Rosiglitazone-Associated Fractures in Type 2 Diabetes

An analysis from A Diabetes Outcome Progression Trial (ADOPT)

Steven E. Kahn, MB, ChB[1]
Bernard Zinman, MD[2]
John M. Lachin, ScD[3]
Steven M. Haffner, MD[4]
William H. Herman, MD[5]
Rury R. Holman, MD[6]
Barbara G. Kravitz, MS[7]
Dahong Yu, PhD[7]
Mark A. Heise, PhD[7]
R. Paul Aftring, MD, PhD[7]
Giancarlo Viberti, MD[8]
for the A Diabetes Outcome Progression Trial (ADOPT) Study Group*

OBJECTIVE — The purpose of this study was to examine possible factors associated with the increased risk of fractures observed with rosiglitazone in A Diabetes Outcome Progression Trial (ADOPT).

RESEARCH DESIGN AND METHODS — Data from the 1,840 women and 2,511 men randomly assigned in ADOPT to rosiglitazone, metformin, or glyburide for a median of 4.0 years were examined with respect to time to first fracture, rates of occurrence, and sites of fractures.

RESULTS — In men, fracture rates did not differ between treatment groups. In women, at least one fracture was reported with rosiglitazone in 60 patients (9.3% of patients, 2.74 per 100 patient-years), metformin in 30 patients (5.1%, 1.54 per 100 patient-years), and glyburide in 21 patients (3.5%, 1.29 per 100 patient-years). The cumulative incidence (95% CI) of fractures in women at 5 years was 15.1% (11.2–19.1) with rosiglitazone, 7.3% (4.4–10.1) with metformin, and 7.7% (3.7–11.7) with glyburide, representing hazard ratios (95% CI) of 1.81 (1.17–2.80) and 2.13 (1.30–3.51) for rosiglitazone compared with metformin and glyburide, respectively. The increase in fractures with rosiglitazone occurred in pre- and postmenopausal women, and fractures were seen predominantly in the lower and upper limbs. No particular risk factor underlying the increased fractures in female patients who received rosiglitazone therapy was identified.

CONCLUSIONS — Further investigation into the risk factors and underlying pathophysiology for the increased fracture rate in women taking rosiglitazone is required to relate them to preclinical data and better understand the clinical implications of and possible interventions for these findings.

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Type 2 diabetes is associated with an increased risk of fractures, with the risk increasing with longer duration of disease (1,2). These fractures affect predominantly the hip, arm, and foot (1–5) and occur despite the fact that bone mineral density is either normal or even increased in patients with type 2 diabetes compared with those who are not hyperglycemic (5–7). Although the reason for this increased risk is unclear, it has been postulated that in older patients some of the risk may be related to disability and falls (8). In the context of specific diabetes therapy, a recent report from the Health, Aging and Body Composition Study—an observational study—noted that older women with type 2 diabetes who were taking thiazolidinediones experienced increased bone loss compared with control subjects, whereas no differences were seen in men (9). However, a recent retrospective study suggested a greater loss of bone mineral density in men taking rosiglitazone (10).

A Diabetes Outcome Progression Trial (ADOPT) was a randomized, controlled clinical trial comparing the effect of the thiazolidinedione rosiglitazone, the biguanide metformin, and the sulfonylurea glyburide on glucose control in drug-naive patients recently diagnosed (<3 years) with type 2 diabetes (11). In the study it was shown that treatment with rosiglitazone produced more durable glycemic control than metformin or glyburide as measured by fasting glucose and A1C. This effect resulted from a greater preservation of β-cell function with rosiglitazone. After unblinding and completion of the prespecified statistical analysis plan, a review of adverse events of special interest uncovered an increase in the number of fractures in women taking rosiglitazone; a brief description of the finding was added as a postscript to the primary manuscript then in press (11). In

From the [1]Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, VA Puget Sound Health Care System and University of Washington, Seattle, Washington; the [2]Samuel Lunenfeld Research Institute, Mount Sinai Hospital and University of Toronto, Toronto, Ontario, Canada; the [3]Biostatistics Center, George Washington University, Rockville, Maryland; the [4]University of Texas Health Science Center at San Antonio, San Antonio, Texas; the [5]Departments of Internal Medicine and Epidemiology, University of Michigan, Ann Arbor, Michigan; the [6]Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford, U.K.; [7]GlaxoSmithKline, King of Prussia, Pennsylvania; and [8]King's College London School of Medicine, King's College London, London, U.K.

Corresponding author: Steven E. Kahn, MB, ChB, VA Puget Sound Health Care System (151), 1660 S. Columbian Way, Seattle, WA 98108. E-mail: skahn@u.washington.edu.

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*A list of members of the ADOPT Study Group can be found in ref. 11. ADOPT was overseen by a steering committee comprising Steven Kahn and Giancarlo Viberti (cochairs), Steven Haffner, William Herman, Rury Holman, Paul Aftring, Nigel Jones, John Lachin, Colleen O'Neill, and Bernard Zinman.

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Abbreviations: ADOPT, A Diabetes Outcome Progression Trial.

women we observed an increased occurrence of bone fractures in the upper and lower limbs, but an increase in hip or vertebral fractures was not noted. An increased fracture risk was subsequently reported in women receiving pioglitazone (12), the other thiazolidinedione currently in clinical use. We now report in greater detail the ADOPT findings related to fractures.

RESEARCH DESIGN AND METHODS

— In ADOPT, 4,360 individuals with type 2 diabetes whose diabetes had been diagnosed within 3 years and who were naive to oral hypoglycemic drugs were randomly assigned. Nine of the randomly assigned subjects never received study medication; 1,456 subjects were assigned to rosiglitazone, 1,454 to metformin, and 1,441 to glyburide therapy. The study was performed in 488 centers in 17 countries in North America and Europe. The protocol was reviewed and approved by institutional review boards for each center, and all subjects gave written, informed consent. The study was a registered clinical trial.

The study protocol has been published previously (13). In brief, ADOPT was a randomized, double-blind, parallel-group trial. Eligible patients with diabetes were aged 30–75 and had a fasting plasma glucose concentration between 126 and 180 mg/dl with lifestyle therapy. Exclusion criteria included clinically significant liver disease, renal impairment, a history of lactic acidosis, unstable or severe angina, known congestive heart failure (New York Heart Association classes I–IV) requiring pharmacological intervention, uncontrolled hypertension, or chronic diseases requiring periodic or intermittent treatment with oral or intravenous corticosteroids or continuous use of inhaled corticosteroids.

Subjects were randomly assigned to receive double-blind treatment with either rosiglitazone, metformin, or glyburide. The initial daily doses were 4 mg rosiglitazone, 500 mg metformin, and 2.5 mg glyburide, and the dose was titrated to the maximum effective daily dose (4 mg rosiglitazone twice daily, 1 g metformin twice daily, and 7.5 mg glyburide twice daily). Forced titration of the dose of medication occurred at each visit when the fasting plasma glucose level was ≥140 mg/dl. The primary outcome was time to monotherapy failure with the maximum tolerated dose of the study drug, which was defined as fasting plasma glucose >180 mg/dl on two successive occasions or by independent adjudication (11).

Concomitant medication use and adverse event reporting

Site investigators recorded all concomitant prescription medication use at baseline and at each clinic visit. Medications were classified using a validated coding system (GSKDrug). Site investigators reported adverse events during the treatment portion of the study, and these were categorized using the Medical Dictionary for Regulatory Activities (MedDRA). Fractures included any preferred term with the text "fracture" within the higher-level group term of "bone and joint injuries." In the case of fractures, the site of the fractures was as reported to or determined by the investigators with no adjudication or subsequent directed assessment performed as part of the study protocol.

Methods, assays, and calculations

Fasting blood samples were drawn for measurement of fasting plasma glucose, A1C, and immunoreactive insulin levels. All assays were performed at a central laboratory (13).

Statistical methods

The cumulative incidence of time-to-event variables was estimated by the Kaplan-Meier method (14), with withdrawals from study medication right censored. The relative risk (hazard ratio [HR]) was estimated from the Cox proportional hazards model (14). These methods allow for differential duration of exposure among groups. Treatment comparison of time to first fracture by body site was also based on Cox proportional hazards regression but with Fisher's exact test if there were zero counts (i.e., no fractures) in one of the treatment groups.

Wilcoxon's rank-sum tests were used to compare baseline variables between groups on the basis of treatment assignment (15). Differences in proportions were tested using the contingency χ^2 test, and differences in quantitative or ordinal variables were tested using the Kruskal-Wallis test (15). Cox proportional hazards models were used to assess the effect of the updated current values of weight, serum creatinine, hematocrit, calcium, A1C, and waist circumference as time-dependent covariates on the risk of fractures.

Data are presented as means ± SD unless specified. Two-sided $P \leq 0.05$ was considered statistically significant. Analyses were conducted using SAS (SAS Institute, Cary, NC).

RESULTS

Demographic and clinical variables at baseline and follow-up

Women and men randomly assigned to the three treatment arms were well matched at baseline (Table 1). As anticipated, the majority of women in the study were aged >50 years (71%) and postmenopausal by self-report (77%). The proportions of patients at baseline using selected categories of medications related to bone health did not differ among the treatment groups within each sex (Table 1), although generally more women than men were using medications associated with better bone health (estrogen-containing hormones, calcium supplements, and bisphosphonates).

The median duration of follow-up was 4.0 years for the rosiglitazone and metformin groups and 3.3 years for the glyburide group. The proportions of patients completing the study were 63, 62, and 56% for the rosiglitazone, metformin, and glyburide groups, respectively. Thus, the number of patient-years of medication exposure was 4,953.8 for the rosiglitazone group, 4,905.6 for the metformin cohort, and 4,243.6 for the glyburide group.

Bone fractures by treatment assignment

Of the 4,351 treated patients, 200 reported a fracture during the course of the study: 92 (6.3%) among those randomly assigned to rosiglitazone, 59 (4.1%) in the metformin group, and 49 (3.4%) in the glyburide group. Accounting for differences in treatment exposure, the incidence of a fracture was 1.86 per 100 patient-years with rosiglitazone, 1.20 per 100 patient-years with metformin, and 1.15 per 100 patient-years with glyburide. Figure 1*A* presents the Kaplan-Meier estimated cumulative incidence of a fracture (95% CI), reaching 9.8% (7.7–11.9) at 5 years with rosiglitazone, 5.6% (4.1–7.1) with metformin, and 5.7% (3.9–7.6) with glyburide. With the Cox proportional hazards model, estimated HRs (95% CI) for risk of fracture with rosiglitazone versus metformin and glyburide were 1.57 (1.13–2.17; P = 0.0073) and 1.61 (1.14–2.28; P = 0.0069), respectively. Interestingly, the

Table 1—*Baseline demographic characteristics, clinical measures, and prior medication use in men and women by treatment assignment*

	Women			Men		
	Rosiglitazone	Metformin	Glyburide	Rosiglitazone	Metformin	Glyburide
n	645	590	605	811	864	836
Age (years)	56.1 ± 10.2	56.7 ± 10.0	56.3 ± 10.7	56.4 ± 9.9	57.0 ± 9.9	56.6 ± 9.8
Postmenopausal	498 (77.2)	463 (78.5)	449 (74.2)	NA	NA	NA
Time since diagnosis of diabetes						
<1 year	275 (42.6)	281 (47.6)	278 (46.0)	375 (46.2)	392 (45.4)	359 (42.9)
1–2 years	351 (54.4)	288 (48.8)	309 (51.1)	407 (50.2)	436 (50.5)	442 (52.9)
>2 years	18 (2.8)	21 (3.6)	18 (3.0)	29 (3.6)	36 (4.2)	35 (4.2)
BMI (kg/m^2)	33.6 ± 7.2	33.8 ± 6.8	33.8 ± 7.1	31.1 ± 6.1	31.0 ± 5.2	31.0 ± 5.3
Waist circumference (cm)	103.4 ± 15.3	104.4 ± 15.2	103.8 ± 16.3	106.7 ± 13.9	106.4 ± 13.6	106.8 ± 14.2
Waist-to-hip ratio	0.90 ± 0.09	0.91 ± 0.09	0.90 ± 0.09	0.99 ± 0.07	0.98 ± 0.09	0.98 ± 0.07
Systolic blood pressure (mmHg)	132.2 ± 15.8	132.9 ± 15.2	132.3 ± 15.1	133.65 ± 15.5	132.8 ± 15.6	133.0 ± 15.6
Diastolic blood pressure (mmHg)	79.0 ± 8.8	79.3 ± 8.5	79.2 ± 8.7	80.4 ± 8.5	80.0 ± 9.2	79.4 ± 9.1
Fasting plasma glucose (mg/dl)	150.9 ± 23.3	150.6 ± 25.6	151.9 ± 27.6	152.0 ± 27.6	151.9 ± 25.6	152.8 ± 27.1
A1C (%)	7.37 ± 0.89	7.36 ± 0.93	7.35 ± 0.88	7.36 ± 0.97	7.36 ± 0.94	7.34 ± 0.95
Fasting insulin (pmol/l)	154.2 ± 99.1	162.6 ± 113.4	167.8 ± 132.3	146.4 ± 114.9	144.5 ± 109.9	137.9 ± 95.1
Estrogen-containing hormones	125 (19.4)	137 (23.2)	114 (18.8)	1 (0.1)	1 (0.1)	0
Calcium supplements	41 (6.4)	52 (8.8)	40 (6.6)	11 (1.4)	15 (1.7)	5 (0.6)
Bisphosphonates	12 (1.9)	11 (1.9)	8 (1.3)	1 (0.1)	2 (0.2)	1 (0.1)
Glucocorticoids*	47 (7.3)	41 (6.9)	51 (8.4)	61 (7.5)	50 (5.8)	53 (6.3)
Thiazide diuretics	120 (18.6)	123 (20.8)	126 (20.8)	109 (13.4)	96 (11.1)	94 (11.2)
Loop diuretics	20 (3.1)	27 (4.6)	23 (3.8)	9 (1.1)	18 (2.1)	16 (1.9)

Data are means ± SD or *n* (%). *Includes all routes of administration. NA, not applicable.

increased risk of fracture with rosiglitazone was first apparent after ~12 months of therapy.

Bone fractures in men

Among the 2,511 men, 89 reported a fracture, with no difference among the groups: 32 (4.0%) of those treated with rosiglitazone, 29 (3.4%) with metformin, and 28 (3.4%) with glyburide. The incidence allowing for the period of exposure was 1.16 per 100 patient-years with rosiglitazone, 0.98 per 100 patient-years with metformin, and 1.07 per 100 patient-years with glyburide. Figure 1*B* presents the Kaplan-Meier estimated cumulative incidence of a fracture, demonstrating no significant difference in risk as estimated from the Cox proportional hazards model. Greater detail of the sites of fractures by treatment assignment in men is listed in Table 1 of the online appendix, available at http://dx.doi.org/10.2337/dc07-2270.

Bone fractures in women

Among the 1,840 women, 111 reported a fracture: 60 (9.3%) of those treated with rosiglitazone, 30 (5.1%) of those treated with metformin, and 21 (3.5%) of those treated with glyburide. The incidence allowing for the period of exposure was 2.74 per 100 patient-years with rosiglitazone, 1.54 per 100 patient-years with metformin, and 1.29 per 100 patient-years with glyburide. The cumulative incidence of a fracture (Fig. 1*C*) reached 15.1% (95% CI 11.2–19.1) at 5 years with rosiglitazone, 7.3% (4.4–10.1) with metformin, and 7.7% (3.7–11.7) with glyburide. With the Cox proportional hazards model, estimated HR (95% CI) for risk of fracture with rosiglitazone versus metformin was 1.81 (1.17–2.80; P = 0.008) and for rosiglitazone versus glyburide was 2.13 (1.30–3.51; P = 0.0029). There was no apparent increased risk of fractures with rosiglitazone over the first 12 months of exposure, the increased risk being manifest beyond 12 months of exposure. Fracture risk did not appear to be related to ethnicity, but numbers in the subgroups were small. Among women with a fracture, 11.7% in the rosiglitazone, 16.7% in the metformin, and 23.8% in the glyburide groups reported an accidental limb injury or fall within 30 days before the fracture. Further, among women who reported a fracture, 18.3% receiving rosiglitazone, 16.7% receiving metformin, and 14.3% receiving glyburide reported more than one fracture.

Among premenopausal women receiving rosiglitazone, 6.8% (10 of 147) reported a fracture versus 3.2% (4 of 127) receiving metformin (P = 0.1709) and 1.9% (3 of 156) receiving glyburide (P = 0.0362). Among postmenopausal women, 10.0% (50 of 498) receiving rosiglitazone, 5.6% (26 of 463) receiving metformin, and 4.0% (18 of 449) receiving glyburide reported a fracture (P = 0.0111 for rosiglitazone versus metformin and P = 0.0003 versus glyburide).

Table 2 presents demographics, clinical characteristics, and selected prior medication use at baseline among women who did and did not report a fracture within each treatment group. Women in the glyburide group who reported fractures were older at baseline; in the rosiglitazone group, more women who reported a fracture were receiving treatment for hypertension at baseline.

Table 2 of the online appendix presents the proportions of selected concomitant medications used by women with a fracture (up until the time of first fracture) and those without a fracture (at any time during the study). There were no clear differences in the patterns of use of estrogen-containing hormones, calcium supplements, bisphosphonates, thiazide and loop diuretics, or glucocorticoids between women who did (up until the time

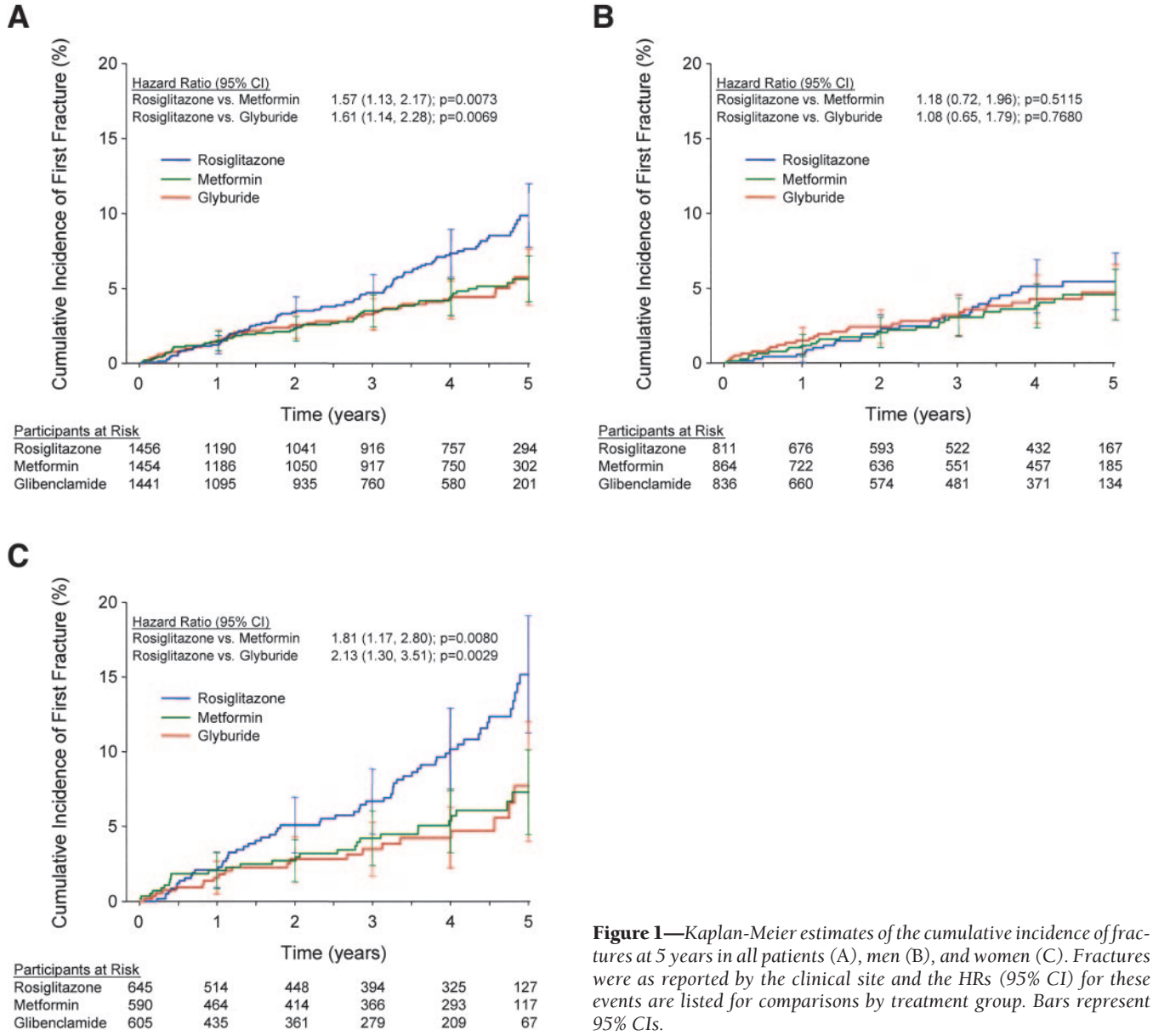

Figure 1—*Kaplan-Meier estimates of the cumulative incidence of fractures at 5 years in all patients* (A)*, men* (B)*, and women* (C)*. Fractures were as reported by the clinical site and the HRs (95% CI) for these events are listed for comparisons by treatment group. Bars represent 95% CIs.*

of first fracture) or did not report a fracture (at any time during the study) within any treatment group. Greater detail of the proportions of concomitant medications used by women with and without a fracture is listed in Table 2 of the online appendix.

Among women in the rosiglitazone group, 5.6% reported a fracture in the lower limb versus 3.1% in the metformin group ($P = 0.0432$) and 1.3% in the glyburide group ($P = 0.0020$), and 3.4% reported a fracture in the upper limb versus 1.7% with metformin ($P = 0.0753$) and 1.5% with glyburide ($P = 0.1188$). There was no difference in the proportion of women who reported a spinal fracture (0.2% with rosiglitazone, 0.2% with metformin, and 0.2% with glyburide). When selected sites are considered, a difference in the proportion experiencing fractures was observed in the foot (3.4% with rosiglitazone, 1.2% with metformin, and 0.7% with glyburide; $P < 0.05$ for rosiglitazone compared with metformin and glyburide), humerus (0.8% with rosiglitazone and 0% for the other treatments), and hand (1.2% with rosiglitazone, 0.7% with metformin, and 0.2% with glyburide; $P > 0.05$ for rosiglitazone compared with metformin and glyburide). Figure 1 of the online appendix illustrates the proportion of women in each group who reported a fracture at selected sites, and a more detailed description of the sites of fractures by treatment assignment is found in Table 3 of the online appendix.

In time-dependent covariate analyses fit separately within each group, the only effect nominally significant at $P \leq 0.05$ was the effect of waist circumference within the glyburide group (HR 1.031 per cm [95% CI 1.001–1.062]; $P = 0.0402$). However, the effect of this covariate did not differ significantly among treatment groups. None of the other covariates had a significant effect (nominal $P \leq 0.05$) on the risk of fractures among women within either group, and the covariate effects did not differ among groups either. Although changes in weight did not significantly affect the risk of fractures among women within any individual treatment group individually, among all females irrespective of treatment there was an increased risk of fracture with increasing body weight

Table 2—*Demographics, baseline characteristics, and selected prior medications by treatment assignment in women with and without fractures*

	Rosiglitazone			Metformin			Glyburide		
	With fractures	Without fractures	*P*	With fractures	Without fractures	*P*	With fractures	Without fractures	*P*
n	60	585		30	560		21	584	
Age									
≤50 years	11 (18.3)	181 (30.9)	0.065	8 (26.7)	153 (27.3)	0.954	3 (14.3)	176 (30.1)	0.012
>50 to ≤60 years	24 (40.0)	205 (35.0)		11 (36.7)	203 (36.3)		5 (23.8)	197 (33.7)	
>60 years	25 (41.7)	199 (34.0)		11 (36.7)	204 (36.4)		13 (61.9)	211 (36.1)	
Race									
White	53 (88.3)	497 (85.0)	0.398	28 (93.3)	485 (86.6)	0.645	20 (95.2)	508 (87.0)	0.805
Black	1 (1.7)	28 (4.8)		2 (6.7)	32 (5.7)		1 (4.8)	38 (6.5)	
Asian	0 (0.0)	15 (2.6)		0 (0.0)	13 (2.3)		0 (0.0)	12 (2.1)	
Hispanic	5 (8.3)	42 (7.2)		0 (0.0)	25 (4.5)		0 (0.0)	25 (4.3)	
Other	1 (1.7)	3 (0.5)		0 (0.0)	5 (0.9)		0 (0.0)	1 (0.2)	
Postmenopausal: yes	50 (83.3)	448 (76.6)	0.235	26 (86.7)	437 (78.0)	0.263	18 (85.7)	431 (73.8)	0.220
Smoking status: yes	4 (6.7)	79 (13.5)	0.132	5 (16.7)	67 (12.0)	0.443	4 (19.0)	71 (12.2)	0.347
Alcohol status: yes	17 (28.3)	173 (29.6)	0.841	11 (36.7)	143 (25.5)	0.180	9 (42.9)	163 (27.9)	0.136
Hypertension drugs: yes	40 (66.7)	306 (52.3)	0.034	12 (40.0)	325 (58.0)	0.052	10 (47.6)	336 (57.5)	0.367
Lipid-lowering drugs: yes	14 (23.3)	138 (23.6)	0.965	7 (23.3)	140 (25.0)	0.837	7 (33.3)	134 (22.9)	0.269
Estrogen-containing hormones	13 (21.7)	112 (19.1)	0.638	5 (16.7)	132 (23.6)	0.383	5 (23.8)	109 (18.7)	0.554
Calcium supplements	4 (6.7)	37 (6.3)	0.918	3 (10.0)	49 (8.8)	0.814	1 (4.8)	39 (6.7)	0.728
Vitamin D	6 (10.0)	47 (8.0)	0.598	3 (10.0)	52 (9.3)	0.896	2 (9.5)	45 (7.7)	0.760
Bisphosphonates	1 (1.7)	11 (1.9)	0.907	1 (3.3)	10 (1.8)	0.542	0	8 (1.4)	0.589
Glucocorticoids*	4 (6.7)	43 (7.4)	0.846	1 (3.3)	40 (7.1)	0.424	2 (9.5)	49 (8.4)	0.854
Statins	10 (16.7)	119 (20.3)	0.498	6 (20.0)	126 (22.5)	0.749	5 (23.8)	111 (19.0)	0.583
Thiazide diuretics	14 (23.3)	106 (18.1)	0.323	4 (13.3)	119 (21.3)	0.298	5 (23.8)	121 (20.7)	0.732
Loop diuretics	2 (3.3)	18 (3.1)	0.913	2 (6.7)	25 (4.5)	0.574	0	23 (3.8)	0.354
Age (years)	58.7 ± 9.70	55.9 ± 10.17	0.041	57.4 ± 9.73	56.6 ± 10.02	0.854	61.1 ± 9.09	56.1 ± 10.76	0.029
BMI (kg/m^2)	33.5 ± 6.42	33.7 ± 7.23	0.936	34.1 ± 5.98	33.8 ± 6.86	0.713	32.6 ± 6.77	33.8 ± 7.08	0.496
A1C (%)	7.49 ± 0.957	7.36 ± 0.879	0.373	7.31 ± 0.821	7.36 ± 0.935	0.883	7.31 ± 1.103	7.36 ± 0.872	0.644
Fasting plasma glucose (mg/dl)	152.8 ± 20.35	150.7 ± 23.56	0.191	149.1 ± 23.37	150.7 ± 25.75	0.686	148.3 ± 17.04	152.0 ± 27.86	0.758
Systolic blood pressure	132.1 ± 13.90	132.2 ± 15.98	0.759	131.0 ± 12.94	133.0 ± 15.31	0.648	129.4 ± 13.97	132.5 ± 15.17	0.497
Diastolic blood pressure	78.7 ± 8.04	79.1 ± 8.89	0.658	77.1 ± 7.77	79.4 ± 8.49	0.160	80.5 ± 7.95	79.2 ± 8.76	0.452

Data are *n* (%) or mean ± SD. *Includes all routes of administration.

(1.04 per kg [1.01–1.07]; $P = 0.0140$). However, accounting for changes in weight over time did not substantially affect the estimated increased risk with rosiglitazone, yielding an adjusted HR for rosiglitazone versus glyburide of 2.06 (95% CI 1.25–3.42) and an HR of 1.60 (0.99–2.60) versus metformin, similar to those in the unadjusted analyses.

CONCLUSIONS — We found that long-term treatment with the thiazolidinedione rosiglitazone is associated with an approximate doubling of the risk of bone fractures in females with type 2 diabetes compared with those taking metformin or glyburide. This increased risk occurs in both premenopausal and postmenopausal women, manifests after 1 year of therapy, and does not appear to be due to increased falls or accidental limb injury. However, the majority of events occurred in postmenopausal women, who had a much higher incidence of fractures. The limited body of data in premenopausal women, although not definitive, is consistent with a similar effect. Over 5 years of follow-up, there was no increased risk of fracture among men.

Our report highlights the value of large, long-term clinical trials. Most clinical studies involving thiazolidinediones are small with a duration of 3–12 months. Given the observation within ADOPT that the cumulative incidence of fractures did not differ with the three therapies until after 1 year, it is not surprising that this adverse effect had not been reported previously. In fact, until we briefly documented this untoward effect of rosiglitazone in ADOPT (11), an increased risk of fractures with a thiazolidinedione had never been clinically demonstrated. The only suggestion that this could occur had come from an epidemiological study of 69 diabetic women aged 70–79 years who manifested increased bone mineral loss with thiazolidinedione treatment (9). After our initial publication, it has been reported that another thiazolidinedione, pioglitazone, is also associated with an ~70% increase in the risk of fractures in women (12), indicating that this adverse effect is probably a thiazolidinedione class effect.

It is well recognized that diabetes is associated with an increased risk of frac-

tures (1–3,5), and this risk has been well documented in the Women's Health Initiative. In that study, >90,000 women were followed for 7 years (5). The cohort included some 5% with diabetes, and in these women it was found that diabetes was associated with a 20% increase in the risk of fractures with the frequency of fractures being increased in the spine, hip, and sites in the upper and lower limbs, with the exception of the lower arm, wrist, and hand. This increased risk of fractures occurred despite the fact that bone mineral density is increased in patients with diabetes compared with those without the disease (5–7). Furthermore, fractures in patients with diabetes are frequently nontraumatic in nature (16).

What, then, may be the mechanism responsible for the increased risk of fractures in thiazolidinedione-treated women? This is not fully understood, but both animal (17) and, more recently, human data (10,18) have demonstrated that thiazolidinedione administration is associated with a reduction in bone mineral density. In humans, this deleterious effect was recently reported to occur in nondiabetic, postmenopausal women who received treatment for 14 weeks and, based on biomarker measurements, was found to be the result of both an acceleration of bone resorption and a reduction in new bone formation (18). These findings are supported by studies in rodents (17) that have, in addition, shown that activation of peroxisome proliferator–activated receptor-γ promotes adipocyte rather than osteoblast differentiation from mesenchymal progenitor cells (19–21) and may reduce IGF-1 levels in bone and thereby also decrease osteoblast formation (22). We reported previously that in ADOPT, 5 years after initiation of treatment with rosiglitazone, the risk of monotherapy failure was decreased by 32% compared with that for metformin and by 63% compared with that for glyburide (11). That fractures were increased in women receiving rosiglitazone despite the agent's greater durability of glucose control suggests that hyperglycemia is not a likely mediator of this deleterious effect of the thiazolidinedione class of drugs. Finally, the time-dependent covariate analysis failed to identify any particular risk factor for the increase in fractures with rosiglitazone and, notably, it was not related to weight gain.

There are limitations to our findings, but they are unlikely to affect the clinical relevance of the observations. First, fracture reports were not systematically collected or adjudicated, and vertebral fractures are often silent, possibly introducing ascertainment bias. Further, the cause and outcome of reported fractures were not systematically followed up. Second, we did not obtain measurements of bone mineral density to assess whether the long-term effect of rosiglitazone included a loss of bone. Third, as the cohort was relatively young and follow-up was for a median of 4.0 years, we cannot exclude the possibility that exposure to medication will not be associated with an increased risk of fractures at other sites later in life.

In summary, we have documented the increased risk of fractures with rosiglitazone relative to metformin or glyburide in women with type 2 diabetes. An increase in fracture risk has also been observed with pioglitazone, and these increases occur in the context of elevated fracture risk among women with type 2 diabetes generally. The mechanism by which these fractures occur is not clear. However, the risk of fracture should be considered in the care of patients with type 2 diabetes, especially female patients, treated with thiazolidinediones, and attention should be given to assessing and maintaining bone health according to current standards of care.

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References

1. Forsen L, Meyer HE, Midthjell K, Edna TH: Diabetes mellitus and the incidence of hip fracture: results from the Nord-Trondelag Health Survey. *Diabetologia* 42: 920–925, 1999
2. Ivers RQ, Cumming RG, Mitchell P, Peduto AJ: Diabetes and risk of fracture: the Blue Mountains Eye Study. *Diabetes Care* 24:1198–1203, 2001
3. Schwartz AV, Sellmeyer DE, Ensrud KE, Cauley JA, Tabor HK, Schreiner PJ, Jamal SA, Black DM, Cummings SR: Older women with diabetes have an increased risk of fracture: a prospective study. *J Clin Endocrinol Metab* 86:32–38, 2001
4. Nicodemus KK, Folsom AR: Type 1 and type 2 diabetes and incident hip fractures in postmenopausal women. *Diabetes Care* 24:1192–1197, 2001
5. Bonds DE, Larson JC, Schwartz AV, Strotmeyer ES, Robbins J, Rodriguez BL, Johnson KC, Margolis KL: Risk of fracture in women with type 2 diabetes: the Women's Health Initiative observational study. *J Clin Endocrinol Metab* 91:3404–3410, 2006
6. Barrett-Connor E, Holbrook TL: Sex differences in osteoporosis in older adults with non-insulin-dependent diabetes mellitus. *JAMA* 268:3333–3337, 1992
7. Strotmeyer ES, Cauley JA, Schwartz AV, Nevitt MC, Resnick HE, Zmuda JM, Bauer DC, Tylavsky FA, de Rekeneire N, Harris TB, Newman AB: Diabetes is associated independently of body composition with BMD and bone volume in older white and black men and women: the Health, Aging, and Body Composition Study. *J Bone Miner Res* 19:1084–1091, 2004
8. Lipscombe LL, Jamal SA, Booth GL, Hawker GA: The risk of hip fractures in older individuals with diabetes: a population-based study. *Diabetes Care* 30:835–841, 2007
9. Schwartz AV, Sellmeyer DE, Vittinghoff E, Palermo L, Lecka-Czernik B, Feingold KR, Strotmeyer ES, Resnick HE, Carbone L, Beamer BA, Park SW, Lane NE, Harris TB, Cummings SR: Thiazolidinedione use and bone loss in older diabetic adults. *J Clin Endocrinol Metab* 91:3349–3354, 2006
10. Yaturu S, Bryant B, Jain SK: Thiazolidinedione treatment decreases bone mineral density in type 2 diabetic men. *Diabetes Care* 30:1574–1576, 2007
11. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G: Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 355:2427–2443, 2006
12. Takeda Pharmaceutical Company: Observation of an increased incidence of fractures in female patients who received long-term treatment with ACTOS (pioglitazone HCl) tablets for type 2 diabetes mellitus (Letter to health care providers). Osaka, Japan, Takeda Pharmaceutical Company, 2007
13. Viberti G, Kahn SE, Greene DA, Herman WH, Zinman B, Holman RR, Haffner SM, Levy D, Lachin JM, Berry RA, Heise MA, Jones NP, Freed MI: A Diabetes Outcome Progression Trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. *Diabetes Care* 25:1737–1743, 2002
14. Lachin JM: *Biostatistical Methods. The Assessment of Relative Risks.* New York, John Wiley, 2000
15. Snedecor GW, Cochran WG: *Statistical Methods.* 7th ed. Ames, Iowa, Iowa State University Press, 1980
16. Strotmeyer ES, Cauley JA, Schwartz AV, Nevitt MC, Resnick HE, Bauer DC, Ty-

lavsky FA, de Rekeneire N, Harris TB, Newman AB: Nontraumatic fracture risk with diabetes mellitus and impaired fasting glucose in older white and black adults: the Health, Aging, and Body Composition Study. *Arch Intern Med* 165: 1612–1617, 2005
17. Rzonca SO, Suva LJ, Gaddy D, Montague DC, Lecka-Czernik B: Bone is a target for the antidiabetic compound rosiglitazone. *Endocrinology* 145:401–406, 2004
18. Grey A, Bolland M, Gamble G, Wattie D, Horne A, Davidson J, Reid IR: The peroxisome proliferator-activated receptor-γ agonist rosiglitazone decreases bone formation and bone mineral density in healthy postmenopausal women: a randomized, controlled trial. *J Clin Endocrinol Metab* 92:1305–1310, 2007
19. Lecka-Czernik B, Gubrij I, Moerman EJ, Kajkenova O, Lipschitz DA, Manolagas SC, Jilka RL: Inhibition of Osf2/Cbfa1 expression and terminal osteoblast differentiation by PPARγ2. *J Cell Biochem* 74:357–371, 1999
20. Akune T, Ohba S, Kamekura S, Yamaguchi M, Chung UI, Kubota N, Terauchi Y, Harada Y, Azuma Y, Nakamura K, Kadowaki T, Kawaguchi H: PPARγ insufficiency enhances osteogenesis through osteoblast formation from bone marrow progenitors. *J Clin Invest* 113:846–855, 2004
21. Ali AA, Weinstein RS, Stewart SA, Parfitt AM, Manolagas SC, Jilka RL: Rosiglitazone causes bone loss in mice by suppressing osteoblast differentiation and bone formation. *Endocrinology* 146: 1226–1235, 2005
22. Lecka-Czernik B, Ackert-Bicknell C, Adamo ML, Marmolejos V, Churchill GA, Shockley KR, Reid IR, Grey A, Rosen CJ: Activation of peroxisome proliferator-activated receptor γ (PPARγ) by rosiglitazone suppresses components of the insulin-like growth factor regulatory system in vitro and in vivo. *Endocrinology* 148:903–911, 2007