Does Sitagliptin Affect the Rate of Osteoporotic Fractures in Type 2 Diabetes? Population-Based Cohort Study

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Context: Type 2 diabetes and osteoporosis are both common, chronic, and increase with age, whereas type 2 diabetes is also a risk factor for major osteoporotic fractures (MOFs). However, different treatments for type 2 diabetes can affect fracture risk differently, with metaanalyses showing some agents increase risk (eg, thiazolidinediones) and some reduce risk (eg, sitagliptin).

Objective: To determine the independent association between new use of sitagliptin and MOF in a large population-based cohort study.

Design, Setting, and Subjects: A sitagliptin new user study design employing a nationally representative Unites States claims database of 72 738 insured patients with type 2 diabetes. We used 90-day time-varying sitagliptin exposure windows and controlled confounding by using multivariable analyses that adjusted for clinical data, comorbidities, and time-updated propensity scores.

Main Outcomes: We compared the incidence of MOF (hip, clinical spine, proximal humerus, distal radius) in new users of sitagliptin vs nonusers over a median 2.2 years follow-up.

Results: At baseline, the median age was 52 years, 54% were men, and median A1c was 7.5%. There were 8894 new users of sitagliptin and 63 834 nonusers with a total 181 139 person-years of follow-up. There were 741 MOF (79 hip fractures), with 53 fractures (4.8 per 1000 person-years) among new users of sitagliptin vs 688 fractures (4.0 per 1000 person-years) among nonusers ($P = .3$ for difference). In multivariable analyses, sitagliptin was not associated with fracture (adjusted hazard ratio 1.1, 95% confidence interval 0.8–1.4; $P = .7$), although insulin ($P < .001$), sulfonylureas ($P < .008$), and thiazolidinedione ($P = .019$) were each independently associated with increased fracture risk.

Conclusions: Even in a young population with type 2 diabetes, osteoporotic fractures were not uncommon. New use of sitagliptin was not associated with fracture, but other commonly used second-line agents for type 2 diabetes were associated with increased risk. These data should be considered when making treatment decisions for those with type 2 diabetes at particularly high risk of fractures. (***J Clin Endocrinol Metab*** **101: 1963–1969, 2016)**

Type 2 diabetes and osteoporosis are both common and chronic conditions that increase with age and so both conditions often coexist in older adults (1, 2). Furthermore, independent of bone mineral density (BMD) and body mass index, type 2 diabetes itself is a major risk factor for typical osteoporosis-related low trauma fractures of the hip, clinical spine, proximal humerus, and distal radius (collectively referred to as major osteoporotic fractures

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Abbreviations: ACG, adjusted clinical group; BMD, bone mineral density; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; MOF, major osteoporotic fracture; RA, rheumatoid arthritis; TZD, thiazolidinedione.

[MOFs]) (2, 3). Although type 2 diabetes is not yet part of the World Health Organization fracture risk assessment tool (FRAX), most studies suggest that it increases the risk of a fracture by at least 20%–30% (1, 2), an increase in risk on the order of that attributable to rheumatoid arthritis (RA) or a family history of hip fracture (3).

Unfortunately, a series of studies ranging from case-series to randomized trials have recently demonstrated that several treatments for type 2 diabetes, such as insulin or sulfonylureas or thiazolidinediones (TZDs), might further increase the risk of osteoporotic fracture (4–9). The biologic plausibility of this increased risk is best typified by the TZDs, which have been demonstrated in preclinical experiments and randomized trials to decrease BMD and approximately double the risk of fracture (4, 7–9). On the other hand, animal models and mechanistic studies suggest that the dipeptidyl peptidase-4 (DPP-4, inhibitors (including sitagliptin and saxagliptin) might be associated with increased BMD and a decreased risk of fracture (4, 10–14). Indeed, a metaanalysis of all the phase 2 and 3 DPP-4 trials (28 studies conducted in 20 000 patients) demonstrated a 40% reduction in the risk of fractures compared with placebo, although this finding was based on only 63 events and was of marginal statistical significance ($P = .045$) (10). Conversely, a secondary analysis from the SAVOR-TIMI 53 Trial of saxagliptin (that was not part of the aforementioned metaanalysis) reported a high rate of fractures over 2-year follow-up and no association between saxagliptin and fracture in more than 16 000 patients who suffered almost 500 fractures (hazard ratio [HR] vs placebo = 1.0, 95% confidence interval [CI] 0.8–1.2) (11). Similarly, Driessen et al reported 2 separate observational studies of about 1 year of sitagliptin exposure and found no association with fracture in either a Danish registry-based case-control study (adjusted odds ratio = 0.97, 95%CI 0.79–1.18) (12) or a United Kingdom Clinical Practice Research Datalink retrospective cohort study (adjusted HR = 1.03, 95%CI 0.92–1.15) (13).

Because of the limited and conflicting data available on the association between DPP-4 and fractures and the clinical importance of the question of how best to choose second and third-line agents for patients with type 2 diabetes who are already at particularly high risk of fractures, we undertook the present study. Our objective was to determine the independent association between new use of sitagliptin and risk of MOFs in a large and representative population of patients with type 2 diabetes.

Materials and Methods

Subjects and setting

We conducted a large population-based cohort study using a nationally representative Unites States claims and integrated laboratory database that included commercially insured patients from all 50 States (Clinformatics Data Mart Database; OptumInsight). This database has been widely used in previous studies (15–17) and includes patient level data collected directly from the clinical encounter, including administrative and sociodemographic information (ie, type of insurance plan, age, sex, income), and all billable medical service claims, including inpatient and outpatient visits and medical procedures (procedure and diagnosis codes), laboratory tests and results (eg, low density lipoprotein, triglycerides, creatinine, A1c), and prescription pharmacy claims based on National Drug Codes (15–17). All clinical diagnoses are recorded according to the International Classification of Diseases, Ninth revision Clinical Modification and procedure codes (according to International Classification of Diseases, Ninth revision and Current Procedural Terminology 4 codes). All data were deidentified and accessed with protocols compliant with the Health Insurance Portability and Accountability Act. The study was approved by the institutional ethics review board of the University of Alberta and the New England Ethics Institutional Review Board, MA.

Study cohort selection

New users of oral antidiabetic agents, defined as no prescription records for any antidiabetic agents including insulin, for 1 year before their index date (ie, date of the first claim for their antidiabetic drug) (16–18), were identified between January 1, 2004 and December 31, 2009. All included patients had to be at least 20 years of age on the index date, be enrolled in a commercial medical insurance plan, and have 1 year of continuous medical insurance (Supplemental Figure 1). Patients were subsequently followed until an outcome or death occurred, insurance was terminated, or the study ended (December 31, 2010), providing a maximum follow-up of 6 years.

Sitagliptin and other antidiabetic drug use (exposure)

Within each 90-day window of follow-up, antidiabetic drug exposure was classified into 6 nonmutually exclusive categories as follows: 1) any sitagliptin use; 2) any metformin use; 3) any sulfonylurea use; 4) any TZD use; 5) any "other" oral antidiabetic drug use (ie, acarbose, meglitinides); and 6) any insulin use. For analyses, each drug exposure class was included in the model as a dummy variable with the reference group being no exposure to the antidiabetic drug of interest (eg, exposure to sitagliptin compared with no exposure to sitagliptin after adjustment for use or nonuse of other antidiabetic drugs). Subjects receiving combination pills (eg, sitagliptin and metformin) were classified as receiving both agents concurrently (ie, any sitagliptin use and any metformin use). Outcomes were attributed to the drugs the patient was receiving at the time of the event and we assumed there were no legacy or carry-over effects from remote exposure to any of the antidiabetic drugs we studied.

MOFs (outcomes)

Our primary outcome was the occurrence of any MOF (defined as any nontraumatic fragility fracture of the forearm, humerus, vertebrae, or hip). This is a commonly used definition of osteoporosis-related fractures that covers the spectrum of potential morbidity (3) and is based on previously validated diagnostic codes captured in physician claims or hospital discharges (2, 19, 20). Although valid and reproducible, methods based on

claims data and diagnostic codes are known to undercapture vertebral compression fractures as perhaps two-thirds of these fractures never come to medical attention (19, 20).

Potentially confounding variables

In addition to the time varying exposure to oral antidiabetic drugs and insulin, baseline covariates (based on the most recent values within 1 y before initiation of glucose lowering therapy) included age, sex, type of medical insurance, laboratory data, and prescription medications (see Table 1 for a complete list). To further control for the total burden of comorbidities, we used the adjusted clinical groups (ACGs) score derived from The John Hopkins ACG System (21), which is a single comorbidity score weighted by the 32 Adjusted Diagnostic Groups that performs equally or better than the Charlson and Elixhauser comorbidity scores (22). Based on this scoring system, we derived the total number of chronic conditions other than diabetes (≤2, 2–5, >5 conditions), and we also included the ACG System derived "frailty" marker (21). Last, we included available risk factors for fracture or falls, such as current alcohol or substance abuse, history of RA, use of oral corticosteroids, or a known osteoporosis diagnosis.

Analytic approach

Because glucose-lowering therapy changes over time, we used time-varying Cox proportional hazards regression to more precisely estimate the drug exposure effect. Exposure to oral antidiabetic drugs or insulin was updated every 90 days based on the expected duration of each prescription using the "days supplied" field within the prescription drug dispensations database (16, 23). In these analyses, time zero was set at the start of the first oral antidiabetic drug use, and each subsequent 90-day window was reassessed for exposures. In addition to time-varying exposure data, we included a time-varying propensity score whereby we updated the propensity or probability of receiving sitagliptin every 90 days throughout the follow-up period using all available data (16, 24). The propensity score was calculated using standard methods and contained 60 variables (model output available upon request from D.T.E.). All analyses were conducted using Stata/MP 14.1 (copyright 1985–2015; StataCorp LP).

Table 1. Baseline Characteristics of 72 738 Patients With Type 2 Diabetes, According to New Use of Sitagliptin

	n (%) or Mean (SD)		
Characteristics	**No Sitagliptin Exposure (n = 63 844)**	**New Sitagliptin Exposure (n = 8894)**	***P* Value**
Sociodemographic			
Age	52 (10)	52 (9)	.6
Age categories			
≤45 y	14 649 (23)	1996 (22)	<.001
46 to ≤60 y	35 975 (56)	5244 (59)	
>60 y	13 220 (21)	1654 (19)	
Male	34 534 (54)	5039 (56)	<.001
Annual income (United States dollar)	48 153 (6063)	48 345 (6196)	.005
Clinical			
ADG comorbidity score	8.35 (9)	8.67 (9)	.001
Ischemic heart disease	7058 (11)	1053 (12)	.03
Heart failure	1592 (2)	256 (3)	.03
Dyslipidemia	31 125 (49)	4415 (49)	.12
Hypertension	38 102 (60)	5209 (59)	.05
COPD	98 (<1)	8 (<1)	.14
Osteoporosis	1841 (3)	229 (3)	.1
RA	30 (<1)	3 (<1)	.6
Substance abuse	394 (1)	51 (1)	.6
CKD (eGFR <60)	3494 (5)	492 (6)	.8
Mean A1c (SD)	7.5 (2)	8.0 (2)	<.001
>2 chronic conditions	29 545 (46)	4323 (49)	<.001
Frail	1990 (3)	276 (3)	.9
Antidiabetic drug use			
Any metformin	54 982 (86)	7691 (86)	.4
Any sulfonylureas	20 088 (31)	3587 (40)	<.001
Any TZDs	17 262 (27)	3308 (37)	<.001
Any insulin	3710 (6)	1048 (12)	<.001
Any other antidiabetic drugs	1277 (2)	405 (5)	<.001
Other medication use			
ACE inhibitor or AR blocker	23 665 (37)	3302 (37)	.9
Statins	20 076 (31)	2554 (29)	<.001
β-Blockers	13 417 (21)	1793 (20)	.06
Nitrates	1675 (3)	209 (2)	.13
Thiazide diuretics	8321 (13)	943 (11)	<.001
Loop Diuretics	2901 (5)	453 (5)	.02
Oral corticosteroids	8682 (14)	1114 (13)	<.005

Sensitivity analyses

Because of the number of variables included in the models as well as the use of a propensity score we were concerned about overfitting models and the potential for "zero cells," as such, and a priori, we did not conduct any sensitivity analyses if the number of outcome events was less than 100. Nevertheless, to evaluate the robustness of our results we did attempt some sensitivity analyses. First, we repeated our main analysis after excluding all patients who used insulin, as insulin may be viewed as a marker for more advanced disease and it is also associated with higher rates of hypoglycemia and falls. Second, we conducted an analysis restricted to women, as they are at much greater risk of fracture than men, and there might even be issues related to effect modification. Last, we restricted analyses to only patients aged 65 years and older as those younger than 65 are at much lower risk of falls and fractures.

Results

General

The final study cohort consisted of 72 738 patients with type 2 diabetes: their median age was 52 years (interquartile range, 46–59), 54% were men, 61% had 2 or more additional comorbidities, and their diabetes was well controlled (median A1c = 7.5) (Table 1). The median follow-up time was 2 years (interquartile range, 1.1–3.6), and the cohort accrued 181 139 person-years of follow-up.

Patterns of antidiabetic drug use

Overall, there were 8894 (12%) new users of sitagliptin, and 86% of these patients also received first-line metformin therapy during the study period. New users of sitagliptin tended to be younger, had fewer comorbidities, were less likely to use insulin, and had somewhat better glycemic control than nonusers of sitagliptin (Table 1). Among nonusers of sitagliptin, the most common agents used in addition to metformin were sulfonylureas and insulin. Of note, 28% of the entire population used a TZD.

Association between sitagliptin and fractures

Over the median 2 years of follow-up, there were 741 MOFs (79 hip fractures) for an overall incidence rate of 4.1 fractures per 1000 person-years. There were 53 fractures (4.8 per 1000 person-years) among new users of sitagliptin vs 688 fractures (4.0 per 1000 person-years) among nonusers of sitagliptin, $P = .3$ for the difference. In propensity adjusted time-varying multivariable analyses, there was no independent association between use of sitagliptin and the risk of fracture (adjusted HR 1.1, 95%CI 0.8–1.4; $P = .7$) (Table 2). There was also no independent association between current use of metformin and fracture (adjusted $P = 1.0$) (Table 2).

Table 2. Independent Correlates of the Risk of Major Osteoporotic Fracture: Multivariable Cox Proportional Hazards Analysis

Correlate	Adjusted Hazard Ratio (95% Confidence Interval)	*P* Value
Antidiabetic agents		
Sitagliptin	1.1 (0.8–1.4)	.7
Metformin	1.0 (0.8–1.2)	1.0
Sulfonylureas	1.3 (1.1–1.5)	.008
TZDs	1.2 (1.04–1.5)	.019
Insulin	2.1 (1.6–2.8)	<.001
Sociodemographic		
Age		
≤45 y	Reference	
46 to ≤60 y	1.7 (1.3–2.1)	<.001
>60 y	2.2 (1.7–2.9)	<.001
Female	1.2 (1.1–1.4)	<.008
Clinical and medication related		
Osteoporosis	1.5 (1.05–2.1)	.03
Loops diuretics	1.4 (1.03–1.8)	.03
Oral corticosteroids	1.3 (1.1–1.6)	.01

Also adjusted for time-updated propensity scores and all variables presented in Table 1.

Other independent correlates of fracture

Older age, female sex, and a history of osteoporosis were independently associated with increased risk of fracture. The use of insulin was significantly associated with a large increased risk of fracture (adjusted HR 2.1, 95%CI 1.6–2.8; $P < .001$), and both sulfonylureas ($P < .008$) and TZDs ($P = .019$) were also independently associated with fracture (Table 2). Otherwise, the only potentially modifiable factors significantly associated with an increased risk of fracture that we observed were related to the use of loop diuretics and oral corticosteroids (Table 2).

Sensitivity analyses with respect to sitagliptin exposure

First, exclusion of patients receiving insulin (n = 4758) did not materially change our results (adjusted HR 1.1, 95%CI 0.8–1.5; $P = .5$). Second, analyses restricted to only the 33 165 women demonstrated higher absolute fracture rates than the overall cohort, but in relative terms, our analyses were unaltered (6.4 for sitagliptin users vs 4.4 for nonusers per 1000 person-years; adjusted HR 1.2, 95%CI 0.8–1.8; $P = .3$). Last, analyses restricted to 14 874 older patients also yielded nearly identical results to the main findings (adjusted HR 1.0, 95%CI 0.6–1.8; $P = .9$) (Figure 1).

Discussion

In a large and nationally representative cohort of insured Americans with type 2 diabetes, we found that fractures

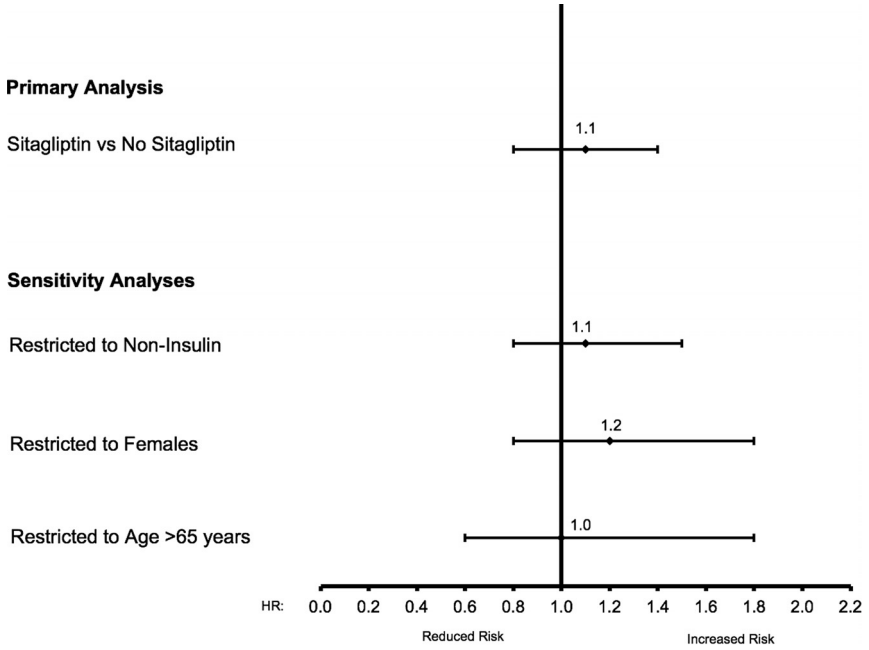

Figure 1. Sensitivity analyses examining the robustness of findings related to the association between sitagliptin use and MOFs.

were not uncommon over 2 years of follow-up, and we observed that various second and third-line treatments for diabetes could affect the likelihood of fracture. In carefully adjusted analyses, we observed that neither sitagliptin nor metformin were independently associated with an increased risk of fracture. Conversely, other commonly prescribed drugs often used as second and third-line treatments for type 2 diabetes, such as sulfonylureas, TZDs, and insulin, all increased the risk of fracture.

Sitagliptin and the other DPP-4 "should" decrease the risk of osteoporotic fracture, and there is a wealth of mechanistic and preclinical data to support this expectation (4). This degree of biologic plausibility had been (seemingly) confirmed by a metaanalysis of 28 DPP-4 trials that demonstrated a significant 40% reduction in fracture over the short term, ie, less than 1 year (10). And yet our results regarding sitagliptin are robustly neutral and consistent with 2 observational studies of sitagliptin (12, 13) and a secondary analysis of a randomized trial of saxagliptin (11). Adding our data to the totality of evidence available suggests that, irrespective of biologic plausibility, it is unlikely that DPP-4 reduce the risk of fracture in a clinically important manner, and that the findings of the Monami et al metaanalysis of less than 100 fracture events were a result of chance or some form of bias (10).

But even the finding that sitagliptin has no effect on the risk of fracture in patients with type 2 diabetes is crucially important given that we (and others) have observed an increased risk of fracture associated the most commonly used second and third-line agents, ie, insulin and sulfonylureas (4–7). In fact, in our study, the 2-fold increased risk in fracture associated with insulin use was as large as the risk attributable to having a diagnosis of osteoporosis and in fact it is larger than the relative risks associated with most of the individual components of the fracture risk assessment tool, ie, FRAX (3). Although there are biological mechanisms that could explain the increased risk of fracture associated with insulin and sulfonylureas (4–7), it could also be that these agents are more likely to provoke symptomatic hypoglycemia and injurious falls and so (indirectly) lead to more fractures (5). This speculation is also supported by our finding that the use of loop diuretics was significantly associated with an increased risk of fracture, perhaps by predisposing to orthostasis and increased falls, in addition to known deleterious effects on BMD (25).

Despite some strengths, our work has several limitations beyond those inherent to all observational studies. First, our population was relatively young (median age, 52 y) and our follow-up relatively short (median, 2 y), meaning that our overall number of fracture events was relatively low, although it seems unlikely we were underpowered for our prespecified analyses of MOFs.

Second, our ascertainment of fractures was based on claims data, and we did not have radiograph confirmation of these events nor did we have enough events to look at different types of fractures. Furthermore, this method of ascertainment will certainly undercapture vertebral fractures, most of which do not come to medical attention (19, 20).

Third, we did not have complete capture of important risk factors for osteoporosis (such as parental history of hip fracture or smoking) or important risk factors for low trauma fractures (such as injurious falls or serious hypoglycemic events). However, there is no reason to believe risk factors for osteoporosis would be distributed differently across sitagliptin exposure on the one hand, and on the other hand, even if we had the information, it would not be appropriate to adjust for falls or hypoglycemic events as these risk factors lay along the potential causal pathway from insulin or sulfonylurea exposure to increased fractures (2, 5).

Fourth, we did not have any markers of bone turnover, or more importantly, measurements of BMD. Although such information may have helped us understand better the mechanistic pathways between diabetes, its treatments, and fractures, it was not the purpose of this observational study. And although we have acknowledged our relatively short follow-up time, it would have been an even greater limitation if we were attempting to look at serial changes in BMD. Although changes in BMD are likely the reason for our findings with respect to TZDs (as demonstrated by others using evidence from randomized trials) (7, 8), it seems unlikely to us that information garnered from BMD scans would have altered our main conclusions, although such data might have helped us better explain our results, it would require a much different study design that incorporated scheduled and serial BMD, scheduled and serial spine radiographs, and a longer follow-up time.

Fifth, regarding sitagliptin exposure itself, we did not consider measures related to adherence, cumulative dose response, or carryover or legacy effects. Nonetheless, by using both time-varying exposure data for sitagliptin and time-updated propensity (to prescribe sitagliptin) scores, we believe we have greatly minimized, although not entirely eliminated, any potential for confounding. Only a randomized trial, or at the least, a secondary analysis of fracture endpoints from a large randomized trial of sitagliptin such as Trial Evaluating Cardiovascular Outcomes with Sitagliptin (~15 000 patients with median 3.0-y follow-up) could confirm and extend our findings, and this would be worthy of future research efforts (26). Last, our study, although large and nationally representative, is based on a cohort of well-insured Americans, and it may not be generalizable to other settings or jurisdictions.

In conclusion, even in a relatively young population with type 2 diabetes, osteoporotic fractures are not uncommon. Sitagliptin is not associated with an increased risk of fracture, although other commonly used agents such as insulin or sulfonylureas were associated with increased fracture risk. These differential effects on bone health and fracture risk should be considered when making treatment decisions in patients with type 2 diabetes who might be at particularly high risk of osteoporosis-related fractures.

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