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TITLE: “Excess of all-cause mortality after a fracture in type 2 diabetic patients: a population-based cohort study.”

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DISCLOSURE PAGE:

(All authors state that they have no conflict of interest.)

DPA has received unrelated research grants from AMGEN, Laboratoires Servier, and UCB Pharmaceuticals. ADP has received unrelated support as speaker or advisor from Amgen, Lilly, UCB, Radius, Mereo and Active Life and institutional research support from Amgen.

BA reports institutional research contracts with Novartis and UCB Pharmaceuticals for epidemiological and pharmacovigilance studies.

SUMMARY: [31 WORDS]

Post-fracture mortality in type 2 diabetes (T2DM) patients has been poorly studied. We report an absolute and relative excess all-cause mortality following a fracture in these patients compared to non-diabetic patients.

ABSTRACT: [247 WORDS]

Purpose: T2DM and osteoporotic fractures are independently associated with a reduced lifespan, but it is unknown if T2DM confers an excess post-fracture mortality compared to non-diabetic fracture patients. We report post-fracture all-cause mortality according to T2DM status.

Methods: Population-based cohort study using data from the SIDIAP Database. All ≥ 50 years old T2DM patients registered in SIDIAP in 2006-2013 and 2 diabetes-free controls matched on age, gender, and primary care center were selected. Study outcome was all-cause mortality following incident fractures. Participants were followed from date of any fracture (AF), hip (HF), and clinical vertebral fracture (VF) until the earliest of death or censoring. Cox regression was used to calculate mortality according to T2DM status after adjustment for age, gender, body mass index, smoking, alcohol intake, previous ischemic heart and cerebrovascular disease.

Results: We identified 166,106 T2DM patients and 332,212 non-diabetic, of which 11,066 and 21,564 respectively sustained a fracture and were then included. Post-fracture mortality rates (1,000person-years) were (in T2DM vs non-diabetics) 62.7 vs 49.5 after AF, 130.7 vs 112.7 after HF, and 54.9 vs 46.2 after VF. Adjusted HR (95% CI) for post-AF, post-HF and post-VF mortality were 1.30 (1.23-1.37), 1.28 (1.20-1.38), and 1.20 (1.06-1.35) respectively for T2DM compared to non-diabetics.

Conclusions: T2DM patients have a 30% increased post-fracture mortality compared to non-diabetics and a remarkable excess in absolute mortality risk. More research is needed on the causes underlying such excess risk, and on the effectiveness of measures to reduce post-fracture morbi-mortality in T2DM subjects.

KEYWORDS:

epidemiology, mortality, osteoporotic fracture, type 2 diabetes mellitus, general population studies.

INTRODUCTION:

Type 2 diabetes mellitus (T2DM) and osteoporosis are two highly prevalent long-term comorbidities. T2DM is a pandemic disease that affects at least 285 million people worldwide, and projections on numbers affected suggest figures will increase to 438 million by the year 2030 [1]. T2DM is associated with a decrease in life expectancy [2] and it is reportedly related to a two-fold excess mortality [3]. Such increased risk of death is partially explained by modifiable clinical variables such as glycemic control and renal complications [4–6]. Macrovascular disease is the principal cause of death amongst T2DM patients, and risk changes over time according to type of complication [7], but cancer and non-cardiovascular non-cancer events are also associated with an increased mortality in this population [8].

In parallel, hip fractures (HF) are associated with the highest mortality of all osteoporotic fractures [9–11], particularly in men [12,13]: about 30% of individuals with hip fracture are estimated to die in the first year post fracture [13], and a second hip fracture increases risk further [14]. Vertebral fractures (VF), the most common osteoporotic fractures [15], are also associated with an increased risk of mortality [9–11,16], particularly when symptomatic (i.e. clinical vertebral fractures) [17]. VF decrease life expectancy, even further in multiple VF patients (compared to those with a single VF) [18], and post-VF mortality peaks during the first months to then decline progressively over time [19]. The impact of non-hip non-vertebral fractures on life expectancy is less well described, but it seems like they increase mortality by 20% [20].

When specific causes of mortality are analyzed it appears like affected patients die most often as a consequence of exacerbations/decompensation of their baseline co-morbidities rather than as a result of direct fracture-related complications [21].

There is a scarcity of data on whether T2DM is associated with an increased post-fracture mortality (compared to non-diabetic fractured patients). We therefore conducted a population-based cohort study to assess the existing association between T2DM status and all-cause mortality risk following different osteoporotic fractures.

METHODS:

Data source:

Data 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/family nurses in 274 primary care practices in Catalonia, Spain, covering over 5 million patients (80% of the Catalan population). The representativeness of the SIDIAP database for the overall Catalan population has been previously demonstrated [22].

SIDIAP contains anonymized information on socio-demographics, primary care visits, referrals, diagnoses -coded using the 10th edition of the International Classification of Diseases (ICD-10)-, measurements (lifestyle factors such as smoking, routine clinical variables such as body mass index/blood pressure, and primary care blood/laboratory results), immunizations, and date of death. SIDIAP is linked to pharmacy invoice data, which provides detailed information on dates, doses, and ATC (Anatomic Therapeutic Classification) codes for drugs dispensed in community pharmacies.

SIDIAP data has been previously used to study many aspects related to T2DM assessment and treatment [23,24], showing a prevalence of T2DM similar to previous studies performed in Spain, as well as to characterize the epidemiology and to describe new predictors of fragility fractures [25–30].

Study population:

We included all subjects ≥ 50 years old registered in the SIDIAP Database with a coded diagnosis for T2DM (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 2006-2013. Up to 2 non-diabetic controls were

matched to each of the T2DM participants 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 controls.

Patients in both the T2DM and the control matched cohort were followed from date of first fracture (index date) to their date of death (outcome) or transfer out/end of study (31/12/2013).

Study outcomes:

All-cause mortality following any incident fracture (AF) (of any skeletal site except face, skull, or digits) was the main study outcome. Secondary analyses were conducted looking at mortality following 1. hip (HF), and 2. clinical vertebral fracture (VF).

Fractures were ascertained using a previously validated list of ICD-10 codes (Appendix 1). Date of death is registered in SIDIAP as provided by the Regional National Health Insurance Database.

Confounders:

We adjusted for a pre-specified list of confounders including age, sex, body mass index, smoking, alcohol drinking, and history of ischemic heart (IHD) or cerebrovascular disease (CVD). Age was measured at the date of fracture, whilst all other confounders were assessed in the up to 5 years prior to T2DM diagnosis, with the one closest to fracture being used for adjustment where more than one measurement (of body mass index, smoking, or alcohol drinking) was available. Missing categories were created for missing values of BMI, smoking, and alcohol drinking, which were then used in the multivariable models to prevent the exclusion of patients with missing data for such variables.

Statistical analyses:

Baseline characteristics were described using mean and standard deviation for continuous variables and frequencies and percentage for categorical ones.

Post-fracture mortality rates were estimated, and Cox regression models were fitted to calculate mortality risk according to T2DM status in three different models: 1. unadjusted, 2. after adjustment for age and sex, and 3. after adjustment for all the previously pre-specified confounders. Absolute difference in mortality rates between T2DM and non-diabetic patients were calculated using the formula by BR Kirkwood and JAC Sterne [31]. Multiplicative terms (T2DM*fracture) were introduced in the survival analysis equation to test for an interaction in the effect of fracture on the relative risk of mortality according to T2DM status. Stata SE ver 12.0 for Mac was used for all the analyses.

RESULTS:

A total of 166,106 T2DM patients and 332,212 non-diabetic were identified. The T2DM cohort had a higher prevalence of previous fracture, as well as of cerebrovascular and ischemic heart disease. Baseline characteristics for both cohorts at the time of inclusion (T2DM diagnosis or matched date in non-diabetic patients) are described in detail in Table 1. A total of 11,066 (6.66%) T2DM and 21,564 (6.49%) non-diabetics sustained a fracture, and were then included for the main analysis. Similarly, 3,861 (2.32%) T2DM and 6,616 (1.99%) non-diabetic subjects sustained a HF; and 2,702 (1.63%) and 5,477 (1.65%) presented a VF, being then included for the proposed secondary analyses.

Compared to patients without incident fracture (and hence not eligible for the post-fracture survival analysis), patients with incident AF, HF, and VF were older and more likely to be women than those who did not fracture during follow-up. Table 2 details socio-demographic and clinical characteristics in patients included (with incident AF, HF, or VF) summarized according to T2DM status.

Overall post-fracture mortality rates (per 1,000 person/year) were 53.93 after AF, 119.23 after a HF, and 49.11 after a VF, and higher in T2DM patients compared to non-diabetics. All-cause mortality was also increased in non-fractured patients, but absolute risk differences were much (more than six-fold) higher following any fracture (Table 3). More than 50% of the observed deaths occurred during the first two years after a fracture, with the higher proportion of them seen in the first year following a HF (Table 4). Age and gender-adjusted Cox regression confirmed an increase in post-fracture mortality for T2DM patients, which remained significant after multivariable adjustment: adjusted HRs 1.30 [95%CI 1.23-1.37] for AF, 1.28 [1.20-1.38] for HF, and 1.20 [1.07-

1.35] for VF patients (Table 5). The test for an interaction in the effect of fracture on the relative risk of mortality according to T2DM status showed an interaction between any fracture and T2DM ($p < 0.001$), between hip fracture and T2DM ($p = 0.007$), but no significant interaction between clinical vertebral fracture and T2DM ($p = 0.70$). Kaplan-Meier curves depict a higher mortality after fractures in T2DM (Figure 1).

Mortality was higher in men (compared to women): fully adjusted HRs 2.10 (1.97 – 2.24) after AF, 1.82 (1.68 – 1.98) after a HF, and 2.03 (1.77 – 2.32) after a VF.

Patients with any fracture had an increased mortality compared to patients without (adjusted HR = 2.17; 95% CI 2.11 – 2.23); such excess mortality was numerically (but not significantly) higher in T2DM (adjusted HR = 2.31; 95% CI 2.11 – 2.42) compared to non-diabetic patients (adjusted HR = 2.11; 95% CI 2.04 – 2.19). Similar results were seen for post-vertebral fracture mortality, which was again non-significantly higher in T2DM (adjusted HR = 2.50 [2.28 – 2.75]) than in non-diabetics (adjusted HR = 2.43 [2.26 – 2.60]). Finally, the effect of hip fracture on mortality was significantly increased in T2DM (adjusted HR = 2.90 [2.74 – 3.06]) compared to non-diabetics (adjusted HR = 2.59 [2.48 – 2.71]).

DISCUSSION:

In our data, T2DM patients have a 30% excess all-cause mortality following any (28% for hip, 20% for vertebral) fracture, compared to non-diabetic patients, and an absolute excess of mortality post-fracture. This is –to our knowledge- the first manuscript to demonstrate such an increased risk of post-fracture death in T2DM patients. A previous unpublished work showed a worse 1-year survival for patients with diabetes (T1DM and T2DM) than those without after sustaining a fracture, with exception of vertebral fractures among adults aged at least 90 years [32]. In the Manitoba cohort, diabetes (T1DM and T2DM) was associated with a higher mortality after a hip, wrist or vertebral fracture compared to non-diabetic patients, especially in patients with long-term diabetes (> 5 years prior to fracture) [33]. Another study observed that diabetes and diabetes with complications were not associated with an increased 30 day mortality following hospital discharge for femoral neck fracture [34].

As expected, T2DM patients in our cohort have a major previous CVD and IHD prevalence, two-fold compared to non-diabetic patients. Both are common macrovascular complications associated to T2DM [35–37] and may explain an excess of early mortality in T2DM patients. Some authors have suggested a relationship between cardiovascular disease and bone disease: a case-control study in patients with metabolic syndrome observed that patients with a coronary event in the last 6 months had a higher vertebral and all fracture prevalence compared to patients without recent IHD [38]. Similarly, when coronary artery disease surrogates (high coronary artery calcium score, obstructive coronary artery disease, and multi-vessel disease) are analyzed by multi-detector computed tomography in postmenopausal women, a higher prevalence of disease is observed in patients with low bone mineral density, independent of cardiovascular risk factors and age [39].

Like in previous studies including patients from the general population, HFs are associated with the highest mortality rates of all osteoporotic fractures [9,10,40–42].

This is also the case in T2DM subjects in our study.

At first sight it may seem surprising that T2DM, which is generally viewed as leading to a two-fold increased mortality risk is only associated with a more modest excess mortality of 20 to 30% in this setting. This does not indicate that a fracture event reduces the excess mortality of diabetes *per se* but only that mortality in fracture patients with T2DM differs less from mortality in other fracture patients, who of course have much greater morbidity and higher mortality than the general population [9,10]. Osteoporotic fracture is in itself such a strong predictor of mortality that concomitant T2DM adds less to the risk than in the general population. The observed increase in mortality attributable to T2DM status resulted in a higher absolute risk of death following fracture/s. Interaction analyses suggest that the impact of any and hip (but not clinical vertebral) fracture on mortality differs significantly by T2DM status.

Similar to other reports of diabetes-free populations, post-fracture mortality appeared higher in T2DM men (compared to women). This is in line with previous studies which have shown an increased risk of post-fracture mortality in men, despite their lower fracture risk [10,12,13,43]. A meta-analysis including 22 cohort studies has confirmed a higher mortality risk in men compared to women after a hip fracture up to five years. Beyond five years, sex-related differences in excess risk for mortality seem to decrease [44].

Strengths and limitations:

The main limitation of our data is the lack of validation of each individual event (both for fracture/s and death). 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) but worse sensitivity. One possible explanation may be that high impact traumatic fractures are seen directly in hospitals or in private health care services [25] and not registered in primary care records. This under-registration should not as any misclassification should be at random and hence affect T2DM and non-diabetic patients similarly. Also, although ICD-10 coding does not distinguish between traumatic and osteoporotic (fragility) fractures, a recent validation of more than 300 fractures coded in SIDIAP participants aged > 50 years old has showed that >90% of hip fractures, >87% of vertebral fractures and >80% of major fractures were fragility/osteoporotic (i.e. not related to high impact trauma) [45]. Any limitations to full capture of fracture events in the study would materially affect the estimates of post-fracture mortality as the sample can be viewed as representative of the full fracture population. Data on cause of death was not available, and thus only all-cause mortality was studied. The onset of T2DM is insidious and many patients will have met the criteria for diabetes for months or years prior to a diagnosis being recorded. This is unlikely to affect the observed differences in mortality, however, as the survival analyses use the date of fracture – a much more robustly defined date than the onset of diabetes – as the index date for comparing mortality. We did not adjust our analyses for the use of anti-diabetic drugs or co-morbidity.

Important strengths of our data are the high number of patients studied and the high representativeness of SIDIAP as a data source, as it covers >80% of the population of Catalonia.

Conclusions:

This is the first manuscript to report an excess risk of post-fracture all-cause mortality in T2DM subjects. Similar to previous studies, most of the observed deaths occurred in the first one to two years following any fracture. More research is needed on the causes underlying the observed increased risk, as well as on the effectiveness of potential measures to reduce post-fracture mortality in T2DM subjects.

FIGURES LEGENDS:

Figure 1: Cumulative mortality probability according to T2DM status after a A) hip fracture, B) vertebral fracture or C) any fracture: Kaplan-Meier plots.

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