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Current concepts in management of weight regain following bariatric surgery

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Abstract

Introduction: Although bariatric surgery is the most effective and durable treatment for obesity, weight regain is common.

Areas covered: In this article, we have critically reviewed data from retrospective and prospective studies pertaining to prevalence and predictors of weight regain following bariatric surgery, as well as the utility of behavioral and pharmacotherapeutic interventions to address post-surgical weight regain.

Expert commentary: The initial step in management of post-surgical weight regain is a comprehensive evaluation of the patient including a thorough assessment of contributing factors. While lifestyle interventions including diet, exercise and behavior modification are fundamental, they have limited efficacy which can be enhanced by pharmacotherapy. The optimal time to commence pharmacotherapy may be at weight plateau to maximize weight loss outcomes after bariatric surgery. Further prospective studies are needed to determine the best combination of behavioral and pharmacological therapies, and also the timing of pharmacotherapeutic intervention.

Keywords: bariatric surgery, weight regain, predictors of weight regain, behavioral interventions, pharmacotherapy

1. Introduction

Body weight is normally maintained within a stable range by homeostatic regulation of energy balance [1]. Weight loss induced by diet and exercise alone is countered by adaptive changes in energy expenditure [2] and an increase in orexigenic hormonal signaling, which opposes the maintenance of a lower body weight and favors weight regain [3]. Bariatric surgery is the most effective and durable intervention for lowering the body weight “set point” due to a combination of anatomical, metabolic and neuro-hormonal mechanisms resulting in amelioration or resolution of metabolic comorbidities, in part through weight-independent mechanisms. In a variable proportion of patients, however, weight regain can occur following bariatric surgery. This increase in weight can result in the reemergence of comorbidities that had initially resolved.

2. Prevalence of weight regain

There is currently no consensus on what constitutes clinically significant weight regain following bariatric surgery and reported weight regain data show considerable heterogeneity in the methods used to define “weight regain” [4,5]. Using a variety of definitions employed in the bariatric surgery literature to the same cohort of patients who had undergone a sleeve gastrectomy, Lauti et al found a wide range of regain rates (9-91%)[5]. The multicenter Swedish Obese Subjects (SOS) study, a large prospective observational study comparing bariatric surgery versus conservative medical management in a group of well-matched patients with obesity, showed that maximal weight loss occurred at one year in the surgical groups. Roux-en-Y gastric bypass (RYGB), vertical banded gastroplasty (VBG) and laparoscopic adjustable gastric banding (LAGB) were associated with total body weight loss (TBWL) of $38 \pm 7\%$, $26 \pm 10\%$ and $21 \pm 10\%$, respectively. However, at 10 years, subjects who underwent RYGB and LAGB regained 34% and 38% of the maximal weight lost at one year, respectively [6]. Other studies have shown that significant weight regain (defined as $\geq 15\%$ regain of maximal weight lost after bariatric surgery) occurs in 25-35% of patients two to five years after the initial bariatric surgical procedure [7]. The Longitudinal Assessment of Bariatric Surgery (LABS) study, a multicenter observational cohort study at 10 US hospitals assessed weight trajectories in 2,348 participants following RYGB (N=1738) and LAGB (N=610)[8]. Seven years following RYGB, mean weight loss was 28.4% of baseline weight; 75% of RYGB participants maintained at least 20% weight loss, with 25% losing less than 20%. Among LAGB participants, 50% maintained at least 16% weight loss through 7 years including participants who underwent a device removal and those who underwent a revision to a new bariatric procedure (73 of the 610 who had LAGB). This study identified distinct trajectories of initial (1-to 3-year) weight change followed by varied patterns of weight fluctuation over the longer-term (3- to 7-year) follow-up. These initial and later patterns of weight change were variable for RYGB and even more so for LAGB; the magnitude and direction/slope of the initial weight loss determined longer-term outcomes in weight. Weight regain between years three and seven reported as a percentage of baseline weight following RYGB was 3.9%, however, 25% of RYGB participants did not maintain 20% weight loss in the long-term. These results while underscoring the durability of bariatric surgery in the majority of patients also suggest that weight maintenance and weight regain are clinically important issues that need further study.

3. Predictors of weight regain and inadequate weight loss

Several studies have shown that inadequate initial weight loss is predictive of weight regain and inferior long-term weight outcomes (7,8). The definition of “successful” or “adequate” weight loss in published literature is arbitrarily defined as weight loss equal to or greater than 50 percent of excess body weight. It is pertinent to note that amelioration or resolution of comorbidities and perceived improvement in quality of life may require less or more than this magnitude of weight loss in individual patients. However, the determination of adequate weight loss based on comorbidity and/or functional responses is exceedingly difficult to quantitate as these outcomes are generally not recorded and there is not a standardized quantitative scale for measuring such effects. The underlying causes of inadequate weight loss and/or weight regain after bariatric surgery are multifactorial and can be divided into preoperative and postoperative predictors

4. Preoperative predictors of weight recidivism and inadequate weight loss

An understanding of the preoperative predictors of inadequate weight loss and weight regain post-bariatric surgery can help identify patients at risk for weight recidivism and offer these patients appropriate resources and counseling. In a recent systematic review, Livhits et al. identified two main preoperative factors: higher baseline body mass index (BMI) and personality disorders [9]. In addition, a few smaller studies identified older age and the presence of type 2 diabetes as other potential preoperative predictors of weight recidivism [10,11]. On the other hand, in the recently published LABS study, among participants who underwent RYGB, the following factors at baseline were associated with worse weight trajectory: male sex, older age, black race, lower BMI, and the presence of type 2 diabetes, low HDL cholesterol, and hypertension. Among participants who underwent LAGB, non-Hispanic ethnicity, male sex, and the presence of low HDL cholesterol and hypertension at baseline were also associated with an inferior weight trajectory [8].

4.1 Higher preoperative BMI

Multiple studies have found that higher preoperative BMI is a predictor of inadequate weight loss post-bariatric surgery. The systematic review by Livhits et al. found that of the 62 studies investigating the link between preoperative BMI and post-surgery weight loss, a majority (37 studies) mostly evaluating excess weight loss (EWL) after RYGB found a negative association between baseline BMI and weight loss [9]. Many studies also report that patients with baseline BMI of $> 50 \text{ kg/m}^2$ achieve less EWL than patients with BMI $\leq 50 \text{ kg/m}^2$ [9]. In a 2013 retrospective analysis of 1,993 patients undergoing either RYGB or LAGB, Ochner et al. found that patients with baseline BMI of $\geq 50 \text{ kg/m}^2$ were more likely to regain significant weight while patients with BMI $< 50 \text{ kg/m}^2$ were likely to continue losing weight 12 months after bariatric surgery [12]. In contrast to the above reported findings, baseline BMI did not predict three year weight change [13] and higher baseline BMI was associated with a more favorable weight trajectory in terms of TBWL over seven years following RYGB [8]. This discrepancy is likely due to the reporting of weight loss data as EWL rather than TBWL in previous studies because weight loss that occurs among lower BMI subjects is greatly exaggerated compared to high-BMI subjects when the weight is reported as EWL.

4.2 Preoperative psychiatric comorbidities

Preoperative psychiatric assessment is important not only to identify appropriate surgical candidates, but also to prepare for counseling and therapy after surgery. These assessments often focus on eating disorders, maladaptive eating habits, substance abuse, and other psychiatric comorbidities such as depression and anxiety. Interestingly, the majority of studies in a 2012 systematic review by Livhits et al. found that these factors are not actually associated with inadequate post-surgery weight loss or weight recidivism [9]. Instead, preoperative personality disorders were found to have a significant negative association with postoperative weight loss, with seven of the 14 studies evaluating 3,360 patients

reporting a negative association between personality disorders and postoperative weight loss [9]. Patients with $\geq 50\%$ EWL compared to those with $< 50\%$ EWL at 12 months had a significantly lower incidence of personality disorder subscales including phobia and paranoia, using the Minnesota Multiphasic Personality Inventory 2 [9,14].

A 2014 review of 19 prospective studies by Wimmelmann et al. reported inconsistent findings between preoperative psychiatric disorders and post-surgical weight loss [15]. In fact, psychological distress related to obesity, such as mild depression, low self-esteem, and poor body image, correlated positively with surgical weight loss. On the other hand, weight loss in individuals with two or more mental disorders including depression, adjustment disorder, posttraumatic stress disorders, anxiety disorder, somatoform disorders and personality disorders was less than in individuals with one or no mental disorder [15, 16]. In addition, the persistence of psychopathology postoperatively predicted poor weight loss outcome. Therefore, postoperative psychiatric disorders may be more direct predictors of weight recidivism than preoperative psychiatric comorbidities [15]. As it is often difficult to predict which patients will develop psychiatric comorbidities following surgery, more studies are needed to understand this relationship and inform patient selection.

5. Postoperative predictors of weight recidivism and inadequate weight loss

Postoperative predictors which include nutritional non-compliance, hormonal/metabolic imbalance, physical inactivity and psychiatric comorbidities may prove to be more directly linked to weight recidivism after bariatric surgery than preoperative predictors, [4, 17]. The LABS-2 study identified the cumulative effects of three postoperative behaviors that explain most of the variability in three-year TBWL following RYGB: weekly self-weighing, continuing to eat when feeling full more than once a week, and eating continuously during the day (grazing). A participant who started to self-weigh, stopped eating when feeling full, and stopped grazing following surgery would be predicted to have 14% greater weight loss compared with participants who made no positive changes in these variables [18].

5.1 Nutritional non-compliance

Although weight loss following bariatric surgery is multifactorial, maintaining weight loss long-term depends largely on sustaining decreased caloric intake. A 2017 prospective longitudinal study of 2,010 patients who underwent bariatric surgery recruited from the SOS study illustrated that decreased caloric intake in the first six months following bariatric surgery was associated with greater weight loss over 10 years [19]. Not only does the quantity of food and number of calories matter, but the macronutrient composition is also important in maximizing weight loss following surgery. Both increasing the proportion of carbohydrates and proteins over fat and eating a higher proportion of protein than carbohydrates were associated with greater weight loss [19]. A 2008 prospective study of 200 patients found that self-reported non-compliance with postoperative dietary recommendations 20 weeks postoperatively significantly predicted lower weight loss at 92 weeks postoperatively [20]. In addition to increased daily caloric intake, maladaptive eating behaviors like grazing can also be important predictors of weight recidivism after surgery [21, 22]. There is insufficient evidence to explain why some patients are more successful than others with dietary compliance postoperatively; this may in part be attributable to the differential effects of surgery on hormonal and metabolic correlates of behavior in individual patients. In addition, the concomitant use of drugs that promote weight gain can make it challenging for some patients to comply with dietary recommendations.

5.2 Hormonal/metabolic imbalance

Bariatric surgery results in weight loss not only through anatomic restriction, but also through metabolic changes, which may be mediated by hormonal regulation and the microbiome [23,24]. It is well established that weight loss induced by behavioral interventions alone is countered by hormonal adaptation to promote weight regain; however, its contribution to weight regain post-bariatric surgery is less well defined. Limited data from a subgroup analysis of 12 patients suggests there is a non-significant increase in ghrelin over five years following a sleeve gastrectomy (SG) [25]. Rodent studies have shown that failure to sustain elevated peptide YY concentrations after RYGB is associated with weight regain [26]. Meal-stimulated gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) levels at 30 minutes were shown to be lower in 10 patients with weight regain compared with 14 patients who successfully maintained weight loss after RYGB [27]. Weight plateau after bariatric surgery may be partly due to the decline in leptin resulting in a state of relative leptin insufficiency. In this vein, Korner et al. sought to determine whether leptin administration to patients following RYGB would promote further weight reduction. In a randomized, double-blind, placebo-controlled cross-over study of 27 women who were at least 18 months post-RYGB and had lost on average 30.8% of their pre-surgical body weight, subjects received either leptin or placebo via subcutaneous injection twice daily for 16 weeks, then crossed over to receive the alternate treatment for 16 weeks [28]. Contrary to their hypothesis, leptin administration did not result in significant weight change. Clearly, more research is needed to delineate the long term effects of bariatric surgery on metabolic and gut hormonal regulation of body weight and the role of these factors in weight regain.

5.3 Psychiatric comorbidities

Postoperative psychiatric comorbidities are strong predictors of inadequate weight loss following bariatric surgery, and they often exert their negative impact on weight loss through eating disorders and other maladaptive eating behaviors. A 2014 review article that focused on binge eating (defined as eating an objectively large amount of food accompanied by a sense of loss of control over eating), binge eating disorder (defined as regular episodes of excessive, uncontrolled overeating associated with psychological distress) and eating with a sense of loss of control (defined as eating accompanied by a sense of loss of control, but not necessarily ingesting an objectively large amount of food) after bariatric surgery found that these maladaptive eating behaviors are associated with less weight loss or more weight regain after surgery [29]. In addition, many psychiatric comorbidities such as depression predict worse postoperative weight loss outcomes and this is at least in part due to their impact on eating behavior. A 2015 prospective 24-month follow-up study of 357 patients who underwent bariatric surgery found that clinically significant depressive symptoms defined as a score of 15 or greater on the Beck Depression Inventory, are significantly associated with less weight loss 6 months and 12 months postoperatively, and predict greater disordered eating through 24 months [30].

5.4 Physical inactivity

Sedentary behavior is known to be associated with an increased risk of obesity [31] and predictably patients with severe obesity are at increased risk for high levels of sedentary behavior following bariatric surgery [32]. Several studies report an increase in physical activity after bariatric surgery; however, there is often discordance between self-reported measures and objective estimates of physical activity. Bond et al. compared self-reported and accelerometer-based estimates of moderate-to-vigorous intensity physical activity (MVPA) before surgery to six months following surgery [33]. Self-reported MVPA increased fivefold from before surgery to six months following surgery whereas accelerometer-based estimates showed nonsignificant decreases in MVPA. Data from the National Weight Control Registry also indicates that patients who have lost weight through bariatric surgery are less physically active than those who have achieved weight loss from non-surgical interventions [34]. On the other hand, some observational data suggest that regular physical activity has a modest effect on improving postoperative

weight loss outcomes [35, 36]. In a systematic review of 13 studies, 11 studies showed a positive association of exercise with postoperative weight loss, and two showed no association. A meta-analysis of three studies revealed that exercise following bariatric surgery appears to be associated with a greater weight loss of ~ 4% of BMI [36]. Given the mixed findings, more studies are necessary to develop methods to quantify physical activity and to characterize the effect of physical activity on post-surgical weight change.

Management of weight regain

6. Behavioral and psychotherapeutic interventions

There is a paucity of published data related to lifestyle interventions targeted specifically for management of postsurgical weight regain. However, there are several small randomized controlled trials and observational studies that have investigated the role of behavioral and psychotherapeutic interventions on postsurgical weight loss that are relevant to the prevention and management of weight recidivism. The goal of behavioral therapy is to help patients make long-term changes through modification and monitoring of both their eating behavior and physical activity level and is largely achieved by controlling cues and stimuli in the environment that trigger eating or sedentary behavior (37). Psychotherapeutic interventions target the psychological factors that correlate with post-surgical weight loss including binge eating, depression, motivation, and coping skills.

A systematic review and meta-analysis of two randomized and seven nonrandomized trials by Beck et al. revealed a statistically significant overall effect of both psychotherapeutic interventions and support groups on post-surgical weight loss with a pooled effect size correlation of 0.18 [38]. No difference was found in the effect sizes of the two interventions. Patients undergoing psychotherapeutic interventions or attending support groups in combination with bariatric surgery appeared to achieve greater weight loss than patients treated with bariatric surgery alone. In a systematic review and meta-analysis of 15 studies published prior to 2012 including five randomized controlled trials, two prospective and eight retrospective cohort trials, Rudolf and Hilbert found that behavioral management had a positive effect on weight loss following surgery although conclusions were limited by the small and heterogeneous samples of studies [39].

More data has now accumulated from randomized controlled trials [40-49] that have assessed the role of intensive behavioral management versus standard care in the management of patients following bariatric surgery [Table 1]. Chacko et al. evaluated a novel mindfulness-based intervention (MBI) designed to control weight after bariatric surgery in a randomized controlled pilot trial of eighteen patients one to five years post-surgery. Participants were randomized to a 10-week MBI or a standard intervention. This novel mindfulness-based approach was highly acceptable to patients post-surgery and was effective in reducing emotional eating, although it did not improve weight or glycemic control in the short term [40]. Lier et al. investigated the impact of preoperative counseling on postoperative treatment adherence in 141 patients who underwent RYGB. The intervention group participated in cognitive behavioral therapy (CBT) sessions weekly for six weeks prior to surgery and three sessions at six, 12 and 24 months after surgery. The control group attended two educational seminars, one pre-operatively and one post-operatively. There were no differences in 12-month weight loss or adherence to treatment guidelines between the two groups [41].

In a randomized, controlled pilot study by Kalarchian et al., participants who had undergone RYGB one year previously were randomly assigned to a structured dietary intervention incorporating portion-controlled foods (intervention, N = 20) or a comparison group (control, n = 20) [42]. Both groups received instruction in behavioral weight loss including one 60-minute session followed by four coaching

telephone calls at monthly intervals. The structured dietary intervention group had reduced calorie intake at four months [-108 vs. 116, $P = 0.05$] and increased weight loss at both four [-4.56% vs. -0.13%, $P = 0.003$] and six months [-4.07% vs. -0.14%, $P = 0.05$]. In a study by Nijamkin et al., 144 Hispanic Americans were randomized to a comprehensive nutrition and lifestyle educational intervention ($n=72$) or a noncomprehensive approach (comparison group $n=72$) beginning six months following RYGB [43]. Those in the comprehensive group participated in education sessions every other week for six weeks in small groups and had frequent contact with a registered dietitian whereas the comparison group received brief, printed healthy lifestyle guidelines. At 12 months following surgery, the participants in the comprehensive group experienced greater EWL (80% vs 64%; $P<0.001$) and reported greater physical activity than the comparison group. Papalazarou et al. also reported improved weight loss outcomes in patients assigned to a dietitian-led multi-faceted lifestyle intervention versus usual care [44]. In contrast to these positive findings, Sarwar et al. reported similar weight loss at four and 24 months in post-operative patients randomized to either brief every-other-week dietary counseling by a registered dietitian for the first four post-operative months or standard care [45]. Swenson et al. also did not observe any difference in BMI or EWL in their dietary intervention study of 32 patients following RYGB who were randomized to either a low-fat diet or a low-carbohydrate, high-protein diet [46]. These disparate findings may be due to the heterogeneity of the interventions which differed both in complexity and intensity.

Ogden et al. assessed the impact of a psychologist-led intervention in 162 patients who underwent either RYGB, LSG or gastric band. In this study, the control group received a standard diet sheet and met with a dietitian and or/nurse at week six and months three, six, and 12. The intervention group received the same care with the addition of three 50-minute individualized sessions with a psychologist (2 weeks pre-operatively, post-operatively in the hospital and at three months). There was no difference in weight loss between the groups one year post-operatively [47].

More recently, there were two published studies that specifically examined patients with documented weight regain following bariatric surgery. Bradley et al. evaluated the feasibility, acceptability, and preliminary effectiveness of a 10-week acceptance-based behavioral intervention to stop postoperative weight regain in 11 patients who had undergone bariatric surgery and regained at least 10% of their maximum lost postoperative weight [50]. The intervention emphasized psychological skills thought to be integral to successful weight control post-surgery and was shown to be feasible and acceptable with 72 % retention and high mean rating (4.25 out of 5.00) of program satisfaction among completers. Participants lost a mean of 3.58 ± 3.02 % of total body weight throughout the 10-week intervention with significant improvements in eating-related and acceptance-related variables.

Internet-based strategies for delivering behavioral intervention have garnered much interest given the scale of the obesity epidemic and the practical challenges patients often face in returning for office-based behavioral counseling. Project HELP (a remotely delivered 10-week behavioral intervention for weight regain after bariatric surgery) was demonstrated to be feasible and acceptable with 70 % retention among those who started the program and had a high mean rating (4.7 out of 5.0) of program satisfaction among study completers [51]. On average, post-surgical weight regain was reversed with a mean weight loss of 5.1 ± 5.5 % throughout the intervention, which was maintained at three-month follow-up. The Bariatric Surgery and Education (BaSE) study, was a randomized, controlled multicenter clinical trial involving 117 patients designed to assess the efficacy of a videoconferencing-based psycho-educational group intervention in patients following bariatric surgery [49]. There were no differences in weight loss, health-related quality of life (HRQOL) score, or self-efficacy between the intervention group versus those assigned to conventional postsurgical visits. However, patients with clinically significant

depression symptoms at baseline who were assigned to the intervention group had significantly lower depression symptoms, better HRQOL scores and a trend towards better EWL one year after surgery compared with the control group.

7. Pharmacotherapy for weight regain

There is limited data on the utility of antiobesity pharmacotherapy for weight regain after weight loss surgery. In a small prospective study, 16 patients with binge eating and inadequate weight loss after adjustable gastric banding were analyzed prospectively for three months while receiving topiramate in doses varying from 12.5 to 50 mg per day [52]. There was a mean increase in EWL from 20.4% to 34.1% without the need for band readjustment. The use of liraglutide for eight to 28 weeks has been reported to induce a mean weight loss of 7.4 kg in a retrospective analysis of 15 patients (RYGB=9; gastric banding= 4; duodenal switch biliopancreatic diversion=1; longitudinal gastrectomy=1) who had EWL <50% after two years of follow-up or had regained more than 15% of their nadir weight [53].

In the largest reported series, Stanford et al. retrospectively assessed the utility of weight loss medications for weight regain or inadequate weight loss in 319 patients [RYGB=258; sleeve gastrectomy =61] treated at two academic institutions [54]. More than half [54%; n = 172] of all study patients lost $\geq 5\%$ [7.2 to 195.2 lbs] of their TBW with medications after surgery. In addition, there were many high responders with 30.3% of patients losing $\geq 10\%$ [16.7 to 195.2 lbs] and 15% losing $\geq 15\%$ [25 to 195.2 lbs] of their total weight. Of the 14 weight loss medications prescribed (both FDA approved and off-label), topiramate was the only medication that demonstrated a statistically significant response for weight loss with patients being twice as likely to lose at least 10% of their TBW when prescribed this medication [odds ratio = 1.9; P = .018]. Furthermore, cumulative weight loss from the combination of surgery plus pharmacotherapy was greater in patients who were prescribed medication at their weight plateau compared to those who had pharmacotherapy initiated after weight regain [32.3% vs 26.8%]. This difference, although clinically relevant, was not statistically significant. Further study is needed to determine the optimal timing for initiation of pharmacotherapy as an adjunct to surgery, as well as the selection of medication following specific operative procedures.

8. Expert commentary

Bariatric surgery is the most effective and durable treatment for obesity and can result in amelioration or resolution of obesity-related co-morbidities. However, long term follow-up data after bariatric surgery indicate that significant weight regain is common despite complex anatomic, metabolic and neuro-hormonal changes engendered by surgical manipulation of the gastrointestinal tract. From a management perspective, the initial step in treating weight recidivism is a comprehensive assessment to determine if weight regain is due to anatomical/surgical failure, medical causes or behavioral issues. If a patient can suddenly tolerate much larger meals, experiences increased hunger or develops new or recurring acid reflux, anatomical complications like band malfunction, pouch enlargement, gastro-jejunal anastomosis dilatation and gastro-gastric fistula should be considered and managed appropriately by the bariatric surgeon. Medical evaluation to exclude endocrine causes of weight regain such as hypothyroidism and rarely Cushing's syndrome (if clinically appropriate) should be considered as well as referral to an Obesity Medicine specialty center.

Detailed medication history may reveal the use of weight-promoting medications within different drug

classes including antidepressants, anticonvulsants, antipsychotics, antihistamines and pharmacotherapies for diabetes and hypertension. Where clinically appropriate, substitution of a weight-promoting medication with a weight-neutral or a potentially weight-reducing medication should be considered. [55,56]. In cases where there are no suitable therapeutic alternatives, use of the minimum dose required to achieve clinical efficacy can limit or prevent drug-induced weight gain. Among antidepressants, paroxetine is considered to be the selective serotonin reuptake inhibitor (SSRI) associated with the greatest long-term increase in body weight, whereas amitriptyline is the most potent inducer of weight gain among the tricyclic antidepressants. On the other hand, SSRIs such as fluoxetine and sertraline have been associated with weight loss during acute treatment and with weight neutrality in the maintenance phase. Bupropion, a dopamine and norepinephrine reuptake inhibitor, can induce weight loss and may be considered for certain patients with depression. Among anticonvulsants topiramate and zonisamide are associated with weight loss whereas gabapentin, pregabalin, valproic acid, vigabatrin, and carbamazepine are generally associated with weight gain and lamotrigine, levetiracetam, and phenytoin can often be weight-neutral. Sedating antihistamines have greater weight gain potential than non-sedating antihistamines. Similarly, a weight-centric approach to the management of type 2 diabetes would prioritize use of metformin, GLP-1 analogs and sodium-glucose co-transporter 2 inhibitors, medications associated with weight loss, and minimize use of weight-promoting agents such as insulin, insulin secretagogues and glitazones [57,58]. In the same vein, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers rather than beta-adrenergic blockers, which can lead to weight gain, are recommended as first-line therapy for the treatment of hypertension in patients with T2DM who are obese. In clinical practice, the weight gaining potential of pharmacotherapies must be carefully weighed against therapeutic efficacy in the individual patient and substitution with alternative pharmacologic agents must be a shared decision process with the patient and other providers where appropriate.

Our current understanding of the predictors of weight recidivism remains limited. From a management perspective, it would be helpful to identify patients at high risk for weight regain in the preoperative period so preemptive measures could be instituted. Despite a plethora of published literature, and the breadth of baseline data collected in the LABS study, it is evident that more work is needed to build a predictive model that adequately explains variability in weight change after bariatric surgery. While older age and the presence of diabetes were identified as being predictive of inferior weight loss outcomes, the effects were small. Participants with diabetes at baseline had 3.7% less weight loss at year three compared to participants without diabetes at baseline, and older age explained less than 1% weight difference for a difference of 10 years. The LABS data also refute the previously held notion that higher baseline BMI predicts poor weight loss outcomes. The addition of genomic and metabolomic data to clinically relevant variables may lead to better prediction of outcomes from weight loss surgery in the future.

The rates of psychopathology are high in bariatric surgery candidates as shown in the LABS-3 psychopathology substudy; 33.7% had greater than one current Axis I disorder, and 68.8% had greater than one lifetime Axis I disorder [59]. Although the presence of preoperative psychiatric co-morbidities did not adversely impact postoperative weight loss outcomes in the LABS study, limited data from other studies suggests personality disorders and multiple psychiatric comorbidities are associated with inferior post-surgical weight loss. This is likely because individuals with such co-morbidities may have more difficulties complying with the behavioral modifications imposed by surgery and therefore may be less likely to achieve successful weight loss. In this vein, the involvement of a psychologist in the postoperative follow-up of patients identified to have multiple psychiatric disorders including personality disorders may be helpful in improving weight loss outcomes and minimizing weight regain.

In the postoperative period, maladaptive behaviors including nutritional non-compliance, physical inactivity and psychiatric comorbidities are key predictors of weight regain. While the majority of patients who undergo bariatric surgery complete several months of preoperative dietary counseling, there needs to be more focus on postoperative dietary counseling especially for those patients who exhibit maladaptive eating behaviors. This can be a practical challenge due to logistical, economic and other factors that often lead to high attrition postoperatively. The use of remote, web-based technology to deliver behavioral intervention is a strategy that can address this problem; this is currently the focus of ongoing research [60] and a tool we have used effectively at our center [61] to facilitate and expand the care of patients with obesity.

Cognitive behavioral therapy is one potential strategy to treat psychiatric comorbidities and improve weight loss outcomes following bariatric surgery. While most patients undergo psychiatric screening before surgery, less attention is focused on screening for psychiatric comorbidities following surgery despite extensive literature on the development of such comorbidities. Post-surgical psychiatric screening could be employed as a strategy not only to diagnose and treat psychiatric conditions, but also to identify associated maladaptive eating behaviors and prevent weight recidivism.

In the aggregate, similar to what is observed in medical weight loss settings, lifestyle interventions have been shown to produce modest weight loss in the post-surgical setting. Several randomized controlled trials RCTs have also failed to show any benefit over usual care. The timing, intensity and comprehensiveness of the interventions, as well as patient selection are factors that may influence weight loss outcomes. In addition, most studies have investigated strategies to augment postoperative weight loss while there are only two small studies that have specifically addressed weight regain. The generalizability of these findings in the setting of weight regain is unclear and highlights a need for more research with greater methodological rigor. Given the limited efficacy of lifestyle interventions alone, the addition of antiobesity pharmacotherapy to optimize weight loss outcomes is both rational and intuitive. Retrospective studies demonstrate efficacy for a variety of weight loss pharmacotherapies. There is currently a lack of data from prospective randomized trials on the relative efficacy of one agent over another. The choice of pharmacotherapy must be individualized to maximize the benefit-to-risk ratio taking into account patients' co-morbidities and contraindications to specific agents. The vast majority of patients received adjunctive pharmacotherapies after significant weight regain; an alternative strategy is to maximize cumulative weight loss from bariatric surgery by initiating weight loss medication at weight plateau before significant weight is regained. As is the case with non-surgical treatments, the magnitude of the initial weight loss following bariatric surgery is predictive of long-term outcomes in weight (8). Therefore, early postoperative efforts to optimize short-term weight loss can potentially impact long-term weight trajectory. Further prospective studies are needed to determine the best combination of behavioral and pharmacological therapies and also the timing of pharmacotherapeutic intervention.

9. Five-year view

Weight regain and inadequate weight loss is common following bariatric surgery; however, an estimate of its true prevalence requires standardization of its definition for reporting. Further research is necessary to gain better understanding of the behavioral and biological correlates of weight regain and provide a rational basis for development of better preventive and treatment strategies. Given the scale of the obesity epidemic, remote web-based behavioral interventions that are accessible to a larger population are expected to become an integral part of weight management. As the field of obesity

medicine evolves with expansion of the pharmacotherapeutic armamentarium, prospective studies will define the best combination of medications to address weight regain following bariatric surgery.

10. Key issues

- Although bariatric surgery is the most effective and durable treatment for obesity, weight regain is common.
- Significant weight regain (defined as $\geq 15\%$ regain of maximal weight lost after bariatric surgery) occurs in 25-35% of patients 2-5 years after the initial bariatric surgical procedure.
- Older age, diabetes, multiple psychiatric disorders including personality disorders are preoperative predictors of weight regain although the effects are small.
- Nutritional non-compliance, hormonal/metabolic imbalance, physical inactivity and psychiatric comorbidities are important postoperative predictors of weight regain.
- The initial step in treating weight recidivism is a comprehensive assessment of the patient by a multi-disciplinary team.
- Behavioral and psychotherapeutic interventions induce modest weight loss in patients with weight recidivism.
- Remote, internet-based lifestyle intervention strategies can increase accessibility and follow-up of patients postoperatively.
- Pharmacotherapy is a useful adjunct to behavioral interventions to improve weight loss outcomes.
- Initiating pharmacotherapy when patients are at their weight plateau may be optimal to maximize cumulative weight loss from surgery.

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Declaration of interest

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Table 1

ACCEPTED MANUSCRIPT

Source	Intervention	Number of patients	Months follow up	Outcomes
Swenson et al (2007)[46]	Low fat (LF) vs. low carbohydrate-high protein (LCHP) diet	LF=13 HPLF=19	3, 6, 12	% EBWL 3 mos LF=-33.5 LCHF=-33.3 (p=0.95) 6 mos LF=-51.0 LCHF=-50.8 (p=0.97) 12 mos LF=-60.3 LCHF=-59.6 (p=0.96)
Papalazarou et al (2010)[44]	Lifestyle intervention (LI) vs. usual care (UC) UC: VLCD (665 kcal) for 4 wks post-operatively, with gradual reintroduction of soft and then normal food by 6 mos, weekly and then monthly visits with a registered dietician. LI: UC plan with an additional 30 individualized 40-min sessions with a registered dietician over 3 years.	30	12, 24, 36	%EWL 12 mos LI=76.4% UC=57.5% (p<0.05) 24 mos LI=74.4% 52.2% (p<0.05) 36 mos LI=74.8% UC=49.1% (p<0.05)
Lier et al (2012)[41]	Cognitive behavioral counseling (CBT) vs. control group (CG) CBT: 6 weekly group sessions pre-operatively and 3 post-operative	CBT=49 CG=48	12	Percent of participants achieving >50 %EBWL CBT=91% CG=85%

	<p>sessions.</p> <p>CG: 1 pre-op and 1 post-op 4-hr educational seminar</p>			(p=0.774)
Nijamkin et al (2012)[43]	<p>Nutritional and lifestyle group (NL) vs. usual care (UC)</p> <p>NL: group sessions with a dietitian every 2 weeks, total 6 sessions UC: given printed guidelines on diet and exercise</p>	<p>NL=72 UC=72</p>	6, 12	<p>%EBWL</p> <p>6 mos NL=54.5% UC=50.7% (p<0.001)</p> <p>12 mos NL=79.6% UC=63.8% (p<0.001)</p>
Kalarchian et al (2012)[48]	<p>Behavioral (B) vs. wait list (WL)</p> <p>Subjects had undergone bariatric surgery ≥ 3 yrs before study entry and had <50% EWL.</p> <p>B: 12 weekly group sessions, 5 biweekly telephone coaching sessions WL: no personal coaching</p>	<p>B=18 WL=18</p>	6, 12 mos	<p>%EBWL</p> <p>6 mos B=6.6% WL=3.1% (p=.29)</p> <p>12 mos B=5.8% WL=0.9% (p=.32)</p>
Sarwer et al (2012)[45]	<p>Dietary counseling (DI) vs. usual care (UC)</p> <p>DI: 15 min in-person or phone sessions with RD every-other-week for 4 mos after surgery. UC- No formal postoperative RD session, appts scheduled as needed.</p>	<p>DC=41 SC=43</p>	2, 4, 6, 12, 18, 24	<p>4 mos DC=20.7% UC=18.5% (p>0.05)</p> <p>6 mos DC=26.1% UC=23.5% (p>0.05)</p>

				<p>12 mos DC=32.8% UC=32.4% (p>0.05)</p> <p>24 mos DC=32.4% UC=33.6% (p>0.05)</p>
Ogden et al (2014)[47]	<p>Psychology-led bariatric rehabilitation service (BRS) intervention vs. usual care (UC)</p> <p>UC: given handout with diet guidelines 2 weeks pre-surgery, follow up with RD or RN at 6 wks, and 3, 6, 12 mos.</p> <p>BRS: In addition to UC, given three 50-min individualized sessions with a psychologist (2 weeks pre-surgery, in hospital, 3 mos follow up)</p>	<p>BRS=82 CG=80</p>	12	<p>Change in BMI</p> <p>BRS=-16.6 UC=-16.37 (p=0.7)</p>
Wild et al (2015) [49]	<p>Psychoeducational intervention (PI) vs. control group = (CG)</p> <p>CG: received conventional surgical visits at 1, 3, 6, 12 mos after surgery PI: In addition to CG plan, received conventional surgical visits and videoconferencing based psychoeducational group intervention (5 face to face group interventions follows by 6 videoconferencing sessions, and then 3 face to face group sessions)</p>	<p>PI=56 CG=58</p>	1, 3, 6, 12	<p>%EBWL</p> <p>6 mos PI=49.5 CG=50.7 (p>0.05)</p> <p>12 mos PI=67.1 CG=65.9 (p>0.05)</p> <p>Subjects with clinically significant</p>

				depression symptoms (CSD) at baseline assigned to PI (n = 29) had better HRQOL ($P = .03$), lower depression scores ($P = .02$), and a trend for better EWL ($P = .06$) 1 year after surgery compared with the control group (n = 20).
Kalarchian et al (2016)[42]	Dietary intervention (DI) vs. control group (CG) CG-monthly phone calls with health coach, provided with daily calorie goals and standard post-operative dietary guidelines. DI-In addition to CG care, given structured dietary intervention with portion-controlled foods, home delivery of meals and snacks once a month, personalized menu plan.	DI=20 CG=20	4, 6	Percent weight loss 4 mos DI=-4.56 CG=-0.13 6 mos DI=-4.07 CG=0.14 Daily calorie intake change from baseline DI=-108 Kcal CG=116 Kcal ($p=0.05$)
Chacko et al (2016)[40]	10-week mindfulness based intervention (MBI) versus standard intervention (SI) MBI: weekly 90 min sessions with mindfulness training, 4 hour meditation retreat mid-way through course SI: 1-hour of individualized counseling with a registered dietician	MBI = 9 SI = 9	3, 6	Change in BMI 3 mos MBI: 0.7 SI: 0.6 ($p=0.92$) 6 mos MBI:1.4 SI: 0.8 ($p=0.28$)

EBWL : excess body weight loss