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ORIGINAL ARTICLE

Incident type 2 diabetes and hip fracture risk: a population-based matched cohort study

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Abstract
Summary There is scarce data on the association between early stages of type 2 diabetes and fracture risk. We report a 20 % excess risk of hip fracture in the first years following disease onset compared to matched non-diabetic patients.
Introduction Type 2 diabetes mellitus (T2DM) is a chronic disease that affects several target organs. Data on the association between T2DM and osteoporotic fractures is controversial. We estimated risk of hip fracture in newly diagnosed T2DM patients, compared to matched non-diabetic peers.
Methods We conducted a population-based parallel cohort study using data from the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) database. Participants were all newly diagnosed T2DM patients registered in SIDIAP in 2006–2011 (T2DM cohort). Up to two diabetes-free controls were matched to each T2DM participant on age, gender, and primary care practice. Main outcome was incident hip fracture in 2006–2011, ascertained using the tenth edition of the International Classification of Diseases (ICD-10) codes. We used Fine and Gray survival modelling to estimate risk of hip fracture according to T2DM status, accounting for competing risk of death. Multivariate models were adjusted for body mass index, previous fracture, and use of oral corticosteroids.
Results During the study period (median follow-up 2.63 years), 444/58,483 diabetic patients sustained a hip fracture (incidence rate 2.7/1,000 person-years) compared to 776/113,448 matched controls (2.4/1,000). This is equivalent to an unadjusted (age- and gender-matched) subhazard ratio (SHR) 1.11 [0.99–1.24], and adjusted SHR 1.20 [1.06–1.35]. The adjusted SHR for major osteoporotic and any osteoporotic fractures were 0.95 [0.89–1.01] and 0.97 [0.92–1.02].
Conclusions Newly diagnosed T2DM patients are at a 20 % increased risk of hip fracture even in early stages of disease, but no for all fractures. More data is needed on the causes for an increased fracture risk in T2DM patients as well as on the predictors of osteoporotic fractures among these patients.

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Introduction

Type 2 diabetes mellitus (T2DM) and osteoporosis are two prevalent long-term comorbidities: in Spain, the prevalence of T2DM varies between 12 and 15 % [1], while the prevalence of osteoporosis in Spanish women exceeds 13 % [2]. The prevalence of both these conditions will increase in coming years in most countries due to population ageing.

T2DM patients have higher bone mineral density (BMD) compared to non-diabetic controls [3, 4]. However, some studies have suggested that older adults with T2DM might not be protected and even could have a higher risk of hip fractures [5]. Data remain controversial, with a number of authors reporting a lack of association [3, 6, 7].

Studies reporting an increased risk tend to show an association between the observed excess risk and either poor metabolic control [8] or the years of evolution of the disease [3]. The association between T2DM and fracture risk was studied in detail among participants of the Rotterdam cohort [3]. According to the authors, T2DM patients had an over 30 % excess risk of non-vertebral fracture, particularly in drug-treated patients. In contrast, pre-diabetes patients (those with impaired glucose tolerance) had a lower fracture risk (hazard ratio (HR)=0.80, 95 % confidence interval (CI) 0.63–1.00). Recently, we also studied this association in the DIAFOS cohort and reported similar fracture risk in pre-diabetic patients compared to non-diabetic patients [9].

However, many factors other than T2DM itself might explain an increased risk of osteoporosis and fractures in these patients: typical T2DM complications such as neuropathy, nephropathy, and cataracts are associated with an increased frequency of falls and consequently fractures [10], and some antidiabetic drugs like insulin and thiazolidinediones have a negative effect on bone [11–14], although this could be due to patients treated with insulin being those with longer duration of or more severe diabetes (confounding) This makes it very difficult to disentangle whether an association between T2DM and an increased fracture risk is due to the disease, its complications, its treatments or all of the above.

To overcome this challenge, we used a population-based database containing routinely collected clinical information to investigate the relationship between recently diagnosed T2DM (when complications and most antidiabetic treatments are infrequent) and hip fracture rates up to 6 years after disease onset. Secondly, we explored the association between T2DM and all osteoporotic fracture rates in the same data.

Methods

Data source

Data for the current study were extracted from the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) database (www.sidiap.org). SIDIAP contains clinical information as coded by general practitioners and community nurses in 274 primary care practices in Catalonia, Spain, covering more than five million patients (80 % of the Catalan population). The representativeness of the SIDIAP database for the overall Catalan population has been previously shown elsewhere [15].

It contains anonymized data recorded in computerized primary care medical records, including sociodemographics, visits to primary care, referrals, diagnoses as coded using the tenth edition of the International Classification of Diseases (ICD-10), clinical measurements (blood pressure, body mass index, etc.), immunizations, and other information. SIDIAP is linked to pharmacy invoice data, which provides detailed information on drugs dispensed in community pharmacies.

SIDIAP data has been previously used to study many aspects related to T2DM assessment and treatment [16], who showed a similar prevalence of T2DM that previous studies performed in Spain, as well as to characterize the epidemiology and to describe new predictors of fragility fractures [17–19].

Study population

We screened SIDIAP to identify patients with a newly coded T2DM diagnosis (ICD-10 codes E11.0, E11.1, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.8, and E11.9) in the period 2006–2011. Up to two non-diabetic controls were matched to each of the participants in the T2DM cohort by age (±2 years), gender, and primary care practice. SIDIAP participants with no T2DM/T1DM coded diagnoses and with no previous use of antidiabetic drugs were eligible as non-diabetic patients in our study.

Both cohorts were then followed from the date when the T2DM patient was diagnosed (index date) until participants died (n=2,501), transferred out of the area (n=1,609), or end of study (31/12/2011), whichever came first.

Study outcomes: hip and osteoporotic fractures

Incident hip fracture was the main study outcome; major osteoporotic and any osteoporotic fracture (all sites, including hip, but excluding skull, fingers, and toes) were the secondary outcomes. All these were ascertained using ICD-10 codes. The list of codes used has previously been validated [20] and is shown as Appendix - Supplementary Table 1.

Confounders

We adjusted for a pre-specified list of confounders including body mass index, history of a previous fracture, and use of oral corticosteroids for 3 months or more (>5 mg of prednisolone or the equivalent).

In further models fitted to explore potential causes for an increased fracture risk in T2DM patients, we also adjusted for history of previous cerebrovascular disease (CVD), previous ischemic heart disease (IHD), previous nephropathy, previous falls, and previous use of bisphosphonates, thiazidic diuretics or antidiabetic drugs (metformin, sulfonylureas, thiazolidinediones, and insulin). Drug utilization was identified using a pre-specified list of World Health Organization Anatomic Therapeutic Classification (WHO ATC) codes, shown as Appendix - Supplementary Table 2.

For body mass index, smoking, and alcohol drinking measurements, only those coded in the up to 5 years before index date were used. For patients with repeat measurements, the one closest prior to index date was considered.

Statistical analyses

Fine and Gray survival models [21] were fitted to model the association between T2DM and hip (and all osteoporotic) fracture risk. These methods account for a competing risk with death, therefore providing a more accurate estimate of the existing association between the study exposure and main outcome. We tested for proportionality of hazards using the Schöenfeld residuals formal test and log-log plots.

Multivariate models were adjusted for the pre-defined confounders listed above, and multiplicative terms were introduced into the regression equations to test for pre-determined interactions (with age, gender, IHD, CVD, chronic kidney disease (CKD), and BMI). Stratified results are reported for significant interactions only [22].

Multiple imputation with chained equations (MICE) methods [23] were used to account for missing information in body mass index.

Stata SE ver 12.0 for Mac was used for all the analyses.

Results

We identified 58,483 T2DM patients and 113,448 controls, who were observed for a median (inter-quartile range) of 2.63 (2.93) years. The T2DM cohort had a higher prevalence of cardiovascular disease, neuropathy, and chronic kidney disease. Baseline characteristics for T2DM and non-diabetic participants are detailed in Table 1.

The median and inter-quartile range duration of T2DM before a fracture was 1.69 (2.25) years. In non-diabetic patients was 1.71 (2.15) years.

In the early years (up to 6) following disease onset, 444/58,483 (0.8 %) T2DM patients sustained a hip fracture (incidence rate (IR) 2.7/1,000 person-years), compared to 776/113,448 (0.7 %) matched non-diabetic controls (IR 2.4/1,000 person-years) (Fig. 1). The fitted survival models showed a borderline-significant association between T2DM and hip fracture risk in the (matched) unadjusted models (subhazard ratio (SHR) 1.11 [95 % CI 0.99 to 1.24]), which became significant after adjustment for pre-defined confounders (SHR 1.20 [1.06 to 1.35]). Included confounders were BMI, previous fracture, and oral corticoids.

Further adjustment for baseline clinical characteristics potentially involved in the causal pathway of the observed association between T2DM status and hip fractures (prevalent CVD, IHD, CKD, and falls history) attenuated this association: fully adjusted SHR 1.10 [0.98 to 1.24]. When we included also antidiabetic drugs, the adjusted SHR were 1.11 [0.86–1.17].

Conversely, a similar proportion of T2DM (2,168/58,483 [3.7 %]) and non-diabetic (4,220/113,448 [3.7 %]) patients suffered at least one osteoporotic fracture in the study period, with rates of 13.4/1,000 and 13.3/1,000 person-years, respectively (Fig. 2). The corresponding SHR was 0.96 [0.90 to 1.03] and 0.97 [0.92 to 1.02] in unadjusted and multivariate adjusted models, respectively. If we considered only major osteoporotic fractures, the corresponding unadjusted SHR was 1.00 [0.95 to 1.05] and adjusted SHR was 0.95 [0.89 to 1.01].

We identified significant interactions between T2DM status and related comorbidities (ischemic heart disease (IHD) and chronic kidney failure (CKD)) as well as with body mass index on hip fracture risk. In the subsequent stratified analyses, the excess risk associated with T2DM was the highest among T2DM patients with prevalent IHD (adjusted SHR 1.39 [0.98 to 1.98]), CKD (adjusted SHR=1.26 [1.03 to 1.55]), or grade 2 obesity (adjusted SHR 1.37 [0.92 to 2.06]) (Table 2).

No significant interactions were seen with age, gender, and previous cerebrovascular disease/stroke.

Discussion

In our data, recently diagnosed T2DM patients have a 20 % higher risk of hip fractures in the first few years following disease onset, compared to non-diabetic patients. Some comorbid conditions typically associated with T2DM, such as prevalent IHD, CVD, and CKD, might partially account for this excess risk, which is higher for diabetic patients (compared to non-diabetic counterparts) with a previous history of IHD and CKD and those with grade 2 obesity at the time of T2DM diagnosis. In our data, no association was observed between T2DM and all osteoporotic fractures grouped together or major osteoporotic fractures (Appendix - Supplementary Tables 1 and 2).

Given our previous work on the validity of fracture coding in SIDIAP, we chose hip fracture as the main study outcome as it is

Table 1 Baseline subject characteristics according to T2DM status

	T2DM patients	Non-diabetic patients	*p* value
Number of patients	58,483	113,448	
Age (years); mean±SD	62.71±11.90	62.52±11.80	0.8960
BMI (kg/m^2); mean±SD	30.86±5.26	28.55±4.62	<0.0001
Missing BMI; *N* (%)	7,857 (13.4)	44,249 (39.0)	<0.0001
Sex (male); *N* (%)	33,147 (56.7)	64,079 (56.5)	0.4400
HbA1c (%); mean±SD	6.53±1.60	5.25±0.65	<0.0001
Missing HbA1c; *N* (%)	5,036 (8.6)	85,137 (75.0)	<0.0001
Creatinine (mg/dl); mean±SD	0.91±0.29	0.91±0.31	<0.0001
Missing creatinine; *N* (%)	3,208 (5.5)	23,696 (20.9)	<0.0001
Alcohol drinking (%)			<0.0001
None	18,057 (30.9)	22,197 (19.6)	
Moderate	17,520 (30.0)	25,581 (22.5)	
Severe	2,058 (3.5)	2,614 (2.3)	
Missing	20,848 (35.6)	63,056 (55.6)	
Smoking; *N* (%)			<0.0001
Never	12,796 (21.9)	25,125 (22.1)	
Current smoker	10,181 (17.4)	16,678 (14.8)	
Ex-smoker	10,247 (17.5)	14,488 (12.8)	
Missing	25,259 (43.2)	57,057 (50.3)	
Previous CVD; *N* (%)	2,851 (4.9)	3,744 (3.3)	<0.0001
Previous IHD; *N* (%)	4,739 (8.1)	5,168 (4.6)	<0.0001
Previous CKD; *N* (%)	6,546 (11.2)	9,469 (8.3)	<0.0001
Previous neuropathy; *N* (%)	295 (0.5)	128 (0.1)	<0.0001
Previous cataracts; *N* (%)	3,796 (6.5)	7,021 (6.2)	0.0145
Previous falls; *N* (%)	596 (1.0)	1,165 (1.0)	0.8790
Oral corticoids use; *N* (%)	4,230 (7.2)	5,672 (5,0)	<0.0001
Bisphosphonates use; *N* (%)	2,550 (4.4)	6,597 (5.8)	<0.0001

CVD cerebrovascular disease, *IHD* ischemic heart disease, *CKD* chronic kidney disease

the one site with the best coding quality [20]. Other fractures with lower coding accuracy are prone to random misclassification, which drives the risk estimate to the null. This could explain at least partially the discrepancy observed in excess risk of hip vs other fractures among diabetic patients. However, more studies are needed to clarify this, and our group is working on the study of predictors of individual fracture sites in the type 2 diabetic population, which might shed some light on the topic.

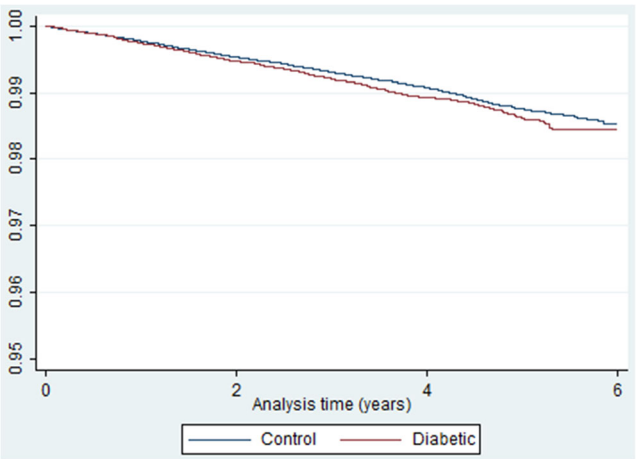

Fig. 1 Cumulative hip fracture probability according to T2DM status: Kaplan-Meier plot, adjusted by BMI, previous fracture, and oral corticoids use

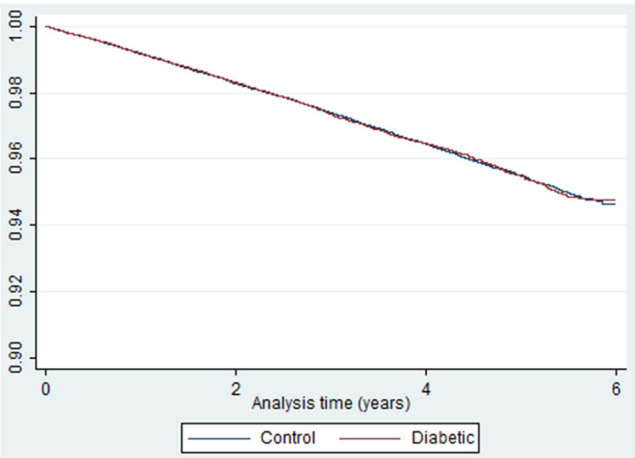

Fig. 2 Cumulative osteoporotic fracture probability according to T2DM status: Kaplan-Meier plot, adjusted by BMI, previous fracture, and oral corticoids use

Table 2 Stratified analyses (SHR adjusted by BMI, previous fracture, and oral corticoids)

	Number (%) affected	Number (%) with an incident hip fracture	Adjusted SHR [95 % CI] for T2DM patients
Prevalent ischemic heart disease (IHD)			
IHD history	9,906	129 (1.3 %)	1.39 [0.98–1.98]
No IHD history	162,022	1,088 (0.7 %)	1.09 [0.96–1.24]
Prevalent chronic kidney disease (CKD)			
CKD history	18,642	374 (2.0 %)	1.26 [1.03–1.55]
No CKD history	152,443	843 (0.6 %)	1.06 [0.92–1.22]
Baseline body mass index			
BMI <25 kg/m^2	28,167	327 (1.1 %)	1.11 [0.86–1.43]
BMI 25 to <30 kg/m^2	65,908	513 (0.7 %)	1.18 [0.98–1.41]
BMI 30 to <35 kg/m^2	50,578	280 (0.6 %)	1.02 [0.80–1.28]
BMI ≥35 kg/m^2	21,852	97 (0.4 %)	1.37 [0.92–2.06]

Further adjustment for antidiabetic treatment use attenuated the association between type 2 diabetes status and hip fractures. However, these treatments might be in the causal pathway of such association, potentially explaining the observed excess risk.

The observed early increase in hip fracture risk associated with T2DM is only moderate but still relevant, as widely used predictive tools used in clinical practice (such as FRAX) do not account for this prevalent disease as a risk factor. Along these lines, two recent studies [24, 25] have shown that FRAX does underestimate fracture risk in T2DM patients.

The association between T2DM and fracture risk was studied in the Rotterdam cohort [3], which showed more than 30 % increased risk of non-vertebral fracture in T2DM, particularly in patients treated with antidiabetic agents. Conversely, pre-diabetic patients (those with impaired glucose tolerance) had a lower fracture risk (HR=0.80, 95 % CI 0.63–1.00). Contrary to these results, the Rochester study [26] and a more recent study [27] have found that the frequency of fractures increased with the duration of diabetes. In the WHI observational study [28], women with a history of prevalent T2DM had a 20 % increased risk of any fracture and a 46 % increase in hip fracture risk.

A recent meta-analysis [4] has shown a 38 % increased hip fracture risk associated with T2DM, higher than that observed in our study. However, their study included patients with long-standing prevalent T2DM while our study focused on recently diagnosed T2DM. Our study participants were therefore less likely to suffer from diabetic complications and to use antidiabetic drugs, offering a cleaner comparison against the general population. Consistent with our data, the cited meta-analysis did not find an increased risk of any fracture (RR=0.96, 95 % CI 0.57–1.61, five studies).

In our study, participants in the T2DM cohort had a higher prevalence of cardiovascular disease, neuropathy, and nephropathy. The association between early stages of T2DM and cardiovascular disease is well known: pre-diabetic patients have an increased risk of cardiovascular death [29–31], and this association increases with the years following disease onset [32]. Other studies have shown the association between cardiovascular disease and fractures [33, 34].

Our study has both strengths and limitations. The main limitation of our data is the lack of validation of each individual fracture. However, coding of fractures in SIDIAP has been compared to classical cohort data and hospital databases and shown to be highly specific (>95 % for all fracture sites tested) and moderately sensitive (almost 70 % for hip fractures) [20]. Sensitivity was low for the coding of fracture sites other than hip, such as clinical spine (50 %) and wrist/forearm (56 %). Also, ICD-10 does not distinguish between traumatic fractures and fragility fractures. A recent study including a random sample of 300 SIDIAP participants aged >50 years old who suffered a fracture during 2012 has shown that >90 % of hip fractures were fragility (not related to high impact trauma) [35]. For this reason, we chose hip fracture as the primary outcome of our study.

Other general limitations of our study are the definition of drug compliance based on pharmacy dispensation data (with no validation within individual subjects), and the time points when lifestyle factors (BMI, alcohol drinking, and smoking) were measured. To minimize misclassification, we only considered information on lifestyle factors as recorded in a maximum of 5 years before index date.

Important strengths of our data are the high number of patients studied, as well as the inclusion of only the incident T2DM patients to enable an accurate assessment of the association between diabetes and fractures before antidiabetic drugs and related complications become highly prevalent.

Ours is the first study to account for the competing risk with death when exploring the association between T2DM and hip fractures. We believe that previous studies failing to account for this may have overestimated the excess risk of

fractures [36, 37], as T2DM is itself a predictor of increased mortality at a population level [38].

Conclusions

We demonstrate that recently diagnosed T2DM patients have a 20 % increased risk of hip fractures up to 6 years after disease onset, compared to matched non-diabetic peers. Diabetic complications and related comorbidities including cardiovascular disease and CKD confer an even higher excess risk in relation to T2DM status.

T2DM must be considered as a predictor of hip fractures even at early stages of disease. Research is urgently needed to establish the key risk factors for fractures in the T2DM population, which might differ from those seen in the general population, as well as to establish the efficacy of available anti-osteoporosis therapies to reduce fractures in diabetic patients.

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Conflicts of interest Daniel Martinez-Laguna, Cristian Tebe, M Kassim Javaid, Xavier Nogues, Nigel K Arden, Cyrus Cooper, Adolfo Diez-Perez, and Daniel Prieto-Alhambra declare that they have no conflict of interest.

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