Continuing Medical Education

The Role of Glucagon-like Peptide-1 (GLP-1)

This drug is used in the treatment of type 2 diabetes and obesity.

BY JEAN CHEN-VITULLI, DPM, MS, AND ANASTASIOS MANESSIS, MD

Goals and Objectives

- Recognizing that GLP-1 receptor agonists as a class of medications are useful in weight loss.
- Recognizing that GLP-1 receptor agonists are useful in diabetes management by lowering HbA1c with cardiovascular and renal protection benefits.
- Acknowledging GLP-1 receptor agonists, especially Rybelsius, may replace Metformin as first-line treatment in Type 2 diabetes.

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*Following this article, an answer sheet and full set of instructions are provided (pg. 112).—**Editor***

The epidemic of obesity in the United States leads to systemic problems such as diabetes and hypertension. Obesity increases the weight on the foot structure which must be supported during stance and ambulation. Hence, being overweight may aggravate arthritic conditions and create undue stress on the plantar fascia, leading to foot pain, including plantar fasciitis. Pain leads to immobility, which also contributes to overall poor health. Several medications on the market help control blood glucose levels in patients with diabetes, but newer drugs also help reduce weight. This article will discuss the role of glucagon-like peptide-1 (GLP-1) in glucose and weight control.

Here are the key takeaways:

- Obesity is a serious problem in the United States, affecting 42.4% of adults and up to 20% of children.[1]
- Older weight loss medications have significant side-effects and contraindications, but newer drugs such as GLP-1 agonists are better tolerated and can help people with and without type 2 diabetes lose weight.
- GLP-1 receptor agonists induce satiety, augment glucose-stimulated insulin secretion, and inhibit inappropriate glucagon secretion.[3]
- Liraglutide, a GLP-1 receptor agonist, is now approved for the treatment of obesity in patients without type 2 diabetes.
- GLP-1 agonists have a protective effect on the kidneys.
- GLP-1 shows real promise for the treatment of diabetes and obesity in patients with type 2 diabetes.
- GLP-1 is now the preferred drug

Continued on page 106

GLP-1 (from page 105)

to add to the regimen when oral metformin by itself is not enough to meet the patient's hemoglobin A1c goal.

- Long-acting GLP-1 controls glycemic levels better than insulin and short acting agents, lowering HbA1c by about 1%.
- GLP-1 is recommended as a first-line or second-line therapy, regardless of hemoglobin A1C in patients with established atherosclerotic cardiovascular disease, high risk of atherosclerotic cardiovascular disease, chronic kidney disease, or heart failure.
- The FDA announced in January 2023 that Rybelsus has now been approved as an initial treatment option for type 2 diabetes.

Prevalence of Obesity

Obesity presents as a significant health problem in the United States due to its relationship with the leading causes of death, including heart disease, stroke, diabetes, and certain types of cancer. A combination of genetics, medications, education and skills, food marketing and availability, dietary patterns, lack of physical activity, and medications contribute to obesity. Those living in a food desert may have difficulty obtaining healthy food. In a world where a salad is more expensive than a hamburger, those with limited income face restricted food access. According to the Centers for Disease Control (CDC), the prevalence of obesity in the United States, defined as a BMI of 30 or higher, is 42.4%.[1] Over the last 20 years, the prevalence has increased from 30.5%. Moreover, the prevalence of severe obesity, defined as a BMI of 40 or higher, has increased from 4.7% to 9.2%.[1] Similarly, childhood obesity is a serious problem. The prevalence ranges from 13% in 2-to 5-year-olds to 20% in 12-to 19-year-olds.[2]

Older Weight-Reducing Medications are Limited

In treating weight reduction, aside from addressing psychological and behavioral interventions in over-eating, there are very few safe, efficacious, and FDA-approved medications that treat appetite and obesity. One available drug is sibutramine, a centrally-acting appetite suppressant limited by side-effects and contraindicated in patients suffering from uncontrolled hypertension and coronary artery disease.[2] Another drug, Orlistat, acts in the gastrointestinal tract to decrease absorption of ingested fat but often is not tolerated well due to side-effects.[2] Phentermine, a sympathomimetic, is also limited by side-effects. It too is contraindicated in patients with uncontrolled hypertension and cardiovascular disease.[2]

Fortunately, the GLP-1 class of medications is available to improve blood sugar control and promote weight loss when combined with lifestyle changes. It offers benefits to people with type 2 diabetes and people with obesity without type 2 diabetes. Hence, GLP-1 medications can be helpful in treatment of diabetic foot ulcers by helping patients achieve glycemic control in wound healing, decrease weight to reduce stress on foot joints, and decrease plantar fascia strain.

According to the American Association of Clinical Endocrinology (AACE)'s guidelines, overweight and obesity should be treated as a chronic disease, stressing the importance of managing it in patients with Type 2 diabetes. GLP-1 Receptor agonist is one of the medications recommended for body mass index (BMI) greater than 27, especially in patients with cardio or renal complications and risk factors, including atherosclerotic cardiovascular disease (ASCVD), cerebrovascular disease, heart failure (HF), and kidney diseases.[3] In those with a BMI greater and equal to 30, recommendations include considering FDA-approved weight loss medications as an adjunct to lifestyle intervention. Bariatric surgery consideration should be considered when the patient's BMI is greater or equal to 35.[3] All the medications in the class of GLP-1 receptor agonists are injectables, except for Rybelsus (oral semaglutide) (Figure 1).

Continued on page 107

Generic (Trade) Name; Manufacturer	Dosing Frequency	Recommended Dosage	Administration Before Meals Required?	Available Dosage Form(s); Needle Requirements
Short-acting				
Exenatide BID (Byetta); AstraZeneca (13)	Twice daily	5 µg subcutaneously twice daily within 60 minutes before meals; after 1 month, may increase to 10 µg subcutaneously twice daily based on clinical response	Yes	5-µg pen, 250 µg/mL (1.2 mL); 29-, 30-, or 31-gauge pen needles
Lixisenatide (Adlyxin); Sanofi (18)	Once daily	10 µg subcutaneously once daily within 1 hour before the first meal of the day; on day 15, increase to 20 µg once daily	Yes	50 µg/mL in 3-mL green prefilled pen (14 10-µg doses); 100 µg/mL in 3-mL burgundy pre-filled pen (14 20-µg doses)
Intermediate-acting				
Liraglutide (Victoza); Novo Nordisk (14)	Once daily	0.6 mg subcutaneously once daily for 1 week, then increase to 1.2 mg once daily; if glycemic control not acceptable, can increase dose to 1.8 mg subcutaneously once daily	No	Multi-dose pen delivers 0.6, 1.2, or 1.8 mg, 6 mg/mL (3 mL); 32-gauge pen needles
Long-acting				
Exenatide QW (Bydureon); AstraZeneca (15)	Once weekly	2 mg subcutaneously once weekly (every 7 days) with or without meals	No	Single-dose 2-mg vial and 2-mg pen (require reconstitution); 23-gauge 7-mm needles supplied with pen
Albiglutide (Tanzeum); GlaxoSmithKline (16)	Once weekly	30 mg subcutaneously once weekly; may increase to 50 mg subcutaneously once weekly for inadequate glycemic control	No	Single-dose 30- and 50-mg pens (require reconstitution for 15 [30 mg] to 30 [50 mg] minutes after mixing); 29-gauge, 5-mm, thin-wall needle supplied with pen
Dulaglutide (Trulicity); Eli Lilly (17)	Once weekly	0.75 mg subcutaneously once weekly; may increase to 1.5 mg subcutaneously once weekly for inadequate glycemic control	No	Single-dose pen or prefilled syringes: 0.75 mg/0.5 mL and 1.5 mg/0.5 mL; 29-gauge needle attached to pen

Figure 1: Chart of Available GLP-1 Receptor Agonists (From *Biopharma PEG: Long Acting GLP-1)Receptor Agonist Drugs Lists and Overview.*[6] https://www.biochempeg.com/article/226.html.

In the early stage, GLP-1 drugs had a short half-life in vivo, requiring frequent injections with poor patient compliance. With the development of long-acting GLP-1 drugs and the extension of their half-life, patient adherence to therapy improved,[6] especially if patients can overcome the fear of needles during self-injection.

GLP-1 (from page 106)

History of GLP-1 Receptor Agonists

In 1987, scientists discovered that GLP-1 promotes insulin secretion. Five years later, an entero-insulin analogue, Exendin-4, which is 53% homologous to GLP-1, was isolated from the saliva of the Mexican giant lizard, later known as exenatide.[7,9] It has GLP-1 receptor agonist activity and a half-life of 2.4 hours. The rapid degradation of GLP-1 in humans is largely due to the fact that the alanine in position 8 of the molecule is readily recognized and cleaved by dipeptidyl peptidase (DPP-4). Whereas, the glycine in position 8 of exenatide made it well resistant to be degraded by DPP-4. In 2005, the FDA approved exenatide (Byetta®) for the treatment of type 2 diabetes mellitus.[6] Since then, several pharmaceutical companies began various developments aimed at GLP-1 receptor stimulation, improving effectiveness and longer duration of action.[6,7]

These include the short-acting agents exenatide twice daily (BID), intermediate-acting liraglutide (administered once daily), and the long-acting agents administered once weekly (QW), including exenatide QW, albiglutide, and dulaglutide. Lixisenatide (administered once daily) has also recently been approved in the United States. In 2019, once a week medication, such as the semaglutide injection (Ozempic®) was approved for the market.[6,7]

GLP-1 Receptor Agonists Mechanisms

Several gastrointestinal hormones help control glucose metabolism, appetite, and body weight. In non-diabetics, glycemic homeostasis is regulated by pancreatic hormones insulin, amylin, and glucagon, as well as by incretin hormones released from the gastrointestinal cells, e.g., GLP-1 and glucose-dependent insulinotropic polypeptide.[4,7] In response to ingestion of glucose, the L and K intestinal cells release incretin hormones that stimulate pancreatic beta cells, leading to insulin secretion.[2,4,7] This mechanism is mainly activated after oral ingestion of glucose and may be impaired in patients with impaired glucose tolerance or non-insulin-dependent diabetes.[2,4,7]

As a result, hyperglycemia occurs. Hence, glucagon suppression of the pancreatic alpha cells and delayed gastric emptying is mediated by incretin's role in reducing hyperglycemia.[2,4] Incretin induces satiety by acting on the central nervous system.[2,4] Incretin hormone is quickly degraded by the enzyme dipeptidyl peptidase-4 (DDP-4). It has a half-life of about one to two minutes. Therefore, researchers have focused on the development of GLP-1 receptor agonists.[2]

Actions of GLP-1 on Targeted Tissues

GLP-1 has a number of potentially beneficial effects in the setting of type 2 diabetes. Intravenous administration of exogenous GLP-1 to patients with type 2 diabetes was shown to reduce plasma glucose concentrations to the normal fasting range, even in patients who had an inadequate response to oral anti-hyperglycemic drugs. The effects of exogenous GLP-1 observed after administration to patients with type 2 diabetes include: (Figure 2)[7,8]

- Decreased glucagon concentrations
- Improved insulin sensitivity
- Decreased A1C
- Slowed gastric emptying
- Increased satiety
- Decreased free fatty acid concentrations
- Decreased body weight

Benefits of GLP-1

Several GLP-1 receptor agonists show improved glycemic control in patients with type 2 diabetes. These agents have been shown to reduce HbA1C by approximately 0.6 to 1.6%[2,7] with low risks of hypoglycemia.[7] They also show improvements in body weight.[2] Other studies have been done to evaluate the weight loss benefits of these medications in patients without diabetes. They show that the chronic use of GLP-1 agonists correlates with significant weight loss.[2] Specifically, the use of liraglutide consistently results in a 4 to 6 kg weight loss.[2] This medication is now FDA approved as a weight reduction agent for patients without diabetes. However, gastrointestinal side-effects and the cost of treatment often lead to discontinuation of therapy. Also, almost all of the GLP-1 receptor agonists, including albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide, only come in injectable forms. The only oral preparation is semaglutide.

Protecting the Brain and Heart

GLP-1 receptor agonists play key roles in reducing reactive oxygen species production, reducing platelet activation, reducing activation of macrophages and monocytes and their consecutive accumulation in the vascular wall, and inhibiting endothelin production. This leads to vasodilation by interfering with several molecular and cellular steps of the atherogenesis process. In essence, GLP-receptor agonists boost the effects of GLP-1 by stabilizing endothelial cells and reducing plaque hemorrhage and rupture.[4,8] Furthermore, GLP-1 slows progression of atherosclerosis[4,5,9] by targeting glycemic control, blood pressure, lipid levels, and renal function, which have been associated with a reduction in cardiovascular and microvascular complications.[7,9]

In a retrospective analysis, patients with type 2 diabetes receiving exenatide (n = 39,275) were less likely than patients receiving other glucose-lowering treatments (n = 381,218) to have a CVD event (hazard ratio [HR] 0.81, P = 0.01), with CVD-related hospitalization (HR 0.88, P = 0.02), or hospitalization for any cause (HR 0.94, P < 0.001), despite a greater prevalence of previous ischemic heart disease, obesity, hyperlipidemia, hypertension, and other comorbidities at baseline.[7] Similar positive cardiovascular results were reported recently for semaglutide, an investigational GLP-1 receptor agonist administered once a week (QW).[7]

Protecting the Kidneys

It is not well understood how GLP-1 receptor agonists protect the kidneys. These drugs do lower hemoglobin A1c, weight, and blood pressure; hence, modifying traditional risk factors for progression of chronic kidney disease and diabetic nephropathy.[4] Moreover, GLP-1 receptors can be found in the renal proximal convoluted tubular cells and preglomerular vascular smooth muscle cells in the kidneys. Direct stimulation of these receptors inhibits the sodium-hydrogen exchanger 3 at the brush border of the proximal convoluted tubular cells, leading to increased natriuresis and consequently reduced blood pressure.[4-6]

Continued on page 108

GLP-1 (from page 107)

Effect on Weight

In rat studies, stimulation of GLP-1 receptors in the hypothalamus by GLP-1 receptor agonists prevented meal initiation and induced meal cessation.[4] Similarly, in humans, injection of GLP-1 receptor agonists showed decreased energy intake, suppressed appetite, and reduced food-craving.[4,9] Patients receiving GLP-1 receptor agonists have had lower preference for fatty and energy-dense food, and less pleasure in eating.[4] These hypothalamic effects are thought to vary among patients treated with GLP-1 receptor agonists.[4]

As a result, observational and interventional studies of the glycemic effects of GLP-1 receptor agonists in patients with type 2 diabetes have noted that patients receiving these drugs lose weight (Figure 3). Several studies also evaluated their weight-loss effect in patients without diabetes and showed reduction of weight.[4,5,7]

Body weight reduction was a common effect observed in clinical trials evaluating GLP-1 receptor agonists in patients with type 2 diabetes. In a mixed-treatment comparison meta-analysis of randomized controlled trials of GLP-1 receptor agonists (exenatide BID and QW and liraglutide) in overweight or obese patients with type 2 diabetes, mean reductions in body weight were greater than with placebo for exenatide 10 µg BID (-1.4 kg), exenatide QW (-1.6 kg), and liraglutide 1.8 mg (-1.5 kg), with no significant differences among these three treatments.

Changes in body weight were reported in clinical studies in the drugs' prescribing information (Figure 3). In clinical trials of once-daily or BID GLP-1 receptor agonists (liraglutide, lixisenatide, or exenatide BID), mean changes in body weight were -2.1 to -2.9 kg for monotherapy and +0.3 to -3.6 kg in combination with oral antihyperglycemic therapies. In trials of weekly GLP-1 receptor agonists (exenatide QW, albiglutide, or dulaglutide), mean changes in body weight were -0.7 to -1.6 kg for monotherapy and +0.3 to -3.1 kg in combination with oral anti-hyperglycemic therapies. Weight loss in patients receiving GLP-1 receptor agonists is thought to occur as a result of slowed gastric emptying and increased satiety. In a study of obese patients with accelerated gastric emptying, treatment with exenatide BID for 30 days resulted in slowed gastric emptying and a modest reduction in caloric intake compared to placebo.[7]

Retinopathy

Retinopathy has been reported to occur at higher rates in patients treated with semaglutide, liraglutide, dulaglutide, and albiglutide. However, difference was statistically significant only for patients who received semaglutide.[4] Most of these patients had retinopathy at baseline, and worsening of retinopathy was similarly reported when insulin was started. This suggests that retinopathy could be attributable to rapid glucose lowering rather than to a drug class effect.[4]

Hypoglycemia

Hypoglycemia has occurred at similar rates in patients receiving GLP-1 receptor agonists.[4] Close monitoring and adjustments of other anti-diabetes medications may be warranted. Signs and symptoms of hypoglycemia should be reviewed with patients, such as hunger, anxiety, cold sweat, nightmares, shakiness, and headaches. The Rule of 15 in treatment of hypoglycemia should be reviewed with patients. This rule states that you should consume 15 grams (g) of carbohydrates when your blood sugar drops under 70 mg/dL, and to check your blood sugar again after 15 minutes. If your blood sugar is still low, you repeat the process.

Effects on Glycemic Control

Results of a meta-analysis of clinical studies indicate that treatment with GLP-1 receptor agonists is associated with A1C reductions (Figure 4) from baseline of -0.42% for exenatide 5 µg

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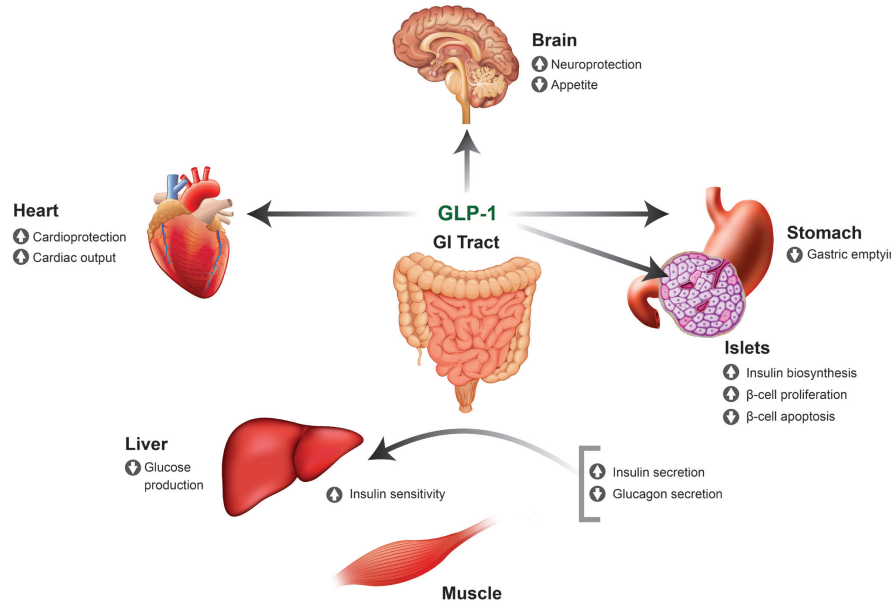

Figure 2: Adapted from *Glucagon-like Peptide 1 Receptor Agonists for Type 2 Diabetes. Diabetes Spectr. 2017 Aug; 30(3): 202–210.* Glucagon-like peptide-1, an incretin hormone inactivated by dipeptidyl peptidase-4 (DPP-4), stimulates insulin secretion after an oral glucose load via the incretin effect. In type 2 diabetes, this process can become blunted or even be absent; however, the utilization of pharmacological levels of GLP-1 can revive insulin excretion. The benefits of this form of therapy to treat type 2 diabetes include delayed gastric emptying and inhibiting the production of glucagon from pancreatic alpha cells if blood sugar levels are high. Furthermore, GLP-1 receptor agonists can decrease pancreatic beta-cell apoptosis while promoting their proliferation. In addition, they lower both systolic and diastolic blood pressure and total cholesterol. In terms of cardiovascular effects, GLP-1 agonists can improve left ventricular ejection fraction, myocardial contractility, coronary blood flow, cardiac output, and endothelial function, while reducing infarction size and overall risks for a cardiovascular event. Other functions of GLP-1 include increased glucose uptake in the muscles, decreased glucose production in the liver, neuroprotection, and increased satiety due to direct actions on the hypothalamus. GLP-1 analogs have also exhibited lower all-cause mortality as well as a hemoglobin A1c reduction of about one percent compared to control groups in patients with type-2 diabetes mellitus.[10]

GLP-1 (from page 108)

BID, -0.50% for lixisenatide 20 µg once daily, -0.69% for albiglutide 30 mg QW, -0.71% for liraglutide 1.2 mg once daily, -0.75% for exenatide 10 µg BID, -1.03% for liraglutide 1.8 mg once daily, and -1.09% for exenatide 2 mg QW, and dulaglutide 1.5 mg QW versus placebo. The mean changes in A1C are reported in clinical studies of 24–52 weeks' duration in the drugs' prescribing information (Figure 4.)[7] In studies of GLP-1 receptor agonists used alone or in combination with oral anti-hyperglycemic therapies, mean changes in A1C ranged from -0.8 to -1.7% for exenatide BID, -0.8 to -1.5% for liraglutide 1.2–1.8 mg once daily, -0.6 to -0.9% for lixisenatide once daily, -0.6 to -0.9% for albiglutide 30–50 mg QW, -0.7 to -1.6% for dulaglutide 0.75–1.5 mg QW, and -1.3 to -1.6% for exenatide QW (Figure 4).[7]

Medullary Thyroid Cancer and Pancreatic Cancer

Medullary thyroid cancer and pancreatic cancer have occurred in rats receiving GLP-1 receptor agonists, but not in human trials.[4] Hence, the FDA requires a black-box warning for GLP-1 receptor agonists regarding the risk of thyroid C-cell tumors. It recommends against using them in patients with a personal or family history of medullary thyroid cell cancer or multiple endocrine neoplasia syndrome type 2a or 2b.[4]

Future Directions

Reversing Fatty Liver Disease

GLP-1 receptor agonists may play a role in slowing and reversing the progression of non-alcoholic fatty liver disease (NAFLD).[4] In the Lira-NAFLD trial, 50 patients who received liraglutide 1.2 mg daily for six months experienced a reduction in liver fat content of 31% ($P < .0001$). Multivariate analysis showed that the reduction in liver fat was associated with decrease in body weight, triglycerides, and hemoglobin A1c.[4] Patients who lost no weight had no reduction in liver fat content compared to baseline.[4]

A meta-analysis of 35 clinical trials showed that these agents were associated with significant reductions in LDL cholesterol (weighted mean difference -3.1 mg/dL [95% CI -4.6 to -1.9]) and total cholesterol (-5.0 mg/dL [95% CI -7.3 to -2.7]) versus control. Hence, improvements in lipid levels have also been observed during treatment with GLP-1 receptor agonists.[4]

In a meta-analysis of eight randomized controlled trials, GLP-1 agonist therapy compared with standard of care, showed significant improvements with alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transaminase, and glycosylated hemoglobin.[9]

Use in Polycystic Ovary Syndrome

Studies in patients with polycystic ovary syndrome showed a significant drop in testosterone levels and body mass index in those receiving liraglutide or exenatide compared with placebo or metformin.[4] Hence, GLP-1 receptor agonists may be beneficial in reducing foot pain by reducing extra strain on the plantar fascia and joints from being overweight. Further studies are still needed to evaluate the benefits

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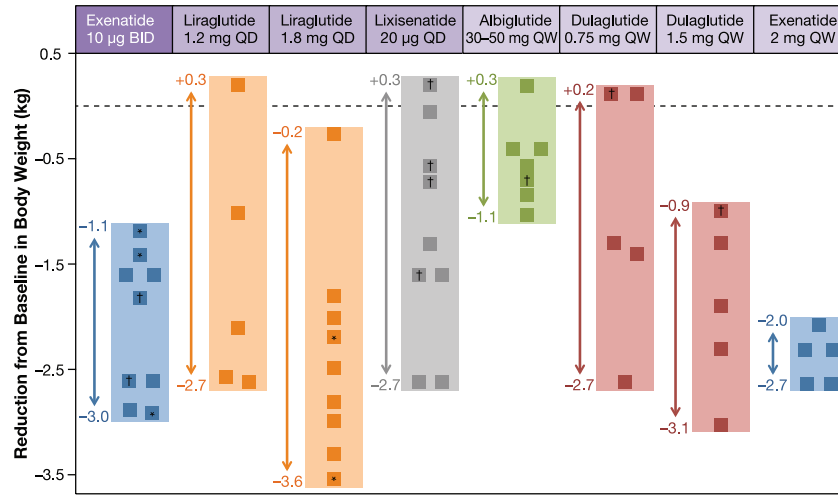

Figure 3: Adapted from *Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes. Diabetes Spectr. 2017 Aug; 30(3): 202–210.* Range of mean changes from baseline in body weight in clinical studies of 24–52 weeks' duration reported in prescribing information for five GLP-1 receptor agonists. Each square represents findings from one study. Drugs were tested as monotherapy or in combination with oral medications, except as noted. Findings were reported as comparator in clinical study in another drug's prescribing information. Finding for drug in combination with insulin. QD, once daily.[7]

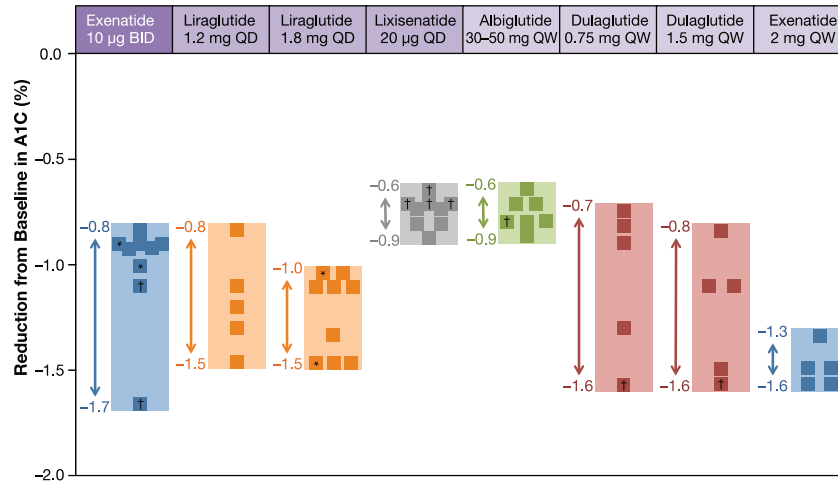

Figure 4: Adapted from *Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes. Diabetes Spectr. 2017 Aug; 30(3): 202–210.* Range of mean changes from baseline in A1C in clinical studies of 24–52 weeks' duration reported in prescribing information for five GLP-1 receptor agonists. Each square represents the finding from one study. Drugs were tested as monotherapy or in combination with oral medications, except as noted. Findings were reported as comparator in clinical study in another drug's prescribing information. Finding for drug in combination with insulin. QD, once daily.[7]

GLP-1 (from page 109)

of GLP-1 receptor agonists in patients with polycystic ovary syndrome and podiatric patients with diabetic foot ulcers and foot pain-related disorders.

Use in Peripheral Arterial Disease (PAD)

In a study of patients with diabetes and PAD, those treated with liraglutide versus those treated with placebo showed a significant 35% reduction in the risk of amputation.[11] At this time, more clinical research is needed to explore the reduction of amputation benefits from GLP-1 receptor agonists.

Use in Type 1 Diabetes

The ADJUNCT ONE™ trial (Efficacy and Safety of Liraglutide as Adjunct Therapy to Insulin in the Treatment of Type 1 Diabetes), the ADJUNCT TWO™ trial, and a large meta-analysis found reductions in hemoglobin A1c, body weight, and total daily dose of insulin. These trials also highlighted in type 1 diabetes mellitus patients an increase in hyperglycemia with ketosis in those receiving liraglutide or exenatide in combination with insulin. This might have been due to insulin dose reductions when liraglutide was initiated. No significant changes in C-peptide were reported in these studies.[4]

Currently, GLP-1 receptor agonists are neither recommended nor FDA-approved for use in type 1 diabetes. However, adding them off-label to insulin in patients with type 1 diabetes can help the patients lose weight and stabilize their blood sugar levels.[4]

Treatment Algorithm

According to the AACE/ACE and ADA diabetes treatment algorithms for glycemic control, GLP-1 receptor agonists are recommended as add-on therapy for patients who do not achieve their A1C target after three months of metformin therapy. GLP-1 receptor agonists also are recommended as an alternative to metformin in first-line therapy in patients who cannot tolerate or are contraindicated for metformin. GLP-1 receptor agonists are well suited for early use in type 2 diabetes since they stimulate release of insulin and suppress glucagon secretion only when blood glucose concentrations are elevated; thus, the risk of hypoglycemia is low.[7,8]

GLP-1 receptor agonists in combination with metformin are recommended for patients who do not achieve A1C goals with metformin alone. For patients requiring triple therapy, GLP-1 receptor agonists can be combined with metformin and a sodium–glucose cotransporter 2 inhibitor in patients with persistent hyperglycemia. Additionally, incretin use with basal insulin may delay the use of bolus insulin at mealtime with reduced risk of hypoglycemia and also help mitigate the weight gain often seen with insulin use.[7]

Rybelsus

The Food and Drug Administration (FDA) announced in January 2023 that Rybelsus (semaglutide), a GLP-1 medication, can now be offered as a first-line treatment option for people with type 2 diabetes. Instead of Metformin, doctors can now prescribe Rybelsus to their patients first.[5] Rybelsus is the only approved GLP-1 medication that can be taken as a pill instead of an injection. This makes it more convenient in patients who fear needles. Rybelsus helps protect the heart. In the PIONEER 6 trial, participants taking Rybelsus experienced cardiovascular protection.[5] One pill that addresses both high blood sugar and heart health can be convenient.

Use of GLP-1 Receptor Agonists and Renal Function

Exenatide BID and QW should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease (ESRD) and should be used with caution in patients with moderate renal impairment (creatinine clearance 30–50 mL/min) or with a history of renal transplantation.[7]

Albiglutide, dulaglutide, and lixisenatide may be used without dose adjustment in patients with mild, moderate, or severe renal impairment (estimated glomerular filtration rate 15–89 mL/min/1.73 m2). Dulaglutide may be used without dose adjustment in patients with ESRD.[7]

Renal function must be monitored in patients with renal impairment who experience severe gastrointestinal adverse effects during treatment with albiglutide, dulaglutide, or lixisenatide because of the potential for dehydration.[7]

Side-effects of GLP-1

The most commonly reported treatment-related adverse effects occurring with GLP-1 receptor agonists are gastrointestinal, primarily nausea (occurring in 25–60% of patients in clinical trials), vomiting (5–15%), and diarrhea (10–20%).[7] In general, the long-acting

Continued on page 111

Editor's Update

Since this article was written, Ozempic in particular has been in the news re: both its possible serious side effects and its ever-widening use for weight loss. Recently reported side effects include gastroparesis, pancreatitis, and kidney disease. And the FDA recently logged a reported shortage of the drug due to an increase in demand. Why? Jabs have been taken at Hollywood celebrities who use Ozempic to stay thin, and more serious concerns have been raised about the drug's lack of availability for diabetics who use it to manage their condition.

Ozempic maker Novo Nordisk previously told E! News that the drug is not FDA-approved for chronic weight management, nor is it marketed as a weight loss aid. "While we recognize that some healthcare providers may be prescribing Ozempic for patients whose goal is to lose weight, Novo Nordisk does not promote, suggest, or encourage off-label use of our medicines and is committed to fully complying with all applicable U.S. laws and regulations in the promotion of our products," the Danish pharmaceutical company said in a statement. "We trust that healthcare providers are evaluating a patient's individual needs and determining which medicine is right for that particular patient." **PM**

GLP-1 (from page 110)

GLP-1 receptor agonists have been associated with lower rates of gastrointestinal adverse events. Also, nausea decreases with time. GLP-1 receptor agonists do not increase the risk of hypoglycemia relative to placebo.[7] Hypoglycemia risk increases compared to placebo when insulin or sulfonyureas are used concomitantly with GLP-1 receptor agonists.[7]

Conclusion

GLP-1 receptor agonist drugs are beneficial in both diabetic patients and non-diabetic patients. They reduce HbA1c, and have cardiac and renal protective properties. Use of this class of medication leads to satiety and weight loss. In terms of podiatric medicine, weight loss leads to less strain on foot joints, ligaments, tendons, and the plantar fascia. There is also a possibility that GLP-1 receptor agonists may be useful in decreasing prevalence of amputation in patients with peripheral arterial diseases; hence, it will be a helpful adjunct for those involved in wound care and amputation prevention centers to consider GLP-1 receptor agonists.

Future podiatric research may substantiate the effect of GLP-1 in reduction of foot pain and lower extremity wounds and amputations. In terms of diabetic foot ulcers, this class of medication will reduce HbA1c to aid in wound healing, and decrease macrovascular and microvascular complications. **PM**

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Jean Chen-Vitulli is a diabetes educator and Science Research Director at Endocrine Associates of West Village.

Anastasios Manessis, MD is an endocrinologist and head of the Endocrine Associates of West Village, specializing in diabetes, obesity, and thyroid disorders.

CME EXAMINATION

SEE ANSWER SHEET ON PAGE 113.

1) Which of the following (is) are used as weight loss drugs?
- **A) Ozempic**
- **B) Orlistat**
- **C) Sibutramine**
- **D) All of the above**

2) Which of the following is not a beneficial effect of GLP-1 receptor agonists?
- **A) Weight reduction**
- **B) Increase of LDL**
- **C) Renal protection**
- **D) Cardiovascular protection**

3) GLP-1 receptor agonists can now be used as:
- **A) Front-treatment of Type 2 diabetes mellitus alone.**
- **B) Used together in combinations with other medications to achieve glycemic control.**
- **C) Can be used in conjunction with basal insulin to delay starting meal time bolus insulin.**
- **D) All of the above**

4) Which of the following medications when used in combination with GLP-1 receptor agonists can increase the risk of hypoglycemia?
- **A) Insulin (Fiasp/Novolog/Humalog)**
- **B) Metformin**
- **C) Glipizide (glucotrol)**
- **D) Glucagon**

5) Currently, there is only one oral GLP-1 receptor agonist drug. Which of the following is in an oral form?
- **A) Ozempic**
- **B) Trulicity**
- **C) Byetta**
- **D) Rybelsus**

Continued on page 112

(Continued from page 111)

6) Which of the following is NOT a benefit of GLP-1 receptor agonists?

A) There is no reduction of HbA1c by 1%.
B) Improved insulin sensitivity
C) Decreased glucagon production
D) Weight loss

7) Which of the following mechanisms is true about the GLP-1 receptor agonists in causing weight loss?

A) Increases satiety
B) Slows gastric emptying
C) Reduces food craving
D) All of the above

8) There is a black box warning for GLP-1 receptor agonists

A) Due to an increase in medullary thyroid cancer in rat studies.
B) Due to an increase in pancreatic cancer in rat studies.
C) Due to an increase in medullary thyroid cancer and pancreatic cancer in human trials.
D) A and B.

9) GLP-1 receptor agonists are also beneficial:

A) In the reduction of blood pressure.
B) In decreasing testosterone in polycystic ovary syndrome.
C) In increasing cardiac output.
D) All of the above

10) Which of the following is NOT a mechanism of GLP-1 receptor agonists?

A) They stimulate insulin secretion after a glucose load.
B) They stimulate glucagon production when blood sugar is high.
C) They decrease pancreatic beta cell apoptosis.
D) They increase glucose uptake by the muscles.

SEE ANSWER SHEET ON PAGE 113.

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EXAM #6/24
The Role of Glucagon-like Peptide-1 (GLP-1)
(Chen-Vitulli and Manessis)

Circle:

1.	A	B	C	D	6.	A	B	C	D
2.	A	B	C	D	7.	A	B	C	D
3.	A	B	C	D	8.	A	B	C	D
4.	A	B	C	D	9.	A	B	C	D
5.	A	B	C	D	10.	A	B	C	D

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Strongly agree [5]	Agree [4]	Neutral [3]	Disagree [2]	Strongly disagree [1]

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6) What overall grade would you assign this lesson?

A B C D

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