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Review article

Management of nonalcoholic fatty liver disease and the role of bariatric surgery: a brief review for surgeons

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Abstract Nonalcoholic fatty liver disease (NAFLD) is closely linked to the metabolic syndrome and is highly prevalent in bariatric patients. The criterion standard to diagnose NAFLD is a liver biopsy specifically to detect inflammatory changes characteristic of nonalcoholic steatohepatitis. Technologic advancements will improve the accuracy of current noninvasive modalities. Modification of risk factors via food management is important to prevent the progression of NAFLD to nonalcoholic steatohepatitis and cirrhosis. Several clinical trials are underway for pharmacologic treatment of NAFLD; currently the mainstay of treatment is insulin sensitizers and vitamin E. There is strong evidence bariatric surgery improves biochemical and histologic features of NAFLD and therefore, bariatric surgery should be considered as a treatment of NAFLD in patients with obesity. Gastric bypass exhibits antilipogenic, antiinflammatory, antioxidant, and antidiabetic properties in the livers of laboratory animals; thereby, providing a unique window to study regulation of body adiposity and insulin resistance. (Surg Obes Relat Dis 2020;16:699–703.) © 2020 American Society for Bariatric Surgery. Published by Elsevier Inc. All rights reserved.

Key words: Liver fibrosis; Cirrhosis; Inflammation; Oxidative stress; Lipid metabolism; Lipogenesis; Fatty acid oxidation; Diabetes; Metabolic syndrome; Insulin resistance; Insulin sensitivity; Guidelines

Nonalcoholic fatty liver disease (NAFLD) is excessive liver adiposity with a range of histologic abnormalities. At least 75 million Americans have NAFLD [1,2] and its worldwide prevalence of 25% to 45% far exceeds that of viral hepatitis C making it the second leading reason patients seek liver transplantation [2,3]. NAFLD is prevalent in >95% of patients who undergo bariatric surgery [4,5] and therefore an understanding of the pathogenesis and current treatment guidelines is paramount to bariatric surgeons.

Definition

The American Association for the Study of Liver Diseases defines NAFLD as radiographic or histologic evidence of fat accumulation in the absence of significant alcohol consumption or use of steatogenic medications [6]. Nonalcoholic fatty liver is the earliest form of NAFLD and is characterized by steatosis without hepatocellular injury. The hallmark of nonalcoholic steatohepatitis (NASH) is inflammatory infiltrates, hepatocyte injury, and fibrosis. Although NASH is clinically silent, it can progress to fibrosis and cirrhosis.

Risk factors

NAFLD disproportionately affects women, blacks, and Hispanics. A body mass index >30 mg/km^2 and metabolic

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Table 1
Independent risk factors for NAFLD

Female
Black
Hispanic
Body mass index >30 mg/km^2
Central obesity
Hypertension
Insulin resistance
Hypertriglyceridemia
Low HDL

NAFLD = nonalcoholic fatty liver disease; HDL = high-density lipoproteins.

syndrome are strong predictive risk factors for NAFLD (Table 1). Other conditions associated with NAFLD are polycystic ovary syndrome and obstructive sleep apnea [7].

Progression to NASH and cirrhosis

NAFLD is a progressive disease. In patients with early nonalcoholic fatty liver only 5% may develop cirrhosis. Once NASH ensues, 20% of patients may progress to cirrhosis [1], of whom at least 80% will have either no improvement or worsening disease. It follows that interventions should be undertaken to halt the progression of NASH because once cirrhosis ensues, 45% of patients develop liver failure within 10 years [8].

Diagnosis

Alanine aminotransferase (ALT) is associated with disease progression but its sensitivity and specificity for the diagnosis of NASH is 45% and 85%, respectively [1]. Similarly, cytokeratin 18, has a sensitivity and specificity of 58% and 68%, respectively, for NASH in a multiethnic cohort [9].

The NAFLD fibrosis score (NFS) uses clinical data, such as body mass index and laboratory values, and is the most validated predictor [10] that identifies patients with severe liver disease who may benefit from a liver biopsy. A low NFS score excludes advanced fibrosis with a sensitivity and specificity of 75% and 58%, respectively. A high NFS score (>.675) identifies advanced fibrosis with a sensitivity and specificity of 33% and 98%, respectively [10–12].

Table 2
Indications for liver biopsy in patients with NAFLD to confirm the diagnosis and to stage NASH

High risk for NASH (steatosis and concomitant metabolic syndrome or diabetes)
Persistent elevation of liver transaminase levels (1.5-fold for >6 mo)
NFS score >.675 (indicating advanced fibrosis)
Evidence suggesting progressive liver disease (AST/ALT >1, hyperbilirubinemia, coagulopathy, thrombocytopenia) or physical examination

NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; NFS = NAFLD fibrosis score; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Ultrasonography is used to screen for steatosis and for longitudinal assessment but cannot differentiate between steatosis and fibrosis. Computerized tomography has a similar role for diagnosis and follow-up. Magnetic resonance imaging and magnetic resonance imaging spectroscopy can detect much lower levels of steatosis (5%–6%) but are expensive and are of limited availability.

Vibration-controlled transient elastography (Fibroscan), and ultrasound with acoustic radiation force impulse are promising modalities to detect fibrosis. Recent approval of Fibroscan will likely make this noninvasive test increasingly available.

Two-dimensional magnetic resonance elastography has excellent predictive accuracy in staging fibrosis with a sensitivity and specificity of 86% and 91%, respectively [13]. Cost and availability of magnetic resonance imaging, however, limit its use to research centers.

The gold standard to diagnose NAFLD is a liver biopsy specifically to detect inflammatory changes characteristic of NASH and to eliminate any competing etiologies. Indications for liver biopsy are summarized in Table 2.

Medical treatment of NAFLD

The mainstay of treatment is weight loss via food management, insulin sensitizers, and myriad other medications. The impact of exercise alone is not well defined. Carbohydrate-restrictive diets are the most effective, and a loss of 3% to 5% weight reverses steatosis, but a 7% to 10% loss is needed to improve histologic features of NASH [14,15].

Pioglitazone improves steatosis, inflammation, insulin resistance, ALT, and aspartate aminotransferase (AST) but not hepatocyte ballooning [16] and should not be used to treat NAFLD without biopsy-proven NASH.

Although Metformin improves insulin sensitivity, cholesterol, and ALT, recent guidelines do not recommend its use to treat NASH [6].

Vitamin E (800 IU/d) improves histologic features of NASH in >40% of patients. Like pioglitazone, vitamin E also reduces ALT/AST levels, steatosis, and lobular inflammation but does not consistently improve fibrosis. There is insufficient evidence for its use in diabetics [6].

Glucagon-like peptide agonist liraglutide improves liver enzymes in diabetics but its effect on liver histology is currently being studied.

In small clinical trials pentoxifylline [17] or obeticholic acid [18] improved steatosis and NASH. Dipeptidyl peptidase 4 inhibitors, such as sitagliptin, decrease ALT/AST when given to diabetics; however, their effect on hepatic steatosis and NASH is not well established [19].

Because the pathogenesis of NAFLD is complex, effective monotherapy thus far has proved elusive, with no treatment demonstrating efficacy in >50% of patients [1,20]. Recently, a phase 2b trial with emricasan did not meet its primary

endpoints in patients with NASH decompensated cirrhosis. Other clinical trials to assess the benefit of cenicriviroc, which targets inflammation and fibrosis in NASH, and PF-05221304 in chronic NAFLD are currently underway in many centers.

Surgical treatment of NAFLD

Laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy (SG), and Roux-en-Y gastric bypass (RYGB) are associated with significant reductions in ALT, AST, alkaline phosphatase, and gamma glutamyl transferase [21]. ALT is improved in 62% of patients and is reduced the lowest by SG and LAGB compared with RYGB. Similarly, alkaline phosphatase is lowered in more patients by LAGB (72%) compared with RYGB (25% of patients). RYGB lowered gamma glutamyl transferase in more patients than LAGB (89% versus 34%, respectively) [22].

Furthermore, in a large cohort of 160 patients with paired biopsies (pre- and postoperative), we demonstrated significant improvement in the histologic features of NAFLD (Table 3). At 31 ± 26 months after bariatric surgery, there was resolution of steatosis and steatohepatitis in 63% and 90% of patients, respectively. Fibrosis of any grade improved in 56% of patients; specifically Grade 2 fibrosis resolved in 58%, improved in 3%, and did not worsen in 11%. Bridging fibrosis resolved in 29%, improved in 29%, and did not worsen in 29% [5].

To further confirm our findings, we undertook a contemporary meta-analysis of 2374 patients procured from randomized controlled trials and observational studies from 1999 to 2016 according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Steatosis improved in 88% and steatohepatitis improved in 59% of patients. More importantly, fibrosis improved or resolved in 30% of patients [22]. RYGB has a greater impact on histologic features of NAFLD compared with LAGB or SG.

As importantly, patients with fibrosis should be followed up closely in collaboration with a hepatologist and monitored with liver tests and Fibroscan to assess for new or worsening features of NASH.

Table 3
Improvement of liver histology in 160 consecutive patients with paired preoperative and postoperative biopsies

Preoperative	Postoperative	%
Steatosis	Resolved	63
	Same	27
	Worse	2
Steatohepatitis	Resolved	90
	Same	5
	Worse	0
Fibrosis	Improved	56
	Same	25
	Worse	16

The patients underwent the first liver biopsy during the index bariatric procedure and a second liver biopsy during an abdominal procedure 31 ± 26 mo after the index bariatric procedure. Most patients had Roux-en-Y gastric bypass.

Future directions

The "multiple hit" theory is proposed to explain the many phenotypes of NAFLD and its progression to cirrhosis. Briefly, insulin resistance, adipokines, high fructose diet, and gut microbiota interact in genetically predisposed patients to induce liver injury [23]. Moreover, a genome-wide association study identified the I148 M variant of PNPLA3 as a major genetic determinant of NAFLD [24]. Understanding epigenetic events that change gene expression without changing DNA structure, and consequently dysregulate metabolic pathways, will improve our insight into "precision" medicine or surgery for NAFLD.

From bedside to bench and back

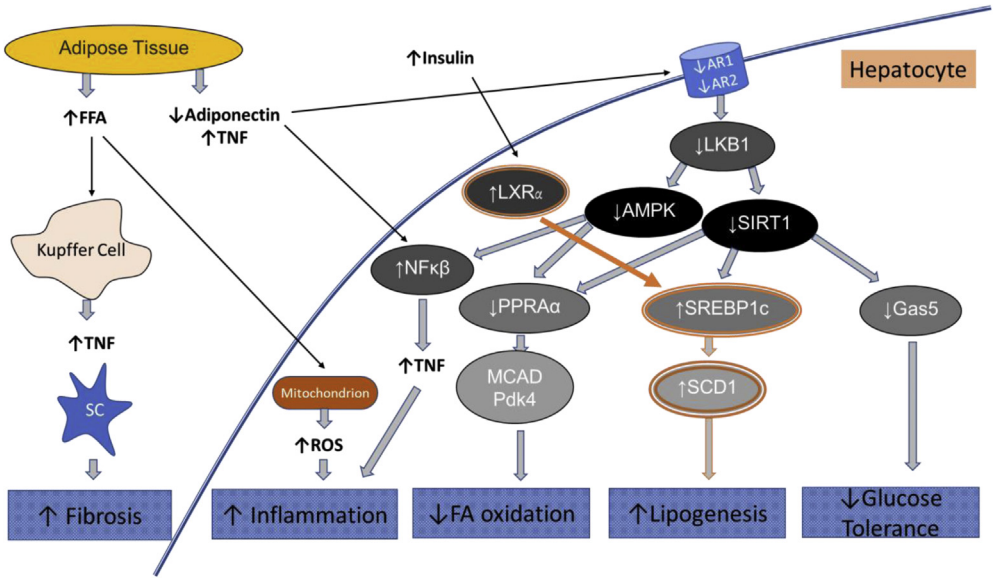
To study mechanistic pathways of the impact of bariatric surgery on NAFLD, we established a rat and mouse models of diet-induced obesity (American Society for Metabolic and Bariatric Surgery Research Grant No. 2008). High-fat diet in these models increased weight, liver weight, and induced steatosis.

In mice [25], obesity-induced steatohepatitis was associated with downregulation of adiponectin and its liver-specific receptor; subsequently, we tested our hypothesis that RYGB may upregulate adiponectin in obese rats (RYGB has very high mortality in mice). Weight loss after RYGB in rats followed a temporal trend similar to humans, but RYGB did not upregulate adiponectin [26].

More importantly, RYGB improved histologic features of steatosis [26], decreased liver weight and triglyceride content by downregulating stearoyl-CoA desaturase-1, a rate-limiting catalyst in the synthesis of hepatic triglycerides, but did not upregulate fatty acid oxidation pathways [26–28]; this suggests that RYGB reduces fat synthesis and storage in the liver.

Furthermore, RYGB improved glucose homeostasis by upregulating 2 key metabolic regulators: Sirtuin1, which controls hepatic lipogenesis and oxidative stress, and 5-amp activated MAP kinase, which has antidiabetic, anti-inflammatory, and antilipogenic properties [28,29]. Additionally, RYGB decreased oxidative stress by lowering reduced nicotinamide adenine dinucleotide phosphate oxidase 2, as well as improved mitochondrial dysfunction in hepatocytes [30].

In other experiments, we investigated how steatosis induced a proinflammatory milieu via activation of Kupffer cells; free-fatty acids increased reactive oxidative stress, tumor necrosis factor-alpha, reduced nicotinamide adenine dinucleotide phosphate oxidase 2, and activated nuclear factor kappa-B via a peroxisome proliferator-activated receptors-gamma–dependent pathway [31].



Proposed obesity-related cellular signaling pathways in the liver. Free fatty acids (FFA) induce pro-inflammatory cytokines from Kupffer cells and that in turn stimulate stellate cells (SC) to produce extracellular matrix proteins resulting in fibrosis. Additionally, FFA induce reactive oxygen species (ROS) in the mitochondria. Inflammation in adipocytes augments pro-inflammatory signaling in hepatocytes through NFKβ and induces lipogenesis via adiponectin receptors (AR1/2) and LKB1. Hyperinsulinemia of obesity induces lipogenesis by activating LXR1. AMPK and SIRT1 are key regulators of lipogenesis via SREBP1c (which is also regulated by LXRα) and SCD1; and fatty acid oxidation via PPRAα, MCAD and Pdk4. Depletion of Gas5 (growth arrest specific 5) increases insulin resistance. We are proposing that RYGB downregulates lipogenesis through LXR1, SREBP1c and SCD1 (double circles) without changes in fatty acid oxidation. LXRα = liver x receptor alpha; SIRT1 = Sirtuin 1; AMPK = 5-amp activated MAP kinase; SCD1 = stearoyl-CoA desaturase-1; NOX2 = NADPH oxidase-2; TNFα = tumor necrosis alpha; NFκB = nuclear factor-kappa B; PPARγ = peroxisome proliferator-activated receptors-gamma; Pdk4 = Pyruvate dehydrogenase kinase-4; MCAD = medium-chain acyl-coenzyme A dehydrogenase; Gas-5 = growth arrest specific 5; SREBP1c = sterol regulatory element binding transcription factor 1.

Others have reported similar findings. RYGB reduces oxidative stress and halts progression of NASH in a mouse model [32]. RYGB or SG reduces hepatic inflammation, mitochondrial dysfunction, and endoplasmic reticulum stress in association with increased relative acylated ghrelin levels in obese rats [33].

In summary, RYGB exhibits antilipogenic, antiinflammatory, antioxidant properties. Nonetheless, its antidiabetic properties are a focus of intense research because of the implications for the worldwide epidemic of metabolic syndrome. Recently, we reported a novel finding that RYGB increases liver, serum, and adipose levels of growth arrest specific 5 [34]; this long noncoding RNA can change gene expression by binding to RNA and has a strong correlation with diabetes [35]. Furthermore, depleting growth arrest specific 5 in human adipose-derived stem cells reduced Sirtuin1 [35]. We hypothesize RYGB increases hepatic growth arrest specific 5 and improves peripheral and hepatic insulin resistance via activation of Sirtuin1 and preferential shift from mammalian target of rapamycin complex 1 to mammalian target of rapamycin complex 2 production (American Society for Metabolic and Bariatric Surgery Research Grant No. 2017).

Conclusions

NAFLD-associated morbidity and mortality worsens with progression of liver injury. Bariatric surgery reverses liver disease across the spectrum of NAFLD, and more importantly, it reverses early stages of fibrosis. There is compelling evidence that surgically induced weight loss should be considered the primary treatment of choice for patients with NAFLD and severe obesity.

Future directions in NAFLD should include studies on how to modify the risk of bariatric surgery in patients with advanced liver disease, establishing a tissue bank to identify metabolic signatures in nonalcoholic fatty liver before and after bariatric surgery, and applying lessons learned from animal models toward translational research efforts.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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