

# *Chapter 5*

## **GLP-1 Based Therapies: Differential Effects on Fasting and Postprandial Glucose**

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## ABSTRACT

Glucagon-like peptide-1 (GLP-1), a gut derived hormone secreted in response to nutrients, has several glucose and weight regulating actions including enhancement of glucose stimulated insulin secretion, suppression of glucagon secretion, slowing of gastric emptying, and reduction in food intake. Due to these multiple effects, the GLP-1 receptor system has become an attractive target for type 2 diabetes therapies. GLP-1 itself, however, has significant limitations as a therapeutic due to its rapid degradation (plasma half-life of 1-2 minutes) by dipeptidyl-peptidase 4 (DPP-4). Two main classes of GLP-1 mediated therapies are now in use: DPP-4 inhibitors that reduce the degradation of GLP-1 and DPP-4 resistant GLP-1 receptor (GLP-1R) agonists. The GLP-1R agonists can be further divided into short-acting and long-acting formulations which have differential effects on their mechanisms of action, ultimately resulting in differential effects on their fasting and postprandial glucose lowering potential. This review summarizes the similarities and differences between DPP-4 inhibitors, short-acting GLP-1R agonists and long-acting GLP-1R agonists. We propose that these different GLP-1 mediated therapies are all necessary tools for the treatment of type 2 diabetes and that the choice of which one to use, should depend on the specific needs of the patient. This is analogous to the current use of modern insulins as short, intermediate, and long-acting versions are all used to optimize the 24-hour plasma glucose profile as needed. Given that GLP-1 mediated therapies have advantages over insulins in terms of hypoglycemia risk and weight gain, optimized use of these compounds could represent a significant paradigm shift for the treatment of type 2 diabetes.

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## INTRODUCTION

Glucagon-like peptide 1 (GLP-1) is an incretin hormone secreted from gastrointestinal L cells predominantly found in the ileum, colon, and rectum in response to nutrients [1-3]. Following food ingestion, GLP-1 appears in the plasma within minutes and due to its rapid degradation by DPP-4, is undetectable by three hours [4-6]. Given that enteroendocrine L cells are predominantly located in the distal gut, it is proposed that rapid appearance of GLP-1 in the plasma following a meal is likely a result of indirect hormonal and/or neural signaling as opposed to direct nutrient contact with GLP-1 secreting cells in the proximal gut lumen [7].

The human GLP-1 receptor (GLP-1R) is a 463 amino acid G-protein coupled receptor expressed on pancreatic islet  $\alpha$  and  $\beta$  cells and many other tissues including the gastrointestinal tract, heart, kidney, lung and the peripheral and central nervous systems [8, 9]. Receptor activation is linked to the cyclic AMP (cAMP) second messenger pathway [10]. Although receptor desensitization has been demonstrated *in vitro*, one week of twice-daily administration of the GLP-1 receptor agonist exenatide to wild-type mice, did not result in downregulation of the glucose lowering effect following and oral glucose load [11].

GLP-1 is thought to play an important physiological role to regulate plasma glucose in the postprandial period through several mechanisms of action: enhancement of glucose stimulated insulin secretion, suppression of glucagon secretion, and slowing of gastric emptying [12-18]. GLP-1 enhances insulin secretion in a glucose-dependent manner [19], augmenting both the first and second phase of secretion [20]. While GLP-1 clearly has direct effects on pancreatic  $\beta$  cells, a portion of the insulin response may be mediated through an indirect afferent nervous system pathway [21]. The effect of GLP-1 on glucagon secretion is also glucose dependent, occurring during euglycemia but does not affect the glucagon response to hypoglycemia ( $\leq 3.7$  mmol/liter) [19]. The mechanisms by which GLP-1 suppresses glucagon secretion could include a direct effect on the pancreatic  $\alpha$  cell but it is conceivable that additional indirect effects include local stimulation of insulin, amylin and somatostatin secretion [7]. GLP-1 is a potent inhibitor of gastric acid secretion and gastric emptying. Although the exact mechanisms by which GLP-1 regulates gastric function are unknown, it is clear that vagal afferents are important [22, 23]. Effects on gastric acid secretion may also be mediated through direct interaction with parietal cells [24]. On balance, the gastric emptying effect may be more important than insulin in controlling postprandial glucose as it limits the rate and extent of meal-derived glucose presented to the  $\beta$ -cell [25]. In fact, infusion of GLP-1 to subjects with type 2 diabetes results in significant and dose-dependent reductions in postprandial glucose and gastric emptying without an increase in plasma insulin [26].

There is also data from the conscious dog suggesting that GLP-1 may augment non-hepatic glucose clearance through a non-insulin mediated mechanism involving neural signalling in the portal vein [27, 28]. In addition, both animal and human studies suggest that GLP-1 may play a role in reducing insulin resistance. The effect has been observed in a variety of insulin resistant diabetic animal models [29] and in human subjects with type 2 diabetes [30]. In humans, the magnitude of the effect appears to be less than that seen with the thiazolidinedione (TZD) class and it is unclear if the effect is independent of the concomitant weight loss often observed. Pair-feeding experiments in nondiabetic, insulin-resistant obese *fa/fa* Zucker rats treated with exenatide for 6 weeks, suggest that a portion of the insulin-sensitizing effect (25%) could not be explained by weight loss [30]. Lastly, GLP-1 appears to play a role in

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mealtime satiety signalling which could impact plasma glucose through a reduction in caloric load ingestion, leading to reductions in bodyweight [12, 18, 31, 32]. In the case of food intake, GLP-1 likely acts centrally by crossing the blood-brain barrier and acts indirectly through vagal mediated pathways [9, 33]. Collectively, these mechanisms work in concert to regulate energy intake and glucose flux during the prandial period, allowing for appropriate consumption and delivery of nutrients from the gut to the circulation, at a time when the endogenous state is optimized for fuel storage without large glucose fluctuations in plasma. In addition, GLP-1R knockout mice have fasting hyperglycemia, suggesting that GLP-1 could play a tonic role in regulating fasting plasma glucose [34]. The mechanisms for such an effect are less clearly discerned. However, the pharmacological potential of this molecule was fully manifested with acute GLP-1 infusion studies in subjects with type 2 diabetes that demonstrated a near-normalization of both fasting and postprandial plasma glucose [30]. The wider biologic role of GLP-1 to positively regulate body weight and the cardiovascular system adds to the pharmacological potential of the hormone

### **GLP-1 Mediated Therapies for Type 2 Diabetes**

The GLP-1 receptor system has become an attractive target for type 2 diabetes therapies due to the multiple glucose, weight and cardiovascular properties attributed to endogenous GLP-1. GLP-1, however, has significant limitations as a therapeutic due to its rapid degradation by DPP-4 (plasma half-life: 1-2 minutes). DPP-4 is a ubiquitous plasma membrane glycopeptidase present on epithelial cells in a host of tissues including the gastrointestinal tract, kidneys, brain, pancreas, lymph nodes, thymus, and vascular bed [35]. A soluble form of DPP-4 can also be found in the plasma and in other body fluids. DPP-4 selectively removes N-terminal dipeptides when alanine or proline are in the second position. Thus, both endogenous and exogenous GLP-1 are rapidly metabolized from GLP-1 (7-36) to GLP-1 (9-36) by DPP-4, rendering it without glucose lowering properties [36].

To circumvent the half-life constraint of GLP-1, two novel classes of glucose lowering therapeutics have emerged: DPP-4 inhibitors and GLP-1R agonists. DPP-4 inhibitors enhance the effects of endogenous GLP-1 by inhibiting the enzyme that inactivates it. GLP-1 receptor agonists mimic the actions of GLP-1 but have DPP-4 resistant properties by virtue of their amino acid sequence and/or through chemical modification. Both classes have demonstrated effective utility for the treatment of type 2 diabetes [7, 33, 37-41]. Differences in their pharmacology, however, result in differential mechanisms of action and ultimately in differences in fasting and postprandial glucose lowering potential. This review focuses on the differences in fasting and postprandial glucose lowering effectiveness of the various classes and sub-classes of GLP-1 mediated therapies.

### **DPP-4 Inhibitors**

DPP-4 inhibitors sitagliptin, saxagliptin, and recently, linagliptin have been approved in the United States for the treatment of type 2 diabetes. In Europe, sitagliptin, saxagliptin and additionally, vildagliptin, are approved. DPP-4 inhibition leads to elevated plasma concentrations of GLP-1, which in turn enhances glucose-dependent insulin secretion and suppresses inappropriately elevated glucagon secretion [42]. In a meta-analysis of randomized controlled studies of at least 12 weeks, DPP-4 inhibitors resulted in a weighted mean reduction in hemoglobin A1c (HbA1c) of 0.74% (95% CI, 0.85% to 0.62%) compared

to placebo [43]. Similar results were observed in a second meta-analysis by Fakhoury et al [41]. Although there are small effects of DPP-4 inhibitors to lower postprandial glucose, the majority of the HbA1c effect results from reductions in fasting glucose [44-46]. Recently, Hjøllund et al. reported that DPP-4 inhibitors have a greater impact on portal vein GLP-1 concentrations (~4-fold) than on concentrations in the peripheral circulation (~2 fold) [47]. One could speculate that DPP-4 inhibitors may therefore exert more of an effect on fasting glucose through augmentation of the portal signal. Glucagon suppression is noted in the prandial state, but stimulation of insulin secretion is modest compared to other GLP-1 based therapies and there is little to no effect on gastric emptying [42, 44, 45, 48].

While both chronic infusions and bolus injections of GLP-1 are associated with weight loss [30, 31], administration of DPP-4 inhibitors typically results in weight neutrality [7, 49-51]. Modest weight loss, however, has been observed with the DPP-4 inhibitor, vildagliptin, in well-controlled patients, and it may reduce intestinal fat absorption [51]. It is not clear if the effects on fat absorption are specific to vildagliptin or if they can be generalized to other DPP-4 inhibitors or GLP-1R agonists.

The reasons for the reduced effect of DPP-4 inhibitors on gastric emptying and bodyweight are not clear. DPP-4 inhibition results in an approximate doubling of active GLP-1 in the peripheral circulation and perhaps these concentrations are insufficient to induce these mechanisms of action. Given that both the gastric emptying and satiety effects of GLP-1 are centrally mediated, higher concentrations of circulating GLP-1 may be required compared to the concentrations necessary to affect insulin and glucagon secretion [52]. Additionally, DPP-4 activates peptide tyrosine-tyrosine (PYY) [53], a gut peptide known to slow gastric emptying and reduce food intake [54]. Thus, if DPP-4 inhibitors reduce active PYY (PYY 3-36) concentrations, the effects of GLP-1 to slow gastric emptying and reduce food intake may be masked by the loss of a PYY effect.

## **GLP-1R Agonists with Intermittent Exposure**

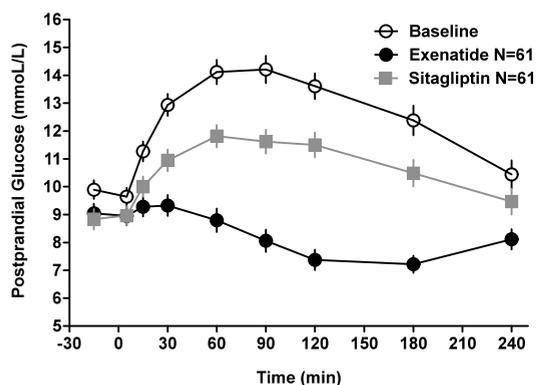
### *Exenatide BID*

The first GLP-1R agonist to be approved for clinical use was exenatide. Exenatide is a synthetic form of exendin-4, a 39 amino acid peptide isolated from the salivary secretions of the gila monster (*Heloderma suspectum*). It shares 53% sequence identity with GLP-1 and is equipotent at the GLP-1R [55]. Exenatide is DPP-4 resistant, resulting in an extended half-life relative to GLP-1 (2.4 hours) [56]. Plasma concentrations of exenatide are detectable for approximately 6-7 hours following a subcutaneous injection in the abdomen, arm, or thigh [57]. Like GLP-1, exenatide slows gastric emptying [58], suppresses glucagon [59, 60], and enhances first-phase and second-phase glucose stimulated insulin secretion, as well as insulin secretion in response to a combined glucose and arginine stimulus [61-63]. Importantly, the actions of exenatide on insulin and glucagon secretion occur during euglycemia, but not during hypoglycemia [62], providing a safeguard against inducing or prolonging hypoglycemia with long-term clinical use. Acute exenatide administration leads to robust dose-dependent reductions in postprandial glucose when bolus subcutaneous injections are administered prior to a meal [59, 60] and to reductions in fasting glucose when administered during an extended fast [59]. When exenatide was subcutaneously infused for 24 hours in patients with type 2 diabetes, dose-dependent reductions in both fasting and postprandial glucose were observed [64]. The reductions in postprandial glucose observed with acute administration of exenatide

were sustained following 28 days of twice a day (BID) or three times a day (TID) treatment [65]. With one year's treatment, exenatide BID improved  $\beta$ -cell function compared to insulin glargine with similar overall reductions in HbA1c [66]. At 52 weeks, C-peptide secretion was increased 2.46 fold with exenatide compared to 1.34 fold with insulin glargine ( $P < 0.0001$ ).

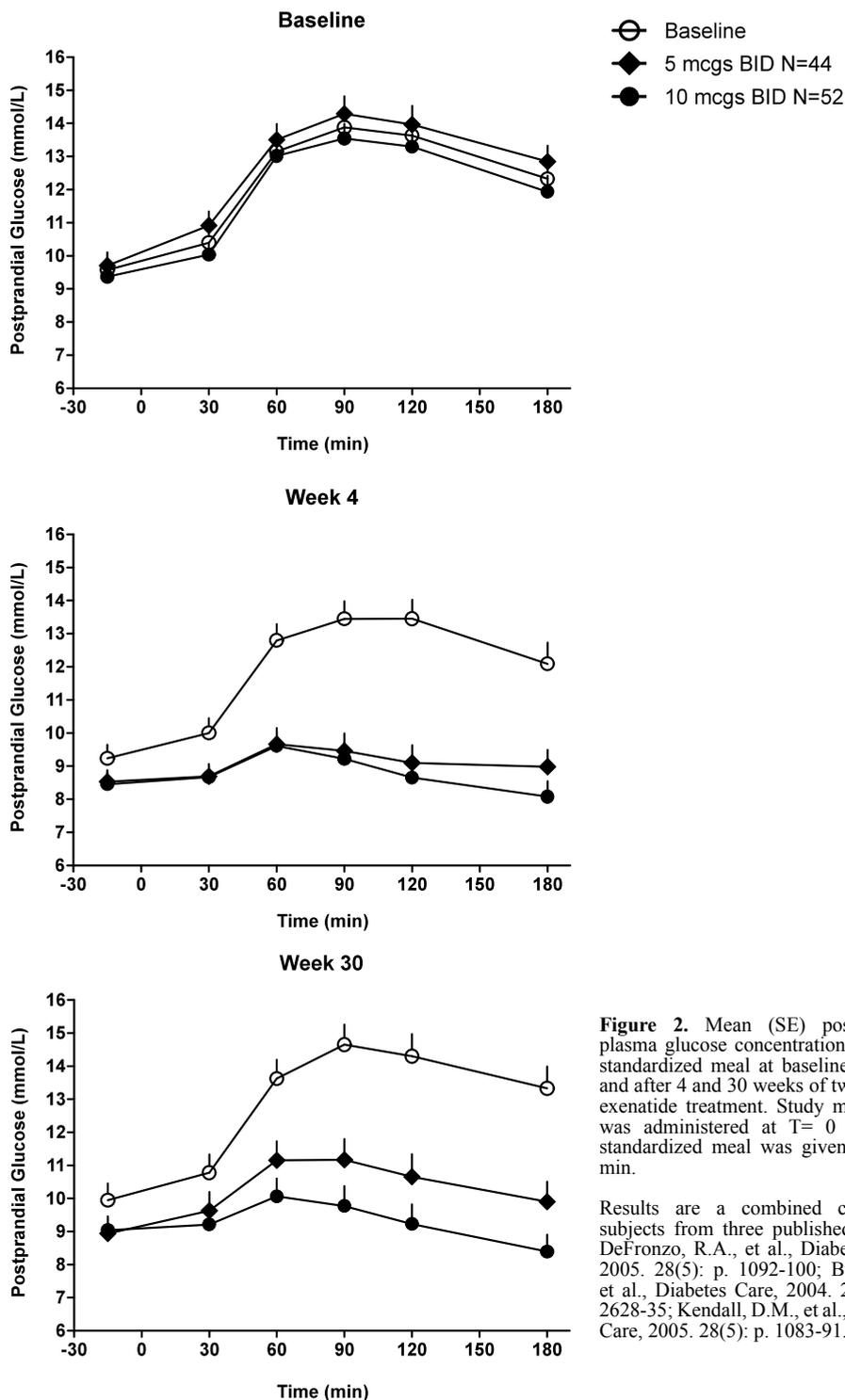
The effects of exenatide and sitagliptin on postprandial glucose metabolism were compared in a randomized 2-week crossover study in patients with type 2 diabetes [44]. Both treatments resulted in reductions in postprandial glucose and glucagon compared to baseline although the magnitude of effect was significantly greater (glucose  $p < 0.0001$ , glucagon  $p = 0.0011$ ) for exenatide compared to sitagliptin (Figure 1). It is noteworthy that with exenatide treatment, the postprandial glucose rise is almost completely blunted following the meal with concentrations falling below the preprandial concentration within one hour. This suggests that the effects on gastric emptying, glucagon secretion and insulin secretion are all contributing to the overall glucose profile. Exenatide 10  $\mu\text{g}$  significantly slowed gastric emptying while sitagliptin 100 mg did not change the gastric emptying rate from baseline. Finally, mean caloric intake during an ad libitum meal was reduced by 134 kcal from baseline with exenatide compared to an increase of 130 kcal from baseline with sitagliptin ( $p = 0.0227$ ).

Treatment with exenatide 10  $\mu\text{g}$  BID (breakfast and dinner) for 30 weeks resulted in mean reductions in HbA1c of 0.9% - 1.0% compared to placebo when added to metformin [67], a sulfonylurea (SFU) [68], or a combination of metformin and a SFU [69]. Consistent with the fact that exenatide is cleared from circulation in 6-7 hours, only modest reductions in fasting plasma glucose (1.0 mM to 1.4 mM) were observed compared to placebo. Placebo corrected weight loss ranged from 0.3 kg to 2.5 kg with the greatest loss observed in metformin treated subjects. A subset of the subjects in these studies underwent a standardized breakfast meal challenge at baseline and after 4 and 30 weeks of treatment. As shown in Figure 2, at 4 weeks, the postprandial rise in plasma glucose was almost completely blunted with exenatide treatment. The postprandial profiles at 30 weeks were slightly higher in all 3 treatment groups (5  $\mu\text{g}$ , 10  $\mu\text{g}$ , and placebo) compared to the 4-week profiles, but the differences between exenatide and placebo remain constant through 30 weeks. This suggests that there is little to no tachyphylaxis of the effect of exenatide on postprandial glucose with intermittent administration.



**Figure 1.** Mean (SE) postprandial plasma glucose concentration during a standard meal at baseline and after treatment with exenatide or sitagliptin. Exenatide was administered at  $T = -15$  min. Sitagliptin was administered at  $T = -30$  min. Standardized meal was given at  $T = 0$  min.

Adapted from: DeFronzo, R.A., et al., *Current Medical Research and Opinion*, 2008, 24(10): p. 2943-52.



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## GLP-1R Agonists with Continuous Exposure

Although the plasma half-life of exenatide is a significant improvement over native GLP-1, the duration of exposure is still limited to 6-7 hours following an injection. Thus, exenatide given twice daily at breakfast and dinner provides intermittent exposure and exerts its main effects during the prandial period of those main meals.

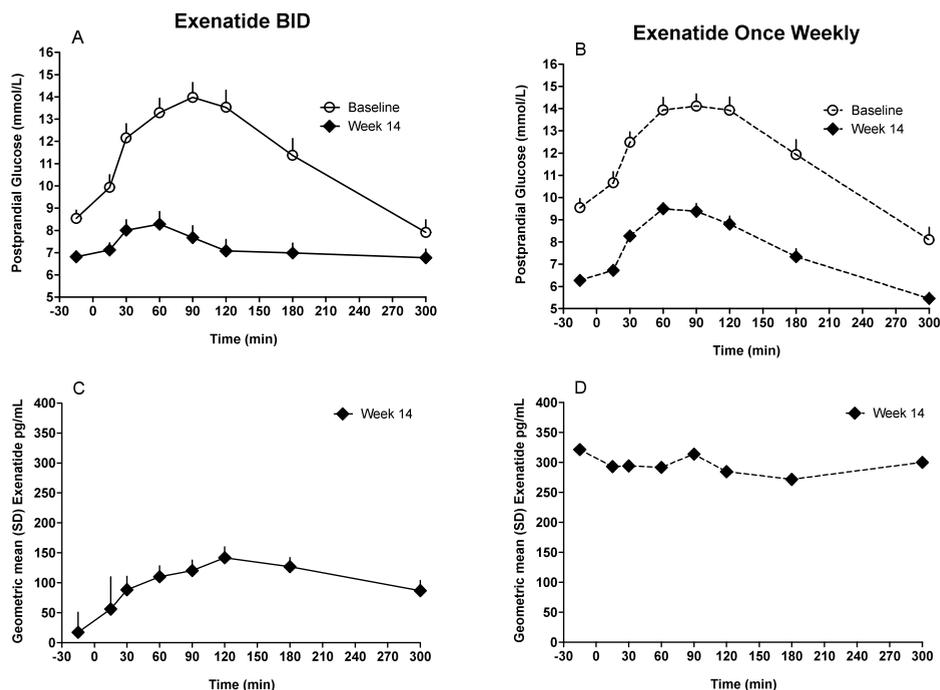
Multiple strategies have been employed to extend the apparent half-life of GLP-1R agonists by slowing the rate of absorption and/or by reducing plasma clearance. Such strategies improve patient convenience by reducing the frequency of administration and enhance the effects on fasting glucose by providing continuous exposure. One such product, liraglutide, is currently available in the United States and Europe. In addition, an extended-release version of exenatide has been developed which is available in Europe and is currently under review at FDA.

### *Exenatide Once Weekly*

The extended-release formulation of exenatide was developed to provide continuous exenatide exposure with once weekly administration. The formulation utilizes biodegradable polymeric microspheres, composed of exenatide in a poly lactide-co-glycolide polymeric matrix. This extended-release formulation is injected subcutaneously and slowly releases native exenatide into the subcutaneous space through a complex process of polymer hydration and degradation [70]. Thus, this absorption rate-limited formulation allows for continuous systemic exposure to exenatide without modification of the native peptide. Once absorbed, the general pharmacokinetic properties of exenatide are unchanged.

In 26- and 30-week controlled trials, the extended-release formulation of exenatide (exenatide once weekly) resulted in HbA1c reductions from baseline ranging from 1.5% to 1.9% [71-74] with more substantial improvements in fasting glucose than had been observed in the exenatide BID studies. The short and long-acting exenatide formulations were directly compared in two studies of 26 [72] and 30-week [74] duration. In the 26-week study, exenatide once weekly resulted in significant improvements in HbA1c compared to exenatide BID (-1.6 % vs. -0.9 %;  $P < 0.0001$ ) with improved fasting plasma glucose (FPG) relative to exenatide BID (-1.94 mmol/L vs. -0.66 mmol/L;  $P = 0.0008$ ). Reductions in mean body weight from baseline to week 24 were not statistically different between groups (-2.3 kg and -1.4 kg). Similar results were observed in the 30-week study (HbA1c: -1.9 % vs. -1.5 %,  $p=0.0023$ ; FPG: 2.3 mmol/L vs. -1.4 mmol/L  $p<0.0001$ ).

The 30-week study also included a standardized meal challenge at baseline and 14 weeks (after exenatide once weekly achieved steady-state plasma exenatide concentrations). Notably, the effects on postprandial glucose excursion and gastric emptying were greater with exenatide BID than with exenatide once weekly (Figure 3 A, B and Table 1). The mean reduction from baseline in 2-hour postprandial plasma glucose was 6.9 mmol/L with exenatide BID vs. 5.3 mmol/L with exenatide once weekly ( $p=0.0124$ ). Gastric emptying was assessed by comparing the absorption of acetaminophen following a 1000 mg oral dose administered before the standardized meal tests. Exenatide BID treatment resulted in a 21% reduction in acetaminophen maximum concentration ( $C_{max}$ ) and a 20% reduction in area under the curve (AUC) compared to baseline. In contrast, exenatide once weekly treatment resulted in only a 5% reduction in  $C_{max}$  and a 4% reduction in AUC.



**Figure 3.** Mean (SE) time profiles of postprandial plasma glucose concentrations at baseline and week 14 during the meal challenge comparing exenatide BID (A) versus exenatide once weekly (B). Geometric mean (SD) time profiles of plasma exenatide concentration at week 14 during the meal challenge for exenatide BID (C) versus exenatide once weekly (D). Meal Challenge subgroup, N=51.

Adapted from Drucker, D.J., et al., *Lancet*, 2008. 372(9645): p. 1240-50.

**Table 1.** Acetaminophen Pharmacokinetic Parameters Following a 1000 mg Oral Dose (N=75)

	Geometric Mean (SE)		Ratio of Week 14/Baseline	
	Baseline	Week 14	Geometric LS Mean	90% CI Of the Mean
<b><math>C_{\max 0-5h}</math> (<math>\mu\text{g/mL}</math>)</b>				
Exenatide QW	11.22 (0.99)	10.61 (0.75)	0.95	0.81, 1.11
Exenatide BID	11.67 (0.80)	9.17 (0.94)	0.79	0.66, 0.93
<b><math>AUC_{0-5h}</math> (<math>\mu\text{g}\cdot\text{min/mL}</math>)</b>				
Exenatide QW	1729 (113)	1651 (141)	0.96	0.84, 1.09
Exenatide BID	1831 (96)	1462 (158)	0.80	0.70, 0.92

$AUC_{0-5h}$  = area under the 5 hour concentration curve,  $C_{\max 0-5h}$  = maximum concentration of the 5 hour concentration curve.  
QW = once weekly.

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The reduced postprandial glucose and gastric emptying effects of exenatide once weekly cannot be explained by lower exenatide plasma exposure, as the geometric mean plasma concentrations were higher with exenatide once weekly (280 to 310 pg/mL) than with exenatide BID (60 to 140 pg/mL) over the 5-hour meal test period [Figure 3 C, D]. The differences also cannot be explained by differences in chemical structure between the two therapies because both release unmodified exenatide into circulation. These data therefore suggest that continuous GLP-1 agonist exposure down-regulates the effects on gastric emptying which in turn reduces the effect on postprandial glucose excursions. This hypothesis is consistent with a recent report by Nauck et al. that demonstrated a reduced gastric emptying and postprandial glucose effect at the lunch meal compared to the breakfast meal during a continuous intravenous infusion of native GLP-1 [75]. Given the short time course (4 hours between meals), the authors proposed that this finding indicated a tachyphylaxis of the gastric emptying effect at the level of the vagal nerve rather than GLP-1 receptor downregulation or desensitization. Interestingly, there appears to be tachyphylaxis of nausea (the most common side effect) with chronic exenatide BID treatment without a loss of effect on gastric emptying or postprandial glucose [67-69, 76] and less nausea is observed with exenatide once weekly than with exenatide BID despite higher plasma concentrations [74].

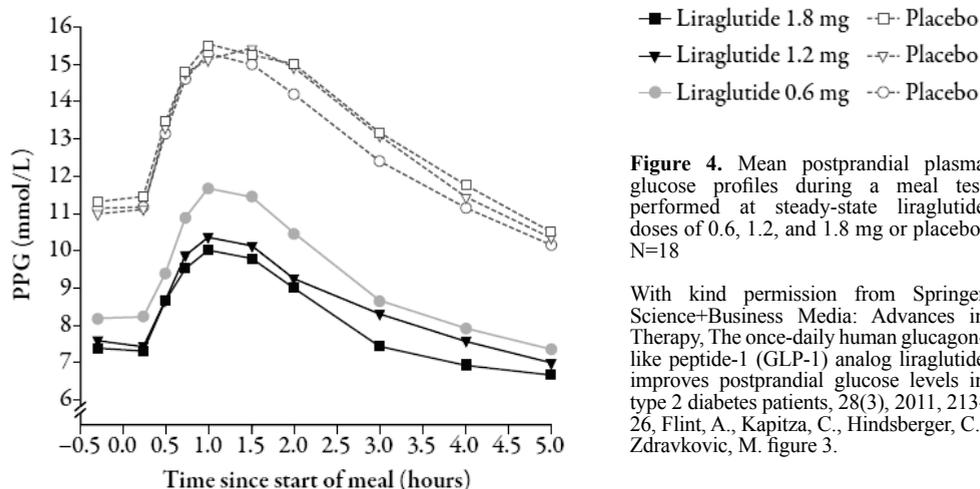
Several groups have described the observation that glucose tolerance is improved at the second meal of the day relative to the first, a phenomenon referred to as the Staub-Traugott effect [77, 78]. Interestingly, Bonuccelli et al, have shown that plasma concentrations of GLP-1 are elevated at the second meal of the day relative to the first, and that the Staub-Traugott effect is mediated through an enhanced insulin response to glucose, and a suppression of hepatic glucose production without changes in the gastric emptying rate [77]. This suggests that augmentation of GLP-1 concentrations by means other than DPP-4 inhibition also does not affect gastric emptying but may improve glucose tolerance through other mechanisms.

### **Liraglutide**

Liraglutide is a DPP-4 resistant GLP-1 analog that achieves slowed absorption and increased half-life through the substitution of arginine for lysine at position 34 and the addition of a C16 fatty acid change at position 26 allowing for reversible binding to albumin [79, 80]. The half-life of liraglutide is 11-15 hours resulting in continuous exposure with once-daily administration [80]. Although the potency of liraglutide is reduced 100-fold relative to GLP-1 (albumin binding is 98%-99%), it retains the basic actions of GLP-1 [1]. Long-term treatment with liraglutide 1.8 mg results in reductions in HbA1c of 1.0% to 1.3% and reductions in fasting glucose of up to 2.4 mmol/L [81-85].

Clinical trial results with liraglutide support the hypothesis that continuous GLP-1R agonism may down regulate the gastric emptying effect. While there are no head-to-head studies available that directly compare the gastric emptying effects of exenatide BID and liraglutide, it appears that liraglutide has a lesser effect on gastric emptying than exenatide BID based on individual observations. In a single dose study of liraglutide on subjects with diabetes, gastric emptying was significantly reduced by 9% compared to placebo as assessed by the 4-hour plasma AUC of 3-ortho-methyl-glucose (3-OMG) following oral administration [86]. No effect on gastric emptying at breakfast or dinner was observed in subjects with type 2 diabetes treated with liraglutide for one week as assessed using the acetaminophen technique [87]. In addition, when gastric emptying was assessed at weekly intervals during

a dose titration of liraglutide 0.6 mg (week 1), 1.2 mg (week 2), and 1.8 mg (week 3), the effects were more pronounced at week 2 than week 3 despite a higher dose at week 3. This is suggestive of tachyphylaxis although definitive conclusions cannot be made [88].



**Figure 4.** Mean postprandial plasma glucose profiles during a meal test performed at steady-state liraglutide doses of 0.6, 1.2, and 1.8 mg or placebo. N=18

With kind permission from Springer Science+Business Media: *Advances in Therapy*, The once-daily human glucagon-like peptide-1 (GLP-1) analog liraglutide improves postprandial glucose levels in type 2 diabetes patients, 28(3), 2011, 213-26. Flint, A., Kapitza, C., Hindsberger, C.; Zdravkovic, M. figure 3.

Consistent with a reduced effect on gastric emptying, liraglutide lowers postprandial glucose mostly through a reduction in pre-prandial glucose (Figure 4) [86-88] although some reduction in the postprandial increment above fasting is evident [88]. The latter can be explained by modest reductions in the rate of gastric emptying and more pronounced effects on glucagon and insulin secretion as is the case with exenatide once weekly [74]. This is in contrast to the postprandial profiles observed with exenatide BID in which little to no rise above fasting can be observed following a meal (Figures 1, 2, 3). The differences between exenatide BID and liraglutide are well illustrated in a 26-week head-to-head study in subjects with type 2 diabetes [89]. In that study, the reduction in HbA1c was greater with liraglutide compared to exenatide BID (1.16% vs. 0.87%) as a result of larger reductions in fasting glucose (treatment difference = 1.0 mmol/L). In contrast, exenatide BID had greater reductions in postprandial glucose compared to liraglutide at breakfast (difference = 1.3 mmol/L) and at dinner (difference = 1.0 mmol/L).

The improvements in fasting glucose observed with liraglutide are likely a result of the higher fasting plasma insulin and lower fasting plasma glucagon concentrations observed with liraglutide vs. exenatide BID, although the glucagon difference did not achieve statistical significance ( $p = 0.144$ ). This difference can be explained by differences in pharmacokinetics as exenatide BID should be cleared from circulation by the time the fasting samples were drawn.

There is currently no data to directly compare the effects of liraglutide and exenatide on fasting insulin and glucagon when both compounds are at their individual plasma therapeutic concentrations. Additionally, there is currently no data to directly compare the effects of liraglutide and exenatide on postprandial plasma insulin and glucagon. Interestingly, it appears

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that short and long-acting GLP-1R agonists have similar effects on bodyweight as described in head-to-head studies [72, 74, 89]. This is somewhat surprising given that exenatide BID administration only results in therapeutic plasma concentrations during the breakfast and dinner meals, and exenatide once weekly and liraglutide administration result in therapeutic concentrations throughout the day (breakfast, lunch, dinner, and snack times). This may suggest that exenatide BID's effect on satiety may last longer than the pharmacokinetics would predict. Alternatively, it may suggest that there is a partial downregulation of the satiety signal with continuous GLP-1R agonism that is compensated for by providing coverage across all meals.

### Summary and Clinical Relevance

The first in class GLP-1R agonist, exenatide BID, was approved by FDA in 2005 and the first DPP-4 inhibitor, sitagliptin, was approved the following year. These novel therapies should be considered significant treatment advancements as each addresses multiple pathophysiologies of type 2 diabetes. A second generation of GLP-1R agonists have more recently been developed to provide continuous exposure and reduced administration frequency. The first of these is liraglutide, which was approved by the European regulatory authorities in 2009 and by FDA in 2010. Exenatide once weekly is expected to be approved in Europe later this year based on the recent recommendation by the CHMP. Although all three classes of GLP-1 mediated therapies (DPP-4 inhibitors, short-acting GLP-1R agonists, and continuous GLP-1R agonists) share the same basic mechanisms, differences in pharmacokinetics and the magnitude of effect for each mechanism, results in differences in fasting plasma glucose, postprandial plasma glucose, and bodyweight effects. Table 2 summarizes the relative effect of each drug on the main mechanisms of action and on their glucose lowering ability in both the fasting and postprandial states.

In their 2009 consensus algorithm, The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommended the use of GLP-1R agonists as Tier 2 interventions especially when hypoglycemia and/or weight gain should be avoided [90]. DPP-4 inhibitors were not included in the current algorithm due to limited data availability at the time the algorithm was created. In contrast, the American Association of Clinical Endocrinologists (AACE) and The American College of Endocrinology (ACE) included both DPP-4 inhibitors and GLP-1R agonists in their 2009 consensus algorithm [91]. Due to their low risk of hypoglycemia, DPP-4 inhibitors were recommended as monotherapy if pre-treatment HbA1c is between 6.5% and 7.5%, particularly if metformin is contraindicated. For dual therapy, GLP-1R agonists, DPP-4 inhibitors, and insulin secretagogues (glinide or SFU) were recommended (in the order listed) to potentiate insulin secretion in combination with an insulin sensitizer (metformin or a TZD). GLP-1R agonists were the preferred choice in this portion of the treatment algorithm due to their postprandial glucose and weight lowering potential despite the greater likelihood of gastrointestinal side effects and the need for twice-daily injections. The National Institute for Health and Clinical Excellence (NICE) also included both GLP-1-mediated therapies in their updated 2009 clinical guideline [92]. In the Banting Lecture of the 2008 ADA annual meeting, Ralph DeFronzo proposed that treatment algorithms should be updated to address the known pathophysiological disturbances in type 2 diabetes [93]. This included using GLP-1R agonists in combination with insulin sensitizers

early in the treatment algorithm. In this regard, GLP-1R agonists have a unique advantage as they can treat disturbances in  $\beta$ -cell function, glucagon secretion, gastric motility, and satiety signals.

**Table 2.** Relative Effects of GLP-1 Mediated Therapies

	DPP-4 Inhibitors	GLP-1R Agonists	
		Short -acting	Continuous
<b>Mechanism of Action in the Fasting State</b>			
Enhance insulin secretion	+	+ / Neutral	++
Suppress glucagon secretion	+	+ / Neutral	++
<b>Mechanism of Action in the Postprandial State</b>			
Enhance insulin secretion	+	+++ <sup>3</sup>	++
Suppress glucagon secretion	+	+++ <sup>3</sup>	++
Slow gastric emptying	Neutral	+++	+
Reduce food intake	Neutral	++	++
<b>Clinical Effects</b>			
Reduce FPG <sup>1</sup>	++	+	+++
Reduce PPG increment <sup>2</sup>	+	+++	++
Reduce bodyweight	Neutral	+	+

<sup>1</sup>Fasting plasma glucose

<sup>2</sup>Postprandial plasma glucose rise above fasting

<sup>3</sup>When considering the lower glycemic load due to gastric emptying effects

At the time these algorithms were developed, exenatide BID was the only GLP-1R agonist clinically available. Thus, no distinction between short-acting GLP-1R agonists and continuous GLP-1R agonists were made. As described in this review, however, DPP-4 inhibitors and the two generations of GLP-1R agonists have distinct properties and each can be used to treat different patient phenotypes and different patient preferences. DPP-4 inhibitors have the advantage of simple oral administration, and they produce clinically relevant reductions in HbA1c. Effects on postprandial glucose are minimal, however. Short-acting GLP-1R agonists have more complex administration (twice daily injections), but robust effects on postprandial glucose. Effects on fasting glucose are less pronounced. The continuous GLP-1R agonists have the advantage of once daily (liraglutide) and once weekly (exenatide) administration and substantial effects on fasting glucose. Effects on the postprandial glucose increment are less robust. In addition, long-acting GLP-1 agonists may have less nausea than observed with short-acting GLP-1 agonists [74, 89]. All three classes of GLP-1 based therapies have a low risk of hypoglycemia when not combined with a hypoglycemic agent such as insulin or an SFU.

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Based on the differential pharmacology of GLP-1 mediated therapies, selection of the agent to use should depend, at least in part, on the glycemic disturbance that is in most need of correction. Monnier et al, demonstrated that fasting hyperglycemia is the major contributor to HbA1c in poorly controlled subjects, while postprandial hyperglycemia is the major contributor to HbA1c in subjects nearing target goals [94]. Thus, short-acting GLP-1R agonists should be considered early in the disease and as part of combination therapy for patients nearing glycemic goals, especially if weight loss would be beneficial. Long-acting GLP-1R agonists should be considered when larger reductions in HbA1c are needed, when fasting glucose elevations are the main problem, and when weight loss would be beneficial. DPP-4 inhibitors could be used in patients with mild to moderate fasting hyperglycemia and in subjects that need to maintain their bodyweight, especially if subcutaneous injections or gastrointestinal side effects limit the use of other GLP-1 mediated therapies. Although no GLP-1R agonist is currently approved for use with basal insulin, short-acting GLP-1R agonists and basal insulin could be a promising combination for treating both fasting and postprandial disturbances with accompanied weight loss [95].

The availability of three unique GLP-1 mediated therapies is analogous to the current use of modern insulins as short, intermediate, and long-acting versions are all used to optimize fasting and postprandial glucose as needed. Unlike the insulins, however, short and long-acting GLP 1R agonists are not currently approved for use in combination with each other, nor are DPP-4 inhibitors approved for use with GLP 1R agonists. Such combinations could potentially be useful, but further exploration is needed to explore their combined safety and efficacy.

## CONCLUSION

GLP-1 based therapies operate through multiple novel mechanisms of action that address many of the pathophysiological disturbances in type 2 diabetes. DPP-4s, short-acting GLP-1R agonists and long-acting GLP-1R agonists each have unique attributes. Selection of the particular therapy should consider safety and tolerability, frequency of administration, concomitant therapies, the need for weight loss or avoidance of weight gain, and the specific glycemic disturbances (fasting and/or postprandial) that need correction.

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