Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis
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CRD summary
This reasonably well-conducted review concluded that long term use of thiazolidinedione doubles the risk of fracture in women with type 2 diabetes but does not produce a significant increase in fracture risk among men with type 2 diabetes. This conclusion accurately reflects the evidence of the review and appears likely to be reliable.

Authors' objectives
To assess the relative and absolute risk of fractures with long-term thiazolidinedione therapy for type 2 diabetes.

Searching
The databases MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials were searched up to June 2008. Search terms were reported. The websites of regulatory authorities, manufacturers' product information sheet and clinical trials registers of GlaxoSmithKline, Takeda Pharmaceuticals and the Clinical Study Results database were searched. The Web of Science Citation Index was also scanned. References of included studies and existing systematic reviews were checked.

Study selection
Randomised controlled trials (RCTs) and controlled observational studies which compared fracture risk in patients with type 2 diabetes or impaired glucose tolerance taking thiazolidinedione with those not on the treatment were eligible for inclusion. Included studies had to be of at least one year's duration. Acceptable comparators were placebo or oral therapy with an active comparator.

Included studies used rosiglitazone or pioglitazone. Most studies used concomitant medications, of which the most common was metformin. There was considerable variation in baseline fracture risk between the studies. Duration ranged from one to four years. See URL for Additional Data field for online appendices containing result tables.

Two reviewers independently assessed the studies for inclusion in the review.

Assessment of study quality
The RCTs were assessed for validity using the criteria of allocation concealment and blinding. Both RCTs and observational studies were assessed for the monitoring and recording of adverse events.

It appears that two reviewers independently assessed the quality of the included studies and that disagreements were resolved through consensus.

Data extraction
Numerical outcome data and participant characteristics were extracted together with information on dose and duration of thiazolidinedione therapy for RCTs and data sources and exposure verification for observational studies.

Two reviewers independently performed the data extraction, with disagreements resolved through consensus.

Methods of synthesis
Pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated using a Mantel-Haenszel fixed-effect model meta-analysis. Numbers needed to harm (NNH) were calculated. Statistical heterogeneity between the studies was assessed using the I² statistic, with a value of 50% or higher considered to indicate substantial heterogeneity. A priori sensitivity analyses were used to investigate the impacts of trial duration and statistical models on effect sizes. The fail-safe number (to assess publication bias) was also calculated.
Results of the review
Ten RCTs (n=13,715) and two observational studies (n=31,679) were included in the review. All RCTs were double-blinded and six had adequate allocation concealment, the remaining four were unclear.

The incidence of fractures was significantly higher in the thiazolidinedione groups compared to control groups (OR 1.45, 95% CI: 1.18, 1.79, p<0.001, 10 RCTs). Statistical heterogeneity was moderate (I\(^2\) = 27%). The analysis was dominated by two large reasonable quality RCTs. Subgroup analysis of the RCTs which reported data separately for men and women, showed that women in thiazolidinedione groups had a significantly higher risk of fracture compared to controls (OR 2.23, 95% CI: 1.65, 3.01, p<0.001, n=4,400) but that there was no significant difference between the groups for men (OR 1.00, 95% CI: 0.73, 1.39, p=0.98, n=7,001). In neither case was there any statistically significant heterogeneity (I\(^2\) = 0%). NNH varied from 55 (95% CI: 34, 103) in young newly diagnosed women to 21 (95% CI: 14, 39) in postmenopausal women. Results from the observational studies supported those of the RCTs.

Authors’ conclusions
Long term use of thiazolidinedione doubles the risk of fracture in women with type 2 diabetes but does not produce a significant increase in fracture risk among men with type 2 diabetes.

CRD commentary
The review question and the inclusion criteria were clear. The authors searched three relevant databases and a number of other sources, reducing the risk of publication bias. The authors reported using rigorous methodology at all stages of the review process. The validity assessment appraised some important aspects of the included studies, but cannot be considered complete. The use of meta-analysis appeared appropriate. This was supported by the low levels of statistical heterogeneity detected using a reliable measure. The authors’ conclusions accurately reflect the results of the review and appear likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that the use of thiazolidinediones in women with type 2 diabetes should be reconsidered, in accordance with updated National Institute for Clinical Excellence (NICE) guidance. Regulatory agencies should restrict the use of thiazolidinediones in women with diabetes who are at risk of fractures.

Research: The authors did not state any implications for further research.

Funding
No external funding.

Bibliographic details

PubMedID
19073651

DOI
10.1503/cmaj.080486

Additional Data URL
http://www.cmaj.ca/content/suppl/2009/01/06/180.1.32.DC2/long-loke-2-at.pdf;
http://www.cmaj.ca/content/suppl/2009/01/06/180.1.32.DC2/long-loke-3-at.pdf

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Bone Density /drug effects; Diabetes Mellitus, Type 2 /drug therapy /epidemiology; Female; Fractures, Bone /chemically induced /epidemiology; Humans; Hypoglycemic Agents /adverse effects /therapeutic use; Male; Thiazolidinediones /adverse effects; Treatment Outcome

AccessionNumber
12009102172

Date bibliographic record published
31/03/2009

Date abstract record published
03/06/2009

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.