Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials
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CRD summary
This well-conducted review concluded that treatment with glucagon-like peptide-1 receptor agonists led to weight loss in overweight or obese patients with or without type 2 diabetes. This conclusion is likely to be reliable for short-term treatment, although the evidence was stronger for people with diabetes than those without.

Authors' objectives
To assess the effects of glucagon-like peptide-1 receptor agonists on weight loss in overweight or obese patients with or without type 2 diabetes.

Searching
The authors searched the Cochrane Library, MEDLINE, EMBASE and Web of Science to May 2011. There were no language restrictions. Search terms were reported. Trial registries were searched using the World Health Organization portal. Reference lists of relevant papers were screened manually. Pharmaceutical companies were contacted for unpublished data.

Study selection
Randomised controlled trials (RCTs) that compared glucagon-like peptide-1 receptor agonists (exenatide given twice daily or weekly; liraglutide given once daily) with placebo, no intervention or anti-diabetic drugs were eligible for inclusion. Randomised comparisons of exenatide and liraglutide were also eligible. Eligible trials recruited adults with or without type 2 diabetes who had a body mass index of 25 or more. Trials had to last at least 20 weeks and assess clinically relevant doses of the glucagon-like peptide-1 receptor agonists. The primary outcome was weight loss; secondary outcomes were reported.

Most included trials recruited patients with type 2 diabetes and were conducted in the USA or Europe. The mean body mass index of participants ranged from 29 to 41; their mean weight ranged from 82 to 111 kg. Trial duration ranged from 20 to 52 weeks. Control groups received placebo or a variety of anti-diabetic drugs. In some trials in patients with diabetes, both groups received an anti-diabetic drug as a co-intervention.

All authors independently selected trials for the review.

Assessment of study quality
Trial quality was assessed based on method of randomisation and allocation concealment. Data were also extracted on: blinding; risk of attrition bias; whether the primary outcome was defined and reported, whether sample size calculations were done and the required sample size achieved; and, for trials terminated prematurely, whether the termination was based on predefined criteria.

It appears that three authors independently assessed trial quality.

Data extraction
Data were extracted to calculate mean differences between groups for continuous outcomes and relative risks for dichotomous outcomes, both with associated 95% confidence intervals (CIs).

Three authors independently extracted data. Disagreements were resolved through discussion.
Methods of synthesis
Trials were pooled by meta-analysis using random-effects models. $T^2$ values and associated p values were used as markers of inter-trial heterogeneity.

Subgroup analyses examined treatment effects in patients with and without diabetes, and in those receiving different glucagon-like peptide-1 receptor agonist regimens. Meta-regression was used to investigate whether body mass index or trial duration predicted treatment effect. Sequential analysis was used to assess the robustness of the results after adjusting for multiple comparisons.

Publication bias and small study effects were assessed by regression analysis of funnel plot asymmetry (Egger's test).

Results of the review
Twenty-five RCTs with 10,560 participants (range 49 to 1,091) were included. Thirteen trials assessed exenatide twice daily, eight assessed liraglutide, and four assessed exenatide once weekly. Three trials compared exenatide twice daily with liraglutide or exenatide once weekly. Randomisation and allocation concealment were considered adequate in all trials.

Glucagon-like peptide-1 receptor agonist treatment was associated with a statistically significant 2.9 kg improvement in weight loss compared with controls (weighted mean difference 2.90, 95% CI -3.59 to -2.22; 21 RCTs, 6,411 participants). Statistically significant heterogeneity was present, but Egger's test did not reveal significant bias or small study effects. Subgroup analyses showed a statistically significant effect on weight loss for patients with and without diabetes and for all three glucagon-like peptide-1 receptor agonist regimens. Differences between regimens were not significant. Body mass index at baseline and trial duration did not significantly predict treatment effect. Sequential analysis indicated that the evidence was sufficient to confirm the intervention effect after adjusting for multiple testing and random error.

Glucagon-like peptide-1 receptor agonists had beneficial effects on blood pressure, plasma cholesterol and measures of glycaemic control, but did not significantly affect plasma concentrations of liver enzymes. Compared with controls, glucagon-like peptide-1 receptor agonists were associated with significant increases in risk of nausea, vomiting and diarrhoea, but not with hypoglycaemia.

Authors' conclusions
Treatment with glucagon-like peptide-1 receptor agonists led to weight loss in overweight or obese patients with or without type 2 diabetes.

CRD commentary
The review question and inclusion criteria were clear. The search covered a range of relevant sources with no language restrictions and included attempts to obtain unpublished data. Risk of publication bias was assessed and no evidence of significant bias was found. Appropriate methods were used to minimise errors and bias in study selection, quality assessment and data extraction.

Quality assessment and synthesis of the included trials were done using standard methods. Statistical heterogeneity was assessed and differences between trials were investigated using subgroup analysis and meta-regression.

The authors’ conclusions reflect the evidence presented and are likely to be reliable, although the short duration of the included trials meant that the review could not address the long-term effects of treatment. Also, as noted by the authors, the evidence base was stronger for patients with diabetes than for those without.

Implications of the review for practice and research
Practice: The authors stated that treatment with glucagon-like peptide-1 receptor agonists should be considered for patients with diabetes who are obese or overweight.

Research: The authors stated that further trials were needed to clarify the effects of glucagon-like peptide-1 receptor...
agonists in patients without diabetes.

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