Efficacy of GLP-1 receptor agonists and DPP-4 inhibitors: meta-analysis and systematic review

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CRD summary
The authors concluded that all the incretin-based therapies significantly reduced glycated haemoglobin and fasting plasma glucose levels. Despite a number of limitations, including unknown variability between trials, poor reporting of trial quality, and unclear review processes, this conclusion appears to be reliable, but the magnitude of the effects is less certain.

Authors' objectives
To summarise the findings from studies of incretin-based therapies, including glucagon-like peptide one receptor agonists and dipeptidyl-peptidase four inhibitors.

Searching
MEDLINE, EMBASE, and BIOSIS Previews were searched for articles published in English, from 1st January 1990 to 30th June 2011. Unpublished studies were excluded. The abstract databases, for 2011, from the American Diabetes Association, and the European Association for the Study of Diabetes, were searched. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) of 10 or more patients with type 2 diabetes, per treatment arm, were eligible for inclusion. Trials had last at least 12 weeks and had to report the change in glycated haemoglobin, as the primary endpoint. Trials were only included if they investigated the effects of one drug, rather than combination therapies. Drugs were eligible if phase III data were available, by 30th June 2011, and if the highest effective maintenance dose was reported. The focus of the analyses was on drugs that were approved for use in the USA, European Union, or both.

Most of the included trials were conducted during phase III development. Almost all trials were published in 2005 or later. Trials lasted from 12 weeks to two years; most of them lasted between 24 and 30 weeks. Most trials used an oral glucose-lowering therapy in addition to the drug of interest. Baseline glycated haemoglobin levels ranged from 7.2 to 10.3%, where reported. Where given, the percentage of female participants ranged from 29.7 to 64.0. A range of therapies was used, at different doses and frequencies, across the trials. The drugs included exenatide and liraglutide (glucagon-like peptide one receptor agonists) and alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin (dipeptidyl-peptidase four inhibitors). Most trials had more than two treatment arms, comparing different drugs or different doses of the same drug, and a control group. Placebo was most commonly used for control groups.

Three reviewers independently assessed studies for inclusion. Disagreements were resolved by discussion with a fourth reviewer.

Assessment of study quality
Studies were assessed for the discontinuation rate, medication changes prior to baseline assessment, comparability of groups at baseline, blinding, and methods of analysis. The number of reviewers, who assessed quality, was not reported.

Data extraction
Study and participant characteristics were extracted, as well as the mean and/or least-squares mean, with 95% confidence interval, for changes from baseline, for glycated haemoglobin, fasting plasma glucose, and weight. Missing data were not imputed.

All data entered into the statistical models were checked by four reviewers against the original references. It was not reported how many reviewers extracted the other data.

Methods of synthesis
Trials were synthesised in two groups: one included those with the highest maintenance dose approved or tested, and the
other included all doses approved for use or tested in a phase III trial. For all analyses, the weighted mean differences, with standard errors, were calculated. Missing standard errors were imputed.

Fixed-effect and random-effects meta-analyses, as well as Bayesian random-effects meta-regression were all performed. $I^2$ was used to assess the heterogeneity between trials to determine whether a fixed-effect or random-effects model should be reported. The investigation of heterogeneity between trials, determined that random-effects meta-analyses were reported. The regression model was used to assess baseline glycated haemoglobin as a moderator of the observed effects.

The risk of publication bias was investigated using funnel plots.

**Results of the review**

Eighty RCTs were included in the review, with over 38,000 patients randomised and analysed (sample sizes were not reported for three trials). Where reported, the analysed sample sizes ranged from 29 to 1,519 patients. Dropout rates ranged from zero to 56.9%, where reported. Sixty-six trials were described as double blind; details of who was blinded were not reported. The funnel plots were not presented, but it was stated that they indicated minimal risk of publication bias. The dose studied for each treatment drug was reported in the supplementary material.

All drugs led to a reduction in glycated haemoglobin. The most effective was exenatide once weekly (WMD -1.59%, 95% CI -1.70 to -1.48; seven trials) and the least effective was linagliptin (WMD -0.60%, 95% CI -0.75 to -0.46; eight trials). All treatments reduced fasting plasma glucose. The most effective was exenatide once weekly (WMD -2.12 mmol/L, 95% CI -2.28 to -1.96; seven trials) and the least effective was saxagliptin (WMD -0.73 mmol/L, 95% CI -0.95 to -0.50; six trials).

The glucagon-like peptide one receptor agonists all caused weight loss of a similar magnitude (for example, exenatide once weekly WMD -2.41kg, 95% CI -2.83 to -1.99; seven trials). Weight loss for the dipeptidyl-peptidase four inhibitors was lower and was only statistically significant for saxagliptin (WMD -0.64kg, 95% CI -1.11 to -0.16; four trials). Further analyses of all doses approved or in late stage development were reported.

**Authors’ conclusions**

All the incretin-based therapies significantly reduced glycated haemoglobin and fasting plasma glucose levels.

**CRD commentary**

The review question was vague, but the inclusion criteria were clear. Some relevant sources were searched, but the exclusion of unpublished studies and those not in English means that relevant trials may have been missed. No evidence of publication bias was reported, but this cannot be verified as the funnel plots were not presented. The basic trial details were missing for some studies. Study selection and data extraction were conducted independently by two people, reducing the risk of reviewer bias and error, but it was unclear how quality assessment was conducted. Trial quality was assessed using non-standardised criteria, which were not described in detail. This makes it difficult to replicate the quality assessment. Adverse events do not appear to have been considered.

Brief results of the quality assessment were reported in the supplemental material. The quality of the included trials was not used in the analyses, making it difficult to assess the impact of quality on the results. Appropriate methods were used to synthesise the trial data and to assess heterogeneity, but the heterogeneity results were not reported, making it difficult to assess the extent of variability between trials. A large number of meta-analyses were reported, but due to the unknown variation between trials, it is unclear if it was appropriate to pool the data.

The quality of the included trials was poorly reported, the search was limited, and some aspects of the review process were unclear, but the authors’ main conclusion, that all the drugs reduced glycated haemoglobin and fasting plasma glucose, appears to be reliable. The magnitude of the effects is less certain.

Several authors reported financial links to pharmaceutical companies, including the developers of exenatide.

**Implications of the review for practice and research**

**Practice:** The authors did not make any recommendations for practice.
Research: The authors stated a need for direct comparative trials between glucagon-like peptide one receptor agonists and dipeptidyl-peptidase four inhibitors, and between the different classes of glucagon-like peptide one receptor agonists.

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