

## EDITORIALS

## Glucagon-like peptide-1 agonists

Cannot be recommended strictly for weight reduction until their benefits and risks are clarified

Raj Padwal *associate professor of medicine*

2F1.26 Walter C Mackenzie Health Sciences Centre, AB, Edmonton, Canada T6G2B7

Over the past century, considerable progress has been made in understanding the role of enteroendocrine signals in regulating glucose. One substantial advance was the delineation of the “the incretin effect,” which refers to the ability of orally administered glucose to stimulate pancreatic insulin secretion to a greater extent than glucose administered intravenously.<sup>1</sup> Glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide are the two key enteroendocrine factors responsible for the incretin effect.<sup>2</sup> GLP-1, secreted from the lower gastrointestinal tract L-cells after nutrient ingestion, stimulates endogenous insulin secretion in a glucose dependent manner, inhibits postprandial glucagon release, delays gastric emptying, and increases satiety.<sup>3</sup> However, GLP-1 is of limited therapeutic use because it is rapidly degraded by dipeptidyl peptidase 4, an enzyme produced at epithelial and endothelial membranes.

In the linked systematic review and meta-analysis (doi:10.1136/bmj.d7771), Vilsbøll and colleagues assess the effect of GLP-1 receptor agonists on weight loss, blood pressure, plasma concentrations of cholesterol and liver enzymes, and glycaemic control.<sup>4</sup> The two currently approved GLP-1 analogues, exenatide and liraglutide, mimic the action of GLP-1 but are resistant to the proteolytic effects of dipeptidyl peptidase 4 and are administered subcutaneously once or twice daily, or less often, depending on the specific drug and formulation.<sup>2</sup> Compared with placebo, GLP-1 agonists reduce mean glycated haemoglobin (HbA<sub>1c</sub>) values by 1.0% (95% confidence interval 0.8% to 1.1%) and are approved for type 2 diabetes as adjunctive treatment to metformin and other agents.<sup>5,6</sup> Vilsbøll and colleagues’ meta-analysis comprised 21 randomised controlled trials (n=6411) with follow-up periods of 20-52 weeks, in which the primary objective was to examine the effect of exenatide and liraglutide on body weight.<sup>4</sup> Compared with placebo or active comparators, GLP-1 agonists reduced weight by 2.9 kg (2.2 to 3.6) in all studies, 3.2 kg (2.1 to 4.3) in three studies of people without diabetes, and 2.8 kg (2.1 to 3.2) in 18 studies of people with diabetes. Small, statistically significant improvements in blood pressure and total cholesterol were also found.

Body weight was a secondary, not primary, end point in 18 of 21 trials. Furthermore, these pooled weight loss estimates were associated with substantial heterogeneity and are difficult to

interpret because they combine the results of trials using placebo and active comparator arms. Of the comparator drugs, insulin, sulphonylureas, and thiazolidinediones increase weight and dipeptidyl peptidase 4 inhibitors are weight neutral. In a subgroup analysis of 10 placebo controlled trials, GLP-1 agonists reduced weight by 1.9 kg (0.9 to 2.9), which is probably a more accurate estimate of the weight reductions that would be expected in clinical practice.

Patients with type 2 diabetes are consistently less responsive to weight loss interventions than those without diabetes.<sup>7</sup> This is partly because of the weight increasing effects of conventional antidiabetic agents other than metformin. In this respect, the comparative weight reducing benefits of GLP-1 agonists are beneficial. However, the overall mean reductions in weight (and reductions in blood pressure and cholesterol) associated with GLP-1 agonists are modest, they are costly (£70 (€82; \$112) to £80 a month in the United Kingdom), and prospective data showing reductions in clinically important end points, such as cardiovascular events or mortality, are lacking.

Given that other antidiabetic and antiobesity agents—most recently thiazolidinediones and sibutramine—have been withdrawn from the market because of unfavourable cardiovascular risk profiles, caution is warranted until studies with hard end points are available (expected after 2015). A meta-analysis of 20 randomised controlled trials (n=10 485) found no evidence of cardiovascular risk with GLP-1 agonists, but it was based on only 114 major cardiovascular events.<sup>8</sup>

Thus, although Vilsbøll and colleagues’ meta-analysis highlights the weight reducing benefits of GLP-1 agonists, it should not alter current clinical practice. Modification of diet and lifestyle remains the cornerstone of the treatment of type 2 diabetes.<sup>9</sup> Treatment with statins and antihypertensive drugs to achieve guideline concordant reductions in cardiovascular risk factors is vital.<sup>9</sup> Metformin should be the first line drug for glycaemic control and HbA<sub>1c</sub> targets should be individualised.<sup>9,10</sup> If indicated, glycaemic control can be further improved by the addition of other agents, including GLP-1 agonists, with the expectation that microvascular but not necessarily macrovascular complications will be reduced.<sup>10</sup> On the basis of current evidence, off label use of GLP-1-agonists for weight loss in people without diabetes cannot be recommended at this time.

Studies evaluating the weight reducing efficacy of GLP-1 agonists in obese people without diabetes and those with prediabetes are ongoing.

Several questions require further clarification in future studies, including delineation of the mechanisms that underlie weight reduction, which seem to be mainly related to a centrally mediated reduction in food intake<sup>11</sup>; examination of the efficacy and safety of longer acting once weekly and once monthly preparations; and elucidation of the clinical relevance of a possible  $\beta$  cell mass preserving effect seen in animal models.<sup>2</sup>

However, the most important unanswered question relates to the safety of GLP-1 agonists. Animal studies have raised concerns of an increased risk of pancreatitis, pancreatic metaplasia, and thyroid C cell tumours.<sup>12</sup> The clinical relevance in humans is unknown and may take decades to assess fully, although data from post-marketing surveillance studies and meta-analyses of the (admittedly) highly selected patient populations enrolled in randomised controlled trials have been reassuring.<sup>12</sup> Nevertheless, continued and close surveillance of these new agents using all available data sources is warranted.

Competing interests: The author has completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declares: no support from any organisation for the submitted work; he is currently a site investigator

for a Novo Nordisk GLP-1 agonist study; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; not externally peer reviewed.

- 1 Kazafeos K. Incretin effect: GLP-1, GIP, DPP-4. *Diabetes Res Clin Pract* 2011;93:S32-6.
- 2 Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006;368:1696-705.
- 3 Drucker DJ. Enhancing incretin action for the treatment of type 2 diabetes. *Diabetes Care* 2003;26:2929-40.
- 4 Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2011;343:d7771.
- 5 Monami M, Marchionni N, Mannucci E. Glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized clinical trials. *Eur J Endocrinol* 2009;160:909-17.
- 6 National Institute for Health and Clinical Excellence. Type 2 diabetes—newer agents (partial update of CG66). 2011. [www.nice.org.uk/guidance/index.jsp?action=byID&o=12165](http://www.nice.org.uk/guidance/index.jsp?action=byID&o=12165).
- 7 Kyrou I, Kumar S. Weight management in overweight and obese patients with type 2 diabetes mellitus. *Br J Diabetes Vasc Dis* 2010;10:274-83.
- 8 Monami M, Cremasco F, Lamanna C, Colombi C, Desideri CM, Iacomelli I, et al. Glucagon-like peptide-1 receptor agonists and cardiovascular events: a meta-analysis of randomized clinical trials. *Exp Diabetes Res* 2011;2011:1-10.
- 9 National Institute for Health and Clinical Excellence. Type 2 diabetes: full guideline. CG66. 2011. <http://guidance.nice.org.uk/CG66/Guidance/pdf/English>.
- 10 Montori VM, Fernández-Balsells M. Glycemic control in type 2 diabetes: time for an evidence-based about-face? *Ann Intern Med* 2009;150:803-8.
- 11 Larsen PJ. Mechanisms behind GLP-1 induced weight loss. *Br J Diabetes Vasc Dis* 2008;8:S34-41.
- 12 Drucker DJ, Sherman SI, Gorelick FS, Bergenstal RM, Sherwin RS, Buse JB. Incretin-based therapies for the treatment of type 2 diabetes: evaluation of the risks and benefits. *Diabetes Care* 2010;33:428-33.

Cite this as: *BMJ* 2011;343:d7282

© BMJ Publishing Group Ltd 2011