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Use of drugs for osteoporosis treatment in patients with type 2 diabetes mellitus: population-based cohort study

Summary

Objective: Ascertain whether there are differences in the prevalence of osteoporosis drugs in patients with type 2 diabetes (DM2) and non-diabetic patients.

Material and methods: Retrospective cohort study with data from the Information System for the Development of Primary Care Research (SIDIAP), which contains anonymous clinical information from more than 5 million patients in Catalonia. All 50-year-old patients diagnosed with DM2, who were matched with two subjects without diabetes, were selected. Information on descriptive variables, prevalent fractures and the use of osteoporosis drugs grouped in bisphosphonates (BF), calcium and vitamin D supplements (CaD), and any osteoporosis drug (OD) were collected. Through logistic regression, the association between the presence of DM2 and the use of OD was calculated, adjusting for confounding variables.

Results: A total of 166,106 patients with DM2 and 332,212 non-diabetics. The DM2 group presented a higher prevalence of fracture than did diabetics (1.3% vs 0.3%). The use of BF in patients with DM2 was 6.6%, compared to 9.3% in non-diabetics (p<0.001). Of CaD, 9.7% vs 12.3% (p<0.001) and OD, 7.6% vs 10.7% (p<0.001). After adjusting for variable confounders, the patients with DM2 presented a lower probability of being treated with BF (OR=0.67, 95% CI: 0.64-0.68), with CaD (OR=0.71, 95% CI: 0.70-0.73) or with OD (OR=0.66, 95% CI: 0.64-0.67) than non-diabetics.

Conclusions: Despite having a higher prevalence of fractures in patients with DM2, they have more than 30% chance of not having received an OD than non-diabetic patients. This may be attributed to an underestimation of risk in these patients..

Key words: *osteoporosis, bisphosphonates, type 2 diabetes mellitus, epidemiology, general population studies.*

Introduction

Osteoporosis is a disease of bone metabolism characterized by increased bone fragility and fracture propensity. In postmenopausal women, these fractures have been associated with a decrease in bone mineral density (BMD)[1]. However, this correlation with low BMD does not occur in all situations; Patients with type 2 diabetes mellitus (DM2) present an increased risk of fractures, especially femoral fractures[2-4], despite presenting higher BMD values compared to the non-diabetic population that fracture[5,6].

Different mechanisms have been postulated through which the risk of fracture in the diabetic population could be increased. These include some complications associated with DM2 (hypoglycemia, neuropathy, nephropathy and diabetic retinopathy)[7-10] and also associated with an increased risk of falls and, consequently, fractures. Also, some antidiabetic drugs, such as sulfonylureas, glitazones and insulin, have been associated with an increased risk of fractures[11,12]. An increased risk of fractures has also recently been reported in patients treated with a sodium 2-glucose co-transporter inhibitor type 2 (iSGLT-2), canagliflozin. This has not been observed so far with other iSGLT-2[13,14]. Another possible explanation would be the effect of deposition of advanced glycosylation products on bone collagen that may decrease bone strength[15-18].

Different osteoporosis drugs (OD) are available for the prevention of osteoporotic fractures. These have been analyzed in a multitude of clinical trials, varying their effect depending on the drug, the population studied and the location of the fracture. However, there is little information on these drugs in normal clinical practice, especially in diabetic patients[19-22].

If patients with T2DM have a higher BMD than non-diabetics and an increased risk of bills, it seems logical to think that the assessment of the real risk of fractures in these patients is underestimated and, consequently, under-treated. Our objective was to determine if there were differences in the prevalence of osteoporosis drugs among patients with DM2 and non-diabetic patients.

Material and methods

Study design:

Population-based retrospective cohort study with data from the Information System for the Development of Primary Care Research (SIDIAP) (www.sidiap.org). The SIDIAP contains the sociodemographic information, clinical records of primary care physicians working at the Catalan Institute of Health (ICS), the main provider of health services in Catalonia, as well as analytical results and pharmacy billing data. It has information of more than 5 million patients (approximately 80% of the Catalan population). The representativeness of SIDIAP over the general population of Catalonia has been previously demonstrated[23]. Previous studies carried out with SIDIAP in patients with DM2 observed a prevalence of the disease similar to studies done in other parts of Spain[24,25]. Various studies are also available that analyze new predictors of fragility fracture[26-30].

Participants:

There were selected all the subjects of 50 or more years of age by diagnosis of DM2 prevalent or incident between 2006 and 2013, using codes CIE10 (E11.0, E11.1, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.8 and E11.9). For every person with DM2, two nondiabetic subjects were selected of the same sex, age (± 2 years) and from the same health center. Those subjects with no diagnosed DM2 or type 1 were considered non diabetic and not to receive any anti-diabetic medication before being included.

Study variables:

Data on age, sex and some clinical variables were collected: body mass index (BMI), smoking (smoker, non-smoker and former smoker) and alcohol consumption (measured by units consumed per week and classified as: low-risk consumption, when consumption in men is less than 17 units or in women to 11, moderate consumption, when in men is between 17 and 28 units or in women between 11 and 17, and consumption of risk when in men is Higher than 28 units or in women at 17, as defined in the Program of Preventive Activities and Health Promotion)[31]. The presence of ischemic heart disease (stable angina, unstable angina or myocardial infarction) and cerebrovascular disease (cerebral infarction or transient ischemic attack) were evaluated at the time of inclusion, using CIE10 codes. Prevalent fractures were also collected (from any location except face or skull, and fingers or toes). The use of drugs for osteoporosis was grouped into three categories: 1) bisphosphonates (BF), 2) supplements calcium and vitamin D (CaD), and 3) any osteoporosis drug (OD). The Anatomical Therapeutic Chemical Classification (ATC) codes were used for this purpose.

Statistical analysis:

The characteristics of the studied population are described by uni-variate descriptive analysis, calculating the mean and standard deviation for the continuous variables, and the absolute frequency and percentage for the categorical variables. Chi square test was used to compare the prevalence of cardiovascular disease and fractures in both groups. The association between the presence of DM2 and the use of OD was calculated through logistic regression; Was adjusted for the following confounding factors, defined a priori according to available literature and biological plausibility: age, sex, BMI, smoking, alcohol consumption, ischemic heart disease (ICH) or previous cerebrovascular disease (CVD) and previous fractures. All statistical tests were performed with a 95% confidence interval (CI) and assuming a bilateral contrast. The statistical package Stata SE version 12.0 for Mac was used for all analyzes.

Ethical considerations:

SIDIAP provided wholly observational data for this study. The SIDIAP data are totally anonymous and identified by an internal code created at the

moment of data inclusion, so it is impossible to identify the subjects included. Approval was obtained from the local Clinical Research Ethics Committee (CEIC IDIAP Jordi Gol), code P15/150.

Results

We identified 166,106 patients diagnosed with DM2 prevalent or incident between 2006 and 2013, and were matched with 332,212 non-diabetic patients. The baseline characteristics of both cohorts are shown in Table 1. Subjects with DM2 had a higher prevalence of IHD and CVD than non-diabetics. They also had a higher prevalence of previous fractures, in general and by specific locations (Table 2).

Patients with DM2 presented a lower proportion of drug use for osteoporosis, both BF and any OD and also for CaD, statistically significant (p<0.001 in all three situations) compared to non-diabetic patients (Figure 1).

When analyzing the likelihood of receiving a drug for osteoporosis in subjects with T2DM, compared to non-diabetic subjects, the unadjusted odds ratios were 0.67 (95% CI: 0.65-0.68) for BF, from 0.74 (95% CI: 0.72-0.75) for CaD, and 0.66 (95% CI: 0.65-0.68) for any OD.

After adjusting for age, sex, BMI, smoking, alcohol consumption, previous IC or CVD and previous fractures, subjects with DM2 were less likely to be treated with BF (OR=0.67; 95% CI: 0.64-0.68), with CaD (OR=0.71, 95% CI: 0.70-0.73) or with any OD (OR=0.66, 95% CI: 0.64-0, 67) than non-diabetics.

Discussion

Patients with DM2, despite having a higher prevalence of previous fractures, had more than a 30% probability of not receiving a drug for osteoporosis, compared to non-diabetic subjects. As in previous studies, we observed a higher proportion of fractures in patients with T2DM compared to non-diabetic patients, especially at the femur level, where the prevalence was multiplied by four. These data coincide with two recent meta-analyzes where 30% more risk of femur fracture is described in patients with DM2[3,32].

Paradoxically, even with a higher prevalence of previous fractures, patients with DM2 are less likely to be treated with a bisphosphonate, calcium and vitamin D supplements, or with any osteoporosis drug. One possible explanation for these events could be an underestimation of the risk of fracture in these subjects. Although we do not have data in our BMD cohort, previous studies comparing patients with T2DM with non-diabetic patients observed that the former had a higher BMD[5]. Therefore, if the fracture risk assessment is performed exclusively by BMD values, patients with DM2 would be undervalued. Another possibility would be the assessment of fracture risk through the use of tools that allow the calculation of the absolute risk of fracture.

In our area, the most commonly used tool is FRAX®, which does not consider DM2 a risk factor.

Different studies[33,34] support the idea of not using FRAX® in patients with DM2, since at the same absolute risk value calculated by FRAX® patients with DM2 present a greater real risk of fractures than non-diabetic patients[35]. In an analysis of the Manitoba cohort, it was observed that patients with DM2 had a higher proportion of observed fractures than expected, both main and femoral fractures, a fact that did not occur in non-diabetic subjects[36]. A third plausible explanation would be that patients with DM2 receive more drugs than non-diabetics, and this could condition the clinician when prescribing a drug for osteoporosis. Although we do not have the number of drugs that our patients received on average, other studies carried out on patients with DM2 from the SIDIAP database[37] describe medication costing almost double compared to non-diabetic patients and, consequently, a greater number of drugs.

As expected, the DM2 patients in our cohort had a higher prevalence of IHD and CVD than nondiabetic patients, almost double. Some authors suggest that there is a relationship between cardiovascular disease and bone metabolism. A case-control study in subjects with metabolic syndrome observed that patients with a coronary event in the last six months had a higher prevalence of vertebral fracture and of any location compared to subjects who had not had a coronary event[38].

One of the limitations of our study is that the data come from the computerized medical history and, unlike the classic cohort studies, there is no case-by-case validation of each fracture. Previous studies have validated SIDIAP data compared to classic cohort studies and hospital discharge databases, with a moderate sensitivity (close to 70%) and high specificity (>95%)[39]. In addition, the ICD-10 coding does not distinguish between trauma fractures and fragility fractures. A recent validation of a sample of more than 300 fractures recorded in patients >50 years of age on the basis of SIDIAP found that more than 90% of femur fractures, more than 87% of vertebral fractures and more than 80% of fractures The main ones were due to fragility (not related to trauma)[40], which gives greater validity to our data. Another possible limitation is that the data in relation to the prescription are collected from the billing data to Pharmacy, in such a way that there may be a stated prescription not withdrawn at the pharmacy and, therefore, not considered. But this fact would occur in both cases in both DM2 and non-diabetic patients.

In contrast, this study has important strengths such as the high number of individuals included, which allows for the detection of statistically significant differences that in other cohort studies with a smaller sample size would not have been detected.

We consider necessary the search for tools that provide a better estimate of the risk of fractures in patients with DM2. One possibility could be to incorporate DM2 as a risk factor in FRAX® or to have a specific tool for patients with DM2 that takes into account both classic and DM2 risk factors. Another option would be the incorporation

Table 1. Baseline characteristics in paired T2D and non-diabetic patients

Variable	Patients with DM2 (n=166,106)	Non-diabetic patients (n=332,212)	Value of p
Gender ♀; n (%)	79,249 (47.7)	158,498 (47.7)	1
Age; mean ± SD	65,4 ± 11.4	63,8 ± 11.8	<0.001

BMI (kg/m²); n (%)
    <24.99
    25-29.99
    >30
    Losses
	
	17,076 (10.3)
	60,404 (36.4)
	75,923 (45.7)
	12,703 (7.6)
		
		55,088 (16.6)
		112,913 (34.0)
		79,220 (23.8)
		84,991 (25.6)
			<0.001

Smoking; n (%)
    Non smoker
    Smoker
    Former smoker
    Losses
	
	78,593 (47.3)
	23,821 (14.4)
	16,835 (10.1)
	45,857 (28.2)
		
		142,888 (43.0)
		42,736 (12.9)
		26,137 (7.9)
		120,451 (36.2)
			<0.001

Consumption of alcohol; n (%)
    Teetotaler
    Low risk
    Harmful consumption
    Losses
	
	100,203 (60.3)
	42,167 (25.4)
	5,257 (3.2)
	18,479 (11.1)
		
		164,381 (49.5)
		81,081 (24.4)
		8,924 (2.7)
		77,826 (23.4)
			<0.001

CVD previous; n (%)	9,762 (5.9)	10,039 (3.0)	<0.001
IHD previous; n (%)	16,416 (9.9)	13,678 (4.1)	<0.001

♀: women; SD: standard deviation; BMI: body mass index; CVD: cerebrovascular disease; IHD: ischemic heart disease.

Table 2. Prevalence of fractures in patients with T2DM and non-diabetic pairs

Localization	Patients with DM2 (n=166,106)	Non-diabetic patients (n=332,212)	Value of p
Any localization n (%)	4,012 (2.4)	1,732 (0.5)	<0.001
Main fracture* n (%)	2,215 (1.3)	1,055 (0.3)	<0.001
Femur n (%)	609 (0.4)	382 (0.1)	<0.001

* Fracture of hip, wrist, forearm, humerus or vertebral.

of new techniques, such as micro-indentation, which allow the assessment of fracture risk independently of BMD[41,42].

Conclusions

Patients with DM2 are about 30% more likely to not receive bisphosphonate, calcium and vitamin D supplements or any osteoporosis drug than non-diabetic patients. We believe that this lower probability of being treated is due to an underestimation of the real risk of fracture in patients with T2DM, which justifies the need for a specific tool for the estimation of fracture risk in these patients.

Conflict of interest: The authors declare no conflict of interest.

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Figure 1. Use of osteoporotic drugs based on the presence or not of DM2
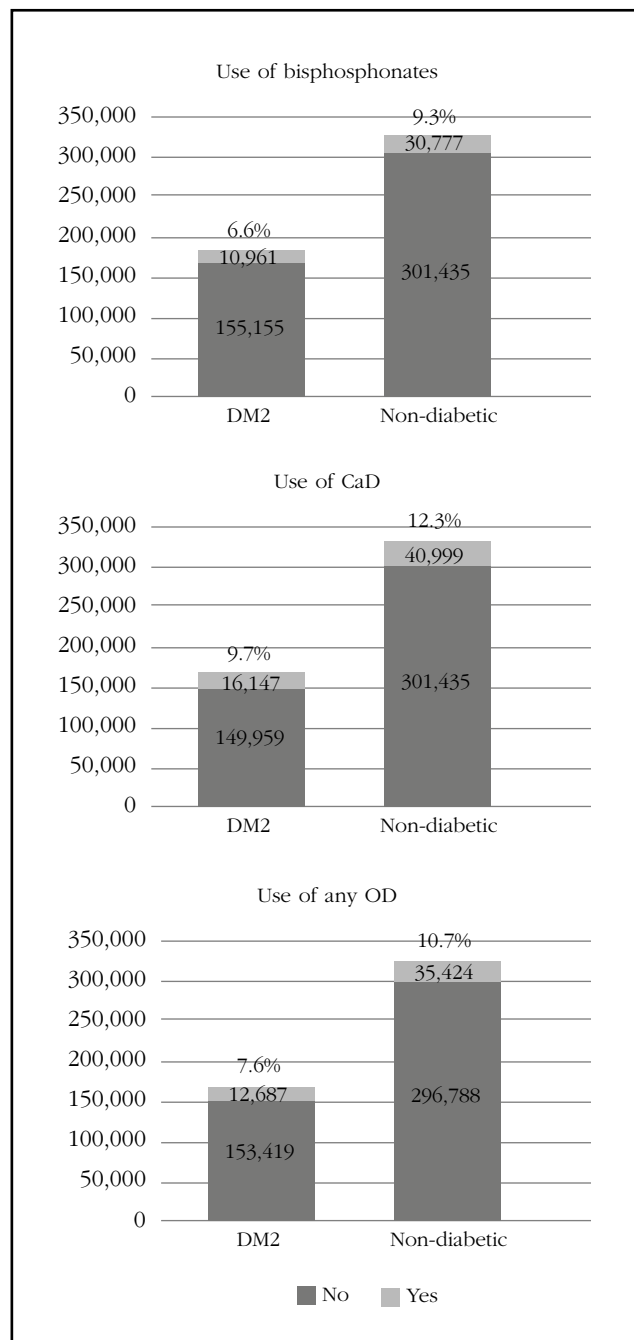
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