Review
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

GLP-1 Receptor Agonists: Nonglycemic Clinical Effects in Weight Loss and Beyond

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Obective: Glucagon-like peptide-1 (GLP-1) receptor agonists are indicated for treatment of type 2 diabetes since they mimic the actions of native GLP-1 on pancreatic islet cells, stimulating insulin release, while inhibiting glucagon release, in a glucose-dependent manner. The observation of weight loss has led to exploration of their potential as antiobesity agents, with liraglutide 3.0 mg day^{-1} approved for weight management in the US on December 23, 2014, and in the EU on March 23, 2015. This review examines the potential nonglycemic effects of GLP-1 receptor agonists.
Methods: A literature search was conducted to identify preclinical and clinical evidence on nonglycemic effects of GLP-1 receptor agonists.
Results: GLP-1 receptors are distributed widely in a number of tissues in humans, and their effects are not limited to the well-recognized effects on glycemia. Nonglycemic effects include weight loss, which is perhaps the most widely recognized nonglycemic effect. In addition, effects on the cardiovascular, neurologic, and renal systems and on taste perception may occur independently of weight loss.
Conclusions: GLP-1 receptor agonists may provide other nonglycemic clinical effects besides weight loss. Understanding these effects is important for prescribers in using GLP-1 receptor agonists for diabetic patients, but also if approved for chronic weight management.

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Introduction

Glucagon-like peptide-1 (GLP-1) is a gut hormone that is secreted by the intestine in response to meal ingestion and potentiates glucose-dependent insulin secretion from the pancreatic beta-cells (1). In addition, GLP-1 suppresses glucagon secretion by alpha-cells, leading to a glucose-dependent reduction in hepatic glucose production (1). Glucagon may be regulated in a paracrine manner, by the secretion of somatostatin from the neighboring delta-cells (2).

GLP-1 receptor agonists mimic the pancreatic actions of native GLP-1, leading to glycosylated hemoglobin (HbA_{1c}) reductions within the range of 1.0–1.5% (3), as well as decreased postprandial plasma glucose levels (4). Several GLP-1 receptor agonists are now approved for use as second-line therapy in the treatment of type 2 diabetes (Table 1) (13).

In addition to improving glycemic control, studies in patients with diabetes show that GLP-1 receptor agonists produce weight loss (3,4). This is an advantage, given that most people with type 2 diabetes are overweight or obese and many also find it difficult to lose weight. Furthermore, there is evidence that weight loss improves glycemic control and has a positive impact on various comorbidities associated with the disease, including cardiovascular risk factors (14).

Accumulating evidence from preclinical and clinical studies indicates that the effects of GLP-1 receptor agonists go beyond glycemic control and weight reduction alone (15,16).

GLP-1 Receptor Agonists: Effects on Body Weight

In addition to their effects on glycemic control, GLP-1 receptor agonists have been shown to produce clinically relevant reductions in weight, body mass index (BMI), and waist circumference in overweight or obese individuals with or without diabetes (17,18). This finding has prompted consideration of GLP-1 receptor agonists as potential weight-loss agents (19). Indeed, liraglutide 3.0 mg day^{-1} was approved for weight management in the US on December 23, 2014 (20), and in the EU on March 23, 2015.

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TABLE 1 GLP-1 receptor agonists approved for treatment of type 2 diabetes

Agent	Recommended dose and schedule	Amino acid sequence of GLP-1 component	Homology to naturally occurring GLP-1
Naturally occurring human GLP-1 (5)	N/A	His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly	N/A
Albiglutide (6)	30 mg QW	His-Gly-Glu-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg	97%; modified GLP-1 dimer fused in series to human albumin. Amino acid substitution at position 8 (glycine to alanine), dimer.
Dulaglutide (7,8)	0.75 − 1.5 mg QW	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly-Gly	90%; synthetic human GLP-1 dimer (8-glycine,22-glutamic acid,36-glycine) fusion protein with peptide (synthetic 16-amino acid linker) fusion protein with immunoglobulin G4 (synthetic human Fc fragment).
Exenatide (9,10)	10 μg BID, ER formulation: 2 mg QW	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2	53%; synthetic version of exendin-4.
Liraglutide (5,11)	1.2 or 1.8 mg QD	His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly	97%; glutamic acid and 16-C free fatty acid addition at position 26. Amino acid substitution at position 34 (lysine to arginine).
Lixisenatide* (12)	20 μg QD	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser-Lys-Lys-Lys-Lys-Lys-Lys-NH_2	Homology not published but, based on amino acid sequence, likely to be <50%. Synthetic version of exendin-4.

*Licensed in Europe. Not approved in the United States.
QW, once weekly; QD, once daily; BID, twice daily; ER, extended release.

The mechanisms by which GLP-1 receptor agonists mediate weight loss are not yet fully understood. However, a study involving obese individuals without diabetes treated with liraglutide 3.0 mg provides some insight. Liraglutide was titrated from a starting dose of 0.6 mg day^{-1} to 3.0 mg day^{-1} at 5 weeks, to minimize nausea and vomiting (21). By 5 weeks, subjects' mean weight was reduced by −2.5 kg, despite them being asked to maintain their usual diet and physical activity. The study demonstrated that liraglutide 3.0 mg day^{-1} increased mean postprandial satiety and fullness ratings, reduced hunger and prospective food consumption, and decreased *ad libitum* energy intake by approximately 16%. Liraglutide 3.0 mg, similarly to the 1.8 mg dose, also delayed gastric emptying. Conversely, energy expenditure in subjects treated with liraglutide 3.0 mg day^{-1} decreased, even when corrected for weight loss, which was probably reflective of metabolic adaptation. Thus, the evidence supports reduced appetite and food intake, without an increase in energy expenditure, as the mechanism underlying weight loss with liraglutide. Body composition studies in humans have shown that weight loss with liraglutide appears to correspond to a reduction in predominantly visceral and subcutaneous fat, rather than lean tissue mass (22,23).

Table 2 summarizes the clinical evidence for weight loss with GLP-1 receptor agonists in patients who are overweight or obese. Of these, liraglutide has been the most extensively studied, with the clinical data presented at scientific meetings (29-34) and in peer-reviewed journals (24,25). Liraglutide phase III studies included populations with overweight and obesity, including prediabetes, hypertension, dyslipidemia, type 2 diabetes, and/or moderate or severe obstructive sleep apnea. In these studies, liraglutide 3.0 mg and lifestyle intervention was associated with a greater weight loss of approximately −5%, compared with placebo and identical lifestyle intervention. Total mean weight loss from baseline in these studies is in the range of −6% to −8% with liraglutide 3.0 mg.

One study (25) tested the effect of liraglutide 3.0 mg vs. placebo following successful initial weight loss on a low calorie diet. Individuals who achieved ≥5% weight loss in the 4- to 12-week run-in period (77% of enrollees achieved this benchmark) were randomly assigned to either liraglutide 3.0 mg or placebo; both groups received diet and exercise counselling. Mean (± standard deviation) percentage weight loss in the run-in period was −6.0% (± 0.9) and, after 56 weeks of therapy postrandomization, subjects in the liraglutide group lost an additional −6.2% (± 7.3) compared with −0.2% (±7.0) in the placebo group (25).

Other GLP-1 receptor agonists also mediate weight loss. Although no systematic long-term clinical trial program has been conducted with exenatide in patients with obesity and it is not currently

TABLE 2 Effects of GLP-1 receptor agonists on weight in patients who are overweight or obese

Study, author, and population	Study design	Sample size and retention	Dose and dosing regimen	Weight loss and time point
Astrup et al., 2009 (24) **Adults with BMI 30-40 kg m^{-2}**	All subjects on −500 kcal deficit diet and increased physical activity; 2-week placebo run-in, followed by randomization 4-week titration from 0.6 mg; 16-week constant dose treatment.	$N = 564$; completers: 85/95 (1.2 mg), 74/90 (1.8 mg), 73/93 (2.4 mg), 82/93 (3.0 mg), 79/98 (placebo), 79/95 (orlistat); total 472/564 completers = 84%	Liraglutide 1.2 mg once daily ($n = 94$)	Change from baseline at 20 weeks: Weight: −4.8 kg; weight loss >5%: 52.1%; weight loss >10%: 7.4%
			Liraglutide 1.8 mg once daily ($n = 90$)	Weight: −5.5 kg; weight loss >5%: 53.3%; weight loss >10%: 18.9%
			Liraglutide 2.4 mg once daily ($n = 92$)	Weight: −6.3 kg; weight loss >5%: 60.8%; weight loss >10%: 22.8%
			Liraglutide 3.0 mg once daily ($n = 92$)	Weight: −7.2 kg; weight loss >5%: 76.1%; weight loss >10%: 28.3%
			Placebo injection ($n = 98$)	Weight: −2.8 kg; weight loss >5%: 29.6%; weight loss >10%: 2.0%
			Orlistat 120 mg TID (open-label) ($n = 95$)	Weight: −4.1 kg; weight loss >5%: 44.2%; weight loss >10%: 9.5%
Astrup et al., 2012 **Adults with BMI 30-40 kg m^{-2}**	2-year extension of above study.	$N = 398$ entered the extension; completers: 46/68 (1.2 mg), 38/59 (1.8 mg), 45/65 (2.4 mg), 47/72 (3.0 mg), 47/67 (placebo), 45/67 (orlistat); total 268/398 completers = 67%	Liraglutide 2.4/3.0 mg once daily pooled group ($n = 92$)	Change from baseline at year 2 (completers): Weight: −7.8 kg; weight loss >5%: 69%; weight loss >10%: 43%
			Orlistat 120 mg TID (open-label) ($n = 45$)	Weight: −5.4 kg; weight loss >5%: 49%; weight loss >10%: 31%
Wadden et al., 2013 (25) **Adults with BMI ≥30 or ≥27 kg m^{-2}**	Obese/overweight participants who lost ≥5% of initial weight during a low-calorie diet run-in were randomly assigned to liraglutide 3.0 mg per day or placebo (subcutaneous administration) for 56 weeks. Diet and exercise counseling were provided throughout the trial.	$N = 422$; completers: 159/212 (3.0 mg), 146/210 (placebo)	Liraglutide 3.0 mg once daily ($n = 207$)	Change from randomization to 56 weeks (full analysis set with last observation carried forward): Weight: −6.0 kg (−6.2%); weight loss >5%: 50.5%; weight loss >10%: 26.1%
			Placebo injection ($n = 206$)	Weight: −0.1 kg (−0.2%); weight loss >5%: 21.8%; weight loss >10%: 6.3%
Rosenstock et al., 2010 (26) **Adults with BMI ≥30 kg m^{-2}**	Obese adults were randomized to exenatide or placebo, combined with lifestyle modification and decreased calorie intake, for 24 weeks.	$N = 152$; 102 completed the 24-week treatment period	Exenatide 10 μg twice daily (following a 4-week 5 μg dose-initiation period)	Weight from baseline compared with lifestyle modification alone: Exenatide −5.1 kg; placebo −1.6 kg; exenatide − placebo ($P < 0.001$); placebo-subtracted difference in percent weight loss −3.3 ($P < 0.001$)

TABLE 2. (continued).

Study, author, and population	Study design	Sample size and retention	Dose and dosing regimen	Weight loss and time point
Kelly et al., 2013 (27) **Adolescents with BMI ≥1.2x the 95th percentile or >35 kg m^{-2}**	26 adolescents (aged 12-19 years) with severe obesity in double-blind, placebo-controlled study; randomized 3-month period, followed by 3-month open-label extension where all subjects received exenatide 10 mg subcutaneously twice daily.	*N* = 26; completers at 3 months: 22 total, 12 on exenatide, 10 on placebo; completers at 6 months: 19	Dose titration from 5 μg twice daily for 1 month and increased to 10 μg twice daily for first 3 months; exenatide (*n* =13) Placebo	Change from randomization to 3 months for completers: BMI −2.90%; BMI −1.18 kg m^{-2}; weight loss −3.26 kg; after open-label extension: BMI −4% from randomization BMI −0.15%; BMI −0.04 kg m^{-2}; weight loss −0.32 kg; after open-label extension: BMI +0.25% from randomization
Dushay et al., 2012 (28) **Obese women without type 2 diabetes**	41 obese women (age 48 ± 11 years), BMI 33.1 ± 4.1 kg m^{-2}; double-blind, placebo-controlled cross-over study; two 16-week treatment periods separated by 3-week washout. No lifestyle intervention.	Exenatide 5 μg twice daily for 2 weeks, then 10 μg twice daily for 16 weeks Placebo	Overall dropout rate 35%; 17% dropped out before randomization and 18% dropped out after randomization	Change from randomization to week 16: Exenatide: Weight −2.77% Placebo: Weight +0.48%

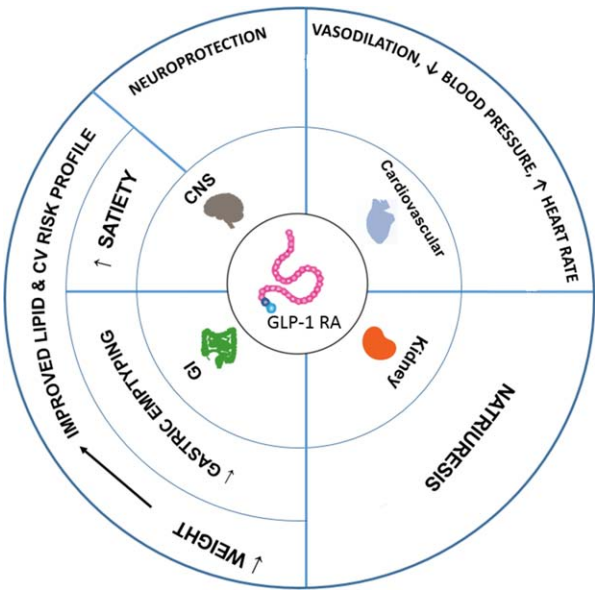

Figure 1 GLP-1RA: Actions beyond glycemic control (15,40,41). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

approved for weight management, a 24-week randomized, placebo-controlled trial involving nondiabetic obese subjects showed that exenatide 10 μg twice daily (BID), combined with lifestyle modification and decreased calorie intake, produced significant weight loss from baseline compared with lifestyle modification alone (−5.1 kg vs. −1.6 kg, $P < 0.001$); the placebo-subtracted difference in percent weight loss was −3.3 kg ($P < 0.001$) (Table 2) (26). There is also evidence, from two small, short-term studies, to indicate that exenatide results in weight loss in nondiabetic adolescents with severe obesity and in obese women (27,28). Furthermore, there is evidence from clinical studies of GLP-1 receptor agonists more recently approved for the treatment of type 2 diabetes, albiglutide, dulaglutide and lixisenatide, of favorable effects on weight loss in diabetes patients (35-37).

Potential pleiotropic effects of GLP-1 receptor agonists beyond glycemia and weight loss

GLP-1 receptors are widely expressed in many tissues beyond the pancreas, including the gastrointestinal system, cardiovascular system, central nervous system and kidneys (15,38,39). Therefore, it is logical to assume that GLP-1 receptor agonists mediate multiple physiological effects, independent of their actions of improving glycemic control and stimulating weight loss (Figure 1).

Cardiovascular effects

Obesity is a substantial contributor to the risk of cardiovascular disease (CVD) (42), but the benefits of lifestyle interventions that reduce weight, although readily demonstrated to improve risk

factors, have not been definitively proven to reduce the rate of cardiovascular events, with studies in different patient populations and different lengths of follow-up providing contrasting results (43,44). Certainly, a favorable effect on cardiovascular risk factors is desirable in medications used for weight loss, and there is a need for agents that have positive effects on cardiovascular risk reduction through mechanisms other than those induced by weight loss *per se* (44,45).

GLP-1 receptor agonists appear to positively influence the cardiovascular risk profile (with the exception of heart-rate elevation, as discussed below) by exerting a range of additional effects, both direct and indirect (16,39,40,46). A meta-analysis of clinical trials in type 2 diabetes showed that GLP-1 receptor agonists were associated with a significant reduction in the incidence of major cardiovascular events, compared with placebo and pioglitazone, and a similar effect as active comparators (sulfonylureas, insulin and dipetidyl-peptidase [DPP]-4 inhibitors) (47). A retrospective study of patients undergoing treatment for type 2 diabetes found that exenatide therapy was associated with a lower risk of cardiovascular events and hospitalizations (CVD-related and all-cause) than treatment with other glucose-lowering therapies, including metformin, alpha-glucosidase inhibitors, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, and insulin (48). The authors speculate on the factors that may account for the beneficial impact of exenatide on such outcomes, including a reduction in hyperglycemia with a lower risk of hypoglycemia, and improvements in cardiovascular risk parameters (48).

Some of the cardiovascular effects observed with GLP-1 receptor agonists are likely to be related to the effects of weight loss and/or glycemic control. For example, several clinical trials have shown that GLP-1 receptor agonists improve lipid profiles in patients with type 2 diabetes through reductions in LDL cholesterol, total cholesterol, triglyceride, and free fatty acid levels (40,47).

Clinical studies have shown that GLP-1 receptor agonists reduce both systolic and diastolic blood pressure, in comparison to placebo and active controls (49,50). Although the mechanism of blood pressure reduction is unclear, it has been hypothesized that this could result from the natriuretic/diuretic effects of GLP-1 agonists on the kidney (51), their vasodilatory effect on the blood vessels (52), and/or interactions with the central nervous system (53).

Interestingly, a preclinical study in transgenic mice also suggested that the antihypertensive effects of GLP-1 receptor agonists may be linked to the release of atrial natriuretic peptide (ANP) (54). In this study, the authors demonstrated that GLP-1 receptor expression is mainly localized to the cardiac atria, and that receptor activation with liraglutide led to the secretion of ANP and reduction of blood pressure. However, a subsequent clinical study was unable to confirm the existence of this gut–heart GLP-1 receptor-dependent and ANP-dependent axis in human subjects (55).

In clinical studies, reduction in blood pressure with GLP-1 receptor agonists tends to occur early on during treatment (after 2 weeks), before significant weight loss is observed, which suggests that these agents have direct hypotensive effects, and that reduction of blood pressure is not due to weight loss alone (49,50).

GLP-1 receptor agonists have also been associated with a slight increase in heart rate, although the underlying mechanism and clinical significance of this effect remains to be determined (50). Evidence suggests that, for liraglutide, the heart-rate increases are not dose dependent, occur soon after drug administration and revert to baseline on drug cessation (16,56). The mechanism underlying the increase in resting heart rate with liraglutide, which is two to three beats per minute on average, is not currently understood, but does not appear to involve increased activation of the sympathetic nervous system, with no increase in urinary catecholamines (56). One proposed mechanism for the heart-rate elevation is that GLP-1 receptors on the sino-atrial node (38) produce the increase.

Preclinical studies suggest that GLP-1 receptor agonists can have a direct role in the prevention of atherogenesis through the modulation of vascular inflammation and improvement of endothelial dysfunction (57,58). One study in apolipoprotein E-deficient (apoE^{-}/$^{-}$) mice demonstrated that the GLP-1 receptor agonist exendin-4 suppressed the accumulation of monocyte and macrophages in the artery wall through the downregulation of various inflammatory and adhesion molecules on these cells (57). Another study in apoE^{-}/$^{-}$ mice demonstrated that liraglutide inhibited atherogenesis in early-onset atherosclerotic disease, and also reduced progression of atherosclerotic plaque formation and enhanced plaque stability (58).

Vascular endothelial dysfunction has a major role in the development of atherosclerosis, usually preceding its development. A clinical study involving 28 subjects with recent-onset type 2 diabetes with impaired glucose tolerance demonstrated that administration of exenatide improved postprandial endothelial dysfunction following a high-fat meal (59). Although part of this improvement was due to the reduction of postprandial triglyceride levels, the authors concluded that exenatide may also improve endothelial function through other mechanisms (59).

There is evidence from preclinical and clinical studies that GLP-1 and GLP-1 receptor agonists have cardioprotective benefits. Several animal models and clinical studies have demonstrated that administration of GLP-1 improves outcomes following cardiac injury (60-62). In a canine model of pacing-induced advanced dilated cardiomyopathy, a 48-h infusion with recombinant GLP-1 dramatically improved left ventricular performance and systemic hemodynamics. These improvements were associated with increased myocardial glucose uptake (60). A small clinical study in patients with myocardial infarction and left ventricular dysfunction following angioplasty found that a 72-h infusion with GLP-1, in combination with standard therapy, significantly improved left ventricular function (61). Another clinical study involving patients with chronic heart failure found that a 5-week GLP-1 infusion, in combination with standard therapy, significantly improved left ventricular function, functional status and quality of life, compared with standard therapy alone (62).

In a mouse model of myocardial infarction, 7 days of liraglutide treatment (200 μg kg^{-1}, twice daily) prior to myocardial infarction increased survival by 57% ($P = 0.0001$), reduced cardiac rupture and infarct size (20.9% ± 1.7% vs. 28.8% ± 3.3%; $P = 0.02$), and improved cardiac output (12.4 ± 0.6 vs. 9.7 ± 0.6 mL min^{-1}; $P < 0.05$), compared with 7 days of treatment with saline (63). Administration of liraglutide was also found to induce expression of several cardioprotective proteins in the mouse heart. Another study conducted in rats showed that the exenatide analogue AC3174 also increased survival and improved cardiac function, postmyocardial infarction (64). Furthermore, rodent studies have demonstrated that lixisenatide

reduces infarct size when used in the acute treatment setting, and also improves cardiac function when administered long-term, following ischemia-reperfusion injury (65).

Few clinical studies have evaluated the cardioprotective effects of GLP-1 receptor agonists in humans. One study, conducted in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention, found that administration of exenatide at the time of reperfusion increases the myocardial salvage index (a measure of cardioprotective effectiveness, calculated as the difference between the myocardial area at risk [AAR] and the final infarct size, divided by the AAR) by 15%, compared with placebo (0.71 ± 0.13 vs. 0.62 ± 0.16; $P = 0.003$) (66).

The mechanisms through which GLP-1 and GLP-1 receptor agonists provide cardioprotective effects are complex and not fully understood. There is evidence from animal studies that GLP-1 exerts direct effects on the myocardium, such as improvements in glucose uptake and metabolism (60), but it is not clear if their actions are mediated dependently or independently of the GLP-1 receptor. The precise localization of GLP-1 receptors in the human heart is a matter of debate, but evidence from recent studies suggest they are predominantly located in the sino-atrial node (38,54).

GLP-1 receptor agonist therapy is associated with improvements in levels of cardiovascular risk biomarkers (67,68). One study in patients with type 2 diabetes found that liraglutide was associated with significant reductions of serum plasminogen activator inhibitor-1 (PAI-1), brain natriuretic peptide (BNP), and a dose-dependent reduction in high-sensitivity C-reactive protein (hsCRP) (67). Liraglutide treatment did not significantly affect levels of adiponectin, leptin, interleukin-6, or tumor necrosis factor-alpha (67). Another study in patients with type 2 diabetes showed that exenatide improved the profile of circulating biomarkers of cardiovascular risk: 1 year of exenatide treatment was associated with a 12% increase in adiponectin levels and a 61% reduction in hsCRP, and these changes were reported to be independent of weight loss during the study (68).

While the results from studies showing cardiovascular benefits with GLP-1 receptor agonists are promising, they mainly derive from preclinical models and short clinical trials, and so require validation in longer-term clinical studies and outcome trials. Indeed, several ongoing studies are evaluating the longer-term effects of GLP-1 receptor agonists on cardiovascular outcomes (69), including lixisenatide (ELIXA study), liraglutide 1.8 mg (LEADER study), exenatide (EXSCEL study) and dulaglutide (REWIND study) (70).

Furthermore, many of the clinical studies were carried out in patients with type 2 diabetes and require confirmation in additional patient populations, including individuals with prediabetes, obesity, hypertension, or dyslipidemia.

Potential neuroprotective effects

There is growing evidence supporting a link between obesity and diabetes and neurodegeneration/cognitive impairment (71,72). The increased incidence of Alzheimer's disease and Parkinson's disease in patients with type 2 diabetes suggest that common mechanisms and/or pathways of cell death underlie these conditions (73).

GLP-1 receptors are expressed by neurons in several areas of the brain, including the pyramidal neurons in the hippocampus and neocortex, and the Purkinje cells in the cerebellum (74). Studies in mice models suggest that many of the new GLP-1 receptor agonists have the ability to cross the blood−brain barrier (75,76), making them attractive therapeutic options for the treatment of neurodegenerative central nervous system disorders (74).

Several studies have demonstrated the neuroprotective effects of GLP-1 receptor (75) agonists in animal models of Alzheimer's disease (41, 75, 77). For example, one study in the amyloid precursor protein/presenilin-1 (APP/PS1) mouse model showed that liraglutide prevented memory impairments in object recognition (75). Treatment with liraglutide restored the ability of APP/PS1, but not wild-type, mice to distinguish between novel and familiar objects, with the overall difference scores vs. saline-treated controls significantly increased (Student's t test, $P = 0.0495$) (75). In the same study, liraglutide prevented synapse loss and deterioration of synaptic plasticity in the hippocampus (75). Liraglutide also reduced the number of amyloid plaques in the brain, and decreased the inflammatory response by ∼50% (75). In the same mouse model, the GLP-1 receptor analog Val8-GLP-1 was shown to prevent or delay age-related synaptic neurodegenerative processes (77). Furthermore, exenatide has also demonstrated neuroprotective effects by reducing the amount of amyloid-beta peptide accumulation in the 3xTg-AD mice model (78).

A single-blind, randomized clinical study evaluating treatment with exenatide or usual medications (control group) in 45 patients with Parkinson's disease has also been published. Although this study was not placebo-controlled, blinded ratings showed clinical improvement in exenatide-treated patients, compared to controls (79). The potential clinical benefits for Alzheimer's and Parkinson's disease patients receiving GLP-1-based therapies is not yet known, although a few clinical studies are investigating this (74).

Effects on kidney function and disease

GLP-1 receptor agonists exert several effects on kidney function, some of which are potentially renoprotective (51,80). GLP-1 receptors have been found in kidney tissue from several types of animal, including rodents (81,82), pigs (83) and cattle (84). In rats and pigs, expression has been detected in the proximal tubular cells (82,83). GLP-1 receptors have also been detected in human and monkey kidney, although renal expression appears to be restricted to smooth muscle cells in the walls of arteries and arterioles (38).

Several studies have demonstrated that GLP-1 promotes natriuresis and diuresis in animal models (85) and humans (86). Moreover, rodent studies have confirmed that GLP-1 receptor agonists also exert these effects (54,87). Sodium excretion is most likely mediated via the inhibition of the Na^+/H^+ ion exchanger isoform 3 (NHE3) in the proximal tubule, and may contribute to the antihypertensive effects of GLP-1 receptor agonists (88).

It is well established that obesity is a risk factor for a range of comorbid conditions, including type 2 diabetes and hypertension, both of which contribute to the development of chronic kidney disease (CKD) (89). In the US, diabetic nephropathy is the leading

cause of CKD (90). Preclinical studies indicate that the use of GLP-1 receptor agonists reduce risk factors of diabetic nephropathy, thereby offering renoprotection (80). Various diabetic rodent models have demonstrated that administration of GLP-1 receptor agonists inhibits the development of hypertension, reduces urine albumin levels, and leads to histological improvements in renal morphology (91-94).

Although some of these renoprotective benefits may have been the result of the improved glycemic control and/or weight loss, it is likely that GLP-1 receptor agonists also have direct effects on renal function. For example, GLP-1 appears to offer renoprotection through its actions on systemic blood pressure and kidney hemodynamics (80). One small clinical study demonstrated that a 3-h GLP-1 infusion decreased glomerular filtration rate (GFR) by 6% in obese, insulin-resistant men, but did not affect GFR in healthy men (86). The authors concluded that reduction of glomerular hyperfiltration was related, via tubuloglomerular feedback, to the direct effect of GLP-1 in promoting sodium excretion in the renal tubule. Obesity and type 2 diabetes are often associated with increased tubular sodium resorption, which may lead to hypertension (86). The findings of this study, together with data from rodent studies, suggest that the actions of GLP-1 and GLP-1 receptor agonists may be more prominent in individuals with obesity/diabetes than in healthy individuals, and protect the kidney damage from the effects of volume expansion, glomerular hyperfiltration, and systemic hypertension (86,88).

Rodent models have also demonstrated that administration of GLP-1 receptor agonists decreases inflammatory cytokines and pro-fibrotic factors associated with the development of nephropathy, including transforming growth factor beta 1 (TGF-β1) and fibronectin (91-93). Clinical studies in patients with type 2 diabetes have also reported reductions of inflammation markers with GLP-1 receptor agonists (95).

Not all the effects of GLP-1 agonists on renal function are beneficial, however, and there have been some case reports of acute kidney injury with these agents (51). Exenatide is primarily eliminated via the kidneys and is not recommended for use in patients with severe renal impairment or end-stage renal disease, while caution is advised during treatment initiation in patients with moderate renal disease (9).

Liraglutide is not eliminated via the kidneys or liver, but completely degraded within the body (most likely by DPP-4 and neutral endopeptidase), as evidenced by the lack of intact liraglutide excreted in the urine and feces (96). The US label for liraglutide use in diabetes advises that it be used with caution in patients with type 2 diabetes and renal impairment, due to limited therapeutic experience in this population (11). In Europe, no dose adjustment of liraglutide 1.2 or 1.8 mg is required in patients with type 2 diabetes with mild or moderate renal impairment (creatinine clearance [CrCl] 60–90 mL min^{-1} and 30–59 mL min^{-1}, respectively) (97). There is no therapeutic experience of liraglutide 1.2 or 1.8 mg in patients with type 2 diabetes with severe (CrCl <30 mL min^{-1}) renal impairment, and liraglutide cannot currently be recommended for such patients or those with end-stage renal disease (97).

There are limited data on albiglutide in severe renal impairment and, in Europe, it is not recommended for this condition (98). Also, the frequency of gastrointestinal events increases as renal function declines, and the albiglutide US label advises caution when using dose escalations in patients with renal function impairment (99). Lixisenatide is primarily cleared through the kidney (100). In Europe, lixisenatide is not recommended for use in subjects with severe renal impairment and caution is advised if subjects have moderate renal impairment (100).

Effects on nonalcoholic fatty liver disease

GLP-1 receptor agonists may have beneficial effects on nonalcoholic fatty liver disease (NAFLD), a condition that is increasing in parallel with the global obesity epidemic (101). While therapeutic experience in patients with hepatic impairment is currently too limited to recommend the use in such patients (97), studies are ongoing to evaluate the efficacy of liraglutide 1.8 mg in patients with nonalcoholic steatohepatitis (NASH) (102). In a small observational study, Japanese subjects who failed to reach HbA_{1c} levels of less than 6.0% and/or alanine aminotransferase (ALT) levels lower than baseline levels following 24 weeks of lifestyle modifications (Stage 1) were treated with 0.9 mg day^{-1} liraglutide (the approved dose in Japan) for an additional 24 weeks (Stage 2) (103). Some patients completed a further 96 weeks treatment with liraglutide (Stage 3). At the end of Stage 2, liraglutide treatment was associated with significant improvements compared with the end of Stage 1 in BMI, visceral fat area, and liver function parameters. At the end of Stage 3, improvements in inflammation, fibrosis, and NAFLD activity score were indicated with liraglutide treatment (103). While the mechanisms by which liraglutide may improve NASH remain to be elucidated, the authors of this study reported correlations between the improvements and reductions in bodyweight and HbA_{1c} (103). Hepatocytes affected by excess fat deposition are more susceptible to ischemic events, such as those induced during liver surgery, heart failure, and cardiogenic shock. Preclinical data suggest that GLP-1 receptor agonists may have a role in protecting both lean and fatty livers from ischemic injury (104).

Effects on saliva, taste, and taste perception

The first GLP-1 agonist, exendin-4, was discovered in the venom and saliva of the Gila monster (105). GLP-1 is not present in human saliva (106) but is expressed in taste buds, especially in type II and III taste cells in rodents and macaques (107). In type II taste cells, GLP-1-expressing taste cells also express α-gustducin and taste 1 receptor 3 (T1R3), whereas in type III taste cells serotonin is coexpressed (107). The GLP-1 cognate receptor is not expressed in taste cells but in the nerve endings innervating the taste bud (107). Interestingly, taste buds contain little or no DPP-IV (107).

The presence of GLP-1 and its receptor in taste buds suggests a role in taste preferences. GLP-1 receptor knockout mice display a significantly reduced response to natural (sucrose) and artificial (sucralose) sweeteners (107), and an increased response to umami (108), in comparison to wild-type controls. No significant differences in taste responses were seen for bitter, salt, or sour stimuli. These findings suggest that GLP-1 is essential to maintain or enhance the taste sensitivity to sweet stimuli and umami. Additionally, the GLP-1-

mediated sweet attraction is reinforced when long-chain fatty acids stimulate the taste buds through the GPR120 lipid-sensor receptor (109).

It is interesting to note that enteroendocrine L cells have chemosensory machinery that is similar to taste cells, and stimulation of α-gustducin, T1R3 and GPR120 in enteroendocrine L cells stimulates the release of GLP-1 (110-113). Furthermore, taste chemosensors in the gut are essential for the regulation and secretion of gastrointestinal hormones, such as GLP-1, OXM, or PYY3-36. For example, in the α-gustducin knockout mouse model, GLP-1 secretion is attenuated after nutrient stimuli to the gut as well as after the rapid increase of GLP-1 following Roux-in-Y gastric bypass (RYGB) (114).

Additionally, bariatric surgery produces a rapid increase in GLP-1 and other gastrointestinal hormones (115), and recent studies have shown that RYGB changes taste preferences by decreasing the preference for sucrose, the perceived sweetness of sucrose and the cravings for sweets and fast foods. RYGB also shifts sweetness palatability from pleasant to unpleasant (116). The effect of bariatric surgery on taste preferences may be mediated by a rapid increase in GLP-1 (117); however, further studies are needed to understand these mechanisms.

The potential to exploit the presence of GLP-1 receptors on taste cells is currently unexplored, though oral GLP-1 therapy might be an avenue for therapeutic intervention to maximize diet efficacy.

Potentially unfavorable nonglycemic actions of glp-1 receptor agonists

No drug can be entirely safe and entirely effective, and this is true for GLP-1 receptor agonists. The potential for adverse renal effects with GLP-1 receptor agonists has been discussed above. Additionally, these compounds are proteins so there is the risk of antibody formation and allergic reactions: anaphylaxis and angioedema (although this is rare in this class of compounds). This topic has been reviewed recently (118), and antibody formation and injection-site reactions are reportedly more frequent for the exendin-4-based compounds (for example, exenatide and lixisenatide), compared with liraglutide. A pooled analysis of the LEAD trials (1, 2, 4, and 5) demonstrated that 8.7% and 8.3% patients had low-level antibodies to liraglutide 1.2 and 1.8 mg, respectively, following 26 weeks of therapy and levels remained low at the end of a 2-year open-label extension period (119). In LEAD-6, 61% patients treated with exenatide 10 μg for 26 weeks had antiexenatide antibodies (119). After switching from exenatide to liraglutide 1.8 mg, 50% and 17% of patients had persistent antiexenatide antibodies at weeks 40 and 78; in comparison, at week 79, only 2.6% and 3.0% of patients who continued on liraglutide or switched from liraglutide to exenatide, respectively, had antiliraglutide antibodies (119). These relatively high frequencies observed with exenatide compared with liraglutide treatment, may be explained by the difference in sequence homology versus native GLP-1, of which exenatide shares only 53% and liraglutide 97% (120).

Obesity, particularly central obesity, is a well-established risk factor for gallstone disease (121). Although infrequent, gallbladder-related adverse events (mainly cholelithiasis and cholecystitis) were observed at a higher frequency with liraglutide 3.0 mg versus placebo (56). Events occurred more frequently in female patients and those who experienced greater weight loss, both of which are associated with a higher risk of gallstone formation, and may explain why similar findings were not observed with lower doses of liraglutide in the type 2 diabetes trials (56). As the increased incidence of gallbladder-related adverse events with liraglutide 3.0 mg was seen across weight-loss categories, however, factors in addition to weight loss would appear to be involved (56).

Both type 2 diabetes and obesity, in particular abdominal obesity, has been associated with an increased risk of acute pancreatitis (122). A small number of cases of pancreatitis have been reported in patients with type 2 diabetes treated in clinical trials with GLP-1 receptor agonists (123). It has not, however, been possible to establish a cause for this relationship because type 2 diabetes, a common comorbidity in obese subjects, is associated with a three-fold increased risk of acute pancreatitis compared with controls without type 2 diabetes (124).

For several drugs in the GLP-1 receptor agonist class (albiglutide, dulaglutide, exenatide extended release, liraglutide), an FDA-approved Risk Evaluation and Mitigation Strategy (REMS) is ongoing in order to provide further information about acute pancreatitis and also medullary thyroid carcinoma. As pancreatitis is a risk factor for pancreatic cancer, concern about the potentially increased risk of such cancer has been raised. The regulatory agencies in the US and in Europe (FDA and EMA) recently issued a joint statement, which included the following paragraph:

"Both agencies agree that assertions concerning a causal association between incretin-based drugs (DPP4 inhibitors and GLP-1 agonists) and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data. The FDA and the EMA have not reached a final conclusion at this time regarding such a causal relationship. Although the totality of the data that have been reviewed provides reassurance, pancreatitis will continue to be considered a risk associated with these drugs until more data are available; both agencies continue to investigate this safety signal" (125).

Thus, it appears that prescribers of GLP-1 receptor agonists should be aware of the association of this class with pancreatitis, and should have a high degree of suspicion should the patient develop severe abdominal pain, with or without nausea and vomiting.

All drugs in this class carry a boxed warning on their package inserts regarding thyroid C-cell tumors. Such tumors have been observed in rodent studies with GLP-1 receptor agonists at clinically relevant exposures, although there has been no association of human C-cell tumors with these drugs. Nevertheless, the labels are required to specify a contraindication, in the case of patients with a personal or family history of medullary thyroid cancer, or with multiple endocrine neoplasia syndrome type 2.

Conclusion

GLP-1 receptors are located throughout the body, and thus are likely to mediate multiple physiological effects, beyond glycemic control and weight loss. There is increasing evidence from preclinical and

clinical studies to suggest that these agents may have a spectrum of beneficial effects, some of which may occur independently of glycemic effects and weight loss. Conversely, there may be some unfavorable effects of GLP-1 receptor agonists, but prescribers should be able to manage these medications by monitoring their patients and by prescribing judiciously.

GLP-1 receptor agonists may reduce the risk of cardiovascular disease through their effects on blood-pressure reduction and the prevention of atherosclerosis, and they may also have a cardioprotective role. The heart-rate elevation may not be an adverse prognostic indicator, but further study is needed to determine the underlying mechanism driving this phenomenon. Cardiovascular outcome trials will, in any event, be the ultimate determinant of overall cardiovascular benefit or risk. There is evidence that GLP-1 receptor agonists may have neuroprotective and renoprotective effects, although consideration of the latter should be balanced with reports of potentially adverse effects in the kidney, especially with exenatide.

Given their potential benefits beyond glycemic control and weight loss, GLP-1 receptor agonists may enhance the treatment of type 2 diabetes and obesity in the future. However, additional clinical studies are needed to further and fully elucidate the pleiotropic effects and potential benefits of these agents. Finally, clinicians must prescribe carefully to avoid potentially harmful effects, while providing opportunity for health improvement in their patients with type 2 diabetes and other obesity-related morbidities. O

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