The Role of Bariatric Surgery in the Era of GLP-1 Receptor Agonists

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ABSTRACT

Obesity continues to be a significant public health issue resulting in morbidity, premature mortality, and substantial costs to the healthcare system. Effective treatments for obesity and its associated co-morbidities exist. Bariatric surgery has been well studied and shown to be safe and effective. Glucagon-like peptide receptor agonists (GLP-1 RAs) are relatively newer but have also been shown to result in substantial weight loss. We reviewed the current literature on both bariatric surgery and GLP-1 RAs and will present the pros and cons of each as well as a discussion of the roles they play in treating obesity. Our goal was to provide a comprehensive reference that can be used by all providers treating obesity to have educated discussions about the current state of treatment options with their patients.

KEYWORDS: Obesity, Bariatric Surgery, GLP-1 Receptor Agonists

INTRODUCTION

Obesity is a widely prevalent medical condition affecting 40% of Americans and 30% of Rhode Islanders.[1,2] The pathophysiology of obesity is still not completely understood and involves a complicated interplay between a variety of hormones and neural pathways as well as the influence of an individual's genetic makeup, environment, socioeconomic status and comorbidities.[1,3] Obesity is associated with increased risk of cardiovascular disease, type II diabetes mellitus (DM), obstructive sleep apnea (OSA), cancer, osteoarthritis, and premature death and results in hundreds of billions of dollars in direct medical costs annually.[1,4,5] The mainstay of treatment for obesity is behavioral change including adopting a healthy diet and increased physical activity; however, this results in insufficient weight loss in a significant number of patients.[6] Since its advent in the 1950s, bariatric surgery has emerged as an increasingly safe and effective option.[6] More recently, anti-obesity medications, specifically glucagon-like peptide receptor agonists (GLP-1 RAs), have become increasingly popular with their use for obesity treatment doubling between 2022 and 2023, while the rates of bariatric surgery during that time decreased by 8.7%.[7] This review will highlight the pros and cons of GLP-1 receptor agonists, compare them to bariatric surgery, and show how the two modalities each have roles both as adjunctive and independent treatments for obesity.

BARIATRIC SURGERY

Long-term data has shown that bariatric surgery is a safe and effective means of achieving significant weight loss. Undergoing bariatric surgery alters more than just a patient's anatomy. It shifts their metabolic setpoint affecting hypothalamic gene expression and changing fat and hormone levels, including increasing GLP-1 secretion, which contributes to changes in caloric intake and energy expenditure.[3,8,9] Currently, bariatric surgery is recommended in patients with a BMI of ≥35 or 30–34.9 with obesity-related co-morbidities such as hypertension, DM, hyperlipidemia, and OSA. The two most common procedures are the sleeve gastrectomy, which accounted for 58.2% of all bariatric procedures in 2023 and the Roux en Y gastric bypass (RYGB), which made up 23.4% of bariatric procedures in 2023.[10] Patients lose, on average, 57% of their excess weight after sleeve gastrectomy and 67% of excess weight after RYGB.[11] Bariatric surgery also effectively treats comorbidities such as DM and cardiovascular disease and has been shown to reduce mortality in studies with long-term follow-up.[1,11-14] A Cochrane review of 22 trials found that, regardless of the procedure, bariatric surgery was more effective than any non-surgical option for achieving weight loss and improvement in associated co-morbidities.[15] There have also been many studies showing that bariatric surgery is cost effective despite the relatively high up-front price tag.[16-19] However, some patients do experience insufficient weight loss or weight regain in addition to post-operative complications, which are procedure dependent but include stenosis (1–19%), leak (.6–7%), internal hernia and marginal ulcer (2.5–5%), nutritional deficiencies, and dumping syndrome in addition to standard peri-procedural risks.[8,20]

GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONISTS

GLP-1 RAs are relatively newer in the world of obesity medicine. They were initially developed to treat diabetes mellitus but were found to result in significant weight loss. Two

GLP-1 RAs, liraglutide and semaglutide, are now FDA-approved to treat obesity and have been shown to result in loss of as much as 20% of excess body weight.[6] Current guidelines support the use of anti-obesity medications in non-pregnant patients with BMI ≥30 or BMI ≥27 with associated co-morbidities who have had an inadequate response to lifestyle changes.[3,21] GLP-1 RAs mimic the action of the hormone glucagon-like peptide acting on the hypothalamus and leading to appetite suppression as well as delayed gastric emptying, increased insulin release, decreased glucagon secretion and increased growth of pancreatic beta cells.[1,8] Treatment with semaglutide, a weekly injectable GLP-1 RA, results in an average of 15% change in body weight at 68 weeks.[12,22] Liraglutide, which is injected daily, results in weight loss of 8% of total body weight at 56 weeks.[23] These medications also help address co-morbidities associated with obesity.[12] The SELECT study included 17,604 patients with obesity and cardiovascular disease and found that 2.4mg of semaglutide weekly decreased the incidence of a composite outcome of death due to cardiovascular events, non-fatal myocardial infarction, or non-fatal cerebrovascular accident (HR 0.80 95%CI 0.72–0.90).[24] However, there are some concerns surrounding the use of these medications. They do have notable side effects including nausea, constipation, diarrhea, headaches, fatigue, pancreatitis, and gastroparesis.[3,25] They also require continued use to maintain their effect. An extension of the STEP 1 trial found that cessation of semaglutide after 68 weeks of treatment was associated with significant weight regain and worsening of cardiometabolic risk factors in the following year.[22] The medications are also expensive and not uniformly covered by insurance. In 2022 Medicare did not cover even FDA-approved anti-obesity medications for the treatment of obesity alone.[1] An analysis by Atlas et al found that, at their current price, neither semaglutide or liraglutide are cost effective.[26] There is also limited availability of these medications and more data on long-term outcomes and the risks of use for the treatment of obesity are needed.[1]

DISCUSSION

Both GLP-1 RAs and bariatric surgery are effective for many users; however, in direct comparison, bariatric surgery has been shown to lead to greater weight loss with at least similar improvement in co-morbidities. In 2022 Sarma and Palcu published a systematic review and meta-analysis comparing weight loss in obese adults treated with GLP-1 RAs versus bariatric surgery.[8] Pooled analysis of 332 patients found significantly greater weight reduction in those who underwent bariatric surgery as compared to those treated with GLP-1 RAs.[8] Their analysis also found equivalent improvement in glycemic control between the two groups, as measured by change in HbA1c at the end of the study period.[8] However, a matched cohort study that looked specifically at patients with obesity and type II DM and compared those who had undergone bariatric surgery with those being treated with GLP-1 RAs actually found that, at two-year follow-up, the surgery patients had a lower risk of major adverse cardiovascular events, significantly higher rates of dyslipidemia remission, and higher rates of cessation of anti-hypertensives compared to patients treated with GLP-1 RAs.[27] Additionally, data show that, in the long run, bariatric surgery is more cost effective than the use of anti-obesity medication.[16] Despite high up-front costs, bariatric surgery has been shown to be cost effective due to its associated reduction in emergency room visits, medication use, and decrease in all cause morality.[16-19,28] GLP-1 RAs, however require ongoing use for continued effect. An analysis by Docimo et al found that, at current medication prices, a sleeve gastrectomy becomes more cost effective than medications after approximately a year of GLP-1 RA use and a RYGB is more cost-effective after 14 months of medication use.[16] Despite the seeming ease of a medication to treat obesity and the growing popularity of GLP-1 RAs, bariatric surgery still results in more significant weight loss at a better medium- to long-term value.

Some surgeons have seen the rise of GLP-1 RAs not as a threat to bariatric surgery but as a useful adjunct. The medications can be used both pre- and post-operatively to augment the results of surgery. Pre-operatively, GLP-1 RAs have been used in very high BMI patients to prepare them for their operations. Higher pre-operative BMI (≥50) is associated with both higher rates of weight regain after surgery and increased peri-operative risk.[3,12,29] A retrospective review of high BMI patients undergoing bariatric surgery found that those who were prescribed GLP-1 RAs pre-operatively lost significantly more weight while awaiting surgery compared to those who did not. There was no delay in time to surgery and no GLP-1 related complications prior to surgery.[29] The group who used GLP-1 RAs had a significantly higher BMI at the start of the study than those who were not taking pre-op medications, 60.7 ± 6.6 kg/m2 versus 54.7 ± 3.8 (p = 0.003); however, there was no difference in peri-operative surgical complication rates and one third of the GLP-1 RA group were able to attain BMIs <50 by the time of surgery.[29] Several other large studies have shown that pre-operative weight loss improves perioperative mortality and these data show that this can be safely achieved through treatment with GLP-1 receptor agonists.[30,31]

GLP-1 RAs can also be used after bariatric surgery to address insufficient weight loss or weight regain. In long-term follow-up, approximately 20–30% of patients experience inadequate weight loss and up to 50% have some weight regain after undergoing bariatric procedures.[32,33] Similarly, a meta-analysis by Yu et al found that 37% of patients will continue to have diabetes after RYGB and long-term data show a 30% risk of relapse in the 63% who do experience initial remission.[34] The etiology of this phenomenon is multifactorial, stemming from environmental, metabolic,

anatomic, psychosocial and nutritional influences.[3] Patients with an anatomic reason for sub-optimal post-operative results often require revisional surgery but alternative treatment modalities may be needed for others in this population.

GLP-1 RAs, specifically liraglutide, have been shown to be an effective treatment for recurrent weight gain. The BARI-OPTIMISE trial investigated liraglutide as an adjunctive treatment to bariatric surgery. The study authors cite prior research showing that patients with poor post-surgical weight loss had lower circulating levels of GLP-1 compared to those with good weight loss after bariatric surgery and hypothesized that treatment with a GLP-1 RA would result in additional weight loss.[35] They performed a double-blind RCT including patients with sub-optimal nutrient-stimulated GLP-1 response and poor weight loss at least 12 months after sleeve gastrectomy or RYGB. Patients were treated with either 3.0 mg of liraglutide daily or a placebo in addition to recommended lifestyle interventions.[36] At 24 weeks, the group treated with liraglutide had significantly greater percent reduction in body weight, reduced fat mass, improved HR-QOL, and favorable changes in fasting glucose, HgbA1c, BP, cholesterol and HDL compared to the placebo group.[36] Another study looked at all patients with weight regain after bariatric surgery and found that, regardless of the procedure, patients who were treated post-operatively with 3.0 mg of daily liraglutide had an average of 5.5% total bodyweight loss over the 7.6 months of treatment.[37] The medication was fairly well tolerated with the most common side effects being nausea (37%), constipation (14.1%) and diarrhea (8.7%).[37] More patients discontinued the medication due to cost (35%) than adverse effects (15%).[37] A similar prospective study looked at all patients with weight regain after RYGB and treated them with 3.0 mg of liraglutide or a placebo. They found that 76% of the liraglutide group lost at least 5% of their body weight at 56 weeks as compared to 17% of patients in the placebo arm.[38] A systematic review and meta-analysis looking at three RCTs, involving 130 patients, found that treatment with liraglutide after bariatric surgery was associated with a significant decrease in BMI and body weight at six months.[39]

The GRAVITAS trial looked specifically at treating diabetes after bariatric surgery. This was a double-blind, randomized controlled trial that included patients with persistent or recurrent type 2 diabetes after bariatric surgery.[40] They found that, when combined with a calorie-restricted diet and increased physical activity, patients treated with 1.8mg of liraglutide daily had significantly better glycemic control and significantly greater weight loss at 26 weeks than those treated with a placebo. By the end of the study period, 46% of patients treated with liraglutide lost 5% or more of their baseline bodyweight compared to only 9% of patients in the placebo group. Additionally, 42% of patients in the medication group had HbA1c levels lower than 48mmol/mol as compared to only 13% of patients treated with a placebo.[40] These results were independent of the type of bariatric surgery and the liraglutide was well tolerated with no difference in adverse events between the intervention and placebo groups.[40]

CONCLUSION

Treating obesity is not simple and we are fortunate to have multiple options to offer patients. GLP-1 RAs are effective at producing weight loss up to 20% of excess bodyweight (EBW) and treating associated cardiometabolic co-morbidities. However, they are costly and require continued use for ongoing effect and long-term data on risks and outcomes are sparse. Bariatric surgery is a significant upfront commitment both in terms of cost and risk; however, it is very effective, producing an average excess body weight loss of 60%, reducing severity and even leading to remission of many comorbidities, and has long-term data showing that it is safe and confers a mortality benefit. Obesity treatment needs to be individualized and both interventions can, and undoubtedly do, have a significant role to play in this field. Despite its track record of safety and efficacy, for some patients, bariatric surgery will just not be the right option. They may have prohibitive co-morbidities, inadequate BMI, or only need short-term weight loss, in which case GLP-1 RAs are a good alternative. In many patients, the answer may be using a combination of the medications and surgery, in addition to lifestyle changes. Pre-operative use of GLP-1 RAs can lower a patient's surgical risk and increase their chances of long-term success. Post-operatively, medications can be used to augment the effects of the operation if desired results are not achieved. Ultimately, the treatment of obesity is multi-disciplinary, and the onus is on all physicians who treat affected patients to be able to effectively educate and counsel their patients about all their options.

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