

Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis

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ABSTRACT

Background: Rosiglitazone and pioglitazone may increase the incidence of fractures. We aimed to determine systematically the risk of fractures associated with thiazolidinedione therapy and to evaluate the effect of the therapy on bone density.

Methods: We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), other trial registries and product information sheets through June 2008. We selected long-term (≥ 1 year) randomized controlled trials involving patients with type 2 diabetes and controlled observational studies that described the risk of fractures or changes in bone density with thiazolidinediones. We calculated pooled odds ratios (ORs) for fractures and the weighted mean difference in bone density.

Results: We analyzed data from 10 randomized controlled trials involving 13 715 participants and from 2 observational studies involving 31 679 participants. Rosiglitazone and pioglitazone were associated with a significantly increased risk of fractures overall in the 10 randomized controlled trials (OR 1.45, 95% confidence interval [CI] 1.18–1.79; $p < 0.001$). Five randomized controlled trials showed a significantly increased risk of fractures among women (OR 2.23, 95% CI 1.65–3.01; $p < 0.001$) but not among men (OR 1.00, 95% CI 0.73–1.39; $p = 0.98$). The 2 observational studies demonstrated an increased risk of fractures associated with rosiglitazone and pioglitazone. Bone mineral density in women exposed to thiazolidinediones was significantly reduced at the lumbar spine (weighted mean difference -1.11% , 95% CI -2.08% to -0.14% ; $p = 0.02$) and hip (weighted mean difference -1.24% , 95% CI -2.34% to -0.67% ; $p < 0.001$) in 2 randomized controlled trials.

Interpretation: Long-term thiazolidinedione use doubles the risk of fractures among women with type 2 diabetes, without a significant increase in risk of fractures among men with type 2 diabetes.

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raised in a footnote of the report of the A Diabetes Outcome and Progression Trial (ADOPT).⁶ The manufacturers of rosiglitazone⁷ and pioglitazone followed this up by issuing warning letters about the risk of fractures.⁷⁻⁹

Women with type 2 diabetes are at an increased risk of non-vertebral fractures,¹⁰ with a near doubling in the risk of hip fractures.¹¹ Any additional risk from thiazolidinedione therapy could have a considerable impact. Our primary objective was to determine systematically the relative and absolute risks of fractures with long-term thiazolidinedione therapy for type 2 diabetes. We also reviewed the effect of thiazolidinedione therapy on bone mineral density to ascertain its biological plausibility.

Methods

Search strategy

We searched MEDLINE, EMBASE and the Cochrane Central Registry of Controlled Trials (CENTRAL) through June 2008. We also searched the websites of regulatory authorities, manufacturers' product information sheets, and the registers of clinical trials of GlaxoSmithKline,¹² Takeda Pharmaceuticals,¹³ and the Clinical Study Results database¹⁴ for unpublished studies. We checked existing systematic reviews and the bibliographies of the studies that were included. Finally, we used the Web of Science Citation Index to identify relevant articles of high impact. Our search strategy is outlined in Appendix 1.

Eligibility criteria

We selected randomized controlled trials and controlled observational studies that compared the risk of fracture among patients with type 2 diabetes who were taking thiazolidinedione therapy and patients not taking this therapy.]

We included randomized controlled trials that met the following inclusion criteria: parallel-design trial of any thiazolidinedione (rosiglitazone, pioglitazone or troglitazone) of at least one year's duration. The participants had impaired glucose tolerance or type 2 diabetes mellitus; each study used either placebo or oral therapy with an active comparator as the control arm; the treatment groups differed only in the use of

Recent systematic reviews have focused on the adverse cardiovascular effects of the thiazolidinediones rosiglitazone and pioglitazone.¹⁻⁵ In late 2006, the risk of fractures with the use of rosiglitazone was

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thiazolidinediones; and the studies reported clearly on fracture outcomes.

For the secondary outcome of effects of thiazolidinediones on bone mineral density, we selected randomized controlled trials and controlled observational studies of any duration that compared changes in bone mineral density in patients with and without thiazolidinedione exposure.

Validity assessment

We assessed the reporting of allocation concealment and the use of blinding in the randomized controlled trials. In accordance with the Cochrane handbook for systematic reviews of interventions, we assessed the strength of data on adverse effects in both the randomized controlled trials and the observational studies by noting how the investigators monitored and recorded adverse effects.¹⁵

Data abstraction

Two reviewers (Y.K.L and S.S.), both independently and as a team, assessed the eligibility and quality of studies for reporting of adverse events. They extracted numerical data on outcomes from the studies included in our analysis. The reviewers achieved consensus on inclusion of the studies and data extraction. Any discrepancies were resolved through discussion. They also contacted authors about items that required clarification.

Study characteristics

From the randomized controlled trials, we recorded the dose and duration of thiazolidinedione therapy and the baseline characteristics of the participants. From the observational studies, we recorded information on the sources of data, the participants, the verification of exposure and the outcomes.

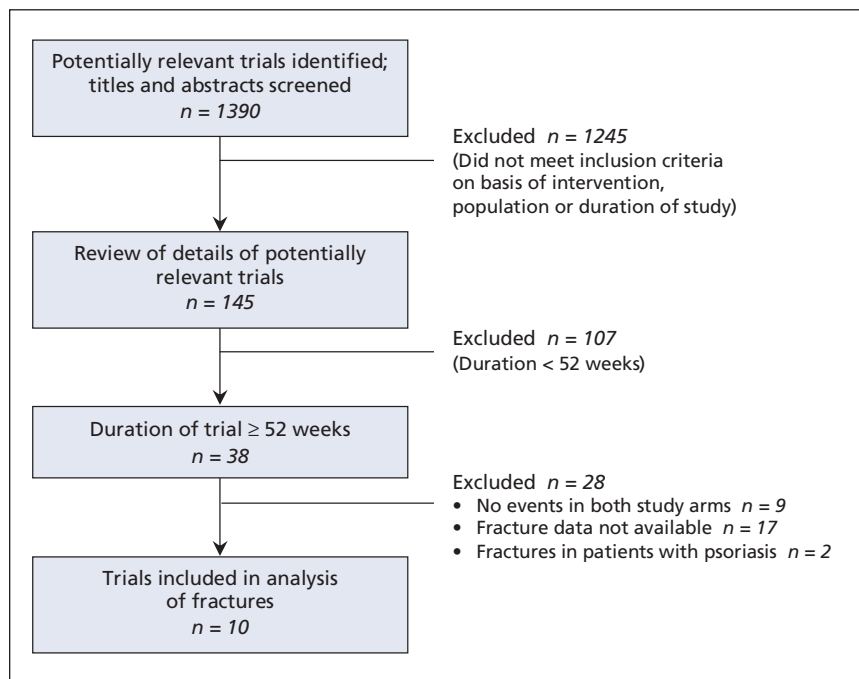


Figure 1: Selection of randomized controlled trials of thiazolidinedione use for meta-analysis of risk of fractures in patients with type 2 diabetes mellitus.

Data synthesis

We used fixed-effects models to calculate pooled odds ratios (ORs), with 95% confidence intervals (CIs), for dichotomous outcomes. We calculated weighted mean differences for continuous outcomes. The fixed-effects Mantel–Haenszel model is the appropriate method for meta-analysis of rare events.¹⁶ All reported *p* values are 2-sided, with significance set at *p* less than 0.05. Statistical heterogeneity was assessed using the *I*² statistic, with 95% CIs.^{17,18} A substantial level of heterogeneity is indicated by *I*² values of 50% or more.¹⁷

We also carried out a predefined sensitivity analysis to determine the influence of trial duration and statistical models on effect size. We estimated the fail-safe number using the Rosenberg method to assess the potential impact of missing data in the meta-analysis (i.e., the number of additional negative trials that would be required to reverse a significant finding in the meta-analysis).¹⁹

We calculated the number needed to harm by applying the pooled OR from the meta-analysis to the control event rate in different populations.^{20,21} The number needed to harm is the number of patients with type 2 diabetes who must be treated with a thiazolidinedione (rather than another intervention) for 1 additional patient to have a fracture. To account for variation in follow-up, we calculated the number needed to harm using person-years as denominators.²²

Results

The selection of trials is summarized in Figure 1. Overall, 10 randomized controlled trials involving a total of 13 715 participants reported on fractures.^{23–32} All of the trials were double-blinded. We judged allocation concealment to be adequate in 6 trials^{23,24,27,30,32} and unclear in 4 trials.^{26,28,29,31} All of the trials included participants with impaired glucose tolerance³¹ and type 2 diabetes.^{23–30,32} The duration was from 1 to 4 years.²³ Data on fractures were available by sex in 5 trials.^{23,24,30,32} The participants in the treatment groups were similar to the control patients with respect to ethnic background, disease duration, glycosylated hemoglobin and body mass index in these 5 trials. Full descriptions of the characteristics of the 10 trials are shown in Appendix 2.

Risk of fractures

Figure 2 shows the pooled data from the 10 randomized controlled trials evaluating the risk of fractures associated with thiazolidinediones overall, and by sex.

We found that thiazolidinediones significantly increased the risk of overall fractures compared with controls (OR 1.45, 95% CI 1.18–1.79; *p* < 0.001); the statistical heterogeneity was moderate (*I*² = 27%) (Figure 2A).

The pooled data from the 5 trials that reported fracture risk by sex (4400 women, 7001 men) showed that thiazolidinediones significantly increased the risk of fractures among women compared with controls (OR 2.23, 95% CI 1.65–3.01; $p < 0.001$) (Figure 2B); there was no statistical heterogeneity among the included trials ($I^2 = 0\%$). Thiazolidinediones did not significantly increase the risk of fractures among men (OR 1.00, 95% CI 0.73–1.39; $p = 0.98$; $I^2 = 0\%$) (Figure 2C). Statistical testing for interaction confirmed a significant difference between the male and female subgroups ($\chi^2 12.01, p < 0.001$).

The characteristics of the 2 observational studies that reported on the association between thiazolidinedione exposure and fractures are shown in Appendix 3.^{33,34} The case-control study by Meier and colleagues³³ showed a significant association between thiazolidinedione exposure (current users with > 8 prescriptions) and fractures among women (OR 2.56, 95% CI 1.43–4.58). In the cohort study, rosiglitazone was significantly associated with fractures when compared with women taking metformin (OR 1.38, 95% CI 1.03–1.82), but no significant elevation of fracture

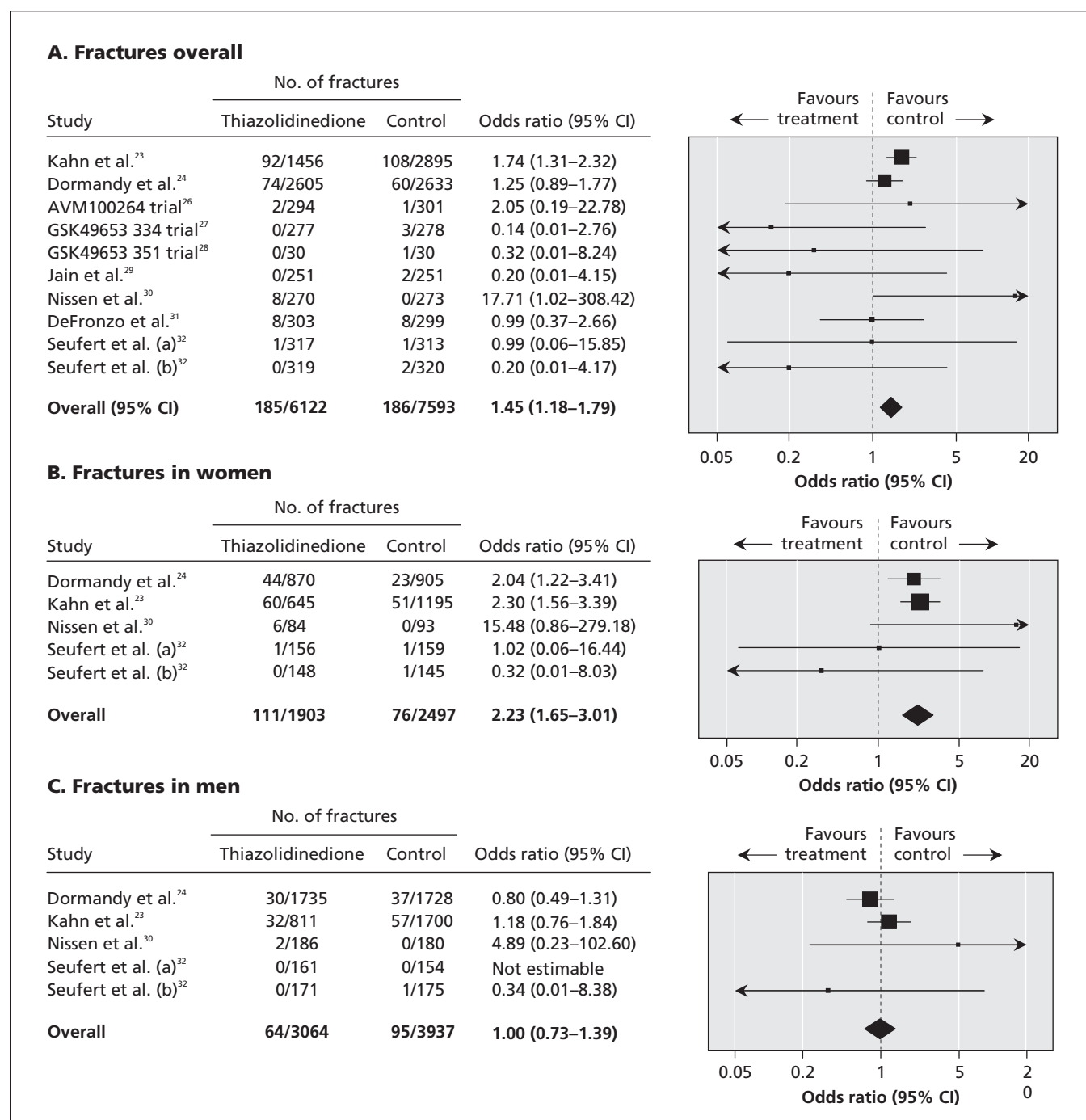


Figure 2: Meta-analysis of fractures in randomized controlled trials of thiazolidinedione versus control.

Table 1: Studies showing the effects of thiazolidinediones on bone mineral density

Study	Design	Population	Treatment groups (no. of patients)	Outcome measures	% of change in bone mineral density, mean (SD)*			
					Hip		Lumbar spine	
					Thiazolidinedione	Control	Thiazolidinedione	Control
Grey et al. ³⁵	14-week double-blind RCT; adequate allocation concealment	50 healthy postmenopausal women in the community; mean age 68 years	<ul style="list-style-type: none"> Rosiglitazone (25) Placebo (25) 	Dual energy radiographic absorptiometry of proximal femur and lumbar spine; biochemical measure of bone resorption	-1.2 (SD 2.1)	-0.2 (SD 2.1)	-1.9 (SD 2.0)	-0.2 (SD 1.6)
Glinborg et al. ³⁶	16-week double-blind RCT; allocation concealment unclear	44 premenopausal women with polycystic ovary syndrome; mean age 32 years	<ul style="list-style-type: none"> Pioglitazone (30) Placebo (14) 	Dual energy radiographic absorptiometry of bone mineral density; biochemical measure of bone metabolism	-1.02 (SD 2.66)	0.34 (SD 2.78)	-0.41 (SD 2.03)	0.67 (SD 2.46)
Yaturu et al. ³⁷	Retrospective controlled cohort study; mean follow-up 16 months	160 men with type 2 diabetes with similar baseline measurements of bone mineral density; mean age 69 years	<ul style="list-style-type: none"> Rosiglitazone (32) Control (128) 	Annualized percentage of change in bone mineral density using dual-energy radiographic absorptiometry	0.69 (SD 2.4)	2.3 (SD 2.9)	-1.19 (SD 1.8)	-0.14 (SD 1.9)
Schwartz et al. ³⁸	4-year prospective cohort study in Health ABC Study	666 older diabetic adults in the community, with and without self-reported thiazolidinedione use; age range 70–79 years	<ul style="list-style-type: none"> Troglitazone (22) Pioglitazone (30) Rosiglitazone (31) 	Annualized percentage of change in bone mineral density using dual-energy radiographic absorptiometry, done every 2 years	Women: -1.23 (95% CI -2.06 to -0.40) additional change per year of drug use Men: -0.25 (95% CI -1.10 to 0.60) additional change per year of drug use	Women: -0.49 (95% CI -1.04 to 0.07) additional change per year of drug use Men: -0.19 (95% CI -0.61 to 0.22) additional change per year of drug use		

Note: CI = confidence interval, RCT = randomized controlled trial, SD = standard deviation.

*Unless stated otherwise.

risk was seen in the comparison of rosiglitazone and sulfonylurea (OR 0.89, 95% CI 0.69–1.14).³⁴ No significant association between thiazolidinedione exposure and fractures among men was found in either study.

Sensitivity analyses

The sensitivity analysis using a random-effects model yielded estimates similar to those of the fixed-effects model for the risk of fractures associated with thiazolidinediones among women (OR 2.19, 95% CI 1.62–2.97; $p < 0.001$). Overall fractures (OR 1.32, 95% CI 0.91–1.92) and fractures among men (OR 1.00, 95% CI 0.73–1.39) were not statistically significant in the sensitivity analysis.

The sensitivity analysis based on the 6 longer-term randomized controlled trials (18 months to 4 years)^{23,24,30–32} showed an elevated risk of fracture (OR 1.51, 95% CI 1.18–1.79; $p < 0.001$). The sensitivity analysis of the 4 smaller trials of 12 months' duration^{26–29} showed a nonsignificant risk of fracture (OR 0.41, 95% CI 0.12–1.44; $p = 0.16$).

Similarly, the association with fractures in the case-control study became apparent among patients who received more than 8 thiazolidinedione prescriptions (corresponding to about 12–18 months of therapy).³³ The cohort study enrolled 27 000 patients with 30 600 patient-years of follow-up, which indicated that, on average, participants were exposed for just over a year.³⁴ With this relatively short duration of exposure, the OR for the rosiglitazone-metformin comparison was elevated only moderately at 1.38, and no significant association was seen in the rosiglitazone-sulfonylurea comparison.

To reverse the significantly increased risk of fractures among women shown in our meta-analysis, we estimated that 42 negative studies with an average sample size of 880 women each would be required.¹⁹

Change in bone mineral density

We identified 2 relevant randomized controlled trials^{35,36} and 2 observational studies^{37,38} (Table 1). All 4 studies showed a consistent decline in bone mineral density associated with thiazolidinediones compared with controls.

The meta-analysis of the percentage point change in bone mineral density in both trials among women who used thia-

thiazolidinediones showed a significant reduction at the lumbar spine (weighted mean difference -1.11% , 95% CI -2.08% to -0.14% ; $p = 0.02$; $I^2 = 0\%$) and at the hip (weighted mean difference -1.24% (95% CI -2.34% to -0.67% ; $p < 0.001$; $I^2 = 0\%$).^{35,36} Adding the observational data from the study by Yaturu and colleagues³⁷ yielded similar findings at the lumbar spine (weighted mean difference -1.36% , 95% CI -2.05% to -0.67% ; $p = 0.001$; $I^2 = 0\%$) and at the hip (weighted mean difference -1.24% , 95% CI -1.78% to -0.70% ; $p < 0.001$; $I^2 = 0\%$) compared with controls (Figure 3).

We excluded 1 observational study from the meta-analysis because its outcome data were reported in a different format.³⁸

Estimated number needed to harm

The relative risk of fractures with thiazolidinediones remained consistently elevated irrespective of age³³ or menopausal status of women.²³ Therefore, we used the single pooled relative risk to estimate the number needed to harm across different age groups.³⁹ Table 2 shows the variation in the number needed to harm and the number of excess fractures with different baseline populations. The patient popula-

tions ranged from patients with newly diagnosed type 2 diabetes at low risk of fractures who were in the metformin arm of the ADOPT study (number needed to harm 55, 95% CI 34–103)²³ to older postmenopausal women with type 2 diabetes at high risk of fracture (number needed to harm 21, 95% CI 14–39).⁴⁰

Interpretation

Our meta-analysis showed that the long-term use of thiazolidinediones doubles the risk of fractures among women with type 2 diabetes, without a significant increase in risk of fractures among men with type 2 diabetes. Overall, use of thiazolidinediones significantly increased the risk of fractures among patients with type 2 diabetes. Thiazolidinedione exposure was also associated with significant changes in bone mineral density at the lumbar spine and the hip.

A posthoc analysis of fracture risk with rosiglitazone in the ADOPT study failed to show any clear relation to ethnicity, hypoglycemia, weight gain or age.²³ However, thiazolidinediones may cause fractures by increasing adiposity of bone marrow,

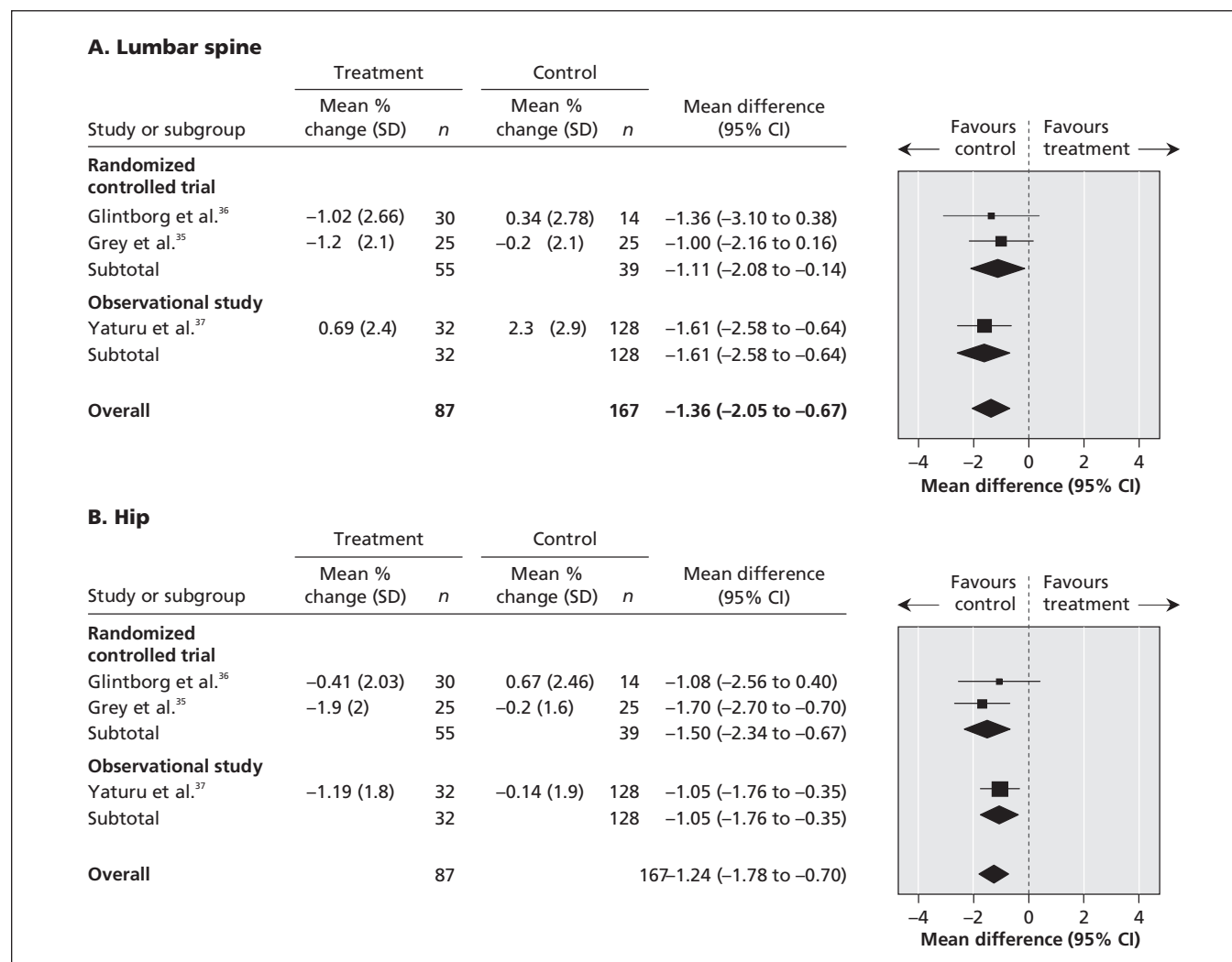


Figure 3: Change in bone mineral density in trials and observational studies.

Table 2: Number needed to harm and number of excess fractures in different populations of women with type 2 diabetes mellitus taking thiazolidinediones

Population	Baseline risk of fractures per 1000 patient-years	Odds ratio of fracture (95% CI) from meta-analysis	1-year number needed to harm* (95% CI)	Excess fractures with thiazolidinedione use per 1000 patient-years (95% CI)
Women in the metformin arm of the ADOPT study; mean age 56 years; diabetes diagnosed within 3 years before study; no previous use of oral hypoglycemic agent ²⁴	15.4	2.23 (1.65–3.01)	55 (34–103)	18 (10–29)
Elderly postmenopausal women in Women's Health Initiative Observational Study; mean age 65 years ¹⁰	28.6	2.23 (1.65–3.01)	31 (19–57)	32 (18–53)
Older cohort of women with diabetes not using insulin; mean age 72 years ⁴⁰	43.5	2.23 (1.65–3.01)	21 (14–39)	48 (26–71)

Note: ADOPT = A Diabetes Outcome and Progression Trial.

*Number of patients with type 2 diabetes who must be treated with a thiazolidinedione, rather than another intervention, for 1 additional patient to have a fracture.

decreasing osteoblast activity or reducing aromatase activity, each of which alters estrogen production and increases bone resorption.³⁸ Thiazolidinediones have a negative effect on markers of bone formation such as alkaline phosphatase and parathyroid hormone.^{35,36,41} In rodent models, rosiglitazone was found to decrease osteoblastic function, which led to bone loss.^{42–44} Thiazolidinediones may also promote osteoclast differentiation and bone resorption.⁴⁵ No proven strategies exist for reducing the risk of fractures induced by thiazolidinediones. Elderly postmenopausal women with type 2 diabetes may not be protected by bisphosphonate therapy.⁴⁶

The underlying mechanism for the apparent sex-specific effect of thiazolidinediones needs further investigation. In animal studies, bone loss occurred with rosiglitazone treatment in rats that had their ovaries removed, but not in rats that were intact.⁴⁷ This indicated that higher levels of sex steroids may protect against fractures in men.⁴⁸

The predominance of fractures in the upper and distal lower limbs with thiazolidinedione therapy, with the relative paucity of hip fractures in the trials, may be attributed to the age of the participants (the mean age was 56 years in the ADOPT study²³). In the observational study by Sanders and colleagues,⁴⁹ the most commonly found fractures in people 55–64 years of age were in the distal upper and lower limbs, whereas the majority (92%) of hip fractures occurred in women over 75 years. The low baseline incidence of hip fractures in the trials' relatively young participants means that the trials lacked the power to detect any significant increase in hip fracture risk (Appendix 4). However, the case-control study involving an older female population (60% were over 60 years) showed that fractures of the hip and femur were significantly associated with thiazolidinedione therapy (OR 4.54, 95% CI 1.28–16.10).³³

The public health impact may be considerable. There were more than 4 million individual users of thiazolidinediones in the United States in 2006.⁵⁰ If one assumes that half of those users were women and that the baseline risk of fractures is similar to that found in the ADOPT study,²³ an estimated 30

000 excess fractures may have occurred if these women had been prescribed thiazolidinediones rather than metformin for more than a year. The excess number of fractures with thiazolidinediones would be 3-fold higher if they experienced fractures at the rates found in population studies^{10,40} rather than at the conservative levels of baseline risk levels of the trials. There is no clear evidence that other oral hypoglycemic agents such as metformin and the sulfonylureas are associated with an increased risk of fractures.⁵¹ Previous observational studies have suggested an increased risk of fracture associated with insulin use, likely due to confounding by severity and duration of diabetes and the presence of comorbidities.^{52,53}

Our results highlight the failure of pharmacovigilance mechanisms that rely on follow-up of spontaneous reports.⁵⁴ We found only a handful of reports of fracture with thiazolidinedione use in the databases of the US Food and Drug Administration in 2006 and Health Canada in 2006.^{55,56} However, in 2001, Quesada-Gomez and Serrano-Alferez⁵⁷ had already called for randomized trials to “examine changes in bone mass and risk for fractures.” Moreover, Rzonca and colleagues⁴³ had warned in 2004 that “rosiglitazone therapy may pose a significant risk of adverse skeletal effects in humans.”

Limitations

Our meta-analysis has several limitations, which are mainly due to the paucity of reported data. None of the trials we included was prospectively designed to measure the risk of fractures. Nevertheless, incidence rates of fractures in the control arms of the trials were consistent with those found in large-scale epidemiologic studies.⁴⁹ We did not have sufficient data to determine whether the risk varied with the particular drug or with different fracture sites. Our estimates of the number needed to harm are valid only for women receiving more than 12 months of thiazolidinedione therapy within the context of specific populations.

We excluded 17 long-term trials of at least 12 months' duration from our analysis because they did not report fracture rates. Although they are unlikely to reverse the direction or

statistical significance of the effect, they may alter the precision of the risk and the confidence intervals. However, not all of the currently unavailable data are negative. An independent interim analysis of fractures in a large long-term rosiglitazone trial that is underway has yielded similar results to those of the ADOPT study.⁷

The only available data from randomized controlled trials on reduced bone mineral density were from healthy women³⁵ and participants with polycystic ovary syndrome,³⁶ rather than patients with type 2 diabetes. However, women with diabetes are likely at similar risk, as shown in the observational studies.³⁸

Conclusion

Despite their limitations, our findings have potential regulatory and clinical implications. Only limited evidence exists that thiazolidinedione-induced glycemic control leads to any reduction in the complications of diabetes.^{58,59} The relatively modest benefits of thiazolidinediones must be balanced against their significant long-term effects on bone and the cardiovascular system. Clinicians should reconsider the use of thiazolidinediones in women with type 2 diabetes. This is in accordance with the updated guidelines of the United Kingdom National Institute of Clinical Excellence.⁶⁰ The guidelines state: "Do not commence or continue a thiazolidinedione in people who have evidence of heart failure, or who are at higher risk of fracture." Regulatory agencies should restrict the use of thiazolidinediones in women with diabetes who are at risk for fractures.

This article has been peer reviewed.

Competing interests: Curt Furberg is a senior investigator and steering committee chair of the National Health, Lung, and Blood Institute-sponsored Cardiovascular Health Study (CHS), a cohort study to examine risk factors of coronary artery disease and stroke in elderly people. In 2004, the study received a grant for \$280 000 from GlaxoSmithKline to determine the relations between LpPLA-2 and various vascular diseases. The grant was primarily for the CHS central laboratory and the CHS coordinating centre. Funding was channeled through Wake Forest University, and Dr. Furberg was the CHS principal investigator. He received no salary support and the funding period ended June 30, 2006. Dr. Furberg has no funding from any other manufacturers of antidiabetic medications. Yoon Loke and Sonal Singh have no competing interests to declare.

Contributors: Yoon Loke and Sonal Singh conceptualized the review, developed the protocol, abstracted and analyzed the data and wrote the manuscript. Curt Furberg reviewed the draft, interpreted the data and provided critical input. Yoon Loke will act as the guarantor for the paper. All of the authors approved the final version of the manuscript submitted for publication.

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Appendix 1 (as supplied by the authors): Specific details of Search Strings June 2008.

PubMed

("rosiglitazone"[Substance Name] OR "rosiglitazone"[All Fields]) OR
("pioglitazone"[Substance Name] OR "pioglitazone"[All Fields]) OR
("troglitazone"[Substance Name] OR "troglitazone"[All Fields])
AND Randomized Controlled Trial[ptyp]

(pioglitazone or rosiglitazone or troglitazone or thiazolidinedione\$) and (bone or fracture\$)

EMBASE

(troglitazone or pioglitazone or rosiglitazone or thiazolidinedione*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
AND (bone or fracture).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
AND "Human" [Subjects]

(pioglitazone or rosiglitazone or troglitazone) {Including Related Terms}
AND trial.mp [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
AND "Human" [Subjects]

Cochrane Controlled Trials Register

Pioglitazone or rosiglitazone or troglitazone

Appendix 2 (as supplied by the authors): Characteristics of randomized controlled trials included in evaluation of fractures

Study ID	Design	Participants	Thiazolidinedione & Comparator	Treatment Duration	Fracture in Thiazolidinedione Arm	Fractures in Control Arm	Monitoring for Adverse Effects.
Kahn 2006 (ADOPT) ^{6, 23}	Double blind, adequate allocation concealment	Type 2 Diabetes Mellitus, diagnosed within past 3 years, treated with diet and exercise only. Mean age 56 years.	Rosiglitazone versus metformin or glibenclamide	4 years	Women: 60/ 645	Women: 51/1195	Investigators looked for adverse events at every study visit. Patients were asked to report number of emergency room visits and hospitalizations, and any days where their activity had been restricted. Baseline characteristics were similar between both groups for ethnicity, disease duration, HbA _{1C} and BMI.
					Men: 32/811	Men: 57/1700	
Dormandy 2006 (PROActiv) ^{24,25}	Double blind, adequate allocation concealment	Type 2 diabetes (median duration 8 years), with known vascular disease. Mean age 62 years. About one-third was on insulin.	Pioglitazone versus placebo	3.5 years	Women: 44/870 ^a	Women: 23/905 ^a	Investigators enquired about adverse events at every study visit. Trial monitors also regularly checked the patients' trial records to ensure that serious adverse events were being reported. Serious events were then checked against the clinical notes. Baseline characteristics were similar between both groups for ethnicity, disease duration, HbA _{1C} and BMI.
					Men: 30/1735 ^a	Men: 37/1728 ^a	
AVM100264 ²⁶	Double blind, unclear allocation concealment	Type 2 Diabetes Mellitus	Rosiglitazone and metformin versus.sulfonylurea and metformin	One year	2/294	1/301	Not stated Baseline characteristics not given

GSK 049653 334 ²⁷	Double blind, adequate allocation concealment	Insulin Resistance Syndrome and Type2 Diabetes	Rosiglitazone versus placebo	One year	0/277	3/278	“Adverse events, laboratory findings and vital signs were closely monitored.” Baseline characteristics were similar between both groups for disease duration, HbA _{1C} and BMI.
GSK 049653 351 ²⁸	Double blind, unclear allocation concealment	Type 2 Diabetes Mellitus with co-existing vascular disease or hypertension	Rosiglitazone versus placebo	One year	0/30	1/30	Not stated
Jain 2006 ²⁹	Double-blind, unclear allocation concealment	Type 2 Diabetes Mellitus	Pioglitazone versus glibenclamide	One year	0/251	2/251	“Adverse events, serious adverse events, and hypoglycaemic events were recorded at each visit. Any untoward medical event concurrent with the use of the study drugs was considered an adverse event.” Baseline characteristics were similar between both groups for ethnicity, disease duration, HbA _{1C} and BMI.
Nissen 2008 (PERISCOPE) ³⁰	Double-blind, adequate allocation concealment	Type 2 Diabetes Mellitus	Pioglitazone versus glimepiride	18 months	Women: 6/84	Women: 0/93	Investigators reported listed adverse events, including hypoglycemia, angina pectoris, peripheral edema, hypertension, and bone fractures. Baseline characteristics were similar between both groups for ethnicity, disease duration, HbA _{1C} and BMI.
					Men: 2/186	Men: 0/180	
DeFronzo 2008 (ACTNow) ³¹	Double-blind, unclear allocation concealment	Impaired Glucose Tolerance	Pioglitazone versus placebo	2.5 years	8/303	8/299	Adverse events were collected as secondary outcomes. Baseline characteristics not given.

Seufert(a) 2008³²	Double-blind, adequate allocation concealment	Type 2 Diabetes Mellitus	Pioglitazone plus metformin versus gliclazide plus metformin	2 years	Women: 1/156	Women: 1/159	Tolerability and safety assessed by monitoring adverse events, physical examination and vital signs and standard clinical laboratory tests. Baseline characteristics were similar between both groups for ethnicity, disease duration, HbA _{1C} and BMI.
					Men: 0/161	Men: 0/154	
Seufert(b) 2008³²	Double-blind, adequate allocation concealment	Type 2 Diabetes Mellitus	Pioglitazone plus sulfonylurea versus metformin plus sulfonylurea	2 years	Women: 0/148	Women: 1/145	Tolerability and safety assessed by monitoring adverse events, physical examination and vital signs and standard clinical laboratory tests. Baseline characteristics were similar between both groups for ethnicity, disease duration, HbA _{1C} and BMI.
					Men: 0/171	Men: 1/175	

^{a.} We extracted fracture data from the manufacturer's Product Information for the PROactive study, as the data on fractures remain unpublished ²⁴

Appendix 3 (as supplied by the authors): Observational studies of thiazolidinedione exposure and association with fractures

Study	Study Type and Data Source	Study Population	Ascertainment of drug exposure	Outcome Ascertainment	Association of thiazolidinediones with fractures
Meier 08 ³³	Case-control. UK General Practice Research Database with medical and prescription records of more than 5 million people	1020 diabetic men and women with low impact fractures (301 wrist/forearm, 274 hip, 222 humerus, 148 rib, 56 vertebral, and 19 not stated). 3728 controls (matched on age, sex and general practice). Adjustments made for potential confounders such as use of other antidiabetic agents, smoking status, BMI and other com-morbidities.	Prescriptions were generated and directly transcribed into computer record, accuracy of the recorded data has been validated in previous studies. Information extracted on drug class and number of prescriptions prior to index date. Analysis was stratified by number of prescriptions, prespecified into 3 categories.	Trained general practitioners recorded medical diagnoses. Previous medical record reviews have shown good accuracy of the recorded diagnoses in the GPRD.	No significant association OR 0.90 (0.46-1.74) for patients with <8 prescriptions (corresponding to 12-18 months use). 3.2% of fracture patients had >8 thiazolidinedione prescriptions, as compared to 1.7% of controls. Adjusted OR for current use of >8 prescriptions vs. non-use was 2.43 (95%CI 1.49 – 3.95). Adjusted OR by gender for >8 prescriptions: Men: 2.50 (95% CI, 0.84-7.41), Women: 2.56 (95% CI, 1.43-4.58) For different fracture sites: Hip/femur: OR 4.54 (1.28 – 16.10) Wrist/forearm: OR 2.90 (1.19-7.10) Fracture risk was independent of age, body mass index and duration of diabetes.
WEUSRTP2181 08 ³⁴	Retrospective cohort, about 9000 patients in each cohort and mean follow-up of just over 12 months. US Ingerix Research Database of patients with medical & prescription coverage in managed care.	Adults initiated on rosiglitazone, metformin or sulfonylurea. Follow-up continued until dispensing of second study drug or insulin, or if patient left the scheme. Cohorts were matched on baseline demographics and factors related to cardiac, but not fracture outcomes. Possibility of residual imbalance remains.	Dispensing records indicating initiation of rosiglitazone, metformin or sulfonylurea, with no record of study drug or insulin use in preceding 6 months. Patients excluded if any other study drugs or insulin dispensed within 30 days of the initial study drug. No stratification by duration of drug exposure, thus missing out on potential differential effects related to cumulative dose or duration.	ICD-9 codes for insurance claims related to fractures. No chart review was carried out, as part of this study, although insurers do regularly audit the accuracy of the claims.	<u>Men:</u> Rosiglitazone 90/4960 (1.81%) Metformin 90/4976 (1.81%) Sulfonylurea 98/4984 (1.97%) OR RSG vs. Metformin: 1.00 (0.99-1.01); p=0.38 OR RSG vs. Sulfonylurea: 0.92 (0.69 – 1.23); p=1.0 <u>Women:</u> Rosiglitazone 118/4017 (2.94%) Metformin 86/4001 (2.15%) Sulfonylurea 132/3993 (3.31%) OR RSG vs. Sulfonylurea: 0.89 (0.69-1.14); p=0.38 OR RSG vs. Metformin: 1.38 (1.03 – 1.82); p=0.03

Appendix 4 (as supplied by the authors): Rates of spine, hip and limb fractures from 5 trials**

Site of Fracture		Thiazolidinedione	Control
Spine	Kahn 2006	4 /1456 (0.27%)	3/2895 (0.10%)
	Other trials	No events	No events
Hip/ Femur	Kahn 2006	3/1456 (0.21%)	3/2895 (0.10%)
	Hedblad 2007	0/277 (0%)	1/278 (0.36%)
	AVM 100264	1/294 (0.34%)	1/301 (0.33%)
	Other trials	No events	No events
Unspecified or Other Lower Limb	Kahn 2006	43/1456 (2.95%)	52/2895 (1.80%)
	Jain 2006	0/251 (0%)	2/252 (0.79%)
	Nissen 2008	7/270 (2.59%)	0/273 (0%)
	Other trials	No events	No events
Upper Limb	Kahn 2006	13/1456 (0.89%)	13/2895 (0.45%)
	Hedblad 2007	0/277 (0%)	2/278 (0.72%)
	Nissen 2008	4/270 (1.48%)	0/273 (0%)
	AVM 100264	1/294 (0.34%)	0/301 (0%)
	GSK 49653 351	0/30 (0%)	1/31 (3%)
	Other trials	No events	No events

*Two trials did not specify the exact fracture sites

+Some patients may have had fractures at more than one site