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Rationale Use of GLP-1 Receptor Agonists in Patients with Type 1 Diabetes

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Abstract Clinicians and patients are rapidly adapting GLP-1 receptor agonists as efficacious and safe therapeutic options for managing type 2 diabetes (T2DM). GLP-1 receptor agonists stimulate insulin production and secretion from the pancreatic β cells in a glucose-dependent manner, improve gastric emptying, favor weight reduction, and reduce postabsorptive glucagon secretion from pancreatic α cells. GLP-1 receptor activity is impaired in patients with T2DM. GLP-1 secretion and subsequent physiologic actions in patients with type 1 diabetes (T1DM) is ill-defined. Some researchers have suggested that the use of GLP-1 receptor agonists in T1DM may reduce excessive postprandial glucagon secretion allowing patients to reduce their total daily dose of exogenous insulin. Hypoglycemia risk may also be minimized in T1DM as glucagon counter-regulation can be preserved to some degree via the glucose-dependent action of the GLP-1 receptor agonists. This paper will consider the physiologic and pharmacologic benefits of adding GLP-1 receptor agonists to therapeutic regimens of patients with T1DM.

Keywords GLP-1 receptor agonists · Type 1 diabetes · Hyperglucagonemia · Liraglutide

Introduction

The physiologic activity of the gut hormones known as incretins was initially noted in 1965. McIntyre et al. determined that the administration of oral glucose increased plasma insulin levels to a greater degree than an equimolar infusion of intravenous glucose [1]. Two hormones, gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) account for the incretin effect. GIP is secreted from the K cells of the duodenum in response to meal stimulation whereas GLP-1 originates from the L cells of the distal ileum within the colon [2•]. Incretin hormones are expressed in the pancreas, central and peripheral nervous system, heart, endothelium, kidneys, lungs, and gastrointestinal tract [3].

In euglycemic individuals, GLP-1 activation within the pancreatic β cells results in the glucose-dependent production and exocytosis of insulin [4]. Thus, insulin release occurs ONLY as β cells are triggered by a rise in ambient glucose levels. Endogenous insulin secretion will decline as plasma glucose levels fall. This will minimize the likelihood of becoming hypoglycemic due to the release of incretins.

The secretion of GIP remains relatively normal in patients with T2DM, although its hormonal action on insulin secretion is severely impaired [5•]. Although GLP-1 receptor site activity is impaired, supraphysiologic stimulation of the receptor with a pharmacologically designed equivalent analog will result in a resumption of GLP-1 hormonal expression [6]. Thus, pharmacologic efforts to develop medications that mimic the actions of GLP-1 have become a target for improving chronic hyperglycemia in patients with T2DM. Table 1 lists the glucose homeostatic actions of GLP-1 in euglycemic individuals.

Once released from the gut in response to a meal stimulus, GLP-1 and GIP are rapidly degraded by dipeptidyl peptidase-4 (DPP-4), an enzyme, which is expressed in many tissues including the liver, lung, kidney, intestines, lymphocytes, and endothelial cells [7]. The physiologic actions directed against both GLP-1 and GIP are swift and efficient. Only 60 % of the GLP-1 remains available for pancreatic β-cell receptor activation within 2 minutes of release from the L-cells of the intestines due to immediate DPP- 4 degradation [8•]. If DPP-4 were not present and active, GLP-1 release would cause hyperstimulation of pancreatic β cells resulting in islet

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Table 1 Physiologic effects of GLP-1 on glucose homeostasis in euglycemic individuals

- Stimulates production and secretion of insulin from pancreatic β cells in a glucose-dependent manner
- Slows gastric emptying
- Induces satiety, thereby reducing caloric intake
- Inhibits glucagon secretion

(Adapted with permission from: Unger J. Diagnosis and management of T2DM. In Diabetes Management in Primary Care- Second Edition. Lippincott, Williams and Wilkins. Philadelphia, PA. 2012;323–412).

hyperplasia and chronic hyperglycemia. Thus, DPP-4 serves as a means by which the body may maintain optimal glucose homeostasis in the postabsorptive state.

GLP-1 Deficiency in T2DM and the Resulting Hyperglucagonemia

Patients with prediabetes and T2DM demonstrate a significant mitigation in the insulinotropic effect of GLP-1 [5•]. Patients with T2DM also appear to downregulate their GIP and GLP-1 receptor activity resulting in resistance in incretin expression within the target tissue [8•]. Glucagon levels in T2DM paradoxically increase and are refractory to glucose administration, yet responsive to GLP-1 replacement therapy [2•].

The counter-regulatory hormone, glucagon, is secreted from pancreatic α cells positioned around the periphery of the islet in response to a hypoglycemic trigger (Fig. 1).

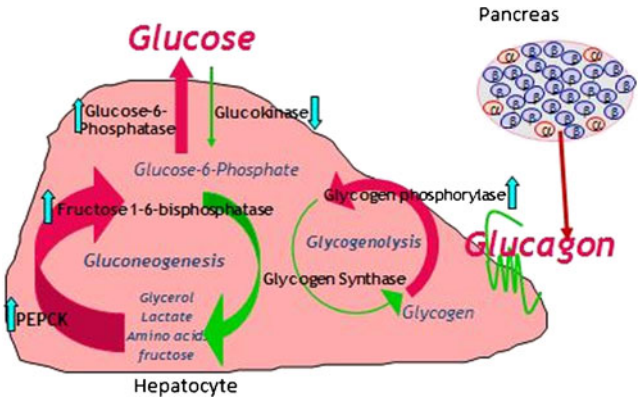

Fig. 1 The physiology of glucagon secretion and action on hepatocytes. Glucagon opposes the action of insulin in peripheral tissues, predominantly in the liver. Although meals generally suppress glucagon secretion from normal α cells, patients with diabetes exhibit disordered control of glucagon secretion leading to excess hepatic glucose production. Glucagon release is stimulated by hypoglycemia and inhibited by hyperglycemia, insulin and somatostatin. GLP-1 also inhibits glucagon secretion. Once released, glucagon increases hepatic glucose production by activating glycogenolysis and gluconeogenesis pathways. (β=pancreatic β cells, which package and secrete insulin. α=α cells, which are the site of glucagon secretion). (Adapted with permission from: Unger J. Diagnosis and management of T2DM. In Diabetes Management in Primary Care- Second Edition. Lippincott, Williams and Wilkins. Philadelphia, PA. 2012:323–412)

Patients with T2DM exhibit elevated basal (fasting) plasma glucagon concentrations and appear to be hypersensitive to the direct stimulatory effect of glucagon on hepatic gluconeogenesis [9••]. Glucagon secretion is regulated, in part, by endogenous insulin secretion. Insulin action on the liver results in storage of glycogen within the hepatocytes. Conditions which disrupt normal glucose homeostasis causing hyperglycemia such as insulin resistance, insulinopenia (as in T1DM), or an increase expression of glucagon activity within sensitized hepatocytes will augment plasma glucose concentrations. Incretin drugs, such as GLP-1 receptor agonists and DPP-4 inhibitors are efficacious in treating patients with T2DM due, in part, to their ability to mitigate the effects of hyperglucagonemia [10, 11••, 12••].

In summary, resistance to the stimulatory effects of the incretin hormones on insulin secretion and glucagon suppression suggest that GLP-1 contributes to the pathogenesis of prediabetes and T2DM. Pharmacologic augmentation of GLP-1 deficiency and resistance results in the glucose-dependent production and secretion of insulin from the pancreatic β cells. The CNS expression of GLP-1 affects satiety, which favors weight reduction. The pharmacologic and physiologic actions of incretin directed therapies for patients with T2DM make these interventions ideal interventional aids.

Pathogenesis of Type 1 Diabetes (T1DM) and Defective Hypoglycemia Counter-regulation

T1DM results from autoimmune B-lymphocyte mediated destruction of pancreatic β cells in susceptible individuals [13]. Hyperglycemia becomes clinically apparent when the number of functioning β cells drops below the threshold required to maintain euglycemia. At the time of their initial diagnosis, patients with T1DM have 20 %–30 % residual β-cell function suggesting that a potential exists for expanding their β-cell mass [14]. Clinically, 10 %–20 % of patients may enter a "honeymoon phase" following a brief, intensive period of insulin therapy, during which time insulin may be discontinued without rebound hyperglycemia [15]. Unfortunately, the autoimmune destruction of the remaining β cells continues with the pace being more rapid for younger patients [15].

Counter-regulatory response to hypoglycemia is dependent upon residual β-cell mass and function [15]. The autoimmune loss of glucose dependent β-cell insulin secretion results in a defective signaling pathway between the α and β cells. As β-cell mass and function declines further glucagon secretory function becomes unregulated. This results in hyperglucagonemia as well as defective glucose counter-regulation (hypoglycemia associated autonomic failure) [16].

The hyperglycemia experienced by patients with T1DM is due to both deficient secretion of endogenous insulin and

reduced suppression of postprandial hyperglycemia [17]. Coupled with the defective counter-regulatory response of glucagon in response to a hypoglycemic event, patients with T1DM are prone to significant glycemic variability [16, 18••]. Simply correcting the defect in insulin secretion may result in excessive dosing of the exogenous insulin in an attempt to control postprandial and fasting glucose levels. Thus, novel therapies, which target the bi-hormonal defects (insulinopenia+-hyperglucagonemia) observed in T1DM should be considered based upon their safety and efficacy profiles.

Endogenous GLP-1 Activity in Patients with T1DM

Few studies have addressed the secretion and physiologic activity of native incretin hormones in patients with T1DM. Lugari et al. [19] suggested that fasting GLP-1 levels were similar between euglycemic individuals and subjects with T1DM. However, postprandial GLP-1 secretion was virtually absent in patients with diabetes. In contrast, Vilsboll et al. [20] noted equal secretion of postmeal GLP-1 and GIP amongst C-peptide negative patients and euglycemic controls. However, fasting levels of the incretin hormones were depressed in T1DM subjects. Other authors speculate that human L-cells express insulin receptors and secrete GLP-1 in response to an insulin stimulus. Furthermore, insulin resistance could result in a loss of this negative feedback mechanism [21].

Glycemic Effect of Exogenous GLP-1 in Patients with T1DM

GLP-1 appears to exert pharmacologic effects in patients with T1DM similar to those with T2DM. Creutzfeldt et al. demonstrated that a continuous infusion of GLP-1 in patients with T1DM reduced fasting hyperglycemia from 241 mg/dL to 180 mg/dL and glucagon concentration by 50 % yet minimally increased endogenous insulin secretion [22]. To demonstrate the glucose-dependent action of GLP-1 in T1DM, a GLP-1 infusion was administered to well insulinized patients without fasting hyperglycemia [23]. The GLP-1 infusion did not influence endogenous glucagon or insulin secretion in these subjects. The glucose concentration remained constant at 144 mg/dL throughout the infusion.

The effects of prolonged use of GLP-1 on human β-cell mass and function are unclear. In vitro studies suggest that GLP-1 may activate protective while inhibit apoptotic (cell destructive) pathways promoting cellular proliferation [24••]. The physiologic and pharmacologic targets of GLP-1 usage in patients with T1DM are noted in Table 2.

Table 2 Possible physiologic and pharmacologic target actions of GLP-1 receptor agonists in T1DM patients

- Reduces paradoxical postprandial and fasting hyperglucagonemia in a glucose dependent manner
- Reduces satiety
- Increases satiety
- Favors weight loss
- Possible protection against pancreatic β-cell loss
- Delays gastric emptying
- Possibly reduces exogenous insulin dose

Clinical Applications of GLP-1 Receptor Agonists in T1DM

GLP-1 receptor agonists such as exenatide, exenatide LAR, and liraglutide are indicated as adjunctive therapy to diet and exercise in adults, age 18 and older, with T2DM. However, clinicians and patients have speculated for years about the possible benefits of using GLP-1 receptor agonists in patients with T1DM. Currently, 11 global clinical trials have been initiated, concluded, or are actively recruiting to study the safety and efficacy of liraglutide in patients with T1DM [25••]. Several investigator initiated trials have been completed and published. The manufacturers of these drugs are insistent that the GLP-1 agonists should ONLY be used for patients with T2DM.

Harrison et al. performed a retrospective chart audit of patients with T1DM at their institution [26••]. Patients were identified who were using both a GLP-1 analog (liraglutide) and an insulin pump. Those patients who had at least 1 follow-up appointment over 20 weeks were noted to have a significant decrease in weight (4.2 % from baseline) and a reduction in A1C from 7.4 % to 7.0 % (P=0.02). The aggregate total daily dose of insulin decreased 19.2 %. There was no increase in hypoglycemia. Thus, patients with T1DM were able to lose weight, improve their glycemic control on less exogenous insulin without experiencing an increase in hypoglycemia when liraglutide was added to insulin pump therapy.

Kielgast et al. treated 19 patients with T1DM (10 with residual β-cell function who were C-peptide positive and 9 without β-cell function who were C-peptide negative) to determine the effect of 4 weeks of liraglutide treatment on glycemic control [26••, 27••]. Insulin doses were optimized prior to entry into the experimental protocol (which could partially account for the reduction in A1C during this short study). Insulin doses were reduced significantly in both cohorts and patients experienced less time spent at glycemic levels<70 mg/dL on continuous glucose monitoring. The C-peptide positive patients decreased their A1C from 6.6 % to 6.4 % over 4 weeks compared with a decline from 7.5 % to 7.0 % in the C-peptide-negative group. Eighteen of nineteen patients lost weight during the study. The most common adverse event was nausea and vomiting, which occurred within the first 2–3 days of dosing and resolved spontaneously or subsequent to dose reduction. During the 4th week of the study, postprandial glucagon levels were significantly reduced, yet increased appropriately during exercise when glucose levels began to fall. This confirms that liraglutide works in a glucose dependent manner even in patients with T1DM.

Figure 2a shows the continuous glucose monitor (CGM) of a 35 year old patient with a 19 year history of T1DM. The patient has used an insulin pump for 9 years and has hypoglycemia awareness autonomic failure (HAAF). Although his A1C was 6.8 %, the patient was experiencing frequent episodes of hypoglycemia and wide intra-day glycemic variability. After being informed about the risks and possible benefits of using a GLP-1 receptor agonist (liraglutide) off-label, he began using liraglutide 0.6 mg daily. He did experience some nausea during the first week, but no vomiting. The dose was subsequently increased after 14 days to 1.2 mg/d as his total daily dose of insulin was decreased by 10 %. A repeat CGM (Fig. 2b) shows the improvement in glycemic variability after 4 weeks of liraglutide 1.2 mg/d plus continuous subcutaneous insulin infusion.

Prescribing Medications Off-Label to Patients

Good medical practice requires that providers use legally available drugs, biologics, and devices according to their best knowledge and judgement. Physicians who use a product for an off-label indication not approved in the product labeling have the ethical and professional responsibility to become well informed about the product, to base its use on firm scientific rationale, and on sound medical evidence (Table 3).The FDA does not regulate how a drug is used or

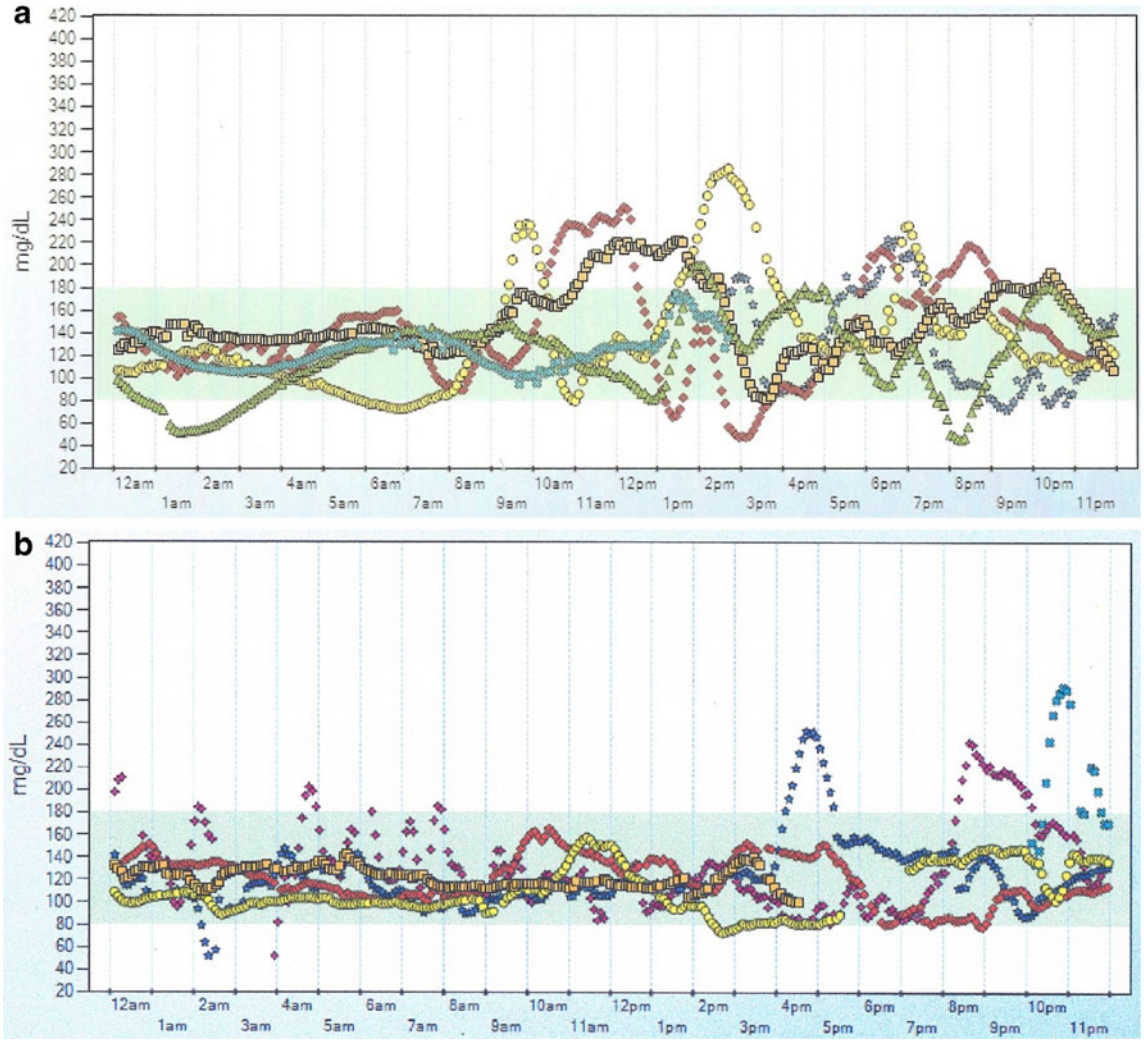

Fig. 2 **a** and **b**, Continuous glucose sensor of a 35-year-old patient with type 1 diabetes before and 4 weeks after adding liraglutide to his insulin pump therapy. The off-label use of liraglutide 1.2 mg/d in addition to rapid acting insulin delivered via continuous subcutaneous insulin infusion, improved this patient's glycemic variability, reduced his total daily insulin requirement by 10 %, reduced his frequency of hypoglycemia, and maintained his A1C of 6.8 %. (Reproduced with permission from: Unger J. Type 1 diabetes in adults. In Diabetes Management in Primary Care- Second Edition. Philadelphia, PA. Lippincott, Williams and Wilkins. 2012:413–52)

Table 3 Basis for off-label use of a drug, biologic agent, or device

1. Physician's own comfort and experience with the prescribed product
2. Peer-reviewed articles which reflect sound scientific evidence supporting off-label use of the product
3. Opinions of local, regional, and national thought leaders on off-label use of the product
4. A sincere desire to directly impart benefit to the patient to whom the off-label use is prescribed

prescribed within one's private practice. However, with each unapproved use of a product, a physician is essentially conducting his/her own clinical trial related to the drug's safety and efficacy. Yet, many of our patients with T1DM are not under satisfactory control despite being excellent diabetes self-managers. For these individuals, using a drug off label which has a "reasonable likelihood of success" and a fairly good safety profile might be considered.

Prior to initiating an off-label drug, physicians should fully inform the patient, and other family members if necessary, as to the potential risks and benefits of the prescribed intervention. Many patients will not even understand the term "off-label use." Patients must be fully informed as to both the standard of care, the reasons for needing an off-label use of a drug, and what may occur if the patient did NOT wish to participate in an off-label product initiation. Physicians will give themselves protection against liability by assuring their off-label uses are (1) made with the patient's informed consent, their disease state, and the necessity to prescribe a drug for off-label use, (2) indicate a firm commitment to directly benefit the patient with the off-label prescription, (3) acknowledge prior experience with the drug both on and off-label, (4) demonstrate a comprehensive understanding of the product through peer reviewed and evidence-based literature, and (5) explain that the choice reflects the general opinion expressed by other clinicians in the specialty [28].

As with all therapies introduced to patients in clinical practice, the side effect profiles of GLP-1R agonists should be proactively discussed. In the phase 3 LEAD T2DM regulatory clinical trials for liraglutide nausea, vomiting, and diarrhea were the most prominent adverse events. These were generally mild, transient, and rarely caused discontinuation of therapy [28]. Liraglutide is approved for use in combination with insulin. Co-administration of insulin detemir with liraglutide 1.8 mg produces an additive glucose lowering effect without changing the pharmacokinetic profile of either agent [29]. Immediately after initiating liraglutide, patients may experience a feeling of satiety. Some patients reduce the caloric intake by as much as 30 %–50 %. If a patient attempts to eat despite experiencing satiety they are likely to become nauseated. In our experience, approximately 5 % of patients with T1DM are unable to tolerate liraglutide in combination with insulin, most often secondary to the GI side effects. A patient with a personal history or family history of medullary thyroid carcinoma should not receive liraglutide. Liraglutide should never be used in a patient with a history of pancreatitis. Any patient who experiences abdominal pain associated with nausea and vomiting while on liraglutide should undergo a workup for acute pancreatitis. The drug should be discontinued if pancreatitis is suspected and not re-initiated if the diagnosis is confirmed.

Pharmaceutical costs should also be factored into the patient's treatment plan. The average cost of a rapid acting insulin pen is $50–$70 whereas each liraglutide pen adds an additional $166 in expense for the patient [30]. Thus, the attempt to reduce glycemic variability by correcting the bi-hormonal defect inherent to patients with T1DM will cost an additional $6000 per year.

Conclusions

The pharmacologic and physiologic defects of GLP-1 are well described in patients with T2DM. In response to an oral glucose stimulated meal, GLP-1 is secreted from the L-cells of the colon and is expressed at receptor sites within the pancreas, heart, brain, and GI tract. GLP-1 action is diminished in patients with T2DM. The use of GLP-1 receptor agonists improve glycemic control in a glucose dependent manner, induce weight loss, enhance satiety, delay gastric emptying, and exhibit β-cell protective and β-cell proliferative effects in some animal studies. The glucose-lowering effect resulting in inhibition of glucagon secretion and satiety may be of benefit to patients with T1DM as well. Although the relationship between GLP-1 targeted action and T1DM is nebulous, patients who use GLP-1 receptor agonists off label often experience improvement in glycemic control, body weight, and total daily insulin dose.

Before GLP-1 receptor agonists can be promoted for use in T1DM, randomized long-term placebo controlled clinical trials will be needed to assess their safety and efficacy in this population.

Physicians who prescribe a GLP-1 receptor agonist off-label to patients with T1DM should fully inform each patient as to the rationale of this therapeutic intervention.

Compliance with Ethics Guidelines

Conflict of Interest Jeff Unger has been on the advisory boards for Novo Nordisk, Sanofi, Janssen, Halozyme, Valeritas; and receives book publishing royalties from Lippincott, Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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