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Effects of GLP-1 and Its Analogs on Gastric Physiology in Diabetes Mellitus and Obesity

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Abstract

The processing of proglucagon in intestinal L cells results in the formation of glucagon, GLP-1, and GLP-2. The GLP-1 molecule becomes active through the effect of proconvertase 1, and it is inactivated by dipeptidyl peptidase IV (DPP-IV), so that the half-life of endogenous GLP-1 is 2–3 min. GLP-1 stimulates insulin secretion from β cells in the islets of Langerhans. Human studies show that infusion of GLP-1 results in slowing of gastric emptying and increased fasting and postprandial gastric volumes. Retardation of gastric emptying reduces postprandial glycemia. Exendin-4 is a peptide agonist of the GLP-1 receptor that promotes insulin secretion. Chemical modifications of exendin-4 and GLP-1 molecules have been accomplished to prolong the half-life of GLP-1 agonists or analogs. This chapter reviews the effects of GLP-1-related drugs used in treatment of diabetes or obesity on gastric motor functions, chiefly gastric emptying. The literature shows that diverse methods have been used to measure effects of the GLP-1-related drugs on gastric emptying, with most studies using the acetaminophen absorption test which essentially measures gastric emptying of liquids during the first hour and capacity to absorb the drug over 4–6 h, expressed as AUC. The most valid measurements by scintigraphy (solids or liquids) and acetaminophen absorption at 30 or 60 min show that GLP-1-related drugs used in diabetes or obesity retard gastric emptying, and this is associated with reduced glycemia and variable effects on food intake and appetite. GLP-1 agonists and analogs are integral to the management of patients with type 2 diabetes mellitus and obesity. The effects on gastric emptying are reduced with long-acting preparations or long-term use of short-acting preparations as a result of tachyphylaxis. The dual agonists targeting GLP-1 and another receptor (GIP) do not retard gastric emptying, based on reports to date. In summary, GLP-1 agonists and analogs are integral to the management of patients with type 2 diabetes mellitus and obesity, and their effects are mediated, at least in part, by retardation of gastric emptying.

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1 Introduction

Secretions from the gastrointestinal tract include hormones and peptides that provide feedback to control gastric function and to stimulate the secretion of insulin from the β cells of the islets of Langerhans in the pancreas. This feedback regulation is referred to as a system of "brakes." The ileal brake is the most recognized and results from feedback regulation of stomach and jejunal function by ileal products such as peptide YY, neurotensin and oxyntomodulin. However, proximal to the ileum, several products of enteroendocrine cells result in inhibitory effects on gastric motor functions that alter gastric reservoir function and induce antral motility and pyloric contractility, leading to retardation of gastric emptying and thereby reducing the rate of delivery of nutrients and their absorption. The upper gastrointestinal hormones and transmitters include cholecystokinin, glucose-stimulated insulinotropic peptide, glucagon and glucagon-like peptide 1 (GLP-1).

GLP-1 analogs or receptor agonists are established treatments for patients with type 2 diabetes mellitus (T2DM) and obesity. Effects of GLP-1 analogs or receptor agonists on gastric emptying are relevant for at least three reasons: first, because the delay in gastric emptying may reduce postprandial glycemia; second, because delay in gastric emptying may reduce kilocalorie intake, providing beneficial effects in obesity; and third, because delay in gastric emptying may cause symptoms that result in the need to slow the increments in doses of these medications. Over the past two decades, there has been increased understanding of the effects of this class of compounds, including the differentiation between the individual medications, as well as probable differences between the effects of short-acting compared to long-acting formulations of the same chemical entity.

This chapter reviews the effects of GLP-1 and its analogs or agonists on gastric physiology in T2DM and obesity. In addition, given the recent introduction of medications with dual effects on GLP-1 and targets of other hormones, the current state of literature is reviewed for changes in gastric functions in anticipation of further applications of dual agonists.

2 Synthesis, Actions, and Degradation of Glucagon-Like Peptide 1

GLP-1 is cleaved from proglucagon, which is expressed in the gut, pancreas, and brain. The processing of proglucagon in intestinal L cells results in the formation of glucagon (a glucose-regulatory hormone), GLP-1, and GLP-2 (an intestinal growth factor). The GLP-1 molecule becomes an active molecule through the effect of proconvertase 1, and it is inactivated by the cleaving of two amino acids at its N terminal by the enzyme, dipeptidyl peptidase IV (DPP-IV) (Moller 2001). There are two equipotent bioactive forms of GLP-1, GLP-1 (17–36) and GLP-1 (17–37), both of which are rapidly inactivated in the circulation by DPP-IV, rendering GLP-1 half-life a mere 2–3 min (Ritzel et al. 1995).

GLP-1 co-localizes in the distal intestine with oxyntomodulin and PYY. The GLP-1 receptor is expressed in the gut, pancreas, brainstem, hypothalamus, and vagal afferent nerves. Ingested nutrients, especially fats and carbohydrates, stimulate GLP-1 secretion, either indirectly through duodenally activated neurohormonal mechanisms or by direct contact of nutrients within the distal intestine (Cummings and Overduin 2007).

GLP-1 actions include activation of the ileal brake, delay in gastric emptying, increase in glucose-dependent insulin release, decrease in glucagon secretion, and increase in pancreatic β cell growth. Studies employing the specific GLP-1 receptor antagonist, exendin-9-39, show that endogenously released GLP-1 controls fasting plasma glucagon, stimulates insulin, and influences mechanisms controlling gastric emptying in humans (Deane et al. 2010a; Schirra and Göke 2005). The reduced glucagon and increased insulin secretion result in diminished postprandial glucose (Drucker 2003). GLP-1 decreases food intake, possibly via vagal and possibly via direct central pathways, mediated specifically by GLP-1 receptors (Cummings and Overduin 2007). Thus, reduction in spontaneous energy intake was demonstrated using an *ad libitum* meal in healthy, normal weight volunteers (Flint et al. 1998).

3 Structures and Formulations of GLP-1 Agonists and Analogs

GLP-1 receptor agonists can be modified from the active fragment of the human GLP-1 (7–36) or derived from exendin-4, a GLP-1 receptor agonist originally isolated from the venom of the Gila monster. Homology with human GLP-1 varies across all GLP-1 receptor agonists, but all can replicate the effects of the human peptide *in vivo*. For example, the exendin-4 derivative, exenatide, shows just 53% amino acid sequence homology with human GLP-1, but binds to the human GLP-1 receptor with affinity equivalent to that of human GLP-1 (Holst 2019). It is thought that, because of this low homology, exenatide would be associated with the most antibodies among the GLP-1 receptor agonists available for clinical use (Garber 2011). Exenatide weekly formulations are more immunogenic than twice daily formulations (Tibble et al. 2013). Those with higher antibody titers were observed to have high incidence of injection site reactions (Fineman et al. 2012).

Given the short half-life of endogenous GLP-1, multiple strategies were used to prolong the duration of action of GLP-1 receptor agonists and, thereby, reduce the need for frequent injections. These strategies include: first, changes in the amino acid sequence of GLP-1 to increase resistance to inactivation by DPP-IV, such as lixisenatide, which is mostly homologous with but slightly modified from exenatide, permitting it to be administered only once instead of twice daily; second, binding to albumin, either covalently (e.g., albiglutide and semaglutide) or noncovalently (e.g., liraglutide), or binding to immunoglobulin G (e.g., dulaglutide), all of which limit renal elimination (Fig. 1). A polymicrosphere preparation allowed exenatide to be

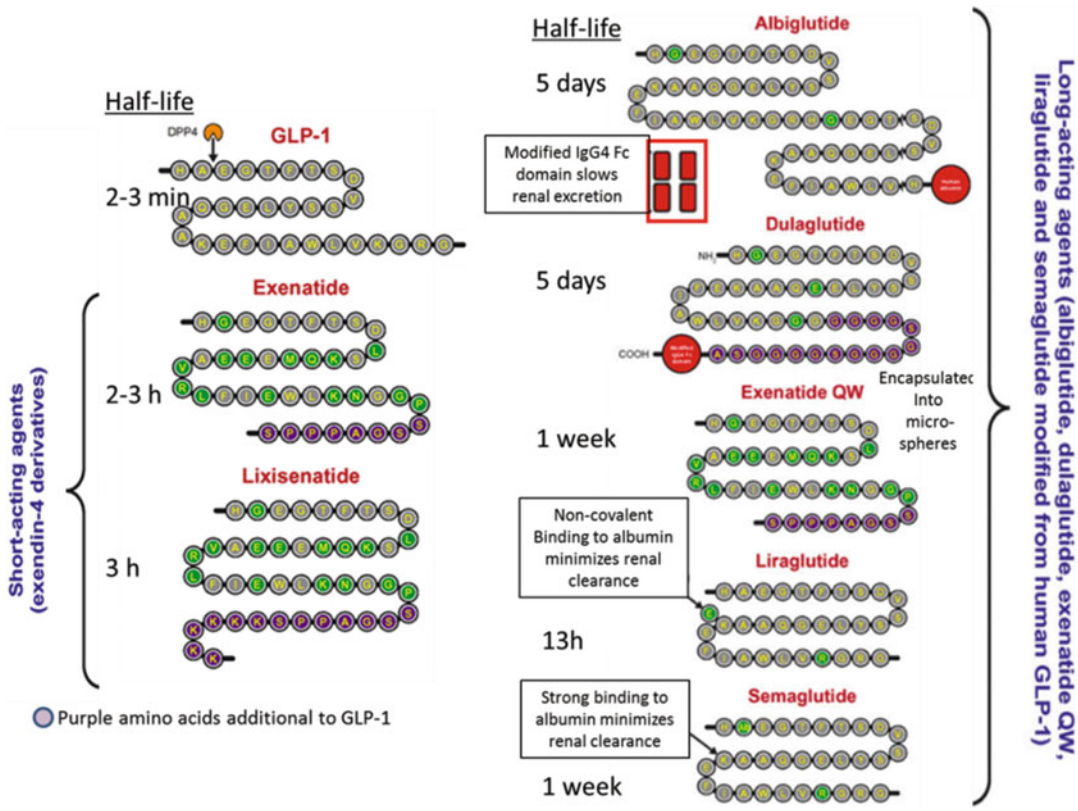

Fig. 1 Structure and properties of glucagon-like peptide 1 receptor agonists. (Reproduced from Gentilella et al. 2019)

continuously released from weekly injections (Gentilella et al. 2019).

4 Effects of GLP-1 on Gastric Functions in Health

Gastrointestinal release of peptides during and after meals has played a critical role in the homeostatic mechanisms regulating caloric intake (Gibbs et al. 1973). GLP-1 has been recognized for a multitude of regulatory functions in humans: secretion of insulin, inhibition of glucagon release, and delay in the emptying of gastric contents into the duodenum. This final feature is referred to as the "ileal brake", a critical inhibitory control mechanism that modulates food consumption and digestive function in health (Read et al. 1984).

GLP-1 secretion is stimulated through a complex cascade of signaling which involves entry of chime into the intestine, release of nesfatin-1 which stimulates CCK secretion, rise in bile salts from gallbladder emptying, and binding of Takeda P protein couple receptor 5 (TGR5) on the basolateral surface of enteric endocrine L cells (Ramesh et al. 2016; Bronden et al. 2018). This endogenous 30-amino acid peptide acts until it is soon degraded within 5 min by DPP-IV (Steinert et al. 2016).

The inhibition of gastrointestinal motility by GLP-1 is mediated through the GLP-1 receptor at the level of the myenteric neurons and downstream signaling of nitregic and cyclic adenosine monophosphate-dependent mechanisms, inhibiting vagal activity (Halim et al. 2018). This results in reduced phasic contractions of the stomach, as well as delay in gastric emptying and diminished gastric acid secretion (Schirra et al. 2002; Imeryüz et al. 1997). GLP-1 also increases fasting and postprandial gastric volumes (Delgado-Aros et al. 2002). These mechanisms require intact vagal innervation; thus, the increased postprandial accommodation induced by GLP-1 is reduced in patients with diabetes and cardiovagal neuropathy (Delgado-Aros et al. 2003). The effects of GLP-1 on gastric functions are confirmed by the reported effects of a GLP-1 receptor antagonist, which increased antral motility and inhibited pyloric tone (Schirra et al. 2006).

The effects of GLP-1 and its analogs are impacted by physiologic principles. First, increases in circulating levels of GLP-1 occur in the fed rather than the fasting state, and they impact the cholinergic mechanisms pertaining to the postprandial upper gastrointestinal motor function, in contrast to the fasting state (Schirra et al. 2009). Second, intragastric calories stimulated far more robust GLP-1 excursion than did intraduodenal infusion (Steinert et al. 2012); however, intraduodenal fat and carbohydrate infusion and absorption stimulate GLP-1 in rats (Lu et al. 2007) and GLP-1 and GIP in humans (Deane et al. 2010a). Third, the effect of GLP-1 to modulate energy intake was augmented substantially by the presence of protein in the stomach (Degen et al. 2006).

These effects of endogenous GLP-1 on gastric motor functions have been co-opted for management of disease states, which will be explored in the next sections.

5 Methodological Assessment of Gastric Emptying

The gold standard for assessing gastric emptying in humans is nuclear scintigraphy (Odunsi and Camilleri 2009); however, this has seldom been implemented in the study of gastric motor function in the context of GLP-1 and GLP-1 receptor agonists or analogs. A few studies have employed gastric emptying breath tests using stable isotopes, which have reasonable correlation with the gold standard of scintigraphy (Szarka and Camilleri 2009; Szarka et al. 2008). The vast majority of studies of gastric emptying and GLP-1 agonists use the paracetamol/acetaminophen absorption test (which will hereafter for simplicity be referred to as acetaminophen absorption test).

This chapter outlines many such studies, but it is worthwhile mentioning a few key limitations of such an assay. First, acetaminophen is typically administered as a liquid such that, even when given with a solid meal, it more closely follows

the exponential pattern of gastric emptying of liquids rather than solids, which are governed by a distinct gastric emptying profile and mechanism (that is, initial retention while solids are triturated to a small particle size before emptying at a relatively constant rate). Second, gastric emptying was calculated by acetaminophen absorption at the end of a 4-, 5-, or 6-h appraisal, at which time much of the acetaminophen will have had the opportunity to be absorbed, consequently missing the potential impact of gastric emptying to the plasma acetaminophen profile. Such studies that express acetaminophen area under the curve (AUC) over 4–6 h undervalue the impact on gastric emptying. Some studies have avoided this potential limitation by assessing acetaminophen AUC from 0 to 1 h, which provides a more precise assessment of gastric emptying. Overall, the literature supports the need to avoid the acetaminophen absorption test to estimate gastric emptying due to the limitations mentioned and to use nuclear scintigraphy which is an accurate, safe, and reproducible method of assessing gastric emptying of solids and liquids.

6 Mechanism of Impairment of GI Motor Function by GLP-1 Agonists

The degree of slowing of gastric emptying by GLP-1 analogs or receptor agonists is dependent on the baseline rates of gastric emptying; thus, the induced delay in gastric emptying is more substantial in those with more rapid baseline gastric emptying (Linnebjerg et al. 2008). In contrast, when baseline emptying is already delayed, there is far less of an effect on gastric emptying from these agents (Marathe et al. 2011). The slowing of gastric emptying induced by GLP-1 agonists is dose dependent (Meier 2012). Delay in gastric emptying, as well as effects on appetite, have not been observed with medications that inhibit the enzyme that breaks down GLP-1 (DPP-IV) (Vella et al. 2007, 2008; Stevens et al. 2012). This is likely due to the lower levels of endogenous GLP-1 activity achieved with the DPP-IV inhibitors compared to the actions of GLP-1 analogs or receptor agonists.

7 Effect of GLP-1 Receptor Agonism in Disease State: Diabetes Mellitus

While much has been published on GLP-1 receptor agonism enhancement in islet cell function (Bunck et al. 2009), the physiologic underpinnings driving improvement in diabetes appear more complex. Indeed, postprandial serum glucose levels were correlated with the degree of slowing of gastric emptying (Linnebjerg et al. 2008; Little et al. 2006; Lorenz et al. 2013; Deane et al. 2010b), and modulation of postprandial serum glucose more closely associated with delay in gastric emptying than it did increase in levels of insulin in the setting of exogenous GLP-1 administration, underscoring the importance of gastric motor functions in homeostatic mechanisms (Little et al. 2006; Willms et al. 1996; Nauck et al. 1997). In addition, when gastric emptying was accelerated by administration of erythromycin, GLP-1 was less able to modulate postprandial serum glucose levels (Meier et al. 2005). This mechanism may also explain why infusion of exogenous GLP-1 improved satiety scores and reduced meal intake in patients with diabetes (Gutzwiller et al. 1999).

The following text and Table 1 summarize key findings of the studies that evaluated gastric emptying in subjects with diabetes mellitus who were exposed to GLP-1 analogs or receptor agonists. The effects of GLP-1 analogs and receptor agonists have ushered in a more "personalized" approach for the management of both type 1 (Marathe et al. 2018) and type 2 diabetes (Holst et al. 2016). Since postprandial glycemic excursions predominate in patients with HbA1c <8% (Monnier et al. 2003), the use of the "short-acting" GLP-1 receptor agonists, exenatide twice daily and lixisenatide alone or in combination with basal insulin, has been proposed as a method to diminish postprandial glycemic excursions, predominantly by slowing gastric emptying (Holst et al. 2016).

Table 1 Summary of clinical trials of the effects of GLP-1 agonists or analogs on gastric emptying and associated features

GLP-1 agonist/ analog	Study design, dose, treatment duration and timing of GE test	Measurement of gastric emptying	Effect on upper GI motor function	References
Dulaglutide (T2DM)	RCT, double-blinded, three-period, cross-over, parallel group, multi-center study of 43 participants with T2DM (F = 65.1%, age 55.3 ± 6.1 years, BMI 30.8 ± 4.0 kg/m^2, HbA1c 7.6 ± 1.1%). Participants received:	Acetaminophen absorption test (480 mg) with a standardized meal	A significant change in $AUC_{0\text{-}12h}$ was observed for the 5 mg dose (decreased by 48%, $p < 0.01$). The time to peak plasma acetaminophen concentration was delayed by 1.5 h for the 8 mg dose relative to placebo, suggesting delay in GE for the 5 and 8 mg doses of dulaglutide at 5 weeks	Barrington et al. (2011)
	Once weekly placebo or			
	Once weekly Dulaglutide (LY2189265) SC at 0.05 mg (n = 3), 0.3 mg (n = 6), 1 mg (n = 5), 3 mg (n = 3), 5 mg (n = 9), or 8 mg			
	GE test: At baseline and after 5 weeks of study			
Exenatide (obesity)	Double-blinded, placebo-controlled, RCT, single center in 20 participants (F = 65%, age 39.3 ± 3.7 years, and BMI 33.9 ± 1 kg/m^2) with obesity and accelerated GE at baseline ($T_{1/2}$ < 90 min). Participants received	Scintigraphy ^{99m}Tc-sulfur colloid solid meal	Delayed GE in exenatide compared to placebo	Acosta et al. (2015a)
	Exenatide 5 μg SC twice daily or		GE at 1 h 12.4% (IQR 8–18.5%) in the exenatide group versus 38.2% (26.6–42.1%) in the placebo group ($p < 0.001$)	
	Placebo		$T_{1/2}$ 187 (141–240) min in the exenatide group versus 86 (73–125) min in the placebo group ($p < 0.001$)	
	GE test: After 30 days of study			
Exenatide (T2DM and obesity)	Single center, placebo controlled, cross-over study of 12 participants with T2DM and obesity (F = 25%, age 44 ± 2 years, BMI 34 ± 4 kg/m^2, HbA1c 7.5 ± 1.5%, T2DM duration 6.6 ± 3.5 years). Participants received treatments on 3 separate occasions, 2–4 weeks apart	Acetaminophen with a solid meal over 6 h	After 6 h, a 58% decrease in mean plasma acetaminophen concentration was observed in the exenatide cohort (840 ± 135 μg/ml) compared with the control cohort (1,995 ± 270 μg/ml) ($p < 0.001$). This suggested a delay in GE in exenatide group	Cervera et al. (2008)
	IV Exenatide (0.05 μg/min 15 min before meal, decreased to 0.025 μg/min 45 min after meal ingestion), or			
	IV saline infusion (control)			
	GE test: after single dose			
Exenatide (T2DM)	RCT, double-blinded, cross over, multi-center study of participants with T2DM (54% female, BMI 33 ± 5 kg/m^2, HbA1c 8.5 ± 1.2%, T2DM duration 7 ± 5 years). Participants received:	Acetaminophen absorption test (liquid, 1,000 mg) over 4 h, with standardized solid meal	Delay in GE seen with exenatide but not sitagliptin.	DeFronzo et al. (2008)
	Exenatide 5 μg twice daily for 1 week, then 10 ug twice daily for 1 week) or		Acetaminophen $AUC_{0\text{-}4h}$ ratio exenatide to sitagliptin: 0.56 ± 0.05 (95% CI 0.46–0.67, $p < 0.0001$)	

	Sitagliptin 100 mg daily for 2 weeks		Delay in GE coincided with a decreased caloric intake	
	GE test: at end of each 2 week treatment arm			
Exenatide (T2DM and obesity)	Randomized, open-label study of 50 participants with T2DM and obesity. Participants received	Acetaminophen absorption test (1,000 mg) with standardized solid meal, tested over 5 h	GE at week 14 delayed compared to baseline with exenatide twice daily but not with once weekly formulation, suggesting tachyphylaxis in effect on GE with long-acting GLP-1 receptor agonists	Drucker et al. (2008)
	Exenatide 2.0 mg SC weekly in 26 patients or SC twice daily (F = 45%, age 55 ± 10 years, BMI 35 ± 5 kg/m^2, HbA1c 8.3 ± 1%, T2DM duration 7 ± 6 years) or			
	Exenatide 5 μg SC twice daily, titrated up to 10 μg twice daily after 28 days in 24 patients (F = 49%, age 55 ± 10 years, BMI 35 ± 5 kg/m^2, HbA1c 8.3 ± 1%, T2DM duration 6 ± 5 years)			
	GE test: at baseline and week 14			
Exenatide (T2DM)	RCT, single-blind placebo-controlled study in 8 participants (F = 37.5%, age 52 ± 8 years, BMI 28.6 ± 5.0 kg/m^2, HbA1c 7.6 ± 1.6%). Participants received on 4 consecutive days a daily SC dose of:	Acetaminophen absorption test with 20 mg/kg liquid acetaminophen over 2 h	Dose-dependent slowing of GE compared to placebo	Kolterman et al. (2005)
	Exenatide daily: 0.02, 0.05, and 0.10 μg/kg or		Mean plasma acetaminophen $AUC_{0–2h}$ lower for exenatide 0.05 μg/kg (907 μg∗min/mL) versus placebo (1,288 μg∗ min/mL) (p = 0.0329), as well as for 0.10 μg/kg exenatide (645 μg∗min/mL) (p = 0.0011)	
	Placebo		Mean plasma acetaminophen concentrations of 13.8, 11.4, and 7.7 μg/mL for 0.02, 0.05, and 0.1 μg/kg exenatide, respectively, compared with 15.6 μg/mL for the placebo group with Cmax lower with exenatide 0.05, and 0.1 μg/kg compared to placebo	
	GE test: during each of 4 consecutive days of injection			
Exenatide (T2DM)	RCT, single-blind, 3 period, cross over of 17 participants (F = 5.9%, age 57 ± 10.1 years, BMI 29.2 ± 3.6 kg/m^2, HbA1c 8.5 ± 1.1%, T2DM duration 6.7 ± 4.5 years). Participants received twice daily:	Scintigraphy with solid meal, 450 kCal, ^{99m}Tc-labeled eggs with ^{111}In-labeled water	Delayed GE for both doses of exenatide	Linnebjerg et al. (2008)
	5 μg Exenatide, 10 μg Exenatide, or Placebo		$T_{1/2}$ of solids was 60 (90% CI 50–70) min for placebo, 111 (90% CI 94–132) min for exenatide 5 μg, and 169 (90% CI 143–201) min for exenatide 10 μg (both vs placebo p < 0.01)	
	GE test: After 5 days of intervention			

(continued)

Table 1 (continued)

GLP-1 agonist/ analog	Study design, dose, treatment duration and timing of GE test	Measurement of gastric emptying	Effect on upper GI motor function	References
Exenatide QW (obesity)	RCT of 32 healthy participants randomized to receive:	Scintigraphy with solid-liquid meal, 330 kCal, ^{99m}Tc-labeled beef with ^{67}Ga-labeled 10% glucose	Exenatide QW slowed GE of solids (AUC 0-120 min: $P < 0.05$) and liquids (AUC 0-120 min: $P = 0.01$), attenuated glucose absorption (iAUC 0-30 min: $P = 0.001$), postprandial rise in plasma glucose (iAUC 0-30 min: $P = 0.008$),and plasma glucagon at 2 h ($P = 0.001$) with no difference in scores for nausea (which were consistently low)	Jones et al. (2020)
	Exenatide QW (2 mg per week subcutaneously) (6 M,10F; age: 59.9 ± 0.9 yr.; BMI: 29.6 ± 0.6 kg/m2) or			
	Placebo (6 M,10F; age: 60.6 ± 1.2 yr.; BMI: 29.5 ± 1.0 kg/m2) for 8 weeks			
	GE test: At baseline and after 8 weeks' treatment		The reduction in plasma glucose at 30 min from baseline to 8 weeks with ExQW was related inversely to $t_{1/2}$ of the glucose drink ($r = -0.55$, $P = 0.03$)	
Exenatide (T2DM and obesity)	RCT, double-blinded, cross over study of 13 participants with T2DM (f = 38.5%, age 56.4 ± 9.2 years, BMI 31.2 ± 3.6 kg/m^2, HbA1c 7.3 ± 0.4%, T2DM duration 3.0 ± 2.6 years); Participants received daily for 9 days in each arm of trial:	Acetaminophen absorption test over 4 h, with a solid meal	No change in GE from placebo was observed based on acetaminophen $AUC_{0\text{-}4h}$	Degn et al. (2004)
	Liraglutide 6 μg/kg SC or			
	Placebo			
	GE test: Day 8 of each arm			
Liraglutide (T2DM)	RCT, double-blinded, parallel, single center study of 100 participants with T2DM who received:	Acetaminophen absorption test (1,500 mg) with standardized liquid meal over 4 h	Week 3: Difference in acetaminophen $AUC_{0\text{-}4h}$ for liraglutide vs placebo was 2.7 (0.2–5.1) mmol/L great for liraglutide ($p = 0.0332$). Time to peak plasma acetaminophen was 19.9 (0.8–39.0) min faster for placebo ($p = 0.0412$)	Dejgaard et al. (2016)
	Liraglutide (n = 50, F = 40%, age 7 ± 13 years, BMI 30.3 ± 3.5 kg/m^2, HbA1c 8.7 ± 0.7%, T2DM duration 20 ± 12 years) or			
	Placebo (n = 50, F = 30%, age 49 ± 12 years, BMI 29.8 ± 3.1 kg/m^2, HbA1c 8.7 ± 0.7%, duration 25 ± 12 years)		Week 24: Difference in acetaminophen $AUC_{0\text{-}4h}$ for liraglutide vs placebo was 3.1 (0.6–5.5) mmol/L greater for liraglutide ($p = 0.0332$). Time to peak plasma acetaminophen was equal for liraglutide and placebo ($p = 0.8793$)	
	Participants received placebo or liraglutide at 0.6 mg SC per day, increased to 1.2 mg SC per day after 1 week, then increased to 1.8 mg per day after 1 week			

	GE test: At baseline and after 3 weeks and 24 weeks of intervention			
Liraglutide (T2DM)	RCT, double-blinded, two period, cross-over single center study of 18 participants with T2DM (F = 0%, age 58.6 ± 6.9 years, BMI 29.7 ± 4.2 kg/m^2, HbA1c 7.8 ± 0.6%)	Acetaminophen absorption test over 5 h	Compared to placebo, acetaminophen $AUC_{0\text{-}5h}$ was 17% lower for 1.2 mg dose ($p < 0.001$) but was not significant for 0.6 mg ($p = 0.287$) or 1.8 mg doses ($p = 0.301$)	Flint et al. (2011)
	Participants received either placebo or liraglutide 0.6 mg daily for 1 week, then 1.2 mg daily for 1 week, then 1.8 mg daily for 1 week. After a washout period, the alternate intervention was given		Acetaminophen $AUC_{0\text{-}1h}$ 43% lower than placebo for 1.2 mg ($p < 0.001$) and 30% lower than placebo for 1.8 mg liraglutide ($p = 0.028$)	
	GE test: At end of each week treatment			
Liraglutide (obesity)	RCT, double-blinded, single center study of subjects with obesity (n = 21, age 37 years [IQR 26–51 years], BMI 34.6 kg/m^2 [IQR 33.4–38.9 kg/m^2]), randomized to receive liraglutide titrated up to 3.0 mg SC daily or placebo. (n = 19, age 42 years [IQR 32–51 years], BMI 37.2 kg/m^2 [IQR 33.6–41.0 kg/m^2])	Nuclear scintigraphy of a solid meal over 4 h	$T_{1/2}$ of solids change from baseline to	Halawi et al. (2017)
			5 weeks was more delayed with liraglutide (median 70 min [IQR 32–151]) compared with placebo (median 4 min [IQR −21-18]) ($p < 0.0001$)	
			16 weeks was delayed with liraglutide (median 30.5 min [IQR −11.0-54.0 min]) compared with placebo (median − 1 min [IQR −19-7 min]) (p 0.025)	
	GE test: At baseline, 5 weeks, and 16 weeks			
Liraglutide (T2DM)	RCT, double-blinded, incomplete cross over, two center study of 46 participants (F = 41%, age 53.5 years [range 38–65 years], BMI 32.6 kg/m^2 [range 27.0–39.9 kg/m^2], HbA1c 7.4% [range 6.5–9.2%]):	Acetaminophen absorption test (1,000 mg) over 5 h, with a standardized liquid meal	GE delayed in liraglutide compared to control groups:	Horowitz et al. (2012)
			Acetaminophen $AUC_{0\text{-}1h}$ liraglutide/placebo ratio 0.62) and glimepiride (acetaminophen $AUC_{0\text{-}1h}$ liraglutide/glimepiride ratio 0.67), ($p < 0.001$ for both)	
	Participants were randomized to two of three arms each given for 4 weeks, followed by a 3 week washout:		Maximum serum acetaminophen concentrations were 20% lower than with liraglutide compared to those with placebo and 15% lower than those with glimepiride ($p \leq 0.006$ for both)	
	Liraglutide followed by placebo,			
	Placebo followed by glimepiride,			
	Glimepiride followed by liraglutide.		Also decreased hunger but not sensations of fullness, satiety, and hunger during test meals	
	Liraglutide was dosed at 0.6 mg SC daily, escalated by 0.6 mg increments weekly to a maximum dose of 1.8 mg daily, maintained for 2 weeks			
	GE test: At end of 4 weeks treatment			

(continued)

Table 1 (continued)

GLP-1 agonist/ analog	Study design, dose, treatment duration and timing of GE test	Measurement of gastric emptying	Effect on upper GI motor function	References
Liraglutide (T2DM)	Single center observational study of 14 participants with T2DM (F = 28.6%, age 60 ± 13.6 years, BMI 26.9 ± 3.8 kg/m^2, HbA1c 9.9 ± 2.6%, T2DM duration 10.4 ± 12.1 years)	Transit time of capsule endoscopy (PillCam®)	Overall gastric transit time (n = 14) was 1:11:53 ± 1:03:17 h at baseline and 1:45:46 ± 1:40:46 h after liraglutide (p = 0.16)	Nakatani et al. (2017)
	Participants received SC liraglutide 0.3 mg, titrated up by 0.3 mg weekly to final dose 0.9 mg.		Participants with:	
	GE test at baseline and 1 week after reaching final dose of 0.9 mg		**No** diabetic neuropathy (n = 7) had gastric transit time of 1:01:30 ± 0:52:59 h at baseline and 2:33:29 ± 1:37:24 h after liraglutide (p = 0.03)	
			Diabetic neuropathy (n = 7) had gastric transit time of 1:12:36 ± 1:04:30 h at baseline and 0:48:40 ± 0:32)52 h after liraglutide (p = 0.19)	
Liraglutide (obesity)	RCT, double-blinded, two-period, incomplete cross over, single center trial of 49 participants with obesity (F = 40.8%, age 48.3 ± 13.2 years, BMI 34.2 ± 2.7 kg/m^2)	Acetaminophen absorption test with standardized solid meal, over 5 h	No difference in GE, based on acetaminophen $AUC_{0\text{-}5h}$, was observed between either liraglutide dose, as well as for liraglutide and placebo	van Can et al. (2014)
	Participants randomly chosen to 2 treatment periods of 5 weeks each, with 6–8 week wash-out		However, acetaminophen $AUC_{0\text{-}1h}$ was 23% less with liraglutide 3.0 mg than placebo (p = 0.007), as well as 13% less than liraglutide 1.8 mg than placebo (p = 0.14), indicative of delayed GE from either liraglutide dose	
	Liraglutide SC 1.8 mg,			
	Liraglutide 3.0 mg, or			
	Placebo			
	GE test: At the end of each 5 week treatment period			
Liraglutide and Lixisenatide (T2DM)	RCT, open-label, multi-center trial in 142 participants with T2DM, divided into three treatment arms given once daily for 8 weeks in combination with insulin glargine:	^{13}C-sodium-octanoic acid containing solid meal with breath test over 4 h	A delay in GE at 8 weeks was observed for all GLP-1 receptor agonists studied. The mean change in $T_{1/2}$ from baseline was as follows:	Meier et al. (2015)
	Lixisenatide 20 μg SC daily (n = 48, F = 31.2%, age 61.6 ± 7.4 years, BMI 30,7 ± 4.3 kg/m^2, HbA1c 7.8 ± 0.7%, T2DM duration 11.4 [range 2.1–32.4] years)		Lixisenatide: 453.6 ± 58.2 min (p < 0.001)	
			Liraglutide 1.2 mg: 175.3 ± 58.5 min (p < 0.05)	
	Liraglutide 1.2 mg SC (n = 47, F = 17%, age 61.4 ± 7.9 years, BMI 30.5 ± 4.0 kg/m^2, HbA1c 7.8 ± 0.8%, duration 10.5 [range 0.2–12.0] years)		Liraglutide 1.8 mg 130.5 ± 60.3 min (p < 0.05)	

	Liraglutide 1.8 mg (n = 47, F = 29.8%, 62.6 ± 9.4 years, BMI 31.2 ± 4.3 kg/m^2, HbA1c 7.9 ± 0.8%, duration 12.5 [range 4.0–31.6] years)			
	GE test: At baseline and 8 weeks later			
Lixisenatide (healthy)	RCT, open-label, cross-over, single-center of 20 participants (F = 50%, age 31 ± 7.3 years, BMI 22.8 ± 2.7 kg/m^2). Participants received lixisenatide SC at 2.5, 5, 10, or 20 μg with 2–7 day washout period	Acetaminophen (1000 mg) absorption over 6 h, liquid meal	For lixisenatide doses of 5 ug or more, $AUC_{0\text{-}1h}$ showed delayed GE vs. placebo ($p < 0.05$)	Becker et al. (2015)
	GE test: 60 min after single dose of lixisenatide or placebo		Cumulative acetaminophen absorption reduced at 6 h compared to placebo for all doses of lixisenatide, including the 2.5 μg dose	
Lixisenatide (T2DM)	RCT, double-blinded, cross-over study of 15 healthy participants (F = 40%, age = 67.2 ± 2.3 years, BMI 24.5 ± 0.8 kg/m^2) and 15 subjects with T2DM (F = 40%, age 61.9 ± 2.3 years, BMI 30.3 ± 0.7 kg/m^2, HbA1c 6.9 ± 0.2%, T2DM duration 5.3 ± 1.2 years). Participants received 10 μg SC lixisenatide or placebo on two separate days	Nuclear scintigraphy over 3 h, with liquid 75 g glucose meal.	Because $T_{1/2}$ could not be determined due to a substantial portion of both cohorts having $T_{1/2}$ > 180 min, GE was instead measured by GE rate (kcal/min) for the first 120 min and showed delayed GE in both cohorts with lixisenatide compared to placebo:	Jones et al. (2019)
	GE test: after single dose of drug		Healthy: 1.45 ± 0.10 kcal/min (placebo) vs 0.60 ± 0.14 kcal/min (lixisenatide) ($p < 0.001$)	
			T2DM: 1.57 ± 0.06 kcal/min (placebo) and 0.75 ± 0.13 kcal/min (lixisenatide) ($p < 0.001$)	
Lixisenatide (T2DM)	RCT, double-blinded, parallel-group study of participants with T2DM randomized to	^{13}C-sodium-octanoic acid containing solid meal with breath test over 4 h	Change in $T_{1/2}$ from baseline to day 28 was 211.5 ± 67.6 min (i.e. delayed) for lixisenatide and − 24.1 ± 32.3 min for placebo ($p = 0.0031$)	Lorenz et al. (2013)
	Lixisenatide SC initiated at 5 μg and increased in increments of 2.5 μg every fifth day to a maximum of 20 μg daily. (n = 21, F = 47.6%, BMI = 31.4 ± 4.1 kg/m^2, HbA1c 8.5 ± 1.0%, T2DM duration 6.1 ± 4.0 y) or		Post-prandial serum glucose inversely related to degree of delay in GE for lixisenatide 20 μg daily	
	Placebo (n = 22, F = 50%, age 53.8 ± 6.6 years, HbA1c 8.9 ± 1.1%, T2DM duration 5.7 ± 3.8 years).			
	GE test: Baseline and 28 days later (4 days at maximum dose of 20 μg lixisenatide)			

(continued)

Table 1 (continued)

GLP-1 agonist/ analog	Study design, dose, treatment duration and timing of GE test	Measurement of gastric emptying	Effect on upper GI motor function	References
Semaglutide (obesity)	RCT, double-blinded, two-period, cross over trial (with 5–7 week washout) of 30 participants with obesity (F = 33.3%, age 42 ± 11 years, BMI 33.8 ± 2.5 kg/m^2) who received weekly injections of:	Acetaminophen absorption test (1,500 mg) over 5 h, with a standardized solid meal	Delay in GE suggested by 27% lower acetaminophen $AUC_{0\text{-}1h}$ reported in the semaglutide arm	Hjerpsted et al. (2018)
	Placebo or		No differences in the acetaminophen $AUC_{0\text{-}5h}$ for semaglutide vs placebo	
	Semaglutide 0.25 mg for 4 weeks, 0.5 mg for 4 weeks, then 1.0 mg for 4 weeks			
	GE test: After 12 weeks of study			

Paracetamol absorption test is written as acetaminophen absorption test. *F* female, *T2DM* type 2 diabetes mellitus, *HbA1c* hemoglobin A1c, *RCT* randomized controlled trial, *GE* gastric emptying, $T_{1/2}$ time to half gastric emptying, *SC* subcutaneous, *AUC* area under the curve, *IQR* interquartile range, *h* hours

Dulaglutide Dulaglutide is a long-acting GLP-1 receptor agonist. One study of dulaglutide at multiple subcutaneous (SC) doses (0.05, 0.3, 1, 3, and 5 mg once weekly) in subjects with T2DM revealed a decrease in acetaminophen $AUC_{0\text{-}12h}$ after 5 weeks of treatment (Barrington et al. 2011). Given the protracted assessment of acetaminophen absorption, the clinical significance of this AUC is not clear. It is possible, as has been seen with other long-acting GLP-1 receptor agonists, that the effect on gastric emptying is minimal to non-existent.

Exenatide Several studies have evaluated the effect of exenatide in short- or long-acting formulations on gastric emptying in subjects with T2DM. Delayed gastric emptying by the gold standard assessment—nuclear scintigraphy of a solid meal—was observed after 5 days' of either 5 μg or 10 μg SC exenatide, twice daily, compared to placebo (Linnebjerg et al. 2008). Four studies evaluated exenatide using acetaminophen absorption. These revealed delayed gastric emptying over a 6-h meal after an intravenous infusion of exenatide (roughly equivalent to one-half the peak concentration of a 5 μg SC dose exenatide) compared to placebo (Cervera et al. 2008); after 4 days of infusion of 0.05 μg/kg and 0.10 μg/kg compared to placebo (Kolterman et al. 2005); after 2 weeks of 10 μg SC, twice daily compared to placebo (DeFronzo et al. 2008); and after 14 weeks of exenatide, 10 μg SC, twice daily, compared to placebo (Drucker et al. 2008). Delay in gastric emptying based on a plasma acetaminophen absorption test was not observed with the once-weekly long-acting formulation compared to baseline (Drucker et al. 2008). However, exenatide QW substantially slowed gastric emptying measured scintigraphically and this relates to the reduction in postprandial glucose (Jones et al. 2020).

Liraglutide Assessments of liraglutide's effects on gastric emptying in subjects with T2DM have primarily used acetaminophen absorption. After eight doses of 6 μg/kg SC daily liraglutide, no difference in gastric emptying was observed, based on acetaminophen $AUC_{0\text{-}4h}$ (Degn et al. 2004). Using a similar treatment duration of 1 week and acetaminophen $AUC_{0\text{-}5h}$, delayed gastric emptying was observed with 1.2 mg liraglutide daily, but not with 0.6 mg or 1.8 mg daily. However, when acetaminophen $AUC_{0\text{-}1h}$ was instead used in the same study, gastric emptying was delayed for both 1.2 mg daily and 1.8 mg daily (Dejgaard et al. 2016). When longer treatment duration was studied, liraglutide, 1.8 mg SC daily, was shown to delay gastric emptying at 3 and 24 weeks, also based on acetaminophen $AUC_{0\text{-}4h}$ (Flint et al. 2011). Similarly, after 4 weeks of treatment with liraglutide, gastric emptying was delayed with liraglutide, 1.8 mg SC daily, compared to placebo, based on acetaminophen $AUC_{0\text{-}1h}$ (Horowitz et al. 2012).

Finally, one study examined gastric emptying effects of liraglutide in subjects with T2DM using gastric transit time of capsule endoscopy. While overall gastric emptying time was not changed from baseline after liraglutide use, when subjects were stratified by presence or absence of diabetic neuropathy, gastric transit time was significantly increased compared to baseline for those without diabetic neuropathy after liraglutide; whereas, those with diabetic neuropathy saw no significant delay in gastric emptying from liraglutide (Nakatani et al. 2017). While there are challenges in interpreting gastric emptying profiles of a solid meal and a capsule, this finding nevertheless illustrates the role of vagal mechanisms in the delay of gastric emptying induced by GLP-1 agonism.

Overall, the reported differences in effects of exenatide and liraglutide on gastric emptying may be more likely related to differences in methods of measurement rather than biological differences, given relatively minor structural differences between the two molecules, as well as the common mechanism of action of binding to the same G-protein-coupled, 7-transmembrane domain GLP-1 receptor. Details of each study are summarized in Table 1.

Lixisenatide Lixisenatide is a relatively more novel, short-acting, once-daily SC GLP-1 receptor agonist. Despite its short half-life (3 h), it is nonetheless administered once daily, most likely

due to its ability to delay gastric emptying (Lorenz et al. 2013; Horowitz et al. 2013). Lixisenatide's effect on gastric emptying was appraised with nuclear scintigraphy using a liquid meal and a scan over 3 h. While this method could not calculate $T_{1/2}$ because $T_{1/2}$ exceeded 3 h in the majority of both healthy and diabetic participants of this study, gastric emptying rate (in kcal/min) for the first 2 h was observed to be delayed in both healthy participants and those with T2DM exposed to lixisenatide compared to placebo (Jones et al. 2019).

Using a ^{13}C-sodium-octanoic acid-containing solid meal with breath test over 4 h, lixisenatide was further observed to delay gastric emptying after 4 weeks at a dose of 20 μg daily, compared to placebo (Lorenz et al. 2013). Lixisenatide, 20 μg daily, after 8 weeks was also shown to delay gastric emptying by the same type of breath test. Because the gastric emptying delay was so profound, particularly compared to the liraglutide doses studied in the same trial, the face values of the gastric emptying times present challenges in interpretation (Meier et al. 2015), especially in view of the documented differences in estimated time to half gastric emptying using different mathematical formulas (Odunsi et al. 2009). Nevertheless, these findings do align with delay in gastric emptying by acetaminophen $AUC_{0\text{-}1h}$ seen after a single dose of lixisenatide (5, 10, or 20 μg) compared to placebo in healthy participants (Becker et al. 2015).

8 Effects on Gastric Emptying with GLP-1 Receptor Agonists in Obesity

The secretion of GLP-1 in obesity has been reported to be reduced in some studies (Carr et al. 2010; Verdich et al. 2001; Adam and Westerterp-Plantenga 2005), although the results are inconsistent, as documented in a comprehensive review of the literature (Steinert et al. 2017). As outlined throughout this chapter, GLP-1 receptor agonism has a multitude of effects which may be useful to exploit for management of obesity. Indeed, several trials have investigated its role in weight management (le Roux et al. 2017; Pi-Sunyer et al. 2015). One such trial of 3.0 mg daily liraglutide observed a weight loss of 8.4 ± 7.3 kg compared to 2.8 ± 6.5 kg in the placebo arm ($p < 0.001$) after 56 weeks of intervention (Pi-Sunyer et al. 2015). It is likely that a contribution to weight loss results from appetite mediation by delay in gastric emptying, which has been observed in both human and animal models (Szayna et al. 2000).

The use of GLP-1 receptor agonism in obesity may be partly related to effects on gastric motor function. While the gastric motor functions in obesity are heterogeneous, a substantial portion of patients has accelerated gastric emptying (Acosta et al. 2015a, b), which may provide an opportunity for "personalized" treatment with a medication that delays gastric emptying. Infusion of exogenous GLP-1 in subjects with obesity, resulted in reduced hunger and calorie intake, and these measures correlated with the degree of gastric emptying delay, measured by the acetaminophen absorption test (Flint et al. 2001; Näslund et al. 1999). Nevertheless, weight loss associated with GLP-1 receptor agonism may be independent of gastric motor changes, and there was similar weight loss with liraglutide and exenatide, despite the differences in gastric emptying (Holst 2013). Weight loss with GLP-1 receptor agonists was not related to adverse gastrointestinal effects (which are largely driven by delays in gastric emptying) in several reports (Nauck et al. 2009; Buse et al. 2004; DeFronzo et al. 2005; Garber et al. 2011; Russell-Jones et al. 2009; Zinman et al. 2007). Another confounder is the fact that there appears to be tachyphylaxis in the retardation of gastric emptying from 5 to 16 weeks of liraglutide treatment, even though, at both times, the gastric emptying delay was significantly correlated with the degree of weight loss (le Roux et al. 2017). Table 1 summarizes key findings in gastric motor functions in the studies that evaluated gastric emptying in subjects with obesity exposed to GLP-1 receptor agonists.

Given the focus of this chapter on gastric effects of GLP-1 and its analogs and receptor

agonists, the central mechanisms will not be extensively discussed. GLP-1 receptors are expressed throughout the central nervous system (Vrang and Larsen 2010), particularly the hypothalamus and brainstem, and they play a role in regulation of appetite (Holst 2013), as well as blood glucose (Alvarez et al. 2005), independent of gastrointestinal effects of GLP-1 and its analogs and receptor agonists. Nevertheless, peripheral stimuli have been shown to interact with central GLP-1 mechanisms to induce weight loss in preclinical studies. For example, gastric body or fundus distention activated GLP-1 containing neurons in the nucleus of the solitary tract (NTS) of rats (Vrang et al. 2003) and this decreased food intake, an effect that was reversed with exendin-9-39, a GLP-1 receptor antagonist, administered directly into the fourth ventricle (Hayes et al. 2009). Apart from the GLP-1 effects on appetite, which appear to have a significant central component, there is evidence that GLP-1 inhibits gastric emptying through mechanisms that involve vagal afferents (Imeryüz et al. 1997), as well as inhibition of central parasympathetic outflow (Wettergren et al. 1998).

Exenatide Exenatide's effects on gastric emptying have been examined in obesity (without concomitant type 2 diabetes mellitus) in one study that measured gastric emptying of solids by nuclear scintigraphy. All subjects in that study had accelerated gastric emptying at baseline. Gastric emptying was delayed compared to placebo after 30 days of exenatide, 5 μg SC twice daily, based on both 1-h gastric emptying and time to half gastric emptying (Acosta et al. 2015a).

Liraglutide One study of liraglutide, 3.0 mg SC daily, showed delayed gastric emptying compared to placebo at both 5 and 16 weeks, measured by nuclear scintigraphy of a solid meal (Halawi et al. 2017). Notably, the delay in gastric emptying was less at 16 weeks compared to 5 weeks, consistent with the tachyphylaxis of GLP-1 agonism on gastric emptying described later in this chapter. Using acetaminophen $AUC_{0\text{-}5h}$, a separate study showed no difference between liraglutide, 1.8 mg or 3.0 mg SC daily, after 5 weeks; however, when acetaminophen $AUC_{0\text{-}1h}$ was used, both doses showed delayed gastric emptying compared with placebo (van Can et al. 2014). This provides a fitting example of the shortcomings of the assessment of gastric emptying based on a prolonged acetaminophen absorption test and how this can be potentially mitigated by testing the absorption over the first hour.

Semaglutide Semaglutide is a long-acting GLP-1 receptor agonist. Despite our understanding of the diminished effects on gastric emptying induced by long-acting GLP-1 agonists (see below), one study did observe a significant reduction in acetaminophen $AUC_{0\text{-}1h}$ (but not acetaminophen $AUC_{0\text{-}5h}$) with 1.0 mg weekly SC semaglutide compared to placebo after 12 weeks of intervention, suggesting that semaglutide may delay gastric emptying (Hjerpsted et al. 2018).

9 Short- vs. Long-Acting GLP-1 Receptor Agonists and Gastric Emptying and Tachyphylaxis

Nauck and colleagues demonstrated that gastric emptying of liquid meals in healthy participants, assessed by double-sampling dye dilution technique over 4 h, was delayed with administration of exogenous GLP-1; they also observed that deceleration of gastric emptying was subject to tachyphylaxis during ingestion of a second meal (Nauck et al. 2011). This loss of the delay in gastric emptying was associated with a statistically significant increase in postprandial glycemia during the second meal. Given this time frame, it is postulated that this tachyphylaxis phenomenon is driven more by the response of the vagal nerve function rather than by GLP-1 receptor downregulation or desensitization. Umapathysivam and colleagues observed similar tachyphylaxis in the delay of gastric emptying from prolonged or intermittent GLP-1 agonism compared to short-acting GLP-1 agonism (Umapathysivam et al. 2014).

There are multiple examples of tachyphylaxis in prolonged GLP-1 agonism. For instance, delay in gastric emptying was observed with short-acting exenatide, but not with the once-weekly, long-acting formulation, compared to placebo (Drucker et al. 2008). In addition, in a separate study, the delay in gastric emptying compared to baseline from 16 weeks of liraglutide (a short-acting GLP-1 receptor agonist) was less substantial than that of 5 weeks of liraglutide (Halawi et al. 2017).

Thus, delay in gastric emptying appears to be more characteristic of short-acting GLP-1 receptor agonists than long-acting GLP-1 receptor agonists (Madsbad 2016; Uccellatore et al. 2015). Tachyphylactic effects on delayed gastric emptying have not been observed with short-acting GLP-1 receptor agonists (Linnebjerg et al. 2008; Drucker et al. 2008; Flint et al. 2011), and may explain the decreased burden of upper gastrointestinal symptoms such as nausea and vomiting observed with long-acting formulations of GLP-1 agonists (Trujillo and Nuffer 2014). On the other hand, it is likely that long-acting formulations, such as albiglutide, dulaglutide, and exenatide long-acting release, improve glycemic control through restoration of balance between insulin and glucagon, rather than robust delays in gastric emptying (Meier 2012).

10 Effects of GLP-1 Agonist on Pharmacokinetics and Pharmacodynamics of Other Medications

An important consideration when prescribing medications in patients with diabetes and/or obesity is the potential of polypharmacy pharmacokinetics. Given the delays in gastric emptying observed with GLP-1 receptor agonists, there are hypothesized effects on other commonly prescribed medications for this demographic. For example, exenatide has been observed to have variable effects on several medications. In healthy volunteers, exenatide did not change steady concentration of digoxin, but it did cause a 17% decrease in mean plasma digoxin and a delay in time to reach steady state (Kothare et al. 2005). Similarly, exenatide was associated with decreased mean lovastatin plasma concentration AUC and time to maximum plasma concentration, although this did not affect 30-week changes in lipid profile (Kothare et al. 2007). Pharmacodynamics of warfarin in healthy volunteers (Soon et al. 2006) or lisinopril in subjects with mild-to-moderate hypertension (Linnebjerg et al. 2009) were not substantially affected by exenatide. Semaglutide was not observed to derange AUC plasma concentrations for lisinopril, warfarin, and digoxin, although the AUC was increased by 32% for metformin, and this may be of limited clinical concern, given the wide therapeutic index of metformin (Bækdal et al. 2019).

11 Variations in GLP-1 Receptor and Responses to GLP-1 Agonists

The minor A allele of GLP-1R (rs6923761) is associated with greater delay in time to half gastric emptying in response to liraglutide and exenatide. These studies provide data to plan pharmacogenetics testing of the hypothesis that GLP-1R influences weight loss in response to GLP-1R agonists (Chedid et al. 2018). The significance of target receptor genetic variation requires further study with other GLP-1 agonists.

12 Oral Semaglutide

Given that most commercially available GLP-1 receptor agonists have been studied in intravenous or subcutaneous injection formulations, oral semaglutide warrants specific mention. The adverse effects from semaglutide are similar to those of other GLP-1 receptor agonists, namely, nausea and vomiting, and these mirror the safety profile of once-weekly injectable semaglutide (Davies et al. 2017). The gastrointestinal side effects appear most consistently with the 14 mg dose, suggestive of a dose-limiting gastrointestinal side effect profile. Overall, there was a small increase in discontinuations compared to other

active drug treatment arms in clinical trials, including liraglutide (le Roux et al. 2017). This underscores the importance of understanding the gastrointestinal related adverse effects from GLP-1 receptor agonists, as well as the potential for therapeutic choice when GLP-1 agents are being considered for treatment of obesity. Given these side effects, it is recommended that dose escalation of oral semaglutide be carried out over 4 weeks or longer (Davies et al. 2017).

13 Effects of Combined GLP-1 and Other Hormone Agonism on Gastric Motor Functions

The evolving landscape of pharmacologic therapy has now incorporated combination therapies with efficacy of GLP-1 receptors and receptors of other hormones, including glucose dependent insulinotropic polypeptide (GIP).

GIP is released from intestinal K cells and, like GLP-1, the release of GIP is triggered by ingestion of nutrients and its activity is modulated by degradation by DPP-IV (Diakogiannaki et al. 2012; Vilsbøll et al. 2006). Dual infusions of GIP and GLP-1 receptor antagonists in healthy participants showed that the combination infusion not only caused poor postprandial glycemic control (compared with placebo and either infusion alone), but also that the combination antagonists accelerated gastric emptying, although perhaps not notably more than the GLP-1 receptor infusion alone (Gasbjerg et al. 2019). In a randomized, cross-over study of overweight or obese subjects, co-infusion of GIP and GLP-1 did not enhance the energy intake or appetite modulating effects of GLP-1 monotherapy, suggesting that GIP likely has little role in altering gastric motor functions, particularly gastric emptying (Gasbjerg et al. 2019). This finding is supported by preliminary data in patients with T2DM, subjected to gastric emptying of a standardized liquid meal (Mathiesen et al. 2019), as well as a phase 1 study of tirzepatide (a novel combination GIP and GLP-1 receptor agonist) using the acetaminophen absorption test (Urva et al. 2019). While many studies of these novel combination agents cite upper gastrointestinal symptoms of nausea and vomiting as relatively frequent and dose-dependent adverse effects from these medications (Coskun et al. 2018; Schmitt et al. 2017; Frias et al. 2018), it is unlikely that these result from a synergistic effect of GLP-1 and GIP on delay in gastric emptying.

There is also a GLP-1 and glucagon receptor dual agonist which results in clinically meaningful reductions in blood glucose, appetite and body weight in obese or overweight individuals with type 2 diabetes mellitus, as well as increase in treatment-emergent gastrointestinal disorders (Ambery et al. 2018). Another GLP-1 and glucagon dual agonist is cotagutide, which enhances insulin release and delays gastric emptying (Parker et al. 2019).

14 Conclusion

GLP-1 agonists and analogs are integral to the management of patients with type 2 diabetes mellitus and obesity. Overall, it appears that their effects are mediated at least in part by retardation of gastric emptying, although the effects on gastric emptying are reduced with long-acting preparations or long-term use of short-acting preparations as a result of tachyphylaxis.

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