Association Between Glycemic Control and Risk of Fracture in Diabetic Patients: A Nested Case-Control Study

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Context: Diabetes mellitus (DM) has been associated with an increased risk of fractures. However, the effect of glycemic control on the risk of fracture is not well understood.

Objective: To evaluate the association between glycemic control and the risk of low-trauma fractures in patients with type 1 DM (T1DM) and type 2 DM (T2DM).

Design: Nested case-control analysis.

Setting: UK-based Clinical Practice Research Datalink.

Patients or Other Participants: The study population was patients whose T1DM or T2DM had been newly diagnosed between 1995 and 2015. The cases were patients with a low-trauma fracture after DM onset. We matched four controls to each case by age, sex, general practice, fracture date, and DM type and duration.

Statistical Analysis: Conditional logistic regression analyses were performed, adjusted for covariates, including body mass index, smoking, DM complications and medications.

Results: The study population included 3329 patients with T1DM and 44,275 patients with T2DM. The median duration between DM onset and fracture date was 4.5 years for both T1DM and T2DM. The risk of fracture was increased in the patients with T1DM with a mean hemoglobin A1c $>$8.0% (adjusted OR, 1.39; 95% CI, 1.06 to 1.83) compared with those patients with T1DM and a mean hemoglobin A1c $\leq$7.0%. No such effect was found in the patients with T2DM. Independently of glycemic control, the risk of fracture was elevated in patients with T2DM and the current use of rosiglitazone and pioglitazone.

Conclusions: The effect of glycemic control on the risk of low-trauma fracture differs between patients with T1DM and T2DM. Poor glycemic control increased the risk of fractures in patients with T1DM but not in those with T2DM. (***J Clin Endocrinol Metab*** **104: 1645–1654, 2019)**

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Abbreviations: BMI, body mass index; CPRD, Clinical Practice Research Datalink; DM, diabetes mellitus; GP, general practitioner; HbA1c, hemoglobin A1c; HR, hazard ratio; MHRA, Medicines and Health Care Regulatory Agency; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Diabetes mellitus (DM) has been associated with an increased risk of fragility fractures. In particular, the risk of hip fractures is increased approximately sixfold in subjects with type 1 DM (T1DM) and two- to threefold in patients with type 2 DM (T2DM) (1).

The pathophysiological mechanisms that contribute to skeletal fragility differ across the two DM types (2). The differences in patient age at disease onset, insulin availability (insulin deficiency *vs* insulin resistance), and the influence of antidiabetic drugs lead to altered skeletal fragility. In patients with a diagnosis of T1DM during adolescence and early adulthood, the deficiencies in insulin and IGF-1 seem to impair osteoblast function, leading to lower bone mass, smaller bone size, and alterations in bone microstructure (2–5).

In contrast, patients with T2DM, who usually experience obesity-related insulin resistance and hyperinsulinemia, will present with normal to increased bone mass and preserved or even increased trabecular bone volume but with increased cortical porosity. This pattern has been found especially in patients with fractures and microvascular complications (3, 6).

In patients with T1DM and T2DM with advanced disease, glucotoxicity, chronic inflammation, and microvascular changes have been thought to be critical factors in accelerating bone aging and the progression of diabetic bone disease (7, 8). In addition, nonskeletal factors (9, 10), such as chronic diabetic complications, comorbidities, and drug effects (11, 12), could increase the risk of falls (6, 13) and, thus, the overall risk of fracture.

It remains unclear to what extent glycemic control has an impact on the risk of fracture. Some studies have reported an association between poor glycemic control and an increased risk of fractures (14–17) or falls (18), but others have not (1, 19–21). In contrast, good glycemic control was also associated with an increased risk of fracture (13, 19) or falls (22) in some studies. Although several studies have examined the effect of glycemic control on the risk of fractures by analyzing hemoglobin A1c (HbA1c) levels (a measure of the average glycemia during an ~12-week period), the results have remained inconsistent owing to methodological heterogeneities. Only a few of these studies included a substantial number of patients (14–16) and analyzed the effect of glycemic control, not only using a single HbA1c measurement (14, 22, 23), but using the mean HbA1c levels during a longer follow-up period (14). The latter might more accurately reflect the degree of glycemic control. Additionally, only Forsén *et al.* (1) analyzed the association between glycemic control and the risk of fracture separately for patients with T1DM and those with T2DM.

Therefore, we conducted a study to evaluate the association between the degree of glycemic control and the risk of nonvertebral low-trauma fractures in patients with newly diagnosed T1DM and T2DM.

Methods

Study design and data source

We conducted a nested case-control analysis within a cohort of patients with incident T1DM or T2DM using data from the UK-based primary care database, the Clinical Practice Research Datalink (CPRD). The study period encompassed 21 years between 1995 and 2015.

The CPRD is a governmental, nonprofit research service and a joint venture from the Medicines and Health Care Regulatory Agency (MHRA) and the National Institute for Health Research (24). This large database of anonymized medical records was established in 1987 and covers the medical records for >11.3 million general practice patients from 674 practices in the United Kingdom (24). The patients are representative of the UK general population in terms of age, sex, and ethnicity (25). The general practitioners (GPs) are trained to record medical information, including medical diagnoses, referrals to specialists and secondary care settings, prescriptions, diagnostic testing, lifestyle information, and demographic data using standard software and standard coding systems (24). The MHRA checks the raw data before release and performs quality control checks. The CPRD is widely used internationally for studies of pharmacoepidemiology and disease epidemiology, including bone fractures (26, 27). The CPRD has been proved to be of high quality (24, 28, 29).

The Independent Scientific Advisory Committee for MHRA database research approved the study protocol (protocol no. 17_061R), and the protocol was available to the journal reviewers.

Study population

We selected patients with an incident diagnosis of T1DM or T2DM from 1 January 1995 to 31 December 2015. The patients with T2DM were required to have a minimum of 3 years of recorded history in the database before the first recorded DM code to ensure that we had only included incident T2DM cases. For the patients with T1DM, we only required 1 year of recorded history, because these patients will usually be much younger at disease onset and might not have a long medical history available.

We identified patients with DM using specific codes for DM and the new use of antidiabetic drugs (oral antidiabetic agents or insulin). We defined the study entry date as the date of the first recorded diabetes code.

We classified patients without specific DM codes indicating the DM type according to the age of DM onset and the prescribed antidiabetic drugs:

- Patients with DM onset before the age of 30 years who had received insulin were classified as having T1DM
- Patients who had received oral antidiabetic drugs with or without insulin were classified as having T2DM
- Patients whose first DM record was after the age of 30 years and who had received only insulin remained unclassified

We did not consider the laboratory test results for the classification of DM type but only the GP-recorded disease

codes and the age and medication of the patients. We excluded all patients with an unclassified DM type from the present study. We further excluded patients with a diagnosis of cancer (except for nonmelanoma skin cancer), alcoholism, or HIV at any point in the patient record, because these patients will usually have many comorbidities and receive many drugs, which could have led to substantial bias and confounding.

Case definition

The cases were patients with a recording of a low-trauma fracture (*e.g.*, nonvertebral fractures of the proximal and distal upper and lower extremities, ribs and thorax, hip and foot) during the study period (*i.e.*, after their incident DM diagnosis). We excluded patients with fractures of the shoulder blade or cranium, because these fractures are not considered low-trauma fractures. We identified fracture cases by the specific codes and assigned the date of the fracture diagnosis as the "index date." We used risk set sampling to identify controls from among the DM patient study population who had not experienced a fracture between DM onset and the index date of their matched case.

We matched the cases to controls 1:4 using age (±3 years), sex, general practice, index date (control present in the database at the case's index date), DM type, and DM duration (±365 days). We assessed DM duration by counting the days between the first recorded DM code and the index date.

Exposure definition

The exposure of interest in the present study was glycemic control after DM onset as defined by the HbA1c levels and expressed as a categorical variable (Table 1). The categories were wider for the patients with T1DM because the patient numbers were smaller and did not accommodate as many levels.

We analyzed the available HbA1c measurements throughout the study period at several points: the initial HbA1c level, mean HbA1c level for the 3 years before the index date, and last HbA1c level before the index date. Only the data for the mean HbA1c level for the 3-year period have been presented because the results were similar for all HbA1c measurements. Missing values are presented in a separate category.

Table 1. Categories for HbA1c Levels in Patients With T1DM and T2DM

Definition	DCCT HbA1c (%)	IFCC HbA1c (mmol/mol)
T1DM		
Good control[a]	≤7.0	≤53
Medium control[a]	>7.0–8.0	>53–64
Poor control[a]	>8.0	>64
Unknown[a]	NA	NA
T2DM		
Very good control	≤6.5	≤48
Good control	>6.5–7.0	>48–53
Medium control	>7.0–7.5	>53–59
Poor control	>7.5–8.0	>59–64
Very poor control	>8.0–9.0	>64–75
Unsatisfactory control	>9.0	>75
Unknown	NA	NA

Abbreviations: DCCT, Diabetes Control and Complications Trial; IFCC, International Federation of Clinical Chemistry; NA, not applicable (owing to missing data).

[a]Categories for the patients with T1DM were wider owing to smaller patient numbers.

Statistical analysis

We used conditional logistic regression to assess the association between HbA1c values and the risk of low-trauma fractures, expressed as ORs and 95% CIs. We assessed a variety of comorbidities and comedications (recorded at any time in the patient records before the index date) for confounding, including those associated with the risk of fracture. For antidiabetic drugs, we assessed the risk of fractures in current users, defined as patients with a prescription for the respective drug recorded ≤60 days before the index date. Additionally, we assessed the association between the patients' number of GP visits within 1 year before the index date and the risk of fracture.

We adjusted the analyses of the patients with T1DM for body mass index (BMI), as a categorical variable (Table 2), smoking (current, past, and never smokers and unknown), previous fractures, chronic renal failure, previous falls, decreased vision (all yes *vs* no), and the use of bisphosphonates, calcium supplements, and metformin. We adjusted the analyses of the patients with T2DM (Table 3) for the same covariates, plus the use of insulin, rosiglitazone, and pioglitazone, but not for chronic renal failure or decreased vision.

No analyzed covariates changed the model by ≥10%. However, we included several covariates in the model according to the established risk factors for fractures and statistically significant univariate ORs. We conducted all analyses using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

We identified 9531 patients with a low-trauma fracture and 38,073 with no fractures (Fig. 1). The types and numbers of nonvertebral low-trauma fractures have been summarized in Table 4. The patient characteristics, selected comorbidities, and drug exposure of the study population are listed in Tables 2 and 3. The risk of fractures associated with the different mean HbA1c values (mean for previous 3 years) is presented in Table 5.

The patients with T2DM had a greater number of recorded HbA1c measurements and better glycemic control compared with the patients with T1DM. In addition, 11.6% of the T1DM cases and 11.9% of the T1DM controls had no reported HbA1c measurements during the 3 years before the index date. This was only the case for 5.6% of the T2DM cases and 4.9% of the T2DM controls. The mean 3-year HbA1c level was 8.7% for the patients with T1DM and 7.3% for all patients with T2DM. However, the patients with T2DM with a prescription for oral antidiabetic drugs or insulin had greater mean HbA1c levels than the patients with medically untreated T2DM. The results, stratified by sex, age, DM duration, and type of DM, were similar to the results from the unstratified analyses and, therefore, were not included.

Table 2. Patient Characteristics and Covariates in Fracture Cases and Controls: T1DM

Characteristic	T1DM Cases, n (%)	T1DM Controls, n (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Age at fracture, y				
<20	254 (37.8)	1021 (38.4)	NA	NA
20–29	91 (13.5)	353 (13.3)	NA	NA
30–39	56 (8.3)	231 (8.7)	NA	NA
40–49	82 (12.2)	329 (12.4)	NA	NA
≥50	189 (28.1)	723 (27.2)	NA	NA
Sex				
Male	363 (54.0)	1438 (54.1)	NA	NA
Female	309 (46.0)	1219 (45.9)	NA	NA
BMI, kg/m^2				
<18.5	19 (2.8)	40 (1.5)	1.78 (1.10–2.87)	1.66 (1.02–2.69)
18.5 to <25.0	206 (30.7)	743 (28.0)	1 (reference)	1 (reference)
25.0 to <30.0	146 (21.7)	603 (22.7)	0.84 (0.67–1.05)	0.86 (0.68–1.08)
30.0 to <35.0	53 (7.9)	306 (11.5)	0.58 (0.42–0.80)	0.62 (0.44–0.87)
35.0 to <40.0	22 (3.3)	74 (2.8)	1.01 (0.65–1.56)	1.03 (0.66–1.62)
≥40.0	11 (1.6)	49 (1.84	0.75 (0.40–1.41)	0.81 (0.41–1.60)
Unknown	215 (32.0)	842 (31.7)	1.10 (0.76–1.59)	1.15 (0.79–1.67)
Smoking status				
Nonsmoker	291 (43.3)	1153 (43.4)	1 (reference)	1 (reference)
Current smoker	106 (15.8)	382 (14.4)	1.12 (0.89–1.41)	1.05 (0.82–1.33)
Ex-smoker	123 (18.3)	497 (18.7)	0.98 (0.78–1.24)	0.98 (0.77–1.24)
Unknown	152 (22.6)	625 (23.5)	0.91 (0.69–1.21)	0.91 (0.68–1.23)
Comorbidities				
Previous fracture	121 (18.0)	307 (11.6)	1.76 (1.43–2.16)	1.67 (1.35–2.07)
Ischemic heart disease	49 (7.3)	136 (5.1)	1.52 (1.09–2.12)	1.50 (1.05–2.14)
Chronic renal failure	25 (3.7)	42 (1.6)	2.45 (1.61–3.74)	2.24 (1.47–3.42)
Diabetic retinopathy	225 (33.5)	756 (28.5)	1.36 (1.12–1.65)	1.29 (1.06–1.57)
Previous falls	90 (13.4)	197 (7.4)	1.97 (1.55–2.51)	1.73 (1.35–2.22)
Decreased vision	37 (6.8)	104 (3.9)	1.44 (1.02–2.04)	1.24 (0.86–1.78)
Comedication				
Insulin	647 (96.3)	2541 (95.6)	1.24 (0.79–1.95)	1.05 (0.66–1.69)
Pioglitazone	7 (1.0)	13 (0.5)	2.13 (0.83–5.44)	2.83 (1.05–7.61)
Rosiglitazone	4 (0.6)	30 (1.1)	0.53 (0.19–1.51)	0.60 (0.20–1.77)
Metformin	99 (14.7)	436 (16.4)	0.82 (0.63–1.07)	0.87 (0.67–1.12)
Bisphosphonates	25 (3.7)	41 (1.5)	2.65 (1.54–4.56)	1.84 (1.09–3.09)
Calcium and supplements	56 (8.3)	121 (4.6)	2.04 (1.43–2.92)	1.39 (0.98–1.98)

Abbreviation: NA, not applicable.

[a] Adjustment for T1DM: BMI, smoking, previous fractures, chronic renal failure, previous falls, decreased vision (all yes *vs* no), and use of bisphosphonates, calcium and supplements, and metformin.

T1DM

Of the 32,273 individuals with incident T1DM, we identified 672 patients with a recorded fracture after the DM diagnosis and 2657 matched DM controls. Overall, the median age at the index date of the patients with T1DM (cases and controls) was 28 years (quartile 1, 14; quartile 3, 52 years), and the mean BMI (last available value before the index date) was 26.5 ± 5.5 kg/m^2. The median interval between the DM diagnosis and fracture was 4.5 years (quartile 1, 2.0; quartile 3, 8.0 years), and 46% of the patients were female. During the study period, the patients with T1DM had a mean of nine recorded HbA1c measurements.

Although the risk of fracture was not increased in the patients with T1DM with moderate glycemic control (3-year mean HbA1c level, >7% to 8%; adjusted OR, 0.99; 95% CI, 0.72 to 1.35), compared with the patients with T1DM and good glycemic control, the risk of fracture for the patients with T1DM and poor glycemic control was slightly increased (3-year mean HbA1c level, >8.0%; adjusted OR, 1.39; 95% CI, 1.06 to 1.83; Table 5).

In patients with recorded comorbidities associated with the micro- and macrovascular complications of DM, such as diabetic retinopathy (adjusted OR, 1.29; 95% CI, 1.06 to 1.57) and chronic renal failure (adjusted OR, 2.24; 95% CI, 1.47 to 3.42), the risk of fracture was also increased compared with patients without the respective comorbidity (Table 2). The number of GP visits was not associated with the risk of fracture.

T2DM

Of the 354,438 individuals with T2DM, we identified 8859 patients with a fracture and 35,416 matched controls. The median age of the patients with T2DM (cases and controls) was 71.7 years (quartile 1, 63; quartile 3, 82), and mean BMI (last available

Table 3. Patient Characteristics and Covariates in Fracture Cases and Controls: T2DM

Characteristic	T2DM Cases, n (%)	T2DM Controls, n (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Age at fracture, y				
<60	1635 (18.7)	6510 (18.4)	NA	NA
60–69	1791 (20.2)	7245 (20.5)	NA	NA
70–79	2576 (29.1)	10,307 (29.1)	NA	NA
80–89	2342 (26.4)	9349 (26.4)	NA	NA
≥90	515 (5.8)	2005 (5.7)	NA	NA
Sex				
Male	2575 (29.1)	10,288 (29.1)	NA	NA
Female	6284 (70.9)	25,128 (71.0)	NA	NA
BMI, kg/m^2				
<18.5	149 (1.7)	346 (1.0)	1.54 (1.30–1.83)	1.41 (1.18–1.68)
18.5 to <25.0	1843 (20.8)	6369 (18.0)	1 (reference)	1 (reference)
25.0 to <30.0	2889 (32.6)	11,688 (33.0)	0.84 (0.79–0.89)	0.85 (0.80–0.90)
30.0 to <35.0	2127 (24.0)	8994 (25.4)	0.79 (0.74–0.84)	0.79 (0.74–0.85)
35.0 to <40.0	1004 (11.3)	4405 (12.4)	0.75 (0.70–0.82)	0.75 (0.69–0.82)
≥40.0	620 (7.0)	2743 (7.8)	0.74 (0.67–0.81)	0.72 (0.65–0.80)
Unknown	228 (2.6)	872 (2.5)	0.90 (0.78–1.05)	0.90 (0.77–1.06)
Smoking status				
Nonsmoker	3678 (41.5)	16,042 (45.3)	1 (reference)	1 (reference)
Current smoker	1137 (12.8)	3739 (10.6)	1.34 (1.26–1.44)	1.30 (1.21–1.40)
Ex-smoker	3937 (44.4)	15,207 (42.9)	1.14 (1.09–1.20)	1.15 (1.10–1.20)
Unknown	107 (1.2)	428 (1.2)	1.07 (0.88–1.31)	1.07 (0.86–1.33)
Comorbidities				
Previous fracture	1910 (21.6)	4879 (13.8)	1.75 (1.66–1.84)	1.63 (1.55–1.72)
Ischemic heart disease	2002 (22.6)	7762 (27.9)	1.04 (0.99–1.10)	1.00 (0.95–1.05)
Chronic renal failure	565 (6.4)	1994 (5.6)	1.16 (1.06–1.27)	1.15 (1.05–1.26)
Diabetic retinopathy	2278 (25.7)	8601 (24.3)	1.11 (1.05–1.17)	1.12 (1.06–1.18)
Previous falls	2621 (29.6)	6849 (19.3)	1.86 (1.77–1.96)	1.75 (1.67–1.84)
Decreased vision	885 (10.0)	3008 (8.5)	1.20 (1.12–1.29)	1.10 (1.02–1.18)
Comedication				
Insulin	1002 (11.3)	3531 (10.0)	1.17 (1.08–1.26)	1.10 (1.02–1.18)
Pioglitazone	694 (7.8)	2267 (6.4)	1.28 (1.16–1.41)	1.36 (1.25–1.49)
Rosiglitazone	501 (5.7)	1653 (4.7)	1.24 (1.12–1.39)	1.32 (1.20–1.46)
Metformin	5366 (60.6)	21,758 (61.4)	1.00 (0.95–1.05)	0.96 (0.91–1.01)
Bisphosphonates	1076 (12.2)	2834 (8.0)	1.64 (1.51–1.77)	1.30 (1.20–1.41)
Calcium and supplements	1579 (17.8)	4670 (13.2)	1.48 (1.39–1.58)	1.15 (1.07–1.23)
Hormone replacement therapy	1739 (19.6)	6550 (18.5)	1.03 (1.03–1.18)	1.03 (0.96–1.09)

Abbreviation: NA, not applicable.

[a]Adjustment for T2DM: BMI, smoking, previous fractures, previous falls, and use of bisphosphonates, calcium and supplements, metformin, insulin, rosiglitazone, and pioglitazone.

measurement before the index date) was 30.2 ± 6.5 kg/m^2. The median interval between the DM diagnosis and the first fracture was 4.5 years (quartile 1, 2.0; quartile 3, 7.9), and 71% of the patients were female. During the study period, the patients with T2DM had a mean of 11 recorded HbA1c measurements before the index date.

Glycemic control was not associated with the risk of fracture in the patients with T2DM with an HbA1c level >6.5% to 7.0% compared with those with T2DM and other HbA1c levels (Table 5). The micro- and macrovascular complications of DM were not clearly associated with the risk of fracture in this patient group.

In analyses stratified for DM treatment, we observed an increased risk of fracture among patients with T2DM and current (last prescription <60 days before the index date) use of pioglitazone (OR, 1.36; 95% CI, 1.25 to 1.49) and rosiglitazone (OR, 1.32; 95% CI, 1.20 to 1.46) compared with nonusers. This effect was independent of glycemic control (Table 3).

Increasing numbers of GP visits were associated with an increased risk of fracture (adjusted ORs for 21 to 30 GP visits, 1.22, 95% CI, 1.14 to 1.31; adjusted ORs, for >30 visits, 1.58; 95% CI, 1.48 to 1.69) compared with patients with ≤20 GP visits in the previous year before the index date (data not shown).

Discussion

Our results suggest that the effect of glycemic control on the risk of nonvertebral low-trauma fractures differs between patients with T1DM and those with T2DM. Although poor glycemic control (HbA1c level >8%) was associated with a slightly increased risk of fracture (OR, 1.39; 95% CI, 1.06 to 1.83) in patients with T1DM

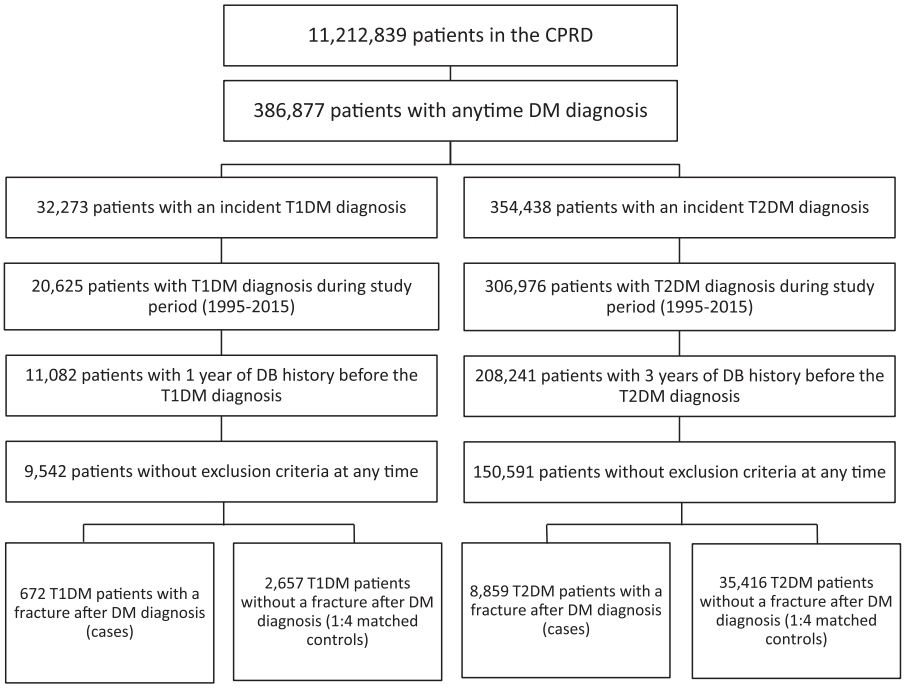

Figure 1. Flowchart showing selection of study population. DB, database.

compared with those with T1DM and good glycemic control (HbA1c level ≤7.0%), we did not observe such an association in patients with T2DM.

We observed an association between comorbidities related to micro- and macrovascular complications, such as diabetic retinopathy and ischemic heart disease, and the risk of fracture in patients with T1DM. In patients with T2DM, the risk of fracture was elevated with the current use of pioglitazone and rosiglitazone, independently of glycemic control, but not in patients with vascular complications. In patients with T1DM and patients with T2DM, the first fracture after DM onset occurred relatively early in the course of the disease (after a mean of 4.5 years).

To date, only a few small studies (1, 30) have assessed the effect of glycemic control on the risk of fracture in those with T1DM. Although the Trondelag Health Survey by Forsén *et al.* (1) reported a trend between glycemic control and the risk of fracture, the association was not statistically significant. This was probably primarily due to the small number of patients with T1DM [only 2.9% (n = 54) of all patients with DM included]. Heap *et al.* (23) demonstrated that glycemic control was associated with whole body bone mineral content in adolescents with T1DM; however, these investigators did not assess the risk of fracture as an outcome in their study. Neumann *et al.* (30) showed that poor glycemic control was associated with an increased risk of fracture in those with T1DM (OR for reported clinical fracture associated with 1-SD increase in median HbA1c, 1.92; 95% CI, 1.09 to 2.75). However, the study was limited by its cross-sectional design and because it had only included 122 patients with T1DM and HbA1c measurements. The study by Conway *et al.* (14), which found an increased risk of fracture in association with both poor (HbA1c, 8% to 9% and >9%) and good (<6.5%) glycemic control compared with HbA1c levels of 7% to 7.9%, had a minimum of two HbA1c measurements per patient and a longer follow-up duration. However, they had not distinguished between T1DM and T2DM (14).

In contrast, we found the risk of incident fracture to be slightly increased for patients with T1DM (adjusted OR, 1.39; 95% CI, 1.06 to 1.83) with poor glycemic control (3-year mean HbA1c >8.0%) compared with patients with T1DM and HbA1c levels ≤7.0%, in a large cohort of 3329 patients with T1DM and a mean of nine HbA1c measurements per patient. However, no such association was found for patients with T2DM.

Table 4. Frequencies of Nonvertebral Low-Trauma Fractures Stratified by DM Type

Low-Trauma Fracture	T1DM, n (%)	T2DM, n (%)
Proximal upper extremity (humerus, elbow)	142 (23.5)	1908 (20.6)
Distal upper extremity (ulna, radius)	87 (14.2)	1084 (11.9)
Ribs	23 (5.1)	428 (4.6)
Hip	6 (0.8)	458 (5.9)
Femur, patella	52 (9.2)	1797 (22.6)
Distal lower extremity (tibia, fibula)	93 (18.6)	1229 (13.3)
Foot	54 (10.9)	550 (5.9)
Unspecified	109 (18.6)	1405 (15.6)

Table 5. Risk of Fractures Associated With HbA1c Levels (3-Year Mean Before Index Date)

Mean HbA1c	Cases, n (%)	Controls, n (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Patients with T1DM				
≤7%	61 (9.1)	284 (10.7)	1 (reference)	1 (reference)
>7%–8%	121 (18.0)	594 (22.4)	0.95 (0.70–1.30)	0.99 (0.72–1.35)
>8%	407 (60.6)	1421 (53.5)	1.37 (1.04–1.79)	1.39 (1.06–1.83)
No record	83 (12.4)	358 (13.5)	1.07 (0.74–1.52)	1.09 (0.76–1.56)
Patients with T2DM				
≤6.5%	2634 (29.7)	10208 (28.8)	1.05 (0.98–1.11)	1.02 (0.96–1.09)
>6.5%–7%	1615 (18.2)	6521 (18.4)	1 (reference)	1 (reference)
>7%–7.5%	1386 (15.7)	6228 (17.6)	0.90 (0.84–0.97)	0.89 (0.83–0.96)
>7.5%–8%	826 (9.3)	3385 (9.6)	0.99 (0.91–1.07)	0.96 (0.88–1.05)
>8%–9%	1009 (11.4)	3964 (11.2)	1.03 (0.95–1.12)	0.99 (0.91–1.08)
>9%	879 (9.9)	3229 (9.1)	1.11 (1.02–1.21)	1.03 (0.94–1.13)
No record	510 (5.8)	1881 (5.3)	1.13 (1.01–1.26)	1.12 (1.00–1.26)

[a] Adjustment for T1DM: BMI, smoking, previous fractures, chronic renal failure, previous falls, decreased vision (all yes vs no), and use of bisphosphonates, calcium and supplements, and metformin. Adjustment for T2DM: BMI, smoking, previous fractures, previous falls, and use of bisphosphonates, calcium and supplements, metformin, insulin, rosiglitazone, and pioglitazone.

Our findings can be explained by the different pathophysiological mechanisms contributing to skeletal fragility in each DM type. During puberty, ~50% to 60% of peak bone mass will be accrued (31). Insulin as an anabolic hormone is thought to have a stimulatory effect on osteoblast function. Therefore, insulin deficiency in T1DM might cause a reduction in osteoblast cell numbers (32), resulting in an impaired peak bone mass. Furthermore, specifically in the first few years after disease onset, rapid bone loss occurs in T1DM, stabilizing thereafter to a steady state in conjunction with disease control. This could be due to a decline in insulin secretion or could result from inadequate control of the diabetes itself (5, 7). Hyperglycemia also seems to play an important role in the pathophysiology of poor bone quality. It appears that hyperglycemia impairs bone mineral acquisition (33) and is associated with decreased bone mineral content (23), impaired vitamin D and calcium metabolism (34), reduced osteoblast differentiation (35), and an increased rate of osteoblast apoptosis (36).

Although some studies did report an association between glycemic control and the risk of fracture in patients with T2DM, we, and several others (1, 19, 37), have failed to confirm this association. Poor glycemic control (HbA1c ≥8%) was associated with increased hospitalization rates because of fractures compared with HbA1c levels <8% in the Atherosclerosis Risk in Communities Study (16). In the Rotterdam Study, patients with HbA1c levels >7.5% had an increased risk of fracture relative to those with a lower HbA1c level [hazard ratio (HR), 1.62; 95% CI, 1.09 to 2.40) (17). Finally, Li *et al.* (15) observed an increased risk of fracture associated with HbA1c levels from 9% to 10% and ≥10% compared with HbA1c levels of 6% to 7% (HR, 1.24; 95% CI, 1.02 to 1.49; and HR, 1.32; 95% CI, 1.09 to 1.58, respectively), in a large geriatric population with T2DM.

Of all the patients with T2DM in our study population, 9081 (21%) had poorly controlled HbA1c levels (>8%). However, the largest proportion (n = 20,978; 47%) presented with good HbA1c control (<7%). In the study by Li *et al.* (15), 43% of the patients with T2DM had HbA1c levels >8%. The study by Schneider *et al.* (16) included only 1195 patients with T2DM; however, 51.6% of them had HbA1c levels >8%. In contrast to these studies (15–17), which were small and had included only one or two HbA1c measurements per person, we were able to analyze the effect of long-term glycemic control using a mean of 11 HbA1c measurements per person in our T2DM population. Additionally, we had access to the medical information for a large cohort of 44,275 patients with T2DM and additional information to adjust for risk factors such as BMI, smoking, comedications, and diabetes-related complications.

One possible explanation for the null effect of glycemic control in patients with T2DM could be the beneficial effect of insulin resistance in early disease (2). Patients with T2DM have superior trabecular indexes owing to obesity-related insulin resistance and hyperinsulinism in the initial years of DM compared with healthy controls (4). Circulating insulin is considered to stimulate osteoblastogenesis and to enhance bone formation (38). Thus, patients with T2DM usually present with a greater bone mass (6, 39) compared with healthy controls.

Independently of glycemic control, several previous epidemiological studies have demonstrated an increased risk of fracture in patients with T2DM (40, 41). Although we did not evaluate the risk of fracture in patients with T2DM overall compared with patients without DM, our findings support the notion that the risk of fracture in patients with T2DM might be related to risk factors that are independent of glycemic control. T2DM is a part of a chronic metabolic disorder and is associated with a range of cardiovascular comorbidities (18). Microangiopathy is thought to be a critical factor in the progression of

diabetic bone disease, inducing accelerated bone loss (7, 8) and increasing the risk of falls and fractures (42). Lee *et al.* (42) recently showed that a substantial portion of this risk can be explained by DM-related comorbidities.

We identified many patients with T1DM and T2DM with DM-related complications despite the relatively short disease duration (the median disease duration before fracture was only 4.5 years). The potential effect of the disease duration itself on the risk of fracture was not the focus of our study. We adjusted for DM duration by matching to separate the effect of glycemic control from a potential effect of disease duration.

The current use of rosiglitazone and pioglitazone was associated with an increased risk of fracture in our study independent of glycemic control. Preclinical (43) and clinical (44) studies have indicated that thiazolidinediones adversely affect bone metabolism, resulting in reduced osteoblastic bone formation and accelerated bone loss and, thus, their use might increase fracture risk. Furthermore, their current use was associated with an approximately two- to threefold increased risk of hip and nonvertebral osteoporotic fractures (45).

The present findings should be interpreted within the context of the study strengths and limitations. The strengths of our study were (i) the large observational nested case-control design within a cohort of patients with newly diagnosed DM; (ii) that our data were from a large and validated primary care database and that the data had been recorded prospectively (thus, avoiding recall bias); and (iii) that we analyzed the effect of glycemic control on the risk of fracture using a mean of 9 and 11 HbA1c measurements for T1DM and T2DM, respectively. Furthermore, we were able to assess the risk of fracture separately for patients with T1DM and T2DM.

However, several limitations should be considered. Our study population included a high proportion of patients with T2DM with good glycemic control who might have been healthier than the T2DM populations analyzed in other studies. Nevertheless, our T2DM population included >30,000 patients with medically treated T2DM, including many with poor glycemic control. Therefore, we expect our results to be applicable to those of other patients with T2DM and poor glycemic control. Furthermore, fractures are associated with a wide range of comorbidities and the use of many drugs. Although we adjusted for a variety of diseases and drugs, we could not rule out that some residual confounding could have been present in our analyses.

Some misclassification of patients as having T1DM and T2DM could have occurred for the patients with a nonspecific DM code. Because the diagnoses of DM (positive predictive value >98%) and fractures (positive predictive value ~90% for hip and vertebral fractures) were well recorded and had been validated in the CPRD, minimal misclassification is likely (46). However, it is possible that we missed some fracture cases. These possible misclassification would likely have been nondifferential and would not have materially changed the results. Also, the cause for the fracture was mostly unknown. We, therefore, could not know whether some fractures could have been caused by diabetic emergencies, such as hypo- or hyperglycemia. These episodes have been, presumably, rather poorly reported in the CPRD. Thus, we did not assess the effect of diabetic emergencies on the risk of fracture. However, this association was not the focus of the study, because the HbA1c levels and fractures were recorded and analyzed independently of the reason for the fracture.

Additionally, the time of disease onset was uncertain, because T2DM can remain undiagnosed for many years, possibly leading to the inclusion of some prevalent (instead of incident) T2DM cases. This was previously shown in the UK Prospective Diabetes study, in which a prevalence of DM tissue damage was shown by the time of the DM diagnosis as a hint of a preexisting DM (47). Therefore, we might have underestimated the time until fracture (after DM onset) in our T2DM study population, which could have potentially affected our matching on DM duration. However, this misclassification is unlikely to have been differential, and we would not expect a major influence on our findings.

In conclusion, the effect of glycemic control on the risk of nonvertebral low-trauma fractures differed between patients with T1DM and T2DM with short-term disease. Although poor glycemic control elevated the risk of fracture in patients with T1DM, we observed no such association in patients with T2DM. This could have resulted from a protective effect of insulin resistance in early disease.

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