REVIEW

Exploiting the antidiabetic properties of incretins to treat type 2 diabetes mellitus: glucagon-like peptide 1 receptor agonists or insulin for patients with inadequate glycemic control?

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Abstract

Type 2 diabetes mellitus is associated with progressive decreases in pancreatic β-cell function. Most patients thus require increasingly intensive treatment, including oral combination therapies followed by insulin. Fear of hypoglycemia is a potential barrier to treatment adherence and glycemic control, while weight gain can exacerbate hyperglycemia or insulin resistance. Administration of insulin can roughly mimic physiologic insulin secretion but does not address underlying pathophysiology. Glucagon-like peptide 1 (GLP-1) is an incretin hormone released by the gut in response to meal intake that helps to maintain glucose homeostasis through coordinated effects on islet α- and β-cells, inhibiting glucagon output, and stimulating insulin secretion in a glucose-dependent manner. Biological effects of GLP-1 include slowing gastric emptying and decreasing appetite. Incretin mimetics (GLP-1 receptor agonists with more suitable pharmacokinetic properties versus GLP-1) significantly lower hemoglobin A1c, body weight, and postprandial glucose excursions in humans and significantly improve β-cell function in vivo (animal data). These novel incretin-based therapies offer the potential to reduce body weight or prevent weight gain, although the durability of these effects and their potential long-term benefits need to be studied further. This article reviews recent clinical trials comparing therapy with the incretin mimetic exenatide to insulin in patients with oral treatment failure, identifies factors consistent with the use of each treatment, and delineates areas for future research.

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Introduction

Type 2 diabetes mellitus (T2D) causes substantial mortality, morbidity, and healthcare expenditures (1). T2D results when insulin secretion by the endocrine pancreas fails to compensate for insulin resistance in peripheral tissues. Once T2D has been diagnosed, β-cell function is reduced by up to 50% (2, 3). Achieving tight glycemic control reduces risks of vascular complications. Epidemiologically, for every 1% increase in hemoglobin A1c (HbA1c) above 5.0%, there is a 20% rise in cardiovascular risk (4). There is no evident threshold below which decreases in mean HbA1c values are not associated with further reductions in vascular risk (5–8).

Given the progressive nature of β-cell dysfunction (9), treatments often escalate, with lifestyle modifications (diet and exercise) giving way to monotherapy with an oral hypoglycemic agent (OHA), then combination of OHA regimens (10, 11). Under conventional treatment paradigms, insulin is introduced when OHAs fail to maintain adequate glycemic control. However, some insulin regimens and other therapies may not always adequately control postprandial glucose (PPG) excursions and may be associated with hypoglycemia and/or weight gain (12–16). Fear of hypoglycemia is considered a barrier to treatment adherence and overall glucose control (17, 18) and has been associated with reduced patient-reported well-being and perceived health status (19). Weight gain may be particularly undesirable, in that up to 80% of patients with T2D are overweight or obese (20, 21), and increasing obesity may worsen insulin resistance and otherwise increase cardiovascular risk and disease burden (22–25). Finally, neither any available OHA nor insulin effectively counters the 'steady, relentless decline in pancreatic (β-cell) function' (26, 27) associated with T2D.

Given these factors, there is an interest in therapies that are weight neutral (or promote weight loss in overweight patients), minimize the risk of hypoglycemia, and exploit physiologic mechanisms to modify T2D. Before the advent of agents exploiting the entero-insular (incretin) axis, only half of Unger's bihormonal (i.e., insulin and glucagon) hypothesis (28) of T2D pathophysiology had been addressed. Through the coordinated actions of glucagon and insulin, the healthy endocrine pancreas maintains glucose homeostasis, preventing both hyper- and hypoglycemia (29).

Incretins, including glucagon-like peptide 1 (GLP-1), are hormones released by entero-endocrine cells in the gut in response to meals. GLP-1 helps to maintain glucose homeostasis through concerted effects on islet α- and β-cells. Glucose-dependent insulinotropic polypeptide (previously termed gastric inhibitory polypeptide, GIP) and GLP-1 stimulate insulin secretion in a glucose-dependent manner (i.e., only in the presence of raised blood glucose). GLP-1 stimulates insulin secretion in a glucose-dependent fashion and can inhibit glucagon secretion, lower plasma glucose and HbA1c, inhibit gastric emptying, and decrease appetite and energy intake (30–34).

These and other findings have helped to spawn the development of incretin mimetics. Given the pivotal role of β-cell dysfunction in the progressive nature of T2D, the fact that certain incretin mimetics promote β-cell replication/neogenesis/mass in animal models is promising from the standpoint of modifying the pathophysiology of this condition (35, 36). The fact that incretin mimetics may help to enhance glycemic control as well as provide weight loss (or a weight-neutral profile) is also promising for many of the T2D patients who are overweight or obese.

This article focuses on endogenous incretins, provides an overview of current and emerging incretin mimetics, reviews data comparing treatment with the incretin mimetic exenatide or with insulin, identifies patient factors consistent with the use of incretin mimetics or insulin, and identifies potential areas for future clinical research. Although certain oral incretin enhancers (dipeptidyl peptidase 4 (DPP-4) inhibitors), such as sitagliptin and vildagliptin, are effective and well-tolerated agents that improve glycemic regulation, these medications have not been evaluated as alternatives to insulin therapy and are not included in the present article (for recent reviews, see Drucker (37) and Åhren (38)).

Incretins in physiologic perspective

Nutrient intake triggers the secretion of gastrointestinal (GI) hormones that play a part in regulating gut and gallbladder motility, digestive enzyme secretion, and postprandial carbohydrate metabolism. Incretin hormones stimulate secretion of insulin by the endocrine pancreas. Through the actions of these hormones, enteral nutrition results in a more potent insulinotropic stimulus compared with an isoglycemic i.v. challenge and this has been termed the 'incretin effect' (39–41).

GLP-1 is a 30-amino acid peptide synthesized and secreted by L-cells mainly within the distal small intestine (ileum) in response to meal intake; it exerts potent effects on GI motility and islet secretory activity, such as delaying gastric emptying and increasing β-cell secretory activity and reducing α-cell secretory activity. GLP-1 exists principally as an amidated form (GLP-1 (7–36) amide) and also as a glycine-extended form

(GLP-1 (7–37)) (42), although both forms have similar biological properties and are equipotent as incretins (43). GIP is a 42-amino acid peptide generated by K cells in the proximal small intestine (duodenum and jejunum), although there is considerable colocalization of GLP-1- and GIP-secreting cells as well as entero-endocrine cells secreting both GLP-1 and GIP (44, 45).

The effects of GIP and GLP-1 on glycemic regulation are transduced via widely distributed specific G-protein-coupled receptors, which can increase intracellular cAMP and calcium concentrations for signal transduction (46). Activation of GIP receptors, which are mainly expressed on islet β-cells, adipocytes, and cells in the central nervous system (CNS), among other actions, helps to prevent apoptosis and foster survival of human β-cells (47).

Activation of GLP-1 receptors amplifies these effects on glycemic regulation, as well as decreasing glucagon secretion, slowing gastric emptying, promoting a sense of satiety, and reducing caloric intake. Potentially beneficial effects of physiologic incretins (and incretin mimetics) on body weight may be mediated through effects on the CNS and adipocytes. Administration of GLP-1 into the cerebral ventricles of rats sharply decreased their energy intakes (48). These effects may have been mediated by interactions of central GLP-1 (released from non-catecholaminergic neurons in the solitary tract nucleus (49)) with hypothalamic and extrahypothalamic nuclei in the brain, as well as via peripheral GLP-1, which can reach the area postrema and subfornical organs with access to hypothalamic centers controlling energy intake (50).

Receptors for glucagon and physiologic incretins (e.g., GIP) are present on adipocytes in animals, but it is not clear if they are also present on human adipocytes; these receptors may play a role in fat metabolism, with GIP promoting lipolysis (51–56). These receptors are down-regulated in certain animal models of T2D. GIP may promote lipolysis partly by stimulating lipoprotein lipase receptors on adipocytes (57).

In addition to increased energy intake and adiposity, many physiologic defects associated with T2D can be addressed via GLP-1 and pharmacotherapies (incretin mimetics and enhancers) derived from the entero-insular axis (Fig. 1) (46). However, GLP-1 itself has a short plasma half-life and is not well suited to intermittent administration.

Overview of current and emerging therapies exploiting the entero-insular axis: incretin mimetics

The insulinotropic effects of GIP are attenuated in patients with T2D, who may experience postprandial elevations in circulating glucagon secondary to reduced postprandial suppression of glucagon by insulin within the endocrine pancreas; these findings are based in part on early work by Samols and colleagues on intra-islet endocrine regulation (58, 59). Therefore, pharmacologic strategies that exploit
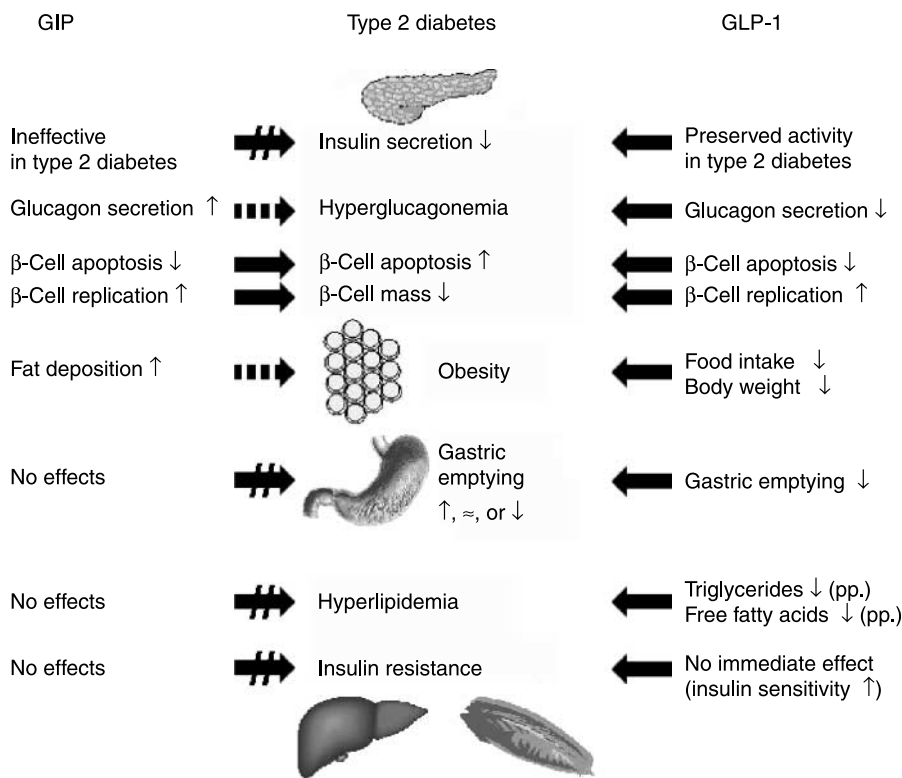
Figure 1 Biological actions of the incretin hormones GIP and GLP-1 addressing central aspects of the pathophysiology of type 2 diabetes. Actions considered to be potentially beneficial for patients with type 2 diabetes are shown as solid arrows, potentially harmful as dashed arrows, and without effect as slashed arrows. Overall, GLP-1 in many aspects exerts biological activity that may be considered therapeutic for patients with type 2 diabetes. For more details and references, see review by Drucker & Nauck (46). GLP-1, glucagon-like peptide 1; GIP, glucose-dependent insulinotropic polypeptide (gastric inhibitory peptide); pp., postprandial.

the entero-insular axis have centered on GLP-1. Incretin mimetics include exenatide (Byetta, Amylin Pharmaceuticals, San Diego, CA, USA; Eli Lilly), a 39-amino acid peptide amide previously termed AC2993 (60–72). Other incretin mimetics include the investigational agents liraglutide (73–78), which is also known as NN2211 (Novo Nordisk, Bagsvaerd, Denmark), and a human recombinant GLP-1-albumin conjugate (known as albugon; GlaxoSmithKline, Human Genome Sciences) (79, 80) and the GLP-1 receptor agonist ZP10 (Sanofi-Aventis, Bridgewater, NJ, USA), of which a prolonged-release formulation is being investigated.

Exenatide

Exenatide is the name for a synthetic product identical to exendin-4, a peptide discovered and named by Raufman and Eng because it was isolated from an exocrine (salivary) gland of lizards (*Heloderma* species) but exerted endocrine effects when administered to mammals (43, 81). This GLP-1 receptor agonist shares $\sim 50\%$ sequence identity with mammalian GLP-1 but is DPP-4-resistant and longer lived (mean $t_{1/2} = 3.3$–4.0 h (82)) with plasma concentrations remaining elevated for up to 6 h after an s.c. injection (67, 82, 83).

Placebo-controlled clinical trials involving s.c. exenatide 5–10 μg administered before breakfast and dinner have evaluated the efficacy and tolerability of exenatide plus OHAs compared with OHAs alone, including metformin (84), sulfonylureas (85), and sulfonylureas together with metformin (86) for ≥ 16 weeks. These studies involved a total of 1680 patients, most of whom were men and Caucasian, with mean ages ranging from 53 to 59 years and HbA1c from 7.9 to 8.6% (26). In an analysis of exenatide, 10 μg treatment twice daily together with metformin and/or a sulfonylurea in individuals with T2D and suboptimal glycemic control on OHAs (mean HbA1c = 8.2%), 217 patients completing 3 years of therapy had a sustained reduction of 1.0% in HbA1c (87). Weight loss from baseline was progressive, reaching 5.3 kg at 3 years ($P < 0.0001$ versus baseline and versus 30 weeks) in these patients (baseline mean body mass index (BMI) = 33.5 kg/m^2). However, only a highly selected subgroup of patients was followed up for 3 years.

The foregoing findings were from an open-label extension study involving patients receiving only exenatide twice daily. However, other clinical data are available to compare the effects of exenatide with placebo on body weight. In 30-week-controlled clinical trials

involving patients with BMI values of 27–45 kg/m^2, treatment with exenatide 10 µg twice daily resulted in a mean weight loss of 1.6–2.8 kg compared with a mean loss of 0.6–0.9 kg on placebo ($P \leq 0.05$ for each comparison of active treatment versus placebo) (84–86). Decreases in body weight tended to be somewhat more pronounced in patients with baseline BMI $\geq$ 30 compared with < 30 kg/m^2 (84).

Across a number of studies (84–86), the weighted mean difference for the absolute change in HbA1c with exenatide compared with placebo was statistically significant at −1.0 percentage point (95% confidence interval (CI) = −1.2 to −0.8%) (26). Other weighted mean differences for exenatide (versus placebo) based on a recent systematic review and meta-analysis included a significant 4.2 risk ratio for achieving HbA1c < 7.0%, an ∼1.5 mmol/l (27 mg/dl) decrease in fasting glucose (FG), and a 1.4 kg decrease in body weight (26). In these studies, nausea occurred in 36 to 51% of patients receiving exenatide but was typically mild or moderate, declined in frequency after the first 2 months of treatment, and infrequently (in ∼5 to 6% of patients) led to treatment discontinuation (84–86).

As with exogenous GLP-1, adverse effects associated with exenatide were chiefly of GI origin, including nausea (and, less frequently, vomiting), which was mostly mild or moderate and typically occurred soon after treatment was initiated or doses increased. However, these adverse effects have resulted in relatively few patients discontinuing exenatide; for instance, in three studies, the proportion of exenatide-treated patients who discontinued because of nausea ranged from ∼5 to 6% during exenatide treatment for 30 weeks to 2 years (84, 85, 88). The incidence of nausea can be reduced via progressive (stepwise) escalation of exenatide doses (89). The frequency of detectable (mostly low; e.g., 1:5–1:125) anti-exenatide antibody titers at any time during exenatide treatment ranged from 41 to 67%, without clinical significance in terms of effects on glycemic control or adverse events (84–86). Placebo-adjusted frequencies of hypoglycemia ranged from 0 to 33% and were generally lower (not different from placebo) in studies using metformin as background therapy; in one such study, the incidence of hypoglycemic episodes (all mild to moderate) was 5.3% in patients receiving 10 µg exenatide, 4.5% in those receiving 5 µg exenatide, and 5.3% in those receiving placebo (all twice daily) (84). Severe hypoglycemia was very infrequent, occurring in one patient in one study (86) and no patients in two other studies (84, 85). However, when exenatide was used with sulfonylureas, the incidence of hypoglycemia increased with improving glycemic control (i.e., lower HbA1c and glucose concentrations) (85).

Liraglutide

As an incretin analog with a $t_{1/2} = 10$–14 h, which is administered once daily, liraglutide is an acylated GLP-1 analog that can bind non-covalently to albumin (78, 90).

In a European study of 165 patients with T2D recently reported by Vilsbøll *et al.* (91), administration of s.c. liraglutide monotherapy once daily (in the evening) for 14 weeks significantly reduced HbA1c, FG, and body weight. Absolute changes in HbA1c were 0.29 percentage point for placebo, −0.98 percentage point for liraglutide 0.65 mg/day, −1.40 percentage points for liraglutide 1.25 mg/day, and −1.45 percentage points for liraglutide 1.90 mg/day (each $P < 0.0001$ versus placebo), +0.3% for placebo, −1.0% for liraglutide 0.65 mg/day, −1.4% for liraglutide 1.25 mg/day, and −1.4% for liraglutide 1.90 mg/day (each $P < 0.0001$ versus placebo). At each dose of liraglutide, FG decreased significantly compared with placebo ($P < 0.0001$). Treatment with liraglutide at the highest dose also significantly decreased fasting glucagon levels and increased the proportions of patients achieving HbA1c < 7% (46% for 1.90 mg/day versus 5% for placebo) and 90-min PPG < 10 mmol/l (180 mg/dl): 46 to 56% for the three meals with liraglutide compared with 15 to 23% with placebo. Liraglutide treatment at each dose was associated with a decrease in body weight, which achieved statistical significance (versus placebo) in the 1.90 mg/day treatment arm: −1.2 kg ($P < 0.04$). Finally, treatment using each dose of liraglutide was associated with significant declines in the proinsulin:insulin ratio. In a previous active comparator study, adjunctive treatment using liraglutide, titrated from 0.5 to 2.0 mg/day over 5 weeks, in tandem with metformin 1000 mg twice daily significantly reduced FG by 3.9 mmol/l (70 mg/dl; $P < 0.05$) and HbA1c by 0.8% ($P < 0.05$) compared with metformin monotherapy and significantly lowered FG by 1.2 mmol/l (22 mg/dl; $P < 0.05$) and body weight by 2.9 kg ($P < 0.05$ compared with metformin together with a sulfonylurea) (74).

As with exenatide, GI symptoms (e.g., nausea, diarrhea) were the chief adverse effects and led to discontinuation in ∼3% of liraglutide patients in the recent European study (91). No patient experienced hypoglycemic episodes (major or minor), and there was no treatment-related anti-liraglutide antibody induction (91). Treatment-related induction of anti-liraglutide antibodies has not been observed in liraglutide studies to date (74, 91).

Albugon

Albugon, a recombinant human peptide-albumin derivative containing an analog of GLP-1 that resists the enzymatic activity of DPP-4, improves insulin secretion, and reduces blood glucose *in vivo* (80). Unlike the 30- to 40-amino acid incretin mimetics exenatide and liraglutide, albugon has less potent anorectic effects in animal studies, although it is not clear if the disparity is secondary to the blood–brain barrier's permeability to the smaller molecules but not to albugon (80). Neither liraglutide nor albugon has been evaluated in direct, active comparator insulin clinical trials.

Incretin mimetics or insulin for patients with T2D inadequately controlled using oral therapies

Exenatide versus insulin active comparator studies

Three published multicenter randomized studies compared 5–10 µg exenatide twice daily with insulin in patients with longstanding (>6 years since diagnosis) suboptimally controlled T2D using OHAs at stable doses: metformin and sulfonylureas in studies 1 and 3 below and metformin or sulfonylureas in study 2:

1) a 26-week open-label parallel-group trial involving 551 patients randomized to exenatide ($n=282$, mean age=59.8 years, HbA1c=8.2%, and BMI= 31.4 kg/m^2) or insulin glargine ($n=267$, mean age=58.0 years, mean HbA1c=8.3%, and mean BMI=31.3 kg/m^2) titrated by patients using a fixed-dose algorithm aiming to achieve a target FG≤5.5 mmol/l (100 mg/dl; not necessarily achieved in all subjects) (92)
2) a 16-week open-label crossover non-inferiority study (93) involving 138 patients (intent-to-treat (ITT) population; mean age=55 years, HbA1c=9.0%, and BMI=31 kg/m^2) treated with either exenatide or insulin glargine for 16 weeks with weekly dose adjustments using a forced-titration algorithm (14) aiming to achieve a target FG≤5.5 mmol/l (100 mg/dl; not necessarily achieved in all subjects)
3) a 52-week open-label parallel-group non-inferiority study involving 501 patients randomized to exenatide ($n=253$, mean age=59 years, HbA1c=8.6%, and mean BMI=30.6 kg/m^2) or premixed biphasic insulin aspart (30/70), with the recommendation to titrate to acceptable glycemic control but without a forced-titration algorithm in 248 patients (mean age=58 years, HbA1c=8.6%, and BMI=30.2 kg/m^2), each of which was administered before the morning and evening meals (94).

In these trials, patients were required to have stable body weights (not varying by >10%) for ≥3 months before screening, HbA1c ranging from 7.0 to 11.0% at the time of screening (upper limit: 10% in one study (92)), BMI ranging from 25 to 45 kg/m^2 (40 kg/m^2 in one study (93)) at screening, as well as ≤3 episodes of severe hypoglycemia within 6 months before screening. Exclusion criteria included the use of insulin, thiazolidinediones, α-glucosidase inhibitors, meglitinides, or weight loss medications within the prior 3–6 months.

Overview of efficacy

Exenatide versus insulin glargine studies In the parallel-group study (92), HbA1c decreased significantly from baseline with each treatment (by 1.1%), and proportions of patients achieving HbA1c≤7.0% at treatment week 26 were also similar in the two treatment groups: 46% (exenatide) and 48% (insulin). However, body weight progressively declined through treatment week 26 (−2.3 kg; −2.6%) in the exenatide group while progressively increasing (+1.8 kg; +2.0%; $P<0.05$ between-group) in the insulin group. Weight reduction tended to be more marked in patients experiencing nausea or vomiting (versus none) and/or longer durations of nausea on exenatide, but significant weight loss (−1.9 kg; −2.2%) occurred even in patients reporting no episodes of nausea (92, 93).

Both treatments significantly lowered blood glucose, but the decrease in FG was significantly greater in patients receiving insulin (−2.9 mmol/l; −52 mg/dl) compared with exenatide (−1.4 mmol/l; −25 mg/dl), as was the proportion of patients achieving a FG value <5.5 mmol/l (100 mg/dl); 21.6% insulin versus 8.6% exenatide; $P<0.001$. According to self-monitored blood glucose (SMBG) profiles, the mean daily blood glucose values were similar in the exenatide (8.1 mmol/l, 146 mg/dl) and insulin (8.0 mmol/l, 144 mg/dl; $P>0.05$) groups. However, patients receiving exenatide had significantly lower PPG excursions. On the other hand, fasting, premeal, and 0300 h glucose values were significantly lower in the insulin glargine group (92).

In the open-label crossover non-inferiority study (93), with results evaluated for the ITT population, both treatments lowered HbA1c significantly from baseline, by 1.4% ($P=0.92$ between-treatments). Based on a 0.01% between-treatment group difference, exenatide was confirmed to be non-inferior to insulin glargine, in that the upper limit of the 95% confidence interval was below the *a priori* margin of 0.4%. Similar proportions of patients achieved HbA1c≤7% with each treatment: exenatide (38%) and insulin glargine (40%). However, a higher proportion of patients in the exenatide group (22%) achieved the treatment target (95) of HbA1c< 6.5% compared with insulin glargine (14%; $P=0.056$). While receiving exenatide, patients experienced significant weight loss (−1.6 kg) compared with a mild weight gain on insulin glargine (least-square mean difference=−2.2 kg). Two-hour PPG excursions were significantly attenuated with exenatide (versus insulin glargine), whereas mean FG values were significantly lower in the insulin group.

On the other hand, replacing insulin treatment with exenatide therapy in patients already receiving insulin does not seem to be advisable, on the basis of findings from a recent pilot study (96, 97).

Exenatide versus premixed biphasic insulin In this parallel-group non-inferiority study, both exenatide (−1.0%) and premixed biphasic insulin aspart (−0.9%; $P=0.069$ versus exenatide) significantly lowered HbA1c from baseline to treatment week 52, with more marked

effects of exenatide on PPG and biphasic insulin aspart on preprandial glucose (94). A significantly higher proportion of exenatide patients (18.3%) achieved HbA1c < 6.5% compared with the insulin group (8.6%; $P=0.0022$). Paralleling findings from the previous exenatide–insulin comparative study (92), body weight declined progressively with exenatide and increased with insulin. The mean change from baseline to week 52 in body weight was -2.5 kg (-2.9%) in the exenatide group and $+2.9$ kg ($+3.5$%) in the biphasic insulin aspart group ($P<0.001$), and the between-treatment disparity was significant at each visit (94). Consistent with the study reported by Heine *et al.* (92), both treatments reduced fasting serum glucose measurements from baseline to endpoint. According to SMBG profile data, both treatments reduced FG and PPG at each time point, with exenatide being generally superior to insulin in lowering PPG and insulin being generally superior to exenatide in lowering FG. At treatment week 52, patients receiving insulin had significantly ($P<0.04$) lower preprandial glucose levels, whereas patients receiving exenatide had significantly ($P<0.002$) lower PPG excursions and/or percent reductions in PPG excursions (94).

In a recent systematic review and meta-analysis, the weighted mean difference in body weight with exenatide (versus insulin) was -4.8 kg (95% CI = -6.0 to -3.5), whereas weighted mean differences in the proportions of patients achieving HbA1c < 7% were not significant between the exenatide and insulin groups (26).

Overview of adverse events/tolerability As in studies in which exenatide was compared with OHAs and/or placebo, exenatide use in the insulin comparator studies was associated with GI-related symptoms as the leading adverse events. These included mild or moderate transient nausea, which occurred in > 50% of patients in one study (92) and 43% in another (93), as well as vomiting, diarrhea, abdominal pain, and/or anorexia/ decreased appetite. In the crossover non-inferiority study, 9.6% of patients reported vomiting on exenatide compared with 3.1% on insulin glargine (93). GI effects led < 6% of patients to discontinue treatment (92, 94). In the recent systematic review and meta-analysis, the risk ratio of nausea in patients receiving exenatide compared with all comparators (including insulin, OHAs, and placebo) was 3.2 (95% CI = 2.2–4.6), vomiting 3.5 (95% CI = 2.6–4.7), and diarrhea 2.3 (95% CI = 1.8–2.9) (26). Among individuals in the exenatide groups within the two parallel-group insulin comparator studies, frequencies of severe nausea (4.6%), discontinuations because of adverse events (9.6%), and discontinuations because of GI adverse events (5.1%) were higher than in the insulin groups (< 1.0% for each) (92, 94).

Based on the recent systematic review and meta-analysis (35), the risk ratio for hypoglycemia was ∼1.0 in patients randomized to exenatide or insulin in the parallel-group comparator studies (relative risk (RR) = 1.0; 95% CI = 0.5–2.3) (26, 92, 94). Overall incidences of hypoglycemia were similar in the exenatide (7.3 events/patient–year) and insulin glargine (6.3 events/patient–year; $P>0.05$) treatment arms in the earlier study (92), as well as in the exenatide (4.7 events/patient–year) and biphasic insulin aspart (5.6 events/patient–year) arms in the latter study (94). In the crossover non-inferiority study, the overall incidences of hypoglycemia were ∼15% in patients on exenatide compared with 25% on insulin glargine treatment (93). In the exenatide/insulin glargine parallel-group comparative study, four patients in each treatment group (1.4 to 1.5%) reported severe hypoglycemia, but none of these episodes required medical treatment or led to treatment withdrawal (92). In the exenatide/insulin open-label glargine crossover non-inferiority study, three patients (∼4%) reported eight episodes of severe hypoglycemia on insulin glargine without treatment discontinuation or dose reduction), while no patient experienced severe hypoglycemia on exenatide treatment (93). In the exenatide/biphasic insulin aspart comparative study, no patients receiving exenatide or insulin reported severe hypoglycemia (94).

The risk of hypoglycemia with exenatide seemed to be largely a function of background OHA treatment. That is, co-administration of exenatide with OHAs not associated with hypoglycemia does not seem to increase the risk of this adverse effect. When sulfonylurea doses were reduced, the incidence of hypoglycemia decreased from 26.9 to 6.1 events/patient–year in the exenatide–biphasic insulin aspart comparator study (94). In the crossover insulin glargine comparator study, incidences of hypoglycemia were similar in patients receiving adjunctive sulfonylureas with exenatide or insulin glargine (30% versus 35%, respectively), which were in turn higher than values for patients receiving adjunctive metformin with either treatment (exenatide + metformin 3% versus insulin glargine + metformin 17%; $P=0.01$) (93). Frequencies of anti-exenatide antibodies ranged from 43% (92) to 45% (94) in the two parallel-group exenatide–insulin comparator studies.

In 2006, a case of acute pancreatitis was reported in a patient with T2D, who was receiving treatment with exenatide and neutral protamine Hagedorn insulin (98). Recently, the US Food and Drug Administration reviewed 30 post-marketing reports of acute pancreatitis in patients taking exenatide. An association between exenatide and acute pancreatitis has been suspected in some of these cases (99); however, it is not clear that the incidence of acute pancreatitis in patients with T2D receiving exenatide is higher than expected in the overall population of such patients. Following these reports, US manufacturer labeling was updated to include the following precaution: 'Postmarketing cases of acute pancreatitis have been reported. Patients should be

informed that persistent severe abdominal pain, which may be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. If pancreatitis is suspected (exenatide) and other potentially suspect drugs should be discontinued, confirmatory tests performed and appropriate treatment initiated. Resuming treatment with (exenatide) is not recommended if pancreatitis is confirmed and an alternative etiology for the pancreatitis has not been identified' (100).

Potential clinical implications, limitations, practical considerations, and future research issues

Potential clinical implications

Compared with insulin glargine and biphasic insulin aspart, treatment with exenatide has been associated with similar decreases in HbA1c, in tandem with significant net declines from baseline in body weight, superior control of PPG excursions, and similar risks of hypoglycemia (which were highest in patients receiving concomitant sulfonylureas). In contrast, insulin treatment was associated with better control of FG elevations. The effects of exenatide may be particularly desirable in overweight or obese patients and/or those with relatively modest elevations in HbA1c, in whom PPG elevations account for a greater proportion of HbA1c than FG elevations (whereas the converse is true for those with more marked HbA1c elevations (101)). Obesity can worsen hyperglycemia, dyslipidemia, and/or insulin resistance, as well as increase the risk of hypertension, other forms of cardiovascular disease, and non-alcoholic fatty liver disease (102–106).

Mechanisms linking obesity (and central adiposity) with cardiovascular disease and mortality, including endothelial dysfunction and atherosclerosis secondary to dyslipidemia, hypertension, inflammation, and changes in the coagulation–fibrinolysis cascades, are also becoming increasingly evident (22). Improved weight management is an important treatment objective for most obese T2D patients (103). For an average loss of 5% of body weight in overweight individuals, HbA1c is expected to decline by 0.6%, and the need for hypoglycemic agents may also decrease (102).

Also promising on a more conceptual level is the finding of exenatide's and liraglutide's beneficial effects on indices of β-cell secretory function (or dysfunction). However, such effects were not assessed in all studies, and their durability is not clear.

Potential limitations

As with many studies of antidiabetic treatments, incretin mimetics and insulin were evaluated according to their effects on surrogate endpoints (e.g., HbA1c, FG, and PPG), not clinical events. In addition to the relatively short-term nature of the insulin comparator studies, the metabolic

and other effects of exenatide have not been compared with a more nearly physiologic basal-bolus approach, which might include insulin glargine (basal component) plus a rapid-acting insulin (regular insulin or analogs, bolus or prandial component). It has also been argued that the exenatide–biphasic insulin aspart study, which did not have a forced-titration design, did not fully optimize the insulin dose, and that neither exenatide–insulin parallel-group comparator study achieved a level of glycemic regulation at endpoint comparable with that achieved using insulin glargine or other insulin formulations (14, 107–109); however, this conclusion is somewhat controversial (13, 110–112), in part because of variation in baseline HbA1c and sulfonylurea use across studies.

In the exenatide–biphasic insulin aspart comparator study (94), physicians were encouraged to target both FG and PPG to attain an optimal balance between HbA1c lowering and hypoglycemic risk. In the absence of a strict dose titration schedule such as the one employed by Riddle *et al.* in the treat-to-target trial (14), it is conceivable that physicians in the exenatide comparator study used a conservative approach when administering biphasic insulin aspart to avert hypoglycemia (versus achieving optimal glycemic control), resulting in lower than optimal insulin doses (94, 110). On the other hand, the use of exenatide and premixed insulin in this study should have closely reflected their real-world use.

Other potential limitations of the exenatide–insulin comparator studies center on the eligibility criteria and sociodemographic and clinical characteristics of the patient populations. These included stable body weight and an absence of recent treatments with OHAs or weight-reducing agents. Mean ages in the insulin comparator studies were below 60 years, and patients of African descent may have been somewhat under-represented.

Practical considerations

On the basis of findings considered in the present review and elsewhere, exenatide therapy can be considered as an alternative to insulin in patients with treatment failure on metformin monotherapy or on metformin together with a sulfonylurea. In the United States and Europe, exenatide is indicated as a treatment adjunct to enhance glycemic regulation in patients with T2D, who are receiving an OHA or a combination of OHAs (100, 113). Potential patient factors that are consistent or inconsistent with the use of incretin mimetics or insulin are presented in Table 1.

Future research issues

The durability of treatment effects on surrogate variables (e.g., HbA1c, PPG, body weight, and β-cell secretory function) should be further evaluated in longer term studies involving larger and more heterogeneous patient populations. For instance, it might be of interest to evaluate the use of incretin mimetics as alternatives to OHAs or

Table 1 Factors more consistent with the use of the incretin mimetic exenatide[a] rather than insulin (and vice versa)[b].

Factors more consistent with treatment using the incretin mimetic exenatide and/or inconsistent with treatment using insulin	Factors consistent with treatment using insulin and/or inconsistent with treatment using the incretin mimetic exenatide
HbA1c < 1.5 percentage point above target	HbA1c ≥ 1.5 percentage point above target
Relatively well-controlled FG concentration	High FG concentration
Primarily PPG concentration peaks	Relatively small PPG concentration peaks
Need to avoid hypoglycemia (caveat: concomitant medications)	No problems associated with hypoglycemia
Failure of measures to control body weight	Some prior success of measures to control body weight
No clinical signs of catabolism	Clinical signs of catabolism
Patient needs treatment that is simple in execution (no dose titration, timing of injection relative to meals not critical)	Patient is willing and able to execute a more complicated treatment regimen (dose titration, exact timing of injection relative to meals not critical)
Patient has little control over (varying) meal sizes, carbohydrate content	Patient has good control over (varying) meal sizes
Patient does not want to perform blood glucose monitoring	Patient is willing to perform blood glucose monitoring

[a]At this writing, the effects of treatment with other incretin mimetics (e.g., liraglutide) have not been compared directly with those of insulin treatment.
[b]These patient-related factors may need to be considered when oral hypoglycemic agents fail to achieve adequate glycemic control and a decision must be made between incretin mimetics and insulin.

insulin in patients with different stages of disease and residual β-cell function. Also of possible interest are studies to further characterize the effects of incretin mimetics on body composition, particularly central adiposity, and determine whether other potential benefits of incretin mimetics (e.g., on blood pressure) are related to, or independent of, changes in body weight. Studies comparing liraglutide, albugon, or other incretin mimetics with insulin might also be useful. Finally, although data suggest that anti-exenatide antibodies have very little impact on safety and other study outcomes (75–77), continued pharmacovigilance for antigenicity is warranted.

Conclusions

Treatment of T2D often escalates from lifestyle modifications to OHA regimens to insulin, but insulin treatment has potential limitations such as inadequate control of PPG excursions, weight gain, and hypoglycemia. Incretins, including GLP-1, help to maintain glucose homeostasis through effects on islet α- and β-cells and stimulate insulin secretion in a glucose-dependent manner. Treatment with incretin mimetics is associated with enhanced glycemic regulation (including reduced PPG excursions), concomitant reductions in (or neutral effects on) body weight, and a low risk of hypoglycemia. On the other hand, treatment with insulin appears to be more effective in lowering FG levels. When oral agents have failed to maintain adequate glycemic control, incretin mimetics may be particularly well suited to the treatment of patients who are overweight or obese, have relatively well-controlled FG with primarily PPG peaks, HbA1c within 1.5 percentage point of target, little control over meal sizes and carbohydrate contents, and prefer simple treatment without the need for glucose monitoring. However, insulin treatment may be better suited to patients with less well-controlled FG levels and small PPG peaks, HbA1c at least 1.5 percentage point above

target, control over meal sizes, and willingness to execute a more complicated treatment regimen and perform blood glucose monitoring. Incretin mimetics may help to expand the T2D clinical paradigm, more meaningfully realize Unger's 'bihormonal hypothesis' (28), and enable more effective treatment of a broader spectrum of patients.

Acknowledgements

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