Systematic review of the effect of telmisartan on insulin sensitivity in hypertensive patients with insulin resistance or diabetes

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CRD summary
This review found that telmisartan conferred significant beneficial effects on fasting plasma glucose and adiponectin levels in patients with hypertension and either insulin resistance or type 2 diabetes mellitus. The lack of a thorough quality assessment and other limitations of the review make the reliability of the authors’ conclusions uncertain.

Authors’ objectives
To evaluate the effect of telmisartan compared to other angiotension receptor blockers on insulin sensitivity in patients with hypertension and either insulin resistance or diabetic states.

Searching
MEDLINE, CINAHL, Scopus and The Cochrane Library were each searched from inception to May 2011 for relevant studies; search terms were reported. References of retrieved relevant studies and systematic and narrative reviews were checked for additional studies. There were no language restrictions. Studies published as abstracts were excluded from the review.

Study selection
Eligible studies were randomised controlled trials (RCTs) in which telmisartan was compared to other angiotension receptor blockers in patients with hypertension and either insulin resistance or type 2 diabetes mellitus. Eligible trials were required to report data on the primary outcome of fasting plasma glucose and secondary outcomes of fasting plasma insulin or a homeostasis model assessment of insulin resistance or adiponectin levels.

Fasting plasma glucose levels at baseline ranged from 100mg/dL to 143mg/dL and fasting plasma insulin ranged from 7.3μU/mL to 49.3μU/mL across the trials. Adiponectin levels at baseline ranged from 4.1 to 12.9μg/dL. Telmisartan dose in most of the trials was 40mg or 80mg. Doses in one trial ranged from 40mg to 80mg. In other trials telmisartan was administered with rosiglitazone. Where stated, lifestyle modification was included in some trials but not in others. Comparator angiotension receptor blockers were eprosartan, losartan, irbesartan, candesartan, olmesartan and valsartan.

Two reviewers performed the study selection; any differences between the reviewers were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed methodological quality using the Jadad five-point scale of randomisation, blinding and treatment of withdrawals and drop-outs. A score of 3 or more was judged to be good quality. Any discrepancies between the reviewers were resolved by a third reviewer.

Data extraction
Data were extracted by two independent reviewers to calculate mean differences (MD) in treatment effect and 95% confidence intervals (CI). Any differences between the reviewers were resolved by a third reviewer.

Methods of synthesis
Pooled weighted mean differences and 95% CIs were calculated using an inverse variance-weighted fixed-effect model. Statistical heterogeneity was assessed using the Q and I² statistics. Where statistical heterogeneity was significant (Q<0.1) a random-effects model was used. Subgroup analyses were undertaken on the basis of telmisartan dose (40mg or 80mg). Potential for publication bias was evaluated by visual appraisals of funnel plots and the Egger’s test.

Results of the review
Eight randomised controlled trials (763 participants, range 40 to 227) were included in the review. Jadad scores showed four trials to be good quality (one trial scored 5 and three scored 3) and four trials to be poor quality (three trials scored 2 and one scored 1). Study duration ranged from three to 12 months.
Statistically significant benefits on fasting plasma glucose were observed with treatment with telmisartan compared to other angiotensin receptor blockers (WMD -8.63mg/dL, 95% CI -12.29 to -4.98; I²=66%, eight trials).

Subgroup analyses according to telmisartan dose showed statistically significant benefits with 40mg telmisartan (WMD -7.00mg/dL, 95% CI -11.14 to -2.85; I²=70%; six trials) and 80mg telmisartan (WMD -14.46mg/dL, 95% CI -20.01 to -8.91; I²=0%; two trials). Significantly greater benefit was seen with 80mg than with 40mg.

There were no statistically significant differences observed between telmisartan and other angiotensin receptor blockers in fasting plasma insulin (seven trials; I²=89%) and insulin resistance measured by homeostasis model assessments of insulin resistance (seven trials; I²=65%).

Subgroup analyses showed statistically significant decreases with telmisartan doses of 80mg in both fasting plasma insulin (WMD -6.06mg/dL, 95% CI -9.27 to -2.84; I²=33%; two trials) and insulin resistance (MD -1.60, 95% CI -3.18 to -0.02; one trial).

Statistically significant increases in adiponectin levels were observed with telmisartan compared with other angiotensin receptor blockers (WMD 0.93ug/dL, 95% CI 0.28 to 1.59; I²=4%; six trials) and with telmisartan administered at a dose of 40mg (WMD 1.03ug/dL, 95% CI 0.25 to 1.81; I²=20%; five trials). One study of telmisartan administered at 80mg found no differences in adiponectin levels compared to irbesartan.

Funnel plots and Egger's test revealed no evidence of publication bias.

**Authors' conclusions**
The results suggest that treatment with telmisartan was associated with significant benefits in improving insulin sensitivity in patients with hypertension and either insulin resistance or type 2 diabetes mellitus. In particular, the effects were greater with doses of telmisartan of 80mg.

**CRD commentary**
The review addressed a clear question. Criteria for inclusion of studies were defined. Appropriate databases were searched without language restrictions for relevant trials. The review was restricted to peer-reviewed studies. The authors evaluated potential for publication bias using validated methods. Steps were taken to minimise reviewer error and bias at each stage of the review process.

There were some differences in study quality and design and in use of lifestyle modification interventions in some trials. However, the authors' decision to combine the results of the review in a meta-analysis appeared to be justified. Some potential sources of statistical heterogeneity were explored through appropriate subgroup analyses. Methodological quality was assessed and the quality scores were presented in the tables. Half of the studies were of poor quality but the authors did not use the results of the quality assessment to interpret the variation in the results. Methods of allocation concealment were not examined and there was no information on the number of drop-outs.

The authors correctly acknowledged limitations of the review from the low quality of some of the trials, small sample sizes, variation in study design, generalisability of results to patients with metabolic syndrome and potential for higher doses of other angiotensin receptor blockers to confer similar beneficial effects as those observed with telmisartan in this review. Caution arising from these limitations was not incorporated into the review conclusions.

The lack of a thorough quality assessment and other limitations of the review make the reliability of the authors' conclusions is uncertain.

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

**Research:** The authors stated that further well-designed trials with well-defined baseline levels of fasting plasma glucose fasting plasma insulin, homeostasis model assessments of insulin resistance and adiponectin were required to clearly establish the group of patients with hypertension and either insulin resistance or type 2 diabetes mellitus who may benefit additionally from telmisartan.
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