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Prehabilitation of overweight and obese patients with dysglycemia awaiting bariatric surgery: predicting the success of obesity treatment

Berkovic MC *et al.* Prehabilitation of overweight and obese patients awaiting bariatric surgery

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Abstract

Bariatric surgery offers the best health results to overweight and obese patients but is not a risk and/or complication-free treatment. In case of additional hyperglycemia, the burden of surgery can be even higher and alter both short-term and long-term outcomes. Although bariatric surgery offers glycemic improvements and in case of early onset diabetes disease remission, weight loss results are lower than for obese patients without diabetes. Different multimodal programs, usually including interventions in patients' performance, nutritional and psychological status as well as currently available pharmacotherapy before the surgery itself might considerably improve the immediate and late postoperative course. However, there are still no clear guidelines addressing the prehabilitation of obese patients with dysglycemia undergoing bariatric surgery and therefore no unique protocols to improve patients' health. In this minireview, we will summarize the current knowledge on prehabilitation before bariatric surgery procedures in patients with obesity and dysglycemia.

Key Words: Bariatric surgery; Obesity; Dysglycemia; Diabetes outcome; Prehabilitation

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Core Tip: The prehabilitation of bariatric surgery patients is an insufficiently investigated area of research. Adequate perioperative preparation for patients awaiting bariatric surgery could present one of the main determinants of predicting the success of surgical treatment, especially in patients with associated dysglycemia. A combination of calorie restrictive diet, structured exercise program, psychological support, and anti-obesity pharmacotherapy should be implemented in the perioperative care of candidates for bariatric procedures. This multimodal approach has the most promising potential to promote 5% weight loss at least thus affecting chronic inflammation and insulin resistance, the main culprits for bariatric surgery resistance.

INTRODUCTION

Obesity is a chronic debilitating disease with many health-related consequences. Nearly 39% of the worldwide adult population in 2019 met the criteria of being overweight and obese and, in addition, having multiple comorbidities^[1,2]. In case of additional derangements in glucose metabolism, such as glucose intolerance or diabetes whose incidence increases with increasing BMI, patients have an even worse long-term prognosis, with accentuated cardiovascular risk, morbidity, and mortality^[3].

Even the accumulation of free fat mass in the legs, arm, and trunk area is reversely associated with diabetes as was demonstrated in a recent study^[4]. Moreover, when weight reduction results (from lifestyle interventions, pharmacotherapy, or metabolic surgery) are compared for obese patients with and without diabetes, later are always more humble, suggesting a necessity for a structured and multimodal approach^[5].

Weight management aimed at weight reduction has favorable metabolic, and mental health benefits for obese patients. A healthy lifestyle, including physical activity, is one

of the pillars of weight management, impacting overall cardiometabolic health and well-being^[6]. In addition, newly available anti-obesity drugs can lead to potent weight loss results, but the most powerful strategy includes bariatric surgery. Different surgical approaches can be selected, some with malabsorptive effects and others, like gastric sleeve-resection without.

Malabsorptive procedures lead to nutritional risk, which might also exist preoperatively, regardless of patients' BMI. Therefore, preoperative nutritional status assessment and cardiorespiratory fitness status might be important parameters in decision making, treatment planning, and psychiatric evaluation. Enhanced Recovery after Bariatric Surgery protocol suggests that a higher preoperative fitness level leads to improved outcomes and fewer postoperative complications^[7]. Unfortunately, current ³ medical care does not routinely include a physical exercise component for the bariatric patient. Moreover, < 10% of bariatric surgery patients meet the current physical activity recommendations, although it has been shown that two weeks before surgery, 40% of obese patients would feel ready to start the exercise^[8].

In addition, prehabilitation might be the key to improving responsiveness to metabolic surgery, especially in patients with dysglycemia, one of the common comorbidities in overweight/obese patients that must be addressed preoperatively^[9].

In this minireview, we will focus on multimodal prehabilitation of patients undergoing bariatric surgery and specifically look into data on patients with coexisting dysglycemia.

ROLE OF EXERCISE

Exercise is a cornerstone of a healthy lifestyle and disease prevention, and sedentarism, lack of exercise, or nonattainment of physical exercise ¹⁰ goals have been strongly correlated with chronic non-communicable diseases such as obesity, metabolic syndrome, and type 2 diabetes mellitus (T2DM)^[10,11]. The inclusion of physical exercise in multimodal preconditioning programs for patients undergoing different surgical procedures has been in the research scope of numerous investigations^[12].

The role of exercise programs before and after bariatric surgery procedures might be important both from the aspect of reduction of perioperative and postoperative complications and as a means of retaining weight loss results achieved by surgery and acquisition of a healthy lifestyle^[13,14]. Unfortunately, despite convincing beneficial outcomes reported from other surgical procedures, structured perioperative exercise programs are barely/rarely used perioperatively for bariatric procedures. According to literature, physical exercise can contribute to approximately 4% excess weight loss, and when exercise is performed post-bariatric surgery, it results in an additional 3.6 kg weight loss^[15]. Well documented are beneficial effects of exercise on anthropometric measures (weight loss, reduction of fat mass, and reduction of neck circumference) accompanied by improvement in physical performance (measured by a 6-min walk test) and quality of life^[15,16]. There are, however, no clear recommendations on validated programs concerning starting the exercise before bariatric surgery, type of exercise, the intensity of exercises, duration of exercise sessions, or comparison of different exercise types concerning short-term and long-term outcomes. Moreover, the literature is mainly oriented on the exercise performed in post-bariatric surgery procedures and how it might help retain weight loss and cut cardiovascular risk compared to preoperative exercise programs^[17,18].

A few studies that have assessed the value of preoperative exercise suggest benefits in fitness level and achievement of presurgery weight loss. Specifically, a 12-wk pre-bariatric surgery program including endurance and resistance exercises suggests improvements in fitness and quality of life-extending one year post-operatively^[16,20,21]. In addition, studies using endurance and resistance training as a pre-bariatric surgery intervention reported improvements in weight and functional capacity, comorbidities, and quality of life^[22,23].

A recently published data from RCT, although having major adherence issues, suggested the benefit of resistance exercises with elastic bands involving large muscle groups of the upper and lower extremities in the perioperative period of obese patients awaiting bariatric surgery together with respiratory prehabilitation^[24].

Obese patients with dysglycemia (prediabetes or diabetes) are at higher risk for diabetes and obesity-related comorbidities^[25].

In a study by Hickey and colleagues^[26] a seven-day 60-min daily exercise program led to a significant decrease in fasting plasma insulin level, suggesting improvements in tissue insulin sensitivity, which is particularly important for overweight/obese patients with dysglycemia. In 24 wk of low-intensity endurance training, in addition to anthropometric parameters, Marcon and coauthors found substantial improvements in systolic and diastolic blood pressure, lipid and glucose levels, and patients' performance^[27]. A study by Woodlief and colleagues⁴ focusing on exercise dose after Roux-en-Y gastric bypass surgery showed that even a modest volume of structured exercise leads to improvements in insulin sensitivity but that higher volumes of exercise are needed for more profound health benefits^[28].

On the other hand, Gilbertson and colleagues investigated the effects of aerobic exercise (30 min/d, 5 d/wk, at home, walking at the intensity of 65%-85% peak heart rate during 30 d) on metabolic and short-term postoperative outcomes of bariatric patients. They found a significant decrease in calorie intake, increase in VO₂peak, decrease in hsCRP, cytokeratin 18 and improvement in quality of life, decreased sugar intake, improved whole-body insulin sensitivity, and glucose levels together with a shorter hospital stay of patients who were in the exercise group^[29]. Moreover, from the aspect of choosing a better exercise type, interval training might be superior to moderate-intensity continuous training in terms of reducing fat mass^[30].

The main problem in objectively assessing the contribution of exercise programs on weight loss outcomes, besides the lack of randomized control trials, is the lack of structured exercise, poor patient adherence, and the self-reported measurement of exercise limiting the result interpretation.

ROLE OF DIET

Restrictive calorie intake is widely advocated for obese patients undergoing metabolic surgery, and a weight loss of 5%-10% is generally mandatory before patients are

considered as candidates for bariatric surgery, primarily as a means of assessing patient's motivation and adherence to follow-up after the surgery^[31].

Currently, different dietary interventions mainly investigated in a non-randomized and uncontrolled manner, such as a low-calorie diet (800/1200 kcal daily) or a very-low-calorie diet (600 kcal per day), were shown to reduce weight preoperatively (4.2% and 5.8%, respectively) with no difference in inducing a reduction in liver volume and having similar effects on surgical complications, length of hospital stay and biochemical parameters^[32]. In addition, very low-calorie ketogenic diets have recently been investigated in the context of weight reduction in obese patients. Although the concern is raised due to their ability to induce katabolism, enhance oxidative stress response, and, through high protein intake, induce a negative metabolic response, data available from a few non-randomized studies suggest mentioned dietary regimen when used 30 d before bariatric surgery and in a sequential way with low calorie and a very low-calorie diet adds beneficial effects in terms of better weight reduction, waist circumference, visceral fat reduction, and improvement in glycemic and lipid profiles accompanied by a mean 30% reduction in liver volume^[33-35].

It is still unclear whether overweight and obese patients benefit from short-term dietary weight loss interventions while changes in the level of circulating mediators of appetite such as leptin, ghrelin, and GIP might favor long-term weight regain^[36]. Moreover, overweight/obese patients might also be at nutritive risk, which might escalate if restrictive diets are not controlled^[37]. Numerous studies reported multiple micronutrient deficiencies in obese patients^[38-40], while Schiavo and colleagues showed that preoperative micronutrient supplementation leads to the prevention of micronutrient deficit in the postoperative period^[41]. Therefore, current guidelines support the preoperative nutritional status screening for all patients awaiting bariatric surgery^[42].

A meta-analysis including 6060 patients showed significant weight reduction achieved through preoperative dietary restriction led to significant weight loss and 27% shorter duration of hospital stay, but with no difference regarding perioperative

morbidity and mortality^[43]. Stefura and colleagues prospectively collected data from 909 bariatric patients treated by ERAS principles and depicted predictors of success in losing > 5% of initial weight as positive (diabetes mellitus, obstructive sleep apnea, and previous surgery) or negative (steatohepatitis, respiratory disorders). Although there was no influence of preoperative weight loss on perioperative morbidity or mortality, patients who lost > 5% in the perioperative period had better weight loss results post-surgery^[44].

Efficacy of calorie restriction (very-low-calorie diet and more recently very low-calorie ketogenic diet) due to weight loss potential are interesting bridging therapy before bariatric surgery but still under debate due to the lack of large randomized studies addressing the issues around their effect on the postoperative complications.

ROLE OF PHARMACOTHERAPY IN PREHABILITATION

A certain number of individuals are resistant to the weight loss effects of bariatric surgery due to multiple reasons such as level of chronic inflammation, presence of T2DM, age, gender, and ethnicity^[45].

Chronic inflammation and ² increased circulating levels of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor- α caused by white visceral adipose tissue could be one of the main reasons for bariatric surgery resistance independent of all other factors^[46]. In responsive individuals, bariatric surgery reduces pro-inflammatory cytokines promoted by weight loss attenuating insulin resistance^[47-49]. Therefore, reducing pre-operative inflammation could improve response to bariatric surgery^[50].

To date, several studies demonstrate that severe dysglycemia, duration of diabetes, and anti-hyperglycemic therapy at the time of surgical procedure are the key factors in predicting response to bariatric surgery^[51-55]. Whether hyperglycemia or insulin resistance are the main culprits for bariatric surgery resistance remains to be seen but improving glycemic regulation and insulin sensitivity could be the most important pre-operative pharmacological targets to improve responsiveness to bariatric surgery.

In addition, unchangeable factors, including aging, female sex^[56,57], and Hispanic and African American races^[58], are associated with higher rates of bariatric surgery failure. Therefore, influencing modifiable risk factors seems to be the most reasonable approach to improve the successfulness of bariatric procedures.

Although lifestyle modifications such as physical activity and diet play a major role in the prehabilitation of bariatric patients, adherence to lifestyle changes remains an elusive and hardly attainable goal^[43]. Implementing pharmacological options that reduce insulin resistance and chronic inflammation by lowering body weight preoperatively in patients with or without diabetes has great potential to improve the response to bariatric surgery.

There are several weight loss agents available on the market. One of the most frequently used is liraglutide, a long-acting ³ glucagon-like peptide 1 receptor agonist (GLP 1 RA) approved for the treatment of T2DM and obesity due to its mechanism of action based on delayed gastric emptying, central reduction of appetite, and stimulation of glucose-dependent insulin secretion^[59,60]. The efficacy and safety of liraglutide 3 mg daily were assessed in phase III clinical trial program SCALE, demonstrating greater improvement compared to placebo regarding HbA1c, ⁸ blood pressure, lipid reduction, and health-related quality of life in overweight people and obese patients^[59-62]. However, most research seems to focus on the role of liraglutide in post-operative management, preventing weight regain, and promoting further weight loss. At the same time, data on perioperative administration is scarce. The effectiveness of liraglutide in the prehabilitation of bariatric patients was demonstrated for the first time in a retrospective cohort analysis by Wood *et al*^[63] in which therapy with ¹ GLP-1 receptor agonists in combination with other anti-diabetic medication prior to bariatric surgery led to higher T2DM remission rates, short and long term, compared to therapy with other anti-diabetic medications alone^[64]. Recently, a case series also demonstrated the potential benefit of short-term therapy with liraglutide prior to bariatric surgery^[65]; however, data from randomized clinical trials are lacking.

Presently, there are several retrospective studies demonstrating the efficacy of liraglutide therapy in patients that underwent bariatric surgery with inadequate weight loss or weight regain^[66,67], including one randomized clinical trial investigating liraglutide effects compared to placebo on total weight loss and excess body weight loss added early after laparoscopic sleeve gastrectomy in obese individuals^[64]. Liraglutide significantly improved the resolution of dysglycemia and weight loss effects of the surgical procedure compared to placebo.

Another promising agent from the same class is semaglutide, a long-acting GLP 1RA with proven effects on diabetes management and weight loss and recently approved by the FDA for both indications.

Semaglutide has improved pharmacokinetic properties compared to liraglutide, enabling once-weekly administration and greater efficacy^[68]. In phase III clinical trial assessing efficacy and safety of semaglutide 2.4 mg in obesity treatment, ¹greater reductions in body weight were observed after 68 wk with once-weekly semaglutide 2.4 mg sc *vs* placebo (mean change from baseline -14.9% *vs* -2.4%; ETD -12.4%; 95CI -13.4 to -11.5; $P < 0.001$)^[69-72]. Similar results were found in a 68-wk ¹phase III study (STEP 3) comparing the effects of semaglutide 2.4 mg *vs* placebo in overweight or obese adults without diabetes. The ¹mean body weight decreased 16% with semaglutide, compared to 5.7% with placebo ($P = 0.0001$)^[71]. No data is available on semaglutide in the prehabilitation of bariatric patients.

Tirzepatide belongs to an emerging new class of drugs called twincretins, ²dual receptor agonists of the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1^[72]. In phase III clinical trial program SURPASS, designed to assess the efficacy and safety of tirzepatide 5, 10, ⁷and 15 mg as a treatment to improve glycemic control in patients with T2DM, tirzepatide demonstrated impressive results in terms of glycemic regulation and weight management^[74,75]. In SURPASS-2 higher dose of tirzepatide (15 mg) had more pronounced weight loss effects compared to semaglutide 1 mg (13.1% *vs* 6.7%) as well as better anti-hyperglycemic effects (2.3% *vs* 1.86%)^[75].

Older ⁹ anti-obesity medications such as orlistat, phentermine/topiramate, and naltrexone/bupropion have low efficacy and cause a drop in body weight up to 3%-7% compared to placebo with unfavorable safety profiles^[76]. Liraglutide also induces similar weight loss but with a more acceptable safety profile. Consequently, the efficacy of semaglutide 2.4 mg and tirzepatide 15 mg in terms of weight loss effects is extremely significant, highlighted by the fact that approximately 75% ² of patients treated with semaglutide 2.4 mg or tirzepatide 15 mg experience 10% to 15% body weight loss accompanied by the well-known side-effects such as nausea, vomiting, diarrhea and obstipation^[77].

Therefore, these new agents could represent a new era in optimizing the medical care of bariatric surgery patients with the potential to significantly influence surgery outcomes. Further prospective randomized trials are necessary to determine the significance of these new classes of anti-obesity medications in the prehabilitation of bariatric surgery patients.

ROLE OF PSYCHOLOGICAL SUPPORT

Numerous studies have demonstrated a link between obesity and psychological disorders in patients awaiting bariatric surgery, the most common being anxiety, depression and binge eating disorders (BED)^[78-80]. Still, the effect of psychological status perioperatively on the success of bariatric surgery remains to be clarified due to large heterogeneity within the same psychiatric diagnosis influencing eating patterns. For instance, in a recently published study, better weight loss was associated with depression and BED diagnosis^[81] as opposed to other findings linking higher levels of psychopathology with the diminished success of weight reduction^[82,83]. Moreover, the results of the latest meta-analysis including published studies about psychological interventions in patients undergoing bariatric surgery were ambiguous regarding the usefulness of psychological support on bariatric surgery outcomes^[84]. Therefore, further research covering this topic is needed to assess if the benefit of psychological therapy really exists.

FUTURE IMPLICATIONS

Without a doubt, lifestyle modifications based on implementing structured exercise programs and nutritional plans offer great benefits in the prehabilitation of patients awaiting bariatric surgery, especially those with associated dysglycemia. The ultimate goal is achieving a minimum 5% weight loss and improving cardiorespiratory fitness and increasing basal rate consequently promoting further postoperative weight loss and bariatric surgery responsiveness as well as reducing postoperative complications and mortality. However, clear recommendations regarding the most efficient exercise protocols and calorie-restrictive diets are lacking and further prospective studies are needed to establish effective and safe protocols to upgrade peri and postoperative care as well as surgery's short and long-term outcomes. One should not forget the influence of patient characteristics, psychological profile, social conditions, and behavioral responses to the operation, which also have a great impact on surgery success requiring the development of protocols for psychological support. Furthermore, present anti-obesity pharmacotherapy such as GLP-1 RA and in the future twincretins offers a significant opportunity to improve the peri and post-operative care of bariatric patients, acting in synergy with exercise and calorie-restrictive diets. Furthermore, the degree of obesity and age influence the choice of treatment strategy or protocol in perioperative care. Still, there are significant shortcomings since most of the research to date has been focused on the postoperative care of bariatric patients, while research on perioperative care has been somewhat neglected.

CONCLUSION

We have tried to summarize current knowledge and propose recommendations for perioperative care of all bariatric patients, but with special emphasis on those with disturbances of glucose metabolism (Table 1). Future studies should focus on the development of perioperative treatment protocols consisting of the most optimal combination of lifestyle changes and pharmacotherapy thus optimizing response to

bariatric surgery, ultimately improving both short and long-term outcomes by reducing the incidence of T2DM and cardiovascular disease.

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