

THE NEW SCIENCE OF GLP-1: EFFECTS BEYOND GLUCOSE CONTROL*

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ABSTRACT

The incretin hormone, glucagon-like peptide-1 (GLP-1) has well-characterized effects on glucose homeostasis that make it an attractive new therapeutic target for type 2 diabetes. In addition to its glucose-lowering properties, GLP-1 has other effects of potential importance in patients with type 2 diabetes. Native GLP-1 administered as a continuous infusion and GLP-1 mimetics increase satiety and decrease appetite and food intake, resulting in weight loss. Cardiovascular risk factors, such as blood pressure and lipid parameters, also improve with chronic GLP-1 mimetic administration. A few small studies have shown a benefit of GLP-1 in patients with ischemic heart disease and chronic heart failure. GLP-1 receptors are widely distributed in the brain and GLP-1 appears to play a role in the central regulation of cardiovascular function and metabolism. Recent studies also suggest that GLP-1 may be neuroprotective. These emerging areas of research suggest that GLP-1 based therapies may have unique long-term benefits beyond glucose control in patients with type 2 diabetes.

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Glucagon-like peptide-1 (GLP-1) is an incretin hormone released from intestinal L cells in the distal ileum and colon in response to food intake.¹ The physiologic actions most commonly associated with GLP-1 are its ability to enhance glucose-dependent insulin secretion, suppress postprandial glucagon secretion, slow gastric emptying, and, in animal models, to promote β -cell proliferation and decrease β -cell apoptosis.² In patients with type 2 diabetes, GLP-1 secretion is reduced and the insulinotropic effects of endogenous GLP-1 are markedly impaired.³ When GLP-1 is continuously infused at supraphysiological doses, fasting and postprandial glucose levels improve in patients with type 2 diabetes.³ Although the benefits of GLP-1 are evident in patients with type 2 diabetes, GLP-1 administration as a treatment strategy is severely limited by its short half-life in vivo of 1 to 2 minutes, due to rapid inactivation by the enzyme dipeptidyl peptidase-4 (DPP-4), and by the impracticality of continuous infusion. Thus, pharmacologic strategies have evolved to overcome these limitations by modifying native GLP-1 to make it resistant to the effects of DPP-4 and prolong its biologic half-life.⁴

Currently, only one GLP-1 mimetic, exenatide, is approved for the treatment of type 2 diabetes. Exenatide is a synthetic GLP-1 mimetic, derived from exendin-4, a naturally occurring GLP-1 receptor agonist isolated from the salivary secretions of the reptile *Heloderma suspectum* (Gila monster). Exenatide activates the GLP-1 receptor similarly to native GLP-1, but is resistant to the proteolytic activity of DPP-4 and consequently has a longer half-life.⁵ It is administered as a twice-daily injection. Exenatide long-acting release, a slow-release depot formulation of exenatide

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that is administered once weekly, is currently in phase III development.⁴ A human GLP-1 analog, liraglutide, recently completed phase III testing and is currently undergoing regulatory review.⁶ Liraglutide has a half-life of approximately 13 hours, allowing for once-daily subcutaneous administration.⁷ Several additional GLP-1 mimetics, including albiglutide (GLP-1 conjugated to albumin) and taspoglutide, a long-acting human GLP-1 analog, are under active investigation, but data are currently limited on these medications.^{4,8}

Glucagon-like peptide-1 mimetics share most of the key attributes of GLP-1. In addition to direct glucose-lowering properties, GLP-1 and GLP-1 mimetics have pleiotropic effects that may be beneficial in type 2 diabetes (Table). These non-glycemic properties, including effects on appetite, weight, blood pressure, cardiovascular risk factors, cardiovascular function, and the central nervous system, are reviewed in subsequent sections.

EFFECTS OF GLP-1 ON APPETITE, SATIETY, AND WEIGHT LOSS

Obesity contributes to the pathogenesis of type 2 diabetes; thus, it is important to explore how GLP-1 affects appetite, satiety, and weight loss. GLP-1 receptors are widely distributed in the brain and are particularly abundant in the hypothalamus in areas implicated in the control of appetite.⁹ Rats given an intracerebral ventricular (ICV) injection of GLP-1, or a GLP-1 mimetic, demonstrate a dose-dependent reduction in food intake.^{9,10} Moreover, repeated daily ICV injections cause weight loss.¹⁰ Although such studies cannot be performed in humans, peripheral GLP-1 infusions suggest similar effects in patients with type 2 diabetes. Gutzwiller et al studied subjects with type 2 diabetes who were given either an infusion of GLP-1 or a saline infusion for 2 hours, during which a meal was served.¹¹ Visual analog scales were used to assess appetite, the amount of food and fluids consumed was measured, and caloric intake calculated. Compared to saline infusion, GLP-1 infusion significantly increased satiety and feelings of fullness and reduced energy intake by 27%.¹¹

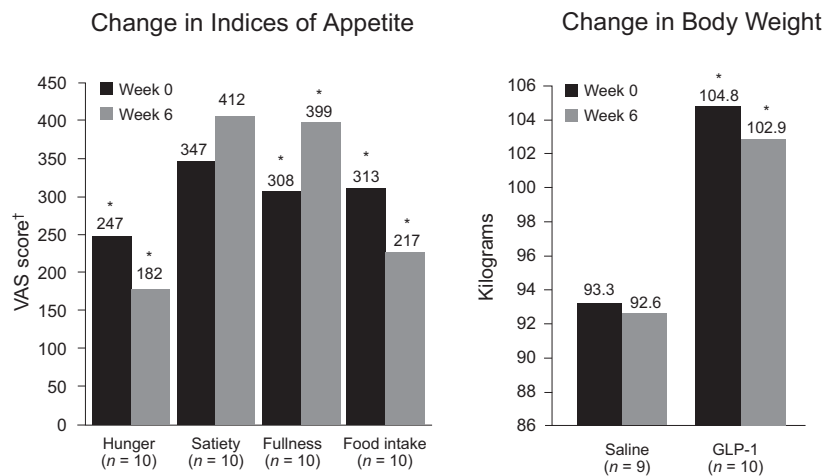
Similar results were seen in a 6-week study by Zander et al, in which patients with type 2 diabetes were randomized either to a continuous subcutaneous infusion of GLP-1 or saline.¹² Hunger, fullness, and prospective food intake changed significantly ($P < .05$) in response to the GLP-1 infusion (Figure 1).¹² Body weight decreased by 1.9 kg ($P = .013$) in the GLP-1 group, even though the subjects were not instructed to lose weight, but was not significantly lower in subjects receiving the saline infusion.¹² This study suggests that

Table 1. Non-glycemic Effects of GLP-1 and GLP-1 Analogs

- Decreased appetite and increased satiety
- Decreased body weight
- Decreased blood pressure
- Decreased cardiac risk factors
- Direct cardiac/vascular effects
- Neuroprotection

GLP-1 = glucagon-like peptide-1.

Figure 1. Effect of 6-Week GLP-1 Infusion on Appetite and Body Weight



* $P < .05$; † Mean area under the curve for VAS score (mm) vs time (h).
 GLP-1 = glucagon-like peptide-1; VAS = visual analog scale.
 Adapted with permission from Zander et al. *Lancet*. 2002;359:824-830.¹²

the effects of GLP-1 on appetite and the sense of fullness translate into meaningful body weight loss over the long term.

The mechanism by which GLP-1 affects appetite and satiety in humans remains speculative. Some studies suggest that GLP-1 has effects in appetite control centers in the human brain. Pannacciulli et al studied 42 healthy, normal volunteers using positron emission tomography imaging of the brain and demonstrated that peak postprandial increases in plasma GLP-1 concentrations were correlated with increases in regional cerebral blood flow in the left dorsolateral prefrontal cortex and the hypothalamus, areas previously shown to be related to food intake.¹³ This study shows in a correlative manner that GLP-1 has an effect in the brain that may act as a stimulus to stop eating during a meal. It is also possible that the effects of GLP-1 are indirect; an injection of GLP-1 has been shown to cause complete cessation of gastric emptying for 30 to 45 minutes.¹⁴ Food sitting longer in the stomach may provide more of a visceral sensation that results in a feeling of satiety. Finally, GLP-1 may modulate appetite and food intake through portal GLP-1 receptors via a vagal loop.⁸

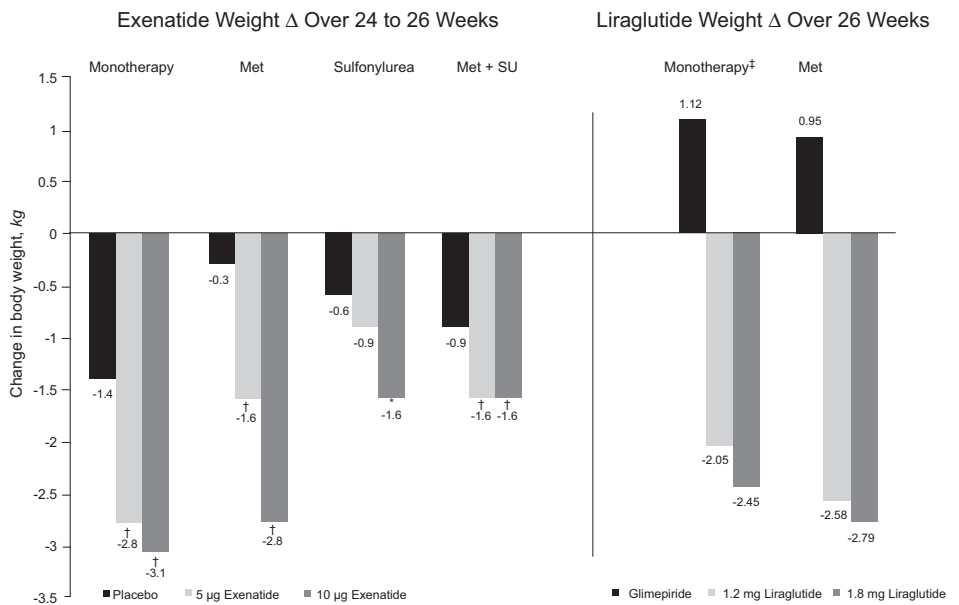
GLP-1 MIMETICS AND WEIGHT LOSS IN CLINICAL TRIALS

Most clinical trials of GLP-1 mimetics have demonstrated modest weight loss, as illustrated for exenatide and liraglutide in Figure 2.¹⁵⁻²⁰ With exenatide, the phase III studies indicate that weight loss occurs particularly when exenatide is given as monotherapy or combined with metformin therapy, but also when combined with a sulfonylurea.¹⁵⁻¹⁸ Nausea is a common side effect of GLP-1 mimetics occurring in up to 59% of subjects initiated on the starting dose of 5 µg twice daily of exenatide and again when titrated to the final dose of 10 µg twice daily.²¹ Although nausea is a

common adverse event, it appears not to be the explanation for the weight loss observed in patients treated with GLP-1 mimetics. In the clinical trials of exenatide, weight loss occurred to a similar degree in patients who did not experience nausea as compared to those who did. Of interest, in patients treated with exenatide in long-term observational studies, the weight loss appeared to be progressive and reached approximately 5 kg at 3 years.²¹ Although provocative, these data need to be interpreted with caution, as they may be an artifact of the study design with a survivor bias; people who are the most successful on the drug continue on it and continue to lose weight.

Weight loss is also found in patients taking liraglutide, as shown in Figure 2 in comparison to patients taking a sulfonylurea.^{19,20} In the LEAD-2 study in which liraglutide was studied as add-on therapy in patients already taking metformin, more than a 2-kg decrease in weight was observed for both liraglutide doses studied; whereas glimepiride, which was approx-

Figure 2. Change in Body Weight with Exenatide and Liraglutide Therapy



* P <.05; † P <.005; ‡ Total study duration for weight loss was 52 weeks. Met = metformin; SU = sulfonylurea. Data from Moretto et al¹⁵; DeFronzo et al¹⁶; Buse et al¹⁷; Kendal et al¹⁸; Nauck et al¹⁹; and Marre et al.²⁰

imately half as effective as liraglutide in lowering glucose, resulted in a 1-kg weight increase.^{19,20} Additional substudies were done in this trial to assess body composition.²² Dual X-ray absorptiometry demonstrated a decrease in body fat, particularly in abdominal regions, in the group treated with liraglutide.²² A significant decrease in intra-abdominal fat as well as subcutaneous fat was also found using computed tomography scans in the same study.²²

In summary, treatment with GLP-1 mimetics is associated with decreases in appetite and body weight. It is likely that the effects of GLP-1 mimetics on appetite and weight loss are mediated through activation of central GLP-1 receptors as well as indirectly through peripheral GLP-1 receptors. On average, the weight loss is modest, but in some individuals it can be significant. The effect appears to be dose dependent, with higher doses of GLP-1 mimetics associated with more weight loss.^{15,20} Weight loss does not appear to be directly related to nausea and it is also unlikely to be the result of delayed gastric emptying, because with the longer-acting medications an equivalent amount of weight loss occurs with less of a delay in gastric emptying.²³ Long-term observational studies with exenatide suggest that the weight loss is durable as long as people continue taking the medication.²³ Finally, it appears that visceral fat is lost in addition to subcutaneous fat.²²

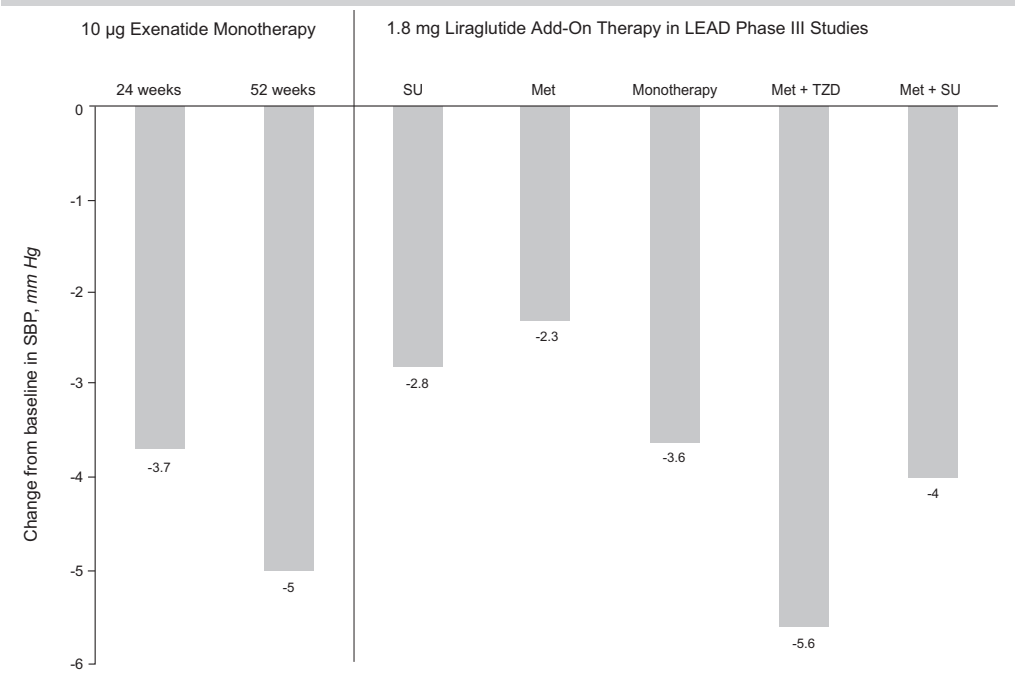
EFFECT OF GLP-1 ON CARDIOVASCULAR RISK FACTORS

Glucagon-like peptide-1 mimetics improve certain cardiovascular risk factors, although it is unclear if the observed benefits are direct effects or indirect effects due to weight loss. Improvements

in systolic blood pressure seen in exenatide and liraglutide trials are illustrated in Figure 3.^{15,19,20,24-27} The decreases in systolic blood pressure range from 2.3 to 5.6 mm Hg. Decreases also occurred in diastolic blood pressure, but were not statistically significant. In the LEAD studies with liraglutide, the decrease in blood pressure occurred within the first 2 weeks, before much weight loss had occurred.^{19,20,25-27} Thus, it seems unlikely that these improvements in blood pressure can be completely ascribed to decreases in body weight that were progressive over the 26-week duration of each study. This suggests that the reduction in blood pressure could be a direct effect of the GLP-1 mimetic. Potential mechanisms for this include a natriuretic effect as well as a direct vasorelaxant effect on the vascular system of GLP-1.²⁸

In 3-year data for exenatide, a significant decrease in triglycerides, low-density lipoprotein cholesterol and total cholesterol, and a significant increase in

Figure 3. Decrease in Systolic Blood Pressure with Exenatide and Liraglutide



LEAD = Liraglutide Effect and Action in Diabetes; Met = metformin; SBP = systolic blood pressure; SU = sulfonylurea; TZD = thiazolidinedione. Data from Moretto et al¹⁵; Nauck et al¹⁹; Marre et al²⁰; Nauck et al²⁴; Garber et al²⁵; Zinman et al²⁶; and Russel-Jones et al.²⁷

high-density lipoprotein cholesterol were observed.²¹ A phase II study also demonstrated that liraglutide treatment was associated with improvements in triglycerides in addition to reductions in plasminogen activator inhibitor-1 (PAI-1).²⁹ PAI-1 is a prothrombotic peptide that circulates in higher levels in patients with diabetes. Because it may contribute to increased cardiovascular risk, a reduction in PAI-1 is likely to be beneficial.

Glucagon-like peptide-1 may also have direct cardiac effects. In a clinical trial by Nickolaïdis et al, 21 patients who experienced an acute myocardial infarction and received an angioplasty were randomized to either a GLP-1 infusion or a saline infusion for 72 hours.³⁰ The patients who received the GLP-1 infusion had a significant improvement in their left ventricular ejection fraction (from 29±2% to 39±2%, $P < .01$) whereas the control group did not show improvement.³⁰ This could be due to improved perfusion, or it could be a direct inotropic effect of GLP-1. Another study showed improvement in left ventricular ejection fraction and functional status in patients with chronic heart failure.³¹ Twelve patients meeting the New York Heart Association class III/IV heart failure classification were given a 5-week infusion of GLP-1 and the results were compared to 9 patients receiving standard therapy.³¹ The patients who received the GLP-1 infusion had a significant improvement in left ventricular ejection fraction, VO_2 max, and 6-minute walking distance.³¹

In summary, there appear to be beneficial effects of GLP-1 on cardiovascular disease risk factors, including blood pressure and lipids. Some of these beneficial effects are due to weight loss, but emerging data suggest that GLP-1 mimetics may have direct effects on the kidneys and vasculature. More research is needed, especially to explore direct cardioprotective effects of GLP-1.

CEREBRAL GLP-1 AND EFFECTS ON NEUROPROTECTION

Another fascinating area of research is the role of cerebral GLP-1. GLP-1 is produced in the brain as well as in the gut.³² GLP-1 receptors are widely distributed in the brain, including in the hypothalamus, the thalamus, the cerebellum, and the cerebral cortex.³³ Animal studies have demonstrated GLP-1 secretion from cells in the nucleus tractus solitarius in the area of postrema, which clearly activate cerebral GLP-1 receptors.³² In animals, this appears to activate the sympathetic nervous system

and an increase in blood pressure and heart rate are seen when GLP-1 is given directly into the brain.³² GLP-1 receptors are prominent in areas of the brain important in appetite and the regulation of metabolism, and GLP-1 has important effects on regulating food and water intake as discussed earlier in this article. The extrapancreatic regulation of glucose metabolism by GLP-1 is also mediated through central pathways.⁸ Activation of central GLP-1 receptors decreases muscle glucose utilization but enhances insulin secretion and net glucose metabolism.³² Therefore, it appears that the effects of GLP-1 are mediated both through direct peripheral effects as well as through central pathways. The net effect, such as a decreased blood pressure or improvements in glucose metabolism, depends on the balance of these 2 actions.

Glucagon-like peptide-1 may also have neuroprotective effects. In a study by Lerche et al, GLP-1 was infused during a glucose clamp with 18-fluorodeoxyglucose as a tracer of glucose flux.³³ Positron emission tomography scans were used to visualize glucose uptake in the brain, and during the GLP-1 infusion glucose transport into the brain was diminished.³³ The authors speculate that through this effect GLP-1 may protect neural cells from the deleterious effects of high glucose levels. Although intriguing, further research is needed before final conclusions can be drawn. Another study suggests that GLP-1 has a direct neuroprotective effect that is not mediated by altering glucose transport.³⁴ This study looked at models of neurocortical damage induced by the neurotoxin amyloid β_{1-42} , the peptide that is implicated in Alzheimer's disease, or ferrous ions, another neurotoxin. When GLP-1 was provided in combination with the neurotoxins, it resulted in a dose-dependent improvement in neuronal survival.³⁴ This effect was mirrored when exenatide was used in the same models.³⁴ If GLP-1 does have neuroprotective effects physiologically, reduced secretion or action of GLP-1 in people with diabetes could be a factor in the increased incidence of cognitive disorders seen in that population.

CONCLUSIONS

Although GLP-1 has been most widely studied for its effects on glucose homeostasis, including its ability to enhance glucose-dependent insulin secretion and suppress postprandial glucagon secretion, other direct and indirect effects of GLP-1 and GLP-1 mimetics are important in patients with type 2 diabetes. GLP-1 has

prominent effects on appetite and energy expenditure, resulting in weight loss. Treatment with GLP-1 mimetics leads to improvements in blood pressure and lipid levels. Some of these beneficial effects are likely due to weight loss, but GLP-1 may also have direct effects. Moreover, emerging research suggests that GLP-1 has direct cardioprotective and neuroprotective effects. As more is learned about the direct and indirect effects of GLP-1 action, there is potential to improve medical conditions not conventionally linked to diabetes, such as heart failure and Alzheimer's disease.

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