Bone 68 (2014) 124–130

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Original Full Length Article

Use of dipeptidyl peptidase-4 inhibitors for type 2 diabetes mellitus and risk of fracture

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ARTICLE INFO

Article history:
Received 16 April 2014
Revised 22 July 2014
Accepted 24 July 2014
Available online 2 August 2014

Edited by: Doug P. Kiel

Keywords:
DPP
Fracture
Diabetes mellitus type 2
Cohort-study
CPRD

ABSTRACT

Introduction: Although patients with type 2 diabetes mellitus have an increased bone mineral density as compared to healthy patients, their risk of fracture is elevated. Incretins, new anti-diabetic drugs, may have a protective effect on bone mineral density. However, data on the effect of incretins on fracture risk are limited. Therefore the aim of this study was to investigate the association between the use of DPP4-I and the risk of fracture.
Methods: A retrospective population based cohort study, using data from the Clinical Practice Research Datalink (CPRD) database (2007–2012), was conducted. Patients ($N = 216{,}816$) with at least one prescription for a non-insulin anti-diabetic drug (NIAD), aged 18+ during data collection, were matched to one control patient. Cox proportional hazards models were used to estimate the hazard ratio of any fracture in DPP4 inhibitor (DPP4-I) users versus controls and versus other NIAD patients. Time-dependent adjustments were made for age, sex, life style, comorbidity and drug use.
Results: The actual duration of DPP4-I use was 1.3 years. There was no different risk of fracture comparing current DPP4-I users to controls (adjusted hazard ratio (adj. HR) 0.89, 95% confidence interval (CI) 0.71–1.13). There was also no increased risk comparing current DPP4-I users to other NIAD users, adj. HR 1.03 (95% CI 0.92–1.15).
Conclusions: DPP4-I use was not associated with fracture risk compared to controls and to other NIAD users. However, the duration of DPP4-I use in our database might have been too short to show an association with fracture risk.

Introduction

Osteoporosis is a common disease and a major public health burden through associated fractures. In 2010, an estimated 2.7 million hip fractures occurred worldwide, of which about 1.8 million were in women [1]. As the incidence of hip fracture continues to increase worldwide, projections indicate that the number of hip fractures occurring in the world each year will rise to 6.26 million by 2050 [2]. Although patients with type 2 diabetes mellitus (T2DM) have an increased bone mineral density (BMD) as compared to controls, their risk of fracture is elevated [3]. This suggests that this elevated risk is due to reduced bone strength or quality. However, some of the anti-T2DM drugs also have been associated with an increased fracture risk, for example thiazolidinediones (TZD) [4–6] and human insulins [7], while others, like metformin have been associated with a reduced fracture risk [8].

In vivo research has shown that glucagon like peptidase - 1 (GLP-1) agonists, a new class of anti-diabetic drugs, might have a beneficial effect on bone [9–11]. This effect might be established by increasing the level of GLP-1 directly (via GLP-1 agonists) or indirectly (via dipeptidyl peptidase-4 inhibitorss) and the GLP-1 receptor which might be present on osteocytes and osteoblasts, as shown in in vitro studies [12,13]. Finally this might lead to an increase in BMD.

Data on the effects of GLP-1 agonists and DPP4-I on fracture risk are limited to a small number of patients and conflicting. A meta-analysis of randomized clinical trials that compared DPP4-Is with a comparator

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http://dx.doi.org/10.1016/j.bone.2014.07.030
8756-3282/

group or placebo confirmed a 40% significant reduction in the risk of fracture [14]. However, this meta-analysis had several limitations: the total number of patients was small ($N = 21{,}055$); there were heterogeneous comparator groups.

In contrast, a study investigating the effect of vildagliptin, a DPP4-I, on bone markers in humans did not show a change in markers representing bone resorption and calcium homeostasis [15]. The possible protective effect of DPP4-I on risk of fracture in humans is not been well established. Therefore the aim of this study was to investigate the association between the use of DPP4-I and the risk of fracture.

Material and methods

Data for this study were obtained from the Clinical Practice Research Datalink (CPRD) in the United Kingdom, previously known as the General Practice Research Database (GPRD) [www.CPRD.com]. The CPRD contains computerized medical records of 625 primary care practices in the United Kingdom, representing 8% of the population. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions, and major outcomes since 1987. Previous studies using CPRD data have shown to be highly valid, with for example for hip fractures over 90% confirmed diagnoses [16].

We conducted a retrospective population based cohort study. The case population consisted of all patients with at least one prescription for a non-insulin anti-diabetic drug (NIAD) and who were aged 18 + during the period of valid CPRD data collection. For this study, data collection started on June 13th, 2007, the date of the first ever prescription of a DPP4-I in CPRD, and ended in August 2012. The index date was defined as the date of the first NIAD prescription since the start of the study period (i.e. the study population was a mix of incident and prevalent NIAD users).

After start of valid data collection a NIAD user was matched by sex, year of birth (within 5 years), and practice to one control. Control patients were patients who never had a prescription of a NIAD or insulin during the entire study period. The index date of the controls was set to the index date of the matched NIAD user and their period of follow-up was divided into intervals of 90 days. Each patient was followed from his or her index date to the end of data collection, the date of transfer out of the practice area, or the patient's death, whichever came first.

The follow-up time of the NIAD users was divided into intervals based on the NIAD and insulin prescriptions, i.e. for every prescription a new interval was created. When there was a washout period of 90 days, an interval was classified as “past NIAD use”, until end of follow-up, or a new prescription of an anti-diabetic drug, whichever came first. Otherwise an interval was classified as “current NIAD use”.

All DPP4-I exposed intervals were classified, according to the time since the most recent prescription, as current (1–90 days), recent (91–180 days), or past (over 180 days) use. At every DPP4-I current use interval, the cumulative prescribed DPP4-I dosage, in sitagliptin dose equivalents, was reviewed and divided by the DPP4-I treatment time (difference in time between the start of the first and last prescription) to estimate the average daily DPP4-I dose. Defined daily doses were used to calculate the sitagliptin dose equivalents [17]. For all current DPP4-I users, a half-year medication possession rate (MPR) was estimated at the date of their latest DPP4-I prescription. The prescribed quantity and the written dosage instruction were used to estimate the duration of treatment. The MPR was determined as the estimated duration of treatment divided by the actual duration (i.e. 182 days). When prescriptions were overlapping, the overlapping days were added to the estimated duration of treatment. A MPR of 80% or more was used as cutoff to categorize patients as compliant (MPR $\geq$ 80%) or not compliant (MPR < 80%).

Patients were followed up from the index date to either the end of data collection, the date of transfer of the patient out of the practice area, the patient's death, or the fracture type of interest, whichever came first. Fractures were classified by use of read codes. We used the following categories to classify fractures: any, hip, radius/ulna, vertebral, and major osteoporotic fracture. A major osteoporotic fracture was defined as a fracture of the hip, vertebrae, radius/ulna or humerus according to the WHO definition [18].

The presence of risk factors was assessed by reviewing the computerized medical records for any record of a risk factor prior to the start of an interval. The following potential confounders were determined at baseline: sex, body mass index (BMI), smoking status and alcohol use. All other risk factors that were considered in this study were determined time-dependently (i.e. at the start of each interval). We considered the following potential confounders: age, HbA1c, falls in 7–12 months before the start of an interval, a history of chronic obstructive pulmonary disease (COPD), previous fracture, rheumatoid arthritis, hypothyroidism, hyperthyroidism, cancer, retinopathy, neuropathy, congestive heart failure and secondary osteoporosis (hypogonadism or premature menopause (<45 year)). In addition, the following drug prescriptions in the 6 months prior to the start of an interval were considered as a potential confounder: oral glucocorticoids, cholesterol lowering drugs, antidepressants, anxiolytics or hypnotics, antipsychotics, anti-Parkinson drugs, antihypertensives (beta-blockers, thiazide diuretics, RAAS inhibitors, calcium channel blockers, loop diuretics), antiarrhythmics, opposed hormone replacement therapy, calcium, bisphosphonates, vitamin D, raloxifene, strontium ranelate, calcitonin, parathyroid hormone, insulin and TZDs.

Regression analysis with Cox proportional hazards models (SAS 9.2, PHREG procedure) was used to estimate the fracture rate of current DPP4-I users compared to control patients (non-NIAD users). This analysis was stratified by major osteoporotic, hip, radius/ulna and clinically symptomatic vertebral fracture, as well as sex and different age categories. As a second analysis the fracture risk of current DPP4-I users was compared to other current NIAD users. The analysis was stratified by major osteoporotic, hip, radius/ulna, and vertebral clinically symptomatic fracture, as well as sex and different age categories. In different analyses we stratified current DPP4-I use by average daily dose, cumulative DPP4-I use and the estimated half-year MPR (low MPR < 80% and high MPR $\geq$ 80%). In all analyses potential confounders were included if they independently changed the beta-coefficient for current DPP4-I exposure by at least 5%, or when consensus about inclusion existed within the team of researchers, supported by clinical evidence from literature.

Results

Table 1 shows the baseline characteristics of the DPP4-I users, the NIAD users, and their matched controls. In total we included 216,816 NIAD users and the same number of controls. The mean age of NIAD users and the controls was 61 years in both groups (standard deviation (SD) 21.0 for both groups). The DPP4-I users were slightly younger at baseline, i.e. 59 years (SD 16.0). The percentage of women was 47.3% within the NIAD user group and the matched controls and 43.0% in the DPP4-I user group. The median follow-up time (from start of follow-up to end of data collection) was 3.7 years (inter quartile range (IQR), 1.61–5.22) and 3.95 years (IQR, 1.79–5.22) for the NIAD users and controls, respectively. The DPP4-I users had a median follow-up time (from the first NIAD prescription until the end of data collection) of 5.0 years (IQR, 2.95–5.16) and a median duration of actual use (from the first DPP4-I prescription until the last DPP4-I prescription) of 1.04 years (IQR, 0.48–1.92).

Table 2 shows that the risk of fracture is similar when comparing the estimated hazard ratio of current DPP4-I use to that of the controls (adjusted hazard ratio (adj. HR) 0.89, 95% confidence interval (CI) 0.71–1.13). Recent DPP4-I users had a significantly increased risk of fracture compared to the controls, adj. HR 1.54 (95% CI (1.08–2.18). The adj. HR of past DPP4-I users was 1.01 (95% CI 0.91–1.13) compared to the controls.