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Research Article

Elevated fracture risk in a Danish cohort with type 2 diabetes mellitus and microvascular diseases

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Abstract

Introduction: Microvascular diseases (MVD) in type 2 diabetes mellitus (T2D) are associated with alterations in the bone microarchitecture, but their association with fracture risk is unclear. We investigated whether MVD (retinopathy, nephropathy, and neuropathy) are associated with higher fracture risk in persons with T2D.
Materials and methods: We identified 10 491 persons with T2D, enrolled in the Danish Centre for Strategic Research in Type 2 Diabetes cohort between 2010 and 2022. The primary outcomes were any hospital-diagnosed fracture (except facial and cranial), and major osteoporotic fractures (MOF), defined as clinical vertebral, hip, humerus, and forearm fractures, in persons with hospital-diagnosed MVD vs without MVD. We used Cox proportional hazard models to calculate crude and adjusted hazard ratios (aHRs).
Results: During a median follow-up of 7.6 yr IQR (3.5; 9.7), the rates of any fracture were higher in persons with T2D and MVD vs no MVD (aHR 1.31; 95% CI [1.15; 1.51]). Similarly, MOF rate was elevated in persons with MVD (aHR 1.33 [1.09; 161]). The rates for any fracture and MOF were highest in persons with neuropathy (aHR 1.49 [1.24; 1.78] and aHR 1.54 [1.19; 1.99], respectively).
Discussion: Fracture risk is elevated in persons with T2D complicated by MVD, particularly in those with neuropathy.

Keywords type 2 diabetes mellitus, microvascular diseases, retinopathy, nephropathy, neuropathy, fractures

Lay Summary

Persons with type 2 diabetes mellitus (T2D) can develop damage to small blood vessels in the eyes, kidneys, or nerves. In a study of 10 491 persons with T2D, those with this type of damage were more likely to break a bone than those without it. This included major fractures of the hip, spine, and arm. The highest risk was seen in persons with nerve damage. Overall, small blood vessel disease in T2D appears to increase the chance of experiencing a fracture.

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Introduction

Type 2 diabetes mellitus (T2D) is a chronic metabolic condition that is characterized by hyperglycemia and insulin resistance.[1] Persons with T2D have a 30% and 35% higher risk of hip[2] and vertebral fractures,[3] respectively, than those without T2D. The elevated fracture risk in T2D is explained by multiple factors including the accumulation of advanced glycation end-products in the bone collagen matrix, which impairs bone material properties,[4] impairment of osteogenic ability of mesenchymal stem cells leading to low bone turnover and poor bone quality,[5] and an increased risk of falls.[6]

Type 2 diabetes mellitus is associated with various complications other than fractures, including microvascular diseases (MVD),[7,8] such as retinopathy,[9] nephropathy,[10] and neuropathy.[9] The pathophysiology of MVD in T2D involves factors including glucose-mediated endothelial damage, and the formation of advanced glycation end-products, thereby resulting in alterations in blood flow and organ dysfunction.[11] Given that some of these mechanisms are also associated with higher fracture risk in T2D,[4] a potential association between MVD and fractures may exist.

Clinical studies generally support that changes in the vasculature may have adverse effects in bone. For example, impaired microvascular blood flow is associated with increased cortical porosity at the distal tibia and radius in persons with T2D and peripheral vascular disease.[12]

Moreover, increased cortical porosity was observed in patients with T2D complicated by MVD.[13] Furthermore, cortical osteocyte lacunar volume is larger and more spherical in persons with T2D and MVD, suggesting that MVD may impair skeletal health.[14] Additionally, premenopausal women with T2D and chronic nephropathy or retinopathy have decreased osteoid thickness,[15] indicating impaired bone formation.

Prior studies investigating the association between MVD and fracture risk in T2D have reported inconsistent findings. Retinopathy is associated with elevated risk of all fractures after adjustment for visual acuity,[16] suggesting that other mechanisms associated with retinopathy may increase fracture risk. In addition, fracture risk was reported to be higher in persons with T2D and neuropathy compared to without neuropathy.[17] In veteran men >65 yr with T2D,[18] 21% of the clinical fractures observed were explained by neuropathy. In contrast, fracture risk has not been found to be elevated in persons with T2D complicated by nephropathy, retinopathy, or neuropathy in a Danish registry-based study.[19] The inconsistency in earlier investigations may be attributed to inadequate information on MVD subtypes at baseline, inclusion of persons with long T2D duration and varying T2D severity, and/or lack of data on variables associated with both T2D and fractures, such as falls and comorbidities. Further research is needed to examine whether the presence of MVD already around the time of T2D diagnosis increase the risk of subsequent fractures.

Therefore, we investigated the association between MVD and fracture risk among persons with T2D, using data from the Danish Centre for Strategic Research in Type 2 Diabetes—the DD2 cohort.[20] This cohort provides thorough patients characterization, comprehensive baseline and physical examinations, and detailed assessment of MVD at baseline. First, we determined whether MVD are associated with elevated risk of any type of fracture and of major osteoporotic fractures (MOF), defined as clinical vertebral, hip, humerus, and forearm fractures. Second, we stratified data to investigate whether MVD subtypes might be associated with different fracture risks.

Materials and methods

Study design and research participants

We used the DD2 cohort to conduct a prospective follow-up study of persons with T2D.[20] In Denmark, general practitioners and hospital outpatient clinics have enrolled persons with recently diagnosed T2D (median duration ~1 yr) in the DD2 study since 2010.[21] In all cases, T2D was clinically diagnosed in members of the DD2 cohort in accordance with the WHO recommendations.[22] The design and implementation of the cohort have been described in a prior publication.[20] Briefly, after enrollment, participants answer a short online questionnaire, undergo a clinical examination, and provide fasting blood and urine samples.[23,24] Using the civil registration number, the DD2 cohort is linked to the Danish National Patient Registry,[25] the Danish Adult Diabetes Registry (DADR),[26] the Danish National Prescription Registry,[27] and the Registry of Laboratory Results,[28] which include additional information on comorbidities, microvascular complications and fractures, hemoglobin A1c, and therapies.

Study cohort

We identified 10 515 persons with T2D who were enrolled in the DD2 cohort between 2010 and 2022. We excluded those who had no residence in Denmark for 1 yr before enrolment ($N = 24$).

MVD definition

Microvascular disease was defined at cohort entry according to hospital records. We used International Classification of Diseases 10th Revision (ICD-10) codes to identify persons with retinopathy, nephropathy, and neuropathy (Table S1).

Outcome definition

The primary outcome was defined as the occurrence of any fracture excluding facial and cranial fractures (Table S2). As a secondary outcome, we also evaluated the occurrence of any MOF, defined as clinical vertebral, hip, humerus, and forearm fractures (Table S2). Major osteoporotic fracture diagnoses have been shown to have high validity in the Danish National Patient Registry.[29] Moreover, pre-specified age- and sex-stratified analyses of the primary outcome were conducted.

Definition of covariates

We defined age at enrolment as a continuous variable, and sex as a binary variable. We defined diabetes duration as the time from the first record of diabetes (initiation of the first glucose-lowering medication, first hospital diagnosis of diabetes, first diabetes record in the DADR, or first HbA1c >6.5%). Covariates including prior fractures were assessed at cohort entry. Excess alcohol intake was defined as >14 alcoholic drinks/wk for women and >21 drinks/wk for men. Self-reported physical activity was categorized into 3 groups: no physical activity, 30 min or more on 1-2 d per week, and 30 min or more at least 3 d per week. Fall-associated

medications were defined as a binary variable (Table S3). The use of glucose-lowering medications was categorized into 3 categories (insulin and analogs therapy, other non-insulin glucose-lowering therapy, or no pharmacological therapy) (Table S4). The Charlson comorbidity index score included 17 disease categories excluding T2D. Waist-to-hip ratio was defined as a continuous variable.

Statistical analyses

We used absolute numbers and percentages to describe categorical variables and median and IQR to describe continuous variables. The date of enrolment in the DD2 cohort was defined as the index date, and participants were followed until the occurrence of the first index fracture, emigration, or death, whatever occurred first. We used the Aalen–Johansen estimator to estimate the cumulative incidence of any fracture and MOF, taking competing risk of death into consideration. Cumulative incidence represents the absolute risk of fracture over time and is distinct from incidence rates based on person-time. Incidence rates were calculated for descriptive purposes only and are presented alongside hazard ratios estimated by Cox proportional hazards models. We computed crude and adjusted hazard ratios (aHRs) using Cox proportional hazard regression models. We built 2 adjustment models based on a directed acyclic graph (Figure S1). Model 1 incorporated covariates that we considered to precede both MVD development and potential fracture risk, such as age at enrollment, sex, T2D duration, alcohol intake, and physical activity. To further investigate whether MVD affected subsequent fracture risk, independently of markers of T2D severity or pathophysiology that may be closely associated with MVD, we used model 2. In model 2, we additionally adjusted for abdominal adiposity, measured according to the waist-to-hip ratio, comorbidity, as assessed with the Charlson index, use of glucose-lowering medications, and the use of fall-associated medications.

Given that fracture risk increases sharply with age and is more pronounced in women than men,[30] we conducted stratified analyses to examine any heterogeneity by age ($<$60 vs $\geq$60 yr) and sex. Also, we ran an interaction analysis to investigate if there is a varying impact of MVD on fracture risk in men and women. In addition, to investigate whether the association was driven by a particular MVD subtype, we reran the models for each individual MVD subtype. Additionally, considering that smoking and prior fractures are associated with elevated fracture risk,[31,32] we performed a sensitivity analysis adjusting for prior fracture and smoking status by using a missing-data indicator, given the absence of smoking status information for 56.2% of our study population.

Statistical significance was defined as an alpha level of 0.05 or lower. We used SAS version 9.4 (SAS Institute Inc.) for the data analyses. Persons received oral and written information before providing signed informed consent to participate in the DD2 cohort. The study was approved by the Regional Committees on Health Research Ethics for Southern Denmark (record number S-20100082) and the Danish Data Protection Agency (record number 2008-58-0035).

Results

Baseline characteristics

We included 10 491 persons with T2D. The baseline characteristics of our study cohort are presented in Table 1. We identified 1794 persons with MVD and 8697 persons without MVD. Persons with T2D and MVD were older (median age 65.1 yr IQR [56.9; 72.0]) than those without MVD (60.6 yr, IQR [51.9; 67.7]). Persons with and without MVD had similar T2D duration at enrolment with a median of 1.8 yr IQR (0.6; 3.5) and 1.3 yr IQR (0.4; 2.8), respectively. Among persons with MVD, 54.4% had an HbA1c $\geq$6.5% compared to 51.0% in persons without MVD. The median waist-hip-ratio was similar at 1.0 IQR (0.9; 1.0) between persons with and without MVD. Among persons with T2D and MVD, 18.2% reported no physical activity at all, 20.1% reported 1-2 d/wk of activity, and 61.7% reported to engage in physical activity for $\geq$3 d/wk. Persons with T2D and no MVD had relatively higher physical activity: 14.1% had no activity at all, 20.3% had activity for 1-2 d/wk, and 65.6% had physical activity for $\geq$3 d/wk. The proportion of persons with excess alcohol intake was approximately 6% in both groups. Macrovascular diseases were more prevalent in persons with MVD (22.9%) than in those without MVD (15.0%). Persons with both T2D and MVD, compared with those with T2D without MVD, more commonly had stroke (6.3% vs 4.0%), coronary artery disease (18.2% vs 11.7%), hypertension (39.1% vs 23.1%), and albuminuria (21.5% vs 14.5%).

Insulin use was more common in persons with than without MVD (10.5% and 5.3%, respectively). Similarly, compared with persons without MVD, persons with MVD had higher use of bisphosphonates (3.2% vs 1.7%), estrogen (8.5% vs 5.4%), glucocorticoids (9.4% vs 5.4%), opioids (20.1% vs 13.2%), antidepressants (4.6% vs 2.3%), benzodiazepines (12.6% vs 7.9%), and antihypertensive medications (80.2% vs 69.3%).

MVD and fracture risk

We identified 1244 fractures over a median follow-up of 7.6 yr IQR (3.5; 9.7). Fracture risk was higher in participants with MVD than without MVD, both for any fracture and for MOF (Figure 1). The 10-yr cumulative incidence of any fracture was 19.5% (95% CI [17.4; 21.6]) in persons with MVD compared to 14.6% (13.7; 15.5) in persons without MVD (Figure 1A). We observed a 51% higher rate of any fracture (HR 1.51 95% CI [1.32; 1.72]) in persons with T2D with rather than without MVD (crude model, Table 2). The hazard rate remained high (aHR 1.36 [1.19; 1.56]) after adjustment for model 1 covariates (model 1, Table 2). After additional adjustment for waist-to-hip ratio, Charlson comorbidity index, use of glucose-lowering medications, and use of fall-associated medications, the rate of any fracture remained higher in persons with than without MVD (aHR 1.31 [1.15; 1.51]) (model 2, Table 2). The aHR of any fracture was numerically but not statistically higher in men with MVD (aHR 1.41 [1.15; 1.72]) than in women with MVD (aHR 1.21 [1.00; 1.46]) (p-interaction = .76) (model 2, Table 2), and aHR was higher in persons $<$60 yr of age (aHR 1.45 [1.14; 1.85]) than persons $\geq$60 yr of age (aHR 1.21 [1.03; 1.44]) (model 2, Table 2).

We identified 577 MOF over a median follow-up of 7.6 yr IQR (3.5; 9.7). The 10-yr cumulative incidence of MOF was 10.3% (95% CI 10.3 [8.7; 12.0]) compared to 6.6% (5.9; 7.2) in persons without MVD (Figure 1B). We observed a 68% higher rate of MOF (HR 1.68 [1.39; 2.03]) in persons with MVD (crude model, Table 3). The hazard rate remained statistically significant but decreased after adjustment for potential confounders including age, sex, diabetes duration, alcohol, and physical activity (aHR 1.37 [1.13; 1.66]) (model 1, Table 3). After further adjustment for the waist-to-hip ratio, Charlson comorbidity index, use of glucose-lowering medications, and the use of fall-associated medications, the aHR remained largely unchanged (aHR 1.33 [1.09; 1.61] (model

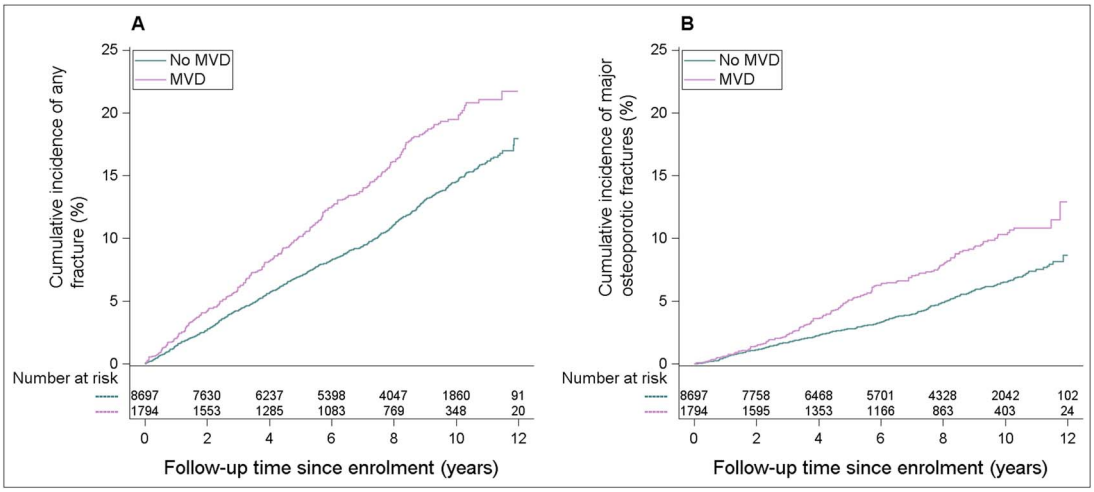


Figure 1 Cumulative incidence of any fracture (A) and major osteoporotic fractures (MOF) (B) as a function of the follow-up period (years) in persons with T2D and MVD and in persons with T2D but no MVD. Abbreviations: MVD, microvascular diseases; T2D, type 2 diabetes mellitus.

2; Table 3). The MOF aHR associated with MVD was numerically albeit not statistically higher in men (aHR 1.43 [1.04; 1.96]) than in women (aHR 1.26 [0.98; 1.61]) (p-interaction = .80) (model 2, Table 3). Persons <60 yr of age had a 49% higher rate of MOF associated with MVD (aHR 1.49 [1.01; 2.21]) while those ≥60 yr of age had a 25% higher rate of MOF with MVD (aHR 1.25 [1.00; 1.56]) (model 2, Table 3).

MVD subtypes and fracture risk

Neuropathy

The rates of any fracture and MOF remained elevated in persons with T2D and neuropathy after adjustment for potential confounders (aHR 1.49 [1.24; 1.78]) and aHR 1.54 [1.19; 1.99], respectively) (model 2, Tables 4 and 5). Compared to those without neuropathy, any fracture and MOF rates were elevated in men with neuropathy (aHR 1.68 [1.30; 2.17] and aHR 1.72 [1.15; 2.58], respectively), and women with neuropathy (aHR 1.34 [1.04; 1.72] and aHR 1.44 [1.03; 2.00], respectively) (model 2, Tables 4 and 5). Any fracture and MOF associations with neuropathy were similar in both sexes (p-interaction = .19 and p-interaction = .46, respectively). Major osteoporotic fracture rates were elevated in individuals <60 yr of age (aHR 1.58 [1.19; 2.10] and aHR 1.74 [1.12; 2.71], respectively), and ≥60 yr of age (aHR 1.43 [1.13; 1.80] and aHR 1.45 [1.06; 1.99], respectively) (model 2, Tables 4 and 5).

Retinopathy

The rates of any fracture tended to be elevated in persons with T2D and retinopathy (aHR 1.20 [1.00; 1.43]) after adjustment for all covariates in model 2 (Table S5). In crude analyses, MOF rate was 65% higher in persons with T2D and retinopathy (HR 1.65 [1.30; 2.10]) (Table S6), but adjustment for potential confounders led to a substantially decreased aHR of 1.16 [0.90; 1.49] (model 2, Table S6).

Nephropathy

The hazard ratios for any fracture and MOF in persons with T2D were similar between persons with nephropathy vs without nephropathy (aHR 1.05 [0.74; 1.49] and aHR [1.25 [0.78; 2.02], respectively) (model 2, Tables S7 and S8).

Sensitivity analysis

After adjustment for prior fracture and smoking status, the hazard rates of both any fracture and MOF remained elevated in persons with T2D and MVD (aHR 1.29 [1.13; 1.48] and aHR 1.31 [1.08; 1.59], respectively). The association were numerically higher in men (aHR 1.40 [1.15; 1.72] for any fracture and aHR 1.43 [1.04; 1.95] for MOF) than in women (aHR 1.18 [0.98; 1.43] for any fracture and aHR 1.25 [0.98; 1.61] for MOF).

Discussion

Among more than 10 000 persons with T2D, MVD were associated with an approximately 33% increased rate for any fractures and MOF. The associations remained after adjustment for T2D duration, comorbidity, lifestyle, or medication use, indicating that MVD may be an independent risk factor for fractures in T2D. The fracture associations with MVD were similar in both sexes, indicating no distinctive fracture mechanism between men and women, and our observations suggested that the association with MVD was independent of age-associated bone loss. Furthermore, neuropathy may be a more important risk factor for fractures than other MVD subtypes.

Our findings align with those from prior studies suggesting that MVD play a role in the elevated fracture risk observed in T2D. In a smaller study assessing fracture risk in 1964 persons with T2D,[17] fracture risk was 30% higher in persons with neuropathy (HR 1.3 CI [1.1-1.6]) than those without the complication. In addition, peripheral neuropathy has been reported to explain 21% of the increased fracture risk associated with diabetes in male veterans 65-99 yr of age.[18] Moreover, in persons with T2D, after adjustment for visual acuity, retinopathy remained associated with an elevated risk of all fractures.[16] However, the study was limited by imprecise assessment of risk factors of fractures in T2D and by overlooking up to 11% of hip fractures diagnoses. Furthermore, in a Danish registry-based case-control study,[19] retinopathy, nephropathy, and neuropathy in T2D were associated with an elevated fracture risk; however, the associations became statistically insignificant after adjustment for several factors including insulin use and cardiovascular diseases. This discrepancy between those findings and our results may stem from

Table 1 Baseline characteristics of the study population.

	T2D without MVD	T2D with MVD
Number of participants (%), *n* = 10 491	8697 (82.9)	1794 (17.1)
Sex (males, [*N*, %]), *n* = 10 491	5155 (59.3)	992 (55.3)
Age (median in years, [IQR])	60.6 (51.9, 67.7)	65.1 (56.9; 72)
Age-group in years (*N*, %)		
<50	1733 (19.9)	202 (11.3)
50-59	2454 (28.2)	392 (21.9)
60-69	2979 (34.3)	637 (35.5)
70-79	1358 (15.6)	452 (25.2)
≥80	173 (2)	111 (6.2)
Year of enrollment (*N*, %)		
2010-2012	1820 (20.9)	443 (24.7)
2013-2015	3721 (42.8)	829 (46.2)
2016-2018	1256 (14.4)	225 (12.5)
2019-2022	1900 (21.8)	297 (16.6)
Diabetes duration (median in years [IQR]), *n* = 10 491	1.3 (0.4; 2.8)	1.8 (0.6; 3.5)
FPG (median in mmol/L [IQR]), *n* = 10 491	7.2 (6.4; 8.2)	7.1 (6.3; 8.3)
HbA1c (*N*, %), *n* = 9482		
<6.5%	3829 (49.0)	762 (45.6)
≥6.5%	3982 (51.0)	909 (54.4)
Waist circumference, *n* = 10 437	107 (97; 117)	107 (98; 117)
Waist-to-hip ratio, *n* = 10 437	1 (0.9; 1)	1 (0.9; 1)
Smoking (*N*, %), *n* = 4587		
Never	1787 (48.6)	447 (49.0)
Former	1186 (32.3)	301 (33.0)
Current	701 (19.1)	165 (18.1)
Excess alcohol intake (*N*, %), *n* = 10 437	502 (5.8)	108 (6.1)
Self-reported physical activity, days/wk (*N*, %), *n* = 10 452		
0	1226 (14.1)	324 (18.2)
1-2	1758 (20.3)	359 (20.1)
≥3	5684 (65.5)	1101 (61.7)
Osteoporosis (*N*, %), *n* = 10 491	163 (1.9)	75 (4.2)
Prior fracture (*N*, %), *n* = 10 491	2027 (23.3)	484 (27.0)
Macrovascular diseases (*N*, %), *n* = 10 491	1305 (15)	410 (22.9)
Stroke (*N*, %), *n* = 10 491	347 (4)	113 (6.3)
Myocardial infarction (*N*, %), *n* = 10 491	375 (4.3)	93 (5.2)
Coronary artery disease (*N*, %), *n* = 10 491	1017 (11.7)	326 (18.2)
Hyperthyroidism, *n* = 10 491	129 (1.5)	45 (2.5)
Hypertension (*N*, %), *n* = 10 491	2012 (23.1)	702 (39.1)
Albuminuria (*N*, %), *n* = 8013	1259 (14.5)	386 (21.5)
Albumin-creatinine ratio (*N*, %), *n* = 8013		
<30 mg/g	5326 (80.9)	1043 (73)
30-300 mg/g	1146 (17.4)	300 (21)
≥300 mg/g	113 (1.7)	85 (6)
Glucose-lowering medications (*N*, %), *n* = 10 491		
Biguanides	7228 (83.1)	1452 (80.9)
Sulfonylureas	398 (4.6)	135 (7.5)
Thiazolidinediones	NA	NA
Dipeptidyl peptidase 4 inhibitors	712 (8.2)	200 (11.1)
SGLT2 inhibitors	316 (3.6)	68 (3.8)
GLP-1 analogs	518 (6)	141 (7.9)
Insulin	465 (5.3)	188 (10.5)
Bisphosphonates (*N*, %), *n* = 10 491	145 (1.7)	58 (3.2)
Estrogen (*N*, %), *n* = 10 491	468 (5.4)	153 (8.5)
Glucocorticoids (*N*, %), *n* = 10 491	468 (5.4)	168 (9.4)
Other medications (*N*, %), *n* = 10 491		
Antihypertensives	6025 (69.3)	1438 (80.2)
Thiazides	1377 (15.8)	329 (18.3)
Loop diuretics	687 (7.9)	344 (19.2)
Anti-psychotic	252 (2.9)	53 (3)
Opioids	1148 (13.2)	361 (20.1)
Antidepressants	197 (2.3)	82 (4.6)
Benzodiazepines	688 (7.9)	226 (12.6)

Abbreviations: FPG; fasting plasma glucose; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; MVD, microvascular diseases; SGLT2 inhibitors, sodium-glucose cotransporter-2 inhibitors; T2D, type 2 diabetes mellitus.

differences in the characteristics of persons with T2D at baseline, as our study population exhibit milder disease presentation than a predominantly inpatient and outpatient sourced registry-based cohort. The severity of health status in a registry-based cohort, may hinder any potential association between MVD and fracture risk. In addition, the enhanced registration of MVD diagnosis and the completeness of our study variables enable the identification of potential associations between MVD and fracture risk.

In our study, we observed similar fracture risk in men and women with MVD. Fracture risk is known to be higher in older women with T2D than younger women with T2D.[2] Given that the median age of our study cohort is >60 yr and the absolute prevalence of fractures is almost doubled in women compared to men, the elevated fracture risk in older women with T2D might partly mitigate the additional relative effect of MVD on fracture risk in women. Moreover, some postmenopausal women may receive medications such as bisphosphonates or hormone replacement therapy that reduce fracture risk.[33] A potential interaction between these medications and fracture risk may obscure the association between MVD and fractures, highlighting the complexity of investigating this association in women with T2D receiving fracture-preventing treatments. However, in our study, the proportion of persons on estrogen at baseline was around 6%, and almost 2% were bisphosphonates users, suggesting minimal impact of these medications on the relationship between MVD and fracture risk.

Although MVD as an aggregate was associated with increased fracture risk in T2D, we observed distinct associations by MVD

Table 2 Hazard ratios (and 95% CI) of any fracture risk in persons with T2D and MVD in the DD2 project cohort.

	Number at risk	Events	IR/1000 person-years (95% CI)	Crude HR (95% CI)	aHR (95% CI) Model 1*	aHR (95% CI) Model 2*
T2D w/o MVD	8697	956	16.1 (15.1; 17.2)	1	1	1
T2D with MVD	1794	288	24.2 (21.6; 27.2)	1.51 (1.32; 1.72)	1.36 (1.19; 1.56)	1.31 (1.15; 1.51)
Stratification by sex						
Men						
T2D w/o MVD	5155	468	13.4 (12.2; 14.6)	1	1	1
T2D with MVD	992	134	20.1 (17.0; 23.9)	1.52 (1.25; 1.84)	1.47 (1.21; 1.78)	1.41 (1.15; 1.72)
Women						
T2D w/o MVD	3542	488	20.0 (18.3; 21.9)	1	1	1
T2D with MVD	802	154	29.4 (25.1; 34.4)	1.47 (1.23; 1.77)	1.25 (1.04; 1.51)	1.21 (1.00; 1.46)
Stratification by age						
<60						
T2D w/o MVD	4187	380	13.2 (11.9; 14.6)	1	1	1
T2D with MVD	594	86	20.2 (16.4; 25.0)	1.53 (1.21; 1.93)	1.50 (1.18; 1.90)	1.45 (1.14; 1.85)
≥60						
T2D w/o MVD	4510	576	18.9 (17.4; 20.5)	1	1	1
T2D with MVD	1200	202	26.5 (23.1; 30.4)	1.42 (1.21; 1.66)	1.26 (1.07; 1.48)	1.21 (1.03; 1.44)

Model 1 was adjusted for age, sex, diabetes duration, alcohol, and physical activity. Model 2 was additionally adjusted for waist-to-hip ratio, Charlson comorbidity index excluding diabetes mellitus, use of glucose-lowering medications, and use of fall-associated medications. Abbreviations: aHR, adjusted hazard ratio; IR, incidence rate; MVD, microvascular diseases; T2D, type 2 diabetes mellitus.

Table 3 Hazard ratios (and 95% CI) of major osteoporotic fractures risk in persons with T2D and MVD in the DD2 project cohort.

	Number at risk	Events	IR/1000 person-years (95% CI)	Crude HR (95% CI)	aHR (95% CI) Model 1*	aHR (95% CI) Model 2*
T2D w/o MVD	8697	430	7.0 (6.3; 7.7)	1	1	1
T2D with MVD	1794	147	11.7 (9.9; 13.7)	1.68 (1.39; 2.03)	1.37 (1.13; 1.66)	1.33 (1.09; 1.61)
Stratification by sex						
Men						
T2D w/o MVD	5155	175	4.8 (4.2; 5.6)	1	1	1
T2D with MVD	992	57	8.1 (6.3; 10.6)	1.69 (1.26; 2.29)	1.55 (1.14; 2.10)	1.43 (1.04; 1.96)
Women						
T2D w/o MVD	3542	255	10.1 (8.9; 11.4)	1	1	1
T2D with MVD	802	90	16.1 (13.1; 19.8)	1.62 (1.27; 2.05)	1.27 (0.99; 1.62)	1.26 (0.98; 1.61)
Stratification by age						
<60						
T2D w/o MVD	4187	138	4.6 (3.9; 5.4)	1	1	1
T2D with MVD	594	32	7.1 (5.0; 10.0)	1.51 (1.03; 2.21)	1.48 (1.01; 2.18)	1.49 (1.01; 2.21)
≥60						
T2D w/o MVD	4510	292	9.2 (8.2; 10.4)	1	1	1
T2D with MVD	1200	115	14.3 (11.9; 17.1)	1.56 (1.26; 1.94)	1.30 (1.04; 1.62)	1.25 (1.00; 1.56)

Model 1 was adjusted for age, sex, diabetes duration, alcohol, and physical activity. Model 2 was additionally adjusted for waist-to-hip ratio, Charlson comorbidity index excluding diabetes mellitus, use of glucose-lowering medications, and use of fall-associated medications. Abbreviations: aHR, adjusted hazard ratio; IR, incidence rate; MVD, microvascular diseases; T2D, type 2 diabetes mellitus.

subtype with fracture risk, particularly in neuropathy. The exact mechanism linking neuropathy to higher fracture risk remains unclear. Neuropathy is associated with an increase in the likelihood of falls attributed to a decrease in balance, strength, and gait,[34] which may be associated with an increased fracture risk. Furthermore, according to bone histomorphometry data,[15] bone quality was reduced in premenopausal women with T2D and concurrent chronic nephropathy or retinopathy. In addition, an increase in bone healing complications in neuropathy, such as nonunion, delayed union, and malunion after foot and/or ankle surgery, has been suggested in a retrospective study of 165 persons with T1D and T2D.[35] Also, neuropathy may dysregulate bone metabolism through the action of neurotransmitters on bone cells.[36] Calcitonin gene-related peptide, a neuropeptide with osteoanabolic potential,[37] is diminished in persons with diabetes mellitus,[38] suggesting impaired skeletal health. Importantly,

Table 4 Hazard ratios (and 95% CI) of any fracture risk in persons with T2D and neuropathy in the DD2 project cohort.

	Number at risk	Events	IR/1000 person-years (95% CI)	Crude HR (95% CI)	aHR (95% CI) Model 1*	aHR (95% CI) Model 2*
T2D w/o neuropathy	9707	1105	16.8 (15.8; 17.8)	1	1	1
T2D with neuropathy	784	139	26.3 (22.3; 31.1)	1.58 (1.32; 1.88)	1.52 (1.27; 1.82)	1.49 (1.24; 1.78)
Stratification by sex						
Men						
T2D w/o neuropathy	5725	532	13.7 (12.6; 14.9)	1	1	1
T2D with neuropathy	422	70	24.4 (19.3; 30.8)	1.78 (1.39; 2.28)	1.74 (1.36; 2.25)	1.68 (1.30; 2.17)
Women						
T2D w/o neuropathy	3982	573	21.1 (19.4; 22.9)	1	1	1
T2D with neuropathy	362	69	28.7 (22.7; 36.4)	1.37 (1.07; 1.76)	1.35 (1.05; 1.74)	1.34 (1.04; 1.72)
Stratification by age						
<60						
T2D w/o neuropathy	4417	410	13.4 (12.2; 14.8)	1	1	1
T2D with neuropathy	364	56	22.3 (17.1; 29.0)	1.66 (1.26; 1.90)	1.60 (1.21; 2.13)	1.58 (1.19; 2.10)
≥60						
T2D w/o neuropathy	5290	695	19.7 (18.3; 21.2)	1	1	1
T2D with neuropathy	420	83	30.1 (24.2; 37.3)	1.54 (1.22; 1.93)	1.47 (1.16; 1.85)	1.43 (1.13; 1.80)

Model 1 was adjusted for age, sex, diabetes duration, alcohol, and physical activity. Model 2 was additionally adjusted for waist-to-hip ratio, Charlson comorbidity index excluding diabetes mellitus, use of glucose-lowering medications, and use of fall-associated medications. Abbreviations: aHR, adjusted hazard ratio; IR, incidence rate; MVD, microvascular diseases; T2D, type 2 diabetes mellitus.

Table 5 Hazard ratios (and 95% CI) of major osteoporotic fractures risk in persons with T2D and neuropathy in the DD2 project cohort.

	Number at risk	Events	IR/1000 person-years (95% CI)	Crude HR (95% CI)	aHR (95% CI) Model 1*	aHR (95% CI) Model 2*
T2D w/o neuropathy	9707	508	7.4 (6.8; 8.1)	1	1	1
T2D with neuropathy	784	69	12.2 (9.7; 15.5)	1.64 (1.28; 2.11)	1.58 (1.22; 2.03)	1.54 (1.19; 1.99)
Stratification by sex						
Men						
T2D w/o neuropathy	5725	203	5.1 (4.4; 5.8)	1	1	1
T2D with neuropathy	422	29	9.4 (6.6; 13.6)	1.86 (1.26; 2.75)	1.85 (1.24; 2.75)	1.72 (1.15; 2.58)
Women						
T2D w/o neuropathy	3982	305	10.7 (9.6; 12.0)	1	1	1
T2D with neuropathy	362	40	15.5 (11.4; 21.2)	1.44 (1.04; 2.01)	1.43 (1.03; 1.99)	1.44 (1.03; 2.00)
Stratification by age						
<60						
T2D w/o neuropathy	4417	147	4.6 (3.9; 5.4)	1	1	1
T2D with neuropathy	364	23	8.5 (5.7; 12.8)	1.82 (1.18; 2.83)	1.71 (1.10; 2.66)	1.74 (1.12; 2.71)
≥60						
T2D w/o neuropathy	5290	361	9.8 (8.9; 10.9)	1	1	1
T2D with neuropathy	420	46	15.6 (11.7; 20.8)	1.59 (1.17; 2.16)	1.50 (1.10; 2.05)	1.45 (1.06; 1.99)

Model 1 was adjusted for age, sex, diabetes duration, alcohol, and physical activity. Model 2 was additionally adjusted for waist-to-hip ratio, Charlson comorbidity index excluding diabetes mellitus, use of glucose-lowering medications, and use of fall-associated medications. Abbreviations: aHR, adjusted hazard ratio; IR, incidence rate; MVD, microvascular diseases; T2D, type 2 diabetes mellitus.

MVD subtypes including neuropathy frequently co-occur in this population. Therefore, the subtype analyses should be interpreted as reflecting the fracture risk associated with the presence of each subtype (regardless of co-occurring MVD). Formal between-subtype comparisons would require a larger dataset with enough cases within mutually exclusive subtype categories.

Strengths and limitations

Our study encompassed a large cohort of persons with T2D residing in Denmark, with complete follow-up for as many as 12 yr. By linking the DD2 data with medical databases, we adjusted for best-known potential confounders that could explain an association between MVD in persons with T2D and fracture risk. An important

limitation of this study is the lack of data on falls precluded us from investigating whether the elevated risk observed between MVD in persons with T2D and fracture risk was distinct from falls. Moreover, information on smoking status was missing in almost half of the study population. To navigate this shortcoming, the missing data indicator was applied; however, this approach may introduce bias if missingness is not at random. Therefore, the smoking-adjusted sensitivity analysis should be interpreted with this caveat in mind. In addition, MVD status and covariates were assessed only at baseline.

Individuals without MVD at baseline may develop MVD during the study, and covariate status may change over time, potentially attenuating associations based on baseline exposure. Therefore, future research should include periodic reassessments of MVD and key covariates to account for their development and progression during the study period. Also, participants might potentially have been misclassified as not having MVD because of the low sensitivity of using MVD diagnosis codes from the registry.[39] In addition, fracture outcomes identified using ICD-10 codes do not allow differentiation between traumatic and fragility fractures, and thus the underlying mechanisms of the recorded fractures cannot be determined. Furthermore, it is possible that some fracture codes such as ICD code M80 were used for prevalent than incident fractures, which may overestimate only any fracture risk but not MOF risk. Also, residual confounding due to unmeasured or incompletely measured factors cannot be fully excluded, despite adjustment for a broad range of demographic, clinical, and medication-related covariates. Finally, two outcomes were examined, which should be considered when interpreting findings.

Conclusion

In this cohort study involving persons with T2D, those with MVD at baseline, particularly those with neuropathy, had clearly higher rates of subsequent fractures and MOF. The findings indicated that the presence of MVD may be used to stratify persons with T2D with higher fracture risk. Fracture risk was particularly elevated in persons with neuropathy, thus suggesting further studies of the direct and indirect effect of nervous system changes on bone fragility are warranted.

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Author contributions

Mohamad I. Nasser (Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing—original draft, Writing—review & editing), Therese K. Grønborg (Data curation, Formal analysis, Software, Visualization), Frederik P.B. Kristensen (Data curation, Formal analysis, Methodology, Software, Validation, Writing—review & editing), Reimar W. Thomsen (Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Allan Vaag (Writing—review & editing), Jens Steen Nielsen (Writing—review & editing), Kurt Højlund (Writing—review & editing), Michael H. Olsen (Writing—review & editing), Peter Vestergaard (Writing—review & editing), Richard Eastell (Writing—review & editing), and Morten Frost (Conceptualization, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Writing—review & editing)

Supplementary material

Supplementary material is available at *JBMR Plus* online.

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Conflicts of interest

M.H.O. has received honoraria for talks by Novo Nordisk A/S, AstraZeneca, and Teva A/S. P.V. reports research grants from Novo Nordisk Foundation and is head of research at Steno Diabetes Center North Denmark funded by the Novo Nordisk Foundation and receipt of drug and placebo free of charge from Novo Nordisk AS for investigator-initiated trials. R.E. receives consultancy funding from Immunodiagnostic Systems, Sandoz, Samsung, Haoma Medica, CL Bio, Biocon, Takeda, meeting presentations for Pharmacosmos, Alexion and Amgen, and grant funding from Roche, Pharmacosmos and Alexion. M.F. reports research grants from Novo Nordisk Foundation; consulting fee from Novo Nordisk AS; and receipt of drug and placebo free of charge from Novo Nordisk AS for an investigator-initiated trial. The Department of Clinical Epidemiology, Aarhus University, receives funding for other studies in the form of institutional research grants to (and administered by) Aarhus University. None of these studies have any reaction to the present study. M.I.N., T.K.G., F.P.B.K., R.W.T., A.V., J.S.N., and K.H. have no potential conflicts of interest to declare.

Data availability

Restrictions apply to the availability of all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions applied.

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