Glucagon-like peptide-1 receptor agonists versus insulin glargine for type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials

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CRD summary
The review concluded that glucagon-like peptide-1 receptor agonists, compared to insulin glargine, significantly decreased weight in patients with type 2 diabetes, but increased gastrointestinal adverse events. The influence on mortality or diabetes-associated complications remained unclear. The authors’ conclusions reflect the limited short-term evidence, but due to limited data and potential for review bias, they should be interpreted with caution.

Authors' objectives
To assess the efficacy and safety of glucagon-like peptide-1 (GLP-1) receptor agonists compared to insulin analogues in type 2 diabetic patients who had not responded to treatment with oral hypoglycaemic agents.

Searching
The Cochrane Library, MEDLINE, EMBASE, Science Citation Index Expanded and Current Controlled Trials Register were searched from inception up to April 2010. There were no language restrictions. Relevant search terms were reported. Reference lists of included studies and related reviews and the United States Food and Drug Administration (FDA) and International Diabetes Federation (IDF) websites were searched. Posters and abstracts from American Diabetes Association (ADA) annual meetings from 2004 to 2009 were searched. Eli Lilly and Company and Novo Nordisk pharmaceutical companies were contacted for additional studies.

Study selection
Eligible studies were randomised controlled trials (RCTs) (parallel and crossover designs) of GLP-1 receptor agonist injection compared to long-acting insulin analogue injection in combination with stable doses of an oral antidiabetic drug for more than 12 weeks. Quasi-randomised controlled trials were excluded.

Eligible participants were aged 18 years or more and had type 2 diabetes diagnosed according to World Health Organization (WHO) 1998 or ADA 2009 diagnostic criteria. Primary end point outcomes included mortality (diabetes related or total), diabetes-related adverse events and health-related quality of life (measured by a validated instrument). Secondary outcomes included glycaemic control, plasma lipid levels, fasting and postprandial insulin and C-peptide levels, weight or body mass index (BMI), blood pressure, waist and hip circumference, waist:hip ratio, mild or moderate hypoglycaemia, adverse events and costs.

Participants in the included studies ranged in mean age from 55 to 60 years. The proportion of males ranged from 32% to 70%. Mean BMI ranged from 31 to 35kg/m². Duration of diabetes ranged from four to 10 years. GLP-1 receptor agonists included either exenatide or liraglutide; these were compared with insulin glargine. These treatments were combined with combinations of metformin, sulfonylurea and thiazolidinedione.

Two reviewers independently selected studies for inclusion in the review. Disagreements were resolved by a third reviewer.

Assessment of study quality
The included studies were assessed for quality; criteria included randomisation procedure, allocation concealment, method of blinding, intention to treat (ITT) analysis and selective outcome reporting. For each trial, criteria were scored as adequate (low risk of bias), unclear (uncertain risk of bias) or inadequate (high risk of bias).

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

Data extraction
For each trial, mean differences (MD) were calculated for continuous data and relative risks (RRs) were calculated for dichotomous data, together with 95% confidence intervals (CIs).

The authors did not explicitly state how many reviewers performed data extraction, but did mention that three reviewers were involved in the data extraction process.

**Methods of synthesis**
A fixed-effect model (or random-effects model where there was evidence of statistical heterogeneity) was used to pool mean differences, relative risks and 95% confidence intervals. Subgroup analysis was performed for different GLP-1 receptor agonists (exenatide and liraglutide). Sensitivity analyses were performed to assess the effect of different types of study design (parallel group or crossover). Statistical heterogeneity was assessed with $X^2$ and $I^2$ (substantial heterogeneity was defined as $p<0.1$ and $I^2>50\%$). A narrative synthesis was undertaken where data were unsuitable for combining in meta-analyses. Funnel plots of primary outcomes and important secondary outcome were calculated to assess publication bias.

**Results of the review**
Five RCTs ($n=1,452$) were included in the review: four trials with a parallel group design and one with a crossover design. All trials had ITT analysis and no indication of selective outcome reporting. None of the trials were blinded. Allocation concealment and randomisation method were adequate for four of the five trials. Trial duration ranged from 16 to 52 weeks.

**Primary outcomes**
None of the trials assessed mortality or diabetes related complications. One trial in a secondary analysis from another paper found no evidence of a difference in health-related quality of life.

**Secondary outcomes**

**Glycaemic control:** Insulin glargine was associated with a significant reduction in fasting blood glucose levels when compared to glucagon-like peptide-1 (GLP-1) receptor agonists (MD 1.31, 95% CI 1.04 to 1.58; $I^2=0\%$; four trials) and a significantly increased percentage of patients who achieved fasting blood glucose of less than 5.6mmol/L (RR 0.35, 95% CI 0.25 to 0.49; $I^2=0\%$; three trials). There was no evidence of a difference in the other measures of glycaemic control (change in glycosylated hemoglobin levels and proportion of patients achieving glycosylated hemoglobin ≤7%) between treatments.

**Postprandial blood glucose levels (four trials):** Three of the trials suggested that GLP-1 receptor agonists were associated with significantly reduced postprandial blood glucose levels when compared with insulin glargine.

**Fasting and postprandial insulin and C-peptide levels (three trials):** GLP-1 receptor agonists were associated with significantly reduced fasting and postprandial insulin (one trial) and C-peptide levels (two trials).

**Plasma lipid levels:** GLP-1 receptor agonists were associated with statistically significant reductions in LDL-C levels when compared to insulin glargine (MD -0.18, 95% CI -0.28 to -0.08, $I^2=0\%$; two trials), but there were no significant differences between treatments for the other lipids (total cholesterol, HDL-C and triglycerides).

**Weight or Body Mass Index:** Compared to insulin glargine, GLP-1 receptor agonists were associated with significantly greater weight reduction (MD -3.96kg, 95% CI -5.14 to -2.77, $I^2=89\%$; five trials), significantly reduced systolic blood pressure (MD -3.59mmHg, 95% CI -5.74 to -1.43; $I^2=0\%$; two trials) and significantly reduced waist circumference (two trials).

**Hypoglycaemia:** There was no evidence of a significant difference in the overall incidence of hypoglycaemia between treatments, but insulin glargine was associated with significantly more nocturnal hypoglycaemic episodes than GLP-1 receptor agonists (two trials).

**Adverse events:** GLP-1 receptor agonists were associated with a significantly greater overall incidence of treatment-
related adverse events than insulin glargine (RR 1.23, 95% CI 1.09 to 1.39; I²=67%; four trials). Most adverse events were gastrointestinal effects such as nausea, vomiting, diarrhoea and abdominal pain.

Subgroup and sensitivity analyses did not significantly alter the results.

There was no evidence of publication bias for the five studies.

**Cost information**

Four publications (based on one of the included RCTs) assessed cost effectiveness. They reported higher direct medical costs with GLP-1 receptor agonists compared to insulin glargine, but comparable or better life expectancy and an improvement in quality-adjusted life years. One trial found that GLP-1 receptor agonists were not cost effective when compared to insulin glargine.

**Authors’ conclusions**

Compared with insulin glargine, GLP-1 receptor agonists were significantly associated with decreased weight, postprandial blood glucose, LDL-C, systolic blood pressure and improved islet beta-cell function, but increased gastrointestinal adverse events. Compared with GLP-1 receptor agonists, insulin glargine significantly reduced fasting blood glucose, but with a higher rate of nocturnal hypoglycaemic episodes and influenza. There was no evidence of a difference between treatments in reduction of HbA1c levels and overall incidence of hypoglycaemia. It was unclear whether GLP-1 receptor agonists influenced mortality and diabetes-associated complications in patients with type 2 diabetes.

**CRD commentary**

The review addressed a clear research question. Inclusion criteria appeared appropriate. Several relevant sources were searched for studies. There were no language restrictions. Attempts made to find unpublished studies by searching a register for ongoing trials and conference abstracts. Too few relevant studies were identified for the authors to assess publication bias. Appropriate methods were used for study selection and this also seemed likely for data extraction, but the authors did not specifically state how many reviewers performed quality assessment. Included studies were assessed for quality using appropriate criteria and were generally at a low risk of bias, although no studies were blinded and only a few studies reported on each outcome.

Study duration ranged from four to 12 months, so long-term efficacy and safety of the treatments was uncertain. No data were available to assess two of the three primary outcomes; the third primary outcome was assessed in a secondary analysis (not meeting the inclusion criteria) of one of the included studies. Methods of synthesis were appropriate; studies were pooled in meta-analyses, where possible, or combined in a narrative format.

The authors’ conclusions reflect the limited evidence base, but lack of data for the primary outcomes, potential for bias in the review process and short follow-up mean the authors’ conclusions should be interpreted with caution.

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

**Practice:** The authors stated that GLP-1 receptor agonists were an option for treatment of diabetic patients, especially those who were overweight or obese or who had not responded to oral hypoglycaemic agents.

**Research:** The authors stated that further research with longer follow-up were required to assess mortality, diabetes-related complications and quality of life; trials should also focus on durability of glycaemic control, weight loss, improvement of beta-cell secretory function, medical costs, safety, quality of life and life expectancy.

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