

The association between type 2 diabetes mellitus, hip fracture, and post hip fracture mortality: a multi-state cohort analysis.

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Conflict of Interest

Cristian Tebé has received lecture fees and honoraria from Boehringer Ingelheim and Amgen outside of the submitted work. Daniel Prieto-Alhambra has received lecture fees and honoraria from Servier, Amgen, and UCB Biopharma SRL outside of the submitted work. Adolf Diez has received lecture fees and honoraria from Amgen, Amgen, Lilly, Gilead, UCB, Roche, Amgen and EchoLight outside of the submitted work. Daniel Martínez-Laguna, Cristian Carbonell, Carlen Reyes, Victor Moreno and Gary S Collins declare that they have no conflict of interest.

Summary [50 words]

Type 2 diabetes mellitus (T2DM) is associated with an excess risk of fractures and overall mortality. This study compared hip fracture and post hip fracture mortality in T2DM and non-diabetics subjects. The salient findings are that subjects in T2DM are at higher risk of dying after suffering a hip fracture.

Abstract [249 words]

Purpose: Previous research suggests that individuals with type 2 diabetes mellitus (T2DM) are at an excess risk of both fractures and overall mortality, but their combined effect is unknown. Using multi-state cohort analyses we estimate the association between T2DM and the transition to hip fracture, post hip fracture mortality, and hip fracture free all-cause death.

Methods: Population-based cohort from Catalonia, Spain, including all individuals aged 65 to 80 years with a recorded diagnosis of T2DM on 01 January 2006; and non-T2DM matched (up to 2:1) by year of birth, gender, and primary care practice.

Results: A total of 44,802 T2DM and 81,233 matched controls (53% women, mean age 72 years old) were followed for a median of 8 years: 23,818 died without fracturing, and 3,317 broke a hip, of whom 838 subsequently died. Adjusted HRs for hip fracture free mortality were 1.32 [95% CI 1.28 to 1.37] for men and 1.72 [95% CI 1.65 to 1.79] for women. HRs for hip fracture were 1.24 [95% CI 1.08 to 1.43] and 1.48 [95% CI 1.36 to 1.60], whilst HRs for post hip fracture mortality were 1.28 [95% CI 1.02 to 1.60] and 1.57 [95% CI 1.31 to 1.88] in men and women respectively.

Conclusion: T2DM individuals are at increased risk of hip fracture, post hip fracture mortality, and hip fracture free death. After adjustment, T2DM men were at a 28% higher risk of dying after suffering a hip fracture and women had 57% excess risk of post hip fracture mortality.

Keywords: Fracture Risk Assessment, Type 2 Diabetes Mellitus, Multi-state models, Osteoporosis, Population-based cohort.

Introduction

Type 2 diabetes mellitus (T2DM) is a serious chronic disease. Its prevalence have been steadily increasing over the past few decades but has risen faster in low- and middle-income countries than in high-income countries¹. T2DM if it's not treated properly can lead to a wide range of serious health problems². T2DM increases patient risk for cardiovascular diseases³, nephropathy⁴, neuropathy⁵, retinopathy⁶ and foot problems⁷. Fragility fractures have recently been incorporated into this collection^{8,9}.

Fragility fractures are those caused by a low impact, such as a fall from a height corresponding to standing, mainly in the humerus, wrist, vertebrae and hip¹⁰. Fragility fractures can be seen as a minor complication but have a great socio-economic impact due to direct and indirect costs^{11,12}. Moreover, fractures, and specially hip fracture, have been associated with significant decrements in patient's quality of life, functional status and life expectation¹³. In most occasion's the best treatment option for hip fractures is surgical¹⁴. Surgical treatment attempts to recover the function and quality of life of the patient prior to fracture. However, results will depend on age, comorbidity level and patient's previous ambulation¹⁵. Hip fracture surgery techniques are somewhat aggressive and requires expert hands to avoid secondary complications¹⁶ such as excessive intraoperative bleeding, infections or functional dependency¹⁷. Complications in older patients or with a fragile status of health could be fatal¹⁸.

Thus, seeing T2DM as a progressive chronic illness the increased hip fracture risk could have severe consequences in patient's life. However, there is little known on the effect of T2DM status on subsequent post-fracture mortality. The aim of this study was to estimate the impact of T2DM on hip fracture, hip fracture free death, and post hip fracture

mortality (Figure 1) in a large population-based cohort using multi-state^{19,20} models analysis.

Methodology

We conducted a population-based cohort study using data from the SIDIAP Database (www.sidiap.org). SIDIAP is an anonymized clinical database that contains information as coded by general practitioners in primary care practices in Catalonia, Spain. SIDIAP is representative of the overall population covering more than five million participants (80% of the Catalan population)²¹. SIDIAP is a validated source of information for epidemiological research and has been previously used to study T2DM as well as for fragility fractures^{8,22–24}.

Eligible participants were men and women aged between 65 and 80 years with a diagnosis of T2DM on 1 January 2006. Up to two non-T2DM individuals, per each T2DM participant included, were matched by year of birth, sex, and primary care facility. All participants were followed up from 1 January 2006 until the earliest of death, transfer out/migration or end of study (31 December 2013).

Main outcomes were incident hip fracture and all-cause mortality. The date of hip fracture was defined as the date general practitioners registered the date of the event in SIDIAP. The date of death was defined as the date of death in the Spanish Mortality Register linked to SIDIAP database. Socio-demographics data, time from T2DM onset, diagnoses as coded using International Classification of Diseases, Tenth Revision [ICD-10] and clinical measurements amongst other clinical information were also included in the database. A validated list of ICD10 codes were used to identify T2DM status, hip fracture, death and confounding factors²².

Statistical analysis

Baseline characteristics of T2DM and non-T2DM participants were described using mean and standard deviation for continuous variables and frequencies for categorical variables. We used Multi-state¹⁹ models to compare several transition risk in T2DM and non-T2DM participants. Multi-state are time-inhomogeneous Markov processes, where the future state of an individual at time t only depends on the current time s (where $s < t$) and on individual's state²⁵. A progressive illness-death model without recovery was planned (Figure 1) with the following transitions states: baseline to hip fracture, baseline to hip fracture free death and hip fracture to death (i.e. post-fracture mortality). Multi-state models allow simultaneous modelling of these different transitions, and estimate cause-specific hazard ratio (HR), cumulative hazards and transition probabilities. Potential confounders considered for adjustment were those known clinically relevant for hip fracture risk such as: age, sex, previous major osteoporotic fracture and previous glucocorticoids use; and for death risk in T2DM and post hip fracture such as: previous nephropathy, previous ischemic heart disease (IHD); previous cerebrovascular disease (CVD). All confounding factors were measured at baseline except age which was treated as a time dependent factor.

Results from the models were presented as cause-specific hazard ratios for hip fracture, hip fracture free death, and post hip fracture death according to T2DM status. Graphs of cumulate incidence functions of each state: death, hip fracture and no event until end of follow up were also presented. All analyses were stratified by sex, which otherwise violated proportionality of hazards (PH). PH assumption was tested graphically with the log-log plot of survival and analytically with the test of proportional-hazards. 95% confidence intervals were reported for all estimates. Statistical significance was defined

at the $P < 0.05$ level. All statistical analyses were conducted using R version 3.4.5 for Windows using the mstate package.

Results

A total of 45,313 people aged between 65 and 80 years with a diagnosis of T2DM on 1 January 2006, and 88,729 matched non-diabetic were eligible. Individuals not diagnosed of T2DM who were either users of anti-T2DM drugs or with two measures of glycated haemoglobin above 6.5% were excluded. Individuals with a recorded hip fracture or death on index date were excluded, irrespective of T2DM. Participants that ended unmatched (i.e. with no matched peer remaining) because of the above exclusion criteria were also excluded. Finally, a total of 44,802 T2DM and 81,233 matched non-T2DM participants were included in the study (figure 2). Participants were followed for a median (inter-quartile range) of 8 (7.3 to 8) years representing a total of 880,867 person-years (p-y) of observation: 304,538 p-y T2DM and 576,329 p-y non-T2DM.

In table 1 baseline demographic and clinical characteristics of study participants are described stratified by T2DM status. Participants with T2DM had a higher prevalence of obesity, cataracts, cardiovascular disease, neuropathy and nephropathy and non-T2DM participants had a higher prevalence of anti-osteoporosis drugs and calcium + vitamin D complements. But similar prevalence was observed in terms of previous osteoporotic major fracture or glucocorticoids prescriptions.

A total of 23,818 participants (10,745 T2DM and 13,073 non-T2DM) died hip fracture free. Median time to death was 4.2 (interquartile range 1.9 to 6.2) years. Unadjusted mortality rates (in hip fracture free participants) in T2DM participants was 36.1 [95%CI 35.4 to 36.7] per 1000 p-y and 23.0 [95%CI 22.6 to 23.4] per 1000 p-y for non-T2DM. In figure 3a mortality rates are presented per age and T2DM status in men and women.

A total of 3,317 participants (1,424 T2DM and 1,893 non-T2DM) suffered an incident hip fracture in the study period. Median (IQR) time from baseline to hip fracture was 4.8 (2.9 to 6.5) years. Unadjusted hip fracture incidence rates in T2DM and non-T2DM participants were 4.7 [95%CI 4.4 to 4.9] per 1000 p-y and 3.3 [95%CI 3.1 to 3.4] per 1000 p-y respectively (figure 3b).

Of those 3,317 participants who broke a hip, 838 (428 T2DM and 410 non-T2DM) subsequently died. Median (IQR) time from hip fracture to death was 1.5 (0.6 to 3) years. Unadjusted mortality rates in those participants who broke a hip were 66.5 [95%CI 60.4 to 73.0] per 1000 p-y and 46.8 [95%CI 42.2 to 51.5] per 1000 p-y for T2DM and non-T2DM participants respectively (figure 3c).

Multi-state Cox model results are presented in tables 2, which show the estimated HR, unadjusted and adjusted, for each transition, stratified by sex. After adjusting for age, previous IHD, previous CVD, previous major fracture, previous nephropathy, corticoids prescriptions, calcium + vitamin D and anti-osteoporosis drugs, T2DM men had a 32% higher hip fracture free mortality risk, and a 24% excess risk of hip fracture, compared to matched non-T2DM during follow-up. In addition, T2DM men were at a 28% higher risk of dying after suffering a hip fracture. After adjusting for the same risk confounders, T2DM women appeared at a 72% higher risk of hip fracture free death, at a 48% more risk of hip fracture, and at a 57% excess risk of post hip fracture mortality during the follow-up period.

Cumulative incidence functions for each transition can be obtained from multi-state models. Thus, for a referent participant it is possible to estimate the probability of being in each transition state (Figure 4). Given 1000 T2DM women aged 72 and with none of the adjusting factors (previous IHD, previous CVD, previous major fracture, previous

nephropathy, corticoids prescriptions, calcium + vitamin D and anti-osteoporosis drugs) 5 years later from index date 14 would broke a hip and remain alive, 3 would broke a hip and die, 83 would die hip fracture free and 900 would remain alive without fracturing (Figure 4). Also, given 1000 T2DM men aged 72 years and with none of the adjusting factors 5 years later from index date 5 would break a hip and remain alive, 2 would break a hip and die, 140 would die hip fracture free and 853 would remain alive without fracturing. Nonparametric estimates of cumulative hazards of the three transitions show also that T2DM participants respect non-T2DM had higher risks for hip fracture, death hip fracture free and death after hip fracture (supplemental figures).

Discussion

This population-based cohort study shows that T2DM participants were at higher risk of death, of hip fracture and of dying after suffering a hip fracture than matched non-T2DM participants. Estimated event probabilities at 5 years suggest that the risk of a hip fracture in T2DM participants is not negligible and neither the subsequent death risk. To our knowledge, this study is the first to explore simultaneously the competing role of death on the relationship of T2DM and hip fracture, and the impact of hip fracture on death risk in T2DM participants.

Excess mortality in T2DM participants is well-known and mainly associated to a higher risk to develop cardiovascular disease, blindness, kidney failure, and lower limb amputation. A recent meta-analysis²⁶ of 35 studies about mortality in T2DM participants showed an 85% increase risk for all-cause mortality (pooled HR 1.85, 95% CI: 1.79–1.92). In men excess of mortality was 57% and two-fold increase in women. In our study this excess of mortality was similar as it was 40% in men and 85% in women.

Different systematic reviews and meta-analyses of observational studies have found a positive association between T2DM and hip fracture with a high variation in estimated effect: Janghorbani et al²⁷ found a two-fold increase of hip fracture risk in T2DM men compared to non-T2DM, and almost three-fold increase of hip fracture risk in T2DM men compared to non-T2DM; Jia et al²⁸ found an 8% increase of hip fracture risk in T2DM participants compared to non-T2DM; Moayeri et al²⁹ found a 20% increase of hip fracture risk in T2DM participants compared to non-T2DM; Dytfeld et al³⁰ have also shown that postmenopausal women with T2DM have higher hip fracture risk with a 30% increase compared to non-T2DM. Furthermore, a significant heterogeneity was found between studies in each meta-analysis. Explanations of this heterogeneity were in part due to differences on participant's age, duration of diabetes, differences on follow-up and local hip fracture incidence. Another key point is the role of death as a competing event, especially in older participants, largely unaccounted for in previous studies. A recent study has found that hip fracture risk in T2DM individuals has been overestimated due to the competing effect of death³¹.

Mortality after hip fracture has been described before in general population^{32–35}. In these studies, key preoperative characteristics associated with the risk of mortality up to 12 months were age, male gender, previous fracture functional status and some comorbidity as dementia or cognitive impairment, diabetes, cancer, chronic obstructive pulmonary disorder and cardiac disease. Risk for death was found largely dependent on age. However at any given age, excess of mortality after hip fracture was found higher in men than in women. In these studies, diabetes was identified as a risk factor in three studies^{18,36,37} and conclusion was that T2DM have a 44% excess risk of death compared to non-diabetic peers along the first year after hip fracture (pooled HR 1.44, 95% CI: 1.13 to 1.82). Our results are largely consistent with these published studies.

A relevant association between some anti-diabetic drugs and fracture risk has been described earlier^{38,39}. Further research on the role of anti-diabetic drugs in transition risks could be of great interest. Ferrari et al⁴⁰ have recently proposed an algorithm for the management of bone fragility in diabetic subjects. The authors suggest treating all diabetic subjects with a previous history of hip, vertebral or with two or more other fragility fractures. They also defend the use of a lower threshold for T-score and a modified version of FRAX to estimate 10-year risk to identify and treat diabetic subjects at increased fracture risk. Our findings, especially on increased death risk after a hip fracture, support these efforts to identify those subjects at increased fracture risk to prevent these from happening.

Individuals with serious chronic illness such as T2DM can experience different relevant events along progression. Assumptions need to be made about dependencies between events. Standard survival analysis involves the analysis of time to an event. Whatever was this event any other event that precludes the interest event can bias results⁴¹. Multi-state analysis¹⁹ adds complexity by allowing the analysis of several events for the same individual. Application of multi-state analysis is sparse in T2DM medical literature. Ting-Shuo et al⁴² used multi-state models to investigate in chronic hepatitis C virus-infected participants the effect of T2DM on the development of hepatocellular carcinoma (HCC) and all-cause mortality after HCC.

Our study has some limitations. The data come from primary care records and no validation of each individual fracture was done and ICD-10 does not distinguish between traumatic and fragility fractures. However, in SIDIAP coding of fractures has been compared to hospital databases and shown to be highly specific (>95% for all fracture sites tested) and moderately sensitive (almost 70% for hip fractures)²³. This cohort was

restricted to individuals older than 65, which imposed a left truncation to the observed time. Also, T2DM patients included prevalent cases, with a variable time of disease duration, and a higher prevalence of obesity, cardiovascular risk, and a lower prevalence of use of anti-osteoporosis drugs and calcium + vitamin D supplements. Obesity is a well-known risk factor for the development of T2DM⁴³, and it is therefore not surprising that it was more commonly seen in our T2DM cohort. Similarly, cardiovascular disease is a known complication related to diabetes, and appeared to be more prevalent in the T2DM population⁴⁴. Additionally, a lower prevalence of antiosteoporosis drugs and calcium/vitamin D supplements has been described in the T2DM previously⁴⁵. This may be related to the underestimation of fracture risk in these subjects, and to the lack of evidence available on their anti-fracture effectiveness in diabetic patients⁴⁶. We adjusted for all these factors in our analysis, but yet residual confounding and related bias could persist due to misclassification or incomplete data in the estimation of the hazard ratios for mortality and death according to T2DM status. It is however also true that some of these factors could be in the causal pathway in the association between T2DM and these events, and over-adjustment would not be desirable either.

Moreover, a recent work has described that 4 in 5 major fractures recorded in SIDIAP are due to fragility, with higher proportions for hip (92%) and vertebral (88%) fractures²². Residual confounding is possible in our study, as some potential risk factors for fracture such as bone mineral density or parental hip fracture history were not available in the database. However, T2DM participants are being associated with a higher bone mineral density⁴⁷.

In summary, we conclude that T2DM participants are at higher risk of hip fracture free death, hip fracture and post hip fracture death and all these risks are higher in women.

Multi-state analysis is a useful technique to analyse, compare and estimate risks in progression chronic illness. Use of this methodology to assess and compare effectiveness of different therapeutic strategies (on men and women) on all these risks transitions is a must.

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Cristian Tebé and Daniel Prieto-Alhambra designed the study, performed data management, statistical analysis, and drafted the paper. Daniel Martínez-Laguna, Cristina Carbonell-Abella, Carlen Reyes, Victor Moreno, Adolf Diez-Perez and Gary Collins supervised epidemiological/analytical aspects, participated in the discussion and interpretation of results, and reviewed and critically edited the paper. All authors read the final version and approved submission.

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