Thiazolidinediones and Fractures: Evidence from Translating Research into Action for Diabetes

Dori Bilik, Laura N. McEwen, Morton B. Brown, Nathan E. Pomeroy, Catherine Kim, Keiko Asao, Jesse C. Crosson, O. Kenrik Duru, Assiamira Ferrara, Victoria C. Hsiao, Andrew J. Karter, Pearl G. Lee, David G. Marrero, Joe V. Selby, Usha Subramanian, and William H. Herman

Departments of Internal Medicine (D.B., L.N.M., C.K., K.A., V.C.H., P.G.L., W.H.H.), Biostatistics (M.B.B.), and Epidemiology (W.H.H.), University of Michigan, Ann Arbor, Michigan 48109; Center for Diabetes and Endocrinology (N.E.P.), Grand Rapids, Michigan 49546; Department of Family Medicine (J.C.C.), University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, Somerset, New Jersey 08873; David Geffen School of Medicine (O.K.D.), University of California, Los Angeles, Los Angeles, California 90095; Division of Research (A.F., A.J.K., J.V.S.), Kaiser Permanente, Oakland, California 94612; and Indiana University School of Medicine (D.G.M., U.S.), Indianapolis, Indiana 46202

Background: Thiazolidinedione (TZD) treatment has been associated with fractures. The purpose of this study was to examine the association between TZD treatment and fractures in type 2 diabetic patients.

Methods: Using data from Translating Research into Action for Diabetes, a multicenter prospective observational study of diabetes care in managed care, we conducted a matched case-control study to assess the odds of TZD exposure in patients with type 2 diabetes with and without fractures. We identified 786 cases based on fractures detected in health plan administrative data. Up to four controls without any fracture diagnoses were matched to each case. Controls were matched on health plan, date of birth within 5 yr, sex, race/ethnicity, and body mass index within 5 kg/m^2. We performed conditional logistic regression for premenopausal and postmenopausal women and men to assess the odds of exposure to potential risk factors for fracture, including medications, self-reported limited mobility, and lower-extremity amputations.

Results: We found statistically significant increased odds of exposure to TZDs, glucocorticoids, loop diuretics, and self-reported limited mobility for women 50 yr of age and older with fractures. Exposure to both loop diuretics and TZDs, glucocorticoids, and insulin and limited mobility and lower-extremity amputation were associated with fractures in men.

Conclusion: Postmenopausal women taking TZDs and the subset of men taking both loop diuretics and TZDs were at increased risk for fractures. In postmenopausal women, risk was associated with higher TZD dose. No difference between rosiglitazone and pioglitazone was apparent. ***(J Clin Endocrinol Metab* 95: 4560–4565, 2010)**

Thiazolidinediones (TZDs), including rosiglitazone and pioglitazone, have been associated with increased risk of fractures in postmenopausal women. Both *in vivo* and *in vitro* results have suggested that TZD activation of peroxisome proliferator-activated receptor-γ may reduce bone formation (1). Previous studies were limited to patients recently diagnosed with type 2 diabetes (2), excluded patients using other antihyperglycemic medications (3) and corticosteroids (4), or did not account for race/ethnicity in the case-control matching criteria (5).

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Abbreviations: ADOPT, A Diabetes Outcomes Progression Trial; BMI, body mass index; CI, confidence interval; HP, health plan; OR, odds ratio; TRIAD, Translating Research into Action for Diabetes; TZD, thiazolidinedione.

The purpose of this study was to examine medication exposures and other factors associated with fractures in patients with type 2 diabetes. We used data from Translating Research into Action for Diabetes (TRIAD), a large, prospective, observational study of diabetes care in managed care, to conduct a matched case-control study. TRIAD studied a geographically, racially, and ethnically diverse population and provided detailed and robust information from multiple sources, including patient surveys, medical records, and administrative data.

Patients and Methods

TRIAD has been described in detail previously (6). Six research centers collaborated with 10 managed care health plans (HPs) and 68 provider groups that served approximately 180,000 patients with diabetes. Institutional review boards at each participating center approved the study. All participants provided informed consent.

TRIAD enrolled 11,927 patients between July 2000 and August 2001. All were at least 18 yr old, not pregnant, community dwelling, English or Spanish speaking, and continuously enrolled in the managed care HP for at least 18 months before the baseline patient survey. Medical record reviews were performed at baseline, and HP administrative data were collected from 18 months before the baseline survey through 2003. We analyzed data for patients with type 2 diabetes (we excluded patients who were diagnosed at <30 yr of age and treated only with insulin), were continuously enrolled, and had a pharmacy benefit as evidenced by multiple medication claims during their enrollment period. We used HP administrative data to ascertain fractures and determine medication exposure. We used patient survey and medical record reviews to assess duration of diabetes, vision problems, self-reported limited mobility, lower-extremity amputation, and Charlson comorbidity index score. We considered a person to be exposed to a medication if they filled a prescription during the 90 d before the fracture date for cases or 90 d before study censor date for controls. The specific medications we examined and their category assignments are listed in the Supplemental Appendix (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

We identified 786 cases based on the earliest diagnosis of a fracture detected in the administrative data using International Classification of Diseases, 9th Revision, Clinical Modification fracture diagnosis codes (with any fourth or fifth digit): 800–829. The 786 cases included 54 women less than 50 yr of age, 457 women 50 yr of age and older, and 275 men. Up to four controls were matched to each case. Controls had no fracture diagnoses detected in the administrative data and were matched on HP, date of birth within 5 yr, sex, race/ethnicity, and body mass index (BMI) within 5 kg/m^2. If there were more than four potential controls for the case, four were randomly selected.

For cases and controls, the study window to assess exposures started 18 months before the baseline survey. For cases, follow up ended with the earliest fracture. For controls, the length of follow up was set equal to that of the matched case by starting 18 months before the baseline survey of the control and extending the same number of days as the follow up of the matched case with the last day assigned to be the censor date of the control.

We compared cases and controls using ANOVA (in which the case-control set was one of the factors) with weighted means and frequency distributions. We used conditional logistic regression to provide unadjusted bivariate exposure Mantel-Haenszel case-control odds ratios (ORs). We used conditional logistic regression for multivariate analyses and for subanalyses by specific TZD (rosiglitazone, pioglitazone, and troglitazone) and TZD dose level. Potential matching variables and risk factors for fracture were identified from the literature (age, sex, race/ethnicity, and BMI, treatment with TZDs, bisphosphonates, glucocorticoids, insulin, or loop diuretics, reduced vision, self-reported limited mobility, and comorbidities). Model variables and interaction terms were selected based on Shtatland's method using stepwise logistic regression, allowing all potential predictors to enter and generating Schwarz and Akaike information criteria to build a parsimonious model (7). The resulting model included the following statistically significant risk factors: exposure to TZDs, bisphosphonates, glucocorticoids, insulins, and loop diuretics, an interaction term for loop diuretics and TZDs, self-reported limited mobility, and lower-extremity amputation. Patients missing values for variables used in this study were excluded. Statistical analyses were performed using SAS (version 9.1.3; SAS Institute, Cary, NC).

Results

Troglitazone was approved by the U.S. Food and Drug Administration in January 1997 and was withdrawn in March 2000 because of liver toxicity. Troglitazone was thus available for 2 yr before the beginning of the administrative data of TRIAD. The first prescription for rosiglitazone was filled in June 1999, and the first prescription for pioglitazone was filled in August 1999. Subsequent uptake of TZD therapy by TRIAD participants was rapid. The cumulative number of patients with prescriptions for rosiglitazone was approximately 500, 970, 1250, and 1400 at 1, 2, 3, and 4 yr after the first prescription was filled. For pioglitazone, it was approximately 500, 800, 1080, and 1300 patients at 1, 2, 3, and 4 yr after the first prescription was filled.

There were 786 cases and 2657 matched controls. Of these, 301 cases (38%) experienced lower-limb fractures, 169 (22%) experienced upper-limb fractures, 116 (15%) experienced pelvis/hip/spine fractures, 72 (9%) experienced multiple fractures, and 128 (16%) did not have the fracture site specified or the site was designated "other." Mean ± SD duration of follow up was 1.9 ± 1.3 yr, maximum follow up was 4.8 yr, and minimum follow up was less than 1 wk. Cases and controls were matched on HP, age, sex, race/ethnicity, and BMI. As shown in Table 1, the cases and controls generally did not differ with respect to the matching criteria. However, the subgroup of women with fractures aged 50 yr and over was slightly older than their matched controls (67.5 *vs.* 66.2 yr, $P = 0.046$).

Table 2 shows the unadjusted odds of exposures to risk factors for fractures. Women aged 50 yr and older with

TABLE 1. Characteristics of patients with fractures and matched controls

	Women ≥50 yr			Women <50 yr			Men		
	Cases	Controls	*P* value	Cases	Controls	*P* value	Cases	Controls	*P* value
n	457	1534		54	177		275	946	
Weighted mean age (SD) (yr)	67.5 (9.7)	66.2 (9.2)	0.046	44.8 (4.0)	44.9 (4.6)	0.88	62.7 (12.3)	62.4 (11.7)	0.75
Weighted mean BMI (SD) (kg/m^2)	31.3 (6.5)	31.3 (5.9)	0.93	36.0 (7.9)	35.4 (7.3)	0.69	30.1 (5.8)	29.9 (4.9)	0.59
Race/ethnicity			1.00			1.00			1.00
Hispanic (%)	16.8	16.8		18.5	18.5		10.9	10.9	
Black (%)	18.8	18.8		16.7	16.7		11.6	11.6	
White (%)	46.2	46.2		38.9	38.9		56.4	56.4	
Asian/Pacific Islander (%)	10.9	10.9		14.8	14.8		11.3	11.3	
Other (%)	7.2	7.2		11.1	11.1		9.8	9.8	
HP			1.00			1.00			1.00
A (%)	8.8	8.8		1.8	1.8		8.0	8.0	
B (%)	7.4	7.4		16.7	16.7		9.1	9.1	
C (%)	15.3	15.3		29.6	29.6		9.5	9.5	
D (%)	16.6	16.6		16.7	16.7		19.6	19.6	
E (%)	21.2	21.2		16.7	16.7		22.9	22.9	
F (%)	2.4	2.4		1.8	1.8		6.5	6.5	
G (%)	5.7	5.7		0	0		5.4	5.4	
H (%)	2.4	2.4		3.7	3.7		5.1	5.1	
I (%)	20.1	20.1		13.0	13.0		13.8	13.8	

fractures, when compared with their matched controls without fractures, were significantly more likely to have filled prescriptions for TZDs, insulin, glucocorticoids, loop diuretics, and bisphosphonates, were less likely to have filled prescriptions for metformin, and were more likely to have longer duration of diabetes, vision problems (blurred or double vision), self-reported limited mobility (some problems walking around or confined to bed), and higher Charlson comorbidity index scores. The smaller sample of women under 50 yr of age showed fewer dif-

TABLE 2. Prevalence of exposure and odds of exposure among patients with fractures

	Women ≥50 yr			Women <50 yr			Men		
	Number (%) of cases	OR	*P* value	Number (%) of cases	OR	*P* value	Number (%) of cases	OR	*P* value
Sulfonylureas	188 (41%)	0.94	0.57	25 (46%)	0.94	0.84	116 (42%)	0.76	0.053
Metformin	120 (26%)	0.71	0.006*	21 (39%)	0.76	0.42	85 (31%)	0.91	0.55
Sulfonylurea/metformin	9 (2%)	1.18	0.70	0	n/a	n/a	5 (2%)	0.97	0.96
Thiazolidinediones	58 (13%)	1.88	0.0004*	5 (9%)	0.56	0.27	38 (14%)	1.79	0.011*
Insulins	128 (28%)	1.36	0.014*	19 (35%)	1.73	0.14	69 (25%)	1.86	0.0003*
Glucocorticoids	67 (15%)	2.08	<0.0001*	10 (19%)	2.83	0.034*	33 (12%)	1.90	0.006*
Thyroid drugs	67 (15%)	1.32	0.078	7 (13%)	2.04	0.16	13 (5%)	1.02	0.96
Statins	125 (27%)	0.89	0.38	11 (20%)	1.05	0.91	94 (34%)	1.13	0.42
Loop diuretics	85 (19%)	1.70	0.0003*	8 (15%)	4.76	0.007*	40 (15%)	1.83	0.004*
Proton pump inhibitors	48 (11%)	1.44	0.052	9 (17%)	1.13	0.79	28 (10%)	1.55	0.07
Estrogen with/without progestin	65 (14%)	0.84	0.27	5 (9%)	0.77	0.64	0	n/a	n/a
Selective estrogen receptor modulators	9 (2%)	1.56	0.31	0	n/a	n/a	1 (0%)	n/a	n/a
Bisphosphonates	16 (4%)	2.16	0.019*	1 (2%)	n/a	n/a	3 (1%)	2.00	0.36
Calcitonin	4 (1%)	2.78	0.13	0	n/a	n/a	0	n/a	n/a
Mean diabetes duration (SD) (yr)	14.9 (12.7)	1.01	0.017*	8.8 (8.0)	1.04	0.08	12.2 (10.2)	1.02	0.016*
Low vision	54 (12%)	1.47	0.029*	8 (16%)	1.45	0.41	20 (8%)	0.98	0.95
Limited mobility	279 (61%)	1.62	<0.0001*	32 (59%)	2.26	0.020*	149 (54%)	2.08	<0.0001*
Amputation	12 (3%)	1.86	0.098	0	n/a	n/a	19 (7%)	2.71	0.002*
Mean Charlson comorbidity index (SD)	2.65 (1.8)	1.10	0.013*	1.98 (1.0)	1.32	0.10	2.94 (2.0)	1.23	<0.0001*

Cases and controls were matched for HP, age, sex, race/ethnicity, and BMI. n/a, Data too sparse. *, $P < 0.05$.

TABLE 3. Multivariate ORs

	Women ≥50 yr OR (95% CI)	Women <50 yr OR (95% CI)	Men OR (95% CI)
Thiazolidinediones	1.71 (1.13–2.58)*	0.38 (0.10–1.39)	1.37 (0.83–2.28)
Bisphosphonates	1.85 (0.94–3.63)		1.69 (0.37–7.85)
Glucocorticoids	1.90 (1.36–2.65)*	2.26 (0.78–6.54)	1.79 (1.11–2.87)*
Insulins	1.12 (0.86–1.45)	1.48 (0.66–3.30)	1.59 (1.11–2.29)*
Loop diuretics	1.49 (1.08–2.06)*	3.31 (0.81–13.44)	1.09 (0.66–1.79)
Interaction loop diuretics and thiazolidinediones	0.99 (0.44–2.24)	2.26 (0.10–48.94)	3.46 (1.06–11.28)*
Limited mobility	1.51 (1.20–1.90)*	2.01 (0.99–4.07)	1.96 (1.45–2.65)*
Amputation	1.30 (0.61–2.79)		2.29 (1.21–4.32)*

Cases and controls were matched for HP, age, sex, race/ethnicity, and BMI. Variables excluded from the model for this population because of insufficient observations. *, $P < 0.05$.

ferences between cases and controls, with cases significantly more likely to have filled prescriptions for glucocorticoids and loop diuretics and more likely to have limited mobility. For men, cases were significantly more likely to have filled prescriptions for TZDs, insulin, glucocorticoids, and loop diuretics and to have longer duration of diabetes, limited mobility, lower-extremity amputations, and higher Charlson comorbidity index scores.

Table 3 shows the adjusted ORs of exposure to various risk factors in cases compared with controls. Among women aged 50 yr and older, cases with fractures were significantly more likely ($P < 0.05$) to be exposed to TZDs [OR of 1.71, 95% confidence interval (CI) of 1.13–2.58], glucocorticoids (OR of 1.90, 95% CI of 1.36–2.65), and loop diuretics (OR of 1.49, 95% CI of 1.08–2.06) and to have limited mobility (OR of 1.51, 95% CI of 1.20–1.90). We did not find TZDs to be significantly associated with fractures in women less than 50 yr of age, although the risk factors associated with fractures were generally similar to those for women aged 50 yr and older. In men, we found fractures to be significantly associated with concurrent use of loop diuretics and TZDs (OR of 3.46, 95% CI of 1.06–11.28), exposure to glucocorticoids (OR of 1.79, 95% CI of 1.11–2.87), and insulin (OR of 1.59, 95% CI of 1.11–2.29), as well as limited mobility (OR of 1.96, 95% CI of 1.45–2.65) and lower-extremity amputation (OR of 2.29, 95% CI of 1.21–4.32).

We examined duration of TZD exposure before fracture for those filling prescriptions for TZDs. We were unable to determine duration of troglitazone exposure because troglitazone treatment may have been initiated before the beginning of our study. For the 84 women aged 50 yr and older, average duration of TZD exposure before fracture was 364 d (interquartile range of 100–582 d). For the eight women under age 50 yr, average duration of TZD exposure before fracture was 521 d (interquartile range of 315–750 d). For the 54 men, average duration of TZD exposure before fracture was 449 d (interquartile range of 180–597 d).

We also assessed the impact of TZD dose on the odds of fracture. We categorized the TZD dose level as "low" or "high." For pioglitazone, 15 mg was assigned low dose and 30–45 mg was assigned high dose. For rosiglitazone, 2–4 mg was assigned low dose and 8 mg was assigned high dose. For troglitazone, 200 mg was assigned low dose and 300–400 mg was assigned high dose. The model included exposure to bisphosphonates, glucocorticoids, insulin, and loop diuretics and limited mobility and lower-extremity amputation. High TZD doses were associated with significantly greater odds of fracture for women age 50 yr and older (OR of 1.42, 95% CI of 1.12–1.79) but not for men or women under age 50 yr.

To assess the risk of fractures associated with rosiglitazone, pioglitazone, and troglitazone, we performed a subanalysis with the individual TZDs as separate variables in models that were otherwise the same as those used above. For women 50 yr of age and older, the odds of exposure was similar for rosiglitazone (OR of 1.64, 95% CI of 0.96–2.80) and pioglitazone (OR of 1.56, 95% CI of 0.89–2.74). For troglitazone, we found the odds of exposure to be 4.23 (95% CI of 1.30–13.75).

Discussion

In this large, prospective, observational study of diabetes care in managed care, we used a matched case-control design and found that women 50 yr of age and older with fractures were more likely to be exposed to TZDs. Women aged 50 yr and older developed fractures after shorter duration of TZD exposure than women under age 50 yr or men. Higher dose of TZD was associated with greater risk. Both rosiglitazone and pioglitazone appeared to be associated with increased risk. Limited mobility was associated with fractures for both women 50 yr of age and older and men. Higher odds of fractures were found for men using both TZDs and loop diuretics and for men with lower-extremity amputations. Duration of diabetes and

Charlson comorbidity index score were not independently associated with fractures.

A Diabetes Outcomes Progression Trial (ADOPT) found higher fracture rates in women randomized to rosiglitazone than in women randomized to metformin or sulfonylureas (2). The association between TZD exposure and fractures in women was confirmed by *post hoc* analyses of earlier clinical trials (8, 9). Subsequent analyses of stored serum samples from ADOPT participants suggested that increased bone resorption may have contributed to increased risk of fractures in women taking TZDs (10). ADOPT was limited to drug-naive patients diagnosed with type 2 diabetes within the previous 3 yr. In our study, the cases and controls averaged over 12 yr since diagnosis. In ADOPT and in our study, the majority of fractures were not typical osteoporotic fractures. In ADOPT, lower-limb fractures accounted for 53% of fractures in women and 28% of fractures in men treated with rosiglitazone. In our study 62% of fractures in women taking TZDs and 43% of fractures in men taking TZDs were lower-limb fractures. In ADOPT, upper-limb fractures accounted for 34% of fractures in women and 31% of fractures in men treated with rosiglitazone. In our study, 20% of fractures in women taking TZDs and 16% of fractures in men taking TZDs were upper-limb fractures. In our study, 44% of all fractures in women and 39% of all fractures in men involved the lower limb, and 25% of all fractures in women and 21% of all fractures in men involved the upper limb.

Additional studies have confirmed an increased risk of fractures in patients taking TZDs. Eight subjects (six women, two men) randomized to pioglitazone in the PERISCOPE study (for Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) experienced fractures. None were reported in the control group (11). A recent cross-sectional study that excluded patients treated with corticosteroids found higher rates of fractures for those taking TZDs compared with those not taking TZDs (4). A retrospective cohort study examining time to fracture found TZD use to be associated with increased fracture risk overall and in women over 65 yr of age (12). An observational study of older, low-income patients in a single state found patients prescribed TZDs as their only oral antidiabetic medication were more likely to develop fractures than patients prescribed a different single oral antidiabetic medication (13). Another prospective cohort study found pioglitazone to be associated with more extremity fractures in men and women but did not find the same effect for rosiglitazone (3). The latter study used a new-user design and excluded patients with sulfonylurea, TZD, or insulin treatment in the previous 2 yr. Our study did not exclude patients based on current medication regimen so the subjects were perhaps more representative of the general population of patients with type 2 diabetes. A recent study found an association between fractures and TZD use and suggested that fracture was associated with higher TZD dose (5). We confirmed the TZD dose-response effect. A self-controlled case-series study using the United Kingdom General Practice Research Database found increased fracture risk during periods of TZD exposure (14). Subjects were selected with evidence of fracture and TZD prescriptions. The study did not include subjects using TZDs who did not experience fractures. The unexposed period was defined as before the initial TZD prescription. Because the unexposed period always preceded the exposed period, the authors adjusted for age, although the approach could be complicated by possible development of comorbidities over time. The study was not able to distinguish type 1 from type 2 diabetes. In TRIAD, we excluded patients with probable type 1 diabetes.

Our finding of increased risk of fracture in men associated with concurrent use of loop diuretics and TZDs was interesting because, in men, loop diuretics or TZDs alone did not confer significant risk. In recent studies, loop diuretics have been associated with fractures in older women (15, 16) and with bone loss in older men (17, 18). If this result is confirmed by others, additional research on potential mechanisms is warranted.

Troglitazone was the only TZD available before the beginning of our study. Our finding of a significant association between fractures and prescriptions for troglitazone in women aged 50 yr and over suggests that increased risk may be associated with longer duration of exposure. Reexamination of historical data on troglitazone-treated patients may help explain the higher fracture risk associated with troglitazone exposure.

Our analyses used multiple sources of data, including surveys, medical records, and administrative data. Our analyses did have several limitations. We relied on pharmacy prescriptions and, if a patient's HP coverage included a limit on pharmacy benefits, patients may have filled prescriptions that we did not detect. We expect this error to be small because we verified that patients were filling prescriptions while enrolled in the HP, and two large HPs submitted pharmacy utilization, not just claims, capturing prescriptions that were not covered. In addition, most HPs included denied claims, further capturing prescriptions that were not covered. Our study included a small number of women under 50 yr of age, and, although the results are shown, we are unable to draw firm conclusions regarding fracture risk associated with TZDs in this small population. We did not inspect x-ray data to confirm fracture diagnoses. We relied on administrative data

sources. Matched case-control studies control for differences in the distributions of the matching variables between cases and controls. In our study, this removed the potential impact of differences in HP, age, sex, race/ethnicity, and BMI on fracture risk. However, matched case-control studies do not adjust for variables that are not matched, and this could have resulted in residual confounding (19).

In conclusion, we confirmed the increased risk of fractures for older women treated with TZDs and identified increased risk of fracture in men who are concurrently taking loop diuretics and TZDs. Risk was associated with higher TZD dose, but no difference between rosiglitazone and pioglitazone was apparent, suggesting a class effect of TZDs on fracture risk. Future studies, particularly long-term, prospective randomized clinical trials, will be needed to conclusively demonstrate small to moderate harm (20).

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Address all correspondence and requests for reprints to: William H. Herman, M.D., M.P.H., 1000 Wall Street, 6th Floor, SPC 5714, Ann Arbor, Michigan 48105. E-mail: wherman@umich.edu.

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