Impact of sitagliptin on markers of beta-cell function: a meta-analysis

Riche DM, East HE, Riche KD

CRD summary
This review assessed whether sitagliptin improved β-cell function in people with diabetes and concluded that although sitagliptin improved two measures of β-cell function it may not have been superior to other therapeutic regimens in terms of increase in HOMA-β. The review was well conducted and the authors’ conclusions reflect the evidence presented.

Authors’ objectives
To assess the effect of the DPP-IV inhibitor sitagliptin on measures of β-cell function in patients with diabetes.

Searching
Electronic searches of MEDLINE (from 1966), EMBASE (from 1990) and The Cochrane Library were carried out to July 2008. Search terms were provided. No language restrictions reported. Proceedings of American Diabetes Association Scientific Sessions (2003 and 2007) and reference lists of primary or review articles were handsearched to identify additional relevant studies.

Study selection
Randomised controlled trials (RCTs) of sitagliptin (alone or as part of a combination therapy) compared to placebo or an active control regimen in patients with diabetes were included. RCTs had to be of at least 12 weeks duration. Data on β-cell function or β-cell dysfunction had to be reported using the outcome measures homeostasis model assessment of β-cell (HOMA-β) index (function) and proinsulin/insulin ratio (PI/IR) (dysfunction).

Dose of sitagliptin was 100mg/day in all included trials; active control regimens included pioglitazone, metformin and glimepiride. Mean patient age was 56 years. The proportion of male participants ranged from 51% to 66%. Mean baseline haemoglobin A1c was around 8%. Mean body mass index (BMI) was 30kg/m$^2$ to 33kg/m$^2$ except for a Japanese study that reported a mean BMI of 25. Trial durations ranged from 12 to 52 weeks (average 25 weeks). Trial drop-out rates were reported to be lower in sitagliptin groups (around 13%) than placebo groups (around 17%).

All potentially relevant articles were reviewed independently by three authors. Disagreements were resolved by consensus.

Assessment of study quality
Trials were assessed for randomisation, random allocation concealment, masking of treatment allocation, blinding and withdrawals.

All included studies were assessed independently by three authors. Disagreements were resolved by consensus.

Data extraction
Data were extracted using a standardised data extraction tool. An attempt was made to contact trial authors for any missing data.

The authors reported that data extraction was conducted independently; they did not state how many reviewers performed the data extraction.

Methods of synthesis
A meta-analysis was performed. Effect sizes were estimated as weighted mean differences (WMD) with 95% confidence intervals (CIs) and pooled using a DerSimonian and Laird random-effects model. Statistical heterogeneity was measured using the Q statistic (p<0.1 was considered statistically significant) and I$^2$ test.
A fixed-effects model (Mulrow-Oxman methodology) was used to pool studies in a sensitivity analysis. Subgroups were analysed for the outcome HOMA-β (limited to sitagliptin versus placebo comparisons): sitagliptin as monotherapy, as combination therapy and in combination with metformin only; trial duration 12 weeks and 24 weeks; sitagliptin administered 50mg twice a day and 200mg/day. Trials of sitagliptin versus glipizide were also analysed separately. Subgroups for the outcome PI/IR were analysed: sitagliptin as monotherapy, combination therapy and in combination only with metformin; analyses limited to trials of 24 weeks duration; trials that administered sitagliptin at 200mg/day.

Presence of publication bias was assessed through visual inspection of funnel plots for asymmetry and using the Egger weighted regression method for all primary and secondary analyses (p<0.05 considered statistically significant).

Results of the review
Twelve RCTs (4,825 participants) were included: 11 assessed effects on HOMA-β (n=3,039) and eight assessed PI/IR (n=2,325). All trials were reported to be randomised and double blinded. No further details of trial validity were provided.

Overall, a statistically significant improvement in HOMA-β was found from sitagliptin compared with placebo (WMD 12.03%, 95% CI 9.45% to 14.60%), which indicated better preservation of β-cell function. A statistically significant reduction in PI/IR was found (-0.06, 95% CI -0.08 to -0.04). Analysis of trials that compared sitagliptin to active control regimens (four RCTs, n=1,425) found better improvement in HOMA-β in the active control group (WMD -5.64%, 95% CI -10.90 to -0.38). The same comparison for PI/IR (three RCTs, n not reported) found no significant difference between sitagliptin and active control regimens.

Subgroup analyses showed that when compared with placebo, a statistically significant improvement in HOMA-β was observed regardless of whether sitagliptin was administered alone or in combination with other drugs, trial duration (12 or 24 weeks) and dosage (50mg twice a day or 200mg/day). When sitagliptin was compared with sulfonylurea (two trials), a statistically significant worsening in HOMA-β was observed (WMD -9.25, 95%CI -16.85, -1.65). Statistically significant decreases in PI/IR were observed compared to placebo for sitagliptin administered alone or in combination, for trials of 24 weeks duration and for dosage of 200mg/day.

Sensitivity analysis (fixed-effects analysis) reportedly did not show a significant difference in results in any primary or subgroup analysis. Statistical heterogeneity was not significant for any primary analysis. Funnel plots were reported to show some evidence of asymmetry. Egger weighted regression models were not statistically significant for either primary analysis.

Authors’ conclusions
The authors concluded that despite significant improvement in measures of beta cell function from sitagliptin compared to placebo, there did not appear to be a benefit from DPP-IV inhibitors over other agents in terms of short term β-cell activity assessed by HOMA-β. They could not rule out prevention of β-cell dysfunction by sitagliptin via reduction in proinsulin, PI/IR and effect of incretin hormones.

CRD commentary
The aim and inclusion criteria for this review were clear and appropriate. The literature search included both electronic and manual elements with an attempt to identify grey literature, which reduced the risk of publication bias. No use of language restrictions was reported, which implied language bias may not have been an issue. The main stages of the review were carried out independently by at least two reviewers, which reduced the risk of reviewer bias. Validity assessment was performed with some indication of the quality features assessed. However, the authors did not give a full description of what they considered to be good quality and only the presence of randomisation and double blinding were reported. The quality assessment results were not used to inform the study synthesis. Apart from the lack of quality assessment detail, other study and patient characterises were provided in table format. The statistical synthesis of included studies and the methods used were appropriate. Subgroup analyses were not well reported and it appeared that no between-subgroup comparison was conducted.

Overall the review was carried out to a good standard and the authors’ conclusions were based on the data presented.
Implications of the review for practice and research

**Practice**: The authors did not state any implications for practice

**Research**: The authors stated that long-term (at least five years follow-up) were needed to clarify the effect of sitagliptin on β-cell salvation and regeneration, particularly in comparison to active control regimens such as glipizide, metformin and thiazolidinediones.

**Funding**
None stated.

**Bibliographic details**

**PubMedID**
19322069

**DOI**
10.1097/MAJ.0b013e31818eb721

**Original Paper URL**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Clinical Trials as Topic; Diabetes Mellitus, Type 2 /drug therapy; Dipeptidyl Peptidase 4 /metabolism; Dipeptidyl-Peptidase IV Inhibitors /pharmacology; Female; Homeostasis; Humans; Insulin /metabolism; Insulin-Secreting Cells /drug effects; Male; Middle Aged; Placebos; Proinsulin /metabolism; Pyrazines /pharmacology; Randomized Controlled Trials as Topic; Sitagliptin Phosphate; Treatment Outcome; Triazoles /pharmacology

**AccessionNumber**
12009106406

**Date bibliographic record published**
02/09/2009

**Date abstract record published**
04/05/2011

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.