Use of thiazolidinediones and the risk of bladder cancer among people with type 2 diabetes: a meta-analysis

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CRD summary
This well-conducted review concluded that thiazolidinediones, particularly pioglitazone, were associated with an increased risk of bladder cancer among adults with type 2 diabetes. The authors acknowledged the limitations of the evidence base and that the incidence of bladder cancer may have been underestimated. The authors' conclusions reflect the evidence presented and are likely to be reliable.

Authors' objectives
To evaluate the risk of bladder cancer among adults with Type 2 diabetes taking thiazolidinediones.

Searching
PubMed, EMBASE, The Cochrane Library, Science Citation Index Expanded, Science Conference Proceedings Citation Index, TOXNET and Scopus databases, Google Scholar, two clinical trials registries and databases of three international drug safety surveillance agencies were searched to March 2012 without language restrictions; the search strategy was available in an online appendix. The proceedings of five international conferences of relevant organizations were searched from 2008. Reference lists of relevant studies were screened and experts in the field were contacted.

Study selection
Randomised controlled trials (RCTs), cohort studies and case-control studies that compared thiazolidinedione exposure with no thiazolidinedione exposure in adults (not defined) with type 2 diabetes were eligible for inclusion. The outcome of interest was incidence of bladder cancer. Most of the participants received pioglitazone; rosiglitazone was also commonly used. Most studies seemed to use only a thiazolidinedione; some also reported using insulin, sulphonylurea and/or metformin. No participant characteristics were reported beyond the inclusion criteria.

Two reviewers independently selected studies for the review. Disagreements were resolved by discussion or consultation with a third reviewer.

Assessment of study quality
The quality of RCTs was assessed using the Cochrane risk of bias tool. Observational studies were assessed using the Newcastle-Ottawa Scale; a score of 5 or less out of 8 was considered to indicate a high risk of bias.

Data extraction
Two reviewers independently extracted data to enable calculation of risk ratios (RR) and 95% confidence intervals (CI); disagreements were resolved by discussion or consultation with a third reviewer. Where necessary, authors were contacted for additional information.

Methods of synthesis
Pooled risk ratios and 95% CI were calculated using an inverse variance Mantel-Haenszel random-effects meta-analysis; adjusted risk ratios were used when derived from observational studies (variables differed across studies) and unadjusted when derived from RCTs. Heterogeneity was assessed using the I² statistic. The level of heterogeneity was classified as low (≤25%), moderate (>25% to 50%) or high (>50% to 75%). Heterogeneity was explored where I² was greater than 25% and pooling was not undertaken where I² was more than 75%. The primary analysis was an evaluation of pioglitazone stratified by study design. Secondary analyses were of rosiglitazone and any thiazolidinedione. Subgroup analyses of pioglitazone or rosiglitazone monotherapy were planned but could not be conducted. The authors stated that there were too few studies to assess publication bias.

Results of the review
Ten studies met the inclusion criteria (2,657,365 patients, range 386 (RCT) to 1,491,060 (cohort study)). Four of the included studies were RCTs, two of which were open-label. Three RCTs were considered to be at high risk of bias (two due to substantial differential losses to follow-up and one due to insufficient reporting of methods and early termination). Six studies were observational, five were cohort studies and one was a case-control study. The case-control study was considered to be at high risk of bias due to inadequately defined cases and unrepresentative controls. Where reported, mean length of follow-up across all studies ranged from 2.4 to six years.

A total of 3,643 patients had newly diagnosed bladder cancer (overall incidence 53.1 per 100,000 person-years).

From three of the RCTs, incidence of bladder cancer was 101.0 per 100,000 person-years among those who used a thiazolidinedione and 65.5 per 100,000 person-years among those who did not. There appeared to be a non-significant increase in the risk of bladder cancer with exposure to any thiazolidinediones (RR 1.45, 95% CI 0.75 to 2.83; I²=2%; four RCTs). There was no association between use of pioglitazone (RR 2.36, 95% CI 0.91 to 6.13; one RCT) or rosiglitazone (RR 0.87, 95% CI 0.34 to 2.23; two RCTs) and bladder cancer.

The cohort studies showed significant associations with bladder cancer with any thiazolidinedione (RR 1.15, 95% CI 1.04 to 1.26; I²=0%; six studies) and for pioglitazone specifically (RR 1.22, 95% CI 1.07 to 1.39; I²=0%; three studies). Studies that evaluated dose-response relationships reported contradictory results.

**Authors' conclusions**
The limited evidence was available to support the hypothesis that thiazolidinediones, particularly pioglitazone, were associated with an increased risk of bladder cancer among adults with type 2 diabetes.

**CRD commentary**
The authors addressed a clear review question and used appropriate inclusion criteria. A comprehensive search included searches for unpublished studies and was conducted without language restrictions. Study selection and data extraction were conducted in duplicate; it was unclear whether such measures to reduce error and bias were employed during the quality assessment. Appropriate criteria were used to assess the quality of included studies and the assessment results were reported in full.

The methods of synthesis were appropriate given the relative rarity of the outcome being assessed. The authors acknowledged that the evidence base was limited and that the review may have underestimated the true number of patients with bladder cancer (although they thought it unlikely to affect the estimates of relative risk).

This was a well-conducted review. The authors' conclusions reflect the evidence presented and are likely to be reliable, but their caution regarding the limited amount of evidence available is important.

**Implications of the review for practice and research**
**Practice:** The authors stated that the review quantified the association between pioglitazone use and bladder cancer and may help inform decisions around safer use of pioglitazone in individuals with type 2 diabetes.

**Research:** The authors stated that future research was required to improve understanding in this area. Studies should include large population-based cohort studies that involve individuals with type 2 diabetes, include a reference group of individuals without diabetes, have a minimum dose and duration of exposure and account for important risk factors for bladder cancer (such as smoking status and history of bladder disease).

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**Bibliographic details**

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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.