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Original Investigation

Proton Pump Inhibitor Use and Risk of Hip Fracture in Kidney Transplant Recipients

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Background: Posttransplantation bone disease is a significant problem, with few well-evidenced therapeutic options. Proton pump inhibitors (PPIs) are associated with hip fracture in the general population and are widely prescribed for kidney transplant recipients.

Study Design: A case-control study.

Setting & Participants: From the US Renal Data System, we identified from diagnoses and procedures 231 kidney transplant recipients with a first hip fracture. Cases were matched at the hip fracture index date with 15,575 controls on age, sex, race, and transplantation year.

Predictor: PPI use.

Outcomes: First hip fracture.

Results: In the year prior to the index date, a PPI was prescribed to 65.4% of cases and 57.4% of controls. Additionally, in 34.6% of cases and 28.9% of controls, a PPI was prescribed for >80% of the year preceding the index date (higher PPI users). Unadjusted ORs of hip fracture associated with any and higher PPI use were 1.55 (95% CI, 1.18-2.05) and 1.65 (95% CI, 1.2-2.27), respectively. When adjusted for baseline demographic, clinical, and pharmacologic covariables, any and higher PPI use remained associated with hip fracture, with ORs of 1.39 (95% CI, 1.04-1.84) and 1.41 (95% CI, 1.02-1.95), respectively.

Limitations: Potential residual confounding through either incorrectly ascertained or unavailable confounders; cohort limited to Medicare beneficiaries receiving low-income subsidy.

Conclusions: In summary, PPI use was associated with hip fracture risk in the US kidney transplant population.

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INDEX WORDS: Proton pump inhibitor (PPI); omeprazole; kidney transplantation; hip fracture; end-stage renal disease (ESRD); drug safety; peptic ulcer prophylaxis; renal transplant recipient; bone disease; modifiable risk factor; outcomes; case-control; US Renal Data System (USRDS).

Hip fracture is associated with increased mortality, decreased mobility, and loss of independence.[1-3] Patients with end-stage renal disease have a considerably elevated risk for hip fracture compared with the general population,[4] and the years immediately following kidney transplantation are an especially high-risk period.[5] Several factors likely contribute to the risk for hip fracture following successful kidney transplantation and include pre-existing chronic kidney disease−associated mineral bone disease, corticosteroid exposure, and osteoporosis.[6]

Many transplantation centers prescribe proton pump inhibitors (PPIs) as peptic ulcer prophylaxis early posttransplantation. However, a significant proportion of kidney transplant recipients remain on PPI therapy beyond the immediate posttransplantation period. Omeprazole alone is the 7th, 6th, and 5th most prescribed drug in years 1, 2, and 3 posttransplantation, respectively.[7] PPI use has been linked to increased fracture risk in the general population.[8,9] However, to our knowledge, no evidence exists specifically linking PPI use and hip fracture risk in the kidney transplantation population. In the present study, we challenged the null hypothesis of no association between PPI use and posttransplantation hip fracture in a contemporary cohort of US kidney transplant recipients.

METHODS

Source Population and Study Design

The source population was defined as all first-time kidney transplant recipients recorded and contributing person-time to the US Renal Data System (USRDS) while having a functioning

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kidney transplant January 1, 2007, to December 31, 2011. The USRDS contains detailed data from the United Network of Organ Sharing and all Medicare claims for eligible patients insured through this federal program. Therein, we conducted this study using a retrospective nested matched case-control design. Hip fracture events were identified using a primary inpatient *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnosis code of 820.xx or 821.xx. We further required that patients have a claim for *ICD-9* procedure codes 78.55, 79.15, 79.35, 81.52, 81.51, 79.05, 79.25, or 81.40 within 7 days of hip fracture diagnosis (Table S1, available as online supplementary material). For each case, the index date was defined as the date of hip fracture diagnosis. Controls were matched (without a fixed matching ratio) with at least 1 case at the index date on transplantation vintage (year of transplantation), age (within 3 years), sex, and race (non–African American vs African American). We used this approach in order to be parsimonious and avoid overfitting in our multivariable models because we could not expect to have large numbers of events. Matching on transplantation vintage, age, sex, and race controls for these variables, but precludes estimation of the associations of these factors with the event of interest.[10] However, associations of these factors with hip fracture risk are well established and hence it was not an objective of our study to confirm these associations, but rather to eliminate confounding of the association of interest by these factors.[11,12] Controls were eligible to subsequently become cases (ie, conditional risk set matching). We excluded patients with a history of nonkidney solid-organ transplantation or recorded history of prior hip fracture. We required that all cases and controls have Medicare Parts A and B as their primary payer and Medicare Part D prescription drug coverage with the low-income subsidy for at least 1 year prior to the index date.

Exposure of Interest

PPI use was the exposure of interest. We identified PPI use in the year prior to the index date using Medicare Part D prescription claims. We defined PPI exposure in 3 different ways: (1) any PPI prescription claim in the 365 days preceding the index date; (2) lesser use, defined as pharmacy-dispensed pills covering $<80\%$ of the 365 days preceding the index date; and (3) higher use, defined as pharmacy-dispensed pills covering $\geq 80\%$ of the 365 days preceding the index date.

Covariables

Patient characteristics were abstracted from the USRDS for each patient and included age, sex, race, body mass index, dialysis vintage prior to transplantation, time since transplantation, living (vs deceased) donor transplant, pretransplantation panel-reactive antibody titers ($\leq 80\%$ vs $>80\%$), and acute rejection episodes. We identified the following comorbid conditions that have been shown to be associated with fracture risk (via changes in bone metabolism or fall risk) based on in- and outpatient claims in the year prior to the index date: diabetes mellitus, cardiovascular disease, cerebrovascular disease, arrhythmia, and rheumatologic disease (Table S1[13-15]). We used Medicare Parts B and D claims to identify relevant immunosuppression use in the year prior to index: (1) tacrolimus, (2) cyclosporine, (3) mycophenolate mofetil or mycophenolic acid, (4) azathioprine, (5) mammalian target of rapamycin (mTOR) inhibitor (sirolimus or everolimus), and (6) corticosteroid use. We also identified bisphosphonate use in the year prior to the index date using Medicare Part D prescription data because prescription of bisphosphonates may occur in particular high-risk patients and is often accompanied by PPI coprescription.

Statistical Analysis

Differences between the case and control groups were evaluated using univariate conditional logistic models after controlling for the case-control matched groups (Table 1). To assess for case-control imbalance, we computed the mean difference between cases and controls within each case-control group for continuous variables and calculated the average proportion of discrepant cases for binary variables (Table S2).

The association of hip fracture with prior PPI use was estimated using both unadjusted and multivariable conditional (on the matching set of hip fracture event and all matched controls; pair identification) logistic regression and was expressed as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). All baseline variables listed in Table 1 except for those hard matched between cases and controls were included in the multivariable model. We specifically tested for effect modification of the PPI (any use)–hip fracture association by calcineurin inhibitor use given their competing metabolism by the cytochrome P450 3A4 enzyme (CYP3A4) in the liver.[16,17]

About 40% of observations had at least 1 variable missing. We assumed the data to be missing at random and performed multiple imputation to generate 40 imputed data sets.[18] We used a fully conditional specification approach.[19] The imputation model included all variables plus a fixed effect for matching set to account for the fact that specific controls were matched to specific cases.

This study was conducted using SAS software (version 9.3; SAS Institute Inc) and StataMP (version 13; Stata Corp) and approved by institutional review boards at Stanford University (IRB-17904) and Baylor College of Medicine (H-36408). The study was granted a waiver of informed consent.

RESULTS

For 2007 to 2011, we identified 231 cases of hip fracture that fulfilled the stated inclusion and exclusion criteria that were then matched with 15,575 controls. The number of matched controls per case ranged between 1 and 225, with a median of 56 (interquartile range, 29-93). In terms of unmatched baseline characteristics, cases had a higher prevalence of diabetes mellitus, cardiovascular disease, cerebrovascular disease, arrhythmia, and rheumatologic disease, as well as higher steroid, mTOR inhibitor, cyclosporine, azathioprine, and bisphosphonate use (Table 1). Mean differences in age and time since transplantation between case and controls within case-control matched group were 1.7 year and 0.3 year, respectively, reflecting good matching within the prespecified bounds (3 years for age and 1 year for time since transplantation; Table S2).

In the year prior to the index date, 65.4% of cases and 57.4% of controls filled a prescription for a PPI; 34.6% of cases and 28.9% of controls were higher PPI users, having filled PPI prescriptions covering at least 292 of the 365 days ($>80\%$) preceding the index date (Table 2).

Unadjusted ORs of hip fracture associated with any, lesser, and higher PPI use compared to no use were 1.55 (95% CI, 1.18-2.05), 1.45 (95% CI, 1.04-2.02), and 1.65 (95% CI, 1.20-2.27), respectively. In adjusted analysis, hip fracture status remained associated with any and high PPI use, with ORs of 1.39 (95% CI, 1.04-1.84) and 1.41 (95% CI, 1.02-1.95), respectively (Fig 1).