0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(9):3349–3354

doi: 10.1210/jc.2005-2226

Thiazolidinedione Use and Bone Loss in Older Diabetic Adults

Ann V. Schwartz, Deborah E. Sellmeyer, Eric Vittinghoff, Lisa Palermo, Beata Lecka-Czernik, Kenneth R. Feingold, Elsa S. Strotmeyer, Helaine E. Resnick, Laura Carbone, Brock A. Beamer, Seok Won Park, Nancy E. Lane, Tamara B. Harris, and Steven R. Cummings, for the Health, Aging and Body Composition (Health ABC) Study

Department of Epidemiology and Biostatistics (A.V.S., E.V., L.P.) and Division of Endocrinology (D.E.S., K.R.F.), Department of Medicine, University of California, San Francisco, San Francisco, California 94107-1762; Department of Geriatrics (B.L.-C.), Reynolds Institute on Aging, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72202; Department of Epidemiology (E.S.S., S.W.P.), Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania 15260; Department of Epidemiology (H.E.R.), MedStar Research Institute, Hyattsville, Maryland 20785; Division of Rheumatology (L.C.), Department of Medicine, University of Tennessee, Memphis, Tennessee 38163; Department of Medicine (B.A.B.), Johns Hopkins University, Baltimore, Maryland 21205; Department of Medicine (S.W.P.), Pochon CHA University, Seoul 135-081 Korea; Department of Medicine (N.E.L.), University of California, Davis, Sacramento, California 95616; Laboratory of Epidemiology, Demography, and Biometry (T.B.H.), National Institute on Aging, Bethesda, Maryland 20892; and Research Institute (S.R.C.), California Pacific Medical Center, San Francisco, California 94120

Context: Activation of peroxisome proliferator-activated receptor-γ by thiazolidinediones (TZDs) results in lower bone mass in mice.

Objective: The objective of the study was to determine whether TZD use is associated with changes in bone mineral density (BMD) in older adults with type 2 diabetes.

Design: We analyzed 4-yr follow-up data from the Health, Aging, and Body Composition observational study.

Setting: The study was conducted in a general community.

Patients: White and black, physically able men and women, aged 70–79 yr at baseline with diabetes defined by self-report, use of hypoglycemic medication, elevated fasting glucose (≥126 mg/dl), or elevated 2-h glucose tolerance test (≥200 mg/dl) participated in the study.

Main Outcome Measures: Whole-body, lumbar spine (derived from whole body), and hip BMD were measured by dual-energy x-ray absorptiometry at 2-yr intervals.

Results: Of 666 diabetic participants, 69 reported TZD use at an annual visit, including troglitazone (n = 22), pioglitazone (n = 30), and/or rosiglitazone (n = 31). Those with TZD use had higher baseline hemoglobin A_{1c} and less weight loss over 4 yr but similar baseline BMD and weight than others with diabetes. In repeated-measures models adjusted for potential confounders associated with TZD use and BMD, each year of TZD use was associated with greater bone loss at the whole body [additional loss of −0.61% per year; 95% confidence interval (CI) −1.02, −0.21% per year], lumbar spine (−1.23% per year; 95% CI −2.06, −0.40% per year), and trochanter (−0.65% per year; 95% CI −1.18, −0.12% per year) in women, but not men, with diabetes.

Conclusion: These observational results suggest that TZDs may cause bone loss in older women. These results need to be tested in a randomized trial. **(*J Clin Endocrinol Metab* 91: 3349–3354, 2006)**

THIAZOLIDINEDIONES (TZDS) ARE an effective and frequently prescribed treatment for diabetes and may have the potential to be used as a prevention treatment in adults and adolescents at high risk of diabetes (1–3). However, the effect of TZDs on bone mass is unclear. TZDs are reported to cause bone loss in some (4–6), but not all (7), rodent models. Rzonca *et al.* (4) and others (5) have reported bone loss with rosiglitazone treatment in mouse models, and Sottile *et al.* (6) found bone loss in ovariectomized rats treated with rosiglitazone, although no effect was seen in intact animals. However, Tornvig *et al.* (7) reported that troglitazone treatment did not cause bone loss in mice.

Little information is available on the effects of TZDs on bone in humans. In a small study of troglitazone use, Watanabe *et al.* (8) found that lumbar spine bone mineral density (BMD) Z-scores were not changed after 12 months of treatment in 25 diabetic patients, including 14 women. In this study levels of urine type 1 collagen *N*-telopeptide and serum bone alkaline phosphatase were reduced after the first month of treatment but returned to baseline levels by 12 months. A study in 33 type 2 diabetic patients also found that troglitazone treatment for 4 wk reduced markers of bone turnover by 7–18% (9). We are not aware of published reports on the effects of pioglitazone or rosiglitazone on BMD or bone markers.

TZDs increase insulin sensitivity and thus improve glycemic control through activation of peroxisome proliferator-

First Published Online April 11, 2006

Abbreviations: A1C, Hemoglobin A_{1c}; BMD, bone mineral density; CI, confidence interval; CV, coefficient of variation; DXA, dual-energy x-ray absorptiometry; FG, fasting glucose; GFR, glomerular filtration rate; Health ABC, Health, Aging, and Body Composition; OGTT, oral glucose tolerance test; PPAR, peroxisome proliferator-activated receptor; TZD, thiazolidinedione.

activated receptor (PPAR)-γ. PPAR-γ activation by TZDs may also affect bone through an increase in bone marrow adiposity and a decrease in osteoblastogenesis, resulting in reduced bone formation (4). In addition, TZDs affect the aromatase pathway, leading to decreased estrogen production and possibly an increase in bone resorption (10). Simultaneously, TZD use causes weight gain that could theoretically preserve bone.

Based on findings that TZDs alter bone metabolism in rodents, the purpose of this study was to assess whether TZD use is associated with changes in BMD in older adults with type 2 diabetes using 4-yr follow-up data from the Health, Aging and Body Composition (Health ABC) cohort study.

Subjects and Methods

Health ABC participants

The Health ABC study is a prospective cohort study investigating whether changes in body composition act as a common pathway by which multiple diseases affect morbidity, disability, and risk of mortality. The study has been previously described in a report on diabetes and BMD (11). Briefly, the cohort consists of 3075 men and women, with approximately equal numbers of black and white participants, aged 70–79 yr recruited at two centers, University of Pittsburgh and University of Tennessee, Memphis. Participants were recruited from a random sample of white Medicare beneficiaries and all age-eligible black community residents in Pittsburgh, Pennsylvania, and Memphis, Tennessee. Participants were excluded if they reported any difficulty with activities of daily living, walking up 10 steps without resting, or walking a quarter of a mile. The study procedures were approved by the institutional review boards of the participating institutions, and written informed consent was provided by all participants. The baseline examination took place during 1997–1998.

Diabetes

At baseline, participants were asked, Has a doctor ever told you that you have diabetes or sugar diabetes? Women were asked not to include diabetes that occurred only during pregnancy. A similar question was asked at each of the annual follow-up visits to identify any recently diagnosed cases of diabetes. An inventory of current medications, including hypoglycemic medications, was taken during the baseline and follow-up interviews, with the exception of the third follow-up visit. Fasting glucose was measured at the baseline, yr 1, and yr 3 visits. A 75-g, 2-h oral glucose tolerance test (OGTT) was performed at baseline. A total of 817 participants had diabetes at baseline or were diagnosed during follow-up. At baseline, previously diagnosed diabetes was found in 468 participants who reported a physician diagnosis of diabetes or use of hypoglycemic medications. An additional 251 participants were found to have diabetes, based on a fasting glucose (FG) 126 mg/dl or greater or a 75-g, 2-h OGTT 200 mg/dl or greater. The participant and the participant's health care provider (if participant gave permission) were notified of any elevated FG or OGTT throughout the study. In addition, 98 incident cases of diabetes were identified during 4 yr of follow-up, based on self-report of a physician diagnosis (all exams), hypoglycemic medication use (yr 1, 2, and 4), and/or elevated FG (yr 1 and 3). At baseline, participants who reported diabetes were asked how many years ago they were diagnosed.

Hypoglycemic medication use

At each annual visit except yr 3, participants were asked to identify prescription and over-the-counter medications used in the previous 2 wk. Medications were coded according to the Iowa Drug Information System (12). The TZDs, troglitazone, rosiglitazone, and pioglitazone, were the medications of central interest in this analysis and were grouped together. Other hypolgycemic medications were classified separately as insulins, sulfonylureas, and metformin. α-Glucosidase inhibitors and meglitinides were combined as other hypoglycemic medications. Years of medication use for each 2-yr period between BMD measurements were assigned in half-year (for the first period) and 1-yr (for the second period) increments, based on reported use at the annual visits.

Bone density measurements

BD was measured at the proximal femur and whole body using dual-energy x-ray absorptiometry (DXA; QDR 4500A; Hologic, Inc., Bedford, MA). Lumbar spine BMD was determined from the subregional lumbar spine BMD in the whole-body scan. DXA quality assurance measurements, including use of daily and cross-calibration phantoms, were performed at both study sites to ensure scanner reliability. The *in vivo* precision for whole-body BMD was evaluated by performing duplicate scans on five volunteers for each scanner. The percent coefficient of variation (CV) for these scans was 1.0% in Memphis and 0.4% in Pittsburgh for whole-body BMD and 2.5 and 3.1%, respectively, for subregional lumbar spine BMD. *In vivo* precision for total hip BMD was not available for these particular instruments but has been reported previously for the QDR 4500A as 0.91% (13) and 1.2% (14). The longitudinal precision of BMD scans was assessed using phantoms. The phantom percent CV for total hip BMD was less than 1% at both sites; the whole-body BMD percent CV was 1.2% at Memphis and 1.8% at Pittsburgh, indicating well-controlled densitometers. Measurements were obtained every 2 yr at baseline, yr 2, and yr 4. Of those with diabetes, 666 participants had at least two BMD measurements and were included in these analyses.

Covariates

Weight was measured with a calibrated balance beam scale at baseline and was repeated at each annual clinic visit. Weight change for each 2-yr interval was calculated as the difference between weight measured at yr 2 and baseline and at yr 4 and 2. Height was measured at baseline with a Harpenden stadiometer (Holtain Ltd., Crymych, UK). Body mass index was calculated as weight divided by height squared (kilograms per square meter). Participants were queried regarding current cigarette smoking, alcohol consumption, and physical activity during the baseline interview.

Use of thiazide diuretics, oral estrogen, statins, oral steroids, bisphosphonates, calcitonin, raloxifene, and calcium and vitamin D supplements was ascertained from the medication inventory at clinic visits described above. In this report, bisphosphonates, calcitonin, and raloxifene were grouped together as osteoporosis medications. Oral estrogen and other bone-active medications listed above were each considered as separate variables. Years of use for each medication for the 2-yr periods between BMD measurements were based on reported use at the annual visits, as described previously for hypoglycemic medication use.

Laboratory measurements

Laboratory measurements were performed at the Laboratory of Clinical Biochemistry at the University of Vermont (Burlington, VT). For measurements of plasma glucose at baseline, yr 1, and yr 3, blood was drawn after an overnight fast (≥8 h). At baseline, immediately after the fasting blood draw, participants ingested 75 g glucose in solution (glucola), and a second blood sample was drawn 2 h later. The 2-h glucose tolerance test was not conducted on participants who reported a history of diabetes. Hemoglobin A_{1c} (A1C) was measured in serum specimens using standard laboratory procedures at baseline, yr 3, and yr 5. These values were used to calculate a weighted average for the A1C level during each 2-yr period of the study. Glomerular filtration rate (GFR) was estimated using the abbreviated Modification of Diet in Renal Disease study equation that includes serum creatinine, age, gender, and race (15).

Statistical analyses

Baseline characteristics of the cohort are presented separately for those with and without any reported TZD use during 4 yr of follow-up. χ^2 tests were calculated for categorical variables, and a t test was used for continuous variables to test for any statistical differences between the two groups.

Linear models were used to assess the association of repeated mea-

sures of change in BMD (baseline to yr 2, yr 2 to yr 4) with duration of use of TZDs during the same interval (16). This approach, implemented using the repeated statement in SAS Proc Mixed (SAS Institute Inc., Cary, NC), explicitly models the inverse covariance between the outcomes in the first and second intervals for each participant. The outcome was annualized percent change in BMD, calculated as the change in BMD from the beginning to end of the interval divided by BMD at the beginning of the interval and length of the interval in years. A test for interaction indicated that the effect of TZDs on change in whole body ($P = 0.002$), lumbar spine ($P = 0.050$), and total hip BMD ($P = 0.099$) differed by gender, so results were modeled separately for women and men. There was no indication of an interaction between race and TZD use (all $P \geq 0.36$).

In the initial model, we adjusted for age, race, baseline weight, baseline BMD, use of other diabetic medications, average A1C (a potential confounder by indication of TZD use), duration of diabetes, and boneactive medications and supplements. To this model we then added change in weight during the interval, a possible mediator that may mask an adverse effect of TZD use on hip BMD by other pathways. In supplementary analysis, we also considered annualized absolute changes in BMD. All statistical analyses were performed in SAS version 9.1 (SAS Institute).

Results

Among the 666 participants with diabetes, 69 reported TZD use at an annual visit. Those with any TZD use during 4 yr of follow-up had higher A1C at baseline and yr 3 and were more likely to use other hypoglycemic medications than those with no TZD use. TZD users experienced less weight loss over 4 yr but had similar baseline BMD and weight than others with diabetes (Table 1). Those with and without TZD use did not differ in smoking status, reported alcohol consumption, or level of physical activity at baseline (data not shown).

At the baseline exam (1997–1998), 11 participants reported troglitazone use. Pioglitazone and rosiglitazone became available in 1999, and troglitazone was taken off the market in 2000. The number of participants reporting TZD use during the 4 yr of follow-up is summarized in Table 2. Of those using a TZD, 19 (28%) also reported use of insulin, 50 (72%) reported use of a sulfonylurea, and 28 (41%) reported use of metformin during the 4 yr of follow-up in Health ABC.

In this cohort of older diabetic adults, the mean annual change in BMD among women who did not report any TZD use was −0.41% for whole body, +1.11% for the whole body lumbar spine subregion, and −0.35% at the total hip. The mean annual change in BMD for men who did not report any TZD use was −0.62% for whole body, +1.27% for the whole body lumbar spine subregion, and −0.35% at the total hip. The increase in spine BMD as measured by DXA is a common finding in older adults and reflects an increase in aortic calcifications, osteophytes, and other degenerative changes rather than an actual gain in bone mass (17, 18).

Change in whole-body bone density

In repeated-measures models adjusted for age and race, longer duration of TZD use in women was associated with greater whole-body bone loss. Each year of TZD use was associated with additional whole-body BMD loss of −0.67% per year [95% confidence interval (CI) −1.03, −0.30%]. Multivariable adjustment had little effect on the association between TZD use and bone loss (Table 3). In men, the association between TZD use and whole-body bone loss was not statistically significant in age- and race-adjusted or multivariable models.

TABLE 1. Characteristics of diabetic participants in the Health ABC study of older well-functioning adults

Variable	Non-TZD users (n = 597)	TZD users (n = 69)
Gender (% women)	46.6	46.4
Race (% black)	48.2	53.6
Age at baseline (yr)	73.6 ± 2.8	73.2 ± 2.5
Baseline weight (kg)	81.2 ± 15.1	82.7 ± 14.5
Four-year weight change (kg)	−1.4 ± 5.5	0.5 ± 6.0[a]
A1C (%)		
Baseline	7.3 ± 1.5	8.4 ± 1.6[a]
3 yr after baseline	6.7 ± 1.4	7.6 ± 1.5[a]
5 yr after baseline	6.6 ± 1.2	7.1 ± 0.9[a]
Duration of diabetes (yr)	7.1 ± 11.3	9.5 ± 10.7
GFR (ml/min per 1.73 m^2)[b]	73.0 ± 17.5	76.9 ± 20.2
Baseline BMD (g/cm^2)		
Whole-body BMD	1.12 ± 0.14	1.14 ± 0.15
Lumbar spine BMD[c]	1.08 ± 0.22	1.11 ± 0.23
Total hip BMD	0.94 ± 0.17	0.96 ± 0.18
Femoral neck BMD	0.79 ± 0.14	0.79 ± 0.15
Trochanter BMD	0.73 ± 0.15	0.75 ± 0.15
Medication use at baseline (% yes)		
Insulin	13.4	18.8
Metformin	7.1	14.5[a]
Sulfonylurea	29.2	55.1[a]
Oral estrogen (women only)	20.5	15.6
Oral steroid	2.7	0.0
Any osteoporosis drugs	2.7	1.4
Thiazide diuretics	22.9	15.9
Statin	14.3	29.0[a]
Calcium supplement	13.9	13.0
Vitamin D supplement	6.2	2.9

Data are mean ± SD or percent.

[a] $P < 0.05$, comparing non-TZD and TZD users.

[b] Estimated with abbreviated Modification of Diet in Renal Disease equation.

[c] Obtained from lumbar spine subregion of whole-body DXA scans.

Change in whole-body lumbar spine subregion bone density

Longer duration of TZD use in women was also associated with bone loss at the lumbar spine. Each year of TZD use was associated with an additional change in lumbar spine BMD of −1.14% per year (95% CI − 1.90, −0.37%) adjusted for age and race. Multivariable adjustment had little effect on this association (Table 3). In men, the association between TZD use and bone loss at the lumbar spine was not statistically significant in age- and race-adjusted or multivariable models.

Change in hip bone density

In women, each year of TZD use was associated with additional bone loss at the total hip (−0.38% per year; 95% CI −0.93, 0.17% per year) adjusted for age and race, but the difference was not statistically significant. With multivariable adjustment, the association between TZD use and bone loss increased but was still not statistically significant (−0.49% per year; 95% CI −1.04, 0.07% per year). Much of this increase was due to the adjustment for weight change. Additional annual bone loss at the trochanter associated with each year of TZD use in women was −0.50% (95% CI −1.02, 0.03%) in age- and race-adjusted models and −0.65% (95% CI

TABLE 2. TZD use in the Health ABC cohort over 4 yr

	Baseline, yr 4 (4 yr)	Baseline, yr 2 (first 2 yr)	yr 2–4 (second 2 yr)
No. reporting use of any TZD[a]	69	32	64
Troglitazone	22	22	13
Pioglitazone	30	5	30
Rosiglitazone	31	7	31
Use of any TZD (yr)[b]	1.67 ± 1.03	1.09 ± 0.60	1.25 ± 0.44

[a] Total number of patients reporting use of the three specific TZDs does not equal those using any TZD because a participant may have used more than one type of TZD during the follow-up period.
[b] Mean ± SD.

−1.18, −0.12%) in a multivariable model. However, additional bone loss at the femoral neck associated with each year of TZD use was smaller in magnitude and was not statistically significant (Table 3). In men, the associations between TZD use and bone loss at the total hip, trochanter, and femoral neck were not statistically significant in age- and race-adjusted or multivariable models (Table 3).

Change in BMD among those using TZDs for at least 2 consecutive years

To assess bone loss in those using TZDs for at least 2 consecutive years, we identified 15 participants who reported use of a TZD at both the yr 2 and yr 4 visits. The unadjusted average annual bone loss (yr 2–4) in these participants was −1.59% (SE 0.59%) at the total hip, − 1.12% (SE 0.72%) at the lumbar spine, and −0.63% (SE 0.64%) for whole body. To assess bone loss in those likely to be compliant with TZD use, we identified six of the 15 participants who experienced an improvement in glycemic control between the yr 3 and yr 5 visits. Among these six participants, unadjusted average annual bone loss (yr 2–4) was −2.5% (SE 1.0%) at the total hip, −1.6% (SE 1.3%) at the lumbar spine, and −0.9% (SE 0.7%) for the whole body.

Discussion

Our data suggest that among older adults with diabetes, TZD use is associated with additional bone loss in women but not men. The magnitude of the additional bone loss associated with a year of TZD use was −0.6% per year for whole body. Over 5 yr for women using TZDs continuously, the average additional bone loss would be 3%. The average whole-body bone loss among diabetic women who were not using a TZD in Health ABC was −0.4% per year. TZD use appears to increase whole-body bone loss by a factor of 2.5. Bone loss is a potent predictor of fracture risk, suggesting that TZD use may be associated with a measurable burden on skeletal health.

Although type 2 diabetes is associated with higher BMD, previous studies suggest that the risk of nonvertebral fractures is increased by 30–60% in older adults with diabetes (19–21). In addition, fracture severity may be worse with greater body mass index (22). We previously reported an association between type 2 diabetes and bone loss in older women (11). The rate of bone loss appears to increase the risk of fracture independent of baseline BMD (23) and may be of particular concern in this population that already has a higher risk of fracture.

For both whole-body and spine BMD, the estimated association with TZD use was not substantially altered by adjustment for potential confounders, including weight gain. However, estimates of hip BMD loss associated with TZD use were greater in multivariable-adjusted models, mainly due to adjustment for weight change. This suggests that TZD use may have opposing effects on bone loss at the hip, increasing

TABLE 3. Additional annualized percentage change in BMD per year of TZD use

Model	Women			Men		
	Estimate (% change)	95% CI	*P* value	Estimate (% change)	95% CI	*P* value
Whole body						
Adjusted for age and race	−0.67	−1.03, −0.30	<0.001	0.00	−0.32, 0.31	0.987
Multivariable[a]	−0.61	−1.02, −0.21	0.003	0.04	−0.30, 0.39	0.810
Lumbar spine[b]						
Adjusted for age and race	−1.14	−1.90, −0.37	0.004	−0.19	−0.96, 0.58	0.627
Multivariable[a]	−1.23	−2.06, −0.40	0.004	−0.25	−1.10, 0.60	0.567
Total hip						
Adjusted for age and race	−0.38	−0.93, 0.17	0.178	−0.12	−0.54, 0.29	0.555
Multivariable[a]	−0.49	−1.04, 0.07	0.087	−0.19	−0.61, 0.22	0.358
Femoral neck						
Adjusted for age and race	−0.26	−0.86, 0.34	0.391	0.09	−0.39, 0.56	0.713
Multivariable[a]	−0.32	−0.94, 0.29	0.303	−0.05	−0.54, 0.44	0.843
Trochanter						
Adjusted for age and race	−0.50	−1.02, 0.03	0.063	−0.17	−0.57, 0.23	0.414
Multivariable[a]	−0.65	−1.18, −0.12	0.016	−0.32	−0.72, 0.09	0.124

[a] Age, race, baseline BMD, baseline weight, weight change, average A1C, insulin, metformin, sulfonylureas, other hypoglycemic medications, diabetes duration, GFR, vitamin D supplements, calcium supplements, oral steroids, osteoporosis drugs (bisphophonates, calcitonin, raloxifene), thiazide diuretics, statins, and oral estrogen (women only).
[b] Obtained from lumbar spine subregion of whole-body DXA scans.

bone loss perhaps through PPARγ activation but at the same time preserving bone through the effects of weight gain.

In contrast to our findings, Watanabe *et al.* (8) reported no effect of troglitazone, administered for 12 months, on lumbar spine BMD Z-score in a study of 25 patients with type 2 diabetes. However, this study included only 14 women and did not report results separately by gender. The results of this previous study are not inconsistent with our observation that TZD use affected only bone loss in women. It is also possible that troglitazone has a different effect than the other TZDs on bone and that our results are driven by effects of TZDs other than troglitazone. This possibility is difficult to evaluate. Given the small numbers of users for each individual TZD, we combined the three TZDs and were unable to investigate the individual effects of each TZD on bone loss.

Our study was not designed to distinguish possible mechanisms by which TZDs may impact bone metabolism. From rodent models, there is evidence that TZDs may affect bone through an increase in bone marrow adiposity and a decrease in osteoblastogenesis, resulting in reduced bone formation (4). TZDs are known to inhibit the aromatase pathway, the main source of estrogen in postmenopausal women (10). TZDs also decrease testosterone levels in women with polycystic ovary syndrome (24, 25). The effect of TZDs on testosterone levels in men is more controversial. Vierhapper *et al.* (26) found decreased levels of testosterone after short-term treatment with pioglitazone in healthy men. However, Patel *et al.* (27) reported that, in nondiabetic insulin-resistant subjects, pioglitazone increased testosterone levels in men and decreased levels in women without polycystic ovary syndrome.

Our finding of increased bone loss with TZD use in women but not men may be the result of increased bone turnover in women, providing a greater opportunity for TZDs to influence bone mass. It is also possible that TZDs may have different effects on androgens, and thus on bone metabolism, in women and men.

Inherent limitations of DXA measurements pose difficulties in studying changes in bone density associated with TZD use. Although DXA is the standard for measuring changes in BMD, increases in body weight, a common side effect of TZD use, may cause artifactual increases in BMD. Because DXA determines BMD by comparing the bone with surrounding soft tissue, changes in fat composition with weight gain may alter BMD results. Increases in tissue thickness, resulting from weight gain, could also introduce artifactual increases in DXA measurements. However, because the weight gain in this cohort was modest, changes in tissue thickness and fat and lean tissue composition should be minimal (28). In addition, the increased weight and body fat associated with TZD use would tend to artificially increase the BMD measurements and artificially reduce any observed bone loss. In this case, the bone loss we observed would tend to underestimate the actual bone loss.

DXA measurements may be artificially lowered by increased bone marrow fat, the opposite effect of weight gain (29). Little is known about bone marrow changes with TZD use in humans. In rodent models, TZD use has been reported to increase (4), and to have no effect on (5), bone marrow fat. We did not have measurements of marrow fat and could not assess the extent or possible impact of any changes on DXA measurement of BMD.

Our measurement of lumbar spine BMD was derived from whole-body scans rather than DXA scans specific for the spine because these were not available in Health ABC. Lumbar spine BMD derived from whole-body scans correlates well with site-specific lumbar spine BMD and has also been shown to predict fracture risk (30).

Some misclassification of TZD use is possible because we relied on self-reported medication use at annual visits. However, such misclassification would likely be nondifferential with respect to the outcome of change in BMD and would therefore attenuate any real association between duration of TZD use and bone loss.

Our models adjusted for potential confounders, including higher A1C levels, longer duration of diabetes, and use of other hypoglycemic medications that are associated with TZD use. However, because our study was observational, rather than a randomized treatment, it remains vulnerable to bias from unmeasured or inadequately measured confounders. These methodological issues could be overcome with a well-designed clinical trial planned specifically to examine the impact of TZD use on bone density.

In conclusion, we found that TZD use is associated with bone loss at the whole body, lumbar spine and trochanter in older women, but not men, with type 2 diabetes. Because older women with type 2 diabetes are at increased risk of fracture, further study of the impact of TZDs on bone density and fracture risk is needed.

Acknowledgments

Received October 12, 2005. Accepted April 4, 2006.

Address all correspondence and requests for reprints to: Ann V. Schwartz, Ph.D., Department of Epidemiology and Biostatistics, University of California, San Francisco, 185 Berry Street, Lobby 4, Suite 5700, San Francisco, California 94107-1762. E-mail: aschwartz@psg.ucsf.edu.

This work was supported in part by the Intramural Research Program of the National Institutes of Health, National Institute on Aging (NIA) (Grants NIA N01-AG-6-2106, N01-AG-6-2101, N01-AG-6-2103, NIA R01 AG17482), and an American Diabetes Association Junior Faculty Award (to A.V.S.).

References

1. **Yki-Jarvinen H** 2004 Thiazolidinediones. N Engl J Med 351:1106–1118
2. **Einhorn D, Aroda VR, Henry RR** 2004 Glitazones and the management of insulin resistance: what they do and how might they be used. Endocrinol Metab Clin North Am 33:595–616, vii-viii
3. **Wysowski DK, Armstrong G, Governale L** 2003 Rapid increase in the use of oral antidiabetic drugs in the United States, 1990–2001. Diabetes Care 26: 1852–1855
4. **Rzonca SO, Suva LJ, Gaddy D, Montague DC, Lecka-Czernik B** 2004 Bone is a target for the antidiabetic compound rosiglitazone. Endocrinology 145: 401–406
5. **Soroceanu MA, Miao D, Bai XY, Su H, Goltzman D, Karaplis AC** 2004 Rosiglitazone impacts negatively on bone by promoting osteoblast/osteocyte apoptosis. J Endocrinol 183:203–216
6. **Sottile V, Seuwen K, Kneissel M** 2004 Enhanced marrow adipogenesis and bone resorption in estrogen-deprived rats treated with the PPARγ agonist BRL49653 (rosiglitazone). Calcif Tissue Int 75:329–337
7. **Tornvig L, Mosekilde LI, Justesen J, Falk E, Kassem M** 2001 Troglitazone treatment increases bone marrow adipose tissue volume but does not affect trabecular bone volume in mice. Calcif Tissue Int 69:46–50
8. **Watanabe S, Takeuchi Y, Fukumoto S, Fujita H, Nakano T, Fujita T** 2003 Decrease in serum leptin by troglitazone is associated with preventing bone loss in type 2 diabetic patients. J Bone Miner Metab 21:166–171
9. **Okazaki R, Miura M, Toriumi M, Taguchi M, Hirota Y, Fukumoto S, Fujita**

T, Tanaka K, Takeuchi A 1999 Short-term treatment with troglitazone decreases bone turnover in patients with type 2 diabetes mellitus. Endocr J 46:795–801
10. **Rubin GL, Zhao Y, Kalus AM, Simpson ER** 2000 Peroxisome proliferator-activated receptor γ ligands inhibit estrogen biosynthesis in human breast adipose tissue: possible implications for breast cancer therapy. Cancer Res 60:1604–1608
11. **Strotmeyer ES, Cauley JA, Schwartz AV, Nevitt MC, Resnick HE, Zmuda JM, Bauer DC, Tylavsky FA, de Rekeneire N, Harris TB, Newman AB** 2004 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
12. **Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin P** 1994 Drug data coding and analysis in epidemiologic studies. Eur J Epidemiol 10:405–411
13. **Baran D, Leahey D, von Stetten E** 1995 Clinical evaluation of a fourth generation fanbeam DXA system. J Bone Miner Res 10:S374 (Abstract)
14. **Fuerst T, Gluer CC, Genant H** 1995 Performance evaluation of a new bone densitometer: Hologic QDR-4500. J Bone Miner Res 10:S370 (Abstract)
15. **Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G** 2003 National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 139:137–147
16. **McCulloch C, Searle S** 2001 Generalized, linear, and mixed models. New York: Wiley
17. **Dawson-Hughes B, Dallal GE** 1990 Effect of radiographic abnormalities on rate of bone loss from the spine. Calcif Tissue Int 46:280–281
18. **Greenspan SL, Maitland LA, Myers ER, Krasnow MB, Kido TH** 1994 Femoral bone loss progresses with age: a longitudinal study in women over age 65. J Bone Miner Res 9:1959–1965
19. **Schwartz AV, Sellmeyer DE, Ensrud KE, Cauley JA, Tabor HK, Schreiner PJ, Black DM, Cummings SR** 2001 Older women with diabetes have an increased risk of fracture: a prospective study. J Clin Endocrinol Metab 86:32–38
20. **de Liefde II, van der Klift M, de Laet CE, van Daele PL, Hofman A, Pols HA** 2005 Bone mineral density and fracture risk in type-2 diabetes mellitus: the Rotterdam Study. Osteoporos Int 16:1713–1720
21. **Strotmeyer ES, Cauley JA, Schwartz AV, Nevitt MC, Resnick HE, Bauer DC, Tylavsky FA, de Rekeneire N, Harris TB, Newman AB** 2005 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
22. **Spaine LA, Bollen SR** 1996 'The bigger they come': the relationship between body mass index and severity of ankle fractures. Injury 27:687–689
23. **Sornay-Rendu E, Munoz F, Duboeuf F, Delmas PD** 2005 The rate of forearm bone loss is associated with an increased risk of fracture independently of bone mass in postmenopausal women. The OFELY study. J Bone Miner Res 20:1929–1935
24. **Azziz R, Ehrmann D, Legro RS, Whitcomb RW, Hanley R, Fereshetian AG, O'Keefe M, Ghazzi MN** 2001 Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. J Clin Endocrinol Metab 86:1626–1632
25. **Arlt W, Auchus RJ, Miller WL** 2001 Thiazolidinediones but not metformin directly inhibit the steroidogenic enzymes P450c17 and 3β-hydroxysteroid dehydrogenase. J Biol Chem 276:16767–16771
26. **Vierhapper H, Nowotny P, Waldhausl W** 2003 Reduced production rates of testosterone and dihydrotestosterone in healthy men treated with rosiglitazone. Metabolism 52:230–232
27. **Patel SM, Szapary P, Ratcliffe SJ, Wolfe ML, Cappola AR,** The effect of pioglitazone on insulin sensitivity and androgen levels in nondiabetic patients with the metabolic syndrome: a double-blind, randomized, placebo-controlled dose escalation trial. Program of the 87th Annual Meeting of The Endocrine Society, San Diego, CA, 2005, p 265 (Abstract P1-393)
28. **Tylavsky FA, Lohman TG, Dockrell M, Lang T, Schoeller DA, Wan JY, Fuerst T, Cauley JA, Nevitt M, Harris TB** 2003 Comparison of the effectiveness of 2 dual-energy X-ray absorptiometers with that of total body water and computed tomography in assessing changes in body composition during weight change. Am J Clin Nutr 77:356–363
29. **Chappard D, Moquereau M, Mercier P, Gallois Y, Legrand E, Basle MF, Audran M** 2004 *Ex vivo* bone mineral density of the wrist: influence of medullar fat. Bone 34:1023–1028
30. **Melton 3rd LJ, Looker AC, Shepherd JA, O'Connor MK, Achenbach SJ, Riggs BL, Khosla S** 2005 Osteoporosis assessment by whole body region *vs.* site-specific DXA. Osteoporos Int 16:1558–1564

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.