	6226 (4.4%)	246 (4.9%)	673 (4.3%)	826 (4.6%)	142 (4.9%)	9967 (4.9%)	322 (5.4%)	824 (5.0%)	935 (5.2%)	139 (5.2%)
Comorbidities										
Rheumatoid arthritis	2356 (1.7%)	73 (1.4%)	250 (1.6%)	356 (2.0%)	69 (2.4%)	6429 (3.2%)	183 (3.0%)	439 (2.7%)	562 (3.1%)	100 (3.8%)
Dementia	12,523 (8.9%)	492 (9.8%)	1237 (7.9%)	1576 (8.7%)	333 (12%)	23,732 (12%)	751 (13%)	1561 (9.5%)	1924 (11%)	373 (14%)
Neurological diseases	42,356 (30%)	2108 (42%)	5070 (32%)	6076 (34%)	1348 (47%)	54,490 (27%)	2114 (35%)	4368 (26%)	4997 (28%)	1147 (43%)
Hypertension	55,843 (40%)	3702 (74%)	9150 (59%)	10,632 (59%)	2234 (78%)	83,937 (41%)	4559 (76%)	9372 (57%)	10,180 (57%)	2053 (77%)
Ischemic heart disease	35,825 (26%)	2330 (46%)	5326 (34%)	6487 (36%)	1444 (50%)	35,032 (17%)	2154 (36%)	3891 (24%)	4864 (27%)	1156 (44%)
Heart arrhythmias	37,600 (27%)	2194 (44%)	4591 (29%)	5330 (30%)	1112 (39%)	42,663 (21%)	2254 (38%)	3939 (24%)	4325 (24%)	855 (32%)
Congestive heart failure	23,094 (17%)	1639 (33%)	3246 (21%)	4679 (26%)	1034 (36%)	27,743 (14%)	1723 (29%)	2904 (18%)	4163 (23%)	895 (34%)
Stroke	22,433 (16%)	1339 (27%)	2922 (19%)	3642 (20%)	803 (28%)	25,536 (13%)	1326 (22%)	2425 (15%)	2920 (16%)	619 (23%)
Chronic obstructive pulmonary disease	11,413 (8.2%)	618 (12%)	1254 (8.0%)	1598 (8.9%)	288 (10%)	13,807 (6.8%)	669 (11%)	1157 (7.0%)	1308 (7.3%)	235 (8.8%)
Chronic liver disease	1544 (1.1%)	124 (2.5%)	269 (1.7%)	407 (2.3%)	108 (3.7%)	1869 (0.9%)	121 (2.0%)	202 (1.2%)	327 (1.8%)	93 (3.5%)
Renal failure	9457 (6.8%)	848 (17%)	1360 (8.7%)	2886 (16%)	770 (27%)	7130 (3.5%)	542 (9.0%)	843 (5.1%)	1979 (11%)	512 (19%)
Malignant tumor (any)	62,174 (44%)	2886 (57%)	7038 (45%)	8411 (47%)	2065 (72%)	89,946 (44%)	3631 (61%)	7730 (47%)	8537 (48%)	1926 (72%)
Diabetes retinopathy	—	258 (5.1%)	1437 (9.2%)	4213 (23%)	1703 (59%)	—	302 (5.0%)	1579 (9.6%)	4308 (24%)	1505 (57%)
Diagnosis of any diabetes complication	—	629 (13%)	2743 (18%)	6929 (38%)	2323 (81%)	—	633 (11%)	2613 (16%)	6271 (35%)	2006 (75%)

continued

Table 2. (*Continued*)

	Men (n = 181,616)					Women (n = 246,689)				
	Non-diabetes (n = 140,036)	T2DM-none (n = 5038)	T2DM-O (n = 15,634)	T2DM-I (n = 18,025)	T1DM (n = 2883)	Non-diabetes (n = 203,567)	T2DM-none (n = 6006)	T2DM-O (n = 16,503)	T2DM-I (n = 17,953)	T1DM (n = 2660)
Medications										
Glucocorticoids	15,543 (11%)	578 (12%)	1501 (10%)	2399 (13%)	365 (13%)	26,870 (13%)	854 (14%)	2174 (13%)	2993 (17%)	405 (15%)
Alendronate	4587 (3.3%)	163 (3.2%)	394 (2.5%)	568 (3.2%)	99 (3.4%)	29,492 (14%)	761 (13%)	1705 (10%)	1947 (11%)	399 (15%)
Metformin	—	—	13,111 (84%)	12,872 (71%)	—	—	—	13,658 (83%)	12,628 (70%)	—
Sulphonylurea	—	—	6502 (42%)	7599 (42%)	—	—	—	711 (43%)	7603 (42%)	—
Pioglitazone	—	—	579 (3.7%)	802 (4.4%)	—	—	—	590 (3.6%)	684 (3.8%)	—
Sitagliptin	—	—	804 (5.1%)	885 (4.9%)	—	—	—	661 (4.0%)	814 (4.5%)	—

Patients stratified according to sex and divided into those without diabetes, those with T2DM and insulin treatment (T2DM-I), T2DM and oral antidiabetics (T2DM-O), and T2DM without any antidiabetic medicines (T2DM-none) or T1DM. Values are presented as no. (%) if not stated otherwise.

consistent for all fracture types) compared with men. Furthermore, women had a larger number of incident fractures during follow-up and very few men were treated with alendronate (Table 2).

The most common non-skeletal fall injuries in regard to location, type of injury, and mechanism of injury are presented in Table 3. There were no clinically significant differences among patients with diabetes compared with non-diabetic individuals. The most common locations for any fall injury were head, hip and thigh, abdomen, lower back, lumbar spine, and pelvis. The most common types of injury were superficial wounds, open wounds, and muscle and tendon injury, and the vast majority fell from the same level, including slipping, tripping, or stumbling.

In Cox regression models adjusted for age, sex, height, and weight and compared with patients without diabetes, the diagnosis of T2DM was associated with an increased risk of hip fracture (adjusted hazard ratio [HR] 1.10 [95% CI 1.05–1.15]) and of non-skeletal fall injury (1.20 [1.15–1.24]). When the models were adjusted for insulin use, the diagnosis itself was still related to non-skeletal fall injury (1.13 [1.08–1.18]) but not to hip fracture (0.99 [0.94–1.05]).

Table 4 presents all the crude incidence rates and adjusted hazard ratios for incident fractures (both hip and other fractures) and non-skeletal fall injury among the different groups of diabetes compared with patients without diabetes. Patients with insulin treatment (regardless of T1DM or T2DM) had increased risk of any of the investigated fracture types (any fracture, hip, upper arm, ankle, and MOF) except for wrist fracture where the risk was not increased. Compared with patients without diabetes, patients with T2DM-none had a significantly lower risk of hip fracture and those with T2DM-O had a significantly lower risk of wrist fracture. Furthermore, all patients with any anti-diabetic medications (T1DM, T2DM-I or T2DM-O) had consistently increased risk of upper arm fracture. All patients with diabetes and any anti-diabetic medication had increased risk for having a non-skeletal fall injury. There was a trend where patients with insulin treatment had the highest risk for fractures and fall injury and those with no anti-diabetic medications had the lowest risk (Table 4). Survival curves corresponding to the final models for patients with T2DM are presented in Fig. 2*A–F*.

Subset analyses in which patients were divided according to sex are presented in Table 5. In general, the risks of having different fractures or non-skeletal fall injury in the different diabetes groups followed the same pattern as in the whole cohort. There were, however, some sex-specific differences as men with diabetes but without insulin treatment did not have increased risk of having any fracture, and men without antidiabetic medications (T2DM-none) had significantly decreased risk of having a hip fracture (adjusted HR 0.78 [95% CI 0.64–0.94]) compared with men without diabetes. In contrast, among women, the risk of having any fracture or hip fracture was slightly increased even in patients with oral antidiabetic medications, and for both men and women, there was an increased risk for non-skeletal fall injury in all patients receiving any antidiabetic medications.

After multivariate adjustment (multivariate 3) where women were compared with men within the same diabetes group, women with T2DM-O (adjusted HR 1.26 [95% CI 1.04–1.53]) or T2DM-I (1.42 [1.19–1.69]) had increased risk of hip fracture compared with men, but for patients with no antidiabetic medications, there was no statistically significant relationship between sex and hip fracture (1.30 [0.95–1.81]). Regarding

Table 3. Summary of the Most Common Incident Non-Skeletal Fall Injuries in Regard to Location, Type of Injury, and Mechanism of Injury

	Non-diabetes ($n = 343,603$)	T2DM-none ($n = 11,044$)	T2DM-O ($n = 32,137$)	T2DM-I ($n = 35,978$)	T1DM ($n = 5543$)
Total number of non-skeletal fall injury	16,193	568	1497	1761	281
Location of injury					
Head	6667 (41%)	213 (38%)	627 (42%)	647 (37%)	112 (40%)
Hip and thigh	3737 (23%)	128 (23%)	317 (21%)	428 (24%)	58 (21%)
Abdomen, lower back, lumbar spine, and pelvis	1208 (7.5%)	45 (7.9%)	110 (7.3%)	137 (7.8%)	20 (7.1%)
Knee and lower leg	1135 (7.0%)	31 (5.5%)	103 (6.9%)	159 (9.0%)	22 (7.8%)
Shoulder and upper arm	1125 (6.9%)	47 (8.3%)	93 (6.2%)	116 (6.6%)	19 (6.8%)
Thorax	843 (5.2%)	33 (5.8%)	89 (5.9%)	98 (5.6%)	17 (6.0%)
Elbow and forearm	525 (3.2%)	20 (3.5%)	40 (2.7%)	49 (2.8%)	10 (3.6%)
Wrist and hand	468 (2.9%)	14 (2.5%)	35 (2.3%)	37 (2.1%)	7 (2.5%)
Ankle and foot	288 (1.8%)	9 (1.6%)	30 (2.0%)	42 (2.4%)	4 (1.4%)
Type of injury					
Superficial wound	8034 (50%)	275 (48%)	718 (48%)	917 (52%)	150 (53%)
Muscle and tendon injury	3244 (20%)	111 (20%)	319 (21%)	329 (19%)	50 (18%)
Open wound	3138 (19%)	106 (19%)	258 (17%)	286 (16%)	53 (19%)
Dislocation, sprain, or strain of joints and ligaments	866 (5.3%)	31 (5.5%)	91 (6.1%)	96 (5.5%)	5 (1.8%)
Mechanism of injury					
Fall on same level from slipping, tripping, and stumbling	9040 (56%)	323 (57%)	808 (54%)	933 (53%)	149 (53%)
Unspecified fall	4485 (28%)	133 (23%)	440 (29%)	496 (28%)	74 (26%)
Other fall on same level	874 (5.4%)	36 (6.3%)	77 (5.1%)	103 (5.8%)	18 (6.4%)
Fall involving bed	690 (4.3%)	32 (5.6%)	55 (3.7%)	84 (4.8%)	15 (5.3%)
Fall on and from stairs and steps	507 (3.1%)	22 (3.9%)	49 (3.3%)	52 (3.0%)	8 (2.8%)
Fall involving wheelchair	322 (2.0%)	15 (2.6%)	30 (2.0%)	57 (3.2%)	11 (3.9%)
Fall involving chair	217 (1.3%)	12 (2.1%)	20 (1.3%)	28 (1.6%)	6 (2.1%)

Patients divided into those with T2DM and insulin treatment (T2DM-I), T2DM and oral antidiabetics (T2DM-O), and T2DM without any antidiabetic medicines (T2DM-none) compared with patients without diabetes. Values are presented as no. (% of total number of non-skeletal fall injuries) if not stated otherwise.

non-skeletal fall injury, there was no significant association between sex and the outcome within the three groups with T2DM (data not shown).

Among patients with T2DM ($n = 79,159$), all available antidiabetic medications were forced into a multivariable Cox regression model adjusted for age, sex, weight, height, previous fracture, rheumatoid arthritis, glucocorticoid and alendronate use, and Charlson comorbidity index. In the model, insulin use was associated with an increased risk of hip fracture (HR 1.24 [95% CI 1.14–1.35]), whereas metformin (1.05 [0.96–1.14]), sulphonylurea (1.06 [0.98–1.15]), sitagliptin (0.85 [0.64–1.12]), and pioglitazone (1.17 [0.93–1.47]) were not. In the same model, but with non-skeletal fall injury as outcome variable, insulin (1.13 [1.06–1.20]) and metformin (1.16 [1.10–1.22]) were independently associated with increased risk, whereas sulphonylurea (0.96 [0.90–1.02]), sitagliptin (0.98 [0.81–1.20]), and pioglitazone (0.88 [0.72–1.07]) were not.

Among all patients with diabetes (T1DM or T2DM, $n = 84,702$), adjusted for age, sex, height, and weight, the presence of any diabetes complication was related to increased risk of hip fracture (1.16 [1.06–1.26]), and this was similar for diabetes retinopathy (1.17 [1.06–1.29]). When the analyses were adjusted for insulin medication, the relationships between these two variables and hip fracture remained but were no longer statistically significant (1.08 [0.99–1.18]) and 1.09 [0.99–1.20]).

Discussion

The main findings from this study were that the risk of fractures differs substantially among patients with diabetes and that patients with T2DM and any kind of antidiabetic medications had increased risk of having a non-skeletal fall injury compared with patients without diabetes. Thus, only those with insulin treatment had significantly increased risk of hip fracture compared with non-diabetic individuals and those without any antidiabetic medications had in fact reduced risk of hip fracture despite increased comorbidities.

The same pattern of increased risk in those with insulin treatment was also found when analyzing other fractures such as any fracture, ankle, or MOF. However, all patients with any (oral and/or insulin) antidiabetic treatment had significantly increased risk of upper arm fracture, and in women the risk of having any fracture or hip fracture was slightly increased even in those with oral antidiabetics. Moreover, when the multivariable models were adjusted for known previous falls, the hazards for future fractures were slightly further reduced. This emphasizes the substantial increased risk of falling in this patient group and, furthermore, the heterogeneity among patients with T2DM that this needs to be taken into consideration for appropriate fracture risk assessment.

These results could be interpreted as already in less severe stages of diabetes, the risk of falling is increased, and when the

Table 4. Hazard Ratios for Patients in Different Groups of Diabetes Compared With Non-Diabetic Individuals

Fractures	Non-diabetes ($n = 343,603$)	T2DM-none ($n = 11,044$)	T2DM-O ($n = 32,137$)	T2DM-I ($n = 35,978$)	T1DM ($n = 5543$)
Any					
Incidence rate/100,000 person-years	5505	4568	4610	5239	6444
Multivariate 1	Reference	0.95 (0.88–1.01)	1.02 (0.98–1.06)	1.21 (1.17–1.26)	1.42 (1.30–1.55)
Multivariate 2	Reference	0.95 (0.88–1.02)	1.03 (0.99–1.08)	1.21 (1.16–1.25)	1.34 (1.23–1.47)
Multivariate 3	Reference	0.95 (0.89–1.02)	1.02 (0.98–1.06)	1.19 (1.14–1.24)	1.33 (1.22–1.45)
Hip					
Incidence rate/100,000 person-years	2404	1791	1896	2115	2650
Multivariate 1	Reference	0.89 (0.80–1.00)	1.04 (0.97–1.11)	1.25 (1.18–1.33)	1.44 (1.26–1.65)
Multivariate 2	Reference	0.88 (0.79–0.98)	1.03 (0.97–1.11)	1.24 (1.16–1.32)	1.38 (1.21–1.58)
Multivariate 3	Reference	0.88 (0.79–0.98)	1.03 (0.96–1.10)	1.23 (1.15–1.31)	1.38 (1.21–1.58)
Wrist					
Incidence rate/100,000 person-years	339	281	197	242	280
Multivariate 1	Reference	0.97 (0.74–1.28)	0.72 (0.59–0.88)	0.95 (0.79–1.14)	1.04 (0.69–1.58)
Multivariate 2	Reference	0.96 (0.73–1.27)	0.73 (0.59–0.89)	0.94 (0.78–1.13)	0.97 (0.64–1.47)
Multivariate 3	Reference	0.94 (0.71–1.24)	0.70 (0.56–0.86)	0.92 (0.77–1.11)	0.93 (0.61–1.41)
Upper arm (collum chir.)					
Incidence rate/100,000 person-years	420	400	412	461	729
Multivariate 1	Reference	1.10 (0.870–1.38)	1.16 (1.01–1.34)	1.36 (1.19–1.56)	2.10 (1.62–2.71)
Multivariate 2	Reference	1.08 (0.86–1.36)	1.18 (1.02–1.36)	1.33 (1.17–1.53)	1.88 (1.45–2.43)
Multivariate 3	Reference	1.08 (0.86–1.37)	1.17 (1.01–1.35)	1.33 (1.16–1.52)	1.34 (1.23–1.46)
Major osteoporotic fracture					
Incidence rate/100,000 person-years	3295	2733	2652	2987	3793
Multivariate 1	Reference	0.97 (0.89–1.06)	1.01 (0.96–1.07)	1.21 (1.15–1.28)	1.45 (1.29–1.62)
Multivariate 2	Reference	0.96 (0.88–1.05)	1.01 (0.96–1.07)	1.20 (1.14–1.26)	1.36 (1.22–1.53)
Multivariate 3	Reference	0.96 (0.88–1.05)	1.00 (0.95–1.06)	1.18 (1.13–1.25)	1.40 (1.35–1.44)
Ankle					
Incidence rate/100,000 person-years	154	168	167	229	328
Multivariate 1	Reference	1.04 (0.72–1.48)	1.01 (0.80–1.27)	1.28 (1.05–1.55)	2.08 (1.42–3.06)
Multivariate 2	Reference	1.03 (0.72–1.47)	1.02 (0.82–1.29)	1.27 (1.04–1.54)	1.93 (1.31–2.84)
Multivariate 3	Reference	1.03 (0.72–1.48)	1.01 (0.80–1.27)	1.24 (1.02–1.52)	1.49 (1.29–1.71)
Non-skeletal fall injury					
Incidence rate/100,000 person-years	3011	3074	3007	3329	3416
Multivariate 1	Reference	1.13 (1.4–1.23)	1.14 (1.08–1.21)	1.29 (1.23–1.36)	1.30 (1.15–1.46)
Multivariate 4	Reference	1.07 (0.98–1.16)	1.12 (1.06–1.18)	1.22 (1.16–1.29)	1.13 (1.00–1.27)

Values are expressed as crude incidence rates/100,000 person-years or hazard ratios and 95% confidence intervals. Patients with T2DM are divided into those with no antidiabetic medicines (T2DM-none), with oral medicines (T2DM-O), and those with insulin treatment (T2DM-I) and those with T1DM. Multivariate 1: Adjusted for age, sex, height, and weight. Multivariate 2: Adjusted for age, sex, weight, height, previous fracture, rheumatoid arthritis, glucocorticoid and alendronate use, and Charlson comorbidity index. Multivariate 3: As multivariate 2 + self-reported known fall injury. Multivariate 4: Adjusted for age, sex, weight, height, previous fall injury, self-reported known fall injury, and Charlson comorbidity index.

disease progresses and becomes more severe, the risk of fracture is ultimately increased, possibly because of direct adverse skeletal effects. It is known that patients with diabetes have increased risk of falling[17] and in accordance with our results but from a much smaller study, diabetes stratified by insulin use was associated with an increased risk of falling.[21] Furthermore, a recent meta-analysis showed a strong relationship between hypoglycemia and the risk of future falls and fractures[22] and this may in part explain the increased risk among patients treated with insulin. Another possible explanation for the increased risk of falls and fractures among insulin-treated patients may be that diabetes treatment may represent a surrogate marker for diabetes duration and disease severity. Indeed, a recent study presented that patients with T2DM and inadequate glucose control had increased risk of hip fracture,[23] and diabetes duration has been associated with increased fracture risk.[24] Nevertheless, as diabetes progresses, patients develop comorbidities such as renal failure, visual impairment, and neuropathy, as well as foot problems and possible accelerated cognitive disorders known to increase fracture

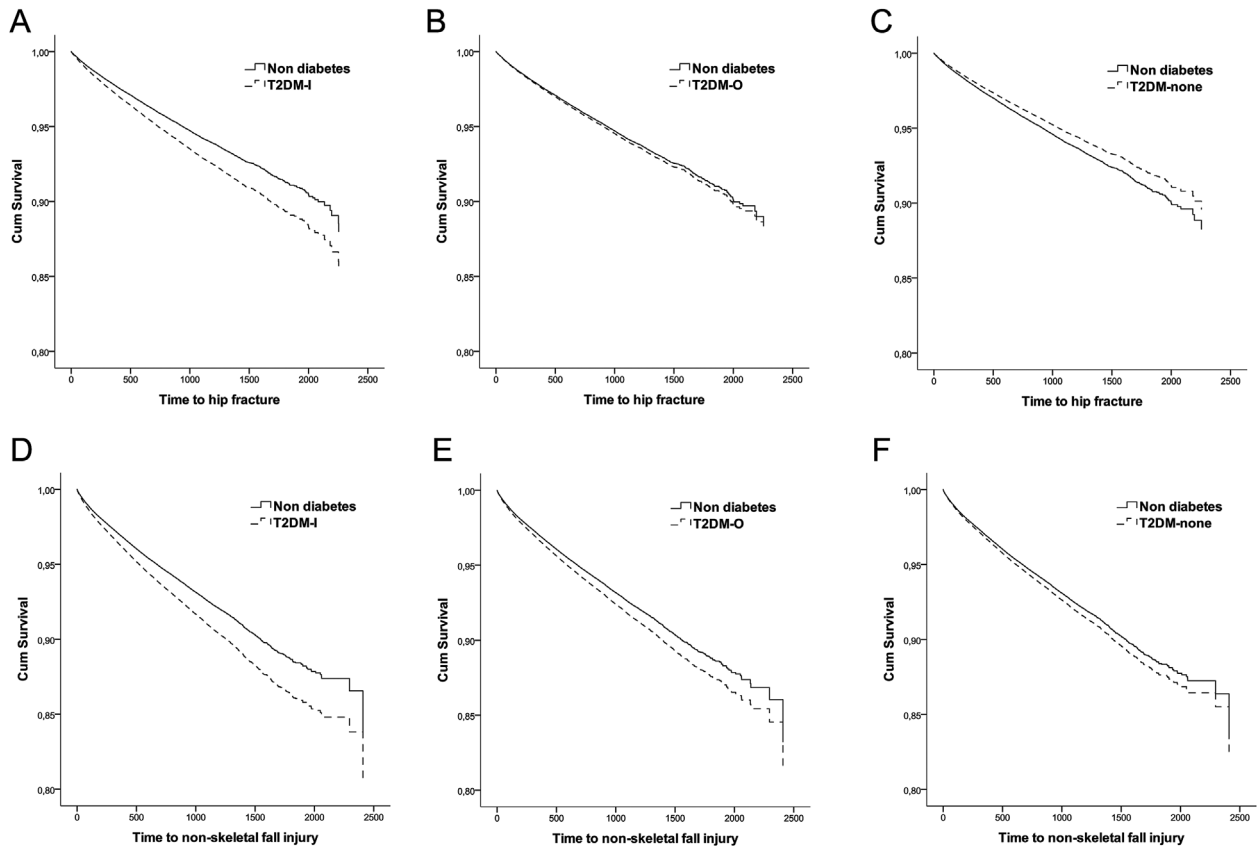

Fig. 2. Survival curves for time to hip fracture or time to non-skeletal fall injury (days). Patients divided into those with T2DM and insulin treatment (T2DM-I), T2DM and oral antidiabetics (T2DM-O), and T2DM without any antidiabetic medicines (T2DM-none) compared with patients without diabetes. (*A–C*) Adjusted for age, sex, weight, height, previous fracture, self-reported fall injury, rheumatoid arthritis, cortisone and alendronate use, and Charlson morbidity index. (*D–F*) Adjusted for age, sex, weight, height, previous fall injury, self-reported known fall injury, and Charlson comorbidity index.

risk.[25–29] Indeed, in the present study, the presence of diabetes retinopathy and other diabetes complications were more frequent in patients with insulin treatment and were near significantly associated with the risk of hip fracture. Furthermore, there are many hypotheses of bone-specific characteristics in patients with severe diabetes such as deteriorated bone matrix properties, low bone turnover, increased cortical porosity, and altered bone marrow adiposity in patients with obesity[16] that may explain some of the association between diabetes and increased risk of fracture.

A previous meta-analysis revealed no specific sex effects of diabetes on the risk of hip fracture.[14] Our results, although presenting a similar pattern among men and women compared with the whole cohort, showed on the contrary that men without insulin treatment did not have increased risk of fractures and men without any antidiabetic medications had in fact decreased risk of hip fracture compared with those without diabetes. In women, the risk of fractures was indeed increased already in those with oral antidiabetic medications, and women with antidiabetic medications had higher risk for fractures compared with men within the same diabetes group. The increased risk of fractures in women could be a result of increased frequency of osteoporosis that is common among postmenopausal elderly women, which in theory would lead to more vulnerability for fractures in the case of falling. Unfortunately, the diagnosis of osteoporosis is rarely registered in the Swedish patient register and could not be properly adjusted for in our study.

A somewhat surprising result was that the group of patients with no antidiabetic medications (T2DM-none) who suffered from many more comorbidities and a near significantly increased risk of non-skeletal fall injuries still had reduced risk of hip fracture compared with patients without diabetes. The group with T2DM-none may consist of a variety of different phenotypes of T2DM where some are patients with "mild diabetes" and some are those with severe disease but with other comorbidities preventing antidiabetic medications. However, after multivariable adjustment for comorbidities, the patients with T2DM-none did not have increased mortality compared with the non-diabetic population (data not shown) and had less frequency of diabetes retinopathy and diabetes complications compared with the other diabetes groups, which strengthens the supposition that a majority of these patients had indeed a less severe diabetes.

Moreover, the risk of incident wrist fracture was not increased in patients with diabetes, and in fact it was significantly decreased in those with oral antidiabetics compared with patients without diabetes. This may seem contradictory but is in fact in accordance with previous studies,[11,21] and in the Women's Health Initiative Observational Study, the risk of lower

Table 5. Hazard Ratios for Patients in Different Groups of Type 2 Diabetes Subdivided into Men and Women

	Men ($n = 41,580$)				Women ($n = 43,122$)			
	T2DM-none* ($n = 5038$)	T2DM-O* ($n = 15,634$)	T2DM-I* ($n = 18,025$)	T1DM* ($n = 2883$)	T2DM-none** ($n = 6006$)	T2DM-O** ($n = 16,503$)	T2DM-I** ($n = 17,953$)	T1DM** ($n = 2660$)
Any fracture								
Multivariate 1	0.91 (0.81–1.03)	0.96 (0.89–1.03)	1.16 (1.09–1.24)	1.56 (1.37–1.78)	0.97 (0.89–1.05)	1.06 (1.00–1.11)	1.24 (1.18–1.31)	1.34 (1.20–1.50)
Multivariate 2	0.90 (0.80–1.02)	0.97 (0.90–1.05)	1.15 (1.08–1.23)	1.43 (1.26–1.64)	0.97 (0.90–1.06)	1.10 (1.07–1.13)	1.24 (1.18–1.30)	1.29 (1.15–1.44)
Multivariate 3	0.90 (0.80–1.01)	0.96 (0.89–1.03)	1.13 (1.06–1.21)	1.40 (1.23–1.60)	0.98 (0.90–1.06)	1.06 (1.01–1.12)	1.23 (1.17–1.29)	1.28 (1.14–1.43)
Hip fracture								
Multivariate 1	0.81 (0.67–0.98)	0.94 (0.84–1.05)	1.16 (1.05–1.29)	1.60 (1.31–1.96)	0.94 (0.83–1.08)	1.10 (1.02–1.20)	1.31 (1.21–1.42)	1.35 (1.13–1.61)
Multivariate 2	0.79 (0.65–0.96)	0.94 (0.84–1.06)	1.15 (1.04–1.28)	1.50 (1.22–1.83)	0.93 (0.82–1.07)	1.10 (1.01–1.19)	1.30 (1.20–1.41)	1.31 (1.09–1.57)
Multivariate 3	0.78 (0.64–0.94)	0.93 (0.83–1.04)	1.12 (1.01–1.25)	1.47 (1.20–1.80)	0.94 (0.83–1.08)	1.09 (1.01–1.19)	1.30 (1.20–1.41)	1.33 (1.11–1.59)
Wrist fracture								
Multivariate 1	0.95 (0.47–1.92)	0.89 (0.57–1.39)	0.68 (0.41–1.11)	2.35 (1.25–4.44)	0.98 (0.73–1.32)	0.69 (0.54–0.86)	1.01 (0.83–1.23)	0.73 (0.42–1.26)
Multivariate 2	0.91 (0.45–1.84)	0.90 (0.57–1.41)	0.66 (0.40–1.08)	2.02 (1.06–3.82)	0.97 (0.72–1.32)	0.69 (0.55–0.87)	1.00 (0.82–1.22)	0.69 (0.40–1.19)
Multivariate 3	0.91 (0.45–1.84)	0.89 (0.57–1.40)	0.64 (0.39–1.05)	1.78 (0.91–3.47)	0.94 (0.69–1.28)	0.65 (0.52–0.83)	0.99 (0.81–1.20)	0.69 (0.40–1.20)
Upper arm fracture (collumchir)								
Multivariate 1	1.09 (0.67–1.77)	1.11 (0.82–1.49)	1.37 (1.05–1.80)	2.44 (1.54–3.87)	1.10 (0.85–1.43)	1.18 (1.00–1.39)	1.36 (1.16–1.59)	1.97 (1.45–2.69)
Multivariate 2	1.06 (0.65–1.73)	1.13 (0.84–1.52)	1.35 (1.03–1.77)	2.10 (1.32–3.34)	1.09 (0.83–1.41)	1.20 (1.02–1.41)	1.33 (1.14–1.56)	1.79 (1.31–2.44)
Multivariate 3	1.01 (0.61–1.66)	1.08 (0.80–1.47)	1.32 (1.00–1.73)	2.10 (1.32–3.33)	1.11 (0.85–1.44)	1.20 (1.02–1.42)	1.33 (1.14–1.56)	1.72 (1.25–2.37)
Major osteoporotic fracture								
Multivariate 1	0.89 (0.76–1.04)	0.95 (0.86–1.04)	1.14 (1.05–1.25)	1.70 (1.44–2.01)	1.02 (0.92–1.14)	1.05 (0.98–1.13)	1.26 (1.18–1.34)	1.31 (1.13–1.52)
Multivariate 2	0.87 (0.74–1.02)	0.96 (0.87–1.05)	1.13 (1.04–1.23)	1.56 (1.32–1.85)	1.01 (0.91–1.12)	1.05 (0.98–1.13)	1.25 (1.17–1.33)	1.25 (1.07–1.45)
Multivariate 3	0.86 (0.73–1.01)	0.94 (0.85–1.04)	1.10 (1.01–1.21)	1.52 (1.28–1.81)	1.02 (0.91–1.13)	1.04 (0.97–1.12)	1.24 (1.16–1.33)	1.25 (1.07–1.45)
Ankle fracture								
Multivariate 1	1.43 (0.23–2.58)	0.66 (0.39–1.10)	1.31 (0.92–1.88)	2.96 (1.65–5.13)	0.88 (0.56–1.39)	1.15 (0.89–1.48)	1.39 (0.98–1.98)	1.68 (1.01–2.81)
Multivariate 2	1.34 (0.74–2.42)	0.66 (0.39–1.10)	1.28 (0.89–1.84)	2.55 (1.41–4.60)	0.89 (0.56–1.41)	1.17 (0.91–1.51)	1.26 (0.99–1.59)	1.60 (0.96–1.04)
Multivariate 3	1.35 (0.75–2.43)	0.66 (0.40–1.11)	1.25 (0.86–1.79)	2.56 (1.41–4.61)	0.90 (0.57–1.42)	1.15 (0.89–1.48)	1.25 (0.98–1.58)	1.59 (0.95–2.66)
Non-skeletal fall injury								
Multivariate 1	1.11 (0.98–1.27)	1.11 (1.02–1.20)	1.26 (1.17–1.35)	1.34 (1.13–1.58)	1.14 (1.02–1.28)	1.17 (1.09–1.26)	1.26 (1.17–1.35)	1.26 (1.07–1.49)
Multivariate 4	1.05 (0.92–1.19)	1.08 (1.00–1.17)	1.17 (1.09–1.26)	1.12 (0.94–1.33)	1.09 (0.97–1.21)	1.15 (1.07–1.23)	1.27 (1.18–1.36)	1.13 (0.95–1.33)

Values are expressed as hazard ratios and 95% confidence intervals. Patients with T2DM are divided into those with no antidiabetic medicines (T2DM-none), with oral medicines (T2DM-O), and those with insulin treatment (T2DM-I) and those with T1DM. Reference groups are men without diabetes (*) and women without diabetes (**). Multivariate 1: Adjusted for age, height, and weight. Multivariate 2: Adjusted for age, sex, weight, height, previous fracture, rheumatoid arthritis, glucocorticoid and alendronate use, and Charlson comorbidity index. Multivariate 3: As multivariate 2 + self-reported known fall injury in history. Multivariate 4: Adjusted for age, sex, weight, height, previous fall injury, self-reported known fall injury, and Charlson comorbidity index.

arm fracture was the only fracture site that was not at all related to diabetes.[9] However, in another large register-based study, men and women with T2DM had indeed increased risk of wrist fracture, although the association was only borderline significant.[6] It should be emphasized that the quality of the register-based data is higher regarding hip fractures (defined both by diagnosis and surgical procedure) than for other fractures, which infers that the observed associations between diabetes and these fractures should be interpreted with caution. Furthermore, the present cohort consists of elderly patients and wrist fractures usually occur earlier in life, as reflected by the relatively low number of radius fractures in our study. Nevertheless, it may be hypothesized that patients with diabetes have more severe falls where the reflex of limiting the traumatic fall by the underarm is impaired. Indeed, a previous study showed that most typical osteoporotic upper-extremity fractures had its own specific injury mechanism.[30]

There are limitations with this study. We did not have access to measurements of HbA1c, BMD, physical activity, smoking, or alcohol use in the databases, and we had to use a surrogate marker of disease severity such as diabetes treatment to characterize the patients. There may still be some misclassification between type 1 and type 2 diabetes, although the prevalence of diabetes and the proportions of patients in each group corresponded well with the expected prevalence of diabetes in this age group. However, the subgroup defined as T1DM may contain patients with T2DM that are misclassified in the registry, especially with respect to the high mean age in each group (where we normally do not expect to find patients with T1DM), and the results for this subgroup must be interpreted carefully. On the other hand, the results still support the hypothesis that the risk of fractures increases along the road as diabetes deteriorates. Another aspect of using treatment strategy as a surrogate marker of disease severity is that prescription of insulin may include a number of other factors such as poor compliance with diet or exercise and perhaps also poor compliance with measurements of blood glucose, intake of insulin in the right doses and times, that could not be adjusted for in the analyses. Nevertheless, a strength of this study was that we used two different registers to classify the patients with diabetes because all patients with diabetes medications are found in the drug dispensatory register (all prescriptions are registered electronically in Sweden) and most patients were indeed registered at hospitals where given diagnoses are transferred to the national patient register. Vertebral fractures are often bypassed and not diagnosed and entered in registers and could not be reliably studied in this cohort and were therefore excluded. On the other hand, we estimate that largely all hip fractures were detected because this diagnosis is established at emergency units and hospital wards, all connected to the national registers, a method that has been validated previously.[31]

In conclusion, this is the first large cohort study of elderly patients with diabetes, classified according to diabetes treatment, with available information regarding the risks of fractures and non-skeletal fall injuries. Patients with insulin-treated T2DM should indeed be considered as a high-risk group for future fractures, but all patients with diabetes and any kind of antidiabetic pharmacological treatment have increased risk of other non-skeletal fall injuries and may benefit from intervention strategies primarily aiming at reducing the risk of falling.

The final explanation for the result is probably multifactorial with some potential bone-specific alterations in patients with severe diabetes, but most of all a complex result of increased frailty and frequent falls owing to diabetic complications such as visual impairment, neuropathy, renal failure, decreased balance and muscle strength, hypoglycemic episodes, and severity of other comorbidities.

Disclosures

All authors state that they have no conflicts of interest.

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