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Risk of fracture with thiazolidinediones: An updated meta-analysis of randomized clinical trials

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ABSTRACT

Objective: The use of thiazolidinediones (TZDs) has been associated with increased fracture risk. We performed a comprehensive literature review and meta-analysis to estimate the risk of fractures with TZDs

Methods: We searched MEDLINE, Embase and the Cochrane Database, from inception to May 2014. We included all randomized trials that described the risk of fractures or changes in bone mineral density (BMD) with TZDs. We pooled data with odds ratios (ORs) for fractures and the weighted mean difference in BMD. To assess heterogeneity in results of individual studies, we used Cochran's Q statistic and the I^2 statistic.

Results: We included 24,544 participants with 896 fracture cases from 22 randomized controlled trials. Meta-analysis showed that the significantly increased incidence of fracture was found in women (OR = 1.94; 95%CI: 1.60–2.35; $P < 0.001$), but not in men (OR = 1.02; 95%CI: 0.83–1.27; $P = 0.83$). For women, the fracture risk was similar in rosiglitazone (OR = 2.01; 95%CI: 1.61–2.51; $P < 0.001$) and pioglitazone (OR = 1.73; 95%CI: 1.18–2.55; $P = 0.005$) treatment and appeared to be similar for participants aged <60 years old (OR = 1.89; 95%CI: 1.51–2.36; $P < 0.001$) and aged ≥60 years old (OR = 2.07; 95%CI: 1.51–2.36; $P < 0.001$). There was a non-significant trend towards increased risk of fractures in different cumulative durations of TZD exposure. TZD treatment was also associated with significant changes in BMD among women at the lumbar spine(weighted mean difference: −0.49%, 95%CI: −0.66% to −0.32%; $P < 0.001$), the femoral neck (weighted mean difference: −0.34%, 95%CI: −0.51% to −0.16%; $P < 0.001$) and the hip(weighted mean difference: −0.33%, 95%CI: −0.52% to −0.14%; $P < 0.001$).

Conclusions: Our results suggest that TZD treatment is associated with an increased risk of fractures in women, effects of rosiglitazone and pioglitazone are similar, fracture risk is independent of age and fracture risk has no clear association with duration of TZD exposure.

Introduction

The thiazolidinediones (TZDs), rosiglitazone and pioglitazone, are peroxisome proliferators-activated receptor γ (PPAR-γ) agonists that alter the transcription of genes influencing carbohydrate and lipid metabolism. In patients with impaired glucose tolerance, they slow the development of type 2 diabetes mellitus (T2DM); in patients with T2DM, TZDs improve glycemic control [1]. On the other hand, their use has been challenged in clinical practice because of side effects which include body-weight gain, congestive heart failure, bone fractures and possibly bladder cancer. This led to warnings and eventually restrictions on the use of rosiglitazone in the United States by the Food and Drug Administration (FDA) [2,3]. As for the other TZDs, pioglitazone too was limited by several side effects. However, FDA recently had determined that recent data for rosiglitazone-containing drugs do not show an increased risk of heart attack compared to the standard type 2 diabetes medicines metformin and sulfonylurea. As a result, they were requiring the removal of the prescribing and dispensing restrictions for rosiglitazone medicines that were put in place in 2010 [4].

By contrast, there were no current guidelines limiting TZD use due to fracture risk. Furthermore, many studies that examined the association between TZDs and risk of fractures had yielded mixed results. Five years ago, a meta-analysis showed that the use of rosiglitazone and pioglitazone was associated with a significantly increased risk of fractures [5]. However, a reanalysis of the same randomized controlled trial data showed that pioglitazone use might not be associated with increased fracture risk in either women or men with T2DM [6]. Subsequently, a series of studies were conducted to reveal the true association between TZD therapy and the risk of fractures [7]. Up to now, most of the data showing the harmful impact of TZDs on bone were consistently obtained from women, especially from older or postmenopausal women. It remains unclear whether the risk is associated with men and whether the risk varied with the particular drug.

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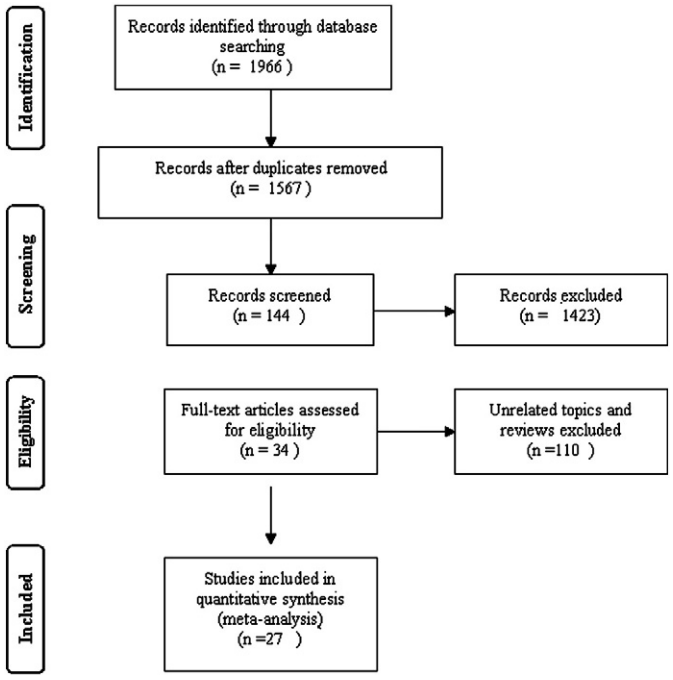

Fig. 1. Flowchart of selecting process for meta-analysis.

Given the newly emerging evidence, we conducted a meta-analysis of randomized clinical trials (RCTs) with the following objectives: (1) to derive a more precise estimation of the association between TZDs and the risk of fractures; (2) to examine the association according to study characteristics;(3) to review TZDs effects on bone mineral density to investigate the etiology of the adverse skeletal effects.

Methods

Search strategy

The meta-analysis is conducted according to the PRISMA guidelines [8]. We searched MEDLINE, Embase and the Cochrane Database of Systematic Reviews through May 2014. We used search terms "pioglitazone", "rosiglitazone", or "thiazolidinediones" in combination with "bones", "skeleton", "bone mineral density", or "fracture". Reference lists from relevant systematic reviews and clinical guidelines are also examined.

Study selection

Study selection was based on an initial screen of identified abstracts or titles and a second screen of full-text articles. Studies were considered eligible if they met the following criteria: (1) the study design was a randomized controlled trial; (2) the main exposure of interest was any TZDs (rosiglitazone, pioglitazone); (3) the outcome of interest was fracture incidence or effects of TZDs on bone mineral density.

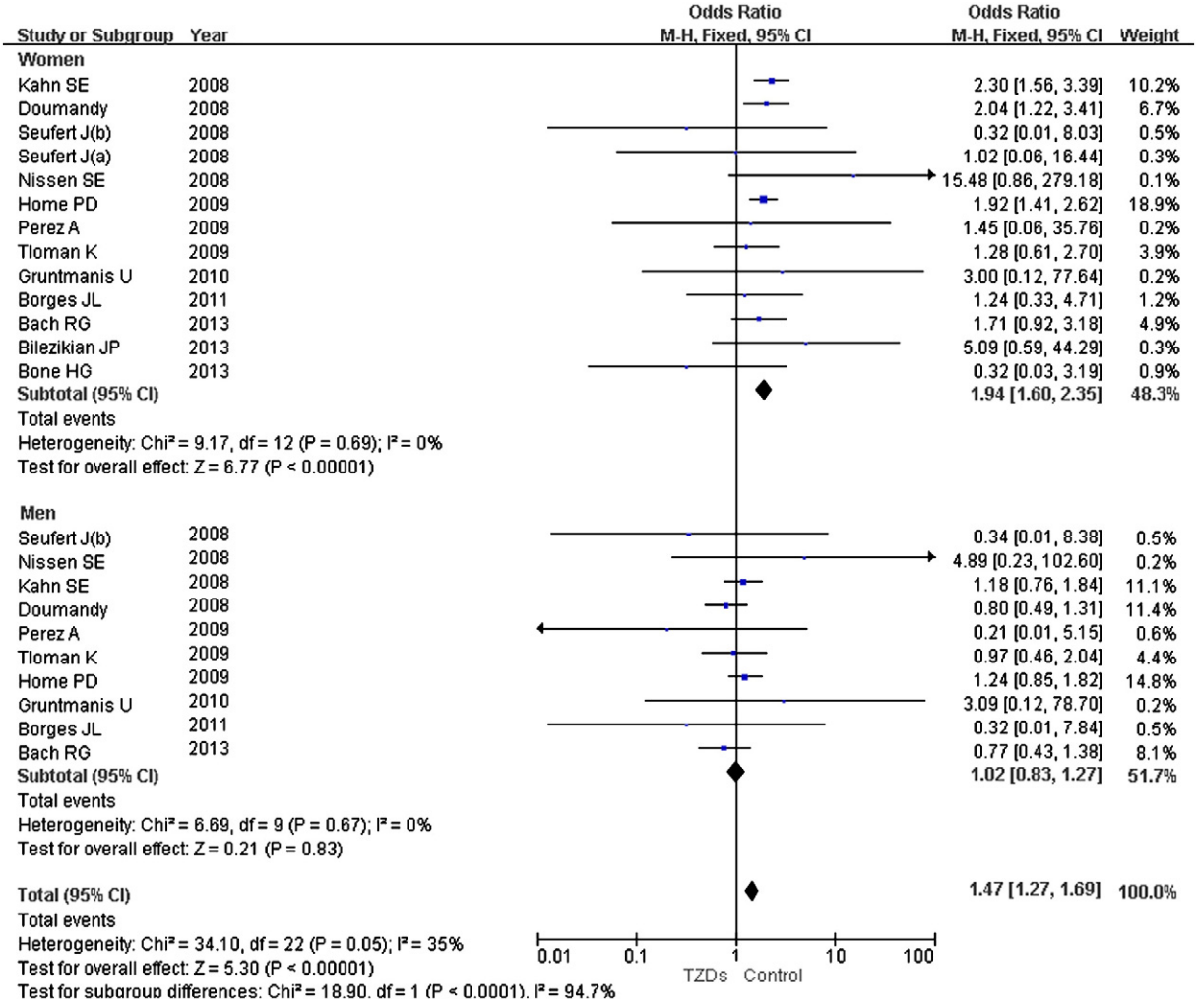

Fig. 2. Forest plot of odds ratio for TZDs and fracture risk.