Factors associated with the effect-size of thiazolidinedione (TZD) therapy on HbA1c: a meta-analysis of published randomized clinical trials

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CRD summary
This review examined factors which impact on the size of the glycated haemoglobin (HbA1c) response to thiazolidinedione therapy in diabetics. The authors concluded that the effect size was significantly affected by the baseline HbA1c value and the duration of the trial. These conclusions should be treated with caution as they are based on a meta-regression of data from trials, the quality of which had not been assessed.

Authors' objectives
To assess factors which impact on the size of the glycated haemoglobin (HbA1c) response to thiazolidinedione (TZD) therapy in patients with diabetes.

Searching
PubMed, EBSCO and SciLit were searched. The search terms were reported, but not the dates over which the searches were conducted. Only studies reported in English were eligible for inclusion in the review.

Study selection
Randomised controlled trials (RCTs) were eligible for inclusion. All of the included RCTs had a parallel design. Eligible studies assessed rosiglitazone or pioglitazone in comparison with either an active comparator or placebo. Studies of troglitazone were excluded from the review. Both TZD monotherapy trials and TZD combination therapy trials were included in the review. Inclusion criteria for the participants were not stated. The mean duration of diabetes was 6.6 years. The majority of patients were using prior oral anti-hyperglycaemic therapy. The majority of included studies enrolled either overweight or obese patients (mean body mass index ranged from 23.4 to 35.1). The mean age of the participants ranged from 53.5 to 61.2 years. The percentage of women in the included studies varied widely, from 8.3 to 87.5%. Studies were required to report both the baseline and the post-intervention HbA1c values for both intervention and comparison groups in order to be eligible for inclusion. The primary review outcome was placebo-subtracted change in HbA1c from baseline.

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 authors reported that they did not assess validity.

Data extraction
Data on sociodemographic and clinical predictors of changes in HbA1c were extracted, as were baseline and post-intervention HbA1c values. The mean reduction in HbA1c was calculated relative to both baseline and placebo values. Variables on a percentile scale were log-transformed to base-10. Smearing estimates (use of percentage change from baseline in each arm) were used to reduce back-transformation bias. Standard errors were obtained by bootstrapping as the data distribution was non-normal.

One reviewer extracted the data and two other reviewers independently checked the data extracted.

Methods of synthesis
The studies were combined in a meta-analysis using a fixed-effect model as no statistically significant heterogeneity was detected. Heterogeneity was assessed using the Q statistic (significance level of 0.10). Weighted regression analysis was used to assess the strength of associations between the mean difference between trial arms in HbA1c and potential predictive factors. A similar regression analysis was performed for the change in HbA1c from baseline.
Results of the review
Forty-two RCTs with 60 TZD trial arms (n= 8,322) were included in the review.

The weighted placebo-subtracted change in HbA\textsubscript{1c} was -0.99% (± 0.02) where the average baseline value was 9.1% (± 1.0%). After controlling for other variables, the baseline HbA\textsubscript{1c} level was significantly inversely associated with both change in placebo-subtracted HbA\textsubscript{1c} (p=0.004) and with change in HbA\textsubscript{1c} from baseline (p=0.002).

There was a significant association between longer trial duration and placebo-subtracted HbA\textsubscript{1c} (p=0.01), but not with change in HbA\textsubscript{1c} from baseline.

Seventy-two per cent of the variation in placebo-subtracted HbA\textsubscript{1c} was explained by the multi-variable models.

Authors’ conclusions
There was a significant negative association between baseline HbA\textsubscript{1c} and the placebo-subtracted change in HbA\textsubscript{1c}, suggesting that the TZD effect size was greater in patients with poorer glycaemic control. There was also a negative association between duration of the clinical trial and placebo-subtracted change in HbA\textsubscript{1c}.

CRD commentary
The review question and the inclusion criteria, with the exception of those for participants, were clear. The authors searched some relevant databases, but limited their search to studies reported in English. This might have increased the possibility that some relevant studies were not included in the review. The authors reported the use of methods designed to minimise bias and error in the extraction of data, but not in the selection of studies for the review. They stated that they did not assess study validity, which, even where exclusively trials described as RCTs are included, means it is difficult to assess the reliability of conclusions based on the trial data. The analysis methods were complex and the main aim of the paper was to perform a meta-regression to identify factors relating to the effects of TZD treatment on HbA\textsubscript{1c}. As the results of the individual trials were not presented in forest plots, it is difficult to assess whether the pooled results are reliable, although the authors did state that there was no evidence of statistical heterogeneity. The lack of a validity assessment and the reliance on a meta-regression, the results of which should be treated as exploratory, mean that the reliability of the conclusions cannot be established.

One author is an employee of, and holder of stock options in, Merck and Co.

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

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