Published in final edited form as:

Obes Surg. 2017 December ; 27(12): 3281–3291. doi:10.1007/s11695-017-2966-1.

Bariatric Surgery Resistance: Using Pre-Operative Lifestyle Medicine and/or Pharmacology for Metabolic Responsiveness

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Abstract

Bariatric surgery is an effective and durable treatment for individuals with obesity and its associated comorbidities. However, not all patients meet weight loss and/or cardiometabolic goals following bariatric surgery, suggesting that some people are “bariatric surgery resistant”. The reason for this resistance is unclear, but potential factors, such as adiposity-derived inflammation, insulin resistance, hyperglycemia, and aerobic fitness prior to surgery have been related to blunted surgery responsiveness. Exercise, diet, and/or pharmacology are effective at reducing inflammation and improving insulin action as well as physical function. Herein, we present data that supports the novel hypothesis that intervening prior to surgery can enhance disease resolution in people who are resistant to bariatric surgery.

Keywords

Bariatric surgery; insulin resistance; diet; exercise; pharmacology; weight loss surgery

Introduction

Nearly 34% of adults are obese (BMI ≥ 30 kg/m^2) in the United States [1]. Obesity impacts public health as its associated comorbidities [2–4] result in higher health care costs [5] and lead to an elevated risk for all-cause mortality [6]. Thus, optimal therapies are drastically needed to combat obesity and reduce healthcare costs.

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CONFLICT OF INTEREST

N.G., A.P., S.K., A.W., J.K., P.H., and S.K.M. declare that they have no conflict of interest.

ETHNICAL APPROVAL STATEMENT

This article does not contain any studies with human participants or animals performed by any of the authors

INFORMED CONSENT STATEMENT

Does not apply.

Lifestyle medicine, including diet and exercise, is established to induce meaningful weight loss and aerobic fitness for cardiometabolic benefit. However, long-term adherence to exercise and diet treatments are poor for the vast majority of patients. In fact, nearly 54% of people experiencing weight loss within the first year of lifestyle modification subsequently experience weight regain [7]. These observations suggest that alternative treatments are required to induce and maintain long-term weight loss. Medication is a reasonable adjunctive therapy to lifestyle treatment, but the optimal combination therapy remains unclear and no current therapies are approved for combination use [8–10]. Bariatric surgery, namely Roux-en-Y gastric bypass (RYGB) or Sleeve Gastrectomy (SG), is an effective treatment for individuals with obesity that often results in greater than 50% loss of excess body weight [11]. In addition, surgery decreases insulin resistance and improves pancreatic function, thereby conferring improved glucose regulation [11]. In fact, approximately 42% of individuals with T2D have remission following bariatric surgery [12–13], and nearly 60% of patients experience resolution of hypertension, hypercholesterolemia, hypertriglyceridemia, obstructive sleep apnea, and gastroesophageal reflux disease [14,15]. Unfortunately, not all patients undergoing bariatric surgery achieve these improvements in metabolic health. The exact reason for this large inter-subject variability to bariatric surgery outcomes is unclear, but pre-operative age, sex, race, body mass index (BMI), and diabetes status are reported determinants associated with non-responsiveness to surgery. Moreover, weight regain is a key underlying factor during the post-operative period that correlates with disease relapse. Herein, we review data in support of the novel hypothesis that pre-surgical interventions may reduce surgical complications, improve recovery and promote metabolic responsiveness post-operation. Thus, the present review will discuss current literature highlighting the clinical and physiologic underpinnings of “bariatric surgery resistant” individuals (Figure 1). In addition, this review will focus on the utility of exercise and diet before surgery as potential therapies that improve sensitivity to surgery and promote weight loss, glycemic control, and cardiometabolic health. Lastly, this review will provide a clinical perspective for optimization of pharmacological agent use to assist with additional weight loss and metabolic health.

Bariatric Surgery Resistance

Multi-factorial elements are associated with an individual’s resistance to bariatric surgery-induced weight loss and CVD risk reduction. Aging has been suggested to predict blunted weight loss after surgery [16–17]. When compared with adults ≥ 60 years, younger individuals experienced significantly greater weight loss at 1 and 5 years post bariatric surgery [18]. These findings may have clinical relevance as older individuals have a 3-fold higher risk of mortality from surgical complications than their younger counterparts [19]. Others have reported that older adults are at increased risk for sarcopenia and insulin resistance, potentially providing an explanation for increased surgical risk and attenuated weight loss with age [20–21]. Sex may also contribute to bariatric surgery resistance. Women have been reported to experience less weight loss than men [16]. Although this finding is consistent with “diet plus exercise” literature [22], it is worth considering that differences in hormones between men and women, including endogenous sex hormones, leptin, and ghrelin, could be in part related to bariatric surgery resistance due to their link to

metabolic disease. A systematic review reported that high levels of testosterone is associated with a higher risk of T2D in women, independent of BMI and central adiposity, but lower risk in men [23]. Leptin concentrations vary between the sexes, as woman have higher concentrations of leptin per unit of fat mass than men [24]. Individuals who are obese are thought to be leptin resistant which alters eating behavior and satiety and could result in a greater caloric intake [25–26]. Women also have elevated ghrelin levels that are associated with a higher total fat mass, while in men, ghrelin is primarily related to central adiposity [27–28]. Given the link between ghrelin promoting insulin resistance [29], and the differential impact ghrelin has in women and men, it is possible that differences in ghrelin hormone profiles may explain why women have reduced weight loss responsiveness to bariatric surgery. Race/ethnicity are additional key clinical factor explaining bariatric surgery resistance. In particular, Hispanic and African American patients experience less weight loss following bariatric surgery than Caucasian patients [30–31]. This observation may be related to observations that Hispanic patients seem to have a higher genetic predisposition for metabolic syndrome, as evidence by the higher disease prevalence compared with African American and Caucasian patients. This suggests that race/ethnicity driven metabolic risk may explain attenuated responses to surgery [32–36]. Although not the purpose of the present review, it is important to consider that psychosocial factors including but not limited to eating behavior, eating disorders, mental illness, substance abuse, and socioeconomic status may also contribute to bariatric surgery resistance [37–40]. In summary, targeting metabolically modifiable risk factors with lifestyle medicine in high-risk populations may be beneficial for bariatric surgery resistant patients.

Independent of age, sex, and race/ethnicity, inflammation is an important etiological factor in obesity that promotes insulin resistance and may affect response to bariatric surgery [3–4]. In particular, increased white adipose tissue in the abdominal visceral region increases the expression of macrophages and inflammatory cytokines including TNF-α and interleukin-6 that in turn leads to elevated systemic inflammation [4, 41]. Moreover, increased inflammation in adipose tissue down-regulates adiponectin, which exacerbates systemic insulin responsiveness in tissues including skeletal muscle and liver. This is problematic as insulin resistance promotes β-cell dysfunction, endothelial dysfunction, hyperglycemia and increased risk for cardiovascular disease [3,4,42]. Bariatric surgery reduces pro-inflammatory cytokines in association with weight loss, and this reduced inflammation correlates with improved insulin sensitivity and brachial artery reactivity [42–44]. These findings are consistent with work by our group showing that individuals who had non-remission of T2D after bariatric surgery were characterized by smaller changes in C-reactive protein and adiponectin compared with those with remission [45]. Thus, pre-operative inflammation may be an important biomarker of bariatric surgery responsiveness [46]. Although others suggest that weight loss is at least partially responsible for changes in inflammation and elevated adiponectin levels [47–49], targeting inflammation has received little attention in the pre-surgical period. Whether reducing inflammation is an important aspect of bariatric surgery responsiveness to promote metabolic health improvement remains to be tested.

Additional factors that may affect individual responsiveness to bariatric surgery are insulin resistance and hyperglycemia. Insulin resistance is a complex physiological response caused

by genetic and environmental factors that lead to dysregulation of metabolic control. Over time, the pancreas is unable to secrete compensatory levels of insulin to maintain glycemic control, thereby resulting in hyperglycemia. As such, it is currently unclear if insulin resistance per se, or the developed hyperglycemia explains attenuated bariatric surgery responses. Indeed, hyperglycemia has been shown to promote toxic effects on the pancreas and decrease insulin secretion capacity, as reflected by reductions in β-cell volume and alterations in pulsatile insulin release [50–51]. This would be consistent with recent work highlighting that pre-operative HbA_{1c} > 10%, T2D duration, and anti-diabetes medication treatment all correlate with T2D non-remission following bariatric surgery [52–55]. Work by our group using the DiaREM score, which is a system to predict the probability of remission of T2D after RYGB surgery, supports the notion that the more severe forms of T2D status prior to surgery relates to non-remission state, even 10 years post-surgery [56]. These studies suggest that hyperglycemia at the time of bariatric surgery may itself play a role in bariatric surgery resistance, or it could be hypothesized that the physiologic factors regulating glucose, including insulin resistance or β-cell dysfunction, may be important targets to improve bariatric surgery outcomes. In support of this hypothesis, Gavin et al. recently reported that people with long duration T2D are characterized as being more insulin resistant prior to RYGB surgery, and thus, are more likely to have blunted T2D remission up to 3 months post-surgery [51]. We showed that long duration T2D is characterized by dampened reductions in HbA_{1c} that were paralleled by having greater β-cell dysfunction prior to bariatric surgery than people with short-duration diabetes [57]. Collectively, these findings suggest that lowering glucose levels and/or improving insulin action prior to surgery can be an important therapeutic target for minimizing surgical complications and improving bariatric surgery sensitivity.

Bariatric Surgery Resistance May Be Associated with Surgical Outcomes

Targeting modifiable risk factors in the pre-operative period may reduce bariatric surgery resistance and possibly improve surgical outcomes. Intra- and post-operative complications from bariatric surgery occur in < 10% of procedures and include, but are not limited to, wound infections, anastomotic leak, and abdominal sepsis [58–59]. The exact reason why these surgical complications vary is unclear, but obesity-induced inflammation and/or hyperglycemia may relate to surgical complications, prolonged operating time, and length of stay. Evidence indicates that surgical risk is associated with the specific bariatric procedure (RYGB > SG) and the patient's age, degree of obesity, and co-morbidities [59–60]. The Longitudinal Assessment of Bariatric Surgery Consortium (LABS) study reported that patients who had a history of deep-vein thrombosis, venous thromboembolism, and elevated BMI were at higher risk for post-surgical death, deep-vein thrombosis, venous thromboembolism, re-intervention, or failure to be discharged by 30 days post surgery [61]. Although no study to date has specifically linked inflammation, insulin resistance or hyperglycemia to the likelihood of bariatric surgery resistance, this prior work [59–61] suggests that there is a relationship between compromised cardiometabolic health and increased surgical risk. In fact, these findings are consistent with data showing that obesity is strongly related to individuals accumulating less than 150 minutes/week of moderate-to-vigorous physical activity and having low functional capacity. The physical inactivity

reported in obese patients may be clinically relevant since the inability to climb 2 flights of stairs or walk 2 city blocks were some of the strongest predictors of blunted weight loss following bariatric surgery [17]. A recent meta-analysis corroborates this observation by showing that lower physical activity levels are associated with attenuated surgery-induced weight loss in bariatric patients [62]. Interestingly, McCullough et al. demonstrated that cardiorespiratory fitness (i.e. VO_2max) < 15.8 ml/kg/min is associated with a longer operating time, intubation duration, and estimated blood loss during surgery as well as more frequent complications including unstable angina, myocardial infarction, and deep venous thrombosis [63]. Although no systematic studies have been conducted to establish a link between surgical complications and a blunted response to bariatric surgery, the intricate interplay of adiposity-derived inflammation, insulin resistance, and physical fitness needs to be better understood to identify their contributions to reduce surgical complications and rescue bariatric surgery resistance.

Exercise as a Pre-Surgical Therapy to Reset Metabolic Responsiveness

Current recommendations to increase aerobic fitness in adults include 150 minutes of moderate or 75 minutes of vigorous physical activity per week. However, < 10% of bariatric surgery candidates meet the activity recommendation prior to surgery [64] and, in turn, are categorized as having “very poor” cardiorespiratory fitness based on their VO_2max [65]. This low level of physical activity may be an explanation for why some individuals have increased composite surgical complications risk. Increasing physical activity levels prior to bariatric surgery could attenuate risk, as Berglind et al. found that pre-surgical physical activity levels were positively associated with post-surgical physical activity levels [66]. Thus, increasing physical activity levels prior to surgery could facilitate a beneficial increase in post-surgery exercise behavior. In fact, over 40% of bariatric patients feel more ready to exercise 2 weeks prior to their surgery [64], and recent work suggests that exercise counseling combined with pedometery may increase physical activity levels approximately 6 months following surgery to a greater extent than standard medical care alone. Unfortunately, there are few randomized controlled trials evaluating the effectiveness of an exercise intervention prior to bariatric surgery. Baillot et al. conducted a semi-supervised endurance and strength training program for 12 weeks prior to surgery and showed that people completed 64.5% of total exercise sessions. The training program resulted in significant weight loss and improvements in both physical fitness, as assessed by a 6-minute walk, and quality of life [67]. These findings were later supported by use of a telehealth approach using a semi-supervised in-home endurance and strength program to increase physical fitness [68]. Whether this increase in fitness and/or strength prior to surgery leads to reduced insulin resistance, inflammation and improved surgical outcomes and responsiveness awaits investigation [11, 69]. Nevertheless, while no study has systematically tested pre-operative exercise interventions in bariatric patients, it has been well established that exercise can improve both insulin resistance [70–71] and inflammation [72–73] in adults across BMI categories. Furthermore, a number of recent randomized controlled trials have been conducted to investigate the effects of exercise imposed post-bariatric surgery to determine whether exercise can effectively promote greater weight loss, fitness, and cardiometabolic health when compared to standard of care alone. Shah et al. demonstrated

that a 12 week exercise program following bariatric surgery improved glucose tolerance compared to standard care [74]. These findings are consistent with data highlighting that moderate intensity aerobic exercise increases insulin sensitivity and glucose effectiveness (i.e. the ability of glucose to facilitate glucose disposal) [75], along with increased VO_2max and mitochondrial adaptation for fat oxidation during bariatric-induced weight loss [76]. Supervised endurance exercise or educational based programs with resistance exercise can also facilitate greater weight loss, improved muscle strength and increased fitness capacity [75–77], suggesting overall that exercise is an effective therapy to improve metabolic health in surgical patients. However, despite higher exercise volumes in the general population appearing to relate to improved glucose regulation [13, 78–79] and cardiometabolic health [80], there is a limitation in the existing body of work on the effects of exercise “dose” on cardiometabolic health maintenance over time as well as on the effectiveness of exercise for the prevention of weight regain. These are important clinical questions that are likely to improve medical practice.

Diet as a Pre-Surgical Therapy to Improve Metabolic Responsiveness

Many bariatric candidates are malnourished due to long-term overconsumption of energy with predominantly low nutrient dense foods, thus leading to low diet quality. Inflammation and insulin resistance are associated with the resulting micronutrient deficiencies (e.g. vitamin D, iron, zinc, vitamin B-12), putting patients at additional risk for resistance post bariatric surgery [81]. The detriment of micronutrient malnourishment on post-surgical outcomes needs to be considered, with requirements of up to 10% weight loss for patients prior to surgery by many surgical centers in the U.S. [82]. This pre-surgical weight loss has been suggested to shorten surgical time, reduce surgical complications, and elicit greater weight loss at 3, 6, and 12 months post surgery when compared with individuals who do not lose weight prior to surgery [83–84]. Independent of macronutrient composition, low calorie diets are the most commonly prescribed dietary interventions since creating the state of negative energy balance is an effective non-surgical venue to reduce body weight [85]. An important reason low-calorie diets are implemented is to optimize weight loss and increase subject safety during surgery, in particular due to the shrinking of the liver, which will be discussed below. Indeed, a very low calorie diet (defined as less than 800 kcal per day) implemented 2 weeks prior to bariatric surgery resulted in significantly fewer post-operative complications in the 30 days after surgery when compared to controls with no pre-operative dietary restrictions [86]. Furthermore, surgeons have reported operations to be easier in patients who have undergone pre-operative diet therapy [86]. However, it is worth noting that some studies report that despite significant amount of weight loss in the pre-surgical period, there was no enhanced weight loss at 24 [87] and 48 [88] months post-surgery compared with those who did not diet pre-surgery. In line with these findings, Pournaras et al. showed that a 2 week very low calorie diet prior to surgery elicited weight loss and improved insulin sensitivity in adults with T2D compared to patients who did not diet. Yet, the group who followed a very low calorie diet pre-operatively did not have greater weight loss or insulin sensitivity at 2 weeks or 1 year post-surgery [89]. Thus, although data indicate that surgery outcomes are beneficially affected by pre-operative diet-induced weight

loss, additional work is required to determine if weight loss and/or metabolic health pre-surgery results in long-term health and well-being in the post-operative period.

Another reason the low-calorie diet is often utilized is to reduce liver size, as nearly 91% of people undergoing bariatric surgery have enlarged livers that are characterized by hepatic steatosis [90]. Enlarged and/or fatty liver is typically observed in individuals with large amounts of excessive body fat. This is problematic since enlarged fatty liver increases the risk of bleeding upon surgical manipulation and reduces operative visibility for the surgeon, thereby contributing to increased operative difficulty [91–92]. Fatty liver also correlates with increased rates of endogenous glucose production that contributes to fasting hyperglycemia and whole body insulin resistance [93]. Thus, dietary interventions that reduce liver size and elicit weight loss may be best for minimizing surgical complications. Edholm et al. evaluated the effectiveness of an 800–1100 kcal/day diet for 4 weeks prior to bariatric surgery, and reported an average weight loss of 7.5 kg, as well as a 12 and 40% decrease in liver volume and fat, respectively. The low calorie diet group had decreased surgical complexity as assessed by surgeons compared to individuals who did not undergo the diet intervention [94]. Brody et al. also studied the effectiveness of a 4 week 1200–1500 kcal/day diet that included specifically two 150 calorie high protein shakes per day during the pre-operative period. Dieting resulted in significant weight loss of approximately 3.1% and decreased left lateral liver volume by nearly 43% [95]. The response to a low calorie diet may be effected by time, as Colles et al. found that 2 weeks is the minimum amount of time for a very low calorie diet (<650 kcal/day) to induce decreased liver volume, while 6 weeks achieved greater reductions in liver size and visceral adipose tissue stores [96]. Thus, following a calorie-restricted diet as a pre-surgical intervention can reduce liver adiposity/size as well as insulin resistance. This in turn can translate to reduced surgical complications and improved surgical outcomes in bariatric candidates [93, 97–100].

One important limitation of following low calorie diets, and in particular the very low calorie liver-shrinking diets, relates to the disproportionally higher loss of skeletal muscle mass due to accentuated protein degradation and decreased rate of protein synthesis during periods of very low energy consumption [101]. Although, to date, no studies have specifically examined the relationship between skeletal muscle mass differences pre-operatively on the response to bariatric surgery, Dodson et al. reported that sarcopenia was an independent predictor of mortality following hepatic inter-arterial therapy [102]. Moreover, Psutka et al. showed that people characterized by sarcopenia were at increased risk of all-cause mortality after radical cystectomy for bladder cancer [103]. These findings suggest that skeletal muscle integrity may play an important role in post-surgical mortality. In fact, the loss of muscle mass from diet alone may be problematic for weight management during the post-operative period in the bariatric population as it results in significantly reduced resting metabolism [104–105], thereby affecting recovery from surgery as well as long-term weight loss.

Exercise is a therapy that can counteract the effects of diet on skeletal muscle loss. Ross et al. demonstrated that 60 minutes of aerobic exercise 5 days/week coupled with a low calorie diet resulted in significantly more adipose tissue loss and greater skeletal muscle mass preservation than diet alone [106], which may contribute to increased insulin sensitivity

[107]. Yokoyama et al. showed that a 3 week calorie restrictive diet (i.e. 25–30 kcal/kg of ideal body weight) plus exercise for 5 days/week also reduces insulin resistance independent of weight loss when compared with diet alone in adults with T2D [108]. These improvements in insulin resistance were determined by HOMA-IR, thereby leaving a gap in our understanding of what insulin-sensitive tissue (i.e. liver, skeletal muscle, etc.) responds most to exercise plus diet in the bariatric population. However, Haus et al. reported that obese adults with impaired glucose tolerance who underwent a hypocaloric diet plus aerobic exercise for 12-weeks derived greater improvement in hepatic, not skeletal muscle, insulin sensitivity when measured by the euglycemic-hyperinsulinemic clamp with intralipid and stable isotope infusion compared with exercise alone [109]. These findings are consistent with other work [110], and suggest that while diet alone is likely an effective therapy for reducing the risk of surgical complications and potentially prolonged metabolic health, adding exercise attenuates risk of muscle loss that can affect long-term bariatric responses for metabolic health.

Pharmacology as a Pre-Surgical Therapy

Despite randomized clinical trials showing the efficacy of lifestyle modification on weight loss and fitness, subject adherence to diet and exercise remains difficult. If conventional approaches to improve glycemic control and weight with lifestyle do not work well or are not feasible, then pharmacological agents that target specific pathological defects contributing to obesity, insulin resistance, and β-cell dysfunction may be necessary for addressing bariatric surgery resistance in the pre-surgical patient. While a goal of surgery is to reduce the number of prescription medications patients are taking, implementing pharmacological interventions in the pre-operative phase may elicit physiological changes that allow patients to better respond to surgery. Nevertheless, health care providers should be cognoscente of their patients' health status in the pre- and post-operative period in order to optimize health and well-being.

Four new weight loss agents with glycemic benefit have been approved for weight loss since 2012 and join orlistat for the long-term management of obesity. These therapies are generally recommended for patients who are obese or overweight (BMI ≥25 kg/m^2) and who suffer from at least one weight-related complication, such as hypertension, T2D, or dyslipidemia. Orlistat is a gastric and pancreatic lipase inhibitor that blocks dietary fat absorption from the gastrointestinal system by ~30%. Both randomized trials and meta-analyses have demonstrated that orlistat treatment can produce weight loss and reduce the incidence of T2D in people with impaired glucose tolerance [111]. Several mechanisms have been proposed to account for the anti-diabetic effect of orlistat, such as improved insulin sensitivity, incomplete dietary fat digestion, partial stimulation of GLP-1 (glucagon like polypeptide-1) release, and decreases in visceral adiposity [112]. Phentermine-extended release (ER) topiramate, lorcaserin, and naltrexone-bupropion are additional medications that elicit weight loss, but do so by acting in the central nervous system to reduce appetite. Clinical trials have shown these medications are effective at reducing HbA_{1c} as well as lowering the progression to T2D [113–118]. Finally, liraglutide, a GLP-1 receptor agonist that is approved for use in T2D, has also been approved for weight loss. Interestingly, GLP-1 (along with GIP, glucose-dependent insulinotropic peptide) is an incretin hormone that not

only plays an important stimulatory role in meal-stimulated insulin secretion, but it also delays gastric emptying and reduces post-prandial glucose levels [119]. Subsequently, many studies have proposed GLP-1 therapy as a novel approach to promote glycemic control and weight loss in obese patients. In fact, Wood et al. showed that the use of GLP-1 receptor agonists combined with anti-diabetic medication prior to bariatric surgery resulted in greater T2D early remission rates and 6 year remission rates than when taking anti-diabetic medications alone [120]. This suggests that GLP-1 receptor agonists may promote metabolic health prior to surgery for enhanced metabolic responsiveness in the post-operative period. More work is needed to understand the effect of GLP-1 receptor agonists, with or without exercise/diet in the pre-surgical bariatric patient, as few studies have studied the combined treatment effects for metabolic health [121–122].

Insulin sensitizers work to improve the regulation of glucose in liver, skeletal muscle, and adipose tissue. Metformin is the most widely prescribed drug to treat hyperglycemia in people with T2D [8]. In fact, metformin is the first-line oral anti-diabetic medication recommended by the American Diabetes Association [123] that aids in blood glucose management and body weight reduction. Current evidence suggests that metformin increases whole-body insulin sensitivity through the suppression of hepatic gluconeogenesis and stimulation of peripheral (mainly skeletal muscle) glucose uptake through activation of adenosine monophosphate-kinase (AMPK) [8].

An older class of insulin sensitizers, the TZDs (thiazolidinediones), act as a ligand for the peroxisome proliferator-activated receptor (PPAR) γ. Although these agents are effective at improving both insulin sensitivity as well as improving/restoring pancreatic β-cell function [124], they often promote weight gain of approximately 2–5 kg [125] and are associated with significant side effects including increased risk for heart failure [126], bladder cancer [127] and bone loss [128–129] and thus, may not be ideal for the pre-surgical obese patient.

A new class of diabetes therapy worth mentioning is the SGLT-2 (sodium-dependent glucose co-transporter-2) inhibitors. This drug acts by blocking the reabsorption of approximately 90% of luminal glucose in the proximal tubule of the kidney. In addition, it has favorable effects on body weight with weight loss of 1.2 to 3.3 kg, in addition to significant impact on glycemic control and systolic blood pressure. Intriguingly, one agent in this class, empagliflozin, was shown to have improved atherosclerotic outcomes in patients at high risk or with known CVD [130]. However, the mechanism by which empagliflozin improves vascular outcomes has not been elucidated.

Sulfonylureas (SUs) are insulin secretagogues that increase pancreatic insulin secretion through the binding of receptors related to potassium channels on β-cells [50]. Unfortunately, SUs do not appear to work effectively in the long term and also carry a risk of promoting weight gain [131–133]. Thus, the role of SUs on preparing patients for surgery is unclear.

Taken together, determining the appropriate pharmacologic agent(s) to prescribe patients pre-operatively will likely vary based on the individual and their current health status, which also includes cost of therapy as the newer agents tend to be more expensive. Further

prospective work is required to define an algorithm for the pre-bariatric surgery patient to foster weight loss and improve metabolic health to reduce surgical complications and improve metabolic responsiveness. Additional work will also be needed to be address how and if individuals should continue agents that promote weight loss even after surgery, particularly as people increase physical activity and improve nutrition. This will be important for optimizing life-long weight management, metabolic health, and well-being in the bariatric patient.

Clinical Perspective and Conclusion

Bariatric surgery causes significant weight loss and improves cardiometabolic health. Individuals undergoing bariatric surgery have significantly lower body weight [87–89] and incidence of comorbidities including T2D and hypertriglyceridemia [134] that persists over time (e.g. 10 years). Post-operative interventions including diet [135], exercise [101], and pharmacotherapy [136] have been explored to a greater extent than pre-operative interventions and have shown to be efficacious. However, newer work highlights that some individuals receiving surgery are “bariatric surgery resistant” and experience blunted weight loss and cardiometabolic health and non-remission of T2D, suggesting the need to intervene prior to surgery. The notion of bariatric surgery resistance therefore raises several important clinical and public health knowledge gaps that need to be addressed. First, what are the characteristics predicting a person being “bariatric surgery resistant”? What treatment(s) may aid resistant individuals prior to surgery to reduce chances of surgical complication, minimize post-operative length of stay, as well as improve recovery in the immediate 30-day period after surgery? How will increasing bariatric surgery sensitivity relate to post-surgical responsiveness, health improvements, and preservation of co-morbidity resolutions? To date, the answers to these questions are unknown, highlighting critical gaps in our current knowledge. These gaps primarily include limited systematic evaluations of pre-operative interventions on improving post-operative outcomes like surgical outcomes, inflammation, insulin resistance, hyperglycemia, and aerobic fitness. We wrote this review to highlight these current gaps, propose hypotheses, and identify possible interventions prior to surgery. A targeted approach to answering these questions, however, may rest in recognition of the known clinical and metabolic determinants of those people likely to be bariatric surgery resistant. Subsequently, targeting tissue-specific modifiable risk factors including obesity, inflammation, hyperglycemia, insulin sensitivity and β-cell function with exercise, diet, and/or pharmacotherapy may be the first steps towards creating a long-life metabolic fitness program in the bariatric patient (Figure 2). Further work to better define the optimal combinations of lifestyle medicine and/or pharmacology for cardiometabolic health in bariatric patients prior to surgery remain to be determined. To date there are no systematic studies that have evaluated individual and/or combined lifestyle interventions prior to bariatric surgery on cardiometabolic outcomes. Thus, clinical trials are needed to understand the correct dose of exercise, diet and/or pharmacology to optimize health in the bariatric resistant patient prior to surgery. Ultimately, development of such a program will set forth a metabolic fitness program that increases the propensity for treatment and prevention of future T2D and CVD.

Acknowledgments

N.G. and S.K.M. were primarily responsible for writing the manuscript. A.P., S.K., A.W., and J.K., P.H. reviewed and edited the manuscript. We thank the members of the Applied Metabolism & Physiology Laboratory for helpful discussion on the manuscript.

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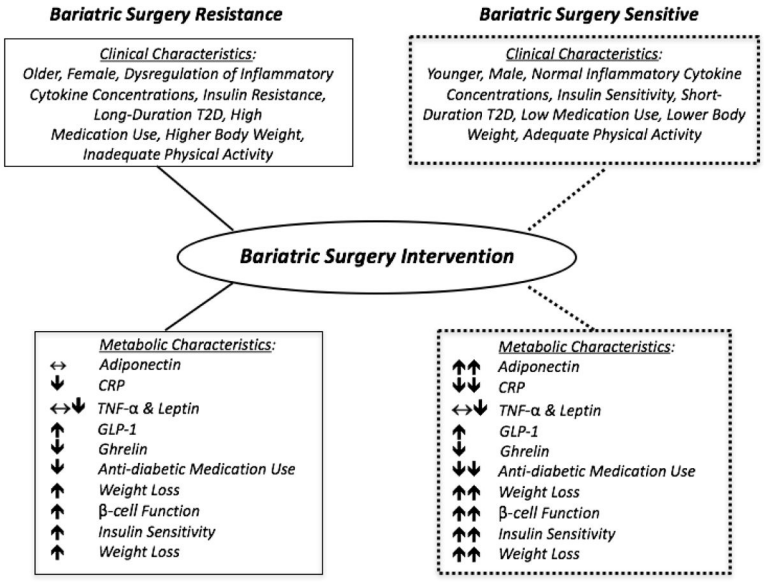

Figure 1.

Summary of potential phenotype and mechanisms underlying the differences in patients with bariatric resistance versus bariatric sensitive before and after surgery. T2D = Type 2 diabetes. CRP = C-reactive protein. TNF-α = tumor necrosis factor-α. GLP-1 = glucagon-like peptide-1. GIP = glucose-dependent insulinotropic polypeptide.

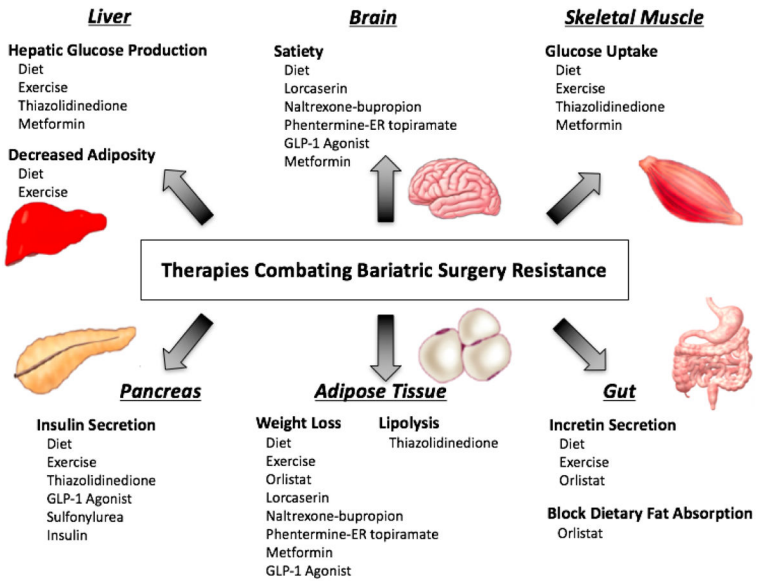

Figure 2.

Summary of lifestyle interventions and pharmaceutical agents that target potential mechanisms of bariatric surgery resistance across various tissues.