Weight Regain after Metabolic Surgery

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Contributor: Juan Salazar, Pablo Duran, Bermary Garrido, Heliana Parra, Marlon Hernández, Clímaco Cano, Roberto Añez, Henry García-Pacheco, Gabriel Cubillos, Neidalis Vasquez, Maricarmen Chacin, Valmore Bermúdez

Patients undergoing metabolic surgery have factors ranging from anatomo-surgical, endocrine metabolic, eating patterns and physical activity, mental health and psychological factors. Some of the latter can explain the possible pathophysiological neuroendocrine, metabolic, and adaptive mechanisms that cause the high prevalence of weight regain in postbariatric patients.

Keywords: metabolic surgery ; obesity ; metabolic syndrome

1. Introduction

The World Health Organization (WHO) defines overweight and obesity as an abnormal, excessive and harmful fat accumulation because it is a well-known independent risk factor for morbid conditions like diabetes mellitus (DM), dyslipidaemia, cardiovascular diseases, and cancer [1]. Over the last four decades, the prevalence of obesity has increased at an alarming rate in countries with Westernized lifestyles, becoming one of the major health concerns as a consequence of morbidity, mortality and the economic burden on national healthcare systems worldwide [2][3][4][5]. In fact, since 1975, obesity prevalence has shown a three-fold increase in adults and a five-fold increase in children and adolescents. Furthermore, according to the latest regional and national projections by the 2023 World Obesity Atlas report on obesity, the majority of the global population (51%, or over 4 billion individuals) will be suffering from being overweight or obesity, defined as a Body Mass Index (BMI) ≥ 25 kg/m^2 and BMI ≥ 30 kg/m^2. If current trends continue, the global economic impact of excess weight could reach $4.32 trillion annually, equivalent to 3% of the global GDP [6][7].

Despite multiple therapeutic strategies for weight loss (WL), combining several nutritional schemes, physical activity, cognitive-behavioral therapy, and pharmacologic intervention, medical obesity management is a challenging endeavor, often yielding limited success, as lifestyle-based interventions alone prove insufficient in achieving significant long-term weight loss in some patients, occasionally leading to a rebound effect where individuals regain more weight than initially present at the beginning [8][9].

On the other hand, the drugs approved for obesity are orlistat, phentermine/topiramate, naltrexone/bupropion, and the Glucagon-like peptide receptor agonists, like Liraglutide or Semaglutide, although these treatments can be expensive and may have adverse effects. Thus, it is important to carefully consider the potential benefits and risks of drug therapy before starting treatment in individuals with obesity [10].

Given this challenge, along with the need for an effective and long-lasting treatment, metabolic surgery (MS) has proved its efficacy in losing massive amounts of both subcutaneous and visceral fat [11], which involves different techniques designed to correct or control obesity, aiming to improve quality of life by achieving adequate and long-lasting WL with minimal complications [12].

In 2022, the American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) states that MS is recommended in case of: BMI ≥ 35 kg/m^2 (regardless of presence, absence, or severity of co-morbidities), patients with T2D and BMI ≥ 30 kg/m^2, individuals with BMI of 30–34.9 kg/m^2 who do not achieve weight loss or co-morbidity improvement using nonsurgical methods. Also, it is important to consider geographic factors; for example, obesity in Asiatic people is recognized as BMI > 25–27.5 kg/m^2, so MS could be performed in these cases. On the other hand, age is not an exclusion or inclusion criteria for MS, and could be performed in Children and adolescents with BMI > 120% of the 95th percentile and a major co-morbidity, or a BMI > 140% of the 95th percentile [13][14][15][16].

MS procedures had traditionally been divided into restrictive, malabsorptive and mixed categories; however, it is now known that MS can cause weight loss not only through these mechanisms but also through appetite control, alterations of hormones of the gut brain axis, alterations in bile acid physiology and intestinal microbiota [17][18][19][20]. Even though MS successfully manages to decrease a significant percentage of body weight, not all patients can maintain the weight loss achieved and could surprisingly regain the lost weight [21]; this undesired scenario could affect the patient's physical and mental health.

2. Metabolic Surgery Complications

As previously mentioned, MS is a low-complication rate procedure with a minimum margin of risk. Overall, the combination of improved surgical techniques, surgeon expertise, patient selection, perioperative care, post-operative management, and advancements in technology and research have resulted in a notable decrease in the incidence of complications linked to bariatric surgery. Nonetheless, it is not exempt from complications, and MS has been associated with adverse surgical complications, including high-mortality complications [22]. Furthermore, Pallati et al. [23], in a systematic review and meta-analysis of 160,000 bariatric patients, reported a post-operative complications rate between 10–17% and a 7% reoperation rate; favorably, the mortality rate remained low (0.08–0.35%).

The perioperative or short-term complications can be divided into minor and major; the most common minor complications are usually at the surgical site (port bleeding or hematoma, skin infections, and post-operative neuropathic pain), hydro electrolyte imbalance, and urinary tract infections. Major complications involve anastomotic leaks, intra-abdominal bleeding, small bowel perforation, myocardial infarction, and pulmonary embolism <30 days after MS. Typically, these early complications frequency is below 1.6%, and the mortality rate is <0.7% [22]. Post-surgical leaks can arise from the gastrojejunal anastomosis of the RYGB (1.68–2.05%); in vertical sleeve gastrectomy, they emerge from the staple line (2.2%). Hemorrhages often begin in the staple line but can also come from anastomotic or gastric remnant ulcers [24].

Moreover, although mid- and long-term complications have been well described, establishing their exact incidence is difficult due to the increasingly significant number of patients who miss their follow-up visits as time goes by. These complications are stenosis, bowel obstruction, marginal ulcers, ventral hernia, fistula, gastroesophageal reflux disease, and metabolic complications like nephrolithiasis and hypoglycemia [25]. In this context, gastrojejunal stenosis is a common complication, with an incidence rate ranging from 4% to 27%, similar to gastroesophageal reflux disease, which occurs in 12% of cases. Meanwhile, gastric stenosis is uncommon, only occurring in 1% of the patients. Internal hernias generally cause small bowel obstructions after gastric bypass or rarely by intraperitoneal adhesions in 2–3% of the patients [25].

Several kinds of ulcers, most marginal, arise within the first 12 months after gastric bypass; their estimated incidence is around 16%, contrasting the much lower incidence of fistulas (1.2%). Unfortunately, fistulas can appear in almost any location of the digestive tract following surgery; gastro-gastric fistulas are an especially alarming RYGB complication. Another rare complication is hernias, which have a frequency of less than 1% in laparoscopic procedures; however, the frequency increases to around 8% for open procedures [24].

Additionally, vitamin and mineral deficiencies are also described as possible complications. Regarding nutritional deficiencies, biliopancreatic diversion leads to a more significant decrease in liposoluble vitamins, copper, and zinc compared to gastric bypass; contrarily, vitamin B12 deficiency, due to decreased levels of its intrinsic factors, is more frequently caused by gastric bypass in comparison to any other procedure [26].

In contrast to these low surgical complications, 10–20% of the patients are expected to regain a significant weight proportion in the long term. Likewise, it has been reported that 20–25% of the lost weight can be regained in a ten-year course, starting nearly 24 months after the surgery; thus, the mean weight regained after the surgery is 10 kg, ranging from 0.5 to 60 kg [27]. In this context, WR is considered clinically significant when WR is greater than or equal to 15% of the lowest weight reached while maintaining this increase for at least six months [28].

3. Risk Factors for Weight Regain after MS: Is It All about the Surgery?

The multifactorial nature behind WR after MS has hampered the comprehension of its mechanisms, and thus, the therapeutic approach. Psychological, behavioral, endocrine metabolic, genetic, and anatomical factors have been associated with WR [29][30].

3.1. Anatomic and Surgical Factors

The leading anatomical abnormality associated with WR is the enlargement of the gastric pouch (>6 cm long or >5 cm wide) and gastrojejunal stoma (diameter > 2 cm), and gastro-gastric fistula (GGF), which are mainly sequelae of procedures such as RYGB and vertical sleeve gastrectomy (VSG) [31][32][33]. A GGF is an abnormal communication between the proximal gastric pouch and the distal gastric remnant. Consequently, food detours to the "previous route" instead of the duodenum, increasing the available gastric volume and food's absorption surface impairing the properties of MS [34][35][36].

By contrast, gastrojejunal stoma dilation leads to accelerated gastric pouch emptying and, therefore, a lack of satiety, instead accommodating larger amounts of food within the gastric pouch. Heneghan et al. [32] assessed the potential causes of WR by gastroscopy in patients submitted to RYGB (*n* = 380), reporting that only 28.8% of those who had WR (*n* = 205) had a normal-sized stoma, contrasting to 63.4% in patients who had successful weight loss (*n* = 175). Simultaneously, univariate statistical analysis demonstrates that the length and dilation of the stoma are the most influencing factors of WR; interestingly, the multivariate analysis only found the latter to be an independent factor for WR. Similarly, a retrospective study carried out by Yimcharoen et al. [33] reported that out of 205 patients with WR after RYGB, 58.9% had dilation of the gastrojejunal stoma, 28% had enlargement of the gastric pouch, and 12.3% had both of these findings.

Similarly, a study in people submitted to RYGB reported that limb length does not influence post-MS weight changes [37]. Still, this could be attributed to the methodology, study sample size, and confounding variables that could induce WR and enlargement of the gastric pouch, such as patients' lifestyles and psychological status.

3.2. Endocrine and Metabolic Factors

RYGB has been associated with episodes of hypoglycemia, a significant clinical component of the dumping syndrome (DS). In a study involving 36 RYGB patients, Roslin et al. [38] assessed their glucose levels six months after the procedure. They found that 11 patients had weight regain exceeding 10%, and six of these experienced hypoglycemia two hours after glucose load. Likewise, a study performed by Varma et al. [39] on 428 American patients who underwent MS determined that the odds of WR were significantly higher in those who had symptoms of hypoglycemia (OR: 1.66; 95% CI: 1.04–2.65). The authors have suggested that the causal relation could be due to metabolic changes produced by glucose homeostasis effects on appetite and gastrointestinal functioning [39]. Additionally, it has been proved that in the long term, post-MS patients with WR exhibit alterations in the levels of gastrointestinal and neuronal peptides related to appetite and satiety, which could indicate that changes in hormonal parameters contribute to WR [40].

3.3. Lifestyle: Eating Patterns and Physical Activity

Implementing lifestyle changes that counter the "obesogenic" environment before surgery is essential to achieve meaningful results in the WL after MS. In this context, it has been described how post-MS patients regain weight by eventually neglecting their lifestyle changes [41]. Furthermore, once the patients reach their target weight, some may increase their caloric intake, an expected eating behavior two years after the surgery [42][43].

Some of patients either fail to keep adequate control of their post-MS nutritional status or refuse entirely to follow the dietary patterns suggested by the weight management team, contrarily, maintain a high caloric intake attributed to a large intake of high-fat food, junk food, sweets, and high-sugar drinks, leading to suboptimal WL or even WR [41][43][44]. Bassan et al. [44][45] conducted a retrospective study that included 80 patients at least 24 months after MS and reported that 23.7% presented a WR greater than 10% of the lowest post-operative weight. Moreover, supported by multivariate analysis, a positive association between Healthy Eating Index and WR was observed (OR 0.95; $p = 0.04$), correlating to similar results found by other authors [44][46].

Furthermore, common maladaptive eating patterns among post-MS patients, such as binge eating and grazing, are considered risk factors for reduced WL [47]. Grazing can be defined as repeated episodes of consuming small quantities of food over a long time and is usually accompanied by feelings of guilt and loss of control [47][48]. A systematic review including 994 post-MS patients showed 16.6–46.6% engaged in grazing and 47% engaged in WR; an association was found between these two variables regardless of the type of MS and the author's definition of grazing [49].

Another factor linked to WR is dysphagia, a frequent complication after RYGB [50]. In a prospective cohort study by Runge et al. [51] on 245 post-MS patients, a higher WR was observed in those with dysphagia (*n* = 49) in comparison to the control group (*n* = 196) (37% vs. 25%). These things considered, patients with dysphagia are more likely to incline their diet partially or even entirely towards soft or liquid food since they are absorbed faster and produce less satiety, favoring a higher caloric intake and thus a positive energy balance that could explain the WR [51][52].

Regarding the food preferences observed after MS, although patients reported a diminished explicit liking for sweet foods at 3 months post-surgery and a lower desire to consume them at both 3- and 12-months post-surgery, intake of high-sugar foods was maintained in another study [53]. In this regard, a meta-analysis showed that bariatric surgery could be effective on energy and fat intake; however, there was no effect on carbohydrate intake [54], being considered another risk factor for developing weight gain after MS.

Besides unhealthy dietary habits, sedentarism or lack of physical activity can also be risk factors for WR. According to Rosenberg et al. [55], only 10–24% of the patients who underwent MS had performed the minimum physical activity to maintain their health status. Moreover, in a study by Yanos et al. [56] on 97 patients submitted to RYGB, 26% exhibited WR, associated with nocturnal eating, alcohol consumption, and diet and physical activity modifications. Correspondingly, Freire et al. [44] reported a lower incidence of WR among post-MS patients who exercised than those who did not.

3.4. Psychological Factors and Mental Health

Neuropsychiatric and Psychological disorders have been linked to WR and can hinder adherence to dietary and behavioral intervention plans during and after MS [46]. Binge eating disorder (BED), defined by The Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) as the uncontrolled consumption of larger and more than usual food quantities within two hours, is one of the main predictors of WR after MS [57]. However, BED prevalence among post-MS patients varies significantly according to the criteria used by different authors, ranging from under 5% to almost 24% [58][59]. Still, it has been demonstrated that BED is related to reduced WL or even WR two years after the procedure, along with developing worse maladaptive eating behaviors than prior MS [47][60]. Similarly, other eating disorders, such as soft food and night eating, have been recognized as predictors of WR after MS [61].

Furthermore, psychiatric disorders increase the risk of WR during post-operative periods; for instance, Rutledge et al. [62] showed that those individuals presenting two or more psychiatric disorders were six times more likely to develop WR post-MS. Under this framework, depression stands out among the most common disorders in bariatric patients, and although the association between this and WR or failure in post-MS WL has been demonstrated, as well as its presence predisposes individuals to be more prone to develop eating disorders, the results of studies tend to contradict each other since some show that depression is diminished after MS or, failing that, no causal relationships are observed in their analyses [56][63][64][65][66]. Similarly, patients with WR have high clinical or borderline anxiety and stress levels; however, these were not associated with higher energy consumption [66][67].

Finally, drug use and alcoholism have been described as influential factors in WR, as post-MS patients may seek relief from other substances through “addiction transfer” to substitute the needs established by the brain reward system for excessive energy consumption prior to MS [60][68][69]. Odom et al. [65] followed up on 203 post-RYGB patients, showing that decreased post-MS well-being, increased need to eat, and preoccupation with drug or alcohol use (addictive behavior) were independent predictors of WR. Thus, it is clear that bariatric patients need pre- and post-MS psychological assessment to ensure expected outcomes in WL and avoid relapse in maladaptive habits related to WR [70].

3.5. Preoperative and Other Factors

Numerous studies have found preoperative factors that may predispose patients to WR. A prospective study of 782 bariatric patients showed that approximately 50% of them presented WR, with patients in the super-obese group having a higher percentage of surgical failure (18.8%) and WR. The authors concluded that individuals with higher BMI before surgery are more likely to WR [71]. In particular, Keith et al. [72], in their retrospective study, described that preoperative factors such as male sex (p = 0.020), white race (p < 0.001), and high socioeconomic level (p = 0.035) were associated with WR. Furthermore, when multivariate analysis was performed, it was observed that socioeconomically advantaged patients were more likely to have WR than the rest (OR: 1.82, CI 1.18 to 2.79). However, other authors have differed with this study since their analyses establish that female sex and black race could be considered risk factors for WR [37][73][74].

Although age has been highlighted as a possible preoperative factor related to WR, results among studies vary significantly, with both young and older adults (>60 years) reported to be prone to WR [73][75][76]. Moreover, time elapsed after surgery, iron deficiency [77], work activity related to eating, and comorbidities such as T2DM have been linked to WR [78].

Remarkably, medications for psychiatric disorders, including tricyclic antidepressants, valproic acid, lithium, and antipsychotics, as well as antidiabetic drugs, steroids, and contraceptives, have been associated with weight gain and positive appetite modulation [79]. In this regard, post-MS patients treated with any of these drugs could theoretically be at high risk for WR [80]. In addition, there are genetic factors related to the development of obesity and adipose tissue (AT) biology that could be implicated in post-MS WR. Among these, genetic polymorphisms of AT adrenoreceptors such as the

ADRB2 gene (*Gly16Arg* and *Gln27Glu*), and those related to leptin, such as *LEPR*-gene (*LEPR Lys109Arg*, *LEPR Gln223Arg*, *LEPR Lys656Asn*), stand out [81].

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