

# Management of Type 2 Diabetes in the Setting of Morbid Obesity: How Can Weight Gain Be Prevented or Reversed?

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## Presentation

The patient is a 48-year-old African-American man with type 2 diabetes diagnosed at age 41 on laboratory testing when his A1C was found to be 10.8%. At diagnosis, he was 73 inches tall and weighed 337 lb (153 kg), resulting in a BMI of 44.5 kg/m<sup>2</sup>. Metformin and premixed insulin NPH/lispro 75/25 were started. He was also noted to have uncontrolled hypertension, with a blood pressure of 174/88 mmHg, and hyperlipidemia.

From age 41 to age 42 years, his diabetes was well controlled, with A1C ranging between 5.9 to 6.8%. However, he gained 46 lb from age 41 to 43. His A1C started to rise and ranged between 7.3 and 8.8% from age 43 to age 45. His primary care provider increased his insulin doses and added sitagliptin to his diabetes therapy regimen. However, the patient continued to gain weight, increasing by 40 lb from age 43 to age 45.

He presented to the endocrinology clinic at age 48 with an A1C of 16.7%. His weight was 497 lb (225 kg), and his BMI was 65.6 kg/m<sup>2</sup>. His total weight gain over the past 7 years was 160 lb. His current diabetes medication regimen consisted of NPH/aspart 70/30 insulin 30 units twice daily (0.27 units/kg/day), sitagliptin 100 mg daily, and metformin 1,000 mg twice daily. His blood glucose levels were in the 400- to 500-mg/dL range. He complained

of severe fatigue, shortness of breath, polyuria, and polydipsia.

His diet was unrestricted, with unlimited portions. He binged on sweets and junk food, consuming an average of eight chocolate cupcakes twice per week. Alcohol use had been heavy for years, and he reported drinking a pint of cognac per day. His main attempts at weight loss in the past included Weight Watchers and walking, resulting in a maximum 25-lb weight loss. He had not been able to walk long distances in the past 2–3 years, however, because of knee and back pain.

His other medical conditions included hypertension, hypercholesterolemia, sleep apnea, osteoarthritis in his back and both knees, depression, and gout. Despite taking three blood pressure medications (lisinopril 40 mg, amlodipine 5 mg, and furosemide 20 mg), his hypertension was still poorly controlled. He was taking simvastatin 40 mg every evening for hyperlipidemia. In addition, he took acetaminophen with codeine and ibuprofen on a daily basis for his back and knee pain.

The patient required assistance to perform activities of daily living, primarily bathing and driving long distances. He used a wheelchair when he was out of the house and a lift chair at home.

On physical exam, he was morbidly obese, with a BMI of 65.6 kg/m<sup>2</sup>. His blood pressure was 165/94 mmHg, and his heart rate was 85 bpm. During the exam, he was markedly short of

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breath when changing position from sitting to standing. He had acanthosis nigricans and skin tags on the posterior neck and bilateral axillae. He had no abnormal striae.

We discussed options for treatment of his poorly controlled diabetes and multiple comorbidities. With an A1C of 16.7% and severe symptomatic hyperglycemia, he required additional insulin in conjunction with aggressive lifestyle changes. We discussed changing his current twice-daily premixed insulin regimen to a more physiological basal-bolus insulin regimen consisting of detemir insulin administered once or twice daily plus three injections of rapid-acting insulin aspart with meals. He was advised to start detemir insulin 40 units twice daily plus aspart insulin 25 units before each meal. Metformin and sitagliptin were continued.

After 1 month, his blood glucose levels improved to the 130- to 260-mg/dL range. His A1C declined to 13%. He eliminated alcohol, stopped drinking all sugary beverages, and markedly reduced his intake of sweets and junk food. However, his diet was still poor. He continued to have an insatiable appetite, causing him difficulty with limiting portion sizes. His weight increased to 541 lb, with a BMI of 71.4 kg/m<sup>2</sup>.

He was referred to a dietitian. His detemir dosage was increased to 50 units in the morning and 50 units at bedtime. His aspart was increased to 35 units before each meal. The goal was to bring his A1C down to ≤9% within 2–3 months. With the improved A1C, his insurance would approve the use of a glucagon-like peptide 1 (GLP-1) receptor agonist. At that time, we would stop sitagliptin and start liraglutide, to be titrated to 1.8 mg every morning, as tolerated. The purpose of using liraglutide is to help with suppression of appetite, limit insulin requirements, and encourage weight loss.

Given this patient's morbidly obese state, multiple uncontrolled comorbid conditions, and low like-

lihood of achieving enough weight loss to ameliorate these conditions with lifestyle and medications alone, he was also referred to the weight loss management program. This program will evaluate him for initiation of a very-low-calorie diet and help him increase his physical activity as a bridge to evaluation for bariatric surgery.

### Questions

1. Medications used to treat diabetes often result in weight gain. Which medications used to treat diabetes can prevent or attenuate weight gain while also improving glycemic control?
2. What is the role of weight loss medications in obese patients with diabetes?
3. When should bariatric surgery be considered for treatment of type 2 diabetes?
4. What is recommended by consensus guidelines for the treatment of type 2 diabetes in morbidly obese individuals?

### Commentary

According to the Centers for Disease Control and Prevention, an estimated 69% of adults >20 years of age are either overweight or obese, with ~35% of these falling into the obese category (1). Obesity is associated with increased morbidity from multiple chronic conditions, including hypertension, dyslipidemia, type 2 diabetes, cardiovascular disease, osteoarthritis, sleep apnea, some cancers, gallbladder disease, and fatty liver disease.

Excess body weight is an established risk factor for type 2 diabetes. Patients with type 2 diabetes are frequently prescribed glucose-lowering medications associated with weight gain. This increase in weight can lead to worsening insulin resistance and the need for intensification of treatment (especially with higher doses of insulin), leading to further weight gain. The effects of diabetes medications on weight need to be taken into consideration to prevent the contin-

uation of this vicious cycle of weight gain and higher insulin doses.

The patient in this case had multiple poorly controlled chronic conditions, including diabetes, hypertension, hyperlipidemia, osteoarthritis, and sleep apnea. The crux of his medical issues was his morbid obesity. However, his most pressing issue at present is his poor glycemic control. The treatment decisions for his diabetes were complicated by his already present morbid obesity, progressive weight gain since diagnosis of diabetes and initiation of treatment, and continued increase in weight with intensification of his diabetes care regimen.

It is important to recognize the association between many glucose-lowering medications and weight gain. The diabetes medications known to be associated with weight gain include sulfonylureas, thiazolidinediones (TZDs), and insulin. With regard to oral medications, the U.K. Prospective Diabetes Study (UKPDS) found that sulfonylureas increased weight by 3.5–4.8 kg in a 3-year period compared to no change in body weight with the use of metformin (2). TZDs are also associated with weight gain of 3–4 kg but have largely fallen out of favor because of concerns regarding increased cardiovascular and fracture risk and cancer. Given the known consequence of weight gain, sulfonylureas and TZDs generally should be avoided in patients who are already overweight, obese, or susceptible to becoming overweight or obese.

Insulin treatment is very effective but results in the greatest amount of weight gain. In the UKPDS, insulin treatment resulted in more weight gain than sulfonylureas. Subjects with type 2 diabetes who took insulin gained an average 7 kg in a 10-year period compared to gains of 3.5–5 kg for those who took sulfonylureas (3).

Intensity of treatment, insulin dose, change in A1C, and frequency of hypoglycemia are all factors influencing the degree of weight gain

(4). A meta-analysis and systematic review showed that increase in body weight is lower with basal insulin than with a twice-daily insulin regimen or a prandial insulin regimen, although higher insulin doses in the latter two regimens may explain the differences (4). Weight gain was also found to be lower with use of detemir versus NPH or glargine; no difference was found in weight gain with NPH compared to glargine (4).

Based on this information, if insulin is required, basal regimen is preferred over a premixed twice-daily regimen or use of only prandial insulin without basal insulin. Detemir is the preferred basal insulin, if needed.

In recent years, alternative medications for diabetes that are weight neutral or promote weight loss have become available. These medications include metformin, GLP-1 receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter 2 (SGLT2) inhibitors.

Metformin should be used as initial pharmacological therapy in type 2 diabetes unless contraindications exist. Metformin has well-known advantages, including the ability to lower A1C by 1–2%, a good safety profile, lack of hypoglycemia when used as monotherapy, no weight gain and possible modest weight loss, and availability as a generic, providing a cost advantage. The UKPDS showed that metformin decreased diabetes-related endpoints in overweight individuals with type 2 diabetes (5). The 10-year follow-up of the UKPDS showed persistent and significant risk reductions in diabetes-related endpoints, myocardial infarction, and death from any cause in the metformin group (6). In terms of weight loss, a 29-week, double-blind, placebo-controlled study of metformin and glyburide, alone and in combination, in obese patients with type 2 diabetes showed that metformin alone resulted in a weight loss of 8 lb compared to a gain of 0.9 lb and a loss of 0.7 lb in

the combination and glyburide-only groups, respectively (7).

The incretin mimetics—GLP-1 receptor agonists and DPP-4 inhibitors—are newer agents recommended for use in overweight or obese individuals with diabetes. GLP-1 receptor agonists lower postprandial glucose excursions by stimulating glucose-dependent insulin secretion, slowing gastric emptying, suppressing postmeal glucagon secretion, and increasing satiety (8). This class of medications includes exenatide twice daily, exenatide extended release, liraglutide, albiglutide, and dulaglutide. These drugs are approved for use as monotherapy or in combination with oral agents. Exenatide twice daily, liraglutide, and albiglutide are also approved for use with basal insulin. GLP-1 receptor agonists significantly improve postprandial glucose levels, lower A1C by 1–2%, have a low incidence of hypoglycemia, and can result in significant weight loss over time (–2–5 kg) (8). Studies comparing GLP-1 receptor agonists to other glucose-lowering agents have shown weight losses up to 5.5 and 8 kg, making this a top choice in patients with type 2 diabetes and obesity (9). The main drawback of GLP-1 receptor agonists includes nausea, which wanes over time and is minimized through slow dose titration. Post-marketing reports of pancreatitis and animal data demonstrating C-cell proliferation and medullary thyroid carcinoma are also potential concerns with use of these drugs.

DPP-4 inhibitors block the enzyme responsible for inactivation of GLP-1, prolonging the beneficial effects of GLP-1 described above. The medications in this class include sitagliptin, saxagliptin, linagliptin, and alogliptin. The benefits of these medications are their safety in patients with chronic kidney disease, lack of hypoglycemia, and weight neutrality. The drawbacks of the DPP-4 inhibitors are lower efficacy, with A1C lowering of 0.6–0.8%, cost, and lack of established long-term safety. These

medications are good second-line agents after metformin in patients who are close to their A1C goal and have concerns regarding hypoglycemia and weight gain.

SGLT2 inhibitors are a relatively new class of oral medication for the treatment of diabetes. The first of this class of drugs, canagliflozin, was approved in March 2013. Other SGLT2 inhibitors approved for use in the United States include dapagliflozin and empagliflozin. SGLT2 inhibitors lower blood glucose and A1C by promoting renal excretion of glucose through blockade of SGLT2 expression in the proximal convoluted tubule of the kidney. The advantages of these medications in obese and overweight individuals with type 2 diabetes are their efficacy, with A1C reduction of 0.6–1%, and associated weight loss of 2–3 kg (10,11).

Choosing medications that are weight neutral or associated with weight loss as initial and subsequent treatment for type 2 diabetes in overweight and obese individuals is in accordance with the American Diabetes Association (ADA) *Standards of Medical Care in Diabetes* (12) and the ADA/European Association for the Study of Diabetes position statement on hyperglycemia management in type 2 diabetes (13). These publications stress a patient-centered approach focusing on patient preferences, cost, potential side effects, effects on body weight, and hypoglycemia risk. The Endocrine Society guidelines on pharmacological management of obesity (14), published in February 2015, also recommend use of metformin, GLP-1 receptor agonists, and SGLT2 inhibitors in individuals with type 2 diabetes and obesity for the dual benefit of weight loss and improved glycemic control. Most available evidence shows the most significant weight loss with GLP-1 receptor agonists, supporting trial of this class of medications in overweight or obese patients with type 2 diabetes whose diabetes is not

controlled with their current regimen or even as monotherapy.

The patient in this case had morbid obesity that was worsening with escalating insulin doses. He had multiple comorbidities and had experienced a significant decline in quality of life, requiring assistance with activities of daily living. After his severe hyperglycemia is addressed and managed, the morbid obesity will need to be evaluated and treated. Obesity is the underlying cause of his poor overall health status and multiple medical problems.

In 2013, the American Medical Association recognized obesity as a disease that should be treated and prevented (15). Greater weight loss produces more benefits, but weight loss of even as little as 3–5% of body weight can improve some cardiovascular risk factors. The American Heart Association/American College of Cardiology/The Obesity Society 2013 guidelines (16) recommend initial weight loss of 5–10% of body weight within 6 months as a realistic and clinically meaningful goal. Weight loss of 5–10% has been shown to significantly reduce development of type 2 diabetes in those with prediabetes (17). In overweight and obese patients with type 2 diabetes, weight loss of 5–10% is associated with reduced A1C, improved fitness, and improvement in all cardiovascular risk factors except LDL cholesterol levels, despite having no effect on the rate of cardiovascular events (18).

Comprehensive lifestyle intervention with a trained nutritional professional is absolutely essential as part of the treatment plan. It is a challenge, however, for obese and overweight patients with type 2 diabetes to achieve adequate weight loss and to maintain any reduction in weight with lifestyle changes alone. As weight is lost, an increase in appetite occurs, and resting energy expenditure declines. Weight loss results in a rise in circulating levels of ghrelin, an orexigenic hormone, and a decline in the anorexigenic hor-

mones peptide YY, cholecystokinin, leptin, and insulin (19). These hormonal changes have been found to persist for at least 1 year after weight loss, resulting in increased appetite and likely weight regain (19).

In the past 1–2 years, weight loss medications targeting this increase in appetite have been developed and approved for use in obese or overweight individuals with related comorbidities. Pharmacotherapy can be used as an adjunct to diet, exercise, and behavioral modification for individuals with a BMI  $\geq 27$ – $29.9$  kg/m<sup>2</sup> and at least one comorbid condition or a BMI  $>30$  kg/m<sup>2</sup> with or without comorbid conditions. These comorbid conditions include hypertension, dyslipidemia, type 2 diabetes, and obstructive sleep apnea.

One question that arises is when to use these pharmacological weight loss medications in overweight or obese individuals with type 2 diabetes. The Endocrine Society guidelines (14) recommend a trial of one or more of the diabetes medications discussed above (metformin, GLP-1 receptor agonists, or SGLT2 inhibitors) before consideration of additional medications designed specifically for weight loss. If chronic weight loss medications are being considered, patients and their providers can choose from five pharmacological agents: orlistat, lorcaserin, combination phentermine-extended release topiramate, combination bupropion-naltrexone, and liraglutide 3 mg daily, a higher dose than is approved for treatment of diabetes. Most of these medications work in the central nervous system, specifically at the arcuate nucleus and pro-opiomelanocortin, to promote satiety. Orlistat, an inhibitor of gastric and pancreatic lipases, has a different mechanism of action that involves impairment of fat digestion. Resulting weight loss from these anti-obesity medications ranges from 3 to 10% compared to placebo (14,20–24).

In this patient with morbid obesity and a BMI 65 kg/m<sup>2</sup>, the

likelihood of achieving clinically sufficient weight loss with lifestyle intervention and the addition of liraglutide was low. Bariatric surgery may be a reasonable option to improve weight-related outcomes and comorbid conditions. Recent randomized, controlled trials comparing medical therapy to bariatric surgery in obese subjects with type 2 diabetes have demonstrated that bariatric surgical procedures can improve glycemic control and reduce cardiovascular risk factors better than medical therapy alone (25–29). The most well-known randomized control trial is the STAMPEDE (Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently) study (27). This trial compared intensive medical therapy alone to intensive medical therapy plus roux-en-Y gastric bypass (RYGB) or a sleeve gastrectomy (SG) in obese patients (BMI 27–43 kg/m<sup>2</sup>) with uncontrolled type 2 diabetes (average A1C  $9.2 \pm 1.5\%$ ). Results at 3 years showed that the primary endpoint of A1C  $\leq 6.0\%$  was achieved by a significantly greater percentage of subjects in the surgical groups than in the medical therapy group (38% gastric bypass, 24% SG, and 5% medical therapy). Beneficial changes were also seen in HDL cholesterol, triglycerides, and albuminuria in the surgical groups, but not the group receiving only medical treatment.

Several major medical societies have published guidelines with regard to which patients are candidates for bariatric surgery (16,30,12). The 2015 ADA *Standards of Medical Care in Diabetes* (12) recommended consideration of bariatric surgery for adults with type 2 diabetes and a BMI  $>35$  kg/m<sup>2</sup>, especially if diabetes or associated comorbidities are difficult to control with lifestyle modification and pharmacological therapy. Small trials have shown some glycemic benefit of bariatric surgery in patients with type 2 diabetes and a BMI of 30–35 kg/m<sup>2</sup>, but there are not yet sufficient data to recommend surgery in these patients (12).

The patient in this case meets the criteria for considering bariatric surgery, but the risks of surgery with his current uncontrolled comorbid conditions must be weighed against the benefits of potential amelioration of his diabetes, sleep apnea, hyperlipidemia, and osteoarthritis. With regard to the choice of bariatric surgical procedure, the American Association of Clinical Endocrinologists/Obesity Society/American Society for Metabolic and Bariatric Surgery 2013 guidelines (30) recommend that individualized goals of therapy (i.e., weight loss, metabolic regulation, and glycemic control), available local expertise, patient preferences, and personal risk stratification be taken into account. Laparoscopic RYGB or SG may be reasonable choices to improve this patient's glycemic control while avoiding the associated nutritional risks associated with biliopancreatic diversion procedure and increased risk for weight regain and lower efficacy of laparoscopic adjustable gastric banding.

### Clinical Pearls

- Obesity is now recognized as a disease that warrants diagnosis, evaluation, treatment, and prevention.
- Obesity is often the crux of a patient's multiple medical problems. The presence of obesity should be recognized in patients with type 2 diabetes and treated along with the diabetes.
- Individuals with type 2 diabetes who are obese or overweight should be treated with glucose-lowering agents that are weight neutral or associated with weight loss unless contraindications exist. These agents include metformin, GLP-1 receptor agonists, or SGLT2 inhibitors, which can be used alone or in combination.
- Additional pharmacological agents designed specifically for weight loss can be considered if weight loss is not sufficient despite the use of glucose-lowering agents

associated with positive effects on weight.

- Bariatric surgery can be considered in adults with a BMI >35 kg/m<sup>2</sup> and type 2 diabetes and/or associated comorbidities that are difficult to control with lifestyle modification and pharmacological therapy.

### Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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