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Optimizing diabetes treatment in the presence of obesity

ABSTRACT

Evidence of a neurophysiologic mechanism that involves hormones from adipocytes, pancreatic islet cells, and the gastrointestinal tract implicated in both obesity and diabetes has led to a search for drugs that not only either target obesity and diabetes or reduce hemoglobin A1c, but also have weight loss as a potential side effect. The authors review medications approved for the treatment of type 2 diabetes mellitus (including pramlintide, also approved for type 1 diabetes) that also have weight loss as a side effect. Drugs discussed include glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, neuroendocrine peptide hormones, alpha-glucosidase inhibitors, and metformin. Where appropriate, the authors comment on the cardiovascular effects of these drugs.

KEY POINTS

The rationale for GLP-1 receptor agonists is that peripheral GLP-1 activates a cascade of centrally mediated signals that ultimately result in secretion of insulin by the pancreas and slowing of gastrointestinal motility. It also exerts an anorexic effect by acting on central pathways that mediate satiation.

SGLT-2 inhibitors have relatively weak glycemic efficacy. Inhibition of SGLT-2 alleviates hyperglycemia by decreasing glucose reabsorption in the kidneys and by increasing excretion in the urine, suggesting urinary loss of glucose (and hence caloric loss). This is thought to contribute to weight reduction in addition to initial weight loss from fluid loss due to osmotic diuresis.

Meta-analyses so far have shown that alpha-glucosidase inhibitors have either a neutral or a beneficial effect on body weight.

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Diabesity was a term coined by Sims et al[1] in the 1970s to describe diabetes occurring in the setting of obesity. Today, the link between type 2 diabetes mellitus (DM), obesity, and insulin resistance is well recognized, and 80% of people with type 2 DM are overweight or obese.[2,3] Unfortunately, weight gain is a known side effect of most agents used to treat type 2 DM (eg, insulin, sulfonylureas, thiazolidinediones), and this often leads to nonadherence, poor glycemic control, and further weight gain.

During the past several years, evidence has emerged of a neurophysiologic mechanism that involves hormones from adipocytes, pancreatic islet cells, and the gastrointestinal tract implicated in both obesity and diabetes.[2] This has led to research for drugs that not only either target obesity and diabetes or reduce hemoglobin A1c (HbA1c), but also have weight loss as a potential side effect.

In this paper, we review medications approved for the treatment of type 2 DM (including pramlintide, also approved for type 1 DM) that also have weight loss as a side effect. Drugs we will discuss include glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, neuroendocrine peptide hormones, alpha-glucosidase inhibitors, and metformin. Where appropriate, we also comment on the effects of the drugs on cardiovascular outcomes.

GLP-1 RECEPTOR AGONISTS

Mechanism of action

GLP-1 is a hormone produced from the proglucagon gene in the alpha cells of the pancreas, in the L cells of intestinal mucosa (predominantly in the ileum and distal colon), and in structures of the nervous system including the brainstem, hypothalamus, and vagal afferent nerves.[4] Food in the gastrointestinal tract, especially if high in fats and carbohydrates, stimulates secretion of GLP-1 in the L cells, which in turn amplifies insulin secretion in a glucose-dependent

manner (the incretin effect).[4] Glucagon secretion is inhibited by GLP-1 during times of hyperglycemia but not hypoglycemia, thereby preventing inappropriately high levels of the hormone.[5] Peripheral GLP-1 activates a cascade of centrally mediated signals that ultimately result in secretion of insulin by the pancreas and slowing of gastrointestinal motility.[5] Lastly, GLP-1 exerts an anorexic effect by acting on central pathways that mediate satiation.[6]

Recent studies suggest that GLP-1 receptor agonist drugs have proliferative, anti-apoptotic, and differentiation effects on pancreatic beta cells, thereby leading to improved glycemic control.[7] **Table 1** summarizes the sites of action and physiologic effects of GLP-1.[7]

TABLE 1
Sites of action and physiologic effects of glucagon-like peptide-1

Site of action	Physiologic effects	Remarks
Pancreas	Stimulates insulin secretion Inhibits glucagon secretion	These actions are glucose-dependent
Vagal afferent neurons	Slows gastric emptying Decreases gastric acid secretion Stimulates pancreatic insulin secretion	Effects mediated via vagal signaling to the gastrointestinal tract and the pancreas
Central nervous system	Suppresses appetite and reduces food intake	Satiety and reward centers of the brain

Based on data from Iepsen et al.[7]

Bioactive forms of GLP-1 are rapidly degraded in the circulation by the dipeptidyl peptidase-4 enzyme. GLP-1 receptor agonists have slightly altered molecular structure and longer duration of action than native GLP-1. Short-acting GLP-1 agonists (eg, exenatide, lixisenatide) have more effect on gastric emptying and lower postprandial blood glucose levels, whereas long-acting GLP-1 agonists (eg, liraglutide, albiglutide, dulaglutide, semaglutide, exenatide) have a greater effect on fasting glucose levels.[4]

Effects on HbA1c and weight loss

As a class, GLP-1 receptor agonists have been proven to cause significant reduction in HbA1c levels. In a meta-analysis of 17 randomized controlled trials involving patients with type 2 DM with suboptimal control on 1 or 2 oral agents, GLP-1 agonists decreased HbA1c levels by 1% (treatment difference 0.5% to 1.6%) compared with placebo.[8] HbA1c reductions from each GLP-1 agonist along with dosing, administration, and weight loss benefit are shown in **Table 2**.[9–14]

Of the current GLP-1 agonists, exenatide and liraglutide have been on the market the longest, thus studied more in terms of weight reduction.

Exenatide. Exenatide BID was the first GLP-1 agonist, approved by the US Food and Drug Administration (FDA) in 2005 for the treatment of type 2 DM. In a 30-week triple-blind, placebo-controlled study of 336 patients already on background therapy with metformin, progressive weight loss was noted with exenatide 5 µg (−1.6 ± 0.4 kg) and exenatide 10 µg (−2.8 ± 0.5 kg) compared with placebo (−0.3 ± 0.3 kg; $P < .001$).[15] A meta-analysis of 14 trials with 2,583 patients showed significant weight reduction with both exenatide 5 µg twice daily (a difference of −0.56 kg, 95% confidence interval [CI] −1.07 to −0.06, $P = .0002$) in 8 trials and exenatide 10 µg twice daily (a difference of −1.24 kg, 95% CI −1.69 to −0.78, $P < .001$) in 12 trials, after treatment for more than 16 weeks.[16]

Liraglutide. Liraglutide has a longer half-life than exenatide and is administered once daily. It is not a first-line therapy for type 2 DM and is recommended as an add-on. Approved daily doses for type 2 DM are 1.2 mg and 1.8 mg.

Multiple studies of glycemic control and weight loss with liraglutide have been conducted since its introduction to the US market in 2010. In the Liraglutide Effect and Action in Diabetes (LEAD) series of trials, liraglutide use as monotherapy or in combination with oral agents was associated with significant dose-dependent weight loss.[17] Liraglutide monotherapy (at 1.2 mg and 1.8 mg) compared with glimepiride in the LEAD-3 trial led to significant weight reduction (2.1 kg and 2.5 kg, respectively, $P < .001$) after 16 weeks, and was sustained up to 52 weeks.[18] Addition of liraglutide (at 1.2 mg and 1.8 mg) to metformin plus rosiglitazone resulted in significant weight loss (1.02 kg and 2.02 kg, respectively) whereas the addition of placebo caused a 0.6-kg weight gain ($P < .001$).[19] The SCALE study randomized 846 adults with type 2 DM who were overweight to obese (body mass index [BMI] ≥ 27 kg/m^2), were taking 0 to 3 oral antihyperglycemic agents (metformin, thiazolidinedione, and a sulfonylurea), and had stable body weight and an HbA1c of 7% to 10% to liraglutide 1.8 mg, liraglutide

TABLE 2
Currently approved glucagon-like peptide-1 receptor agonists for diabetes mellitus

Generic name (Brand name)	Administration[a]	Dose	Hemoglobin A1c reduction (%)	Weight change (kg)
Exenatide BID (Byetta)[9]	Within 60 minutes before breakfast and dinner	5 µg BID 10 µg BID	0.5 to 0.7 0.7 to –1.7	–1.1 to –2.7 –1.5 to –2.9
Liraglutide (Victoza)[10]	Once daily at any time of day	0.6 mg QD 1.2 mg QD 1.8 mg QD	 0.8 to 1.1 0.5 to 1.5	 +0.3 to –2.6 –0.2 to –2.8
Exenatide QW (Bydureon)[11]	Once every 7 days at any time of day	2 mg QW	1.3 to 1.6	–2.0 to –2.7
Albiglutide (Tanzeum)[12]	Once every 7 days at any time of day	30 mg QW 50 mg QW	0.7 to 0.8 0.6 to 0.9	–0.4 to –1.2
Dulaglutide (Trulicity)[13]	Once weekly at any time of day	0.75 mg QW 1.5 mg QW	0.7 to 1.6 0.8 to 1.6	+0.2 to –2.8 –0.9 to –3.1
Lixisenatide (Adlyxin)[14]	Within 60 minutes before main meal	10 µg QD 20 µg QD	0.6 to 0.9	+0.31 to –2.7

[a] All drugs administered by subcutaneous injection.
BID = twice daily; QD = once daily; QW = once every 7 days

Data based on package inserts.[9–14]

3.0 mg, or placebo. Mean weight loss after 56 weeks was 6.0% (6.4 kg) with liraglutide 1.8 mg, 4.7% (5.0 kg) with liraglutide 3.0 mg, and 2.0% (2.2 kg) with placebo.[20]

In 2016, high-dose once-daily liraglutide 3.0 mg (Saxenda) was approved by the FDA for weight loss. In a double-blind randomized trial of liraglutide 3.0 mg vs placebo in patients who had a BMI of at least 30 or who had a BMI of at least 27 plus treated or untreated dyslipidemia or hypertension, Pi-Sunyer et al[21] reported a mean weight reduction of 8.4 ± 7.3 kg with liraglutide vs 2.8 ± 6.5 kg with placebo (a difference of −5.6 kg, 95% CI −6.0 to −5.1, $P < .001$) after 56 weeks. Furthermore, 63.2% of patients in the liraglutide group lost at least 5% of body weight vs 27.1% with placebo, and 33.1% in the liraglutide group lost 10% or more of body weight vs 10.6% in the placebo group ($P < .001$).[21] Of note, liraglutide 3.0 mg is not indicated for type 2 DM per se.

In a 2012 meta-analysis of randomized controlled trials of adults with and without type 2 DM, with a BMI of 25 or greater, and who received GLP-1 receptor agonists at clinically relevant doses (exenatide ≥ 10 µg/day, exenatide ≥ 2 mg/week, or liraglutide ≥ 1.2 mg/day), those taking GLP-1 receptor agonists had more weight loss than those on a control intervention (oral antihyperglycemic, insulin, or placebo) at a minimum of 20 weeks, with a weighted mean difference −2.9 kg (95% CI −3.6 to −2.2) in 21 trials and 6,411 participants.[22]

GLP-1 agonists currently being investigated for obesity treatment are lixisenatide, albiglutide, taspoglutide, and oxyntomodulin.[23]

Cardiovascular outcomes

The presence of GLP-1 receptors in blood vessels and myocardium has led to the hypothesis that GLP-1 receptor agonists can improve cardiovascular disease outcomes.[24] In the pivotal Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, 9,340 patients with type 2 DM and increased cardiovascular disease risk were randomized to liraglutide vs placebo.[25] The hazard ratio (HR) for time to the primary end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was 0.87 ($P = .01$ for superiority, $P < .001$ for noninferiority) for liraglutide compared with placebo after 3.8 years. The incidence of death from any cause or cardiovascular cause was also lower with liraglutide.[25]

Adverse effects

Tolerable transient nausea and vomiting are reported adverse effects; these symptoms occur early in therapy, usually resolve in 4 to 8 weeks, and appear to

be associated with greater weight loss.[26] Although no causal relationship between GLP-1 receptor agonist use and pancreatitis or pancreatic cancer has been established to date, several cases of acute pancreatitis have been reported.[25] Alternative therapies should be considered in patients with a history of or risk factors for pancreatitis.

Combined with insulin

A product that combines insulin glargine and lixisenatide (Soliqua) is FDA-approved for patients with type 2 DM. In a 30-week randomized controlled trial of the combination product vs insulin glargine alone in patients with type 2 DM not controlled on basal insulin with or without up to 2 oral agents, the combination product resulted in an HbA1c reduction from baseline of 1.1% vs 0.6% for insulin glargine alone ($P < .001$).[27] Mean body weight decreased by 0.7 kg with the combination product and increased by 0.7 kg with insulin glargine ($P < .001$).[27] In a 24-week study of a lixisenatide-insulin glargine combination vs insulin glargine in insulin-naïve patients taking metformin, there was a reduction in HbA1c of about −1.7% from baseline in both groups, while the combination group had a 1-kg weight reduction compared with a 0.5-kg weight increase in the insulin glargine group ($P < .001$).[28]

SGLT-2 INHIBITORS

Mechanism of action

In a healthy normoglycemic person, about 180 g of glucose per day is filtered into the glomerular filtrate and reabsorbed into the circulation.[29] SGLT-2 facilitates the reabsorption of glucose in the proximal convoluted tubule of the kidneys. Approximately 90% of glucose reabsorption is mediated by SGLT-2 found in the S1 and S2 segments of the proximal convoluted tubule, and the remaining 10% by SGLT-1 in the S3 segment. At serum glucose levels above 180 g, the reabsorptive capacity of the nephron is overwhelmed, resulting in glycosuria.[30] SGLT-2 expression is also increased in patients with diabetes, thus leading to increased glucose reabsorption into the circulation, further contributing to hyperglycemia.[30] Inhibition of SGLT-2 alleviates hyperglycemia by decreasing glucose reabsorption (30% to 50% of filtered glucose) in the kidneys and by increasing excretion (50 mg to 80 mg of glucose) in the urine.[31] SGLT-2 inhibitors currently FDA-approved are canagliflozin (Invokana), dapagliflozin (Farxiga), and empagliflozin (Jardiance).

HbA1c

SGLT-2 inhibitors have relatively weak glycemic efficacy. A meta-analysis of SGLT-2 inhibitors vs other antidiabetic medications or placebo found that SGLT-2 inhibitors appeared to have a "favorable effect" on HbA1c, with a mean difference vs placebo of −0.66% (95% CI −0.73% to −0.58%) and a mean difference vs other antihyperglycemic medications of −0.06% (95% CI 0.18% to 0.05%).[32]

Weight loss

The same meta-analysis found that SGLT-2 inhibitors reduced body weight (mean difference −1.8 kg, 95% CI −3.50 kg to −0.11 kg).[32] And in a randomized controlled trial, monotherapy with canagliflozin 100 mg/day and 300 mg/day resulted in body weight reduction of 2.2% (1.9 kg) and 3.3% (−2.9 kg), respectively, after 26 weeks.[33] A Japanese study showed a dose-related total body weight loss with empagliflozin vs placebo ranging from 2.5 ± 0.2 kg (5-mg dose) to 3.1 ± 0.2 kg (50-mg dose) after 12 weeks.[34] Bolinder et al[35] reported that adding dapagliflozin 10 mg to metformin in patients with type 2 DM reduced total body weight by −2.96 kg (95% CI −3.51 to −2.41, $P < .001$) at week 24. Whole-body dual-energy x-ray absorptiometry and magnetic resonance imaging findings in this study revealed a decrease in fat mass and visceral and subcutaneous adipose tissue after treatment with dapagliflozin, thus suggesting urinary loss of glucose (and hence caloric loss) contributing to weight reduction in addition to initial weight loss from fluid loss due to osmotic diuresis.[35] A continuous decline in total body weight was observed in a 78-week extension study resulting in −4.54 kg (95% CI −5.43 to −3.66 kg) at week 102, along with further reduction in total body fat mass as measured by dual-energy x-ray absorptiometry.[36]

Cardiovascular outcomes

The landmark study Empagliflozin, Cardiovascular Outcomes and Mortality in Type 2 Diabetes (EMPA-REG) involving 7,020 patients was the first large cardiovascular outcomes trial in patients with type 2 DM and overt cardiovascular disease. A relative risk reduction of 14% (12.1% to 10.5%, HR 0.86, 95% CI 0.74 to 0.99) in major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) was observed with empagliflozin.[37] Rates of all-cause mortality and hospitalization for heart failure relative risk reductions were 32% (8.3% to 5.7%; HR 0.68 [0.57, 0.8]) and 35% (4.1% to 2.7%; HR 0.65 [0.50, 0.85]), respectively, with empagliflozin. The mechanism behind this cardiovascular benefit is unknown but is currently being explored.[37]

Adverse effects

Increased risk of urinary tract and genital infections are known adverse effects of SGLT-2s. Other effects noted include postural hypotension from volume depletion and a transient increase in serum creatinine and decrease in glomerular filtration.[29]

NEUROENDOCRINE PEPTIDE HORMONE: AMYLIN ANALOGUES

Mechanism of action

Amylin is a 37-amino-acid neuroendocrine peptide hormone secreted primarily by pancreatic beta cells. It promotes early satiety, and its anorexigenic effects are mediated by its action on the neurons of the area postrema in the brain.[38] After a meal, amylin decreases gastric acid secretion and slows gastric emptying. It is co-secreted with insulin in a 1:20 amylin-to-insulin ratio and inhibits glucagon secretion via a centrally mediated mechanism.[39]

Pramlintide (Symlin) is an amylin analogue administered subcutaneously immediately before major meals. It decreases postprandial glucose levels and has been approved by the FDA as an adjunct to prandial insulin in patients with type 1 and type 2 DM.[40]

HbA1c

Amylin secretion is impaired in type 1 and type 2 DM, and small but significant reductions in HbA1c have been observed with addition of pramlintide to usual insulin regimens. In patients with type 1 DM, HbA1c levels were reduced by 0.4% to 0.6% after 26 weeks on 30 µg 3 times daily to 60 µg 4 times daily of pramlintide added to insulin.[41,42] And pramlintide 120 µg added to usual antihyperglycemic therapy in patients with type 2 DM has been reported to decrease HbA1c by 0.7% at week 16 or 26.[43,44]

Weight loss

A meta-analysis of 8 randomized controlled trials assessed the effects of pramlintide on glycemic control and weight in patients with type 2 DM treated with insulin and in obese patients without diabetes.[45] In these trials, patients took at least 120 µg of pramlintide before 2 to 3 meals for at least 12 weeks; a total of 1,616 participants were included. In the type 2 DM group, pramlintide reduced body weight by 2.57 kg (95% CI −3.44 to −1.70 kg, $P < .001$) vs control, over 16 to 52 weeks.[45] The nondiabetic obese group had a weight loss of −2.27 kg (95%CI −2.88 to −1.66 kg, $P < .001$) vs control.[45]

Pramlintide and a pramlintide-phentermine combination are currently under investigation for treatment of obesity.[23]

Cardiovascular outcomes

Cardiovascular outcomes in patients treated with pramlintide have not been studied to date, but reductions have been observed in markers of cardiovascular risk including high-sensitivity C-reactive protein and triglycerides.[46]

Adverse effects

Transient mild-to-moderate nausea is the most common adverse effect of pramlintide. Hypoglycemia has also been reported, more frequently in patients with type 1 DM, which is possibly associated with inadequate reduction in insulin.

ALPHA-GLUCOSIDASE INHIBITORS

Mechanism of action

Alpha-glucosidase inhibitors competitively inhibit the alpha-glucosidase enzymes at the brush border of the small intestine. Taken orally before meals, these drugs mitigate postprandial hyperglycemia by preventing the breakdown of complex carbohydrates into simpler monosaccharides, thus delaying their absorption.[47] These agents may be used as monotherapy or in combination with other antihyperglycemic agents. They work independently from insulin, although they have been shown to potentiate GLP-1 secretion.[48] Acarbose and miglitol are currently approved in the United States. Acarbose has been more extensively studied worldwide.

HbA1c

Alpha-glucosidase inhibitors have been reported to reduce mean HbA1c by 0.8% (95% CI −0.9% to −0.7%), as well as fasting and postprandial glucose, and postprandial insulin levels.[49]

Weight loss

There is conflicting evidence on whether alpha-glucosidase inhibitor therapy has a neutral or beneficial effect on body weight. A Cochrane meta-analysis observed significant BMI reduction with acarbose, although no effect on body weight was noted,[49] whereas in another meta-analysis, body weight was significantly reduced by 0.96 kg (95% CI −1.80 to −0.12 kg) when acarbose was added to metformin.[50] A review of pooled data from worldwide post-marketing studies for acarbose reported a weight reduction after 3 months of 0.98 ± 2.11 kg in overweight patients and 1.67 ± 3.02 kg in obese patients.[51]

Cardiovascular outcomes

In the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM), when compared with

placebo, treatment of patients with impaired glucose tolerance with acarbose significantly reduced the incidence of cardiovascular events (HR 0.51, 95% CI 0.28 to 0.95, $P = .03$), myocardial infarction (HR 0.09, 95% CI 0.01 to 0.72, $P = .02$), and newly diagnosed hypertension (HR 0.66, 95% CI 0.49 to 0.89, $P = .006$).[52]

Adverse effects

Although mild, gastrointestinal effects of flatulence and diarrhea can be bothersome and result in discontinuation of the drug in most patients.

METFORMIN

Mechanism of action

Metformin is the first-line antihyperglycemic agent for type 2 DM recommended by the American Diabetes Association and European Association for the Study of Diabetes.[53,54] The main action of metformin is to decrease glucose production in the liver. In the small intestine, metformin stimulates the L cells to produce GLP-1, and in skeletal muscle, it increases glucose uptake and disposal.[55]

HbA1c

As monotherapy, metformin has resulted in HbA1c reductions of 0.88% to 1.2%.[55]

Weight loss

Reduced food intake[56,57] and gastrointestinal intolerance[58] occurring early in therapy have been noted to account for weight loss in short-term studies of nondiabetic obese patients treated with metformin.[59] Long-term trials of patients with and without diabetes have yielded mixed results on weight reduction from metformin as monotherapy or adjunct therapy. In the United Kingdom Prospective Diabetes Study (UKPDS), metformin had resulted in approximately 1.5 kg of weight gain (slightly less than the 4-kg weight gain in the glibenclamide group).[60] Improved antihyperglycemic efficacy of other antihyperglycemic agents (insulin, sulfonylureas, and thiazolidinediones) with addition of metformin led to dose-lowering of the antihyperglycemic agents, ultimately resulting in amelioration of weight gain; this has also led to small weight reductions in some studies.[59] In the Diabetes Prevention Program study of patients with impaired glucose tolerance, metformin treatment resulted in an average weight loss of 2.1 kg compared with placebo (−0.1 kg) and lifestyle intervention (−5.6 kg; $P < .001$).[61]

Cardiovascular outcomes

Metformin has been observed to decrease micro- and macrovascular complications. Compared with diet alone, metformin was associated with a 39% reduction in the risk of myocardial infarction, and a 30% lower risk of a composite of macrovascular diseases (myocardial infarction, sudden death, angina, stroke, and peripheral disease).[60]

Adverse effects

The most common adverse effect of metformin is gastrointestinal intolerance from abdominal pain, flatulence, and diarrhea.[62] Metformin-associated lactic acidosis is a serious and potentially life-threatening effect; and vitamin B_{12} deficiency may occur with long-term treatment.[62]

TAKE-HOME POINTS

As more medications and interventions are being developed to counter obesity, it also makes sense to select diabetes medications that do not contribute to weight gain in patients who are already overweight or obese. The effects of available medications can be maximized and treatment regimens individualized (based on patients' needs and preferences, within the limitations of drug costs and side effects), along with lifestyle modification, to target diabesity.

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