CLINICAL VIGNETTE

GLP-1 Receptor Agonist Use for Uncontrolled Type 2 Diabetes and Insufficient Weight Loss after Bariatric Surgery

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Case

A 52-year-old male with type 2 diabetes mellitus returns for follow up. His past medical history includes: obesity, dyslipidemia, hypertension, and prior sleeve gastrectomy six years ago. Before his sleeve gastrectomy, his diabetes was managed with insulin glargine & lixisenatide injection 60 units daily, empagliflozin 10 mg daily, and metformin 1000 mg twice daily. His BMI was 35.8, weighing 221 pounds, with height of 5 foot 7 inches. Labs were significant for a hemoglobin A1c of 8.7%. He lost 50 pounds three years after his bariatric surgery, with a nadir of 171 pounds. Insulin glargine was reduced to 14 units daily. At this point, he began gaining weight and his blood sugars increased. Empagliflozin was started for its weight loss benefit and was discontinued due to overnight polyuria. He switched to dulaglutide 0.75 mg weekly, which was better tolerated. Dulaglutide was titrated to 1.5 mg weekly, and insulin was stopped. Hemoglobin A1c improved to 6.6%. Dulaglutide was further increased to 3 mg weekly for additional glucose control and weight loss. He continues to tolerate dulaglutide without any side effects or hypoglycemia. His weight was now 165 pounds, and his A1c of 6.2% (see Table 1).

Discussion

Obesity and uncontrolled diabetes mellitus remain challenges for some patients after bariatric surgery (BS), with various outcomes. Approximately 20–25% of patients report either regain of weight or insufficient weight loss (<50% excess weight loss), which hinder remission of comorbidities.[1,2] Due to regain of weight or insufficient weight loss, patients may experience only partial remission of comorbidities.[2] Despite the increasing use of bariatric surgery, there remains insufficient data to address post BS, the treatment of relapsed type 2 diabetes and weight regain. To optimize metabolic outcomes for patients with type 2 diabetes and morbid obesity, understanding the pathophysiology after BS, the frequency of type 2 diabetes relapse post-BS, and reviewing data on the use of glucagon-like peptide 1 (GLP-1) receptor agonists after BS is essential.

Depending on the procedure, weight loss after BS is due to a combination of gastric restriction, malabsorption, and possibly hormonal changes. Our patient underwent a sleeve gastrectomy, the most commonly chosen BS.[3] Sleeve gastrectomy can remove up to 80% of the fundus of the stomach, thereby reducing ghrelin levels.[4,5] All peripheral hormones from the intestines and adipose tissue, as well as nutrients, act on first-order central neurons in the arcuate nucleus of the hypothalamus. These peripheral hormones activate either the weight-gaining (NPY/AgRP) pathway or the weight-loss (POMC/CART) neuron system. Ghrelin is an orexigenic hormone, and the reduction of this hormone leads to a significant decrease in appetite via decreased activity of the NPY/AGrP orexigenic pathway.[6] After a sleeve gastrectomy, there is also improved insulin secretion and exaggerated postprandial rise in GLP-1. The weight loss from the surgery contributes to improved insulin sensitivity, and neurohormonal changes contribute to satiety and improved function of endogenous insulin in patients with diabetes.[3,5]

While the general mechanism for weight loss after a sleeve gastrectomy is known, the exact pathophysiologic mechanism for weight loss and diabetes remission another, common BS Roux-en-Y gastric bypass (RYGB) is less well understood.[3,7] Fifty to seventy-five percent of post-RYGB weight loss is related to gastric restriction, and 5% of the weight loss can be attributed to malabsorption. The remaining post-RYGB weight loss remains unexplained. Most likely, neurohormonal changes, such as increases in GLP-1 and PYY levels, also impart anorectic effects.[5,7] Other hypotheses explaining weight loss include increased resting energy expenditure and dumping syndrome.[5] Weight loss, avoidance of stimulation of cells producing the anti-incretin factor, and earlier and/or increased GLP-1 production lead to improved insulin function and sensitivity in patients with diabetes.[7]

The majority of patients with type 2 diabetes who undergo BS need continued monitoring and treatment of their diabetes and weight. It is now well-recognized that a majority of patients will continue to have type 2 diabetes, either from lack of initial remission of type 2 diabetes or relapse of type 2 diabetes, years after their BS.[2,8,9] The Swedish Obese Subjects (SOS) study included 342 subjects with preexisting type 2 diabetes. Seventy-two percent of subjects had diabetes remission two years after BS, but only 36% of these subjects remained diabetes-free at 10-year follow-up, a 50% relapse rate.[10] The majority of the surgeries included either vertical banded gastroplasty or gastric banding. A more recent study included a cohort of 736 patients with type 2 diabetes who underwent primary RYBG or sleeve gastrectomy. Fifty-eight percent of patients experienced diabetes remission in the first year after surgery, 62% after RYBG and 41% after sleeve gastrectomy. After eight years

follow-up, 32% of the patients who initially achieved diabetes remission experienced relapse with type 2 diabetes.[2]

Patients with type 2 diabetes after BS continue to require diabetes treatment and optimization of their weight. GLP-1 receptor agonists and other incretin therapy can be used adjunctively with BS. Our patient demonstrates the benefit of using a GLP-1 receptor agonist after sleeve gastrectomy to help with insulin cessation, optimization of glycemic control, and further weight loss. At the time of his sleeve gastrectomy, existed on safety and efficacy of GLP-1 receptor agonists after BS. Use of GLP-1 receptor agonist on top of insulin were recommended to reduce insulin burden and optimize his weight. New data are now available which demonstrate the safety of GLP-1 receptor agonists after BS. A 2022 retrospective observational study published by Jensen et al. showed no serious adverse events in fifty patients receiving GLP-1 receptor agonist treatment post-BS.[11] After six months of GLP-1 receptor agonist treatment, there was a significant reduction of 8.8% in total body weight and BMI decrease of 2.9 kg/m2, correlating to 67.4% of weight regain.[11] Our patient experienced a 10 pound weight loss and an A1c reduction of 0.9% on dulaglutide 3 mg weekly, achieving to his A1c goal of <6.5%.

Our patient highlights the challenge of treating obesity and type 2 diabetes after BS. While BS offers significant potential for weight loss and remission of type 2 diabetes, weight regain and insufficient weight loss challenges, affecting the long-term management. Understanding the pathophysiological mechanisms underlying different BS procedures, such as sleeve gastrectomy and RYGB, is crucial for optimizing outcomes. Long-term studies, like the SOS study, demonstrate need for continued monitoring and treatment of type 2 diabetes post-BS, given the significant relapse rates observed. Incorporating adjunctive therapies like GLP-1 receptor agonist and other new incretin therapies shows promise in improving glycemic control and aiding weight management. Recent research demonstrates their safety and efficacy post-BS. Our patient further highlights the potential benefits of such therapies in achieving glycemic goals and addressing weight concerns in patients post-BS. Future research is needed to refine treatment approaches and enhancing outcomes for individuals with type 2 diabetes and obesity following BS.

Table 1: Diabetes Therapy, A1c, Weight, and BMI Before and After Sleeve Gastrectomy

Date	Diabetes therapy	A1c	Weight	BMI
5/5/2017	Insulin glargine & lixisenatide injection 60 units daily, empagliflozin 10 mg daily, and metformin 1000 mg twice daily	8.7%	221 lbs (100.6 kg)	35.8
12/5/2017	Insulin glargine 15 units daily; other diabetes medicines discontinued Note: Sleeve Gastrectomy performed	7.8%	215 lbs (97.8 kg)	34.8
9/25/2018	Insulin glargine 14 units daily and empagliflozin 10 mg daily added	8.1%	171 lbs (77.8 kg)	26.9
6/17/2020	Insulin glargine 14 units daily and dulaglutide 0.75 mg weekly added	7.3%	175 lbs (79.4 kg)	27.4
7/20/2020	Dulaglutide increased to 1.5 mg weekly and insulin stopped	--	175 lbs (79.4 kg)	27.4
11/15/2021	Dulaglutide 1.5 mg weekly increased to dulaglutide 3 mg weekly	6.6%	175 lbs (79.4 kg)	27.4
7/19/2023	Dulaglutide 3 mg weekly	6.2%	165 lbs (75 kg)	25.9

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