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Bariatric outcomes of high BMI patients with preoperative anti-obesity medications

Alex D. Obermark[1] · Da Young Seo[1] · Avery Bernazard[2] · Jesse R. Richards[3] · Stephen Phillippe[4] · Zhamak Khorgami[4] · Geoffrey S. Chow[4]

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Abstract

Introduction Treating severe obesity (BMI > 50 kg/m^2) poses unique challenges. Glucagon-like peptide-1 (GLP-1) receptor agonists have shown significant efficacy in treating obesity and can be integrated into a multimodal comprehensive treatment of obesity. This study evaluates the perioperative outcomes and efficacy of anti-obesity medications (AOMs) for prehabilitation and preoperative weight loss in a high BMI cohort.

Methods This retrospective cohort study analyzed patients who underwent bariatric surgery from April 2018 to February 2023 in the University of Oklahoma-Tulsa Comprehensive Weight Loss and Bariatric Surgery program. Patients with an initial program BMI ≥ 49.5 kg/m^2 were included. The primary outcome of interest was preoperative weight loss; the secondary outcome was total weight loss at 1 year postoperatively. Data on AOM type and duration were collected. Weight and BMI were measured at multiple standard intervals throughout the program. Available results of genetic obesity testing were included. Preoperative weight loss was compared between groups using the Kruskal–Wallis Test.

Results 206 patients underwent bariatric surgery during the study period; 79 had a BMI ≥ 49.5 kg/m^2 (age: 44 ± 11.2 years, 75.9% female). 34 (43%) had obesity-related genes. The average weight and BMI of the sample at the start of the program were 165.9 kg and 58.5 kg/m^2. The median preoperative weight loss for lifestyle only, oral AOM, GLP-1 or GLP-1/GIP agonist, and combo medical therapy was 3.1, 8.5, 10.3, and 10.4 kg, ($P = 0.01$). The mean total weight loss and excess weight loss percentage were 61.97 ± 20.9 kg and 65.6 ± 20.8%.

Conclusion GLP-1 therapies induced the highest weight loss preoperatively and a greater decrease in BMI than any other strategies. Preoperative GLP-1 therapy in high-risk patients is effective in maximizing preoperative weight loss and should be considered in high BMI patients before surgery. Additional studies are needed to determine optimal duration, durability, and cost-effectiveness of AOMs before and after metabolic surgery.

Keywords GLP-1 agonist · Bariatric surgery · Morbid obesity · Severe obesity · Anti-obesity medications · Preoperative treatment

Obesity has emerged as a global health crisis and is associated with numerous chronic diseases, including type 2 diabetes mellitus, dyslipidemia, hypertension, heart disease, multiple malignancies, and others. Obesity is a multifactorial disease with many contributing factors, including genetics, environmental factors, lifestyle, and healthcare. This makes a multifaceted approach to combating obesity necessary. Lifestyle modifications can realistically produce a 4–6% decrease in total body weight within a year [1, 2]. Patients with a body mass index (BMI) above 40 kg/m^2 are unlikely to achieve a normal weight with lifestyle modifications alone. Individuals in this population may face significantly higher incidences of comorbidities, reduced quality of life, and decreased effectiveness in responding to treatments.

✉ Geoffrey S. Chow
Geoffrey-Chow@ouhsc.edu

[1] School of Community Medicine, University of Oklahoma, 1919 S Wheeling Ave Ste. 600, Tulsa, OK 74105, USA

[2] University of Duke, Durham, NC, USA

[3] Department of Internal Medicine, University of Oklahoma, Tulsa, USA

[4] Department of General Surgery, University of Oklahoma, Tulsa, USA

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However, patients can achieve sufficient weight loss with surgery or multimodal therapy [3].

Comprehensive bariatric programs have been shown to be an effective treatment for obesity. These programs include a team of surgeons, physicians, dieticians, and mental health experts who support patients by optimizing their nutrition and physical conditioning, providing psychological support, offering expertise on pharmacotherapeutics, and providing Metabolic and Bariatric Surgery. Pharmacological interventions for obesity have gained significant popularity in recent years with the use of many different anti-obesity medications (AOMs). These medications promote weight loss and have significant potential in reducing weight, optimizing comorbid conditions and improving physical health before surgery.

Glucagon-like peptide-1(GLP-1) receptor agonists (Semaglutide, Liraglutide, etc.) have recently had a significant presence in medical and non-medical media, resulting in increased popularity and usage. GLP-1 is a naturally released gastrointestinal hormone that is central in promoting insulin release, suppressing glucagon release, slowing gastric emptying, and promoting satiety. GLP-1 agonists mimic these effects, leading to decreased appetite, reduced food intake, and, ultimately, weight loss. Older oral AOMs such as Phentermine, Orlistat, and Topiramate typically result in a 5–10% total body weight reduction, compared to GLP-1 agonists, resulting in 10–15% total body weight loss in a year [4, 5]. Additionally, GLP-1 agonists are effective in treating weight-related comorbidities, such as Type 2 Diabetes Mellitus, Obstructive Sleep Apnea, Dyslipidemia, Hypertension, and Non-Alcoholic Fatty Liver Disease (NAFLD) [4, 6, 7].

Alongside lifestyle modifications and pharmacological therapies, bariatric surgery remains the most durable and effective strategy for long-term weight loss and does not require long-term continuation of additional pharmacotherapy. Bariatric surgery has been shown to produce an average excess weight loss of 61.2% and significant reductions in weight-related comorbidities. As laparoscopic techniques have improved, the rates of bariatric surgeries have also increased [8]. Bariatric surgery is invasive gastrointestinal surgery and can have complications. The range of surgical complications includes infection, anastomotic leaks, bleeding, vitamin deficiencies, postprandial hypoglycemia, major adverse cardiac events, and hernias. Bariatric surgery rarely results in mortality, and rates will likely continue to decrease due to improvements in perioperative management and surgical techniques [8, 9]. Patients with BMI > 40 kg/m^2 are classified as ASA grade III (severe systemic disease) and often have weight-related comorbid conditions which may put these patients at greater perioperative risk [9]. As such, optimizing presurgical treatments are critical for patients with BMI > 50 before undergoing bariatric surgery.

This study aims to explore the use of GLP-1 agonists and other AOM as preoperative treatment for obesity in patients with BMI ≥ 50 kg/m^2. Preoperative use of GLP-1 agonists has the potential to elicit significant weight loss in these patients and prevent perioperative complications associated with severe obesity. Additionally, GLP-1 agonists could help promote psychological well-being by giving patients greater control over their eating habits before surgery.

Methods

This retrospective cohort study was approved by the University of Oklahoma Institutional Review Board and conducted and conducted in compliance with STROBE guidelines. It included all patients who underwent Bariatric surgery within the University of Oklahoma-Tulsa Comprehensive Weight Loss and Bariatric Program from April 2018 to February 2023.

Sample selection

The total number of patients enrolled in the program from April 2018 to February 2023 was 206. Patients with a BMI of < 49.5 kg/m^2 were excluded ($n = 127$). The remaining patients ($n = 79$) were stratified based on the type of treatment they received preoperatively into lifestyle modifications only ($n = 15$), Oral AOMs ($n = 19$), GLP-1/GIP ($n = 24$), or combo medical therapies ($n = 22$) (Fig. 1). All patients receiving combo medical treatments received a GLP-1/GIP agonist and an Oral AOM and all patients received primary bariatric surgery during this period.

Preoperative exposure

Prior to surgery, all patients received standard preoperative counseling, including medical, surgical, psychiatric, and nutritional evaluation, as part of a comprehensive Weight loss program. Upon entering the program, patients underwent a comprehensive medication evaluation. The decision to initiate or continue Anti-Obesity Medications (AOMs) use, including GLP-1 agonists, was based on shared decision-making, insurance coverage, and the discretion of an obesity medicine specialist.

For patients with a BMI ≥ 50 kg/m^2, the recommended surgical options included Roux-en-Y Gastric Bypass (RYGB), Vertical Sleeve Gastrectomy (VSG), or Single Anastomosis Duodenal-Ileostomy (SADI-S). The choice of surgery was determined by factors such as BMI, comorbidities, and collaborative decision-making between the surgeon and patient. All procedures were performed at a Metabolic and Bariatric Surgery Accreditation and Quality

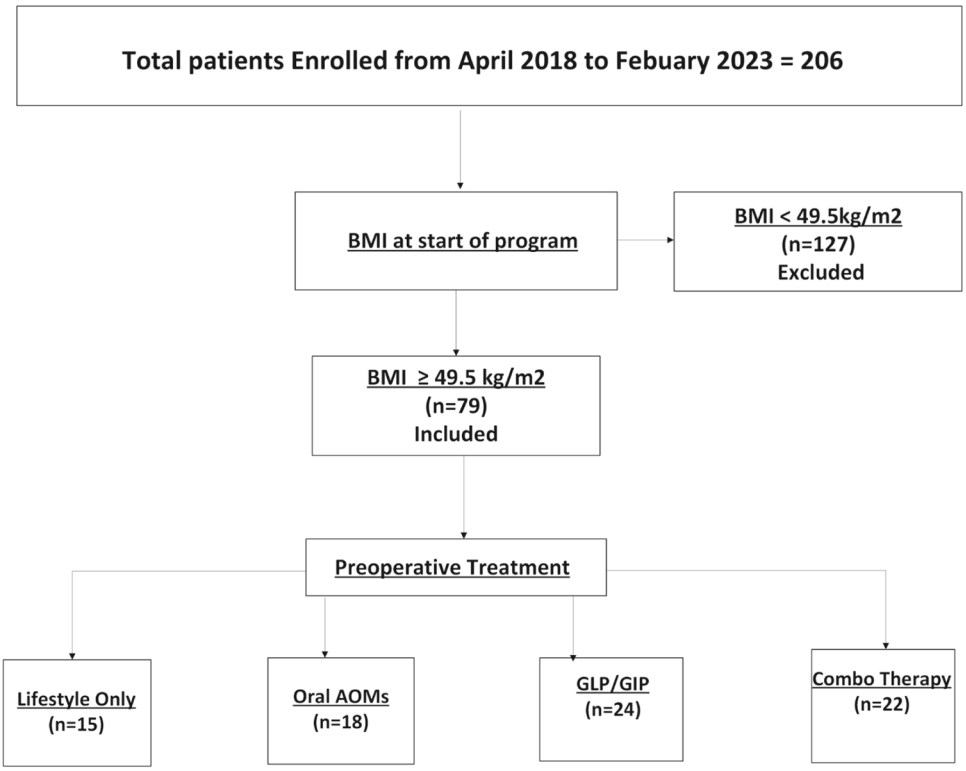

Fig. 1 Flow diagram for patients included in this study, with respective preoperative treatments

Improvement Program (MBSAQIP)-accredited center of excellence using minimally invasive techniques.

Data collected

- Weight and BMI at the start of the program, at surgery, 3-, 6-, 9-, and 12-month postoperative
- Type of Bariatric surgery
- Preoperative AOM use
- Perioperative complications
  - Patients' charts were reviewed for common complications, including infection, bleeding, anastomotic leaks, deep vein thrombosis, nausea or vomiting lasting more than 1 month postoperative, incisional complications, dumping syndrome, strictures or stenosis, bowel obstruction, gallstones, and ulcerations.
- Genes associated with obesity
- Weight-related comorbidities at the start of the program:
  - Type II diabetes mellitus (T2DM), hypertension (HTN), hyperlipidemia (HLD), gastric esophageal reflux disease (GERD), coronary artery disease (CAD), congestive heart failure (CHF), obstructive sleep apnea (OSA), chronic kidney disease (CKD), asthma, osteoarthritis (OA), non-alcoholic fatty liver disease (NAFLD), and polycystic ovarian syndrome (PCOS).

Genetic testing

- Patients were screened for childhood onset obesity, family history of obesity, and hyperphagia symptoms as well as comorbidities suspicious for syndromic or monogenic obesity. Patients who had a positive screening test received genetic testing.
- Patients were tested for mutations in the leptin-melanocortin pathway using the sponsored Uncovering Rare Obesity panel from prevention labs which test for 79 genes and also copy number variants.
- The test is available at no cost to patients who meet the above screening criteria.

Statistics

Data were analyzed using the SPSS version 29 software program (IBM Corp., Armonk, NY). A non-parametric test (Kruskal–Wallis) was applied to assess the difference in weight loss among different treatment groups. Linear regression was used to perform multivariate analysis, assessing if GLP-1 use (with or without oral AOM) vs. non-GLP-1 (lifestyle and oral AOM) has a significant association with preoperative weight loss while adjusting for initial weight, age, gender, T2D, and Bardet–Biedl Syndrome (BBS) diagnosis. A P value of < 0.05 was considered significant.

Results

Descriptive statistics for the patient population can be seen in Table 1. Most of the sample identified as the female gender (75.95%), with the largest portion of the sample coming from the 40–49 age range. Patients all received bariatric surgery, with 35 (44.30%) RNY procedures, 33 (41.77%) VSG procedures, and 11 (13.92%) SADI procedures. All surgeries were primary bariatric surgeries, and no cases were revisional. The most common comorbidity seen preoperatively is HTN (74.68%), followed by OA and OSA (73.42%). Additional weight-related comorbidity data can be seen in Table 1. There were a total of 34 (43.04%) patients who had known gene mutations associated with obesity.

There were no instances of perioperative mortality. There were two instances of surgical site infection. Two patients experienced leakage around surgical wounds, with one requiring surgical repair. The most common reported complication was transient abdominal pain (5 patients), with all instances resolving with appropriate postoperative care.

The average weight and BMI at the start of the program were 165.88 kg and 58.53 kg/m^2, respectively. There was an average duration of preoperative treatment of 7.66 ± 5.3 months. All patients receiving medical therapies reported no adverse effects from their perspective of preoperative pharmacotherapy. All patients receiving combo medical treatments received a GLP-1/GIP agonist and an Oral AOM. The mean weight loss and decrease in BMI at 1-year postoperative follow-up were 61.66 ± 20.90 kg and 21.83 kg/m^2, respectively. There were a total weight loss and excess weight loss percentage at one-year postoperative visits of 36.70 and 65.57%, respectively (Table 2).

The median preoperative weight loss for lifestyle only, oral AOM, GLP-1 or GLP-1/GIP agonist, and combo medical therapy was 3.1, 8.5, 10.3, and 10.4 kg, respectively ($P = 0.01$). There was a mean preoperative excess weight loss percentage of lifestyle only (5.01%), oral AOMs (9.04%), GLP/GIP (13.80%), and combo medical therapy (13.05%) (Fig. 2).

A multivariate analysis using linear regression showed GLP-1 use (with or without oral AOM) vs non-GLP-1 optimization (lifestyle and oral AOM) had a significant association with preoperative weight loss after adjustment for initial weight, age, gender, T2D, and BBS diagnosis ($t = 2.685$, $P = 0.009$).

At one year postoperatively, the median weight loss for lifestyle only, oral AOM, GLP-1 or GLP-1/GIP agonist, and combo medical therapy was 36.8, 65.7, 60.5, and 59.6 kg, respectively. The corresponding decreases in BMI were 18.5, 25.1, 22.2, and 19.9 kg/m^2 (Fig. 3).

Figure 4 illustrates a line graph that depicts weight loss for each preoperative treatment group, showing changes

Table 1 Demographic characteristics of the cohort

Variable	N(%)
Sex	
Men	19(24.05)
Female	60(75.95)
Age	
10-19	3(3.80)
20-29	3(3.80)
30-39	20(25.32)
40-49	30(37.97)
50-59	18(22.78)
60-69	4(5.06)
70-79	1(1.27)
Type of Surgery	
RNY	35(44.30)
VSG	33(41.77)
SADI	11(13.92)
Comorbidities	
DMII	36(45.57)
GERD	50(63.29)
CAD	7(8.86)
CHF	10(12.66)
HTN	59(74.68)
OSA	58(73.42)
CKD	4(5.06)
Asthma	20(25.32)
PCOS	14(23.33)*
HLD	33(41.77)
OA	58(73.42)
NAFLD	15(18.99)

RNY roux-en-Y gastric bypass, *VSG* vertical sleeve gastrectomy, *SADI* single anastomosis duodenal switch, *DMII* diabetes mellitus type II, *GERD* gastroesophageal reflux disease, *CAD* coronary artery disease, *CHF* complete heart failure, *HTN* hypertension, *OSA* obstructive sleep apnea, *CKD* chronic kidney disease, *PCOS* polycystic ovary syndrome, *HLD* hyperlipidemia, *OA* osteoarthritis, *NAFLD* non-alcoholic fatty liver disease

*Percentage was calculated from only the female population of the sample

Table 2 Quantitative data of BMI ≥ 50 kg/m^2 cohort

Variable	N±std dev
Mean Starting Weight(kg)	165.88±30.66
Mean Starting BMI(kg/m^2)	58.53±7.52
Mean Preoperative Duration (Months)	7.66±5.32
Mean Total Weight Loss 1-year post-op (%)	36.07±20.90
Mean Excess Weight Loss 1-year post-op (%)	65.57±20.81

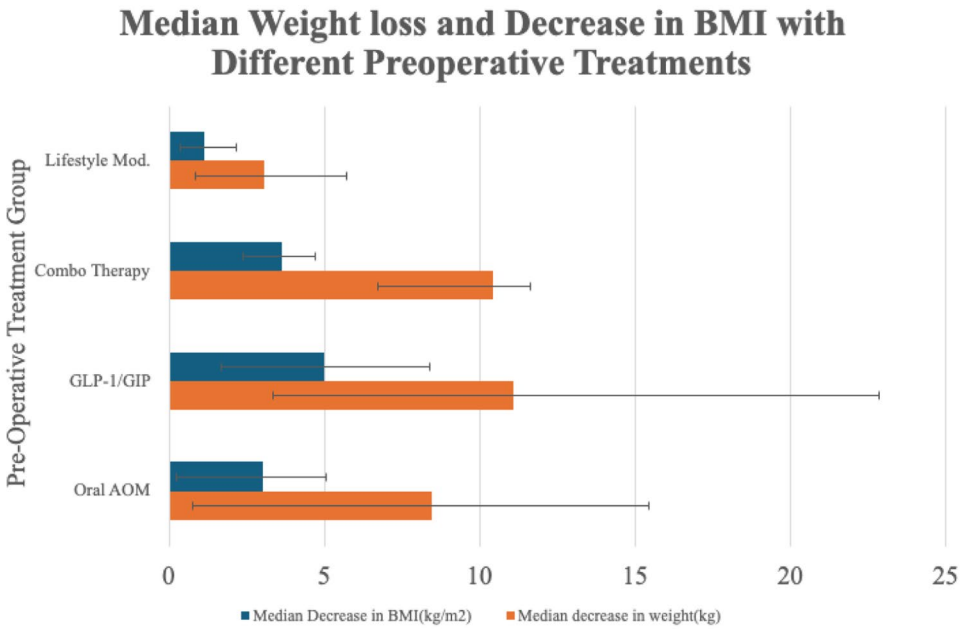

Fig. 2 Comparison of preoperative weight loss and decrease in BMI with IQR

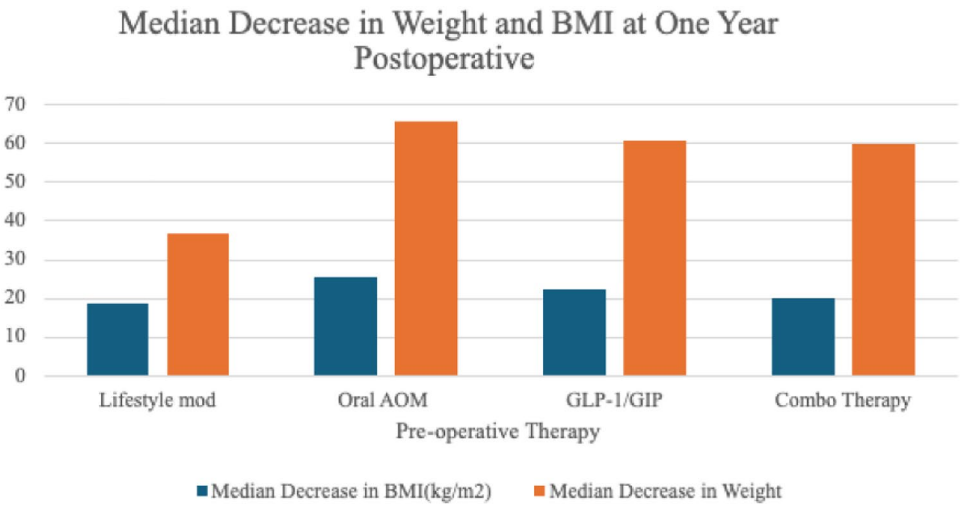

Fig. 3 Median decrease in weight and BMI at 1-year postoperative follow-up grouped based on preoperative treatment

from the program's start to the beginning of AOM, at the date of surgery, and again at the one-year postoperative visit.

The average total weight loss after 1-year post-surgery categorized by surgery type for each treatment group is represented in Table 3.

Among patients who were found to have any obesity-associated gene variant, there was variability in treatment. The lifestyle modifications group had 2 (13%) gene-positive patients, oral anti-obesity medications group had 11 (61%) gene-positive patients, GLP/GIP therapy group had

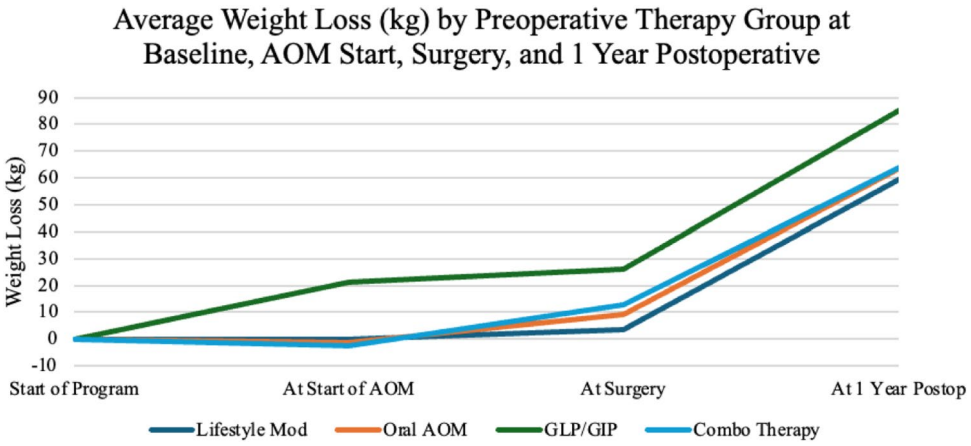

Fig. 4 Line graph of average weight loss by preoperative treatment group at baseline, AOM start, surgery, and 1-year postoperative

Table 3 Average total weight loss at one-year postoperative visit by type of surgery in each treatment group

	Average Total Weight Loss (Kg) by Preoperative Treatment Group			
Type of Surgery	**Lifestyle modification**	**Oral AOM Therapy**	**GLP-1/GIP Therapy**	**Dual Medical Therapy**
RNY	75.7	65.3	55.3	55.7
VSG	42.2	69.6	64.9	71.4
SADI	-*	50.9	60.8	62.5

*No 1 year data

10 (42%) gene-positive patients, and combo medical therapy group had 11 (50%) gene-positive patients.

Discussion

Traditionally, lifestyle changes and bariatric surgery have been considered the main treatments for obesity, although the long-term effect of these therapies on obesity is limited [10, 11]. There are many studies to suggest that bariatric surgery can significantly reduce BMI and other obesity-related conditions, and non-surgical therapies are unlikely to achieve normal weight in patients who present with BMI ≥ 50 kg/m^2 [12]. However, even with evidence of the benefits and durability of bariatric surgery, these interventions are very underutilized. Specifically, in patients with BMI ≥ 50 kg/m^2, there is increased hesitation due to the increased risk of surgical complications and difficulty in obtaining normal weight with a single modality. Therefore, many patients may benefit from preoperative weight loss and a decrease in BMI prior to surgery [13].

The results of this retrospective cohort study demonstrate the benefits of GLP-1/GIP agonists as a pharmacological treatment to precede bariatric surgery for patients with BMI ≥ 50 kg/m^2. Patients that used preoperative GLP-1/GIP agonists or combined therapy of oral anti-obesity medications and GLP-1/GIP agonists saw a significant decrease in weight compared to their counterparts that solely used oral anti-obesity medications or lifestyle changes. Postoperatively, all groups experienced significant weight loss, on par with typical results from these surgeries. These results support other research studies highlighting the use of GLP-1 agonists and lifestyle changes, resulting in significant weight loss [10, 14, 15]. However, there are limited articles that compare weight loss between GLP-1 agonists used in combined therapy or compared to oral AOMs prior to and in conjunction with bariatric surgery. Few studies specifically observe the effects of these treatments in patients with BMI ≥ 50 kg/m^2.

As part of the multidisciplinary care of these patients, AOM were held at least 1 week prior to surgery, and typically held after surgery. In patients who needed additional pharmacotherapy for control of diabetes, patients who did not have full remission were started on appropriate anti-hyperglycemic therapy. If patients had access to GLP-1 agonists, these were started if considered the best therapy from a medical standpoint. Occasionally, patients were started on GLP-1 agonists after surgery if they had a phenotype with hyperphagia as a clinical symptom in the first year after bariatric surgery.

One aspect of our study that may potentially benefit from further investigation is the role of GLP-1 agonists in patients with genetic causes of obesity. There have been many genes identified that are associated with an increased risk of obesity and weight-related comorbidities. Mutations in the hypothalamic Melanocortin 4 receptor (MC4R) and Bardet–Biedl Syndrome (BBS) are associated with defects in regulating metabolism and appetite. Medical treatments can

effectively manage the hyperphagia symptoms associated with these mutations [16]. For patients with these genetic defects who have BMI ≥ 50 kg/m^2, bariatric surgery combined with GLP-1 agonists and targeted gene therapies can be significantly beneficial. The increased access to genetic testing, along with rates of gene positivity in this population, suggests that rates of genetic obesity may be higher than previously reported rates, and there may be a role for standardized testing in patients with BMI ≥ 50 kg/m^2.

With the increasing demands and prices of GLP-1 agonists, it is becoming more difficult for patients to access GLP-1 agonists [17]. It has been shown that bariatric surgery or lifestyle changes alone are not sufficient to achieve target weight loss in patients with severe morbid obesity [18]. It is imperative to continue researching the efficacy and safety of these medications and develop pathways that integrate newer medical therapies that require long-term compliance with surgical therapies, which often can reduce of the number and amount of medications required for patients. Additionally, long-term medical therapy is associated with increased costs for ongoing medical treatments along with the risk of adverse events due to ongoing medical therapy.

Despite the promising benefits of GLP-1 agonists in a comprehensive bariatric program, challenges remain. The long-term safety and efficacy of GLP-1 agonists in the bariatric population require ongoing investigation. Patient responses to AOMs vary with some patients experiencing gastrointestinal symptoms and others tolerating medications well. Patients with a BMI > 50 kg/m^2 benefit from personalized obesity treatment perioperatively to improve the efficacy of surgery, improve weight-related comorbidities, and reduce perioperative mortality.

Limitations

There are some notable limitations to this study. This is a retrospective study, with a primary focus on preoperative weight loss. Patients were not randomized to surgical intervention, and the preoperative therapies were independent from the choice of surgical procedure. Surgical procedures were performed using shared decision-making, incorporating patient goals and wishes, and comorbidities and pre-op weight loss may also affect patient surgical decisions. Some patients were on AOMs prior to joining the program, which was not captured, and there may be variable durations that patients spent utilizing pharmacological therapy prior to surgery. The duration of therapy is variable across all patients in this study, and there is no standardized duration or specific weight goal required before patients are scheduled for surgery. Despite these limitations, this study demonstrates a significant benefit to GLP-1/GIP agonist use in weight loss of patients with severe obesity.

In conclusion, oral AOMs, GLP-1 agonists, and multimodal approaches to obesity have demonstrated superior preoperative weight loss compared to patients who do not have any preoperative AOM therapy. GLP-1 agonist therapies result in significantly greater preoperative weight loss than non-GLP-1 therapies. Integrating GLP-1 therapies into a comprehensive bariatric program has significant benefits for patients, especially those who have struggled to lose weight with other methods. These medications have the potential to reduce weight-related comorbidities and complications of surgery in a high BMI population.

Additional research is required to determine the optimal application of these therapies. Key questions remain regarding the most effective timing, duration, and cost-effective treatment use before bariatric surgery. Further long-term studies are needed on the long-term durability of weight loss and the cost-effectiveness of these medications. For patients with BMI ≥ 50 kg/m^2, there is a need for standardized pathways to develop cost-favorable healthcare policies to decrease long-term expenses while increasing preoperative and long-term weight loss for high-risk patients.

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Declarations

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