Glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized clinical trials
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CRD summary
The review concluded that the prophylactic use of glucagon-like peptide-1 receptor agonists for type 2 diabetes effectively reduced glycosylated haemoglobin and postprandial glucose; it had a similar effect to insulin in patients unresponsive to sulphonylurea or metformin. The safety profile was reassuring. The review had no major flaws, but the presence of heterogeneity makes the reliability of the conclusions unclear.

Authors' objectives
To evaluate the safety and effectiveness of the prophylactic use of glucagon-like peptide-1 receptor agonists in the treatment of type 2 diabetes.

Searching
MEDLINE, EMBASE, BIOSIS Previews, and the Cochrane Central Register of Controlled Trials, were searched with various search dates reported up to December 2008 for publications in English. Search terms were reported. Unpublished trials were identified by searching various websites (www.clinicaltrials.gov; www.novonordisk-trials.com; www.clinicalstudy-results.org), and by a manual search of the abstracts of the annual congresses in 2008 of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Further trials were found during the preparation of the manuscript and added to the meta-analysis.

Study selection
Randomised controlled trials (RCTs), with either a cross-over or a parallel series design, comparing glucagon-like peptide-1 receptor agonists with either placebo or other active drugs in patients with type 2 diabetes, were eligible for inclusion. Included trials had to have a duration of at least 12 weeks. The primary outcome was glycosylated haemoglobin (HbA1c) level. The secondary outcome was body mass index at the end of the trial. Data on adverse events were also extracted. Trials were excluded if they were incomplete or had been interrupted, or if relevant data was not accessible. Both unpublished and published trials were identified.

The included trials were of two glucagon-like peptide-1 analogues, liraglutide (dosage 0.045 to 1.9 mg/day) and exenatide (dosage 0.8 to 20 μg/day). The comparator groups in the included trials were placebo, insulin or active comparators (metformin, glimepiride and glargine). Exenatide is usually given twice a day and liraglutide once a day, but one study of exenatide used a long-acting release formula with a higher dose (0.8 to 2 mg/week). The duration range of the trials was 12 to 52 weeks. The mean duration of diabetes in the patients in the included trials was 7.3 years (range 2.0 to 11.8 years); their mean age was 56 years (range 53 to 61 years). Details of the sex of the patients in the included trials were not provided.

Two independent researchers were involved in the literature search, and disagreements were resolved by a third reviewer.

Assessment of study quality
Methodological quality was assessed using a scaled-down version of the method developed by Jadad and Schulz. Criteria included: adequacy of randomisation and blinding; loss to follow-up recorded; and intention-to-treat.

It was not clear how many reviewers performed the quality assessment.

Data extraction
Weighted mean differences (WMD) were extracted for glycosylated haemoglobin and body mass index, the incidence
of severe or any hypoglycaemia and other adverse events, and death from any cause, for each RCT (further details are given). Principal authors of RCTs were contacted to access missing data.

Two independent researchers extracted the data with disagreements resolved by a third reviewer.

**Methods of synthesis**

Weighted mean differences for glycosylated haemoglobin levels and body mass index were pooled using a random-effects model. Mantel-Haenszel odds ratio (OR) with 95% confidence intervals (CI) were calculated for hypoglycaemia and adverse events using a random-effects model. Where possible, separate analyses were carried out for trials with different glucagon-like peptide-1 receptor agonists. Heterogeneity between trials was determined using $I^2$ tests to compare placebo-controlled and comparator-controlled trials.

Publication/disclosure bias was assessed using the Begg and Mazumdar rank correlation test: Kendall’s tau without continuity correction, and one-sided $p$ values, were calculated. Interaction was assessed using the method of Altman and Bland. The statistical power to detect a clinically relevant difference of at least 0.5% in glycosylated haemoglobin for placebo-controlled and active-comparator trials was assessed using the method of Thorlund et al. Bias associated with publication date was assessed by calculating $z$ values for glycosylated haemoglobin.

**Results of the review**

Twenty one RCTs (n=8482 patients) were identified. Twelve RCTs were placebo-controlled; six were active comparator studies; the remaining three RCTs had both a placebo group and an active drug control group. Nine trials investigated liraglutide and twelve studies, exenatide. Randomisation was classed as adequate in ten RCTs; blinding was adequate in nine studies and reported as 'open label' in five RCTs; loss to follow-up was reported as adequate in 19 RCTs; and an intention-to-treat analysis was performed in all but one RCT.

**Efficacy**: Glucagon-like peptide-1 receptor agonists gave a significant improvement (decrease) in glycosylated haemoglobin (HbA1c) levels compared to placebo (WMD -1.0 mmol/L, 95% CI: -1.1 to -0.8). Similar significant results were reported for subgroup analyses of liraglutide and exenatide. The effect was similar in both shorter term (less than 26 weeks) and longer term trials (more than 26 weeks) and in unpublished trials and published trials. When glucagon-like peptide-1 receptor agonists were compared with other active drugs, there was no significant difference in HbA1c level when compared with insulin (five RCTs), sulphonylurea (glimepiride) (three RCTs of liraglutide), and metformin (one RCT of liraglutide). However, for four RCTs comparing exenatide with insulin, exenatide significantly reduced self-monitored postprandial glucose after breakfast (WMD -0.67 mmol/L, 95% CI: -0.56 to -0.78) and after dinner (WMD -0.66 mmol/L, 95% CI: -1.14 to -2.73), but had no significant effect on postprandial glucose after lunch. There was a high level of heterogeneity for HbA1c, and both placebo-controlled ($I^2=83.6\%$) and active comparator-controlled ($I^2=83.2\%$) trials (both $p<0.001$). For HbA1c and publication bias, Kendall’s tau was -0.25 ($p=0.11$) for placebo-controlled trials and 0.14 ($p=0.36$) for active comparator-controlled trials. For published trials alone, the corresponding values were -0.28 ($p=0.15$) or placebo-controlled trials and 0.07 ($p=0.43$) for active comparator-controlled trials, indicating an absence of significant publication bias.

**Body mass index**: Glucagon-like peptide-1 receptor agonists gave a significant reduction in body mass index compared to placebo (WMD -0.44 kg/m², 95% CI: -0.78 to -0.10; 11 RCTs), which was also significant for exenatide compared to placebo (WMD -0.62 kg/m² (95% CI: -1.14 to -0.10) but not significant for liraglutide compared to placebo. When compared to insulin, glucagon-like peptide-1 receptor agonists also gave a significant reduction in body mass index (WMD -1.57 kg/m², 95% CI: -1.98 to -1.15; five RCTs).

**Safety and adverse events**: In placebo-controlled trials, exenatide significantly increased the risk of hypoglycaemic episodes (OR 2.92, 95% CI: 1.49 to 5.75; 10 RCTs), but the risk was only increased where the drug was combined with sulphonylurea (OR 4.62, 95% CI: 1.89 to 11.21; 10 RCTs). In RCTs which compared exenatide and insulin, exenatide was not associated with an increased risk of hypoglycaemic episodes. Liraglutide was not significantly associated with increased risk of hypoglycaemic episodes compared to placebo (five RCTs). Glucagon-like peptide-1 receptor agonists significantly increased the risk of nausea (OR 3.88, 95% CI: 2.79 to 5.42), vomiting (OR 4.23, 95% CI: 2.67 to 6.13), and diarrhoea (OR 2.36, 95% CI: 1.67 to 3.33). Similar significant results were reported for subgroup analyses of liraglutide and exenatide. There was no significant risk of severe glycaemic episodes, increased
mortality, major cardiovascular events, pancreatitis, or angioedema associated with the use of either exenatide or liraglutide.

Authors’ conclusions
Glucagon-like peptide-1 receptor agonists were effective in reducing glycosylated haemoglobin and postprandial glucose. In patients not responding to sulphonylurea and metformin, glucagon-like peptide-1 receptor agonists had a similar effect to insulin. The safety profile was reassuring, with low hypoglycaemic risk and low cardiovascular disease risk. Glucagon-like peptide-1 receptor agonists which induced weight loss had gastrointestinal side-effects. The efficacy and tolerability of liraglutide, requiring once-a-day administration, was comparative to exenatide, which required twice-a-day administration.

CRD commentary
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched in any language, and unpublished studies were also considered. Publication bias was assessed. Study quality was assessed using suitable criteria. Some study details were not reported. Statistical heterogeneity was assessed and there was evidence for a high level of heterogeneity for glycosylated haemoglobin. The statistical method used for the meta-analysis of the RCTs seemed appropriate. The authors disclosed a number of financial relationships with pharmaceutical companies. The review had no major flaws, but the presence of heterogeneity makes the reliability of the authors’ conclusions unclear.

Implications of the review for practice and research
Practice: The authors stated that liraglutide could be a valid alternative to exenatide in selected patients (as indicated by the Consensus algorithm issued by the ADA/EASD), in whom glucagon-like peptide-1 receptor agonists can be used. Liraglutide must used only once a day, whereas exenatide must be used twice a day. In some patients glucagon-like peptide-1 receptor agonists can be used in addition to metformin.

Research: The authors did not report any relevant implications for research.

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