

## Metabolic syndrome and liver disease in the era of bariatric surgery: What you need to know!

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### Abstract

Metabolic syndrome (MS) is defined as the constellation of obesity, insulin resistance, high serum triglycerides, low high-density lipoprotein cholesterol, and high blood pressure. It increasingly affects more and more people and progressively evolves into a serious issue with widespread healthcare, cost, and quality of life associated consequences. MS is associated with increased morbidity and mortality due to cardiovascular or chronic liver disease. Conservative treatment, which includes diet, exercise, and antidiabetic agents, is the mainstay of treatment, but depends on patient compliance to medical treatment and adherence to lifestyle modification recommendations. Bariatric surgery has recently emerged as an appropriate alternative treatment with promising long-term results. Sleeve gastrectomy and Roux-en-Y gastric bypass constitute the most commonly performed procedures and have been proven both cost-effective and safe with low complication rates. Liver transplantation is the only definitive treatment for end-stage liver disease and its utilization in patients with non-alcoholic steatohepatitis has increased more than fivefold over the past 15 years. In this review, we summarize current state of evidence on the surgical treatment of MS.

**Key Words:** Metabolic syndrome; Bariatric surgery; Sleeve gastrectomy; Gastric bypass; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Liver transplantation

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**Core Tip:** Metabolic syndrome (MS) is increasingly common in developed countries, and is associated with cardiovascular disease, hyperlipidemia, and non-alcoholic steatohepatitis. Diet, exercise, and weight loss are the milestones of conservative management. Bariatric surgery has emerged as a promising treatment in severely obese patients or in patients with MS resistant to conservative measures. Sleeve gastrectomy and Roux-en-Y gastric bypass are the most commonly performed bariatric procedures. The only definitive treatment in patients with MS and end-stage liver disease secondary to non-alcoholic steatohepatitis is liver transplantation (LT). The optimal timing for bariatric surgery, when required along with LT, has yet to be determined.

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## INTRODUCTION

Metabolic syndrome (MS), also known as syndrome X, is a complex entity consisting of insulin resistance, obesity, hypertriglyceridemia, increased waist circumference and hypertension<sup>[1,2]</sup>. According to National Heart, Lung and Blood Institute, at least three of the following metabolic risk factors should be met to establish the diagnosis of MS: (1) Obesity (waist circumference  $\geq 102$  cm for men and  $\geq 88$  cm for women); (2) Triglycerides  $\geq 150$  mg/dL; (3) High-density lipoprotein (HDL) cholesterol  $< 40$  mg/dL for men and  $< 50$  mg/dL for women; (4) Systolic blood pressure  $\geq 130$  mmHg and/or diastolic  $\geq 85$  mmHg; and (5) Fasting serum glucose  $\geq 100$  mg/dL<sup>[2-4]</sup>. The incidence of MS, following the patterns of obesity and type 2 diabetes mellitus (T2DM), is approximately 30% in the adult population in the United States<sup>[1,5,6]</sup>. Data suggest that even populations with relatively lower body mass index (BMI), such as Asian Americans, can be affected by MS<sup>[7]</sup>. The prevalence of MS has significantly increased over the last decades, with less physically active and older individuals being increasingly affected<sup>[6]</sup>. It is quite evident that MS evolves into a global epidemic health problem that mandates timely and effective action<sup>[1,8]</sup>. Therefore, we sought to review the complications associated with MS with a particular focus on diseases of the liver, as well as the available treatment options focusing mostly on bariatric and liver surgery.

## COMPLICATIONS ASSOCIATED WITH MS

MS has been associated with an increased risk of cardiovascular morbidity and mortality, and has been identified as an independent predictor of nonfatal stroke, ischemic heart disease, and cardiovascular death<sup>[9]</sup>. Wilson *et al*<sup>[10]</sup>, in a prospective study of 3323 adults followed over 8-years, reported an increased incidence of cardiovascular disease in patients who developed MS, while 30% of all myocardial infarctions and coronary heart disease deaths in men and 16% in women could be attributed to MS.

MS can also lead to insulin resistance, and consequently T2DM. The mean weight, BMI, and prevalence of obesity in the United States population have increased significantly from 1960 to 2000<sup>[11]</sup>. The prevalence of T2DM has also increased from 1.8% to 5.8% over the same period, due to the increased prevalence of obesity, as well as due to the increased detection and awareness in previously undiagnosed patients<sup>[11]</sup>. In addition to obesity, other factors play a key role in the rising T2DM trend, such as the lack of physical activity, dietary changes, and other environmental factors<sup>[8,11]</sup>.

Moreover, MS may affect the liver resulting in a wide spectrum of clinical conditions ranging from non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) to cirrhosis and, eventually, hepatocellular carcinoma (HCC). NAFLD is the most common cause of chronic liver disease in western countries<sup>[12,13]</sup>,

and is defined as  $\geq 5\%$  fatty permeation of the liver parenchyma in the absence of an alcohol abuse history<sup>[12]</sup>. It occurs in up to one-third of the general population<sup>[14]</sup>, and in up to 80% of patients with MS<sup>[15]</sup>. Risk factors predisposing to NAFLD include older age ( $> 50$  years), hypertriglyceridemia, insulin resistance, and central obesity<sup>[13,16]</sup>. Liver steatosis is considered to be one of the earliest signs of MS<sup>[17]</sup>, and early diagnosis and management are warranted to prevent the occurrence of irreversible histopathologic changes of the liver parenchyma<sup>[15]</sup>, which can lead to NASH, cirrhosis, and HCC<sup>[12,14]</sup>. Notably, Ekstedt *et al*<sup>[18]</sup> reported three out of 129 (2.3%) recruited NAFLD patients developed HCC. Data suggest that the excessive fat stored in the hepatocytes promotes the release of pro-inflammatory cytokines, such as tumor necrosis factor, which stimulate pro-oncogenic pathways, including the nuclear factor kappa-light-chain-enhancer of activated B cells and the c-Jun N-terminal kinase pathways<sup>[19]</sup>. Additionally, it has been shown that the loss of function of several tumor suppressor genes is involved in this process<sup>[12]</sup>. The definitive pathophysiologic mechanisms predisposing to the development of HCC in patients with NAFLD have yet to be elucidated.

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## CONSERVATIVE MANAGEMENT

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According to the current state of evidence, the cornerstone of MS management consists of lifestyle changes, such as restricted consumption of calories combined, regular exercise, and weight loss<sup>[20]</sup>. Previous studies have shown promising results with pioglitazone, metformin and vitamin E for the management of NASH<sup>[20,21]</sup>. Recently, obeticholic acid was found to be effective in the FLINT and REGENERATE trials and is expected to become the first FDA approved drug for the treatment of NASH<sup>[22-26]</sup>. Amphetamine derivatives, such as phentermine and desoxyephedrine, as well as statins have been occasionally utilized and showed promising results against NASH<sup>[27,28]</sup>. The addition of liraglutide to lifestyle changes has demonstrated better results than lifestyle changes alone<sup>[29]</sup>. Finally, vitamin D and zinc sulfate seem to be beneficial in children with MS<sup>[30,31]</sup>.

Nevertheless, the overall impact of lifestyle changes in MS and NASH highly depends on patient compliance, while conservative treatment is mostly effective in limiting the progression of obesity<sup>[32]</sup>. Despite the progress in pharmacologic treatment, non-surgical treatment is not always adequate to yield fruitful outcomes in obese patients (BMI  $> 30$ ).

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## SURGICAL MANAGEMENT

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Bariatric surgery can result in significant weight loss, and potentially complete resolution of MS. In addition, operative MS management results in reduced rates of hypertension, cardiovascular risk, and plasma lipids, while it may also lead to improvements in glucose tolerance<sup>[27]</sup>. In addition, surgery has a significant advantage over conservative methods in lowering the level of hemoglobin A1c (HbA1c) in T2DM patients<sup>[33]</sup>. Regarding its latter effect, bariatric surgery may even result in the complete remission of T2DM<sup>[34-36]</sup>. In fact, the duration of T2DM and preoperative serum C-peptide levels have been identified as predictive factors of postoperative benefit in glucose tolerance<sup>[37,38]</sup>. Recent recommendations suggest lifelong supplementation after all bariatric surgeries<sup>[39]</sup>. The loss of weight after bariatric surgery is also beneficial for patients with NAFLD and NASH, considering that a loss of  $\geq 10\%$  of body weight might facilitate a significant decrease in liver fibrosis<sup>[40]</sup>.

Bariatric surgical management was historically classified into restrictive and malabsorptive procedures. Restrictive procedures aim to decrease the amount of ingested food through a modification of the stomach capacity, while malabsorptive procedures aim to remove or bypass part of the small intestine thus leading to a decrease in gastrointestinal absorptive surface. In general, malabsorptive procedures are more beneficial in terms of lipid parameters than restrictive procedures<sup>[41]</sup>. Usually, both types of procedures are utilized in the management of MS. However, recent data suggest that factors other than restriction or malabsorption mediate the benefits of bariatric surgeries. For instance, gut hormones and enteroplasticity have been proven to play also an important role in terms of weight loss<sup>[42]</sup>, while alteration of the intestinal microbiome, gut hormone production, neural signaling, hepatic and pancreatic function, and gastrointestinal nutrient-sensing affect the glucose homeostasis and insulin sensitivity<sup>[43]</sup>. Bariatric procedures are most commonly

performed laparoscopically (96%) and include the following: Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), biliopancreatic diversion (BPD) with duodenal switch, and placement of laparoscopic adjustable gastric band (LAGB)<sup>[44]</sup>.

### **RYGB**

RYGB involves the formation of a 50-mL gastric pouch, as well as an antecolic Roux-en-Y gastrojejunostomy. Immediate effects of RYGB include the restricted intake of calories, the rapid entry of nutrients into the small intestine, and the increased nutrient and bile delivery to the distal small intestine, while it concurrently excludes the proximal intestine from nutrients<sup>[43]</sup>. RYGB can lead to significant mean weight loss (from 136.9 kg to 100.6 kg) and decrease in BMI (from 45.5 kg/m<sup>2</sup> down to 33.3 kg/m<sup>2</sup>) at 4 years postoperatively<sup>[38]</sup>. MS resolution during the first postoperative year can occur in up to 75.8% of the patients<sup>[45]</sup>, while a beneficial effect on blood pressure can be seen in up to 65% of MS patients<sup>[45]</sup>. Similar effects have been observed in other parameters associated with MS, including fasting lipids and glucose metabolism. In T2DM patients with a mean HbA1c level of 8.6%, the 1-year postoperative remission of T2DM after RYGB has been reported to be as high as 73.5%<sup>[40]</sup>. However, data suggest that during the 5-year postoperative period, the observed T2DM benefits may abate, mostly due to the insufficient amount of pancreatic beta cells reservoir in some patients<sup>[33]</sup>. Similarly, the beneficial effects on hyperlipidemia and hypertension are greater during the first 2 years after surgery, while these conditions may reemerge at 10 years post-procedure<sup>[46]</sup>. This finding signifies the potential importance of lifelong treatment with antihypertensive and lipid-lowering medications.

RYGB is considered a safe and effective therapeutic modality with low rates of postoperative complications, such as anastomotic leakage (0.63%), hemorrhage (0.52%), and bowel obstruction (0.4%)<sup>[38,47]</sup>. A common type of hernia observed after RYGB is Petersen's hernia, which is characterized by the herniation of a small bowel helix through the mesenteric gap created during the operation<sup>[48]</sup>. A recent meta-analysis revealed that this complication can be prevented with routine mesenteric gap closure after laparoscopic RYGB, with similar results in terms of other complication rates or weight loss<sup>[49]</sup>. Other postoperative complications include vitamin B<sub>1</sub>, vitamin B<sub>12</sub>, iron and calcium deficiency, as well as peptic ulcer disease<sup>[50]</sup>. Moreover, the need for reoperation or endoscopic intervention (anastomotic leak, infection, internal hernia, small bowel obstruction, insufficient weight loss) in patients undergoing RYGB is up to 22.1%<sup>[51]</sup>. Additional complications that may affect the quality of life include postprandial dumping syndrome, hypoglycemia, calcium oxalate nephrolithiasis and chronic kidney disease<sup>[52-54]</sup>. The 5-year postoperative mortality rate is around 3%<sup>[55]</sup>.

### **SG**

SG is mainly a procedure that results in caloric restriction, rapid entry of nutrients in the small intestine, and enhanced nutrient and bile delivery to the distal jejunum and ileum<sup>[43]</sup>. SG involves resection of approximately 80% of the stomach. SG is the most widely applied surgical procedure in the management of MS worldwide and results in improvement of all MS constituents, except for hypertriglyceridemia<sup>[47]</sup>.

Although both RYGB and SG can lead to weight loss and decrease in BMI, these effects are less pronounced with SG. In a meta-analysis, comparison of RYGB and SG demonstrated significantly higher percentage excess weight loss in RYGB patients (65.7% *vs* 57.3%,  $P < 0.0001$ )<sup>[52]</sup>. Despite being a simple procedure, SG offers significant benefits, including improved glycemic control, weight loss, improved insulin sensitivity, and decreased need for hypoglycemic agents, in patients with MS, diabetes, and obesity. Postoperatively, most insulin-dependent patients tend to reduce or even stop taking their insulin dose, and their management can be changed to oral hypoglycemic agents only<sup>[56-58]</sup>. At 6 mo after surgery, up to 84% of diabetic patients present with resolution or remission of T2DM<sup>[59]</sup>. However, 30% to 50% of patients exhibit recurrence of diabetes in the long-term<sup>[60]</sup>. The effectiveness of SG in lowering glucose levels might be associated to the fact that fasting glucagon-like peptide 1, an incretin that promotes glucose homeostasis through insulin secretion, increases significantly after SG<sup>[61]</sup>. Significant improvements after SG have also been reported in terms of HDL cholesterol levels and hypertension<sup>[57]</sup>. In addition, when compared to RYGB, SG does not increase the risk of nephrolithiasis and chronic kidney disease<sup>[53,62]</sup>.

SG is considered to be safer than RYGB, but both share the same spectrum of postprocedural complications except for the nutritional deficiencies, which are typically seen in lower rates after SG compared to RYGB. However, SG patients may present with postoperative iron, vitamin B12, and vitamin D deficiencies and ongoing monitoring with supplementation is necessary<sup>[63,64]</sup>. Reflux esophagitis is a relatively common complication after SG, while it is also deemed to be a contraindication for

SG<sup>[52]</sup>. In the long-term, a small percentage of patients may require a supplementary endoscopic or surgical intervention<sup>[65]</sup>, while some patients complain of nausea and vomiting after excess food intake<sup>[50]</sup>. In extremely obese patients (BMI > 60 kg/m<sup>2</sup>), the rate of postoperative complications appears to be high and comparable to the rate of other bariatric procedures<sup>[52]</sup>.

### **BPD with duodenal switch**

BPD with duodenal switch resembles RYGB, both in terms of procedure and mechanisms that mediate the effect on glucose homeostasis and weight loss. BPD is the most effective procedure in terms of weight loss, but requires higher levels of expertise and surgical skill and is considered as the least safe bariatric procedure. BPD can be effective in extremely obese patients (BMI > 60 kg/m<sup>2</sup>) or in patients with MS resistant to other modalities, since it provides very strong metabolic effects and durable 35%-45% weight loss<sup>[66]</sup>. BPD with duodenal switch constitutes only 1.5% of all bariatric procedures performed worldwide<sup>[67]</sup>.

Postoperatively almost 90% of BPD patients achieve normal HDL cholesterol levels<sup>[68]</sup>, while fasting serum glucose levels may remain normal for up to ten years<sup>[69]</sup>. Serum total cholesterol and triglycerides levels commonly normalize too, while complete resolution of hypertension has also been documented with three-fourths of the patients presenting with normal blood pressure values at ten years postoperatively<sup>[69]</sup>. An up to 70% weight loss may also be achieved and it may be preserved for more than ten years<sup>[70]</sup>.

Immediate postoperative complications include wound infection, anastomotic leak, and bowel obstruction<sup>[70]</sup>. Extensive small bowel resection can result in severe malabsorptive complications, such as anemia, nutritional deficiencies, hypoproteinemia, and bone demineralization<sup>[47,70]</sup>. BPD patients will require strict lifelong nutritional supplementation, including supplementation of lipid soluble vitamins, since they commonly exhibit vitamin A, D, E, and K deficiency<sup>[52,71]</sup>. Similarly to RYGB, patients undergoing BPD are at increased risk of nephrolithiasis<sup>[53,62]</sup>.

### **LAGB placement**

LAGB procedure involves the placement of an inflatable silicone device over the cardia of the stomach, which results in the formation of a small gastric pouch. This device includes a subcutaneous port to adjust the gastric band and the width of the gastric pouch<sup>[72]</sup>. LAGB can result in sufficient weight loss, while the reduction in BMI can be as high as 6.56 kg/m<sup>2</sup> in only 1 mo after the operation<sup>[48]</sup>. One significant advantage of LAGB placement over the other bariatric procedures is that the LAGB placement does not induce renal damage nor promotes renal stone formation<sup>[72,73]</sup>. In fact, urinary oxalate excretion was reported to be lower after LAGB placement than after RYGB, and similar to that of normal controls<sup>[74]</sup>.

Nevertheless, this technique is infrequently used mostly due to complications, including erosion, infection, band slippage, esophagitis, esophageal dilation, and port dysfunction<sup>[50]</sup>. LAGB placement may be technically easier than the other bariatric operations, but it has been associated with a higher reoperation rate<sup>[15]</sup> with approximately 20% of the patients requiring a reoperation at 4.5 years postoperatively<sup>[72,75]</sup>. In addition, although LAGB placement can achieve a significant loss of weight, the results are inferior to those seen with either SG<sup>[35]</sup> or RYGB<sup>[50]</sup>. Other aspects of MS are less improved, and these findings are to a certain extent attributed to the unchanged postoperative plasma ghrelin levels<sup>[40]</sup>. Last but not least, LAGB placement has not been deemed effective in the management of NASH<sup>[15]</sup>.

### **Comparison of bariatric procedures**

Despite the large number of patients in need of bariatric surgery, no official guidance on patient allocation to the various treatment modalities has been published to date. There is a growing body of evidence that the several bariatric procedures could be ranked in ascending order based on their effectiveness (weight loss percentage and duration of weight loss maintenance) as follows: (1) LAGB placement; (2) SG; and (3) RYGB, and (4) BPD with duodenal switch<sup>[67]</sup>. Despite its increased effectiveness, BPD with duodenal switch has been associated with high rates of postoperative complications, while all bariatric procedures require varying lifelong supplementation due to nutritional deficiencies. In general, higher rates of morbidity and mortality have been observed in bariatric patients with comorbidities associated with MS, especially in the first 30 d after surgery<sup>[76]</sup>. These data render BPD suitable only for extremely obese patients, when RYGB and SG are thought of as inadequate or for patients suffering from less severe MS-related conditions. The use of LAGB placement has been

decreasing in western countries, since SG and RYGB can achieve superior rates of MS resolution with much lower morbidity rates, and a decreased need for postoperative monitoring. As previously mentioned, SG is currently the most frequently performed bariatric procedure worldwide.

### **The role of bariatric surgery in NAFLD/NASH**

Although recommendations from the American Association for the Study of Liver Diseases<sup>[77]</sup> advocate for the use of vitamin E (in non-diabetics) and pioglitazone for NASH, caution is warranted with these agents due to their long-term risk of prostate and bladder cancer development, respectively<sup>[78,79]</sup>. Although nonsurgical weight loss can effectively improve all histological features of NASH and NAFLD (including fibrosis), most patients had early-stage fibrosis<sup>[80]</sup>. Therefore, other options including bariatric operations have been explored for the management of NASH and NAFLD. In fact, NAFLD at all stages is more common in those who meet criteria for bariatric surgery, which can indeed lead to sustained weight loss<sup>[77]</sup>. The most commonly used system for the assessment of necro-inflammatory lesions in NAFLD is the NAFLD Activity Score (NAS) from the NASH Clinical Research Network, which is comprised of 4 semi-quantitatively assessed histology features [steatosis (0-3), lobular inflammation (0-2), hepatocellular ballooning (0-2), and fibrosis (0-4)] and 9 histologic features recorded as either present or absent<sup>[81]</sup>.

A recent prospective study demonstrated the bariatric surgery, namely one-anastomosis gastric bypass, led to a significant decrease in the grades of fatty infiltration, cell ballooning, lobular inflammatory changes and total NAS at 15 mo postoperatively<sup>[82]</sup>. More specifically, the histological features of NASH disappeared in 41.7% of NASH cases and in 50.0% of borderline NASH cases<sup>[82]</sup>. Another recently published prospective study supports these findings by demonstrating histological resolution of NASH with no worsening of fibrosis in 84.4% of the patients<sup>[83]</sup>. There is a growing body of evidence suggesting that the vast majority of patients with NAFLD and NASH will experience improvements in histology after any type of bariatric surgery (Table 1). On the other hand, compared to those without cirrhosis (0.3%), caution is warranted when recommending bariatric surgery for patients with compensated or decompensated cirrhosis due to the higher mortality rates (0.9% and 16.3%, respectively<sup>[84]</sup>). In a systematic review summarizing the outcomes of bariatric surgery in 122 cirrhotics (96.5% Child-Pugh A, and 3.4% Child-Pugh B), early and late mortality were found to be 1.6% and 2.45%, respectively<sup>[85]</sup>.

The American Association for the Study of Liver Diseases recommends considering bariatric surgery in otherwise eligible obese NAFLD or NASH patients<sup>[77]</sup>. However, the current state of evidence does not allow us to deduce meaningful conclusions whether bariatric surgery can be used for the management of NASH specifically, but experienced bariatric surgeons can offer this option in eligible patients with compensated NASH on a case-by-case basis<sup>[77]</sup>.

### **Liver transplantation and bariatric surgery**

A significant percentage of patients may eventually require both bariatric surgery and liver transplantation (LT) for MS-related liver conditions; however, the sequence and appropriate interval between bariatric surgery and LT are still under investigation. The typical approach includes bariatric surgery one year prior to LT<sup>[86]</sup>. The main advantage of this approach is that the bariatric procedure can act as a “bridge” for patients to reach the predetermined BMI requirement for LT. Besides, data suggest that LT may result in a 5 kg weight gain at one year and a 10 kg weight gain at three years post-LT<sup>[72]</sup>. Theoretically, this approach would improve the LT outcomes and would result in fewer postoperative complications, less final weight, and lower graft rejection rates. On the other hand, serious adverse events associated with the bariatric operation, such as portal hypertension<sup>[86]</sup>, anastomotic leakage, wound infection, bleeding, and kidney injury<sup>[87]</sup> could possibly complicate the subsequent LT. It has also been shown that patients with non-compensated cirrhosis have an increased mortality rate after bariatric surgery (16.3%), in contrast to patients with compensated cirrhosis or patients without liver disease (< 1%)<sup>[84]</sup>. Severe hepatic dysfunction has also been noted as a complication after RYGB<sup>[88]</sup>. Therefore, this likelihood for an increased mortality in cirrhotic patients, renders this “bridging” strategy questionable<sup>[84,88-90]</sup>.

Recently, the “simultaneous” approach for LT and bariatric surgery has emerged as an alternative to the “bridging” approach<sup>[86,91]</sup>. The bariatric procedure most commonly performed along with LT is SG, because it does not involve manipulations around the biliary tract, while malabsorption is also not typically seen after SG<sup>[92]</sup>. This approach may lead to decreased length of hospital stay, postoperative pain, cost, and stress<sup>[44]</sup>. Postoperative complications of SG during LT include the leak from gastric staple line,

Table 1 Bariatric surgery studies with histological assessment of liver biopsy

| PMID     | First author | Year | Country       | Study design | Patients | Type of surgery     | Steatosis <sup>1</sup> | Hepatocyte ballooning <sup>1</sup> | Inflammation <sup>1</sup> | Fibrosis <sup>1</sup> | NAS <sup>1</sup> | Deterioration <sup>2</sup> | Follow-up (mo) |
|----------|--------------|------|---------------|--------------|----------|---------------------|------------------------|------------------------------------|---------------------------|-----------------------|------------------|----------------------------|----------------|
| 32553765 | Lassailly    | 2020 | France        | P            | 180      | RYGB, LAGB, BPD, SG | Yes                    | Yes                                | Yes                       | Yes                   | Yes              | Yes                        | 60             |
| 32556752 | Salman       | 2020 | Egypt         | P            | 67       | OAGB                | Yes                    | Yes                                | Yes                       | Yes                   | Yes              | No                         | 15             |
| 32153044 | Salman       | 2020 | Egypt         | P            | 81       | SG                  | Yes                    | Yes                                | Yes                       | Yes                   | Yes              | Yes                        | 18             |
| 32152677 | Salman       | 2020 | Egypt         | P            | 71       | SG                  | Yes                    | NA                                 | NA                        | Yes                   | Yes              | Yes                        | 30             |
| 32124215 | Nikai        | 2020 | Japan         | R            | 28       | SG                  | Yes                    | Yes                                | Yes                       | Yes                   | Yes              | No                         | 24             |
| 32360804 | Bazerbachi   | 2020 | United States | P            | 20       | IGB                 | Yes                    | Yes                                | Yes                       | No                    | Yes              | Yes                        | 6              |
| 29126863 | Garg         | 2018 | India         | P            | 32       | RYGB, LAGB, SG      | Yes                    | Yes                                | Yes                       | Yes                   | NA               | Yes                        | 12             |
| 27697327 | Manco        | 2017 | Italy         | P            | 20       | SG                  | Yes                    | Yes                                | Yes                       | Yes                   | Yes              | No                         | 12             |
| 27405478 | Aldoheyani   | 2017 | Saudi Arabia  | P            | 27       | SG                  | Yes                    | Yes                                | Yes                       | Yes                   | Yes              | No                         | 3              |
| 26077701 | Froylich     | 2016 | United States | R            | 25       | RYGB, SG            | Yes                    | Yes                                | Yes                       | Yes                   | Yes              | Yes                        | 18             |
| 27594839 | Schneck      | 2016 | France        | P            | 9        | RYGB                | Yes                    | Yes                                | Yes                       | Yes                   | Yes              | Yes                        | 55             |
| 25537957 | Taitano      | 2015 | United States | R            | 160      | RYGB, LAGB          | Yes                    | NA                                 | Yes                       | Yes                   | NA               | Yes                        | 31             |
| 26003897 | Praveen Raj  | 2015 | India         | P            | 30       | RYGB, SG            | Yes                    | Yes                                | Yes                       | Yes                   | Yes              | No                         | 6              |
| 25917783 | Lassailly    | 2015 | France        | P            | 30       | RYGB, LAGB, BPD, SG | Yes                    | Yes                                | Yes                       | Yes                   | Yes              | No                         | 12             |
| 25379859 | Caiazzo      | 2014 | France        | P            | 413      | RYGB, LAGB          | Yes                    | NA                                 | Yes                       | Yes                   | Yes              | NA                         | 60             |
| 22161114 | Tai          | 2012 | Taiwan        | P            | 21       | RYGB                | Yes                    | Yes                                | Yes                       | Yes                   | Yes              | Yes                        | 12             |
| 23355916 | Vargas       | 2012 | Spain         | P            | 26       | RYGB                | Yes                    | Yes                                | Yes                       | Yes                   | Yes              | No                         | 16             |
| 22108808 | Moretto      | 2012 | Brazil        | R            | 78       | OAGB                | Yes                    | Yes                                | Yes                       | Yes                   | NA               | Yes                        | NA             |
| 20460923 | Weiner       | 2010 | Germany       | R            | 116      | RYGB, LAGB, BPD     | Yes                    | NA                                 | Yes                       | Yes                   | NA               | No                         | 19.4           |
| 19409898 | Mathurin     | 2009 | France        | P            | 211      | RYGB, LAGB, BPD     | Yes                    | Yes                                | No                        | No                    | Yes              | Yes                        | 60             |
| 17376042 | Furuya       | 2007 | Brazil        | P            | 18       | RYGB                | Yes                    | Yes                                | Yes                       | Yes                   | Yes              | No                         | 24             |
| 16076987 | Clark        | 2005 | United States | R            | 16       | RYGB                | Yes                    | Yes                                | Yes                       | Yes                   | Yes              | No                         | 10.2           |

<sup>1</sup>Did the parameter improve after the bariatric operation?

<sup>2</sup>Did any patient experience worsening in any of the parameters after the bariatric operation?

BPD: Biliopancreatic diversion with duodenal switch; IGB: Intra-gastric balloon placement; LAGB: Laparoscopic adjustable gastric banding; NA: Not available; OAGB: One-anastomosis gastric bypass; P: Prospective; R: Retrospective; RYGB: Roux-en-Y gastric bypass; SG: Sleeve gastrectomy.

and rarely excessive weight loss<sup>[86]</sup>.

Performing a bariatric procedure after LT is not considered to be an optimal option. The most important complication, wound dehiscence, is attributed to the use of corticosteroids and immunosuppressive medications in LT recipients<sup>[86]</sup>. It has been proven that immunosuppressive regimens are a strong predictive factor for 30-day mortality in patients undergoing bariatric surgery<sup>[86,93]</sup>. Post-LT adhesions might also turn a routine bariatric procedure into a particularly challenging operation<sup>[44,72,86]</sup>.

Currently, LT is the only treatment option that can definitively lead to complete resolution of NASH in bariatric patients. It is worth mentioning that in the early 2000s, only 3% of the LTs were performed for end-stage liver disease secondary to NASH, while in 2011 this percentage increased to 19%<sup>[12]</sup>. By 2020, NASH is expected to come first as a cause for LTs, at least in western countries<sup>[92]</sup>. The 5-year survival rate after LT for end-stage liver disease attributed to NASH is 60%-85%<sup>[94]</sup>.

Despite of these promising results, LT in NASH patients has been associated with increased risk of postoperative complications compared to patients undergoing LT for other indications, such as renal dysfunction, sepsis, cardiovascular complications, wound infection, and prolonged mechanical ventilation. In the long-term, hypertension, obesity and hyperlipidemia may also deteriorate post-LT, mostly due to the state of immunosuppression, while recurrence of MS has been observed in around 50% of LT patients with preoperative MS<sup>[89]</sup>. Interestingly, up to 12% of transplant patients may require re-transplantation: (1) Due to NASH recurrence, which can be attributed to genetic causes, immunosuppressive agents, and the presence of excess adipose tissue<sup>[44,70,95]</sup>; or (2) Due to acute graft rejection, which is also higher compared to that seen after LT for other conditions<sup>[12,92]</sup>.

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## CONCLUSION

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MS is a common disease entity, particularly in western countries. It is usually accompanied by cardiovascular disease, dyslipidemia, and NASH, and is associated with increased morbidity and mortality. Although diet, exercise and weight loss are the cornerstone of initial management, bariatric surgery has emerged as an alternative approach, particularly in severely obese patients or in those with MS resistant to conservative treatment. SG and RYGB are the most commonly utilized bariatric procedures. The only definitively therapeutic modality in MS patients with end-stage liver disease secondary to NASH is LT, while the optimal time frame for bariatric surgery, when required in combination with LT, has yet to be determined.



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