Meta-analysis of the effect of thiazolidinediones on serum C-reactive protein levels

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CRD summary
This review assessed the effects of thiazolidinediones (TZDs) on serum C-reactive protein (CRP) levels in randomised controlled trials. Serum CRP levels appear to be significantly reduced by treatment with TZDs, the effect being more pronounced in patients with type 2 diabetes mellitus than in non-diabetic patients. However, given the problems encountered in the analysis, the robustness of the final meta-analysis is questionable.

Authors’ objectives
To determine the effects of thiazolidinediones (TZDs) on serum C-reactive protein (CRP) levels in randomised controlled trials RCTs).

Searching
The authors searched PubMed (individual databases not specified) from January 1991 to June 2005; the search terms were reported. In addition, the Cochrane Library (the Cochrane Controlled Trials Register and the Cochrane Database of Systematic Reviews) was searched from January 1997 to June 2005. The reference lists of retrieved articles and review articles were screened for further references. Only articles published in the English language were included; conference proceeding abstracts were excluded.

Study selection
Study designs of evaluations included in the review
RCTs were eligible for inclusion in the review.

Specific interventions included in the review
Studies comparing any TZD with a control group were eligible for inclusion in the review. Studies that compared TZDs with other antidiabetic agents and did not have a control group were excluded. Studies of troglitazone were also excluded, as this drug has been withdrawn from use in the USA. All the studies included in the review assessed either pioglitazone or rosiglitazone compared with a placebo control; the doses ranged from 4 mg twice daily to 8 mg four times daily for pioglitazone, and from 15 to 45 mg four times daily for rosiglitazone. The duration of treatment ranged from 8 to 26 weeks.

Participants included in the review
The authors did not specify what types of participants were eligible for inclusion in the review. The majority of participants who took part in the included studies had diabetes mellitus type 2 and/or coronary artery disease. Other diseases affecting participants but only found in single studies included ischaemic attack or stroke, human immunodeficiency virus and metabolic syndrome. The participants were usually middle-aged.

Outcomes assessed in the review
Studies that measured changes in serum CRP levels from baseline to the end of the treatment period were eligible for inclusion in the review.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The validity of the primary studies was assessed using the Jadad scale, with each individual study awarded a score from 0 (low) to 5 (high) points. Two reviewers acting independently abstracted data from the studies and resolved any discrepancies through consensus.
**Data extraction**
Two reviewers independently abstracted data from the studies using a standardised form. Any discrepancies were resolved through consensus.

The difference between intervention and control groups in terms of changes in serum CRP levels from baseline to follow-up were calculated for each study and reported as means with standard deviations (SDs). Where these data were not reported, variances were calculated from standard errors, confidence levels (CIs) or P-values. If the exact variance was not derivable, the authors used figures that were imputed by inverting the boundary P-values (e.g. P<0.05 into P=0.05) or by assuming that there was a correlation between the initial and final serum CRP levels with a coefficient of 0.5. Methods described by Hozo et al. (see Other Publications of Related Interest) were used to convert medians and interquartile ranges into means and SDs.

**Methods of synthesis**

How were the studies combined?
Means and SDs were combined using a random-effects model to give an overall mean change with 95% CIs. A P-value (two-tailed) of 0.05 was considered statistically significant. Publication bias was assessed using a funnel plot and Egger's regression method.

How were differences between studies investigated?
Differences between the studies were assessed using chi-squared and I-squared tests for heterogeneity. In addition, the association between changes in serum CRP levels and haemoglobin A1c was investigated using a meta-regression analysis. The analysis was repeated, removing one study at a time, in order to investigate whether one study had undue influence over the overall findings.

**Results of the review**
Thirteen studies (n=1,276) were included in the review: 10 double-blind RCTs (n=987) and 3 randomised case-controlled studies (n=289). In total, 231 patients were treated with pioglitazone and 485 with rosiglitazone.

Study quality ranged from 1 to 5 points on the Jadad scale: one study (a case-controlled study) scored 1 point, five (including 2 case-controlled studies) scored 2 points, two scored 3 points, three scored 4 points and two scored 5 points. Four studies did not report information on patient drop-outs.

No evidence of publication bias was observed in either the funnel plot or when using Egger's regression method.

The overall mean change in serum CRP level was -0.82 (95% CI: -1.15, -0.49) in favour of TZD in comparison with control. However, significant heterogeneity was associated with this result (chi-squared 1,120.60, d.f.=13, P<0.00001; I-squared 98.8%) (13 studies, n=1,371; 14 comparisons since 1 study included 2 comparisons). Repeating the analysis and removing one study at a time did not significantly alter the results, suggesting that no one study had undue influence on the overall findings.

**Authors’ conclusions**
The review data suggest that serum CRP levels are significantly reduced by treatment with TZDs. This effect was more pronounced in patients with type 2 diabetes mellitus, but levels decreased in both diabetic and non-diabetic populations.

**CRD commentary**
This review was based on a clear research question but the authors did not specify which populations were eligible for inclusion. The searches for relevant data seemed reasonable, although relevant data might have been missed by the exclusion of conference abstracts and articles not published in English. The authors failed to specify which PubMed databases were used in their searches and made no specific attempts to locate unpublished material, although checks the authors made suggest that publication bias is not a problem. Attempts to reduce bias and errors in the quality assessment...
and data abstraction appear to have been made. However, it was unclear whether similar attempts were made to reduce selection bias since the authors did not report how studies were selected for inclusion, or how many reviewers were involved.

The authors' methods of analysis were reasonable, although they themselves mentioned that the conversion of non-normally distributed data (median and range) to normally distributed data (mean and SD) might have introduced errors. They were also unable to explain the heterogeneity associated with their findings. The inclusion of two comparisons from one study also resulted in the duplication of data from this study's control group. Therefore, although the findings appear to favour TZD over the control group, the robustness of the final overall mean change in serum CRP levels is unclear and these data should be interpreted with caution. It was unclear how any of these findings translate into clinical benefits.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research to assess the long-term effects of TZDs, particularly in relation to cardiovascular end points, is required. One such trial is currently underway (the PROspective Pioglitazone clinical trial in macrovascular events, PROactive).

Bibliographic details

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Other publications of related interest

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Subject indexing assigned by NLM

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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.