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Risk of fracture associated with states prior to the diagnosis of diabetes mellitus type 2: Nested case-controlled study (DIAFOS cohort)

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Summary
Background: In phases prior to the diagnosis of diabetes mellitus type 2 there is an increased risk of cardiovascular disease, but it is not known if this is the case in relation to the risk of fractures.
Objective: To compare the prevalence of fracture in cases of diabetes mellitus and in matched controls.
Material and method: Nested case-control study in a population-based cohort. All patients diagnosed with type 2 diabetes in the period 2006-2011 were included, as were, for each of these patients, two control subjects of the same age, gender, and from the same medical centre, without diabetes. Any fractures, cerebro-vascular accidents and ischemic cardiopathy prevalent in these patients were identified using ICD codes 10. The prevalence of osteoporotic, major and hip fractures, and of cardiovascular disease at the time of diagnosis for the diabetic subjects, and on the same date for the matched controls, were calculated. Using conditional logistical regression the odds ratios (OR) were calculated, adjusting for body mass index, smoking, alcoholism, use of statins, cardiovascular disease and diabetic complications.
Results: 58,931 diabetic patients and 117,862 controls were identified. At the date of diagnosis the diabetic patients had a higher prevalence of cerebro-vascular accident (4.9% vs 3.5%; p< 0.001) and ischemic cardiopathy (8.1% vs 4.7%; p< 0.001). On the other hand, the prevalence of osteoporotic fracture (2.8% vs 2.7%; p= 0.22), hip fracture (0.4% vs 0.4%; p=0.63) and major fracture (1.5% vs 1.5%; p=0.97) was similar in both groups. The adjusted ORs were: 1.2 (CI 95%: 0.96-1.09), 1.08 (CI 95%: 0.90-1.28), and 0.99 (CI 95%: 0.91-1.09), respectively.
Conclusions: The type 2 diabetic patients had a higher prevalence of cardiovascular disease at the time of diagnosis. However, their risk of fracture was similar to the non-diabetic control subjects.

Key words: diabetes mellitus type 2, osteoporotic fractures, cardiovascular disease, prevalence.
Introduction
Diabetes mellitus and osteoporosis are two diseases which are highly prevalent in our environment. According to the estimates of the International Diabetes Federation, nearly 245 million people suffered from diabetes mellitus type (DM2) in 2006. The prevalence of DM2 in adults in Spain varies between 12 and 15%. Similarly, the overall prevalence of osteoporosis in our environment is 12.7% in women and 4.15% in men.

Although the relationship between diabetes mellitus and cardiovascular disease is well known, less data is available regarding the possible relationship between DM2 and osteoporosis. Different epidemiological studies indicate an increase in bone mass in type 2 diabetic patients while contrary to what would be expected, there is an increased risk of fracture, both in the femur and the vertebrae and other locations.

According to the natural history of DM2, patients may pass through an average of 5-10 years in a number of prior states characterised by alterations in carbohydrate metabolism: pre-diabetes. What is meant by pre-diabetes is those intermediate situations between normality and diabetes. Two states may be distinguished: impaired glucose tolerance (IGT), defined by the American Diabetes Association (ADA) as a value of glycemia after an oral glucose tolerance test with 75 g of glucose taken orally; and impaired fasting glucose (IFG) defined as a baseline glycemia of between 100 and 125 mg/dl. What is meant by pre-diabetes is those intermediate situations between normality and diabetes. Two states may be distinguished: impaired glucose tolerance (IGT), defined by the American Diabetes Association (ADA) as a value of glycemia after an oral glucose tolerance test with 75 g of glucose taken orally; and impaired fasting glucose (IFG) defined as a baseline glycemia of between 100 and 125 mg/dl. Although they should not be considered to be diseases, these pre-diabetic states are associated with an increased cardiovascular morbimortality, which is greater in patients with IGT than in those with IFG. There is little data available on the risk of fracture in these states; the Rotterdam study showed that those patients with IGT had a significant reduction in the risk of fracture.

As a consequence, this study was designed with the objective of analysing the prevalence of fractures at the time of diagnosis of DM2 in a population-based cohort.

Material and method
This is an nested case-controlled study in a population-based cohort (DIAPOS cohort). The data were obtained from the SIDIAP database, which contains the clinical information recorded by primary care doctors working in the Catalan Institute of Health (Instituto Catalán de la Salud (ICS)), the main provider of health services in Catalonia, as well as pharmacy invoice data, analysis data from reference laboratories and reports from hospitals in the public health system. This database includes information from approximately 5.8 million patients (approximately 80% of the Catalan population). After a quality control, information from almost 5 million people was available, demographically representative of this population. The quality of the information which SIDIAP contains has been validated; earlier studies validated the records of incidents of fracture in comparison with classical cohorts and the data related to the records of DM2.

From all the patients included in SIDIAP, those who had a diagnosis of DM2 in a period between 01/01/2006 and 31/12/2011 were identified, using the CIE codes 10. From all those diabetes-free (types 1 and 2) SIDIAP participants two controls per case were randomly selected, matched by year of birth, sex and health centre.

Data was collected regarding descriptive variables: age, sex, body mass index, presence of complications associated with diabetes mellitus (cata-racts, nephropathy and diabetic neuropathy), smoking (smoker, non-smoker, ex-smoker), alcohol consumption (in average units of weekly consumption, classified as: low risk consumption, when in men it was between 17 and 28, or in women, between 11 and 17 units; risky consumption, when in men it was higher than 28 and in women higher than 17 units) and use of statins (ATC codes C10AA1 to C10AA08). The presence of ischemic cardiopathy (stable angina, unstable angina or myocardial infarction) and cerebrovascular disease (cerebral infarction or transitory ischemic accident) at the time of diagnosis with DM2 using CIE codes 10. In addition, all the clinical fractures recorded in the computerised clinical history prior to the diabetes mellitus diagnosis were collected by means of a review of CIE codes 10; The SIDIAP database does not contain imaging test information, for which reason it was not possible to radiologically confirm the fractures. Three different types of fracture were distinguished: osteoporotic fractures (in any location except fingers or toes, face or cranium); major fractures according to FRAX (hip, wrist, forearm, humerus and vertebrae) and hip fracture.

Statistical analysis
The characteristics of the population studied were described by means of a descriptive univariate analysis, calculating the mean and standard deviation for continuous variables and absolute frequency and percentage for categorical variables. To compare the prevalence of cardiovascular disease and of fracture in both groups the chi squared test was used. Using conditional logistic regression the unadjusted odds ratios were calculated for cardiovascular disease and fractures, and adjusted for the following confusion factors defined a priori according to the available literature and biological plausibility: body mass index, smoking, alcoholism, use of statins, cardiovascular disease, cataracts, nephropathy and diabetic neuropathy. All the statistical tests were carried out with a confidence (CI) of 95% and assuming a bilateral contrast.

The SIDIAP database provided purely observational data for this study. The SIDIAP data are totally anonymous and identified by an internal code created at the time of incorporation of the data, a fact which makes impossible the identification of the subjects included in the study. The approval was obtained of the local ethics committee for clinical research (CEIC IDIAP Jordi Gol).
Table 1. Baseline characteristics of the patients with DM2 (cases) and of the patients without DM2 (controls)

<table>
<thead>
<tr>
<th></th>
<th>Cases DM2</th>
<th>Matched controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>58,931</td>
<td>117,862</td>
<td></td>
</tr>
<tr>
<td>Age in years. average (SD)</td>
<td>62.79 (11.97)</td>
<td>62.80 (11.97)</td>
<td>0.896</td>
</tr>
<tr>
<td>Men. N (%)</td>
<td>33,562 (56.6%)</td>
<td>66,724 (56.6%)</td>
<td>1</td>
</tr>
<tr>
<td>Women. N (%)</td>
<td>25,369 (43.4%)</td>
<td>51,138 (43.4%)</td>
<td>1</td>
</tr>
<tr>
<td>Overweight patients. N (%)</td>
<td>19,169 (32.5%)</td>
<td>31,962 (27.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Obese patients. N (%)</td>
<td>26,472 (44.9%)</td>
<td>23,673 (20.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients with moderate alcohol consumption and risk. N (%)</td>
<td>19,651 (33.5%)</td>
<td>28,298 (24%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Active smokers. N (%)</td>
<td>10,228 (17.3%)</td>
<td>17,342 (14.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous cataract patients. N (%)</td>
<td>3,849 (6.5%)</td>
<td>7,333 (6.2%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Patients with prior renal disease. N (%)</td>
<td>6,546 (11.1%)</td>
<td>9,469 (8.03%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients with previous diabetic neuropathy. N (%)</td>
<td>295 (0.5%)</td>
<td>128 (0.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients receiving statins. N (%)</td>
<td>26,071 (44.2%)</td>
<td>29,535 (25.1%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Results

58,931 patients were diagnosed with DM2 between 01/01/2006 and 31/12/2011, and 117,862 matched controls were selected. In Table 1 the baseline characteristics of both cohorts are described, which were, as to be expected, same sex and similar age, but with a higher proportion of patients who were obese or overweight, smokers and receiving statins among the diabetics.

In relation to the presence of cardiovascular disease at the time of diagnosis, 4,799 (8.1%) cases and 5,535 (4.7%) controls had ischemic cardiopathy prior to the index date (p<0.0001); and 2,895 (4.9%) and 4,125 (3.5%), respectively, had cerebrovascular disease (p<0.0001). The corresponding ORs were 1.79 (95% CI: 1.73-1.87; p<0.0001) for ischemic cardiopathy and 1.42 (95% CI: 1.36-1.49; p<0.0001) for cerebrovascular disease.

The prevalence of osteoporotic fractures, major and hip, was similar and without statistically significant differences (Table 2). Those patients with DM2 had at the time of diagnosis a similar risk of fracture to the non-diabetic controls (Figure 1). The adjusted ORs were: for osteoporotic fractures, 1.02 (95% CI: 0.96-1.09; p=0.46); for major fractures, 0.99 (95% CI: 0.91-1.09; p=0.93); and for hip fracture, 1.08 (95% CI: 0.90-1.28; p=0.39).

In analysing patient sub-groups according to their exposure to tobacco, use of statins or degree of control of the DM2 starting (defined by HbA1c <7% or ≥7%), no statistically significant differences in the risk of osteoporotic fractures, major or hip, were observed (Table 3). Those patients with an initial HbA1c above 7% have a risk of fracture of the femur very close to being statistically significant (adjusted OR=1.30; 95% CI: 0.96-1.75; p=0.09).

Discussion

The patients with DM2 have an increased risk of around 70% and 40% of ischemic cardiopathy and cerebrovascular disease respectively, compared with the matched controls. A recent meta-analysis15 of patients with pre-diabetes (including patients with IGT and IFG) concluded that these have an increase of 26% in cerebrovascular disease (RR=1.26; 95% CI: 1.10-1.41; p<0.001). A study of patients with IFG16, according to the criteria of the ADA (American Diabetes Association), found and increase in the risk of ischemic cardiopathy in women (OR=1.70; 95% CI:1.0-3.0; p=0.049).

However, according to the results of our study, the patients with DM2 did not have a higher probability of suffering a fracture (major or hip osteoporotic fracture) than the rest of the population at the time of diagnosis with diabetes. This suggests that the increase in risk associated with DM2 does not appear in the initial phases of the disease but with the development of the disease itself.

The mechanism by which DM2 favours the appearance of fractures is not clearly defined, even though different substances have been described which have a crucial role in the pathogeny of this association17-18. In carrying out an analysis by sub-groups we have observed that those patients with an initial HbA1c above 7% have a risk of hip fracture at the limit of statistical significance. Previous studies19 show that a degree of deficient metabolic control is associated with higher levels of sclerostin, provoking a risk of fractures. Furthermore, high levels of glucose leads to an accumulation of degradation products in the bone matrix, which results in bone which is biomechanically less strong20. Although our study did not have available data on these substances, it not
having found a higher incidence of fractures at the time of diagnosis of DM2 may support this hypothesis. The temporariness between the association of diabetes and fracture will be the object of a new prospective study in the follow up of the DIAFOS cohort.

As is to be expected, the patients with DM2 at the time of diagnosis have an increased risk of ischemic cardiopathy, as well as cerebrovascular disease, in comparison with the general population. Different epidemiological studies have shown that patients with glucose intolerance have a greater cardiovascular morbimortality\(^2\). Different mechanisms associated with hyperglycemia have been postulated as favouring arteriosclerosis, among which are endothelial dysfunction, oxidative stress and the formation of degradation products\(^3\). It is of interest to note that in the population of patients with DM2 in our study the proportion of patients who were overweight-obese and who were already receiving statins (indirect indicator of the presence of lipid metabolism disorder) was higher than in the controls. This may be explained by the fact that obesity and lipid metabolism disorders favour the appearance of carbohydrate metabolism disorder (impaired fasting glucose, glucose intolerance, diabetes or metabolic syndrome). In addition, the presence of a higher proportion of active smokers among those with diabetes type 2 may increase both the risk of suffering a cardiovascular event and fractures. The use of statins has been associated with a lower incidence of osteoporotic fractures\(^2\), possibly due to the fact that it interferes in the same metabolic pathway, that of mevalonate, on which the bisphosphonates also act. A direct effect of statins has also been demonstrated in vitro in primary cultures of human osteoblasts\(^2\). However, its effects on bone are not very marked and do not, in our opinion, explain the lack of difference in the incidence of fractures. In any case, our analysis was adjusted for this possible confusion factor.

One of the limitations of our study is that the data comes from computerised clinical histories and, differently from the classical cohort study, may be underreported. This may result in bias in the random classification, which may lower the association between the predictor factors and the event of interest. In fact, the record of fractures in SIDIAP has been validated in comparison with the classical cohort studies and hospital discharge databases, and the data have a moderate sensitivity (nearly 70%) and a high specificity (>95%)\(^12\). On the other hand, this study has significant strengths, such as the high number of individuals, which allows the detection of statistically signifi-

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### Table 2. Prevalence of earlier fractures groups in patients with DM2 and those without DM2

<table>
<thead>
<tr>
<th></th>
<th>Cases DM2</th>
<th>Matched controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Osteoporotic fractures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>1,654</td>
<td>3,192</td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>2.8%</td>
<td>2.7%</td>
<td>0.224</td>
</tr>
<tr>
<td><strong>Major fractures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>891</td>
<td>1,785</td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>1.5%</td>
<td>1.5%</td>
<td>0.967</td>
</tr>
<tr>
<td><strong>Hip fractures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>232</td>
<td>482</td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>0.4%</td>
<td>0.4%</td>
<td>0.633</td>
</tr>
</tbody>
</table>

Figure 1. Risk of having a fracture at the time of diagnosis of DM2 (unadjusted OR) according to the location of the fracture

![Risk of having a fracture at the time of diagnosis of DM2](image-url)
cant differences, even in cases where this is very limited. Therefore, we think that the lack of an increase in fractures at the time of diagnosis of DM2 is a consistent finding.

Conclusions
The DIAFOS cohort is made up of a population of patients newly diagnosed with diabetes mellitus type 2 in which the intention is to analyse the association between the diabetes and the presence of fractures. In this first analysis, using a nested case-controlled design within this cohort, we can conclude that at the time of diagnosis the diabetic patients did not have a higher risk of suffering a fracture than the general population, so that it appears to be the case that pre-diabetes does not cause an increased risk of suffering fractures, contrary to what happens with cardiovascular disease. So, these results do not support the need for specific evaluation of the risk of fractures in patients with a diagnosis of DM2 beyond what is normal in the general population.

Conflict of interest: The authors declare that they have no conflicts of interest.

Bibliography