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Use of glucose-lowering drugs and risk of fracture in patients with type 2 diabetes☆

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ABSTRACT

Background: Diabetes mellitus is associated with an increased risk of hip fracture. The aim of this cohort study was to investigate whether glucose-lowering drugs influence the risk of hip fracture in patients with incident diabetes.
Methods: A study was performed on a cohort of patients with incident type 2 diabetes. Diabetes diagnosis was defined using information from the Danish National Patient Registry and reimbursement information of glucose-lowering drugs from the Register of Medicinal Product Statistics. The period of observation was from 01.01.1996 till 31.12.2011. The primary exposure was glucose-lowering drugs and the primary endpoint was hip fracture. Unadjusted, adjusted, and propensity score adjusted Cox regressions were performed.
Results: 5244 patients with type 2 diabetes with a mean follow up of 5.5 years were included in the study. Use of sulphonylureas within the last 90 days was associated with hip fracture in patients with type 2 diabetes, hazard ratio 1.64 (95% confidence interval: 1.54,1.75), whereas ever use of sulohonylyreas was not associated with an increased risk of fractures. Use of sulphonylureas within the last 90 days was also associated with an increased risk of fractures at other sites. Use of glitazones within the last 90 days was associated with an increased risk of hip fracture, hazard ratio 2.07 (95% confidence interval: 1.39,3.07), whereas ever use was not associated with an increased risk.
Conclusions: Current use of sulphonylureas was associated with hip fracture in patients with type 2 diabetes. Speculatively, this may be due to hypoglycemia resulting in falls.

1. Introduction

The risk of a hip fracture is 1.4 fold increased in type 2 diabetes compared to non-diabetes individuals [1]. Bone mineral density and other common fracture risk factors underestimate the risk of hip fracture in patients with type 2 diabetes [2]. Current fracture predictors are inadequate, however diabetes related complications, comorbidities, and medication may explain the increased risk of fracture. Detrimental effects on bone have already been established for women but not men using glitazones [3–6]. Other glucose-lowering drugs have shown neutral effects or opposing associations on fracture outcome. In observational studies metformin is associated with an decreased risk of fracture, whereas sulphonylureas have been associated with both an increased and decreased risk of fracture [7,8]. Insulin use, glucagon like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase IV inhibitors (DPPIV-i) have neutral outcomes in observational studies [7,9,10]. In Randomized controlled trials metformin and sulphonylureas are superior in terms of bone health compared with glitazone [7–15]. In vitro metformin and sulphonylureas are related to increased osteoblast differentiation and GLP-1 is related to decreased osteoclast activity and both drugs may thus be beneficial for the bone [16].

However, based on the current evidence it is difficult to conclude, with the exception of glitazones, whether the specific treatments are beneficial, harmful or have no effect on bone fracture.

The primary aim of this study was to evaluate whether specific glucose-lowering drugs increase the risk of hip fracture in patients with incident type 2 diabetes. Secondary goals were to assess the relationship between use of glucose-lowering drugs and incident type 2 and fractures at other sites than hip.

Abbreviations: (ATC), anatomical therapeutic classification; (CCI), Charlson comorbidity index; (DPPIV-i), dipeptidyl peptidase IV inhibitors; (ICD), International Classification of Diseases; (GLP-1), glucagon like peptide-1; (HR), hazard ratio.

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2. Materials and methods

The study was designed as a population-based cohort study. In Denmark every person is assigned a civil registration number, which is a unique personal identifier that allows linkage between several registries [17]. From 1977 to 1995 all inpatient visits are registered in the Danish National Patient Registry. From 1996 outpatient visits and emergency room contacts are also registered in the Danish National Patient Registry. Diagnoses are coded by the International Classification of Diseases (ICD) 8 in the period 1977–1993 and coded by ICD 10 from 1994 and forward. All ICD diagnosis codes used in this study are displayed in the Supplemental Tables 1 and 2.

2.1. Study population

A cohort of diabetes patients ($n = 501.724$) was defined based on diagnoses from the Danish National Patient Register and reimbursement data from the Register of Medicinal Product Statistics. The validity and capture of the diabetes diagnosis is high [18]. All patients with type 1 diabetes were excluded. Type 1 diabetes was defined by diagnosis of type 1 diabetes from the Danish National Patient Registry, usage of insulin, and no use of other glucose-lowering drugs. A diagnosis of type 2 diabetes was defined by a diagnosis of type 2 diabetes and/or usage of non-insulin glucose-lowering drugs. All individuals with a diagnosis or reimbursement of a glucose-lowering drug before 1996 were excluded to restrict the population to patients with incident diabetes. Patients with a diagnosis of pancreatitis or use of oral glucocorticoids were excluded as they are shared risk factors for diabetes and fracture. Information on diagnoses and drug reimbursements were collected from 01.01.1977 until the censoring date (death, emigration or end of study at the 31.12.2011).

2.2. Exposure

Information on pharmaceuticals was coded by the anatomical therapeutic classification (ATC) system. Information on the ATC codes used is presented in Supplemental Table 3. Individuals who had at least three reimbursements of a glucose-lowering drug were classified as users in order to increase the likelihood that the drug was consumed and that the individual was less likely to be non-adherent due to poor compliance or side effects. Individuals with less than three reimbursements of glucose-lowering drugs were classified as non-users. Reimbursements were recorded for the entire period from index date until end of study (or censoring). Users of glucose-lowering drugs were grouped as ever users or as current users. Current users were defined as an individual with a reimbursement within 30 days, 90 days or six months before end of study (or censoring date). These cut-offs were used because in Denmark, antidiabetic drugs are prescribed in packages for 30 days (GLP-1 receptor agonists), 90 days (sulphonylureas) or longer periods (metformin). Thereby current users would be correctly identified in the analyses. Current users could also have reimbursements before this period and include both chronic and new users. Current users were divided into strata consisting of users who had a reimbursement within the last 30 days, 90 days, or six months. Time-stratified models based on these strata were investigated in order to limit the risk of misclassification of current users as non-users or long-term users.

2.3. Endpoint

The primary endpoint was a hip fracture based on registration in the Danish National Patient Registry. Fracture at major osteoporotic sites (humerus, distal forearm, vertebrae, and hip), forearm, vertebrae, or fracture at any site were secondary endpoints. The coding of a fracture was at the discretion of the discharging physician in the Emergency room for outpatients and the department for in-patients based on X-rays and where appropriate MRI or CT and surgical findings as well as clinical findings. In general the validity of a fracture report is very high. Individuals with an endpoint within the first year after being diagnosed with diabetes were excluded from the analysis in order to reduce possible confounding by other conditions than diabetes and glucose-lowering drugs.

2.4. Follow-up

The cohort was followed from the time of diabetes diagnosis and ended at time of fracture or the censoring date (death, emigration or end of study at the 31.12.2011). The follow-up times reported are equal to the diabetes duration.

2.5. Confounders

Information on confounders was based on ICD and ATC codes from the Danish National Patient Registry and the Register of Medicinal Product Statistics. Diagnoses before end of study or censoring date was used to calculate the Charlson Comorbidity Index (CCI). The CCI consists of major diseases and predict ten-year mortality [19], however we excluded diabetes and diabetes with end-organ damage from the calculations of the CCI as diabetes was a selection criterion and complications were handled as specific exposures. Information on concurrent prescription medicine use was retrieved from the national registry. Age was defined as age at the date of diabetes diagnosis and categorized in 10-year intervals (0–10 years old, 10–20 years old, etc., and >90 years old). Registry-based information on fall- and hypoglycemia-related hospital admissions was included in the analyses. In the models each glucose-lowering drug was included separately in order to adjust for multiplicity of glucose-lowering drugs used by patients in clinical practice.

2.6. Statistical analysis

Unpaired *t*-test was performed to compare characteristics of patients with and without hip fracture. Bartlett's test determined whether or not an unequal variance should be used. Hazard ratios (HR) for primary and secondary endpoints were calculated using Cox regression models. Proportionality was tested before modeling of any of the Cox regressions, and both unadjusted and adjusted analyses were conducted. Adjustment was performed by age (10 year categories), sex, previous major osteoporotic site fracture, CCI, neuropathy, retinopathy, nephropathy, previous hypoglycemic events, falls, an alcohol related diagnosis, use of either statin, antihypertensive, thiazide, loop diuretic, potassium saving diuretic, combination drug of diuretics, antipsychotic, calcineurin inhibitor, and ever/current use of glucose-lowering drugs. Sensitivity analyses were conducted for ever users and by the current user strata of glucose-lowering drugs. Furthermore, sensitivity analyses were conducted using A) collection of one reimbursement as the definition of a user and B) newly started users defined as those who had collected the first reimbursement within 90 days of the end of study (or censoring date). Gender stratified analyses were also performed. To further disentangle the associations of different sulphonylureas subanalyses were performed on these. For the primary endpoint, a sub-analysis including only current users of metformin was performed in order to assess the effect of treatment with metformin in combination with other glucose-lowering medication on the risk of a hip fracture. The analysis was based on metformin users in order to distinguish between potential effects on hip fracture risk of additional glucose-lowering treatment with glitazones, sulphonylureas, GLP-1 receptor agonists, DPPIV-I, and insulins as second in line glucose-lowering drugs on the effects on the risk of fracture.

Propensity score adjustment reduces the bias by confounding [20]. In the statistical analysis of observational data, propensity score attempts to estimate the effect of a treatment or other intervention by accounting for the covariates that predict receiving the treatment. The