Meta-analysis of the clinical effect of ligustrazine on diabetic nephropathy

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CRD summary
This review concluded that ligustrazine had a significant therapeutic effect on improving renal function and reducing urine protein in patients with diabetic nephropathy. Due to potential limitations in the included evidence and in the reporting and conduct of the review, this conclusion may not be reliable.

Authors' objectives
To evaluate the clinical effect of ligustrazine (bioactive component of *Ligusticum chuanxiong*) on diabetic nephropathy.

Searching
Ten databases were searched including PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and six Chinese databases. The search was not restricted by language or date of publication. Search terms and dates were not reported.

Study selection
Randomised controlled trials (RCTs) that evaluated intravenous administration of 20mg/mL ligustrazine in patients with diabetes mellitus and stage III-IV diabetic nephropathy (based on the Morgensen criteria) were eligible for inclusion.

Among the included trials, ligustrazine dose ranged from 40 to 400mg daily. Treatment duration ranged from 10 days to 12 weeks. All participants were based in China.

It was unclear how many reviewers selected studies for inclusion.

Assessment of study quality
Included RCTs were assessed for randomisation, allocation concealment, blinding, attrition, intention-to-treat analysis, and reporting of diagnostic and outcome criteria. Trial quality was rated as A (adequate), B (unclear), or C (inadequate).

It appeared that two blinded reviewers independently assessed study quality, with disagreements resolved by a third.

Data extraction
Standardised mean differences (SMDs) were calculated for the following continuous outcomes: blood urea nitrogen, serum creatinine, 24-hour urine protein, urine micro-albumin, and urine albumin excretion rate. Missing data were obtained from study authors where possible.

Two blinded reviewers independently extracted data from included trials, with disagreements resolved by a third reviewer.

Methods of synthesis
Standardised mean differences, with 95% confidence intervals (CIs), were pooled using a random-effect model. Statistical heterogeneity was assessed using $X^2$ and $I^2$.

Results of the review
Twenty-five RCTs (1,645 patients) were included in the review.

Statistically significant benefits associated with ligustrazine treatment were reported for blood urea nitrogen (SMD -1.24, 95% CI -2.02 to -0.46; 10 RCTs; 709 patients), serum creatinine (SMD -18.31mmol/L, 95% CI -30.94 to -5.68; 10 RCTs; 709 patients), 24-hour urine protein (SMD -0.36g, 95% CI -0.56 to -0.17; 10 RCTs; 716 patients), urine micro-albumin (SMD -50.78mg/24hours, 95% CI -72.20 to -29.36; 10 RCTs; 689 patients), and urine albumin
excretion rate (SMD -21.42μg/min, 95% CI -29.01 to -13.83; five RCTs; 289 patients). No adverse effects were reported among the included trials.

There was a high degree of between-study statistical inconsistency for all outcomes (I²=82% to 98%)

**Authors’ conclusions**
Ligustrazine had a significant therapeutic effect on improving renal function and reducing urine protein in patients with diabetic nephropathy.

**CRD commentary**
The research question for this review was broadly defined for the intervention, participants, and study designs of interest. Attempts appeared to have been made to identify all the relevant published literature, and to minimise the potential for errors and bias in the extraction of data from included trials.

The authors assessed trial quality, but the details of this assessment were not reported beyond a statement that quality was "not very high". Crucial data on the included trials (including comparison treatments and patient characteristics) were not reported, which made it difficult to establish how appropriate the analysis was and how it might be interpreted. No attempt appeared to have been made to identify unpublished studies which could have potentially provided less positive findings. The pooled outcomes were highly heterogeneous.

Given these limitations, the authors' conclusions may not be reliable.

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

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