Sitagliptin in the treatment of type 2 diabetes: a meta-analysis
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CRD summary
The review found that sitagliptin was efficacious and well tolerated in the treatment of adults with type 2 diabetes compared to placebo. Possibilities of publication and language biases and the inclusion of many trials with an unclear risk of bias mean that the reliability of the review is uncertain.

Authors' objectives
To assess the efficacy and safety of sitagliptin in adults with type 2 diabetes.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched to 24 March 2010 for published studies. The search included articles in English; it was unclear whether trials published in Chinese were also eligible. The search strategy was reported. Bibliographies of primary studies and review articles were searched by hand. Abstracts were excluded.

Study selection
Randomised controlled trials (RCTs) of sitagliptin to treat adult patients diagnosed with type 2 diabetes using standard diagnostic criteria were eligible. Sitagliptin could be used alone or with other oral hypoglycaemics; comparison groups were placebo or other oral hypoglycaemics. Trials needed to include patients treated for at least 12 weeks and include change in glycosylated haemoglobin (HbA1c) from baseline to follow-up as a main outcome. Secondary outcomes included beta-cell function (measured by homeostasis model of assessment of β-cell, HOMA-β) fasting plasma glucose and adverse events. Trials were excluded if they were of non-adults, participants with type 1 diabetes, unstable cardiac disease or significant renal impairment.

In the included studies, all summary data were reported by treatment groups. The mean age of participants ranged from 50.9 to 61 years and between 21% and 66% were male (where stated). Mean body mass index (BMI) ranged from 24.9kg/m² to 32.5kg/m² and mean HbA1c at baseline ranged from 7.1% to 9.3%. Sitagliptin was given at a dose of 100mg four times per day, alone or with at least one anti-hyperglycaemic agent (including pioglitazone, insulin, metformin or glimepiride). Control groups received placebo and/or at least one anti-hyperglycaemic agent (including metformin, vildagliptin, glipizide, glimepiride, rosiglitazone, pioglitazone or insulin). Follow-up ranged from 12 to 54 weeks.

Two reviewers independently selected studies for inclusion. Any disagreement were resolved by consensus or a third reviewer.

Assessment of study quality
Risk of bias was assessed using the Cochrane Risk of Bias tool to classify studies according to adequacy of description for allocation generation, allocation concealment, blinding of participants, outcome assessors and investigators, addressing incomplete outcome data, being free of selective reporting and being free of other sources of bias. Each item was classed as adequate, unclear or inadequate.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data were extracted to calculate mean differences in change from baseline for continuous outcomes and risk ratios (RR) for categorical outcomes, with 95% confidence intervals (CI).

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Fixed-effect meta-analysis was used to estimate weighted mean differences (WMD) and pooled risk ratios; random-effects models were used where significant heterogeneity was found using X² and I² statistics.
Results of the review
Eighteen studies (8,327 participants, range 38 to 1,172) were included in the review. Overall risk of bias was unclear for most studies; three studies were considered to have a high risk of bias. All studies were double blind but in some cases it was not clear who was blinded. In no cases was incomplete outcome data addressed.

**Sitagliptin versus placebo:** Sitagliptin was significantly associated with a reduction in HbA1c (WMD 0.74, 95% CI 0.63 to 0.85; I²=45%; 11 studies), fasting plasma glucose (WMD 1.20, 95% CI 1.03 to 1.38; I²=31%; 11 studies) and HOMA-β (WMD -10.94, 95% CI -14.07 to -7.8; I²=0%; 12 studies) compared to placebo. Similar results were found in studies in which patients used other oral hypoglycaemics and those in which they did not.

**Sitagliptin versus active control:** Other oral hypoglycaemic monotherapy was significantly associated with a greater reduction in HbA1c than sitagliptin monotherapy (WMD -0.14, 95% CI -0.24 to -0.04; I²=7%; three studies) and fasting plasma glucose (WMD -0.73, 95% CI -1.32 to -0.13; I²=78%; three studies). Using sitagliptin as an add-on therapy was as efficacious as other oral hypoglycaemics. Sitagliptin as either monotherapy or an add-on therapy was not effective in altering HOMA-β.

**Safety outcomes:** There was no difference in incidence of hypoglycaemia or serious adverse events in sitagliptin compared to active control groups or in the incidence of serious adverse events in sitagliptin compared to placebo. Sitagliptin as an add-on therapy was associated with a higher risk of hypoglycaemia than placebo as an add-on therapy (RR 2.21, 95% CI 1.53 to 3.18; I²=55%; six studies).

**Authors’ conclusions**
Sitagliptin provided a clinically meaningful reduction in HbA1c and fasting plasma glucose and no difference in serious adverse effects compared to placebo; it was thus efficacious and well tolerated.

**CRD commentary**
The review addressed a clear question. Inclusion criteria were clear and appropriate. The search covered several sources and the search strategy appeared appropriate. Attempts were made to reduce error and bias during the study selection; it was unclear whether data extraction and quality assessment were also performed in duplicate. A relevant quality assessment tool was applied; it appeared that the reliability of most trials was uncertain. The authors acknowledged that publication or language bias might have affected their results as only published studies in English and Chinese were included; no tests for publication bias were performed. Study details were presented clearly.

The meta-analysis was appropriate and steps were taken to report results separately for monotherapy versus add-on therapy. The authors acknowledged that data on long-term effects were lacking and stated that different definitions of hypoglycaemia were used in the included studies.

Possibilities of publication and language biases and the inclusion of many trials with an unclear risk of bias mean that the reliability of the review is uncertain.

**Implications of the review for practice and research**
**Practice:** The authors stated that sitagliptin offered a novel therapeutic approach for patients with type 2 diabetes.

**Research:** The authors stated that further large trials of sitagliptin were required to provide better evidence on the long-term effects of the drug.

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