Liver injury and acute liver failure after bariatric surgery an overview of potential injury mechanisms

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Liver Injury and Acute Liver Failure After Bariatric Surgery
An Overview of Potential Injury Mechanisms

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Abstract: The obesity epidemic has caused a surge in the use of bariatric surgery. Although surgery-induced weight loss is an effective treatment of nonalcoholic fatty liver disease, it may precipitate severe hepatic complications under certain circumstances. Acute liver injury (ALI) and acute liver failure (ALF) following bariatric surgery have been reported in several case series. Although rare, ALI and ALF tend to emerge several months after bariatric surgery. If so, it can result in prolonged hospitalization, may necessitate liver transplantation, and in some cases prove fatal. However, little is known about the risk factors for developing ALI or ALF after bariatric surgery and the mechanisms of liver damage in this context are poorly defined. This review provides an account of the available data on ALI and ALF caused by bariatric surgery, with emphasis on potential injury mechanisms and the outcomes of liver transplantation for ALF after bariatric surgery.

Key Words: gastric bypass, liver cirrhosis, liver transplantation, nonalcoholic fatty liver disease, protein-energy malnutrition

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KEY POINTS

- Acute liver injury (ALI) and acute liver failure (ALF) are rare but severe complications of bariatric surgery.
- A disproportionally long alimentary loop and nonadherence to nutritional support are risk factors for postoperative liver dysfunction.
- Protein-energy malnutrition, lipotoxicity, bacterial overgrowth, and a compromised intestinal barrier may all trigger hepatic dysfunction after bariatric procedures.
- Prompt initiation of total parenteral nutrition in ALI (and ALF) cases after bariatric surgery is mandatory.
- Liver transplantation is required for ALF cases or nonresponders to nutritional therapy.

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INTRODUCTION

The obesity epidemic has caused a rise in the use of bariatric surgery, with several hundred thousand procedures being performed worldwide annually.[1] It includes various procedures that can be categorized as causing restrictive, malabsorptive, or combined effects. Long-term studies show that bariatric surgery causes significant long-term weight loss, recovery from diabetes, improvement in cardiovascular risk factors, and a reduction in mortality.[2] However, the changes in intestinal anatomy and metabolism may precipitate severe hepatic complications under certain circumstances. Over the last decades, severe ALI and ALF requiring liver transplantation (LTx) have been reported in small series after jejunoileal bypass (JIB) or biliopancreatic diversion (BPD),[3–5] which are only indicated in patients with a body mass index (BMI) of $>60\,kg/m^2$.[6] However, similar reports are now surfacing following more contemporary techniques, such as Roux-en-Y gastric bypass (RYGB) and one-anastomosis (mini) gastric bypass (OAGB).[7–9]

Although the exact incidence of severe ALI and ALF after bariatric surgery is unclear, current literature suggests that it may only affect a handful of patients per year globally.[10] ALI and ALF typically emerge several months after bariatric surgery. If so, it can result in prolonged hospitalization, may necessitate LTx, and in some cases prove fatal.[10,11] Little is, however, known about the risk factors for developing ALI and ALF after bariatric surgery and the mechanisms of liver damage in this context are poorly defined. This review therefore provides an account of the available data on ALI and ALF caused by bariatric surgery, with emphasis on possible injury mechanisms and the outcomes of LTx for ALF following bariatric surgery. Throughout the manuscript, severe ALI is defined as the combination of liver injury (elevated transaminases and jaundice) in conjunction with coagulopathy (international normalized ratio of >1.5) in patients without preexisting liver disease, while ALF applies to cases where severe ALI occurs in combination with hepatic encephalopathy.[12]

BARIATRIC SURGERY

Background

Since conventional approaches such as reducing calorie intake, increasing physical activity, and/or pharmacological treatment have yielded unsatisfactory results,

various surgical interventions to lose weight have been developed.[13] These bariatric techniques have accomplished sustainable weight loss, thereby improving cardiovascular risk profiles and reducing overall mortality.[14] As a result, several hundred thousand of procedures are performed each year.[1] Bariatric surgery is currently indicated in patients with severe obesity who fail to lose sufficient weight by nonsurgical means. Severe obesity is defined as a BMI of $>40\ kg/m^2$ or a BMI between 35 and $40\ kg/m^2$ with concurrent comorbid conditions, including diabetes, hypertension, and nonalcoholic fatty liver disease (NAFLD).[15]

Bariatric procedures are categorized as restrictive, malabsorptive, or a combination of both. Restrictive procedures limit gastric volume to reduce food intake. Malabsorptive procedures divert food from digestive fluids such as bile and bypass a portion of the small intestine, thereby limiting nutrient uptake. Most bariatric procedures combine both principles.[16] The following bariatric procedures have been developed: (1) BPD with duodenal switch (DS, Scopinaro technique), (2) RYGB, (3) OAGB, and (4) sleeve gastrectomy (SG). An overview of the aforementioned techniques is shown in Figure 1. Laparoscopic RYGB has been considered the gold standard for several decades.[15] However, SG has gained popularity in recent years due to the low complication rate.[17] Although RYGB still predominates in Europe, SG has become the most common bariatric procedure in the United States.[18,19]

Metabolic Effects of Bariatric Surgery

Large, randomized trials comparing bariatric surgery to lifestyle changes and pharmacological interventions describe postoperative weight loss of 25% to 30% of total body weight at 1 to 5 years follow-up. In doing so, bariatric surgery provides better glycemic control than conventional therapy in patients with type 2 diabetes, while also significantly improving blood pressure and lipid profiles.[20,21] As bariatric surgery typically leads to sustained weight loss,[22] it improves the 10-year survival rate in obese individuals when compared with nonsurgical treatment.[2,23,24] In addition, weight reduction surgery is safe, with current mortality rates (ie, $<1\%$) similar to laparoscopic cholecystectomy or appendectomy.[25,26]

Bariatric surgery also affects the liver.[27] NAFLD is considered the hepatic manifestation of the metabolic syndrome and favorable effects in patients with NAFLD have been noted. In morbidly obese patients with biopsy-confirmed nonalcoholic steatohepatitis (NASH), a reduction in the histologic NAFLD activity score was seen in liver biopsies 1 year after various types of bariatric surgery. These histologic improvements were accompanied by normalization of liver damage parameters, such as serum alanine aminotransferase and γ-glutamyl transferase levels.[28] The effect of weight loss surgery on NAFLD is supported by 2 prospective cohort studies investigating obese patients with biopsy-confirmed NASH or hepatic fibrosis, showing marked histologic improvement 2 years after laparoscopic adjustable gastric banding and SG.[29,30] Supporting evidence showed normalization of the international normalized ratio of coagulopathy and a reduction in transaminase levels in severely obese individuals with biopsy-confirmed NAFLD 1 year after bariatric surgery, attesting to improved liver function and reduced liver damage, respectively.[31,32] However, bariatric surgery can also adversely affect the liver under certain circumstances, which are described next.

POTENTIAL MECHANISMS LEADING TO LIVER INJURY

Over the last decades, ALI and ALF have been described as rare postoperative complications after JIB or BPD(-DS).[3–5] JIB has therefore been largely (but not completely) abandoned as a method for weight reduction.[33] However, similar complications are now surfacing after RYGB and OAGB.[7–9] Although poorly understood, several mechanisms have been proposed to induce ALI and ALF in patients following bariatric surgery, including protein-energy malnutrition, lipolysis and lipotoxicity, and compromised intestinal barrier function.

Protein-energy Malnutrition

Alterations in gastrointestinal (GI) anatomy and physiology following bariatric surgery can cause nutritional deficiencies, such as protein-energy malnutrition.[34] Current guidelines therefore recommend the postoperative use of oral vitamins and micronutrient supplements.[35,36] Several lines of evidence link amino acid deficiencies to the onset of hepatic steatosis and consequent liver damage. The most important evidence comes from 3 fatal cases. Two patients refused nutritional support after bariatric surgery due to psychiatric comorbidity, while another patient became vegetarian and withdrew from postoperative nutritional support after OAGB.[37,38]

Protein malnutrition can be caused by limited nutrient intake, a lack of therapy adherence, and/or excessive surgical limb exclusion, all leading to reduced amino acid bioavailability.[39,40] The most prominent amino acid deficiencies noted after RYGB include serine, histidine, phenylalanine, lysine, glycine, alanine, methionine, and threonine.[39] A lack of amino acids per se is sufficient to trigger hepatocyte triglyceride accumulation in vitro, with most pronounced effects reported for arginine and threonine.[41] In vivo, a methionine-deficient and choline-deficient diet fed to rats rapidly culminates in (macrovesicular) steatosis and considerable hepatopathology,[42] which compromises the liver's resilience against various forms of injury.[42,43] Although reduced concentrations of methionine have been observed 12 months after RYGB,[39] rats fed a methionine-deficient diet did not exhibit hepatic fat accumulation without concomitant choline deficiency.[41] However, replenishing methionine stores protected mouse livers from apoptosis and oxidative stress under conditions of protein starvation.[44] Also, methionine deficiency triggered hepatic inflammation and fibrosis in both mice and rats, suggesting that methionine depletion following bariatric surgery may be harmful for the liver, even when it does not directly causes hepatocyte fat loading.[41,45,46]

In contrast to methionine, a choline-deficient diet in humans induces NAFLD and liver damage,[47] meaning that lack of choline alone is enough to elicit harmful hepatic fat accumulation.[48] Two reports have described decreased choline levels after bariatric surgery.[49,50] A combined lack of methionine and choline leads to impaired β-oxidation and diminished production of very low-density lipoproteins, while choline deficiency per se impairs very low-density lipoprotein secretion, resulting in macrovesicular steatosis, oxidative stress, and hepatocyte apoptosis,[45,51] eventually reducing liver function.[52]

Shortage of methionine and choline following bariatric surgery may be explained by a combination of factors. Methionine and choline are primarily absorbed in the jejunum and ileum by carrier-mediated transport.[53–56] As bariatric surgery bypasses the duodenum and proximal part of the jejunum, uptake of methionine and choline is hampered.[57] Also, the reduction in gastric volume decreases the pH in the digestive system. Because methionine is primarily absorbed by

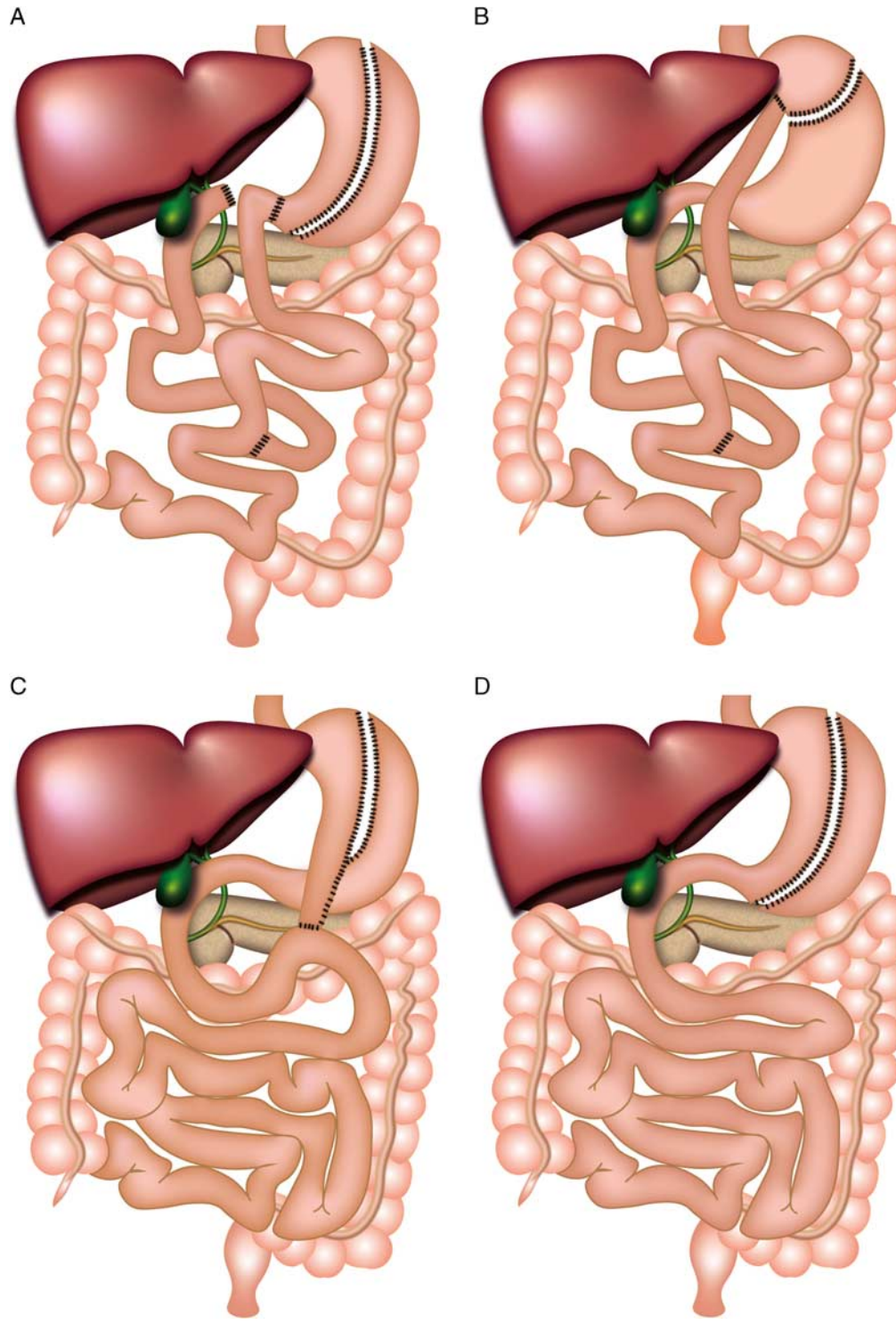

FIGURE 1. Common types of bariatric surgery. A, Biliopancreatic diversion with duodenal switch. B, Roux-en-Y gastric bypass. C, One-anastomosis gastric bypass. D, Sleeve gastrectomy. full color online

a pH-dependent transporter, pH changes negatively affect methionine uptake.[58] In addition, the general population does not even meet the recommend daily choline intake.[59] In bariatric patients, in which choline uptake is already impaired, choline bioavailability will likely be even more compromised. Choline deficiency can also be caused by changes in gut microbiota following bariatric surgery.[60] Some bacterial strains, which convert choline to trimethylamine, become more abundant after bariatric surgery.[61] Thus, colonization with trimethylamine-producing bacteria further reduces choline

bioavailability.[62] In addition, folate and vitamin B_{12} deficiencies, which are regularly observed after bariatric surgery,[63] increase choline requirements. Since folate and choline both methylate homocysteine to produce methionine, a folate deficiency leads to a compensatory increase in choline consumption and, thereby, a secondary choline deficiency.[64]

Compromised Intestinal Barrier Function

Small intestinal bacterial overgrowth (SIBO) is a common complication of RYGB, occurring in >70% of cases.[65] SIBO may facilitate hepatic injury by compromising the intestinal mucosal barrier. Manipulation of the GI tract disrupts mechanisms that normally control enteric bacterial populations.[66] When this balance is perturbed after bariatric surgery, bacterial dysbiosis results in the production of inflammatory cytokines and endotoxins, causing mucosal injury and increased gut permeability.[61] Impaired function of the mucosal barrier may subsequently facilitate translocation of these toxic macromolecules into the portal venous system, causing liver damage or exacerbation of hepatic injury induced by other mechanisms (see above).[3] SIBO can also stimulate the synthesis of interleukin-6, which has shown to induce insulin resistance in adipocytes.[67] Insulin resistance enhances hepatic fat accumulation by no longer suppressing lipolysis, which increases free fatty acid delivery to the liver, and stimulation of de novo lipogenesis, causing hepatocellular damage and liver dysfunction.[67,68]

Several factors may promote SIBO after bariatric surgery, including (disproportional) intestinal limb exclusion, bowel dysmotility, decreased gastric acidity, intestinal bile deprivation, and undigested food reaching the colon.[69] First, limb exclusion and decreased motility of the biliopancreatic limb induce mechanical stasis, providing the ideal environment for bacterial colonization. Second, intestinal delivery of gastric acid, which normally inhibits bacterial proliferation in the digestive system, is limited due to surgical exclusion of the majority of the stomach, allowing bacterial overgrowth in the alimentary limb.[66] Third, bypassing the duodenum results in the absence of antimicrobial bile acids in the alimentary limb, such as cholic acid and deoxycholic acid, promoting colonization of bacterial flora[70] and dysbiosis.[60] Last, as digestive enzymes such as bile and pancreatic secretions do not enter the alimentary limb until the jejunojenostomy, undigested food can become a substrate for bacterial fermentation, leading to SIBO.[71]

The most persuasive evidence linking SIBO to postbariatric liver damage comes from a trial using the antibiotic metronidazole. This study demonstrated complete or partial reversal of biopsy-confirmed, surgery-induced hepatic steatosis in postbariatric patients after treatment with metronidazole. During subsequent periods of alternating antibiotic therapy with drug-free intervals, hepatic steatosis repeatedly diminished when metronidazole was administered and increased when metronidazole was withdrawn.[72]

Lipolysis and Lipotoxicity

Although a clear linear relation between the speed and/or extent of weight loss after bariatric surgery and the onset of liver dysfunction is lacking, one report described that rapid weight loss of >1.6 kg/week induces portal inflammation and fibrosis.[73] Disproportionate weight loss after bariatric surgery may induce liver dysfunction by triggering excessive lipolysis in visceral adipose tissue, leading to hepatic lipotoxicity.[74] In support of this hypothesis, 2 patients with a history of bariatric surgery who experienced a significant symptom-free period (with a stable weight) developed ALI directly after suddenly losing an excessive and unexplained amount of weight.[9] Weight loss after bariatric surgery normally involves a drop in endogenous insulin production due to improved peripheral insulin sensitivity, which subsequently triggers the release of free fatty acids stored in adipose tissue.[75] However, as excess weight loss (ie, the amount of weight above the ideal body weight) equaled ±110% in these patients, compared to only ±60% to 70% after regular RYGB and OAGB, the extent of lipolysis was likely substantially higher than commonly observed after bariatric surgery.[9,76] As a result, an excess of free fatty acids reaches the liver through the portal circulation, exceeding the liver's capacity to metabolize free fatty acids through mitochondrial β-oxidation in hepatocytes.[74] Disproportionate activation of β-oxidation has shown to generate toxic reactive oxygen species in mice receiving a high fat diet.[77] Generation of reactive oxygen species may trigger mitochondrial injury and the production of proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-6, which impede liver function.[51,78]

Histologic Changes

On a histopathologic level, ALF after bariatric surgery manifests as advanced steatohepatitis, resembling an aggressive form of NAFLD.[7,38,69] Postbariatric steatohepatitis is characterized by microvesicular and macrovesicular steatosis and is associated with centrizonal scarring, hepatocellular ballooning, and the presence of Mallory-Denk bodies.[4,7] Hepatic biopsies from patients with ALF after bariatric surgery also demonstrated focal ductular reaction and hepatocanalicular cholestasis, reflecting an inflammatory reaction caused by the release of endotoxins and cytokines.[7,38,79,80] Pericellular fibrosis, which is typically seen in patients with postbariatric liver injury, is often accompanied by perivenular fibrosis, representing fibrous wall thickening, intimal fibrosis, or total venous sclerosis with luminal obliteration.[4,7] Other histologic features, including confluent bridging necrosis, lymphocytic and neutrophilic infiltrates, and cirrhosis have also been reported in patients with postbariatric ALF.[4,9,79,80]

ALI AND ALF AFTER BARIATRIC SURGERY

RYGB

In 1967, Mason and Ito introduced the gastric bypass for patients with severe obesity as an alternative to JIB, a technique that completely excluded the small intestine from the alimentary stream, leading to both unsatisfactory weight loss and a high complication rate, including 4% mortality.[33,81–84] The original procedure involved segmentation of the stomach to create a small gastric pouch, followed by the construction of a loop gastrojejunostomy, resulting in food bypassing the majority of the stomach, duodenum, and the first 40 to 50 cm of the jejunum.[85] Over time, the loop gastrojejunostomy was replaced by a Roux-en-Y configuration to avoid bile reflux.[86] Although RYGB was originally developed as a restrictive procedure, it also caused malabsorption by bypassing a major part of the GI tract.[57] During the last years, RYGB has been advanced into its current laparoscopic form, reducing recovery time and perioperative complications compared to open RYGB.[87]

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TABLE 1. Liver Failure After RYGB

Outcome	Patient No.	Type of Procedure	Gender	Age	Initial BMI (kg/m²)	Preexisting Liver Disease	Liver Biopsy Before/ During BS	BMI Minimum (kg/m²)	BMI (kg/m²)	Maximum Weight Loss (kg)	Onset of LF After Surgery	Liver Biopsy After BS	Meeting ALF Criteria	Cause of Death
Recovery with nutritional support	1[7]	RYGB	Female	37	46	No	NA	32	14	40	NA	Panacinar steatosis, ballooned hepatocytes, Mallory-Denk bodies	ALI	
	2[88]	Extended RYGB	Female	37	61	No	NA	NA	NA	48	7 mo	Steatosis and mild fibrosis	ALF	
Recovery with revision* or conversion† of the bariatric surgery	3[9]*	RYGB	NA	NA	53.4	No	NA	26.6	26.8	NA	24 mo	Macrovesicular steatosis	Liver dysfunction	
	4[9]*	Distal RYGB	NA	NA	50.2	No	NA	28.7	21.5	NA	85 mo	NA	ALI	
	5[9]*	Distal RYGB	NA	NA	44.1	No	NA	20.3	23.8	NA	12 mo	NA	ALI	
	6[9]†	RYGB	NA	NA	48.2	No	NA	21.9	26.3	NA	84 mo	Macrovesicular and microvesicular steatosis	ALI	
Recovery with liver transplantation	7[7]	RYGB	Female	37	59.4	No	NA	26.5	32.9	91	NA	Micronodular cirrhosis, azonal steatosis, ballooned hepatocytes, Mallory-Denk bodies	ALI	
	8[89]	RYGB	Female	56	50.9	No	NASH	24.5	26.4	65.2	2 y	NA	ALF	
Dead	9[7]	RYGB	Female	33	45.3	No	Steatosis and centrizonal pericellular fibrosis	38.4	6.9	18	NA	Panacinar steatosis, ballooned hepatocytes, Mallory-Denk bodies, bridging fibrosis	ALF	Unknown
	10[7]	RYGB	Female	37	55.1	No	NA	36.5	22.2	45	NA	Azonal steatosis, ballooned hepatocytes, Mallory-Denk bodies	Liver dysfunction	Unknown
	11[9]	RYGB	NA	NA	58	No	NA	28.7	29.3	NA	2 mo	NA	ALF	Decompensated liver disease and septic shock
	12[88]	Extended RYGB	Female	54	49	No	NA	NA	NA	35	7 mo	Steatohepatitis and cirrhosis	ALF	Gastric carcinoma with peritoneal metastases
	13[90]	Distal RYGB	Male	33	80	No	Cirrhosis	NA	NA	NA	9 mo	NA	ALF	Hepatic failure

TABLE 1. (*continued*)

Outcome	Patient No.	Type of Procedure	Gender	Age	Initial BMI (kg/m^2)	Preexisting Liver Disease	Liver Biopsy Before/During BS	BMI Minimum (kg/m^2)	BMI (kg/m^2)	Maximum Weight Loss (kg)	Onset of LF After Surgery	Liver Biopsy After BS	Meeting ALF Criteria	Cause of Death
	14[90]	Redo RYGB	Female	40	64.4	No	Cirrhosis	NA	NA	NA	1 mo	NA	ALF	Hepatic failure and hepatorenal syndrome after ascitic fluid leak
Awaiting transplantation	15[88]	Extended RYGB	Female	34	86	No	NA	NA	NA	128	17 mo	Steatohepatitis and cirrhosis	ALI	

*Recovery after revision.
†Recovery after conversion.
ALF indicates acute liver failure; ALI, acute liver injury; BMI, body mass index; NA, not available; NASH, nonalcoholic steatohepatitis; RYGB, Roux-en-Y gastric bypass.

Although rare, cases of acute liver dysfunction following RYGB have been described in a small case series (Table 1).[7,9,88–90] In total, 15 patients with different stages of liver dysfunction after RYGB were identified: 2 (13%) patients with mild liver dysfunction, 6 (40%) patients with ALI, and 7 (47%) patients with ALF. Eight of 15 (53%) patients recovered: 2 (13%) with nutritional support, 4 (27%) after revision or conversion of the RYGB, and 2 (13%) by means of LTx. Six patients died (40%): 1 (7%) due to septic shock, 1 (7%) after developing gastric carcinoma with peritoneal metastases 6 years after LTx, 2 (13%) due to progressive hepatic failure without considering LTx, and 2 (13%) as a result of an unspecified cause. One (7%) patient was still awaiting LTx at the time of publication.

Of all the 15 patients that developed liver dysfunction, ALI, or ALF after RYGB, 6 (40%) patients underwent a distal or extended version of the bariatric procedure, suggesting a negative impact of a disproportionally long alimentary loop on liver function.[9,88,90] Accordingly, elongation of the common channel led to significant improvement in laboratory parameters in 2 of these patients.[9] This suggestion is reinforced by 2 patients who developed ALF after extended or distal RYGB, but in whom lengthening of the reabsorption limb was not performed due to unspecified reasons. At the end, both of these cases proved fatal.[88,90] It should however be noted that a gastric carcinoma was identified on postmortem examination in one of these patients, which brings into question the causal relationship between bariatric surgery and death in this case.[88]

Even though a significant number of patients died, some of these deaths were probably not related to the previous bariatric procedure. As an illustration, 2 patients (13%) showed unspecified manifestations of cirrhosis perioperatively, most likely due to severe obesity, increasing the likelihood of developing acute-on-chronic liver failure after RYGB. One patient died due to fulminant hepatic failure in combination with hepatorenal syndrome after developing an ascitic fluid leak during the early postoperative course.[90] As this patient underwent conversion of a failed horizonal gastroplasty to RYGB, poor preoperative physical condition may have contributed to the fatal outcome.

OAGB (Mini/Omega Loop)

OAGB, also known as mini-gastric bypass or omega loop gastric bypass, was first described by Rutledge.[91] The procedure, which was initially proposed as an alternative to RYGB, consists of a single gastrojejunal anastomosis between a long gastric pouch and a jejunal omega loop ~200 cm distal from the ligament of Treitz.[92,93] This surgical procedure provides similar results as RYGB but is technically less demanding and easier to revise.[94] OAGB causes weight loss by both restriction and malabsorption and carries the same characteristics as RYGB.[95] Although OAGB raised severe criticism due to controversial aspects of this procedure,[96] several studies reported favorable outcomes concerning weight loss and obesity-related comorbidities, such as diabetes and hypertension.[76,91,94] Nevertheless, OAGB is still disputed since bile is brought into direct contact with the gastric mucosa, theoretically creating biliary reflux and possibly increasing the risk of gastric and esophageal cancers.[97]

Despite its recent introduction, several stages of liver dysfunction, including ALF, have been reported after OAGB (Table 2).[9,38,93,98] One case series and 3 case reports described 8 patients suffering from impaired liver function

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TABLE 2. Liver Failure After OAGB

Outcome	Patient No.	Type of Procedure	Gender	Age	Initial BMI (kg/m^2)	Preexisting Liver Disease	Liver Biopsy Before/ During BS	BMI Minimum (kg/m^2)	BMI (kg/m^2)	Maximum Weight Loss (kg)	Onset of LF After Surgery (mo)	Liver Biopsy After BS	Meeting ALF Criteria	Cause of Death
Recovery with revision* or conversion† of bariatric surgery	1[9]†	OAGB (BPL 370 cm, CL 320 cm)	NA	NA	42.9	No	NA	20.8	22.1	NA	12	Cirrhosis	Liver dysfunction	
	2[9]†	OAGB (BPL 265 cm, CL 395 cm)	NA	NA	40.8	No	NA	21.7	19.1	NA	35	Cirrhosis	ALI	
	3[9]†	OAGB (BPL 200 cm, CL 375 cm)	NA	NA	57.6	No	NA	22.40	35.2	NA	36	Macrovesicular and microvesicular steatosis	ALF	
	4[9]†	OAGB (BPL 95 cm, CL 275 cm)	NA	NA	64	No	NA	30.5	33.5	NA	20	Macrovesicular steatosis	ALI	
	5[93]*	OAGB	Female	57	42.8	No	Ballooning and mild steatosis	25.7	17.1	NA	8	Prominent ballooning, steatosis, and neutrophilic satellitosis	Liver dysfunction	
Recovery with liver transplantation	6[9]	OAGB (BPL 175 cm, CL 500 cm)	NA	NA	33.3	No	NA	22.03	11.3	NA	5	Cirrhosis	ALF	
Death	7[98]	OAGB	Female	37	44	NA	NA	24	20	52,5	12	Nonspecific inflammation in portal spaces and fatty change	ALF	Multiorgan failure after gastrogastrostomy
	8[38]	OAGB	Female	29	55.7	NA	NA	NA	NA	NA	8	Steatohepatitis, intracellular cholestasis, and multifocal lobular and periportal fibrosis	ALF	Hepatic failure (died on list)

*Recovery after revision.
†Recovery after conversion.
ALF indicates acute liver failure; ALI, acute liver injury; BMI, body mass index; BPL, biliopancreatic limb; CL, common limb; NA, not available; OAGB, one-anastomosis gastric bypass.

TABLE 3. Liver Failure After BPD and DS (Scopinaro)

Outcome	Patient No.	Type of Procedure	Gender	Age	Initial BMI (kg/m^2)	Preexisting Liver Disease	Liver Biopsy Before/ During BS	BMI Minimum (kg/m^2)	BMI (kg/m^2)	Maximum Weight Loss (kg)	Onset of LF After Surgery	Liver Biopsy After BS	Meeting ALF Criteria	Cause of Death
Recovery with nutritional support	1[102]	BPD-DS	Female	31	41	NA	NASH	NA	NA	NA	2 wk	NA	Liver dysfunction	
	2[102]	BPD-DS	Female	43	61	NA	NA	NA	NA	NA	6 mo	Steatosis	Liver dysfunction	
	3[102]	BPD-DS	Female	45	40	NA	NA	NA	NA	NA	1 mo	NA	Live dysfunction	
	4[102]	BPD-DS	Female	26	44	NA	NASH	NA	NA	NA	3.5 mo	NA	Live dysfunction	
	5[102]	BPD-DS	Female	20	60	NA	NA	NA	NA	NA	1 mo	NA	Liver dysfunction	
	6[102]	BPD-DS	Male	34	45	NA	Steatosis	NA	NA	NA	1 wk	NA	Liver dysfunction	
	7[102]	BPD-DS	Male	25	47	NA	NA	NA	NA	NA	1 mo	NA	ALI	
	8[102]	BPD-DS	Female	42	49	NA	NA	NA	NA	NA	NA	NA	ALI	
	9[102]	BPD-DS	Female	50	61	NA	NASH	NA	NA	NA	NA	NA	Liver dysfunction	
	10[103]	BPD-DS	Female	41	57	NA	NA	24	33	NA	11 mo	Steatosis, fibrosis, liver cirrhosis	ALF	
Recovery with liver transplantation and revision* or conversion† of the bariatric procedure	11[4]*	BPD	Female	29	63	No	NA	26	37	NA	10 mo	Cholestatic hepatitis and macrovesicular steatosis	ALF	
	12[3]*	BPD					Details could not be extracted from the original report						ALF	
	13[3]*	BPD					Details could not be extracted from the original report						ALF	
	14[3]*	BPD					Details could not be extracted from the original report						ALF	
	15[3]* after 8 wk+ retransplantation	BPD	Male	19	41	No	NA	20	21	40	62 mo	Steatosis and necrosis	ALF	
	16[79]†	BPD	Female	41	46	No	Mild macrovesicular steatosis	26.3	19.7	NA	8 mo	Necrosis, cholestasis, and steatosis	ALF	
	17[104]†	BPD-DS	Female	33	49	NA	NA	23	26	NA	20 mo	Disappearance of hepatocytes, cholangiolar metaplasia, and bile stasis	ALF	

	18[80]	BPD-DS	Female	37	54	No	NA	30	24	NA	8 mo	Acute hepatitis with confluent bridging necrosis, mixed inflammatory infiltrates, and ductular reaction	ALF	
Dead	19[4]	BPD	Female	38	56	No	NA	29.9	26.1	NA	7 mo	Necrosis	ALF	Pulmonary infection, sepsis, and multiorgan failure after LTx without revision or conversion of the bariatric procedure
	20[4]	BPD	Female	29	60	No	Mild hepatic steatosis and fibrosis	35	25	NA	6 mo	Cirrhosis and necrosis	ALF	Hepatic failure (died on list)
	21[3]	BPD	Male	38	40	No	NA	22	18	53	21 mo	NA	ALF	Hepatic failure (died on list)
	22[3]	BPD	Male	40	47	No	NA	25	22	50	14 mo	NA	ALF	Hepatic failure (died on list)
	23[3]	BPD					Details could not be extracted from the original report						ALF	Multiorgan failure after LTx with revision of the bariatric procedure
	24[3]	BPD					Details could not be extracted from the original report						ALF	Lung carcinoma 6 y after LTx with revision of the bariatric procedure
	25[102]	BPD-DS	Female	41	64	NA	Steatosis	NA	NA	NA	2 mo	NASH	ALF	Hepatic failure (died on list)
	26[104]	BPD-DS	Female	41	58	NA	NA	39	19	NA	6 mo	NASH	ALF	Hepatic failure (died on list)
	27[105]	BPD	Female	49	53.3	No	NA	28.7	24.6	NA	3 mo	NA	ALF	Multidrug resistant sepsis, septic shock
	28[106]	BPD	Male	35	NA	NA	NA	18	NA	NA	12 mo	Hepatic necrosis, macrovesicular and microvesicular steatosis	ALF	Multidrug resistant refractory septic shock after LTx and revision of BPD
	29[107]	BPD	Female	53	NA	NA	NA	NA	NA	NA	3 y	Steatosis	ALF	Hepatic failure after refusing surgical intervention

TABLE 3. (*continued*)

Outcome	Patient No.	Type of Procedure	Gender	Age	Initial BMI (kg/m^2)	Preexisting Liver Disease	Liver Biopsy Before/ During BS	BMI Minimum (kg/m^2)	BMI (kg/m^2)	Maximum Weight Loss (kg)	Onset of LF After Surgery	Liver Biopsy After BS	Meeting ALF Criteria	Cause of Death
	30[69]	BPD	Female	24	40	NA	NA	20.2	19.8	NA	5 y	Fibrosis, macrovesicular steatosis, infiltrates, and cholangitis lenta	ALF	Recurrent hepatic failure after 3 failed LTx and conversion of the bariatric procedure after 8 wk
Awaiting transplantation	31[3]	BPD	Male	29	40	No	NA	20	20	60	84 mo	NA	ALF	

*Recovery after revision.
†Recovery after conversion.
ALF indicates acute liver failure; ALI, acute liver injury; BMI, body mass index; BPD, biliopancreatic diversion; DS, duodenal switch; LTx, liver transplantation; NA, not available; NASH, nonalcoholic steatohepatitis.

after OAGB: 2 (25%) patients with mild liver dysfunction, 2 (25%) patients with ALI, and 4 (50%) patients with ALF. Six (75%) patients recovered: 5 (63%) after revision or conversion of the bariatric procedure and 1 (13%) following LTx. Two (25%) patients died due to fulminant hepatic failure, one in which technically successful revision surgery failed to improve liver function. Both patients were not eligible for LTx due to hemodynamic instability.

Four (50%) patients showed clinical stabilization or even full recovery after conversion of OAGB to RYGB combined with elongation of the common channel.[9] Since only one of these patients suffered from ALF, the question remains whether revision surgery is able to relieve ALF in this patient category. As described for RYGB, the onset of liver dysfunction after OAGB seems related to the length of the excluded bowel segment. Yet, due to the limited number of described cases, firm conclusions are difficult to draw.

SG

To our knowledge, no cases of ALI or ALF following SG have been reported. Considering that SG reduces gastric volume without bypassing intestinal segments, it is expected that hepatic ramifications of this technique will remain limited. Similarly, hepatic complications of endoscopic bariatric techniques such as gastric balloons or endoscopic sleeve gastroplasty have not been reported and will most likely remain rare.

BPD (Scopinaro) and DS

BPD, also eponymously known as the Scopinaro technique, was developed in 1979 and has 4 components: (1) partial distal gastrectomy, (2) transection of the small bowel, (3) Roux-en-Y gastroenterostomy creating an alimentary limb, and (4) an anastomosis between the biliopancreatic limb and the alimentary limb approximately 50 cm before the ileocecal junction.[82] However, due to side effects, 2 modifications were introduced: (1) the DS, which preserves the lesser curvature, antrum, pylorus, and first part of the duodenum, and (2) an ileoileal anastomosis, which doubles the length of the common channel.[99] Since BPD-DS involves removal of the stomach in combination with bypassing a large part of the small intestine, it provides both malabsorptive and restrictive effects.[100] Given the relatively high risk for postoperative complications, BPD(-DS) is currently only utilized in patients with a BMI >60 kg/m^2.[6,101]

Cases of acute liver dysfunction following BPD(-DS) have been described in a small series (Table 3).[3,4,69,79,102–107] Eleven studies describing 31 cases of acute liver dysfunction after BPD(-DS) were retrieved: 7 (23%) patients with mild liver dysfunction, 2 (6%) patients with ALI, and 22 (71%) patients with ALF. Eighteen of 31 (58%) patients recovered: 10 (32%) with nutritional support and 8 (26%) by means of LTx. Seven (23%) patients that recovered with LTx also underwent revision or conversion of the bariatric procedure: 6 (19%) simultaneous with LTx and 1 (3%) 8 weeks post-LTx. Twelve (39%) patients died: 5 (16%) following LTx, 5 (16%) due to progressive hepatic failure while awaiting a donor liver, 1 (3%) as a result of ALF after refusing any surgical intervention, and 1 (3%) due to a hospital-associated complication. Of the patients who died following LTx, 3 (10%) died after developing sepsis-induced multiorgan failure in the direct postoperative period, 1 (3%) after developing lung carcinoma 6 years post-LTx, and 1 (3%)

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after undergoing 3 LTx and revision of the BPD 8 weeks after the initial transplantation.

In the latter case, a liver biopsy excluded rejection as a potential cause of recurrent graft failure.[69] Late dismantling of the BPD could also be eliminated, as steatohepatitis recurred after the second and third LTx, while intestinal anatomy had already been restored following the first LTx. Although unlikely in the aforementioned patient, late revision or conversion of the BPD may have caused ALF in other patients. As an illustration, 1 patient needed retransplantation owing to rapid redevelopment of ALF due to late revision of the BPD 8 weeks post-LTx.[3]

These statistics suggest that nutritional support is able to restore liver function, but only in certain patients.[102,103] To illustrate this, 9 of 10 patients that recovered with nutritional support showed signs of liver damage, but without coagulopathy or hepatic encephalopathy, suggesting only mild liver dysfunction.[102] To date, only 1 case with ALF has been successfully resolved with total parenteral nutrition.[103] In that respect, therapy response seems inversely correlated to the severity of hepatic dysfunction.

Several factors have to be taken into consideration when interpreting these findings. Since a liver biopsy was not routinely performed, the extent of hepatic parenchymal injury at the time of bariatric surgery could not be determined. This hampers the assessment of the true etiology of liver dysfunction after bariatric surgery. For cases of ALI or ALF that did not respond to nutritional support or that occurred many years after the index procedure, the onset of ALI or ALF could not be unequivocally linked to previous weight loss surgery. In that respect, several reports also lack information about alcohol and drug use or whether other causes of ALI or ALF such as viral hepatitis were excluded.

In conclusion, both aggressive nutritional support and revision of the bariatric procedure seem justified in patients with ALI caused by bariatric surgery. Patients with ALF should be managed in liver transplant centers and considered for LTx, as the chance of recovery with nutritional support only are slim, based on currently available data.

FUTURE PERSPECTIVES

ALI and ALF are rare complications of bariatric surgery and because of the low incidence, little evidence-based guidance is available. Based on the available data, the following points seem important to consider. To mitigate the risk of ALI and ALF after bariatric surgery, procedures that feature the most extreme alterations in GI anatomy, such as JIB and BPD, should be avoided when possible. Bariatric surgery should be very carefully considered in patients with preexisting liver disease such as cirrhosis, although it is not an absolute contra-indication.[108] When performing a RYGB, the main precipitant for postoperative liver injury seems to be a disproportionally long alimentary limb, which should obviously be avoided. In the postoperative period, patients with psychiatric comorbidity and/or poor therapy adherence seem to have an increased risk for liver-related sequelae. When managing patients with severe ALI related to bariatric surgery, early recognition and aggressive nutritional support are mandatory, while cases of ALF should be managed in liver transplant centers.

Risk stratification is an important goal for future research, in particular to distinguish patients that benefit from nutritional support only from patients that require LTx to recover. Identifying biomarkers that accurately reflect nutritional status would be helpful in this respect. In addition, defining preoperative risk factors for developing liver injury after bariatric surgery would enable the selection of patients best treated with a technique with less hepatic complications, such as SG.

REFERENCES

1. Angrisani L, Santonicola A, Iovino P, et al. IFSO Worldwide Survey 2016: Primary, Endoluminal, and Revisional Procedures. *Obes Surg*. 2018;28:3783–3794.
2. Carlsson LMS, Sjöholm K, Jacobson P, et al. Life expectancy after bariatric surgery in the Swedish obese subjects study. *N Engl J Med*. 2020;383:1535–1543.
3. Geerts A, Darius T, Chapelle T, et al. The multicenter Belgian survey on liver transplantation for hepatocellular failure after bariatric surgery. *Transplant Proc*. 2010;42:4395–4398.
4. D'Albuquerque LA, Gonzalez AM, Wahle RC, et al. Liver transplantation for subacute hepatocellular failure due to massive steatohepatitis after bariatric surgery. *Liver Transpl*. 2008;14:881–885.
5. Grimm IS, Schindler W, Haluszka O. Steatohepatitis and fatal hepatic failure after biliopancreatic diversion. *Am J Gastroenterol*. 1992;87:775–779.
6. Bennett JMH, Mehta S, Rhodes M. Surgery for morbid obesity. *Postgrad Med J*. 2007;83:8–15.
7. Tsai JH, Ferrell LD, Tan V, et al. Aggressive non-alcoholic steatohepatitis following rapid weight loss and/or malnutrition. *Mod Pathol*. 2017;30:834–842.
8. Mahawar KK. Liver dysfunction with both Roux-en-Y and one-anastomosis gastric bypass is almost exclusively seen with longer than standard limb lengths. *Obes Surg*. 2018;28:548–549.
9. Eilenberg M, Langer FB, Beer A, et al. Significant liver-related morbidity after bariatric surgery and its reversal—a case series. *Obes Surg*. 2018;28:812–819.
10. Addeo P, Cesaretti M, Anty R, et al. Liver transplantation for bariatric surgery-related liver failure: a systematic review of a rare condition. *Surg Obes Relat Dis*. 2019;15:1394–1401.
11. Keleidari B, Mahmoudieh M, Gorgi K, et al. Hepatic failure after bariatric surgery: a systematic review. *Hepat Mon*. 2019;19:e86078.
12. Wendon J, Cordoba J, Dhawan A, et al. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. *J Hepatol*. 2017;66:1047–1081.
13. Arterburn DE, Courcoulas AP. Bariatric surgery for obesity and metabolic conditions in adults. *BMJ*. 2014;349:g3961.
14. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA*. 2004;292:1724–1737.
15. Wolfe BM, Kvach E, Eckel RH. Treatment of obesity: weight loss and bariatric surgery. *Circ Res*. 2016;118:1844–1855.
16. Billeter AT, Fischer L, Wekerle A-L, et al. Malabsorption as a therapeutic approach in bariatric surgery. *Viszeralmedizin*. 2014;30:198–204.
17. Angrisani L. 2014: The year of the sleeve supremacy. *Obes Surg*. 2017;27:1626–1627.
18. The Dutch Institute for Clinical Auditing (DICA). Jaarrapportage DATO; 2017.
19. Schroeder R, Harrison TD, McGraw SL. Treatment of Adult Obesity with Bariatric Surgery. *Am Fam Physician*. 2016;93:31–37.
20. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet*. 2015;386:964–973.
21. Ikramuddin S, Korner J, Lee WJ, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the

Diabetes Surgery Study randomized clinical trial. *JAMA*. 2013;309:2240–2249.
22. Kothari SN, Borgert AJ, Kallies KJ, et al. Long-term (>10-year) outcomes after laparoscopic Roux-en-Y gastric bypass. *Surg Obes Relat Dis*. 2017;13:972–978.
23. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med*. 2007;357:753–761.
24. Sjöström L, Narbro K, Sjöström CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med*. 2007;357:741–752.
25. Villamere J, Gebhart A, Vu S, et al. Utilization and outcome of laparoscopic versus robotic general and bariatric surgical procedures at Academic Medical Centers. *Surg Endosc*. 2015;29:1729–1736.
26. Nguyen NT, Nguyen B, Shih A, et al. Use of laparoscopy in general surgical operations at academic centers. *Surg Obes Relat Dis*. 2013;9:15–20.
27. Lassailly G, Caiazzo R, Ntandja-Wandji LC, et al. Bariatric surgery provides long-term resolution of nonalcoholic steatohepatitis and regression of fibrosis. *Gastroenterology*. 2020;159:1290–1301.e5.
28. Lassailly G, Caiazzo R, Buob D, et al. Bariatric surgery reduces features of nonalcoholic steatohepatitis in morbidly obese patients. *Gastroenterology*. 2015;149:379–388; quiz e15-6.
29. Salman AA, Sultan AAEA, Abdallah A, et al. Effect of weight loss induced by laparoscopic sleeve gastrectomy on liver histology and serum adipokine levels. *J Gastroenterol Hepatol*. 2020;35:1769–1773.
30. Dixon JB, Bhathal PS, Hughes NR, et al. Nonalcoholic fatty liver disease: Improvement in liver histological analysis with weight loss. *Hepatology*. 2004;39:1647–1654.
31. Kalinowski P, Paluszkiewicz R, Ziarkiewicz-Wróblewska B, et al. Liver function in patients with nonalcoholic fatty liver disease randomized to roux-en-y gastric bypass versus sleeve gastrectomy: a secondary analysis of a randomized clinical trial. *Ann Surg*. 2017;266:738–745.
32. Cherla DV, Rodriguez NA, Vangoitsenhoven R, et al. Impact of sleeve gastrectomy and Roux-en-Y gastric bypass on biopsy-proven non-alcoholic fatty liver disease. *Surg Endosc*. 2020;34:2266–2272.
33. Singh D, Laya AS, Clarkston WK, et al. Jejunoileal bypass: a surgery of the past and a review of its complications. *World J Gastroenterol*. 2009;15:2277–2279.
34. Lupoli R, Lembo E, Saldalamacchia G, et al. Bariatric surgery and long-term nutritional issues. *World J Diabetes*. 2017;8:464–474.
35. Mechanick JI, Youdim A, Jones DB, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Obesity (Silver Spring)*. 2013;21(suppl 1):S1–S27.
36. Heelkunde NVV. Richtlijn Morbide Obesitas. 2011.
37. Lammers WJ, van Tilburg AJ, Apers JA, et al. Liver failure caused by prolonged state of malnutrition following bariatric surgery. *World J Hepatol*. 2018;10:396–399.
38. Kermansaravi M, Abdolhosseini MR, Kabir A, et al. Severe hypoalbuminemia and steatohepatitis leading to death in a young vegetarian female, 8 months after mini gastric bypass: a case report. *Int J Surg Case Rep*. 2017;31:17–19.
39. Nicoletti CF, Morandi Junqueira-Franco MV, dos Santos JE, et al. Protein and amino acid status before and after bariatric surgery: a 12-month follow-up study. *Surg Obes Relat Dis*. 2013;9:1008–1012.
40. Sgambato D, Cotticelli G, de Sio I, et al. Liver failure in an obese middle-aged woman after biliointestinal bypass. *World J Clin Cases*. 2013;1:52–55.
41. Nishi H, Yamanaka D, Kamei H, et al. Importance of serum amino acid profile for induction of hepatic steatosis under protein malnutrition. *Sci Rep*. 2018;8:5461.
42. Marsman HA, Heger M, Kloek JJ, et al. Reversal of hepatic steatosis by omega-3 fatty acids measured non-invasively by (1) H-magnetic resonance spectroscopy in a rat model. *J Gastroenterol Hepatol*. 2011;26:356–363.
43. Marsman HA, Heger M, Kloek JJ, et al. Omega-3 fatty acids reduce hepatic steatosis and consequently attenuate ischemia-reperfusion injury following partial hepatectomy in rats. *Dig Liver Dis*. 2011;43:984–990.
44. Caballero VJ, Mendieta JR, Lombardo D, et al. Liver damage and caspase-dependent apoptosis is related to protein malnutrition in mice: effect of methionine. *Acta Histochem*. 2015;117:126–135.
45. Van Herck MA, Vonghia L, Francque SM. Animal models of nonalcoholic fatty liver disease—a starter's guide. *Nutrients*. 2017;9:1072.
46. Stephenson K, Kennedy L, Hargrove L, et al. Updates on dietary models of nonalcoholic fatty liver disease: current studies and insights. *Gene Expr*. 2018;18:5–17.
47. Zeisel SH, Da Costa KA, Franklin PD, et al. Choline, an essential nutrient for humans. *FASEB J*. 1991;5:2093–2098.
48. Mazidi M, Katsiki N, Mikhailidis DP, et al. Adiposity may moderate the link between choline intake and non-alcoholic fatty liver disease. *J Am Coll Nutr*. 2019;38:633–639.
49. Yoshida N, Kitahama S, Yamashita T, et al. Metabolic alterations in plasma after laparoscopic sleeve gastrectomy. *J Diabetes Investig*. 2021;12:123–129.
50. Troseid M, Hov JR, Nestvold TK, et al. Major increase in microbiota-dependent proatherogenic metabolite TMAO one year after bariatric surgery. *Metab Syndr Relat Disord*. 2016;14:197–201.
51. Reiniers MJ, van Golen RF, van Gulik TM, et al. Reactive oxygen and nitrogen species in steatotic hepatocytes: a molecular perspective on the pathophysiology of ischemia-reperfusion injury in the fatty liver. *Antioxid Redox Signal*. 2014;21:1119–1142.
52. Mehedint MG, Zeisel SH. Choline's role in maintaining liver function: new evidence for epigenetic mechanisms. *Curr Opin Clin Nutr Metab Care*. 2013;16:339–345.
53. Phillips WA, Webb KE Jr, Fontenot JP. Characteristics of threonine, valine and methionine absorption in the jejunum and ileum of sheep. *J Anim Sci*. 1979;48:926–933.
54. Mastrototaro L, Sponder G, Saremi B, et al. Gastrointestinal methionine shuttle: priority handling of precious goods. *IUBMB Life*. 2016;68:924–934.
55. Hegazy E, Schwenk M. Choline uptake by isolated enterocytes of guinea pig. *J Nutr*. 1984;114:2217–2220.
56. Horie A, Ishida K, Watanabe Y, et al. Membrane transport mechanisms of choline in human intestinal epithelial LS180 cells. *Biopharm Drug Dispos*. 2014;35:532–542.
57. Karmali S, Johnson Stoklossa C, Sharma A, et al. Bariatric surgery: a primer. *Can Fam Physician*. 2010;56:873–879.
58. Ulker İ, Yildiran H. The effects of bariatric surgery on gut microbiota in patients with obesity: a review of the literature. *Biosci Microbiota Food Health*. 2019;38:3–9.
59. Wallace TC, Blusztajn JK, Caudill MA, et al. Choline: the underconsumed and underappreciated essential nutrient. *Nutr Today*. 2018;53:240–253.
60. Shen N, Caixàs A, Ahlers M, et al. Longitudinal changes of microbiome composition and microbial metabolomics after surgical weight loss in individuals with obesity. *Surg Obes Relat Dis*. 2019;15:1367–1373.
61. Ciobârcă D, Cătoi AF, Copăescu C, et al. Bariatric surgery in obesity: effects on gut microbiota and micronutrient status. *Nutrients*. 2020;12:235.
62. Romano KA, Vivas EI, Amador-Noguez D, et al. Intestinal microbiota composition modulates choline bioavailability from diet and accumulation of the proatherogenic metabolite trimethylamine-N-oxide. *mBio*. 2015;6:e02481.
63. Komorniak N, Szczuko M, Kowalewski B, et al. Nutritional deficiencies, bariatric surgery, and serum homocysteine level: review of current literature. *Obes Surg*. 2019;29:3735–3742.
64. Kim YI, Miller JW, da Costa KA, et al. Severe folate deficiency causes secondary depletion of choline and phosphocholine in rat liver. *J Nutr*. 1994;124:2197–2203.
65. Andalib I, Shah H, Bal BS, et al. Breath hydrogen as a biomarker for glucose malabsorption after Roux-en-Y gastric bypass surgery. *Dis Markers*. 2015;2015:102760.

66. Dukowicz AC, Lacy BE, Levine GM. Small intestinal bacterial overgrowth: a comprehensive review. *Gastroenterol Hepatol (N Y)*. 2007;3:112–122.
67. Lagathu C, Bastard JP, Auclair M, et al. Chronic interleukin-6 (IL-6) treatment increased IL-6 secretion and induced insulin resistance in adipocyte: prevention by rosiglitazone. *Biochem Biophys Res Commun*. 2003;311:372–379.
68. Utzschneider KM, Kahn SE. Review: The role of insulin resistance in nonalcoholic fatty liver disease. *J Clin Endocrinol Metab*. 2006;91:4753–4761.
69. Lefere S, Hoorens A, Raevens S, et al. Refractory subacute steatohepatitis after biliopancreatic diversion. *Hepatology*. 2017; 66:289–291.
70. Urdaneta V, Casadesús J. Interactions between bacteria and bile salts in the gastrointestinal and hepatobiliary tracts. *Front Med (Lausanne)*. 2017;4:163.
71. Bures J, Cyrany J, Kohoutova D, et al. Small intestinal bacterial overgrowth syndrome. *World J Gastroenterol*. 2010; 16:2978–2990.
72. Drenick EJ, Fisler J, Johnson D. Hepatic steatosis after intestinal bypass–prevention and reversal by metronidazole, irrespective of protein-calorie malnutrition. *Gastroenterology*. 1982;82:535–548.
73. Andersen T, Gluud C, Franzmann MB, et al. Hepatic effects of dietary weight loss in morbidly obese subjects. *J Hepatol*. 1991;12:224–229.
74. Verna EC, Berk PD. Role of fatty acids in the pathogenesis of obesity and fatty liver: impact of bariatric surgery. *Semin Liver Dis*. 2008;28:407–426.
75. Jaworski K, Sarkadi-Nagy E, Duncan RE, et al. Regulation of triglyceride metabolism. IV. Hormonal regulation of lipolysis in adipose tissue. *Am J Physiol Gastrointest Liver Physiol*. 2007;293: G1–G4.
76. Lee WJ, Ser KH, Lee YC, et al. Laparoscopic Roux-en-Y vs. mini-gastric bypass for the treatment of morbid obesity: a 10-year experience. *Obes Surg*. 2012;22:1827–1834.
77. Cardoso AR, Kakimoto PA, Kowaltowski AJ. Diet-sensitive sources of reactive oxygen species in liver mitochondria: role of very long chain acyl-CoA dehydrogenases. *PLoS One*. 2013;8:e77088.
78. Csak T, Ganz M, Pespisa J, et al. Fatty acid and endotoxin activate inflammasomes in mouse hepatocytes that release danger signals to stimulate immune cells. *Hepatology*. 2011; 54:133–144.
79. Castillo J, Fabrega E, Escalante CF, et al. Liver transplantation in a case of steatohepatitis and subacute hepatic failure after biliopancreatic diversion for morbid obesity. *Obes Surg*. 2001;11:640–642.
80. Auclair M, Martel G, Lapointe R. Successful orthotopic liver transplantation after biliopancreatic diversion with duodenal switch. *Surg Obes Relat Dis*. 2013;9:e46–e48.
81. Scopinaro N, Adami GF, Marinari GM, et al. Biliopancreatic diversion. *World J Surg*. 1998;22:936–946.
82. Scopinaro N, Gianetta E, Civalleri D, et al. Bilio-pancreatic bypass for obesity: II. Initial experience in man. *Br J Surg*. 1979;66:618–620.
83. Andersen T, Juhl E, Quaade F. Fatal outcome after jejunoileal bypass for obesity. *Am J Surg*. 1981;142:619–621.
84. Mason EE, Ito C. Gastric bypass. *Ann Surg*. 1969;170:329–339.
85. Seeras K, Acho RJ, Lopez PP. Roux-en-Y Gastric Bypass Chronic Complications. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing StatPearls Publishing LLC; 2022.
86. Colquitt JL, Picot J, Loveman E, et al. Surgery for obesity. *Cochrane Database Syst Rev*. 2009;2:Cd003641.
87. Schauer PR, Ikramuddin S, Gourash W, et al. Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. *Ann Surg*. 2000;232:515–529.
88. Cotler SJ, Vitello JM, Guzman G, et al. Hepatic decompensation after gastric bypass surgery for severe obesity. *Dig Dis Sci*. 2004;49:1563–1568.
89. Marszalek R, Ziemianski P, Lagiewska B, et al. The first Polish liver transplantation after Roux-en-Y gastric bypass surgery for morbid obesity: a case report and literature review. *Ann Transplant*. 2015;20:112–115.
90. Brolin RE, Bradley LJ, Taliwal RV. Unsuspected cirrhosis discovered during elective obesity operations. *Arch Surg*. 1998; 133:84–88.
91. Rutledge R. The mini-gastric bypass: experience with the first 1,274 cases. *Obes Surg*. 2001;11:276–280.
92. Robert M, Espalieu P, Pelascini E, et al. Efficacy and safety of one anastomosis gastric bypass versus Roux-en-Y gastric bypass for obesity (YOMEGA): a multicentre, randomised, open-label, non-inferiority trial. *Lancet*. 2019;393:1299–1309.
93. Motamedi MAK, Rakhshani N, Khalaj A, et al. Biopsy-proven progressive fatty liver disease nine months post mini-gastric bypass surgery: a case study. *Int J Surg Case Rep*. 2017;39:168–171.
94. Rutledge R, Walsh TR. Continued excellent results with the mini-gastric bypass: six-year study in 2410 patients. *Obes Surg*. 2005;15:1304–1308.
95. Wang W, Wei PL, Lee YC, et al. Short-term results of laparoscopic mini-gastric bypass. *Obes Surg*. 2005;15:648–654.
96. Mahawar KK, Carr WR, Balupuri S, et al. Controversy surrounding 'mini' gastric bypass. *Obes Surg*. 2014;24:324–333.
97. Alexandrou A, Davis PA, Law S, et al. Esophageal cancer in patients with a history of distal gastrectomy. *Arch Surg*. 2002; 137:1238–1242.
98. Motamedi MAK, Barzin M, Ebrahimi M, et al. Severe fatal protein malnutrition and liver failure in a morbidly obese patient after mini-gastric bypass surgery: case report. *Int J Surg Case Rep*. 2017;33:71–74.
99. Anderson B, Gill RS, de Gara CJ, et al. Biliopancreatic diversion: the effectiveness of duodenal switch and its limitations. *Gastroenterol Res Pract*. 2013;2013:974762.
100. Nguyen NT, Varela JE. Bariatric surgery for obesity and metabolic disorders: state of the art. *Nat Rev Gastroenterol Hepatol*. 2017;14:160–169.
101. Angrisani L, Santonicola A, Iovino P, et al. Bariatric surgery worldwide 2013. *Obes Surg*. 2015;25:1822–1832.
102. Baltasar A, Serra C, Perez N, et al. Clinical hepatic impairment after the duodenal switch. *Obes Surg*. 2004;14:77–83.
103. Aasheim ET, Frigstad SO, Sovik TT, et al. Hyperinsulinemic hypoglycemia and liver cirrhosis presenting after duodenal switch: a case report. *Surg Obes Relat Dis*. 2010;6:441–443.
104. Baltasar A. Liver failure and transplantation after duodenal switch. *Surg Obes Relat Dis*. 2014;10:e93–e96.
105. Mocanu ICS, Costa P, Palma R. Liver failure after bariatric surgery—clinical case and literature review. *J Gastroenterol Metabol*. 2018;1:104.
106. Rodriguez Silva C, Fernandez Aguilar JL, Sanchez Perez B, et al. Acute liver failure secondary to bariatric surgery: An indication for liver transplantation. *Cir Esp*. 2016;94:113–114.
107. Langdon DE, Leffingwell T, Rank D. Hepatic failure after biliopancreatic diversion. *Am J Gastroenterol*. 1993;88:321.
108. Patton H, Heimbach J, McCullough A. AGA clinical practice update on bariatric surgery in cirrhosis: expert review. *Clin Gastroenterol Hepatol*. 2021;19:436–445.