Differential effects of GLP-1 receptor agonists on components of dysglycaemia in individuals with type 2 diabetes mellitus

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Abstract

Metabolic consequences of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are the result of enhanced glucose-stimulated insulin secretion, inhibition of glucagon release, delayed gastric emptying and increased satiety. These attributes make GLP-1 agonists a treatment option in type 2 diabetes mellitus (T2DM). To optimise treatment choice, a detailed understanding of the effects of GLP-1 RAs on glucose homeostasis in individuals with T2DM is necessary. Although the various GLP-1 RAs share the same basic mechanisms of action, differences in pharmacokinetic/pharmacodynamic characteristics translate into differential effects on parameters of glycaemia. Head-to-head comparisons between long-acting non-prandial (liraglutide once daily and exenatide once weekly) and shorter-acting prandial (exenatide twice daily and lixisenatide once daily prandial) GLP-1 RAs confirm their differential effects on fasting plasma glucose (FPG) and post-prandial glucose (PPG). Liraglutide once daily and exenatide once weekly demonstrate greater reductions in FPG but lesser impacts on PPG excursions plasma than exenatide twice daily. Prandial GLP-1 RAs have a profound effect on post-prandial glycaemia, mediated by delaying gastric emptying, which is not subject to the tachyphylaxis occurring due to the sustained elevated plasma GLP-1 concentrations after treatment with long-acting GLP-1 RAs. Lixisenatide once daily prandial, in contrast to liraglutide, strongly suppresses post-prandial glucagon secretion, further contributing to the more pronounced PPG-lowering effect found with lixisenatide. Evidence suggests that the GLP-1 RAs that predominantly target the prandial glucose excursions, such as exenatide twice daily and lixisenatide once-daily prandial, are therefore best used as combination therapy with basal insulin and will form an important new treatment option for individuals with T2DM.

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Keywords: GLP-1 receptor agonists; Incretin; Prandial; Type 2 diabetes mellitus

Résumé

Différences dans les effets des agonistes du GLP-1 sur les glycémies chez les diabétiques de type 2.

Les conséquences métaboliques des analogues du GLP-1 (agonistes des récepteurs du GLP-1 ou ARs du GLP-1) proviennent d’une augmentation de la stimulation de la sécrétion insulinique, d’une inhibition de la production de glucagon, d’un ralentissement de la vidange gastrique et d’une augmentation de la sensation de satiété. Toutes ces propriétés font des ARs du GLP-1 une option thérapeutique dans le diabète de type 2 (DT2). Pour optimiser le choix thérapeutique, il est nécessaire d’avoir une compréhension détaillée des effets des ARs du GLP-1 sur l’homéostasie glucidique chez les individus ayant un DT2. Bien que fondés sur un mécanisme d’action commun, les ARs du GLP-1 diffèrent dans leur pharmacocinétique et leur pharmacodynamie, ce qui se traduit par une différence d’effets sur les paramètres glycémiques. Les études comparatives entre agonistes à durée d’action prolongée et basale (liraglutide une fois par jour et exénatide une fois par semaine) et agonistes à durée d’action courte et prandiale (exénatide biquotidienne et lixisenatide une fois par jour) confirment qu’ils n’exercent pas des effets identiques sur la glycémie à jeun et post-prandiale. Le liraglutide une fois par jour et l’exénatide retard injecté une fois par semaine sont plus efficaces sur la glycémie à jeun que sur la glycémie post-prandiale quand ils sont comparés à l’exénatide administré 2 fois par jour. Les agonistes à effet prandial ont un effet marqué sur les glycémies qui suivent les repas. Cet effet, qui est médité par le ralentissement de la vidange gastrique, n’est pas sujet à la survenue de l’effet de tachyphylaxie provoqué par la présence d’une élévation chronique des concentrations plasmatiques du GLP-1 après un traitement par des analogues du GLP-1 à action prolongée. Par rapport au liraglutide, le lixisenatide une fois par jour exerce un effet inhibiteur plus puissant sur la sécrétion.
1. Introduction

The main incretin hormones, glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1), are released predominantly from L- and K-cells, which are situated primarily in the proximal or distal intestine, respectively, following nutrient ingestion [1]. Both incretins promote insulin secretion, although GLP-1 is much more effective and also inhibits glucagon release, delays gastric emptying and enhances satiety, resulting in weight loss [2]. The early recognition that the incretin effect is insufficient in type 2 diabetes mellitus (T2DM) led to the evolution of incretin-based therapies. Two strategies have been developed in an attempt to restore and maintain the GLP-1 effect: [1] inhibition of the ubiquitous enzyme dipeptidyl peptidase-4 (DPP-4), which rapidly degrades GLP-1 in vivo, by the use of orally administered inhibitors; and [2] parenteral administration of GLP-1 mimetics that are DPP-4-resistant (GLP-1 receptor agonists [GLP-1 RAs]) [2].

The metabolic effects of GLP-1 RAs, complemented by potential extra-glycaemic properties (e.g. cardioprotection and vasodilatory actions), are particularly suited for the treatment of T2DM. The blood glucose-lowering actions of GLP-1 RAs manifest only in the setting of hyperglycaemia; thus, treatment minimises the risk of hypoglycaemia in the absence of concomitant insulin secretagogues or insulin supplementation therapy. The main tolerability issue with GLP-1 RAs is gastrointestinal intolerance, such as nausea and vomiting. These events are usually transitory and are rare after the first few weeks of therapy, although the frequency appears to vary between GLP-1 RAs [3].

Currently, four GLP-1 RAs are clinically available for the treatment of T2DM: exenatide twice daily; a long-acting formulation of exenatide, exenatide once weekly; lixisenatide once-daily; and liraglutide, once-daily prandial [4]. Other GLP-1 RAs in development include albiglutide once weekly and semaglutide once weekly [5]. The differential effects of native GLP-1 and the prandial- and non-prandial GLP-1 RAs in different body systems are shown in Fig. 1.

An important consideration in the assessment of GLP-1 RAs for the management of hyperglycaemia in T2DM is their ability to attenuate post-prandial plasma glucose (PPG) excursions. In normal physiology, the incretin system is adapted to facilitate the regulation of nutrient ingestion and disposal, thereby limiting excessive post-prandial hyperglycaemia and its potential deleterious effects on the vascular endothelium, which are precursors for cardiovascular disease. Traditional oral antidiabetic drugs (OADs), such as the sulfonylureas (SUs), do not independently curtail PPG, with only the alpha-glucosidase inhibitors and the short-acting glinides being capable of obtunding PPG excursions. In individuals advanced on to basal insulin therapy, only 60% achieve a glycated haemoglobin (HbA1c) target of 7% owing to a variety of reasons, including a delay in initiating basal insulin therapy and/or inadequate titration. There is also the need to address PPG excursions in those failing to achieve the glycaemic goal, for which the alternative is to introduce and titrate short-acting insulin pre-prandially with frequent self-monitoring of blood glucose, hence the attractive alternative of introducing a GLP-1 RA. The purpose of this paper is to review the effect of different GLP-1 RAs on hyperglycaemia, with particular focus on the differential impact on fasting plasma glucose (FPG-) and PPG-lowering potential with the different agonists.

2. Pharmacological profile of GLP-1 RAs

2.1. Prandial GLP-1 RAs: exenatide and lixisenatide

Structurally, exenatide and lixisenatide once-daily prandial are similar. Exenatide is a synthetic form of exendin-4, a 39-amino-acid peptide isolated from the salivary secretions of the Gila monster, which shares partial sequence homology with GLP-1 and is a potent agonist of the human GLP-1 receptor [2]. Exenatide has a half-life of approximately 2 h, necessitating twice-daily dosing. Lixisenatide is a 44 amino-acid exendin-4 analogue with an extended C-terminus [6]. Both agonists are short-acting, with time-to-peak concentration [t\text{max}] of around 2 h [7]; lixisenatide has a half-life of 2.8 h [4]. The binding affinity of lixisenatide to the human GLP-1 receptor is four-fold greater than native GLP-1, whereas exenatide has approximately the same affinity as native GLP-1 [8].

2.2. Non-prandial GLP-1 RAs: extended-release exenatide, liraglutide, albiglutide and semaglutide

Extended-release exenatide (exenatide once weekly), liraglutide, albiglutide and semaglutide are non-prandial GLP-1 agonists that rely on different mechanisms to delay their absorption from the subcutaneous tissue and extend their duration of action. Extended-release exenatide is a formulation that encapsulates exenatide in microspheres made of poly-(D,L,lactic-co-glycolic acid), a biodegradable medical polymer that enables controlled drug delivery over an extended period of time and has a 2-week half-life, allowing once-weekly administration to provide continuous exposure above the therapeutic threshold [9].

Liraglutide is an analogue of human GLP-1 with 97% sequence homology. To extend its duration of action, liraglutide contains a C16 palmitoyl fatty-acid side chain at Lys26 and a replacement of lysine with arginine at position 34. The addition of the fatty-acid chain allows liraglutide to form heptamers when injected subcutaneously, which, along with its binding
to albumin, delays its absorption [10]. It reaches a maximum concentration at 9–12 h after dosing, and plasma levels remain stable for up to 13 h after a single subcutaneous injection [11].

Albiglutide is a dimer of GLP-1 that is fused to human albumin [12]. The amino-acid at position 8 of each of the GLP-1 subunits has been substituted, increasing its resistance to degradation by DPP-4. Like liraglutide, albiglutide shares 97% homology with native GLP-1. Albiglutide reaches maximum concentration after 3–5 days, and has a half-life of 6–7 days, suggesting the possibility of once-weekly dosing.

Semaglutide is a unique monoacylated human GLP-1 analogue. The mode of action behind blood glucose reduction and a decrease in body weight follows identical principles to liraglutide but with a longer intrinsic half-life of approximately 6–7 days [5]. The semaglutide molecule, therefore, has a pharmacokinetic profile that is appropriate for once-weekly subcutaneous administration.

3. Review of post-prandial glucose-lowering by GLP-1 RA treatment

The results of the different trials are summarized in Table 1. Detailed data are reported in Tables S1–S4, Supplementary data.

3.1. Exenatide 10 µg twice daily

3.1.1. Phase III registration studies

Exenatide 10 µg twice-daily prandial was evaluated in three Phase III, 30-week, placebo-controlled registration trials in individuals with T2DM who are suboptimally controlled on SU [13], metformin [14], or metformin + SU [15] (Table S1, Supplementary data). In these studies, exenatide reduced HbA1c level by 0.8–0.9% from baseline versus 0.1–0.2% for placebo. In the latter two studies [14,15], the impact of incretin therapy on PPG excursions was evaluated with standardised meal-tolerance tests. In subjects on metformin, exenatide produced a 34% decrease in PPG area under the curve (AUC) over 15–180 min, which was apparent by week 4 [14]. In subjects on metformin + SU, exenatide produced an 87% reduction in PPG excursion AUC over 15–180 min, and the 2-h post-breakfast PPG fell by approximately 3.6 mmol/L at 30 weeks compared to an increase of 0.4 mmol/L in the placebo arm [15].

3.1.2. Post-marketing studies

3.1.2.1. Studies with no background glucose-lowering therapy. In a 24-week study of exenatide 5 or 10 µg twice daily as monotherapy, exenatide 10 µg twice daily led to a significant reduction in HbA1c, and a modest reduction in PPG versus placebo \( (P<0.001) \) [16]. Mean daily PPG fell by 1.4 mmol/L and the 2-h post-breakfast reduction, estimated from self-monitoring of plasma glucose (SMBG), decreased by approximately 2.2 mmol/L with exenatide 10 µg twice daily versus 0.2 mmol/L with placebo (Table S1, Supplementary data).

3.1.2.2. Suboptimal glycaemic control on metformin. Four randomized active-comparator studies in individuals with T2DM inadequately controlled on metformin alone have reported changes in PPG after a standardised test meal (Table S1, Supplementary data) [17–20]. In a randomised crossover trial, the effects of exenatide 5 µg twice daily for 1 week followed
Table 1
Summary of clinical trials with different GLP-1 receptor agonists. The efficacy of each tested receptor agonist was assessed against a comparator treatment by calculating, at endpoint, the differences between the increments or decrements from baseline of each parameter for the tested GLP-1 and its comparator. In order to simplify the reporting of the data, the dispersion for each cluster of studies, as indicated in each row, is quoted using the lowest and highest values of differences. For each tested parameter, the sign –ve or +ve indicates a result in favour of either the GLP-1 receptor analogue or its comparator, respectively. Oral agents include oral hypoglycaemic drugs that were given as either monotherapy or combined therapy. Detailed data can be obtained by consulting the Supplementary data.

<table>
<thead>
<tr>
<th>Type of tested GLP-1 receptor agonists</th>
<th>No of studies</th>
<th>Background treatment (references)</th>
<th>Comparator(s)</th>
<th>Differences (Δ) between the tested GLP-1 receptor agonist and its comparator at endpoint</th>
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<td>ΔHbA1c (%)</td>
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<td>Oral agents [17–25,27,28,34,65]</td>
<td>Placebo [16,25]</td>
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<td></td>
<td>2</td>
<td>Glargine + oral agents [26,66]</td>
<td>Placebo [26] or oral agents [66]</td>
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<td>Long-acting exenatide DURATION studies</td>
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<td>Oral agents [28,29,31,32]</td>
<td>Oral agents [29,30]</td>
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<td>Lisinidastatide</td>
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<td>Placebo [35–37,39]</td>
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<td>Or none [38]</td>
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<td>Glargine [36]</td>
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<td>GetGoal studies</td>
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<td>Oral agents [40,42,44,45,47,49]</td>
<td>Placebo [40,42–45,49]</td>
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<td>Or none [43]</td>
<td>Exenatide [47]</td>
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<td>3</td>
<td>Insulin + oral agents [16,18,41]</td>
<td>Placebo [41,46,48]</td>
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<td>NR: not reported.</td>
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by 10 μg twice daily in the second week were compared to the oral DPP-4 inhibitor sitagliptin, with metformin therapy being continued in both arms [17]. Exenatide produced a rapid reduction in PPG of 6.2 mmol/L from baseline versus a reduction of 2.1 mmol/L for sitagliptin. All PPG parameters (AUC, average concentration [Cave], and maximum concentration [Cmax]) were significantly lower with exenatide versus sitagliptin (P < 0.0001). After crossover, substitution of exenatide in those previously treated with sitagliptin resulted in a 4.2 mmol/L reduction in 2-h PPG (Table S1, Supplementary data).

In a 20-week, randomised, open-label study [18], in addition to their metformin regimen, the participants received exenatide, rosiglitazone or a combination of both agents. Although FPG was significantly reduced to a similar extent in all treatment groups, exenatide + rosiglitazone produced a greater reduction in HbA1c, reflecting the differences in PPG excursions seen in response to a standardised meal. At study end, the PPG excursion (AUC) was also significantly lower with the combination of exenatide and rosiglitazone (P = 0.004). The average 2-h post-meal PPG reduction from baseline was approximately 4 mmol/L with exenatide alone or when combined with rosiglitazone [18] (Table S1, Supplementary data).

Two 52-week studies have compared exenatide with the SUs glibenclamide and glimepiride [19,20]. In these studies, exenatide reduced 2-h post-meal PPG by 1.7 and 2.5 mmol/L versus 2.1 and 2.6 mmol/L for the glibenclamide and glimepiride studies, respectively (Table S1, Supplementary data).

3.1.2.3. Suboptimal glycaemic control on metformin with sulfonylurea combination. Two randomised controlled studies have compared exenatide versus insulin therapy—insulin glargine [21] or biphasic insulin aspart [22]. In these studies, HbA1c was reduced by exenatide and by both of the insulins. As expected, the reduction in FPG was greater with insulin glargine than with exenatide, whereas the change was similar with exenatide versus biphasic insulin (Table S1, Supplementary data). Compared with insulin glargine, exenatide produced a lower mean SMBG 2 h after the morning (P < 0.001) and evening (P < 0.001) meals. In a subgroup that undertook a standardised meal test, 2-h PPG was reduced by 3.4 mmol/L from baseline with exenatide and 0.8 mmol/L with insulin glargine. In the biphasic insulin study, greater reductions in PPG excursions following morning (P < 0.001), midday (P = 0.002) and evening (P < 0.001) meals were observed with exenatide versus insulin, with an average reduction of −3.8 mmol/L 2 h post-breakfast.

Other studies comparing exenatide with insulin have been conducted [23,24], but these studies have not reported the effect of therapy on PPG levels (Table S1, Supplementary data).

3.1.2.4. Suboptimal glycaemic control on thiazolidinedione with or without metformin. The addition of exenatide to thiazolidinedione (TZD) ± metformin led to a reduction in HbA1c and FPG versus placebo [25]. Exenatide was associated with reductions in glucose excursions after the morning and evening meals (mean −1.7 mmol/L). The 2-h PPG reduction from baseline, estimated from SMBG values, was 3.2 mmol/L for exenatide and 0.3 mmol/L for placebo (Table S1, Supplementary data).

3.1.2.5. Suboptimal glycaemic control on basal insulin with or without metformin and/or thiazolidinedione. In subjects inadequately controlled on insulin glargine ± metformin, TZD or both, the addition of exenatide reduced HbA1c to a greater extent than titration of insulin glargine alone (difference −0.7%) [26]. The 2-h PPG post-breakfast reduction from baseline was 2.0 mmol/L versus 0.2 mmol/L for placebo (Table S1, Supplementary data).

3.2. Extended-release exenatide

The Phase III clinical development programme of exenatide once-weekly non-prandial involved a series of trials known as the “DURATION” trials. These studies were designed to compare the safety and efficacy of exenatide once weekly with exenatide twice daily (DURATION-1 and -5) [27,28], sitagliptin or pioglitazone (DURATION-2) [29], metformin, pioglitazone or sitagliptin (DURATION-4) [30], liraglutide (DURATION-6) [31], and insulin glargine (DURATION-3) [32], (Table S2, Supplementary data). Studies reporting PPG values included DURATION-1, -4 and -5.

3.2.1. Studies with no background glucose-lowering therapy

In DURATION-4, exenatide once weekly was evaluated as monotherapy versus metformin, pioglitazone and sitagliptin in a 26-week study of 820 treatment-naïve people with T2DM [30]. Exenatide once weekly produced a significant reduction in HbA1c and a reduction in FPG. The mean reduction in SMBG PPG excursions was similar among all treatment groups. The 2-h post-breakfast PPG reduction was approximately 3.6 mmol/L from a pre-treatment baseline value of 12.2 mmol/L, which was mainly due to a reduction in fasting rather than post-meal glucose levels (Table S2, Supplementary data).

3.2.2. Suboptimal glycaemic control on metformin/SU combination

DURATION-3 [32] was a randomised open-label study in which exenatide once weekly was compared with insulin glargine titrated to target using the INITIATE (Insulin by Aggressive Titration and Education) dosing algorithm [33]. Reductions in HbA1c were greater with exenatide than with insulin glargine, with people receiving exenatide being an average of 4 kg heavier. Although there was a greater reduction in FPG with insulin glargine, exenatide once weekly was superior in lowering PPG after both the morning and evening meals. At the end of the study, the 2-h post-breakfast PPG reduction was approximately 3.5 mmol/L for both exenatide once weekly and insulin glargine (Table S2, Supplementary data). Individuals treated with exenatide once weekly had a lower incidence of hypoglycaemia but a greater incidence of gastrointestinal adverse events (AEs), which led to a higher rate of discontinuations due to AEs, including injection-site reactions, versus...
3.3. Liraglutide

The “LEAD” studies were a series of six randomised trials of 26–52 weeks’ duration, that assessed the efficacy and safety of liraglutide (0.6–1.8 mg) once-daily alone or in combination with OADs in 5796 individuals with T2DM (Table S3, Supplementary data). The reductions in PPG 1.5 h from the beginning of a meal were reported in all six studies, but without baseline values in four of the studies [34–37].

In the only 52-week study, LEAD-3 [38], liraglutide (1.2 and 1.8 mg) produced dose-dependent reductions in HbA1c and FPG versus glimepiride. FPG concentrations fell during the first 2 weeks after randomisation in the liraglutide groups and during the first 4 weeks in the glimepiride group, remaining stable thereafter. Liraglutide was superior to glimepiride in reducing PPG; based on the mean values taken after the three meals of the day by SMBG, liraglutide reduced PPG by an estimated −1.7 and −2.1 mmol/L versus −1.4 mmol/L with glimepiride. Liraglutide was associated with weight loss, whereas glimepiride resulted in weight gain (Table S3, Supplementary data).

In the 26-week LEAD-1 trial, liraglutide, rosiglitazone or placebo was added to background SU therapy [39]. Liraglutide 1.2 mg and 1.8 mg significantly reduced HbA1c versus rosiglitazone (P < 0.00001). A small increase in HbA1c was observed in the placebo group. Reductions in PPG (90 min post-meal from baseline) with liraglutide 1.2 mg or 1.8 mg daily were −2.5 mmol/L and −2.7 mmol/L, respectively, versus 1.8 mmol/L and 0.4 mmol/L with rosiglitazone and placebo, respectively (Table S3, Supplementary data) [39].

In LEAD-2 [35], dose-dependent reductions in PPG (mean of three meals based on SMBG-derived profiles) were similar for liraglutide 1.2 mg and 1.8 mg and glimepiride (Table S3, Supplementary data).

In LEAD-4 and LEAD-5, investigated triple therapy with liraglutide was given on a background of metformin and an additional OAD (rosiglitazone in LEAD-4 and glimepiride in LEAD-5) [36,37]. In LEAD-4, similar reductions versus placebo in PPG were observed with both liraglutide doses (1.2 mg and 1.8 mg). LEAD-5 assessed the efficacy of liraglutide 1.8 mg daily versus placebo and open-label insulin glargine, all in combination with metformin and glimepiride. The PPG reduction with liraglutide (1.8 mmol/L) was comparable with the reduction seen with insulin glargine (1.6 mmol/L); there was no change in the placebo group (Table S3, Supplementary data).

3.4. Lixisenatide once-daily prandial

The Phase III “GetGoal” programme comprised 11 randomised studies that evaluated the efficacy and tolerability of lixisenatide 20 µg once-daily prandial in more than 5000 individuals with T2DM. Results from the trials that have been published or presented as abstracts are represented in Table S4, Supplementary data [40–50]. References to PPG values were available from seven studies: GetGoal-Mono [43], GetGoal-M [40], GetGoal-S [45], GetGoal-L [41], GetGoal-L-Asia [48], GetGoal-M-Asia [49] and GetGoal-Duo-1 [46]. PPG values were a secondary endpoint and were reported as mean change from baseline at 2 h post-prandially following a standardised meal. The evaluated cohorts differed in terms of the duration of T2DM at study entry (mean duration: 1.1–14.1 years) and type of background therapy, ranging from no current glucose-lowering therapy to one or two OADs ± basal insulin.

3.4.1. Studies with no background glucose-lowering therapy

Lixisenatide once-daily prandial was evaluated as monotherapy versus placebo in the 12-week, GetGoal-Mono-Japan study [43]. Lixisenatide produced significant improvements in HbA1c, FPG and PPG versus placebo. The 2-h PPG was markedly lowered from a baseline of 14.6 mmol/L by 5.5 mmol/L with the one-step increase and by 4.5 mmol/L from a baseline of 14.8 mmol/L with the two-step increase (P < 0.0001 for both) (Table S4, Supplementary data).

3.4.2. Suboptimal glycaemic control on metformin-only baseline therapy

In the 24-week GetGoal-M study in patients with suboptimal glycaemic control on metformin therapy only, lixisenatide (both morning or evening administration) reduced HbA1c versus placebo [40]. Lixisenatide morning administration was associated with a major reduction in the 2-h PPG after a standardised meal of −5.7 mmol/L from baseline versus only a −1.2 mmol/L reduction for placebo (Table S4, Supplementary data).

3.4.3. Suboptimal glycaemic control on metformin/SU combination baseline therapy

In a similar 24-week study in individuals treated with a SU ± metformin (GetGoal-S), lixisenatide significantly reduced HbA1c versus placebo (P < 0.0001), with a pronounced reduction in the 2-h PPG following a standardised meal test of 6.2 mmol/L versus a reduction of 0.2 mmol/L for placebo (Table S4, Supplementary data) [45].

3.4.4. Suboptimal glycaemic control on basal insulin plus OADs

In a 28-day, randomised, double-blind, placebo-controlled, parallel-group Phase II study in patients with T2DM, treatment with once-daily prandial lixisenatide after a standardised breakfast contributed significantly to slowing the rate of gastric emptying. Delayed gastric emptying has been associated with lower PPG levels, but no such relationship was found for the placebo group in this study [51].

Three Phase III studies (n = 1253 in total) have examined the impact of lixisenatide once-daily prandial on PPG values in subjects with suboptimal glycaemic control using basal insulin [41,46,48]. In GetGoal-L-Asia, 311 Asian subjects inadequately controlled on basal insulin ± SU were randomised to lixisenatide 20 µg once-daily or placebo for 24 weeks [48]. With lixisenatide, 2-h PPG fell dramatically from a high baseline of 17.8 mmol/L to 9.9 mmol/L after the standardised meal test.
versus little or no change with placebo. This pronounced PPG reduction was associated with a reduction in HbA1c level of 0.77% compared with an increase of 0.11% for the placebo group (P < 0.0001) (Table S4, Supplementary data).

In GetGoal-L, the 2-h PPG after the standardised meal test was reduced with lixisenatide by 5.5 mmol/L (from a baseline of 16.4 mmol/L) and by only 1.7 mmol/L with placebo (from a baseline of 15.9 mmol/L). These reductions were associated with a reduction in HbA1c of 0.7% with lixisenatide and 0.4% with placebo [41] (Table S4, Supplementary data).

GetGoal-Duo-1 adopted a different study design to GetGoal-L and GetGoal-L-Asia [46]. Those subjects with suboptimal glycaemic control whilst in receipt of various oral agents, mainly metformin but also SU or TZD agents, were treated for 12 weeks with basal insulin glargine, titrated to a target FPG of less than 5.6 mmol/L. At the start of run-in, SU therapy was stopped. Individuals failing to achieve the target HbA1c of ≤7% at 12 weeks and FPG of ≤140 mg/dL were then randomised to lixisenatide or placebo. During the 12-week run-in period, the addition and titration of insulin glargine resulted in a reduction in HbA1c of approximately 1%. Thereafter, during the randomised 24-week study period, the mean HbA1c was further reduced by −0.7% with lixisenatide and −0.4% with placebo. At study end, lixisenatide once-daily prandial had produced significant reductions in 2-h PPG (mean difference versus baseline of −3.1 mmol/L versus 0.1 mmol/L with placebo) (Table S4, Supplementary data).

3.5. Albiglutide and semaglutide

The efficacy and safety of albiglutide once weekly is being investigated in the Phase III Harmony programme, involving eight studies and (to date) approximately 5000 individuals with T2DM. These studies are investigating albiglutide once weekly as monotherapy and as add-on to OADs and insulin. Results from two studies, Harmony-6 (albiglutide vs prandial insulin lispro) [52] and Harmony 7 (albiglutide vs lixisenatide) [53], have been reported. In both studies, albiglutide reduced HbA1c versus the comparator, but PPG data have not yet been reported.

The Phase III global development programme for semaglutide, “SUSTAIN”, is currently being initiated, with the first late-stage trial having commenced in April 2013. A Phase II trial showed clinical efficacy and safety that was generally similar to lixisenatide [5].

4. Comparisons between GLP-1 RAs on PPG excursions

4.1. Exenatide twice daily versus lixisenatide

A direct comparison of the efficacy, safety and tolerability of lixisenatide twice daily and exenatide twice daily was performed in the LEAD-6 trial [34]. Individuals failing to reach the set glycaemic target with metformin, SU or both were randomised to lixisenatide 1.8 mg once-daily or exenatide 10 μg twice daily. At study end, exenatide had substantially decreased PPG 90 min post-breakfast compared with lixisenatide (estimated treatment difference, −1.3 mmol/L; P < 0.0001) and also substantially decreased PPG after dinner (estimated treatment difference, −1.0 mmol/L; P = 0.0005) (Table S3, Supplementary data).

4.2. Exenatide twice daily versus exenatide once weekly

DURATION-1 compared the safety and efficacy of exenatide twice daily versus exenatide once weekly over an initial period of 30 weeks [28], followed by 1.5 years of treatment with exenatide once weekly, for a total of 2 years of exenatide treatment [54]. By week 14, exenatide twice daily reduced 2-h PPG from baseline and, at the end of the 30-week initial period, a greater reduction was observed versus exenatide once weekly (−6.9 mmol/L vs −5.3 mmol/L, respectively; P = 0.0124) (Fig. 2 and Table S2, Supplementary data), although at 30 weeks, the patients given exenatide once a week had significantly greater changes in HbA1c than those given exenatide twice a day (−1.9% vs −1.5%, P = 0.0023).

4.3. Lixisenatide versus lixisenatide

Lixisenatide 20 μg once-daily prandial has been directly compared with lixisenatide 1.8 mg once-daily in a Phase II, 4-week, randomised, open-label trial in 148 subjects with T2DM inadequately controlled on metformin [55]. Lixisenatide produced a significantly greater mean reduction from baseline in PPG versus lixisenatide, reducing PPG excursion by 8.6 mmol/L and ΔAUC0:30–4:30h by 8.6 h·mmol/L (P < 0.0001) more than lixisenatide after a meal test (Fig. 3 and Table S4, Supplementary data). Lixisenatide also significantly decreased post-prandial glucagon AUC0:30–4:30h from baseline to day 28 versus lixisenatide (estimated treatment difference: −21.2 h·pg/mL; P = 0.032).

5. Discussion and clinical relevance

The introduction of GLP-1 mimetics has provided an additional dimension to therapy for individuals with T2DM. The most recent joint position statements by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) for the personalised management of hyperglycaemia in T2DM acknowledged that GLP-1 RAs have a low risk of hypoglycaemia and the possibility for weight loss [56]. Since 2009, the clinical evidence base and clinical experience with GLP-1 RAs has expanded dramatically and these agents are now being prescribed widely in combination with other oral agents and basal insulin. Although the GLP-1 agents share the same basic mechanism of action, differences in pharmacokinetics translate into important differential effects on parameters of glycaemic control and effects beyond glycaemic control (Fig. 1). Both exenatide twice daily and lixisenatide once-daily prandial are associated with relatively large, dose-dependent reductions in PPG, as originally described in Phase II dose-finding studies. In randomised trials, consistent, pronounced reductions in PPG are apparent with both agents. These agents could therefore be considered as prandial GLP-1 RAs.
For exenatide twice daily, 2-h PPG reductions from baseline varied between 1.7 and 6.6 mmol/L according to whether subjects were concurrently receiving no treatment or additional OADs alone or in various combinations. The addition of exenatide twice daily to insulin glargine reduced the SMBG-reported 2-h post-breakfast excursion by 2.0 mmol/L [26]. Lixisenatide once-daily prandial achieved reductions in 2-h PPG of 5.5 to 6.2 mmol/L from baseline in patients either receiving no background treatment or metformin ± SU. For those receiving lixisenatide on top of basal insulin, the 2-h PPG reductions ranged from 3.1 (GetGoal-Duo-1) to 8.0 mmol/L (GetGoal-L-Asia). The more modest reduction in (GetGoal-Duo-1) probably also reflects the relatively better overall glycaemic control in this population at baseline (HbA1c 7.6% at randomisation) [46]. Unfortunately, no comparative PPG values were recorded in the GetGoal-X head-to-head comparison between exenatide and lixisenatide [47].

In the direct comparison between exenatide twice daily and exenatide once weekly, the twice-daily dose produced less of an effect on PPG but superior reductions in PPG versus the once-weekly dose [28]. The inhibition of gastric emptying was greater with exenatide twice daily, resulting in blood glucose $C_{\text{max}}$ and an AUC reduction of 21% and 20%, respectively, versus 5% and 4%, respectively, with exenatide once weekly. The sustained elevated plasma concentrations of exenatide reported with the once-weekly formulation induce tachyphylaxis – that is, progressive loss of inhibition of gastric emptying [57]. The slowing of gastric emptying is a key factor related to the reduction in PPG with exenatide twice-daily dosing, which maintains its inhibition of gastric emptying owing to the acute and short-lived peak GLP-1 concentrations that are observed post-administration.

Comparison of exenatide twice daily and liraglutide once-daily provides evidence of differences between the prandial and non-prandial GLP-1 RAs on FPG and PPG, with a superior FPG reduction being achieved with liraglutide and a superior lowering of PPG by exenatide twice daily [34]. There are no data available that directly compare the effects of exenatide and liraglutide on post-prandial plasma insulin or glucagon concentrations.

The comparison between liraglutide once-daily and lixisenatide once-daily further illustrates how pharmacodynamic differences may bring about this preferential PPG-lowering effect of the short-acting agents [55]. Lixisenatide prevented the PPG rise during the test meal, with the 2-h post-meal values being lower even than the fasting values, suggesting the possible contribution of additional factors beyond the delayed gastric emptying effect of lixisenatide, such as glucagon suppression following the test meal. This finding was accompanied by a significant lowering of the post-prandial insulin AUC (Fig. 4) [55].

Recent evidence has suggested that the rapid tachyphylaxis of the inhibition of gastric emptying by continuous infusion of GLP-1 is mediated through adaptation of the autonomic nervous system via the vagus nerve, but this effect does not seem to extend to the islet hormone response [57].

5.1. Clinical relevance

There is evidence that both FPG and PPG are independent predictors of cardiovascular disease [58], and a strong physiological and pharmacological rationale exists for combining insulin and GLP-1 RAs in T2DM. Given the substantial effect of lixisenatide on PPG, the multicentre ELIXA study
(NCT01147250) will determine the future potential of lixisenatide once-daily prandial in preventing cardiovascular events in patients with T2DM [59]. In clinical practice, insulin is the most consistent blood glucose-lowering therapy but is subject to the combined risk of hypoglycaemia and weight gain. By contrast, GLP-1 RAs are reliant on residual beta-cell function to normalise the blood glucose to complement their other actions on gastric emptying and insulin sensitivity via weight loss.

GLP-1 RAs are useful in addressing fasting/pre-prandial hyperglycaemia. Combining the complementary actions of basal insulin and incretin therapies, especially the prandial GLP-1 RAs, is therefore logical, to address both the fasting/pre-prandial hyperglycaemia and PPG excursions and to minimise the risk of hypoglycaemia and weight gain.

The ADA/EASD position statement acknowledges the addition of short-acting insulin at mealtimes to correct PPG excursions due to the loss of beta-cell responsiveness to a nutrient challenge [56]. Although achieving equivalent glycaemic control to basal insulin, prandial insulin places the individual at a greater risk of hypoglycaemia and weight gain and, consequently, a poorer quality of life. GLP-1 RA-based therapies now provide the opportunity to use a lower dose of insulin in an attempt to reduce the risk of hypoglycaemia, which, along with the weight-reducing property of the GLP-1 RAs, negates any potential weight gain as a direct consequence of the insulin therapy.

HbA1c elevation is due to multiple defects and, if individuals have achieved target FPG, persistently abnormal HbA1c is likely to be corrected by agents with a biological action that targets PPG. The ability of a GLP-1 RA to decrease HbA1c for most individuals, who were previously unable to achieve a target HbA1c level <7% on optimised basal insulin therapy, confirms the need to address both FPG and PPG. There remains debate regarding the individual contribution of post-meal and post-challenge glycaemia to cardiovascular risk and other outcomes, such as retinopathy and cognitive dysfunction, but the relative contributions of FPG and PPG to overall glycaemia have been clarified [60]. For those individuals with suboptimal glycaemic control on OADs, fasting hyperglycaemia dominates over a wide range of HbA1c levels. However, in individuals on titration-intensified basal insulin therapy, PPG contributes approximately 50% to the overall glycaemic burden in those with HbA1c 7.5–7.9%.

The different pharmacological profiles of the GLP-1 RAs contribute to the differential impact on FPG and PPG levels, suggesting that the selection of a GLP-1 RA should be guided by the predominant dysglycaemic state according to blood glucose monitoring. In addition, although overall glycaemic control is the treatment aim for all T2DM patients, the decision to use short- or long-acting GLP-1 RAs may be partly dependent on the T2DM disease profile. The contribution of FPG and PPG hyperglycaemia to overall glycaemic control changes with disease progression, with PPG excursions contributing more to hyperglycaemia in patients with moderate T2DM, and PPG excursions contributing more in later-stage T2DM [61]. For patients where FPG is the primary treatment goal, long-acting non-prandial GLP-1 RAs may be more suitable, whereas short-acting prandial GLP-1 RAs have a stronger reducing effect on post-prandial glucose levels owing to their effect on delaying gastric emptying. Thus, short-acting prandial GLP-1 RAs may be more suitable for moderate hyperglycaemia, mainly due to elevated PPG, whereas long-acting non-prandial GLP-1 RAs may be more effective in patients with pronounced hyperglycaemia, mainly due to elevated FPG; additional studies are necessary to further investigate this [62].

Further studies are ongoing to examine more fully the glycaemic impact of the differential FPG:PPG effect seen with GLP-1 RAs. In this respect, lixisenatide 20 μg once-daily prandial is currently being compared with liraglutide 1.2 mg once-daily or 1.8 mg once-daily for reducing PPG during a standardised breakfast meal test after a period of 8 weeks in individuals with T2DM who are inadequately controlled with insulin glargine ± metformin (ClinicalTrials.gov number NCT01596504).

The administration of a prandial agent (exenatide twice daily and lixisenatide once-daily) is linked to a meal, whereas the administration of a non-prandial agent is not linked to meal timing. Once-daily usage was confirmed in a dose-ranging study of four doses and two regimens, where a 20 μg once-daily dose of lixisenatide showed the best efficacy-to-tolerability ratio differentiation, where it was found to be equally effective compared with the twice-daily dose given before the meal. For this reason, the once-daily dose before breakfast was selected for the Phase III programme [63]. The convenience of dosing regimens make treatment with long-acting, non-prandial, once-weekly GLP-1 RAs and short-acting once-daily prandial GLP-1 RAs an attractive option for T2DM patients with varying daily routines, and increases the likelihood of patient treatment compliance. Where patient weight control is an issue, long-acting non-prandial GLP-1 RAs have a marginally greater effect on weight loss than short-acting prandial GLP-1 RAs. Short-acting prandial GLP-1 RAs, however, are ideally suited in patients receiving basal insulin for whom weight gain is not acceptable. The strong reducing effect on PPG levels by short-acting prandial GLP-1
RAs complements the FPG reducing ability of basal insulin, while having a beneficial effect on weight.

GLP-1 RAs exhibit differences in their safety profiles, with short-acting GLP-1 RAs having slightly higher gastrointestinal side effects compared with long-acting GLP-1 RAs, specifically transient nausea and vomiting [64]. In a head-to-head trial of exenatide once weekly versus exenatide twice daily, 50% of the patients receiving exenatide twice daily reported nausea versus 39% of those receiving exenatide once weekly [28].

In conclusion, GLP-1 RAs address several pathophysiologic abnormalities that are characteristic of T2DM. Both the prandial (exenatide and lixisenatide once-daily prandial) and non-prandial GLP-1 RAs (liraglutide, exenatide once weekly, albiglutide and semaglutide) offer many benefits; however, there are important differences. Short-acting preparations predominantly reduce PPG as a result of a delay in gastric emptying and are not subject to tachyphylaxis due to the intermittency of exposure and thus may be defined as “prandial”. The emerging clinical trial data on the combination of prandial GLP-1 RAs (exenatide and lixisenatide) given with basal insulin (insulin glargine, insulin detemir and NPH insulin) to address PPG excursions suggests an important new treatment option for individuals with T2DM.

Disclosure of interest

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L. Monnier has no conflicts of interest to declare in relation to this review.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2013.09.004.

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