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META-ANALYSIS

The effect of thiazolidinediones on bone mineral density and bone turnover: systematic review and meta-analysis

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Abstract
Aims/hypothesis Thiazolidinediones (TZDs) are associated with an increased risk of fracture but the mechanism is unclear. We sought to determine the effect of TZDs on bone mineral density (BMD) and bone turnover markers.
Methods PubMed, EMBASE and Cochrane CENTRAL databases were searched from inception until January 2015 for randomised controlled trials comparing TZDs with metformin, sulfonylureas or placebo, and those reporting changes in BMD and/or bone turnover markers. The primary outcome was percentage change in BMD from baseline and results were pooled with random effects meta-analyses.
Results In all, 18 trials were included in the primary analyses and another two were included in the sensitivity analyses (n=3,743, 50% women, mean age 56 years, median trial duration 48 weeks). TZDs decreased BMD at the lumbar spine (difference −1.1% [95% CI −1.6, −0.7]; p<0.0001), total hip (−1.0% [−1.4, −0.6]; p<0.0001) and forearm (−0.9% [−1.6, −0.3]; p=0.007). There were statistically non-significant decreases in BMD at the femoral neck (−0.7% [−1.4, 0.0]; p=0.06) and total body (−0.3% [−0.5, 0.0]; p=0.08). Five trials (n=450) showed no statistically significant difference in percentage change in BMD between the TZD group and controls up to 1 year following TZD withdrawal. In 14 trials, the effect of TZD treatment on turnover markers varied considerably between individual studies.
Conclusions/interpretation Treatment with TZDs results in modest bone loss that may not be reversed 1 year after cessation of treatment.

Keywords Bone density · Diabetes mellitus · Meta-analysis · Pioglitazone · Rosiglitazone · Systematic review · Thiazolidinediones

Abbreviations

ADOPT	A Diabetes Outcome Progression Trial
BMD	Bone mineral density
bsALP	Bone-specific alkaline phosphatase
CTX	β-C-terminal telopeptide of type I collagen
IGT	Impaired glucose tolerance
PINP	Procollagen type I N-terminal propeptide
PPAR-γ	Peroxisome proliferator activated receptor-γ
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
TZD	Thiazolidinedione

Introduction

Thiazolidinediones (TZDs), such as rosiglitazone and pioglitazone, are agonists of the peroxisome proliferator activated receptor-γ (PPAR-γ) isoform that promote insulin sensitisation [1]. These agents improve glycaemic control in patients with type 2 diabetes and slow the development of diabetes in persons with impaired glucose tolerance (IGT) [2, 3].

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However, TZDs have also been associated with an increased risk of fracture [4, 5]. Post-hoc analyses of large randomised controlled trials (RCTs) have demonstrated a 1.5- to 2-fold increased risk of distal extremity fracture in women with diabetes receiving TZDs [6–8]. In addition, observational studies have reported an increased risk of fracture in the axial skeleton with TZD use in both women and men [9, 10].

The mechanism by which TZDs increase fracture risk remains unclear. At a cellular level, PPAR-γ acts on mesenchymal stem cells to preferentially promote differentiation into adipogenic cell lineages at the expense of osteoblastogenesis [11]. Some clinical studies report increased loss of bone mineral density (BMD) with TZDs [12–15], but the effects on bone turnover markers have been inconsistent, with evidence for both reduced bone formation [14, 16, 17] and increased bone resorption [12, 17, 18]. It is possible to detect biologically significant effects in surrogate endpoints for fracture, such as BMD and bone turnover, in much smaller cohorts than are required for investigation of effects on fracture incidence. Therefore, we conducted a systematic review and meta-analysis of all RCTs that assessed the effects of TZDs on BMD and bone turnover markers to determine whether or not bone loss, due to an uncoupling of bone formation and resorption, may account for the increased risk of fracture in patients taking TZDs. We also investigated whether or not the effect of TZDs on BMD and bone turnover markers varies depending on patient characteristics (sex, hormonal status, comorbidities) or intervention characteristics (type of TZD, dose, treatment duration), and whether or not withdrawal of therapy results in reversal of any TZD-induced changes in BMD.

Methods

In January 2014, we searched PubMed, EMBASE and Cochrane CENTRAL databases from inception, without limits, for RCTs of TZDs with BMD and/or bone turnover markers as an endpoint. The complete search strategy is shown in the electronic supplementary material (ESM) Table 1. We also searched three clinical trials registries (www.clinicaltrials.gov, www.controlled-trials.com/mrct and www.anzctr.org.au, all accessed 20/01/2014) for ongoing trials, and hand-searched the reference lists of identified articles and recent review articles for relevant studies. An updated literature search of all databases was performed in January 2015.

We included RCTs carried out in adults aged ≥18 years that compared TZD treatment with a control group that received placebo, metformin or a sulfonylurea, and reported changes in BMD or bone turnover markers during the intervention period. Titles and abstracts were screened by one author (E. O. Billington) and the full text of potentially eligible articles were reviewed by two authors independently (E. O. Billington, M. J. Bolland). The process of selection for inclusion in the systematic review and meta-analysis is shown in Fig. 1.

We extracted information from each study on participant characteristics, interventions, study design, outcome measures, funding source and investigator conflicts of interest. Where necessary, we clarified data uncertainties with the study authors. Data were extracted by a single author (E. O. Billington) using a pre-specified extraction form and checked by a second author (M. J. Bolland). Any discrepancies were resolved through discussion. Risk of bias was assessed as recommended in the Cochrane review handbook [19] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The primary endpoint was percentage change in BMD from baseline to the end of the intervention period at the lumbar spine, femoral neck, total hip, forearm and total body. Secondary endpoints were percentage change in bone turnover markers (procollagen type I N-terminal propeptide [PINP], osteocalcin, β-C-terminal telopeptide of type I collagen [CTX] and bone-specific alkaline phosphatase [bsALP]) from baseline to the end of the intervention period, and percentage change in BMD and bone turnover markers

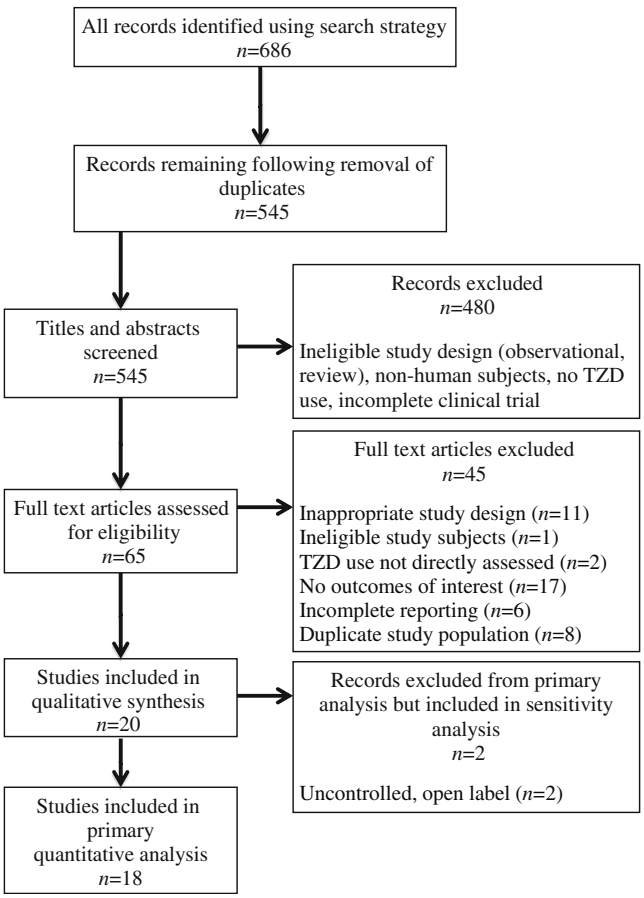

Fig. 1 PRISMA flow sheet indicating process of selection of studies for inclusion in systematic review and meta-analysis

following withdrawal of the intervention. Fractures were not assessed as most of the studies designed to assess change in BMD were underpowered and of inadequate duration to assess fracture outcomes. Furthermore, the risk of fractures with TZD use has been previously established in meta-analyses [4, 5]. Where data were presented in figures, we used digital calipers to extract the data. For studies that presented absolute data rather than percentage change from baseline [13, 16, 20–23], we calculated the mean percentage change from the raw data and calculated the SD of the percentage change using the approaches described in the Cochrane review handbook [24].

Data were pooled using random effects meta-analysis and heterogeneity was assessed using the I^2 statistic (I^2>50% was considered significant heterogeneity). Funnel plots and Egger's regression model were used to assess for the likelihood of publication bias. We undertook sensitivity analyses in pre-specified subgroups (sex, hormonal status, indication for TZD, type of TZD, treatment dose, trial duration). All tests were two-tailed, and p values <0.05 were considered statistically significant. Analyses were performed using Comprehensive Meta-Analysis (Version 2, Biostat, Englewood, NJ, USA).

Results

Literature search results We identified 18 RCTs that met all the inclusion criteria [12–15, 17, 18, 21–23, 25–33]. Two open-label studies had a control group that received no treatment [16, 20] and these were included only in the sensitivity analysis. In our initial search, we identified one completed study at www.clinicaltrials.gov (accessed 20/01/2014) that met our inclusion criteria, but no results had been reported [34]. Results were subsequently published on www.clinicaltrials.gov (accessed 05/01/2015), but neither BMD nor bone turnover marker outcomes were reported and these variables have been removed from the list of outcomes. We requested data from the study contact, but they were unable to provide us with any study results. One conference abstract [35] was potentially eligible for inclusion but did not contain enough information for adequate data extraction and we were unable to contact the study author to obtain further data.

Study characteristics The study design and selected baseline characteristics of the 18 RCTs in the primary analyses and the two open-label studies included in the sensitivity analysis are summarised in Table 1. These 20 studies involved 3,743 participants, of whom 50% were women and the mean age was 56 years. Baseline BMD data are shown in ESM Table 2. Seven studies included only women and one included only men; 12 studies involved patients with type 2 diabetes or IGT, one study had patients with metabolic syndrome, four studies included patients with HIV, one study had women with polycystic ovarian syndrome and two studies involved healthy postmenopausal women.

Rosiglitazone was studied in 12 trials and pioglitazone in eight studies. One multi-arm study administered pioglitazone in one arm and balaglitazone in the other two arms [29]. Results from these three TZD arms were pooled for the primary analyses. One study had a 2×2 factorial design, whereby one treatment arm consisted of rosiglitazone or placebo and the other treatment arm consisted of metformin or placebo [27]. For the primary analyses, we compared the two pooled groups who received rosiglitazone with the two pooled groups who did not. The control group received placebo in 12 studies, metformin in four studies, metformin or placebo in one study, and metformin and glibenclamide (known as glyburide in the USA and Canada) in one study. Eight studies were of ≤6 months duration and 12 were of >6 months duration. Three studies extended beyond 12 months, but none were longer than 25 months [13, 16, 26]. Five studies included follow-up periods after withdrawal of TZD treatment, ranging 24–52 weeks [12, 14, 15, 25, 28]. Fourteen studies reported BMD and 14 reported bone turnover marker outcomes.

ESM Table 3 shows our assessment of the risk of bias; in all, 16 trials were assessed as having a low risk of bias [12–15, 17, 22, 23, 25–33], two as having a moderate risk [18, 21] and two as having high risk of bias [16, 20]. Ten studies were conducted and/or funded by industry, and investigator conflicts of interest were reported for eight studies.

Changes in BMD Fourteen studies (n=1,734 patients) were included in the primary analyses [12–15, 21–23, 25–30, 32]. Figure 2 shows that TZDs decreased BMD compared with controls at the lumbar spine (difference −1.1% [95% CI −1.6, −0.7]; p<0.0001), total hip (−1.0% [−1.4, −0.6]; p<0.0001) and forearm (−0.9% [−1.6, −0.3]; p=0.007). Statistically non-significant decreases were seen in BMD at the femoral neck (−0.7% [−1.4, 0.0]; p=0.06) and total body (−0.3% [−0.5, 0.0; p=0.08]). Inclusion of the open-label RCT [16] in a sensitivity analysis did not change the effect estimates although the femoral neck result became statistically significant (p=0.002). No consistent evidence of publication bias was found for any of these outcomes based on visual inspection of funnel plots and results from the Egger's test.

We performed pre-specified sensitivity analyses in subgroups to determine whether or not restricting the pooled analysis to studies with certain patient or intervention characteristics would alter our findings. The results of analyses restricted to women, postmenopausal women, cohorts with diabetes mellitus or IGT, RCTs of rosiglitazone, RCTs of pioglitazone, RCTs of low-dose TZDs (average daily dose ≤4 mg rosiglitazone or ≤30 mg pioglitazone), RCTs lasting ≤26 weeks, RCTs lasting >26 weeks, RCTs with metformin as a control and RCTs of placebo as a control were all similar to the results for the primary analyses (summarised in ESM

Table 1 Characteristics of RCTs assessing the effect of TZDs on BMD and bone turnover markers in adults

Name	Trial length (weeks)	Withdrawal duration (weeks)	Location	Population	*n*	Mean age (years)	Sex (% women)	Mean BMI (kg/m^2)	Intervention (daily dose)	Control	Outcomes
Berberoglu[a], 2007 [20]	12	None	Turkey	DM2, PM	56	60	100	34	Rosi (4 mg)	None	BTM
Grey, 2007 [14]	14	52	New Zealand	Healthy PM	50	68	100	27	Rosi (8 mg)	Pl	BMD, BTM
Glintborg, 2008 [23]	16	None	Denmark	PCOS	30	33	100	34	Pio (30 mg)	Pl	BMD, BTM
Schindler, 2009 [22]	26	None	Austria	HIV	44	46	8	23	Rosi (4 mg)	Pl	BMD
Berberoglu[a], 2010 [16]	104	None	Turkey	DM2, PM	56	60	100	35	Rosi (4 mg)	None	BMD, BTM
Gruntmanis, 2010 [18]	26	None	USA	DM2	150	56	41	34	Rosi (8 mg)	Pl	BTM
Kanazawa, 2010 [21]	52	None	Japan	DM2, PM	45	66	40	23	Pio (15–30 mg)	Met	BMD, BTM
Tungsiripat, 2010 [32]	48	None	USA	HIV	78	50	17	26	Rosi (8 mg)	Pl	BMD
Zinman, 2010 [17]	52	None	17 countries	DM2	1,605	57	43	33	Rosi (8 mg)	Met and G	BTM
Borges, 2011 [13]	80	None	Nine countries	DM2	209	51	47	33	Rosi (8 mg) and Met	Met	BMD, BTM
Harris, 2011 [27]	16	None	USA	HIV	70	44	39	28	Rosi (4 mg)	Pl and Met	BMD, BTM
Harslof, 2011 [28]	14	26	Denmark	Healthy PM	57	65	100	27	Rosi (8 mg)	Pl	BMD, BTM
Henriksen, 2011 [29]	26	None	Denmark, Sweden, Finland	DM2	409	61	38	34	Pio (45 mg), Bala (10–20 mg)	Pl	BMD, BTM
Ross, 2012 [31]	48	None	USA	HIV	71	50	17	26	Rosi (8 mg)	Pl	BTM
van Lierop, 2012 [33]	24	None	The Netherlands	DM2, men	71	56	0	29	Pio (30 mg)	Met	BTM
Bilezikian, 2013 [12]	52	24	Eight countries	DM2, PM	226	64	100	31	Rosi (8 mg)	Met	BMD, BTM
Bone, 2013 [25]	52	26	USA	IFG or IGT, PM	156	60	100	16	Pio (45 mg)	Pl	BMD, BTM
Bray, 2013 [26]	108[b]	None	USA	IGT	232	49	70	35	Pio (45 mg)	Pl	BMD
Grey, 2014 [15]	52	52	New Zealand	DM2 or IGT	86	64	49	31	Pio (30 mg)	Pl	BMD, BTM
Maalouf, 2014 [30]	52	None	USA	Met synd	42	53	64	33	Pio (45 mg)	Pl	BMD

[a] Open-label studies in which the controls received no treatment; included in sensitivity analyses only

[b] Duration 108 weeks or until development of overt type 2 diabetes

Bala, balaglitazone; BTM, bone turnover markers; DM2, type 2 diabetes mellitus; G, glibenclamide; IFG, impaired fasting glucose; Met, metformin; Met synd, metabolic syndrome; PCOS, polycystic ovarian syndrome; Pio, pioglitazone; Pl, placebo; PM, postmenopausal; Rosi, rosiglitazone

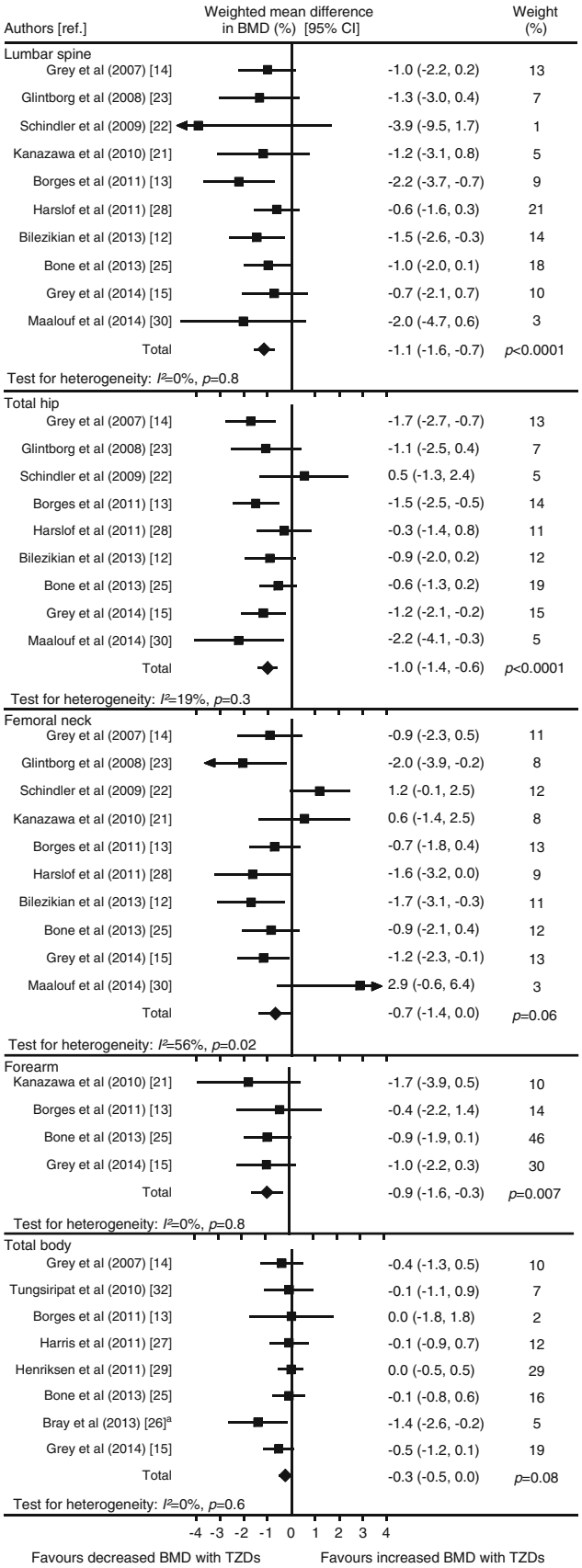

Fig. 2 Meta-analyses of the effects of TZDs on the percentage change in BMD from baseline at five skeletal sites. [a]Subtotal body BMD

Table 4). For this reason, and because most subgroups contained fewer than five studies, we did not formally test for interactions between the subgroups. The number of studies was insufficient to assess effects in men or in cohorts with HIV.

Five studies reported on changes in BMD following withdrawal of TZD treatment for 24–52 weeks [12, 14, 15, 25, 28]. Figure 3 shows that there were no statistically significant differences in percentage change in BMD between the TZD group and controls following treatment withdrawal.

Changes in bone turnover Change in bone turnover markers varied considerably between individual studies and significant heterogeneity was observed for all turnover markers, except osteocalcin. The pooled summary statistics (CTX difference 11.0% [95% CI 0.5, 21.5]; p=0.04; bsALP 1.0% [−5.6, 7.6]; p=0.80; PINP 3.7% [−5.1, 12.5]; p=0.40; osteocalcin −0.8% [−5.2, 3.6]; p=0.70) may, therefore, not be generalisable. Of

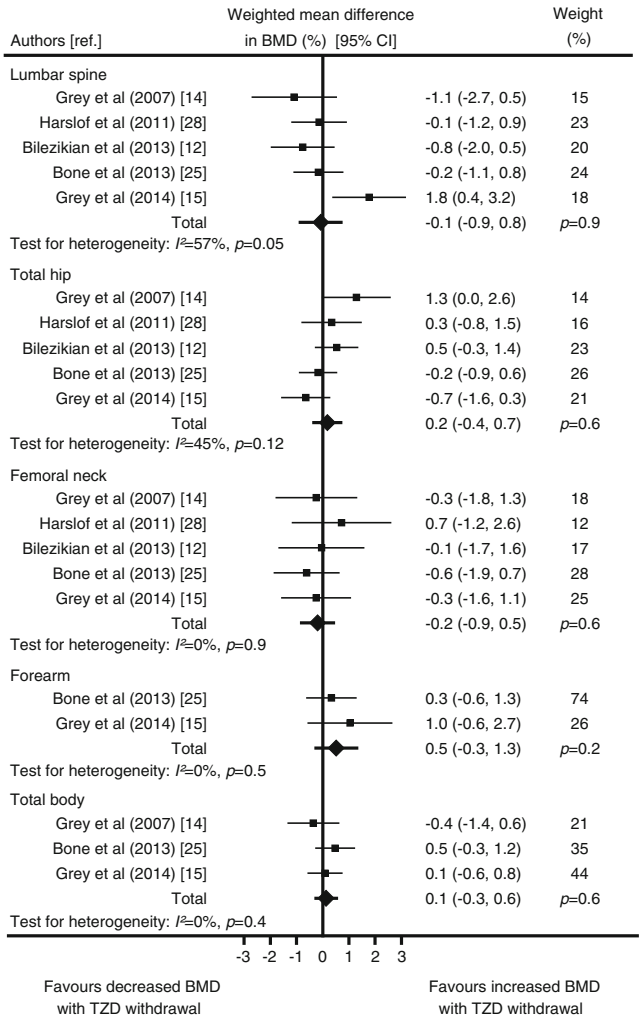

Fig. 3 Meta-analysis of the effects of TZD cessation on the percentage change in BMD at five skeletal sites from the time of TZD withdrawal until the end of the follow-up period

10 studies reporting on CTX, five reported significant increases with TZDs [12, 17, 18, 28, 33] and five showed no effect [13–15, 25, 31]. Of the five studies reporting on bsALP, one reported a significant increase with TZDs [12] and no effect was seen in four [13, 17, 25, 28]. Of the 11 studies reporting on PINP, three reported significant increases with TZDs [12, 18, 33], two showed significant decreases [27, 31] and six found no effect [13–15, 17, 25, 28]. Of the six studies that reported on osteocalcin, one demonstrated a significant decrease with TZDs [14] and five showed no effect [21, 23, 25, 28, 31]. Inclusion of the results of an open-label RCT [20] in a sensitivity analysis did not alter our findings. We did not formally assess for statistically significant interactions between pre-specified subgroups because there were insufficient studies; however, heterogeneity between studies did not appear to be related to patient characteristics, type of TZD, TZD dose, type of control or study duration.

Only two studies reported withdrawal data for markers of bone turnover [12, 25]. Pooling of these results did not identify significant changes in turnover markers following cessation of treatment with TZDs (data not shown).

Discussion

In these meta-analyses, treatment with TZDs for 3–24 months reduced BMD at the lumbar spine, proximal femur and forearm by 0.7%–1.1% compared with placebo or metformin. After cessation of TZD therapy, there was no further loss of BMD, but there was also no regain of the earlier BMD loss. The decreases in BMD were consistent in different RCTs, across different patient populations, in RCTs of different TZD agents and doses, in RCTs with metformin or placebo as a control and in trials lasting ≤6 or >6 months. By contrast, there was marked heterogeneity in changes of most bone turnover markers with TZDs.

Our analyses demonstrate that TZDs cause modest bone loss, an effect that is apparent by 6 months of treatment. An important clinical question is whether or not this bone loss persists with ongoing treatment. If there is little further BMD loss after 1 year of TZD treatment, the decreases in BMD of 0.7%–1.1% observed in the meta-analyses are likely to be clinically insignificant as they are much smaller than the normal variation of BMD in the population, and are equivalent to the average loss of BMD over 1 year in postmenopausal women [36]. However, if BMD loss was cumulative at a rate of 1% per year, such decreases would be clinically important after 5–10 years of treatment. Existing clinical trials are unable to provide a definitive answer to this question. While bone loss appeared to be similar in studies of ≤6 months and >6 months duration, the meta-analyses did not have sufficient power to detect small differences in BMD changes between these subgroups of trials as only three studies extended beyond 1 year [13, 16, 26]. In one of these extended studies, BMD loss at the lumbar spine was greater after 80 weeks than after 56 weeks, arguing against a plateau [13]. Results of an observational cohort study by Schwartz and colleagues suggest that long-term treatment with TZDs may result in progressive bone loss [37]. They found that persons who used TZDs for at least 2 years demonstrated progressive annual bone loss of −1.6% at the total hip and −1.1% at the whole body lumbar spine sub-region. By contrast, the annual change in BMD amongst non-TZD users was −0.4% at the hip and + 1.1% at the lumbar sub-region. However, this was not a controlled trial, and only 15 patients received >2 years of therapy. Given the nature of type 2 diabetes as a chronic, life-long disease, many patients will be prescribed TZDs with the expectation of continuing treatment for at least 5–10 years. Therefore, determining the long-term effects of TZDs on BMD is an important safety question that needs to be addressed with high priority.

Our results raise the possibility that TZDs may increase skeletal fragility by mechanisms other than decreasing BMD. The results of the A Diabetes Outcome Progression Trial (ADOPT) suggest that the 2-fold increased risk of fracture does not become evident until almost 2 years of treatment [8], and an extrapolation of the results from our meta-analyses would suggest a 2% decrease in BMD by this time. This is unlikely to fully explain the changes in fracture risk seen in ADOPT and other RCTs [6–8]. The majority of fractures in patients taking TZDs in randomised trials occur at cortical sites (humerus, distal forearm, tibia) [4, 5], but we did not observe a greater magnitude of bone loss at cortical sites than trabecular sites. Studies in both rodents and humans indicate that TZD exposure is associated with changes in cortical microarchitecture, which will not necessarily be evident on dual-energy x-ray absorptiometry [38–40]. Animal studies have also demonstrated that TZD exposure results in increased cortical porosity and decreased cortical thickness in the absence of significant changes in volumetric BMD [38, 39]. In women using TZDs, reduction in polar strength strain index at highly cortical sites has been observed [40]. Therefore, while TZD-mediated declines in BMD may result in an increased propensity for fracture, particularly if bone loss is sustained with long-term treatment, the excess distal extremity fractures observed in patients taking TZDs may be better explained by changes in microarchitecture at cortical sites.

Assessment of the effect of TZDs on bone turnover markers did not help to elucidate the mechanism by which these medications increase fracture risk. Change in bone turnover markers varied considerably between individual studies. While HIV, anti-retroviral treatment, diabetes, glycaemic control and the postmenopausal state are all known to influence concentrations of turnover markers [41–43], no consistent changes in these markers were observed within the different study populations incorporated in this meta-analysis. Our

findings corroborate the results of animal studies, which have also reported inconsistent effects of TZDs on bone turnover [11]. In addition to being heterogeneous, changes in bone turnover markers did not correspond with the observed changes in BMD in this meta-analysis. Furthermore, several included studies that assessed both turnover markers and BMD did not observe a correlation between the two [12, 13, 23, 29]. This is not surprising as the assessment of turnover marker concentrations is associated with considerable within-patient variability [41] and they do not always correspond with small changes in BMD [44]. Within the subgroup of the ADOPT trial in whom bone turnover markers were measured, Zinman et al did not observe differences amongst those who fractured and those who did not [17]. Therefore, turnover markers appear to have a limited role in the assessment of skeletal response to TZD therapy.

This is the first meta-analysis to assess the effect of TZD discontinuation on BMD. BMD did not change significantly at any site following TZD withdrawal, suggesting that the BMD loss with TZD therapy is not reversible in the year following discontinuation. Although the mechanism by which TZDs act on bone is complex and not yet fully understood, these agents appear to have a direct effect on the differentiation of both osteoblasts and osteoclasts [11, 45]. PPAR-γ has been shown in preclinical studies to promote the differentiation of mesenchymal stem cells into adipocytes rather than osteoblasts [46], and to promote osteoclast differentiation and increase osteoclast numbers [45]. In addition, exposure to TZDs appears to induce osteoblast and osteocyte apoptosis [47–49]. A reduction in the number of osteocytes and osteoblasts has the potential for prolonged negative effects on bone, given the relatively long differentiation periods and lifespans of these cell types [50]. This may explain why there does not appear to be any regain of lost BMD following cessation of TZDs.

This meta-analysis has several limitations. Although we identified 20 eligible RCTs, there were not enough studies to carry out detailed subgroup analyses and only three studies had outcome data beyond 1 year. There was marked heterogeneity amongst studies of bone turnover markers and we were unable to draw conclusions regarding the effect of TZDs on turnover markers. Despite its limitations, this study has several strengths. It is the largest meta-analysis to evaluate the effect of TZDs on bone density and bone turnover markers, and the only one to assess the effect of TZD withdrawal on these variables. We are aware of two previous meta-analyses of the effect of TZDs on BMD [4, 51]. The earlier analysis identified two small RCTs published prior to June 2008 involving 95 participants [4]. The more recent analysis included seven studies [51]. Our meta-analysis provides important additional information by including more studies, previously unpublished data from some studies, more BMD sites, data from withdrawal studies and data from bone turnover markers.

For physicians who treat patients with TZDs, these results raise an important safety flag. Longer-term studies assessing the effects of both TZD treatment and withdrawal on BMD are needed, together with a better understanding of the mechanism by which TZDs affect fracture risk. Until this information is available, it may be prudent for clinicians to periodically monitor BMD in older patients taking TZDs and to consider avoiding these agents altogether in individuals at high risk of fracture, such as postmenopausal women with clinical risk factors for fracture.

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Duality of interest AG is a shareholder in Auckland Bone Density, which provides bone density measurements. All other authors declare that there is no duality of interest associated with their contribution to this manuscript.

Contribution of authors All authors (EB, AG, MB) made significant contributions to the creation of this manuscript. EB, AG, and MB developed the research question and study design. The literature search was conducted by EB. Data extraction was carried out by EB and MB. Writing and revision of the manuscript was done by all three authors. MB is responsible for the integrity of the work as a whole. All three authors have approved the final version of this manuscript for publication.

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