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REVIEW

# Surgical treatment of nonalcoholic fatty liver disease in severely obese patients

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**Abstract:** Obesity is a multi-organ system disease with underlying metabolic abnormalities and chronic systemic inflammation. Nonalcoholic fatty liver disease (NAFLD) is a hepatic manifestation of obesity metabolic dysfunction and its associated cardiovascular- and liver-related morbidities and mortality. Our current understanding of NAFLD pathogenesis, disease characteristics, the role of insulin resistance, chronic inflammation, gut–liver and gut–brain crosstalk and the effectiveness of pharmacotherapy is still evolving. Bariatric surgery significantly improves metabolic and NAFLD histology in severely obese patients, although its positive effects on fibrosis are not universal. Bariatric surgery benefits NAFLD through its metabolic effect on insulin resistance, inflammation, and insulinotropic and anorexinogenic gastrointestinal hormones. Further studies are needed to understand the natural course of NAFLD in severely obese patients and the role of weight loss surgery as a primary treatment for NAFLD.

**Keywords:** NAFLD, severe obesity, bariatric surgery

## Introduction

Nonalcoholic fatty liver disease (NAFLD) occurs in both the young and old as well as in every ethnic population group.[1] It is quickly becoming a world health problem as a function of the rise in obesity and as the relationship between NAFLD and obesity is recognized.[2] NAFLD in obese patients is a frequent metabolic dysfunction with significant associated comorbidities. The incidence of NAFLD in the general population is variable, with a reported prevalence between 6% and 51%.[3] In patients with obesity, NAFLD incidence is between 24%–98%.[4] NAFLD patients have increased overall risk of death relative to the general population,[5] with cardiovascular disease as the most common cause of death.[6] The cardiac risks are predictable, considering the powerful association of NAFLD with metabolic syndrome (MS), and inflammation with atherosclerosis.[5,7,8] NAFLD also has liver-related complications such as progression to cirrhosis and hepatocellular carcinoma.[9] Once progression to nonalcoholic steatohepatitis (NASH) develops, there is a 4%–27% risk of cirrhosis over 10 years with a 12% risk of liver-related death.[10] Currently, NAFLD is the number one cause of liver function abnormalities and chronic liver disease in adults.[11] It is predicted to be the most common indication for liver transplantation over the next 10 years, making it an impending public health crisis of the century. Since obesity is a multi-organ system disease with chronic relapsing characteristics, NAFLD disease course is likely to follow the metabolic profile of obesity, necessitating a multidisciplinary approach combining lifestyle modifications with weight reduction, medications, and bariatric

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surgery. Early diagnosis and aggressive treatment of NAFLD is therefore indicated because of the associated morbidities. Severely obese patients are particularly at risk for liver-related mortality and should be the focus of treatment strategies for fatty liver disease. This article will provide a brief review of the underlying pathogenesis and current medical treatment as the background for an update on the current role of weight loss surgery on the outcome of NAFLD.

## Obesity and MS

The epidemic of obesity has now become a global health issue. In the United States alone, the 2012 population data show that 32% of adults are overweight with 34.9% of adults considered to be obese.[12] The prevalence did not differ between men and woman. The highest percentage of obesity was seen in the non-Hispanic black population with 47.8% being classified as obese. Current definitions for obesity are based on overall body mass index (BMI). The World Health Organization (WHO) defines obesity as BMI $\geq$30 kg/m$^2$. Obesity is further classified as Class I: BMI 30–34.9 kg/m$^2$, Class II: BMI 35–39.9 kg/m$^2$, and Class III: BMI $\geq$40 kg/m$^2$. Morbidly or severely obese patients have a BMI $\geq$40 kg/m$^2$. Currently, 6.6% of the US population is considered to be severely obese.[13] National Institutes of Health BMI criteria for weight loss surgery are BMI $>$40 kg/m$^2$ or $\geq$35 kg/m$^2$ with one obesity-related comorbidity, such as fatty liver disease. Most of the complications of obesity are related to the associated MS. A review of MS can be found in many excellent in-depth articles.[14,15] Briefly, MS is defined by the Adult Treatment Panel III[14] or the International Diabetes Federation Task Force[16] as the presence of three or more components of 1) severe obesity, central obesity by waist circumference, 2) type 2 diabetes mellitus, insulin resistance (IR) measured by fasting serum insulin and glucose, 3) hypertension, and 4) dyslipidemia. MS is a known metabolic predictor of atherosclerosis and cardiovascular mortality risks,[17] placing obese patients at an increased hazard ratio for all causes of mortality.[18] MS has the central features of IR, visceral adiposity, dyslipidemia, endothelial dysfunction, hypercoagulability, chronic stress, and hypercortisolism. These global pathologic changes lead to an increased risk for diabetes mellitus, hypertension, dyslipidemia, ischemic heart disease, cerebrovascular disease, and liver disease. The underlying causes are not clear but excess visceral fat, adipocyte dysfunction, chronic low-grade inflammation, and genetic predisposition have been invoked. Because of the strong association between MS and NAFLD, NAFLD is considered to be part of the spectrum of obesity-related metabolic dysfunctions.[19]

## NAFLD

NAFLD is seen in 24% of the adult population.[20] This figure rises to 74% in severely obese adult patients.[21] NAFLD describes a spectrum of hepatic conditions ranging from simple steatosis (defined as hepatic fat infiltration in $>$5% of the liver), to the inflammatory form of NAFLD or steatohepatitis (also called NASH) characterized by hepatic inflammation, necrosis, and hepatocyte ballooning, with or without fibrosis. NASH is associated with the risks for progression to end-stage cirrhosis and liver failure.[22] The American Association for the Study of Liver Disease has proposed three classifications for NAFLD: 1) nonalcoholic fatty liver or simple steatosis without inflammation; 2) NASH, the advanced form of NAFLD, and 3) borderline NASH.[22] When diagnosing NAFLD in obesity, other causes of fatty liver need to be excluded such as viral, infectious, drugs, toxins, autoimmune, and metabolic conditions (eg, cystic fibrosis, Wilson's disease). A careful social history must be taken to exclude excessive alcohol consumption ($>$10 g of ethanol per day) as a cause of steatosis.[23]

Several histological grading systems for NAFLD based on liver biopsy have been developed, with the Brunt[24] and the NASH–Clinical Research Network Activity Score (NAS)[25] being the main cataloging systems. NAS classification relies on individual histologic scores of steatosis, inflammation, and hepatocyte ballooning. The more widely used Brunt grading and staging system classifies steatohepatitis into one of three categories: mild, moderate, or severe[24] with a four-score staging system for fibrosis: perisinusoidal fibrosis (stage 1), periportal fibrosis (stage 2), bridging fibrosis (stage 3), and cirrhosis (stage 4).

Clinically, NAFLD is difficult to diagnose. The majority of patients are asymptomatic. However, some patients may complain of malaise, right upper quadrant abdominal pain, or hepatomegaly. Many of the clinical evaluations are undertaken in the absence of symptoms because of incidental abnormal liver function tests, especially alanine transaminase (ALT).[26,27] Normal liver function tests, however, cannot be used exclusively to diagnose NAFLD, nor to rule out advanced NAFLD.[28] Unfortunately, the progression of fatty liver disease is sometimes only apparent after the signs and symptoms of cirrhosis have already developed.

Noninvasive imaging techniques such as abdominal ultrasound, computed tomography, and magnetic resonance imaging can detect steatosis, although a negative test cannot rule out more advanced NAFLD.[26,29]

Diagnostic panels including FibroTest, NAFLD fibrosis score based on many variables such as age, BMI,

hyperglycemia, platelet count, albumin, and aspartate aminotransferase/alanine transaminase ratio; and diagnostic biomarkers such as proinflammatory molecules, apoptosis-associated cytokeratin 18 fragments, and microRNA,[30] have been advocated, but not universally accepted for a noninvasive identification of NAFLD patients with bridging fibrosis and or cirrhosis.[31] Liver biopsy remains the gold standard for the diagnosis and the staging of NAFLD and NASH.[1] Because of the cost, invasiveness, and morbidity of the procedure, it is not practical to perform a liver biopsy on all at-risk patients. Currently, there are no definitive guidelines to screen, image, or biopsy patients for NAFLD diagnosis. A liver biopsy should be considered in patients who are at an increased risk for having steatohepatitis and advanced fibrosis,[22] such as individuals with obesity, MS, and persistently abnormal liver chemistries.

## Pathogenesis: obesity and NAFLD

The pathogenesis of NAFLD has been aggressively researched but remains incompletely understood. IR and MS are most commonly associated with NAFLD. Because of the powerful association between MS and NAFLD, NAFLD is considered to be a manifestation of MS. Many recent articles have provided in-depth reviews of NAFLD molecular pathways.[32–34] Research has centered on the relationship between three cell types: adipocytes, hepatocytes, and the intestinal epithelial cells. There are two proposed organ system interactions underlying NAFLD during obesity: the fat–liver interaction and the gut–liver interaction.

The fat–liver axis involves pathologic changes and adaptations of the hypertrophied fat-laden adipocytes during obesity and the development of IR. During obesity, adipocytes acquire a new proinflammatory molecular signature and abnormal free fatty acid release.[35] Free fatty acids activate stress kinases such as c-Jun NH2 terminal kinase (JNK), which, in concert with proinflammatory cytokines, cause derangement in the insulin-signaling pathway in adipocytes and hepatocytes.[36–38] These pathways impair pancreatic endocrine cell function to further exacerbate IR. Both the stress kinases and hyperinsulinemia additionally cause abnormal responses of hepatic lipogenic transcription factors, leading to excess gluconeogenesis, de novo lipid synthesis, and abnormal lipid transport.[39,40] Lipid burden in hepatocytes induces cellular production of oxygen-free radicals. Oxidative stress activates JNK, perpetuates IR, induces mitochondrial and endoplasmic reticulum stress, cell death, and injures hepatocytes.[41] Inflammation and phagocytosis of apoptotic hepatocytes by macrophage results in the activation of hepatic stellate cells into myofibroblast-like cells to initiate a profibrogenic response.[42]

Pathologies underlying obesity and NAFLD may be more complicated than simple abnormal fat–liver interactions. The second proposed mechanism of NAFLD development in obesity relates to the gut–liver crosstalk. The gut is a large lymphoid organ with an active, diverse bacterial microflora. This microflora supports intestinal metabolic, digestive, hormonal, and trophic activities. It also interacts with the host immune response to pathogens. With obesity, increased consumption of fructose and lipids also alters the microbiota of the gut. It has been shown that patients with NAFLD have increased intestinal permeability and small intestinal bacterial overgrowth.[43] As the first organ responder to bacterial translocation, the liver innate immune response and hepatic inflammation are induced,[44] furthering hepatic IR.

Additional intestinal molecular pathways are regulated by bile acids and gut peptides such as incretins (glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide). Incretins[45] are nutrient sensors with diverse effects on cardiovascular function, satiety, gastric emptying, insulin production, and glucagon release to affect hepatic IR and lipid metabolism.[46,47] As major ligands for G-protein-coupled receptor Transforming Growth Factor 5, bile acids indirectly activate GLP-1 to improve insulin sensitivity. Bile acids also bind to lipid-sensing nuclear hormone receptors such as farnesoid X receptor to modulate hepatic cholesterol, lipoprotein, and glucose metabolism.[48]

More recently, non-coding RNA molecules known as microRNA involved in the regulation of gene transcription have been linked to the pathogenesis, progression, and severity of NAFLD through their effects in cell growth, apoptosis, and inflammation as well as lipid and fatty acid metabolism, suggesting that they can be used as biomarkers or as targets for therapy.[49] Consistent with this, visceral fat from morbidly obese patients has been shown to have a signature profile of microRNA which correlates with the severity of NAFLD.[50,51]

## Management of NAFLD

### Pharmacologic

Nonoperative management of fatty liver disease has centered on the treatment of obesity and of the individual components of MS. Encouraging results have been obtained with lifestyle modifications in obese patients with fatty liver disease and the mainstay of treatment for steatosis remains weight reduction. Eckard et al have shown that diets low in fat or processed carbohydrates and moderate exercise can be effective in

improving steatosis in NAFLD as shown by follow-up liver biopsy.[52] Current recommendations call for a loss of 5% of excess weight for steatosis and a 10% excess weight loss for NASH,[53] but long-term compliance is problematic and the effectiveness of weight loss for NASH is inconclusive.[54–56] Lifestyle modifications have not been shown to be a reliable long-term management strategy in the treatment of obesity for the majority of individuals.[57]

Since steatosis has been considered to be a benign, non-progressive disease, pharmacologic or invasive interventions are not indicated. The treatment of NASH has focused on a variety of modalities including lifestyle modification, and pharmacologic and surgical interventions. No current cure for NASH exists, but many studies have investigated pharmacotherapy for the treatment of the IR and hyperlipidemia components of MS to alter the course of NASH. Several pharmacologic treatments such as orlistat,[58] pioglitazone,[59] metformin,[60] atorvastatin,[61] ursodiol,[61] vitamin E,[62] omega-3 fatty acids,[63] and many others have been proposed. Improvements in liver biopsy findings have been demonstrated with pioglitazone, rosiglitazone, atorvastatin, and ursodiol. However, these therapies have associated pharmacologic adverse effects and the efficacies have not been consistently reproduced in clinical trials,[64,65] putting in question their role as definitive treatment for NASH. Integrative analyses of obesity-associated molecular pathways are being actively pursued toward identification of genetic, transcriptomic, and proteonomic signatures to provide drug-based interventions.[66] With insufficient general acceptance for NASH pharmacologic treatment, weight reduction through bariatric surgery is increasingly used as a therapeutic modality to improve the metabolic dysfunction with secondary gain on improving NASH. It is worth noting that the lipostatic model of body mass regulation postulates that each individual has a central set-point for hunger and energy balance.[67] This may account for weight gain recidivism after the initial successful weight loss in some bariatric patients with long-term follow-up.[68] It follows that some obese patients may benefit from multipronged weight loss approaches incorporating bariatric procedures with maintenance pharmacotherapeutics such as GLP-1 analogs to sustain long-term weight loss and metabolic benefits.

## Bariatric surgery

Bariatric surgery is currently indicated for severely obese individuals with a BMI >40 kg/m$^2$ or with a BMI ≥35 kg/m$^2$ and obesity-related comorbid conditions. Weight loss by bariatric surgery is effective in improving and/or resolving metabolic abnormalities with up to a 40% reduction in long-term obesity-related morbidity.[69] With a causal link established between NAFLD and the obesity-related MS, bariatric surgery interventions promoting weight loss would be expected to improve NAFLD. No randomized controlled studies have been performed to specifically examine the efficacy of bariatric surgery as a primary indication for the treatment of NAFLD, but several studies have been published addressing NAFLD as a secondary outcome of bariatric surgery. A meta-analysis of 21 studies examining the effect of surgery on NAFLD in morbidly obese patients reported significant improvement or resolution of steatosis (92%), NASH histology (82%), and fibrosis (66%).[70] Because progression of fibrosis has been noted in some patients, the article concluded that bariatric surgery impact on NASH disease course remains to be proven. A recent review of the bariatric literature provided similar findings of consistent histological improvement in steatosis, inflammation, and fibrosis following weight loss, but with new onset or progression of NASH or of hepatic fibrosis in some patients.[71] The American College of Gastroenterology, the American Gastroenterological Association, and the American Association for the Study of Liver Diseases published the consensus statement that while bariatric surgery is not contraindicated in otherwise eligible obese patients with NAFLD, it is not an "established option for NASH treatment."[22] Concerns about progression of NAFLD to cirrhosis described in patients undergoing jejunoileal bypass[72,73] or with rapid weight loss following bariatric surgery[74,75] provide the additional rationale for the position that the safety and efficacy of bariatric surgery in patients with established cirrhosis are not proven. It is worth mentioning that a prospective study of 1,775 bariatric patients with a matched medical cohort reported sustained improvement in liver function enzymes following bariatric surgery at 2 and 10 years of follow-up.[76] In the absence of long-term follow-up for liver-related comorbidities, the current disease course assessment for NAFLD has been limited to short term follow up of liver histology evaluation as a primary outcome. We conducted a review of the published bariatric reports using liver biopsy as the gold standard to diagnose and evaluate NAFLD. Most of the publications are retrospective analyses with many confounding biases, small sample size, lack of sequential systematic follow-up biopsies, variable methodologies for reporting histological features, and scant information on patient selection criteria and associated metabolic data. With these limitations in mind, the effect of the different bariatric surgical techniques: 1)

restrictive or 2) restrictive and malabsorptive procedures on NAFLD histology are summarized below with highlights on articles of particular interest.

### Restrictive

The restrictive procedures reduce the stomach volume and thereby, caloric intake. A 2009 prospective study by Mathurin et al described 381 consecutive patients with initial liver biopsy at the time of bariatric surgery, of which 56% underwent gastric banding.[77] The majority of the patients underwent planned follow-up liver biopsies at 1-year (85% patients) and 5-year (81% patients).[77] Substantial weight loss and improvement in metabolic parameters were achieved. The global NAS scores, the individual steatosis and ballooning degeneration scores and the incidence of NASH all significantly improved. The inflammation and fibrosis NAS scores were unchanged, although 96% of the patients had low fibrosis scores of ≤1 (no fibrosis or focal fibrosis), and fibrosis improved in 80% of the patients. At 1 and 5 years, 4/258 patients and 2/203 patients with underlying fibrosis progressed to bridging fibrosis. No patient developed de novo bridging fibrosis except for a patient with alcoholic abuse. Patients with persistent IR were more likely to have less favorable evolution of their hepatic disease.

A retrospective analysis by Luyckx et al reviewed 69/528 vertical gastroplasty patients who had paired liver biopsies within an average of 3 years of the initial gastroplasty biopsies.[21] Steatosis significantly improved. Perisinusoidal inflammation worsened in 26% with 88% characterized as mild and 13% as moderate disease. Stratopoulous et al's retrospective evaluation of 51/216 gastroplasty patients with baseline and subsequent liver biopsies at an average of 18 months[78] showed regression of NASH, and marked improvement in steatosis, inflammation, and fibrosis; with unchanged fibrosis in 41% but worse fibrosis in 12% (six patients). Dixon et al reported 60 patients with follow-up biopsies showing consistent lower histologic NAS scores in steatosis, inflammation, and fibrosis with 80% resolution of NASH and 13% stable disease in the 30 patients with baseline NASH.[79] No liver disease progression was noted.

### Malabsorptive/restrictive

Two malabsorptive/restrictive procedures, the biliopancreatic diversion with duodenal switch (BPD-DS) as well as the Roux-en-Y gastric bypass (RYGB) capitalize on caloric intake reduction from the restrictive component of the procedure and nutrient malabsorption by diverting the flow of intestinal enzymes and ingested nutrition to enhance weight loss. Both surgical approaches have become widely accepted in the treatment of morbid obesity because they provide rapid and substantial weight reduction.

Significant responses in MS and its related pathologies have been demonstrated with the BPD-DS.[80] For example, diabetes is cured in over 90% of patients based on medication cessation. Reports of the effect of BPD-DS on NAFLD are limited. The available data come from two large studies by Kral et al in 2004 and Keshishian et al in 2005.[81,82] Kral et al prospectively studied 104/689 BPD-DS patients with follow-up liver biopsy at 41±25 months. Steatosis and fibrosis semiquantitative grading decreased with weight loss. Fibrosis increased in 42% of the patients, but mostly from grade 0 to 1. Three patients had new onset cirrhosis but they also had underlying biliary tract obstruction, alcohol abuse, and intractable diarrhea. Notably, cirrhosis was encountered in 11 or 2% of the patients at the time of BPD-DS. At an average of 112 months of follow-up, the remarkable finding was that improvement or regression of cirrhosis occurred in 9/11 patients. The remaining two patients continued to have disease progression, one with intractable diarrhea and pancreatitis and one with hemosiderosis. These data suggest that severely obese patients with compensated cirrhosis may benefit from weight loss procedures. Keshishian et al retrospectively evaluated 78/697 patients with follow-up liver biopsy between 6 and 36 postoperative months after BPD-DS.[82] NASH histology initially worsened with concurrent rise in liver function tests at 6 months but steadily improved at follow-up. The initial histological deterioration was attributed to the initial acute weight loss.

The majority of the literature assessing the effect of bariatric surgery on the course of NAFLD involves RYGB patients because it is the most commonly performed malabsorptive/restrictive procedure. Thirteen studies investigated the changes in liver histology after RYGB.[83–94] Four studies by Furuya et al,[90] Barker et al,[87] Tai et al,[95] and de Almeida et al[89] are worth mentioning because of the availability of planned paired biopsies. In Furuya et al's prospective study, 18 patients underwent repeat control percutaneous liver biopsies at 2 years post-surgery. Significant improvement of the metabolic parameters[90] paralleled lower overall NAS and fibrosis scores for all patients, with 75% regression of NASH and 50% regression of fibrosis, and no progression of disease in all patients. Similarly, Tai et al prospectively evaluated 21 patients with planned repeat liver biopsies at 1 year post-RYGB. Improvement in all histological categories was seen with no disease progression. Barker et al performed follow-up biopsies in 19 patients

with prior diagnosis of NASH after an average interval of 21 months. NASH resolved in 89% of the patients. One patient had mild worsening of fibrosis score from 0 to 1 with an additional patient having portal fibrosis score progression from stage 2 to stage 3.[87] In de Almeida's study, 16 patients with repeat liver biopsies at a median follow-up of 20 months after having been diagnosed with NASH from the initial biopsy had similar decreases in NAS scores in all categories. NASH regressed in 15/16 of the patients and improved in 1/16.[89]

Publications reporting post-surgical progression of hepatic fibrosis are worth mentioning. They were all retrospective RYGB studies where repeat biopsies were performed on a very small subset of prior bariatric patients because of the opportunities for biopsies at the time of reoperative surgery. A common theme is the overall improvement of metabolic results, steatosis, NASH parameters, and the lack of change in portal tract pathologies except for isolated cases of new onset or progression of liver fibrosis. In Mattar et al's study of 70/3,000 bariatric patients with repeat biopsies, the percentage of patients with grade 1 NASH increased from 26% to 50% on repeat biopsy at an average of 15 postoperative months.[85] In 91/613 of Silverman et al's liver rebiopsies at a postoperative average of 18 months, one patient had new perisinusoidal fibrosis, while fibrosis improved or regressed in the remaining patients.[83] Of the 16/557 RYGB patients with rebiopsies at 18 months in Csendes et al's report, one patient had progression from steatosis to pericellular fibrosis.[88] In Moretto et al's study of 78/644 RYGB patients,[93] baseline NASH histology regressed in 23/39 patients and fibrosis improved in 52% of patients at an average of 12 months after the first biopsy. Of note, 2/79 patients developed new onset fibrosis stage 1 and 2, and three patients progressed from stage 1 to stage 3 bridging fibrosis. Liu et al's report of 39 patients with repeat liver biopsies showed that NAS grading improved for all histological categories with 100% resolution of NASH.[91] Two patients had increased lobular inflammation from grade 1 to 2, and six patients developed new portal inflammation. In all of these studies, the basis for disease progression in the individual patients was not apparent.

In summary, while rigorous data are limited, the vast majority of bariatric patients have consistent improvement of steatosis, inflammation, and fibrosis and no disease progression, providing strong support for bariatric salutary effect on obesity-related NASH. For the majority of the few patients in whom inflammation or fibrosis worsened after restrictive bariatric surgery, the degree of histological changes was mild. Patient-specific factors such as rapid weight loss and loss of macronutrients, bacterial overgrowth, poor metabolic response to weight reduction, discordant results between the first and the repeat biopsies from sampling variability and interpretation error inherent to liver biopsies,[96] histological progression as the natural course of the fatty liver disease, procedure-related specific complications are all possible causes for disease progression that cannot be substantiated from the articles. Severely obese patients with NASH therefore should not be excluded from undergoing restrictive bariatric surgery to treat the underlying obesity and metabolic dysfunction because of the secondary gain in liver histologic improvement. Since simple steatosis is considered to be a benign histological finding, it does not meet the criterion as an indication for National Institutes of Health bariatric guidelines in patients with BMI $\geq$35 kg/m$^2$.

Due to BPD-DS's higher perioperative and postoperative morbidity, its underlying procedure-related risks for bacterial stasis from blind loop syndrome, (which may further exacerbate liver disease), and its potential association with an acute decline in NAFLD histology from drastic weight loss, this procedure should be used with caution in patients at risk for and/or in patients with advanced NAFLD. Quality prospective studies should be performed to definitively address the safety of BPD-DS in NAFLD patients.

## Potential mechanisms of bariatric surgery effect on NAFLD

The beneficial effects of bariatric surgery on metabolic dysfunction have redefined weight loss bariatric surgery as "metabolic surgery,"[97] with possible procedure-related differences in the degree of metabolic efficacy.[98] Its mechanisms are more complex than simple weight reduction from caloric restriction and malabsorption. Following bariatric surgery, the loss of excess body fat can enhance adipocyte function, improve IR and systemic inflammation to restore metabolic balance; and the alteration in the intestinal microenvironment can modify the course of NAFLD. The intestinal bypass procedures may have additional hormonal advantages such as alterations in gastrointestinal peptides with the net effect of promoting satiety and insulin sensitivity.

A 2004 meta-analysis study demonstrated an overall 61.2% reduction in excess body fat following restrictive or restrictive/malabsorptive procedures.[99] Since excess body fat has been linked to IR and MS, lower fat mass following

weight reduction in bariatric patients decreases lipid burden (as demonstrated by declines in circulating lipid profiles including fatty acids, low-density lipoprotein, triglycerides, and lipoprotein A levels)[100] and improves IR.[101] Similarly, systemic inflammation is attenuated as shown by favorable alteration in the profile of circulating proinflammatory and anti-inflammatory cytokines such as C-reactive protein, interleukin 6, interleukin 18, and tumor necrosis factor α,[102,103] or anti-atherogenic, anti-inflammatory, and anti-diabetogenic adiponectin[104] following gastric bypass.

In the intestines, changes in the microbiota[105] (such as increased Proteobacteria and reduced Firmicutes species)[106] favor a non-obesogenic profile, improve the energy profile, and heighten insulin sensitivity after bariatric surgery. Likewise, secondary increases in the levels of gut incretins GLP-1, glucose-dependent insulinotropic polypeptide, polypeptide YY, and oxyntomodulin in response to proximal intestinal exclusion and accelerated nutrient delivery to the distal intestines following RYGB can improve hepatic IR.[107,108] In the liver, GLP-1 promotes hepatic lipid export and oxidation, reduces hepatic proinflammatory cytokines, and decreases endoplasmic reticulum stress.[109] Along with anorexigenic ghrelin[110] and polypeptide YY,[111] GLP-1 has additional extraintestinal effects on the gut–brain axis[112] to regulate central satiety, and diminish hunger and food intake. The combinatorial effects of bariatric surgery in reducing fat mass, altering neurohormonal regulation of appetite, or favoring less obesogenic intestinal microbiota may help enhance insulin sensitivity and diminish systemic inflammation to improve NAFLD. Further studies are required to prove the underlying mechanisms.

## Conclusion

Morbid obesity has become a worldwide epidemic, bringing with it a multitude of metabolic abnormalities including NAFLD. Pharmacologic interventions for NAFLD targeting inflammation or IR remain unproven. Because of safety concerns, lack of consistent efficacy, and the requirement that patients are enrolled in clinical trials for drug eligibility, pharmacotherapy has limited practical clinical use. The role of bariatric surgery as a primary indication for NAFLD treatment has yet to be systematically studied. However, despite imperfect information, the preponderance of the data suggests that NASH improves following bariatric surgery, with an outcome closely linked to the metabolic end results. The benefits of bariatric surgery on the course of NASH are not universally consistent, calling for the need for quality longitudinal studies to better understand the natural history of NAFLD after bariatric surgery. Without long-term follow-up, the sustainability of these outcomes also remains unclear. Further information is needed on the safety and efficacy of specific procedure-related bariatric surgery in improving NASH histology in severely obese patients, with particular attention to the subset of patients who continues to have NAFLD disease progression. Additional studies are also needed to facilitate further understanding of the pathogenesis of NAFLD and the mechanisms of bariatric surgery effects on NAFLD. In the absence of effective noninvasive alternatives, bariatric surgery offered within the context of well-designed studies offers the most promise in the treatment of NAFLD in severely obese patients.

## Disclosure

The authors report no conflicts of interest in this work.

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