Effect of thiazolidinediones on albuminuria and proteinuria in diabetes: a meta-analysis

Sarafidis PA, Stafylas PC, Georgianos PI, Saratzis AN, Lasaridis AN

CRD summary
The authors concluded that treatment with thiazolidinediones significantly decreased urinary albumin and protein excretion in patients with diabetes. This was a well conducted review, but the uncertain quality of the included studies and high levels of variability between studies suggest that the results should be treated with caution.

Authors' objectives
To evaluate the effectiveness of thiazolidinediones (rosiglitazone and pioglitazone) on urinary albumin and protein excretion in patients with diabetes mellitus.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restrictions from 1991 to September 2009 for peer-reviewed studies; search terms were reported. Reference lists of relevant studies and previous reviews were examined.

Study selection
Randomised controlled trials (RCTs) that compared thiazolidinediones (rosiglitazone and pioglitazone) with placebo or other antidiabetic agents in adult diabetic patients were eligible for inclusion. Study duration had to be at least 12 weeks. The effects of thiazolidinediones on changes in urine albumin or protein excretion were assessed using time-specified urine collections or spot urine specimens.

In the included trials, all patients had been diagnosed with type 2 diabetes between 4.9 and 17.1 years (where stated). Five trials compared rosiglitazone with placebo or active treatment and 10 studies compared pioglitazone with placebo or active treatment. Twelve trials enrolled patients with either normo- or microalbuminuria at baseline. Three trials enrolled patients with microalbuminuria or proteinuria. In more than half of the trials, patients could be treated with a renin-angiotensin system (RAS) blocker. Mean haemoglobin A1c at baseline ranged from 7.7% to 9.9%. Hypertension was present at baseline in most trials. Mean patient age ranged from 51.9 to 65.5 years. Most patients were male.

Two authors independently undertook the selection process; disagreements were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed trials quality using a risk of bias graph that assessed sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential sources of bias. A third reviewer checked data for accuracy. Disagreements were resolved through consensus.

Data extraction
Two reviewers independently extracted changes from baseline to study end in urine albumin or protein excretion to calculate mean differences and 95% confidence intervals (CIs) between the thiazolidinedione and control groups. Authors were contacted for additional information where necessary. Missing standard deviations were imputed based upon reported p values or interquartile or full ranges. Correlations from other included studies were used to estimate change from baseline standard deviations. A third reviewer checked the data for accuracy.

Methods of synthesis
Studies were pooled using a random-effects model. Results were presented as weighted mean differences (WMDs) or standardised mean differences (SMDs), with 95% confidence intervals (CIs). Results were reported separately for trials that reported changes in time-specified urine collections and those that reporting changes in spot specimens. Studies were grouped according to baseline levels of urine albumin or protein excretion into groups of patients with normo- and/or microalbuminuria and of those with macroalbuminuria (albumin excretion >300mg/g creatinine) or proteinuria (protein excretion >500 mg/d).
Subgroup analyses were undertaken by type of thiazolidinedione. Statistical heterogeneity was assessed using Cochran Q test and the $I^2$ statistic. Sensitivity analysis were conducted to assess the impact of assumptions made about the standard deviation of effect sizes. Publication bias was assessed using Begg's and Egger's tests.

**Results of the review**
Fifteen RCTs (n=2,860 participants, range 28 to 639) were included in the review. Follow-up ranged from 12 to 52 weeks.

**Normo- or microalbuminuria (12 RCTs):** Compared with controls, thiazolidinedione treatment was associated with a significant decrease in the proportional change in urinary albumin excretion measured using time-specified collections (WMD -64.8%, 95% CI -75.6 to -53.9, $I^2$=0%; five study arms) and proportional changes in albumin-creatinine using spot specimens (WMD -24.8%, 95% CI -39.6 to -10.0, $I^2$=95%; eight study arms) in patients with baseline normo- or microalbuminuria.

Thiazolidinedione treatment in participants with normo- and microalbuminuria at baseline was associated with a significant decrease in urinary albumin excretion and urine albumin-creatinine (SMD -0.6, 95% CI -0.8 to -0.4, $I^2$=78%).

**Macroalbuminuria or proteinuria (three RCTs):** Compared with controls, thiazolidinedione resulted in a significant decrease in urinary protein excretion and urine protein-creatinine in patients with proteinuria at baseline (SMD -1.1, 95% CI -1.8 to -0.4, $I^2$=71%).

Sensitivity analysis suggested that the findings were robust.

There was no evidence of publication bias.

**Authors' conclusions**
Treatment with thiazolidinediones significantly decreased urinary albumin and protein excretion in patients with diabetes.

**CRD commentary**
The review question was clear and supported by potentially reproducible inclusion criteria. The search strategy included relevant sources and was not restricted by language, which reduced the possibility of language bias. The restriction to published studies meant that some potentially relevant data may have been missed. Risk of publication bias was assessed and no evidence of it was found. All parts of the review process were performed in duplicate, which minimised risks of reviewer errors or bias. Study quality was assessed using an appropriate tool, but the results were not reported. Adequate details of primary studies were provided. There was only a small number of studies that assessed macro/proteinuria. Given the high levels of heterogeneity it was questionable whether the methods of synthesis were appropriate. Sources of heterogeneity in the meta-analyses were investigated. There were large differences in the results reported using weighted mean differences compared to those that used standard mean differences; in light of the differences it appeared that standard mean differences might have been more appropriate.

This was a well conducted review, but the uncertain quality of the included studies and high levels of variability between studies suggest that the results should be treated with caution.

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

**Research:** The authors stated that well-designed long-term randomised clinical trials with hard renal outcomes as primary endpoints were required to assess the potential benefits of thiazolidinediones on diabetic nephropathy. Further studies were required in patients with proteinuria.
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