**Name of Journal:** *World Journal of Hepatology*

**Manuscript NO:** 57493

**Manuscript Type:** REVIEW

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

Ziogas IA *et al*. Metabolic syndrome, liver disease and bariatric surgery

Ioannis A Ziogas, Konstantinos Zapsalis, Dimitrios Giannis, Georgios Tsoulfas

**Ioannis A Ziogas,** Department of Surgery, Division of Hepatobiliary Surgery and Liver Transplantation, Vanderbilt University Medical Center, Nashville, TN 37232, United States

**Konstantinos Zapsalis,** Aristotle University of Thessaloniki, Thessaloniki 54124, Greece

**Dimitrios Giannis,** Center for Health Innovations and Outcomes Research (CHIOR), The Feinstein Institute for Medical Research, Manhasset, NY 11030, United States

**Georgios Tsoulfas,** The First Department of Surgery, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece

**Author contributions:** Ziogas IA and Zapsalis K contributed to this paper equally. Tsoulfas G and Ziogas IA contributed to conception and design; Zapsalis K, Ziogas IA, Giannis D, and Tsoulfas G contributed to acquisition, analysis, and interpretation of data; Ziogas IA, Zapsalis K, and Giannis D contributed to drafting of the manuscript; Ziogas IA, Zapsalis K, Giannis D, and Tsoulfas G contributed to critical revision and final approval.

**Corresponding author: Georgios Tsoulfas, FACS, FICS, MD, PhD, Associate Professor,** The First Department of Surgery, Aristotle University of Thessaloniki, 66 Tsimiski Street, Thessaloniki 54124, Greece. tsoulfasg@auth.gr

**Received:** June 11, 2020

**Revised:** August 10, 2020

**Accepted:** September 1, 2020

**Published online:** October 27, 2020

**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

**Citation:** Ziogas IA, Zapsalis K, Giannis D, Tsoulfas G. Metabolic syndrome and liver disease in the era of bariatric surgery: What you need to know! *World J Hepatol* 2020; 12(10): 709-721

**URL:** https://www.wjgnet.com/1948-5182/full/v12/i10/709.htm

**DOI:** https://dx.doi.org/10.4254/wjh.v12.i10.709

**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.

**INTRODUCTION**

Metabolic syndrome (MS), also known as syndrome X, is a complex entity consisting of insulin resistance, obesity, hypertriglyceridemia, increased waist circumference and hypertension[1,2]. 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 ≥ 102 cm for men and ≥ 88 cm for women); (2) Triglycerides ≥ 150 mg/dL; (3) High-density lipoprotein (HDL) cholesterol < 40 mg/dL for men and < 50 mg/dL for women; (4) Systolic blood pressure ≥ 130 mmHg and/or diastolic ≥ 85 mmHg; and (5) Fasting serum glucose ≥ 100 mg/dL[2-4]. 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[1,5,6]. Data suggest that even populations with relatively lower body mass index (BMI), such as Asian Americans, can be affected by MS[7]. The prevalence of MS has significantly increased over the last decades, with less physically active and older individuals being increasingly affected[6]. It is quite evident that MS evolves into a global epidemic health problem that mandates timely and effective action[1,8]. 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[9]. Wilson *et al*[10], 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[11]. 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[11]. 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[8,11].

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[12,13], and is defined as ≥ 5% fatty permeation of the liver parenchyma in the absence of an alcohol abuse history[12]. It occurs in up to one-third of the general population[14], and in up to 80% of patients with MS[15]. Risk factors predisposing to NAFLD include older age (> 50 years), hypertriglyceridemia, insulin resistance, and central obesity[13,16]. Liver steatosis is considered to be one of the earliest signs of MS[17], and early diagnosis and management are warranted to prevent the occurrence of irreversible histopathologic changes of the liver parenchyma[15], which can lead to NASH, cirrhosis, and HCC[12,14]. Notably, Ekstedt *et al*[18] 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[19]. Additionally, it has been shown that the loss of function of several tumor suppressor genes is involved in this process[12]. The definitive pathophysiologic mechanisms predisposing to the development of HCC in patients with NAFLD have yet to be elucidated.

**CONSERVATIVE MANAGEMENT**

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[20]. Previous studies have shown promising results with pioglitazone, metformin and vitamin E for the management of NASH[20,21]. 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[22-26]. Amphetamine derivatives, such as phentermine and desoxyephedrine, as well as statins have been occasionally utilized and showed promising results against NASH[27,28]. The addition of liraglutide to lifestyle changes has demonstrated better results than lifestyle changes alone[29]. Finally, vitamin D and zinc sulfate seem to be beneficial in children with MS[30,31].

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[32]. Despite the progress in pharmacologic treatment, non-surgical treatment is not always adequate to yield fruitful outcomes in obese patients (BMI > 30).

**SURGICAL MANAGEMENT**

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[27]. In addition, surgery has a significant advantage over conservative methods in lowering the level of hemoglobin A1c (HbA1c) in T2DM patients[33]. Regarding its latter effect, bariatric surgery may even result in the complete remission of T2DM[34-36]. In fact, the duration of T2DM and preoperative serum C-peptide levels have been identified as predictive factors of postoperative benefit in glucose tolerance[37,38]. Recent recommendations suggest lifelong supplementation after all bariatric surgeries[39]. The loss of weight after bariatric surgery is also beneficial for patients with NAFLD and NASH, considering that a loss of ≥ 10% of body weight might facilitate a significant decrease in liver fibrosis[40].

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[41]. 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[42], 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[43]. 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)[44].

***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[43]. RYGB can lead to significant mean weight loss (from 136.9 kg to 100.6 kg) and decrease in BMI (from 45.5 kg/m² down to 33.3 kg/m²) at 4 years postoperatively[38]. MS resolution during the first postoperative year can occur in up to 75.8% of the patients[45], while a beneficial effect on blood pressure can be seen in up to 65% of MS patients[45]. 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%[40]. 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[33]. 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[46]. 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%)[38,47]. 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[48]. 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[49]. Other postoperative complications include vitamin B1, vitamin B12, iron and calcium deficiency, as well as peptic ulcer disease[50]. 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%[51]. Additional complications that may affect the quality of life include postprandial dumping syndrome, hypoglycemia, calcium oxalate nephrolithiasis and chronic kidney disease[52-54]. The 5-year postoperative mortality rate is around 3%[55].

***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[43]. 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[47].

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)[52]. 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[56-58]. At 6 mo after surgery, up to 84% of diabetic patients present with resolution or remission of T2DM[59]. However, 30% to 50% of patients exhibit recurrence of diabetes in the long-term[60]. 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[61]. Significant improvements after SG have also been reported in terms of HDL cholesterol levels and hypertension[57]. In addition, when compared to RYGB, SG does not increase the risk of nephrolithiasis and chronic kidney disease[53,62].

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[63,64]. Reflux esophagitis is a relatively common complication after SG, while it is also deemed to be a contraindication for SG[52]. In the long-term, a small percentage of patients may require a supplementary endoscopic or surgical intervention[65], while some patients complain of nausea and vomiting after excess food intake[50]. In extremely obese patients (BMI > 60 kg/m²), the rate of postoperative complications appears to be high and comparable to the rate of other bariatric procedures[52].

***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/m²) or in patients with MS resistant to other modalities, since it provides very strong metabolic effects and durable 35%-45% weight loss[66]. BPD with duodenal switch constitutes only 1.5% of all bariatric procedures performed worldwide[67].

Postoperatively almost 90% of BPD patients achieve normal HDL cholesterol levels[68], while fasting serum glucose levels may remain normal for up to ten years[69]. 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[69]. An up to 70% weight loss may also be achieved and it may be preserved for more than ten years[70].

Immediate postoperative complications include wound infection, anastomotic leak, and bowel obstruction[70]. Extensive small bowel resection can result in severe malabsorptive complications, such as anemia, nutritional deficiencies, hypoproteinemia, and bone demineralization[47,70]. 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[52,71]. Similarly to RYGB, patients undergoing BPD are at increased risk of nephrolithiasis[53,62].

***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[72]. LAGB can result in sufficient weight loss, while the reduction in BMI can be as high as 6.56 kg/m² in only 1 mo after the operation[48]. 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[72,73]. In fact, urinary oxalate excretion was reported to be lower after LAGB placement than after RYGB, and similar to that of normal controls[74].

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

***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[67]. 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[76]. 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[77] 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[78,79]. Although nonsurgical weight loss can effectively improve all histological features of NASH and NAFLD (including fibrosis), most patients had early-stage fibrosis[80]. 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[77]. 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[81].

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[82]. More specifically, the histological features of NASH disappeared in 41.7% of NASH cases and in 50.0% of borderline NASH cases[82]. 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[83]. 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[84]. 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[85].

The American Association for the Study of Liver Diseases recommends considering bariatric surgery in otherwise eligible obese NAFLD or NASH patients[77]. 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[77].

***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[86]. 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[72]. 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[86], anastomotic leakage, wound infection, bleeding, and kidney injury[87] 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%)[84]. Severe hepatic dysfunction has also been noted as a complication after RYGB[88]. Therefore, this likelihood for an increased mortality in cirrhotic patients, renders this “bridging” strategy questionable[84,88-90].

Recently, the “simultaneous” approach for LT and bariatric surgery has emerged as an alternative to the “bridging” approach[86,91]. 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[92]. This approach may lead to decreased length of hospital stay, postoperative pain, cost, and stress[44]. Postoperative complications of SG during LT include the leak from gastric staple line, and rarely excessive weight loss[86].

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[86]. It has been proven that immunosuppressive regimens are a strong predictive factor for 30-day mortality in patients undergoing bariatric surgery[86,93]. Post-LT adhesions might also turn a routine bariatric procedure into a particularly challenging operation[44,72,86].

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%[12]. By 2020, NASH is expected to come first as a cause for LTs, at least in western countries[92]. The 5-year survival rate after LT for end-stage liver disease attributed to NASH is 60%-85%[94].

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[89]. 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[44,70,95]; or (2) Due to acute graft rejection, which is also higher compared to that seen after LT for other conditions[12,92].

**CONCLUSION**

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.

**REFERENCES**

1 **Saklayen MG**. The Global Epidemic of the Metabolic Syndrome. *Curr Hypertens Rep* 2018; **20**: 12 [PMID: 29480368 DOI: 10.1007/s11906-018-0812-z]

2 **Metabolic Syndrome**. National Heart, Lung, and Blood Institute (NHLBI) [Internet]. [cited 2020 January 29]. Available from: https://www.nhlbi.nih.gov/health-topics/metabolic-syndrome

3 **Diabetes Canada Clinical Practice Guidelines Expert Committee**, Punthakee Z, Goldenberg R, Katz P. Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome. *Can J Diabetes* 2018; **42** Suppl 1: S10-S15 [PMID: 29650080 DOI: 10.1016/j.jcjd.2017.10.003]

4 **Alberti KG**, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr; International Diabetes Federation Task Force on Epidemiology and Prevention; Hational Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; **120**: 1640-1645 [PMID: 19805654 DOI: 10.1161/CIRCULATIONAHA.109.192644]

5 **Alberti KG**, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome--a new worldwide definition. *Lancet* 2005; **366**: 1059-1062 [PMID: 16182882 DOI: 10.1016/S0140-6736(05)67402-8]

6 **Moore JX**, Chaudhary N, Akinyemiju T. Metabolic Syndrome Prevalence by Race/Ethnicity and Sex in the United States, National Health and Nutrition Examination Survey, 1988-2012. *Prev Chronic Dis* 2017; **14**: E24 [PMID: 28301314 DOI: 10.5888/pcd14.160287]

7 **Palaniappan LP**, Wong EC, Shin JJ, Fortmann SP, Lauderdale DS. Asian Americans have greater prevalence of metabolic syndrome despite lower body mass index. *Int J Obes (Lond)* 2011; **35**: 393-400 [PMID: 20680014 DOI: 10.1038/ijo.2010.152]

8 **O'Neill S**, O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. *Obes Rev* 2015; **16**: 1-12 [PMID: 25407540 DOI: 10.1111/obr.12229]

9 **Jeppesen J**, Hansen TW, Rasmussen S, Ibsen H, Torp-Pedersen C, Madsbad S. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease: a population-based study. *J Am Coll Cardiol* 2007; **49**: 2112-2119 [PMID: 17531661 DOI: 10.1016/j.jacc.2007.01.088]

10 **Wilson PW**, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation* 2005; **112**: 3066-3072 [PMID: 16275870 DOI: 10.1161/CIRCULATIONAHA.105.539528]

11 **Gregg EW**, Cadwell BL, Cheng YJ, Cowie CC, Williams DE, Geiss L, Engelgau MM, Vinicor F. Trends in the prevalence and ratio of diagnosed to undiagnosed diabetes according to obesity levels in the U.S. *Diabetes Care* 2004; **27**: 2806-2812 [PMID: 15562189 DOI: 10.2337/diacare.27.12.2806]

12 **Cauchy F**, Fuks D, Zarzavadjian Le Bian A, Belghiti J, Costi R. Metabolic syndrome and non-alcoholic fatty liver disease in liver surgery: The new scourges? *World J Hepatol* 2014; **6**: 306-314 [PMID: 24868324 DOI: 10.4254/wjh.v6.i5.306]

13 **Byrne CD**, Targher G. NAFLD: a multisystem disease. *J Hepatol* 2015; **62**: S47-S64 [PMID: 25920090 DOI: 10.1016/j.jhep.2014.12.012]

14 **M I**, Singh C, Ganie MA, Alsayari K. NASH: The Hepatic injury of Metabolic syndrome: a brief update. *Int J Health Sci (Qassim)* 2009; **3**: 265-270 [PMID: 21475547]

15 **Caravatto PP**, Cohen R. The Role of Metabolic Surgery in Non-alcoholic Steatohepatitis Improvement. *Curr Atheroscler Rep* 2017; **19**: 45 [PMID: 28986720 DOI: 10.1007/s11883-017-0681-y]

16 **Wardani HA**, Rahmadi M, Ardianto C, Balan SS, Kamaruddin NS, Khotib J. Development of nonalcoholic fatty liver disease model by high-fat diet in rats. *J Basic Clin Physiol Pharmacol* 2019; **30**: [PMID: 31760381 DOI: 10.1515/jbcpp-2019-0258]

17 **Martins MJ**, Ascensão A, Magalhães J, Collado MC, Portincasa P. Molecular Mechanisms of NAFLD in Metabolic Syndrome. *Biomed Res Int* 2015; **2015**: 621080 [PMID: 26078958 DOI: 10.1155/2015/621080]

18 **Ekstedt M**, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, Kechagias S. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology* 2006; **44**: 865-873 [PMID: 17006923 DOI: 10.1002/hep.21327]

19 **Johnson PJ**. How do mechanisms of hepatocarcinogenesis (HBV, HCV, and NASH) affect our understanding and approach to HCC? *Am Soc Clin Oncol Educ Book* 2013 [PMID: 23714479 DOI: 10.1200/EdBook\_AM.2013.33.e132]

20 **Aguilar-Olivos NE**, Almeda-Valdes P, Aguilar-Salinas CA, Uribe M, Méndez-Sánchez N. The role of bariatric surgery in the management of nonalcoholic fatty liver disease and metabolic syndrome. *Metabolism* 2016; **65**: 1196-1207 [PMID: 26435078 DOI: 10.1016/j.metabol.2015.09.004]

21 **Rotman Y**, Sanyal AJ. Pioglitazone for the treatment of NASH in patients with prediabetes or type 2 diabetes mellitus-authors' response. *Gut* 2018; **67**: 1372 [PMID: 28468762 DOI: 10.1136/gutjnl-2017-314263]

22 **Alkhouri N**. NASH and NAFLD: emerging drugs, therapeutic targets and translational and clinical challenges. *Expert Opin Investig Drugs* 2020; **29**: 87 [PMID: 31984804 DOI: 10.1080/13543784.2020.1721169]

23 **Neuschwander-Tetri BA**, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, Chalasani N, Dasarathy S, Diehl AM, Hameed B, Kowdley KV, McCullough A, Terrault N, Clark JM, Tonascia J, Brunt EM, Kleiner DE, Doo E; NASH Clinical Research Network. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet* 2015; **385**: 956-965 [PMID: 25468160 DOI: 10.1016/S0140-6736(14)61933-4]

24 **Eslam M**, Alvani R, Shiha G. Obeticholic acid: towards first approval for NASH. *Lancet* 2019; **394**: 2131-2133 [PMID: 31813639 DOI: 10.1016/S0140-6736(19)32963-0]

25 **Siddiqui MS**, Van Natta ML, Connelly MA, Vuppalanchi R, Neuschwander-Tetri BA, Tonascia J, Guy C, Loomba R, Dasarathy S, Wattacheril J, Chalasani N, Sanyal AJ; NASH CRN. Impact of obeticholic acid on the lipoprotein profile in patients with non-alcoholic steatohepatitis. *J Hepatol* 2020; **72**: 25-33 [PMID: 31634532 DOI: 10.1016/j.jhep.2019.10.006]

26 **Younossi ZM**, Ratziu V, Loomba R, Rinella M, Anstee QM, Goodman Z, Bedossa P, Geier A, Beckebaum S, Newsome PN, Sheridan D, Sheikh MY, Trotter J, Knapple W, Lawitz E, Abdelmalek MF, Kowdley KV, Montano-Loza AJ, Boursier J, Mathurin P, Bugianesi E, Mazzella G, Olveira A, Cortez-Pinto H, Graupera I, Orr D, Gluud LL, Dufour JF, Shapiro D, Campagna J, Zaru L, MacConell L, Shringarpure R, Harrison S, Sanyal AJ; REGENERATE Study Investigators. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet* 2019; **394**: 2184-2196 [PMID: 31813633 DOI: 10.1016/S0140-6736(19)33041-7]

27 **Shah K**, Johnny Nergard B, Stray Frazier K, Geir Leifsson B, Aghajani E, Gislason H. Long-term effects of laparoscopic Roux-en-Y gastric bypass on metabolic syndrome in patients with morbid obesity. *Surg Obes Relat Dis* 2016; **12**: 1449-1456 [PMID: 27387692 DOI: 10.1016/j.soard.2016.03.017]

28 **Athyros VG**, Boutari C, Stavropoulos K, Anagnostis P, Imprialos KP, Doumas M, Karagiannis A. Statins: An Under-Appreciated Asset for the Prevention and the Treatment of NAFLD or NASH and the Related Cardiovascular Risk. *Curr Vasc Pharmacol* 2018; **16**: 246-253 [PMID: 28676019 DOI: 10.2174/1570161115666170621082910]

29 **Capristo E**, Panunzi S, De Gaetano A, Raffaelli M, Guidone C, Iaconelli A, L'Abbate L, Birkenfeld AL, Bellantone R, Bornstein SR, Mingrone G. Intensive lifestyle modifications with or without liraglutide 3mg vs. sleeve gastrectomy: A three-arm non-randomised, controlled, pilot study. *Diabetes Metab* 2018; **44**: 235-242 [PMID: 29398254 DOI: 10.1016/j.diabet.2017.12.007]

30 **Belenchia AM**, Tosh AK, Hillman LS, Peterson CA. Correcting vitamin D insufficiency improves insulin sensitivity in obese adolescents: a randomized controlled trial. *Am J Clin Nutr* 2013; **97**: 774-781 [PMID: 23407306 DOI: 10.3945/ajcn.112.050013]

31 **Kelishadi R**, Hashemipour M, Adeli K, Tavakoli N, Movahedian-Attar A, Shapouri J, Poursafa P, Rouzbahani A. Effect of zinc supplementation on markers of insulin resistance, oxidative stress, and inflammation among prepubescent children with metabolic syndrome. *Metab Syndr Relat Disord* 2010; **8**: 505-510 [PMID: 21028969 DOI: 10.1089/met.2010.0020]

32 **Vitiello A**, Angrisani L, Santonicola A, Iovino P, Pilone V, Forestieri P. Bariatric Surgery Versus Lifestyle Intervention in Class I Obesity: 7-10-Year Results of a Retrospective Study. *World J Surg* 2019; **43**: 758-762 [PMID: 30430189 DOI: 10.1007/s00268-018-4847-8]

33 **Ikramuddin S**, Korner J, Lee WJ, Thomas AJ, Connett JE, Bantle JP, Leslie DB, Wang Q, Inabnet WB 3rd, Jeffery RW, Chong K, Chuang LM, Jensen MD, Vella A, Ahmed L, Belani K, Billington CJ. Lifestyle Intervention and Medical Management With *vs* Without Roux-en-Y Gastric Bypass and Control of Hemoglobin A1c, LDL Cholesterol, and Systolic Blood Pressure at 5 Years in the Diabetes Surgery Study. *JAMA* 2018; **319**: 266-278 [PMID: 29340678 DOI: 10.1001/jama.2017.20813]

34 **Cazzo E**, Gestic MA, Utrini MP, Machado RR, Geloneze B, Pareja JC, Chaim EA. Impact of Roux-en-Y gastric bypass on metabolic syndrome and insulin resistance parameters. *Diabetes Technol Ther* 2014; **16**: 262-265 [PMID: 24299427 DOI: 10.1089/dia.2013.0249]

35 **Sethi P**, Thillai M, Nain PS, Ahuja A, Vayoth SO, Khurana P. Effects of Laparoscopic Sleeve Gastrectomy on Central Obesity and Metabolic Syndrome in Indian Adults- A Prospective Study. *J Clin Diagn Res* 2017; **11**: PC01-PC04 [PMID: 28273998 DOI: 10.7860/JCDR/2017/24477.9232]

36 **Nugent C**, Bai C, Elariny H, Gopalakrishnan P, Quigley C, Garone M Jr, Afendy M, Chan O, Wheeler A, Afendy A, Younossi ZM. Metabolic syndrome after laparoscopic bariatric surgery. *Obes Surg* 2008; **18**: 1278-1286 [PMID: 18401668 DOI: 10.1007/s11695-008-9511-1]

37 **Vinzens F**, Kilchenmann A, Zumstein V, Slawik M, Gebhart M, Peterli R. Long-term outcome of laparoscopic adjustable gastric banding (LAGB): results of a Swiss single-center study of 405 patients with up to 18 years' follow-up. *Surg Obes Relat Dis* 2017; **13**: 1313-1319 [PMID: 28602794 DOI: 10.1016/j.soard.2017.04.030]

38 **Nassour I**, Almandoz JP, Adams-Huet B, Kukreja S, Puzziferri N. Metabolic syndrome remission after Roux-en-Y gastric bypass or sleeve gastrectomy. *Diabetes Metab Syndr Obes* 2017; **10**: 393-402 [PMID: 29033596 DOI: 10.2147/DMSO.S142731]

39 **Tabesh MR**, Maleklou F, Ejtehadi F, Alizadeh Z. Nutrition, Physical Activity, and Prescription of Supplements in Pre- and Post-bariatric Surgery Patients: a Practical Guideline. *Obes Surg* 2019; **29**: 3385-3400 [PMID: 31367987 DOI: 10.1007/s11695-019-04112-y]

40 **Yu H**, Di J, Bao Y, Zhang P, Zhang L, Tu Y, Han X, Jia W. Visceral fat area as a new predictor of short-term diabetes remission after Roux-en-Y gastric bypass surgery in Chinese patients with a body mass index less than 35 kg/m2. *Surg Obes Relat Dis* 2015; **11**: 6-11 [PMID: 25547054 DOI: 10.1016/j.soard.2014.06.019]

41 **To VT**, Hüttl TP, Lang R, Piotrowski K, Parhofer KG. Changes in body weight, glucose homeostasis, lipid profiles, and metabolic syndrome after restrictive bariatric surgery. *Exp Clin Endocrinol Diabetes* 2012; **120**: 547-552 [PMID: 23070831 DOI: 10.1055/s-0032-1323738]

42 **Mulla CM**, Middelbeek RJW, Patti ME. Mechanisms of weight loss and improved metabolism following bariatric surgery. *Ann N Y Acad Sci* 2018; **1411**: 53-64 [PMID: 28868615 DOI: 10.1111/nyas.13409]

43 **Batterham RL**, Cummings DE. Mechanisms of Diabetes Improvement Following Bariatric/Metabolic Surgery. *Diabetes Care* 2016; **39**: 893-901 [PMID: 27222547 DOI: 10.2337/dc16-0145]

44 **García-Pajares F**, Peñas-Herrero I, Sánchez-Ocaña R, Torrres-Yuste R, Cimavilla-Román M, Carbajo-López A, Almohalla-Alvarez C, Pérez-Saborido B, Muñoz-Conejero E, Gonzalez-Sagrado M, Caro-Patón A, Sánchez-Antolín G. Metabolic Syndrome After Liver Transplantation: Five-Year Prevalence and Risk Factors. *Transplant Proc* 2016; **48**: 3010-3012 [PMID: 27932133 DOI: 10.1016/j.transproceed.2016.07.038]

45 **Martini F**, Anty R, Schneck AS, Casanova V, Iannelli A, Gugenheim J. Predictors of metabolic syndrome persistence 1 year after laparoscopic Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2015; **11**: 1054-1060 [PMID: 25868838 DOI: 10.1016/j.soard.2015.02.019]

46 **Sjöström L**, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjöström CD, Sullivan M, Wedel H; Swedish Obese Subjects Study Scientific Group. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004; **351**: 2683-2693 [PMID: 15616203 DOI: 10.1056/NEJMoa035622]

47 **Consalvo V**, Salsano V, Sarno G. Three-Port Laparoscopic Adjustable Gastric Banding (LAGB): Surgical Technique and Three Years Follow-Up. *Surg Technol Int* 2017; **30**: 93-96 [PMID: 28537646]

48 **Blackbourne LH**. Surgical recall. Philadelphia: Lippincott Williams & Wilkins; 2015

49 **Magouliotis DE**, Tzovaras G, Tasiopoulou VS, Christodoulidis G, Zacharoulis D. Closure of Mesenteric Defects in Laparoscopic Gastric Bypass: a Meta-Analysis. *Obes Surg* 2020; **30**: 1935-1943 [PMID: 31955371 DOI: 10.1007/s11695-020-04418-2]

50 **Major P**, Wysocki M, Pędziwiatr M, Pisarska M, Dworak J, Małczak P, Budzyński A. Risk factors for complications of laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass. *Int J Surg* 2017; **37**: 71-78 [PMID: 27956112 DOI: 10.1016/j.ijsu.2016.12.012]

51 **Peterli R**, Wölnerhanssen BK, Peters T, Vetter D, Kröll D, Borbély Y, Schultes B, Beglinger C, Drewe J, Schiesser M, Nett P, Bueter M. Effect of Laparoscopic Sleeve Gastrectomy *vs* Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss in Patients With Morbid Obesity: The SM-BOSS Randomized Clinical Trial. *JAMA* 2018; **319**: 255-265 [PMID: 29340679 DOI: 10.1001/jama.2017.20897]

52 **Våge V**, Nilsen RM, Berstad A, Behme J, Sletteskog N, Gåsdal R, Laukeland C, Mellgren G. Predictors for remission of major components of the metabolic syndrome after biliopancreatic diversion with duodenal switch (BPDDS). *Obes Surg* 2013; **23**: 80-86 [PMID: 23011463 DOI: 10.1007/s11695-012-0775-0]

53 **Lieske JC**, Mehta RA, Milliner DS, Rule AD, Bergstralh EJ, Sarr MG. Kidney stones are common after bariatric surgery. *Kidney Int* 2015; **87**: 839-845 [PMID: 25354237 DOI: 10.1038/ki.2014.352]

54 **Nasr SH**, D'Agati VD, Said SM, Stokes MB, Largoza MV, Radhakrishnan J, Markowitz GS. Oxalate nephropathy complicating Roux-en-Y Gastric Bypass: an underrecognized cause of irreversible renal failure. *Clin J Am Soc Nephrol* 2008; **3**: 1676-1683 [PMID: 18701613 DOI: 10.2215/CJN.02940608]

55 **Weiner RA**, El-Sayes IA, Theodoridou S, Weiner SR, Scheffel O. Early post-operative complications: incidence, management, and impact on length of hospital stay. A retrospective comparison between laparoscopic gastric bypass and sleeve gastrectomy. *Obes Surg* 2013; **23**: 2004-2012 [PMID: 23846474 DOI: 10.1007/s11695-013-1022-z]

56 **Sharples AJ**, Mahawar K. Systematic Review and Meta-Analysis of Randomised Controlled Trials Comparing Long-Term Outcomes of Roux-En-Y Gastric Bypass and Sleeve Gastrectomy. *Obes Surg* 2020; **30**: 664-672 [PMID: 31724116 DOI: 10.1007/s11695-019-04235-2]

57 **Arica PC**, Aydin S, Zengin U, Kocael A, Orhan A, Zengin K, Gelisgen R, Taskin M, Uzun H. The Effects on Obesity Related Peptides of Laparoscopic Gastric Band Applications in Morbidly Obese Patients. *J Invest Surg* 2018; **31**: 89-95 [PMID: 28635510 DOI: 10.1080/08941939.2017.1280564]

58 **Dolan K**, Hatzifotis M, Newbury L, Lowe N, Fielding G. A clinical and nutritional comparison of biliopancreatic diversion with and without duodenal switch. *Ann Surg* 2004; **240**: 51-56 [PMID: 15213618 DOI: 10.1097/01.sla.0000129280.68540.76]

59 **Helmiö M**, Victorzon M, Ovaska J, Leivonen M, Juuti A, Peromaa-Haavisto P, Nuutila P, Vahlberg T, Salminen P. Comparison of short-term outcome of laparoscopic sleeve gastrectomy and gastric bypass in the treatment of morbid obesity: A prospective randomized controlled multicenter SLEEVEPASS study with 6-month follow-up. *Scand J Surg* 2014; **103**: 175-181 [PMID: 24522349 DOI: 10.1177/1457496913509984]

60 **Andalib A**, Aminian A. Sleeve Gastrectomy and Diabetes: Is Cure Possible? *Adv Surg* 2017; **51**: 29-40 [PMID: 28797344 DOI: 10.1016/j.yasu.2017.03.003]

61 **Yang J**, Gao Z, Williams DB, Wang C, Lee S, Zhou X, Qiu P. Effect of laparoscopic Roux-en-Y gastric bypass *vs* laparoscopic sleeve gastrectomy on fasting gastrointestinal and pancreatic peptide hormones: A prospective nonrandomized trial. *Surg Obes Relat Dis* 2018; **14**: 1521-1529 [PMID: 30449509 DOI: 10.1016/j.soard.2018.06.003]

62 **Chang AR**, Grams ME, Navaneethan SD. Bariatric Surgery and Kidney-Related Outcomes. *Kidney Int Rep* 2017; **2**: 261-270 [PMID: 28439568 DOI: 10.1016/j.ekir.2017.01.010]

63 **Dix CF**, Bauer JD, Wright OR. A Systematic Review: Vitamin D Status and Sleeve Gastrectomy. *Obes Surg* 2017; **27**: 215-225 [PMID: 27815862 DOI: 10.1007/s11695-016-2436-1]

64 **Kwon Y**, Kim HJ, Lo Menzo E, Park S, Szomstein S, Rosenthal RJ. Anemia, iron and vitamin B12 deficiencies after sleeve gastrectomy compared to Roux-en-Y gastric bypass: a meta-analysis. *Surg Obes Relat Dis* 2014; **10**: 589-597 [PMID: 24582411 DOI: 10.1016/j.soard.2013.12.005]

65 **Scopinaro N**, Papadia F, Marinari G, Camerini G, Adami G. Long-term control of type 2 diabetes mellitus and the other major components of the metabolic syndrome after biliopancreatic diversion in patients with BMI < 35 kg/m2. *Obes Surg* 2007; **17**: 185-192 [PMID: 17476869 DOI: 10.1007/s11695-007-9045-y]

66 **O'Brien PE**, Hindle A, Brennan L, Skinner S, Burton P, Smith A, Crosthwaite G, Brown W. Long-Term Outcomes After Bariatric Surgery: a Systematic Review and Meta-analysis of Weight Loss at 10 or More Years for All Bariatric Procedures and a Single-Centre Review of 20-Year Outcomes After Adjustable Gastric Banding. *Obes Surg* 2019; **29**: 3-14 [PMID: 30293134 DOI: 10.1007/s11695-018-3525-0]

67 **Castagneto Gissey L**, Casella Mariolo JR, Mingrone G. How to Choose the Best Metabolic Procedure? *Curr Atheroscler Rep* 2016; **18**: 43 [PMID: 27229936 DOI: 10.1007/s11883-016-0590-5]

68 **Loy JJ**, Youn HA, Schwack B, Kurian M, Ren Fielding C, Fielding GA. Improvement in nonalcoholic fatty liver disease and metabolic syndrome in adolescents undergoing bariatric surgery. *Surg Obes Relat Dis* 2015; **11**: 442-449 [PMID: 25820083 DOI: 10.1016/j.soard.2014.11.010]

69 **Scopinaro N**, Marinari GM, Camerini GB, Papadia FS, Adami GF. Specific effects of biliopancreatic diversion on the major components of metabolic syndrome: a long-term follow-up study. *Diabetes Care* 2005; **28**: 2406-2411 [PMID: 16186271 DOI: 10.2337/diacare.28.10.2406]

70 **van den Berg EH**, Douwes RM, de Meijer VE, Schreuder TCMA, Blokzijl H. Liver transplantation for NASH cirrhosis is not performed at the expense of major post-operative morbidity. *Dig Liver Dis* 2018; **50**: 68-75 [PMID: 28935188 DOI: 10.1016/j.dld.2017.08.022]

71 **Homan J**, Betzel B, Aarts EO, Dogan K, van Laarhoven KJ, Janssen IM, Berends FJ. Vitamin and Mineral Deficiencies After Biliopancreatic Diversion and Biliopancreatic Diversion with Duodenal Switch--the Rule Rather than the Exception. *Obes Surg* 2015; **25**: 1626-1632 [PMID: 25595384 DOI: 10.1007/s11695-015-1570-5]

72 **Yu H**, Zhang L, Bao Y, Zhang P, Tu Y, Di J, Han X, Han J, Jia W. Metabolic Syndrome After Roux-en-Y Gastric Bypass Surgery in Chinese Obese Patients with Type 2 Diabetes. *Obes Surg* 2016; **26**: 2190-2197 [PMID: 26809584 DOI: 10.1007/s11695-016-2074-7]

73 **Penniston KL**, Kaplon DM, Gould JC, Nakada SY. Gastric band placement for obesity is not associated with increased urinary risk of urolithiasis compared to bypass. *J Urol* 2009; **182**: 2340-2346 [PMID: 19762051 DOI: 10.1016/j.juro.2009.07.041]

74 **Semins MJ**, Asplin JR, Steele K, Assimos DG, Lingeman JE, Donahue S, Magnuson T, Schweitzer M, Matlaga BR. The effect of restrictive bariatric surgery on urinary stone risk factors. *Urology* 2010; **76**: 826-829 [PMID: 20381135 DOI: 10.1016/j.urology.2010.01.037]

75 **Ibrahim AM**, Thumma JR, Dimick JB. Reoperation and Medicare Expenditures After Laparoscopic Gastric Band Surgery. *JAMA Surg* 2017; **152**: 835-842 [PMID: 28514487 DOI: 10.1001/jamasurg.2017.1093]

76 **Lak KL**, Helm MC, Kindel TL, Gould JC. Metabolic Syndrome Is a Significant Predictor of Postoperative Morbidity and Mortality Following Bariatric Surgery. *J Gastrointest Surg* 2019; **23**: 739-744 [PMID: 30430431 DOI: 10.1007/s11605-018-4035-z]

77 **Chalasani N**, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018; **67**: 328-357 [PMID: 28714183 DOI: 10.1002/hep.29367]

78 **Lewis JD**, Ferrara A, Peng T, Hedderson M, Bilker WB, Quesenberry CP Jr, Vaughn DJ, Nessel L, Selby J, Strom BL. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care* 2011; **34**: 916-922 [PMID: 21447663 DOI: 10.2337/dc10-1068]

79 **Klein EA**, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, Minasian LM, Ford LG, Parnes HL, Gaziano JM, Karp DD, Lieber MM, Walther PJ, Klotz L, Parsons JK, Chin JL, Darke AK, Lippman SM, Goodman GE, Meyskens FL Jr, Baker LH. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2011; **306**: 1549-1556 [PMID: 21990298 DOI: 10.1001/jama.2011.1437]

80 **Vilar-Gomez E**, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, Friedman SL, Diago M, Romero-Gomez M. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. *Gastroenterology* 2015; **149**: 367-78.e5; quiz e14-5 [PMID: 25865049 DOI: 10.1053/j.gastro.2015.04.005]

81 **Kleiner DE**, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, Liu YC, Torbenson MS, Unalp-Arida A, Yeh M, McCullough AJ, Sanyal AJ; Nonalcoholic Steatohepatitis Clinical Research Network. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005; **41**: 1313-1321 [PMID: 15915461 DOI: 10.1002/hep.20701]

82 **Salman MA**, Salman AA, Omar HSE, Abdelsalam A, Mostafa MS, Tourky M, Sultan AAEA, Elshafey MH, Abdelaty WR, Salem A, Khaliel OO, Elshafey HE, Atallah M, Shaaban HE, Yousef M, Nafea MA. Long-term effects of one-anastomosis gastric bypass on liver histopathology in NAFLD cases: a prospective study. *Surg Endosc* 2020 [PMID: 32556752 DOI: 10.1007/s00464-020-07725-y]

83 **Lassailly G**, Caiazzo R, Ntandja-Wandji LC, Gnemmi V, Baud G, Verkindt H, Ningarhari M, Louvet A, Leteurtre E, Raverdy V, Dharancy S, Pattou F, Mathurin P. Bariatric Surgery Provides Long-term Resolution of Nonalcoholic Steatohepatitis and Regression of Fibrosis. *Gastroenterology* 2020 [PMID: 32553765 DOI: 10.1053/j.gastro.2020.06.006]

84 **Mosko JD**, Nguyen GC. Increased perioperative mortality following bariatric surgery among patients with cirrhosis. *Clin Gastroenterol Hepatol* 2011; **9**: 897-901 [PMID: 21782772 DOI: 10.1016/j.cgh.2011.07.007]

85 **Jan A**, Narwaria M, Mahawar KK. A Systematic Review of Bariatric Surgery in Patients with Liver Cirrhosis. *Obes Surg* 2015; **25**: 1518-1526 [PMID: 25982807 DOI: 10.1007/s11695-015-1727-2]

86 **Suraweera D**, Dutson E, Saab S. Liver Transplantation and Bariatric Surgery: Best Approach. *Clin Liver Dis* 2017; **21**: 215-230 [PMID: 28364810 DOI: 10.1016/j.cld.2016.12.001]

87 **Tasca A**. Metabolic syndrome and bariatric surgery in stone disease etiology. *Curr Opin Urol* 2011; **21**: 129-133 [PMID: 21191301 DOI: 10.1097/MOU.0b013e3283435cbc]

88 **Eilenberg M**, Langer FB, Beer A, Trauner M, Prager G, Staufer K. Significant Liver-Related Morbidity After Bariatric Surgery and Its Reversal-a Case Series. *Obes Surg* 2018; **28**: 812-819 [PMID: 28965313 DOI: 10.1007/s11695-017-2925-x]

89 **Kosola S**, Lampela H, Makisalo H, Lohi J, Arola J, Jalanko H, Pakarinen M. Metabolic syndrome after pediatric liver transplantation. *Liver Transpl* 2014; **20**: 1185-1192 [PMID: 24923737 DOI: 10.1002/Lt.23931]

90 **Geerts A**, Darius T, Chapelle T, Roeyen G, Francque S, Libbrecht L, Nevens F, Pirenne J, Troisi R. The multicenter Belgian survey on liver transplantation for hepatocellular failure after bariatric surgery. *Transplant Proc* 2010; **42**: 4395-4398 [PMID: 21168706 DOI: 10.1016/j.transproceed.2010.07.010]

91 **Diwan TS**, Rice TC, Heimbach JK, Schauer DP. Liver Transplantation and Bariatric Surgery: Timing and Outcomes. *Liver Transpl* 2018; **24**: 1280-1287 [PMID: 30080949 DOI: 10.1002/Lt.25303]

92 **Adair A**. Bariatric surgery for obese patients undergoing liver transplantation. *HPB (Oxford)* 2018; **20**: 1-2 [PMID: 28528269 DOI: 10.1016/j.hpb.2017.02.446]

93 **Andalib A**, Aminian A, Khorgami Z, Jamal MH, Augustin T, Schauer PR, Brethauer SA. Early Postoperative Outcomes of Primary Bariatric Surgery in Patients on Chronic Steroid or Immunosuppressive Therapy. *Obes Surg* 2016; **26**: 1479-1486 [PMID: 26647068 DOI: 10.1007/s11695-015-1923-0]

94 **Mikolasevic I**, Filipec-Kanizaj T, Mijic M, Jakopcic I, Milic S, Hrstic I, Sobocan N, Stimac D, Burra P. Nonalcoholic fatty liver disease and liver transplantation - Where do we stand? *World J Gastroenterol* 2018; **24**: 1491-1506 [PMID: 29662288 DOI: 10.3748/wjg.v24.i14.1491]

95 **Davis BC**, Shadab Siddiqui M. Liver Transplantation: the Role of Metabolic Syndrome. *Curr Treat Options Gastroenterol* 2017; **15**: 316-331 [PMID: 28432575 DOI: 10.1007/s11938-017-0135-1]

**Footnotes**

**Conflict-of-interest statement:** All the authors would like to declare that there is no conflict of interest

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Corresponding Author's Membership in Professional Societies:** American Association for the Study of Liver Diseases, No. 111687; American Gastroenterological Association, No. 378360; American Society of Transplant Surgeons; American Society of Transplantation; The Transplantation Society; American College of Surgeons, No. 03054282.

**Peer-review started:** June 11, 2020

**First decision:** July 30, 2020

**Article in press:** September 1, 2020

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Greece

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Shabbir A **S-Editor:** Ma YJ **L-Editor:** A **P-Editor:** Li JH

**Table 1 Bariatric surgery studies with histological assessment of liver biopsy**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **PMID** | **First author** | **Year** | **Country** | **Study design** | **Patients** | **Type of surgery** | **Steatosis1** | **Hepatocyte ballooning1** | **Inflammation1** | **Fibrosis1** | **NAS1** | **Deterioration2** | **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 | Aldoheyan | 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 |

1Did the parameter improve after the bariatric operation?

2Did any patient experience worsening in any of the parameters after the bariatric operation?

BPD: Biliopancreatic diversion with duodenal switch; IGB: intragastric 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.