Current Gastroenterology Reports (2018) 20: 49
https://doi.org/10.1007/s11894-018-0653-6

STOMACH AND DUODENUM (J PISEGNA AND J BENHAMMOU, SECTION EDITORS)

Treatment of NASH with Gastric Bypass

Pichamol Jirapinyo[1,2] · Christopher C. Thompson[1,2]

Published online: 22 September 2018

Abstract

Purpose of Review Nonalcoholic steatohepatitis (NASH) is a spectrum of nonalcoholic fatty liver disease (NAFLD). It is defined as the presence of fatty liver along with inflammation and hepatocyte injury. To date, weight loss achieved via lifestyle intervention remains the mainstay of NASH treatment. However, given the known benefit of weight loss on NASH and the known effect of bariatric surgery on weight loss, several studies have explored the potential role of bariatric surgery on the treatment of NASH.

Recent Findings This review article summarizes the evidence on the effect of Roux-en-Y gastric bypass (RYGB), a common bariatric surgery, on NASH therapy. Specifically, studies show that RYGB is associated with an improvement of all NASH histologic features at 1 year.

Summary Compared to adjustable gastric band, RYGB appears to be superior at treating NASH. Randomized controlled trials and long-term studies are underway to better clarify the role of these procedures specifically for NASH therapy.

Keywords NASH · NAFLD · Fatty liver · Obesity · Gastric bypass · RYGB · Bariatric endoscopy · EBMT

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a growing cause of chronic liver disease (CLD) worldwide. In the US, NAFLD is the most common cause of CLD representing greater than 75% of CLD as of 2008 [1]. In 2011, the prevalence of NAFLD was estimated to range from 6.3 to 33% in the general US population depending on the diagnosing modality [2]. In patients with obesity, however, the prevalence of NAFLD is estimated to be as high as over 90% with up to 5% having unexpected cirrhosis [2]. With a rise in the obesity pandemic, it is expected that the prevalence of NAFLD will continue to increase. By 2020, it is predicted that NAFLD will be the leading indication for liver transplantation [3].

Compared to the general population, patients with NAFLD have increased overall mortality with the most common cause being cardiovascular diseases (CVD) [4, 5]. Other causes of deaths among patients with NAFLD include liver-related mortality and cancer-related mortality [6]. In 2016, it was estimated that $103 billion was spent on treating patients with NAFLD in the U. S [7]. This number is predicted to increase to $1.005 trillion in 10 years given the increasing burden of obesity and NAFLD [8].

NAFLD represents a spectrum of liver conditions ranging from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) and finally to cirrhosis. Compared to NAFL, or simple steatosis, NASH is a more aggressive form of NAFLD with an intermediate risk of progressing to cirrhosis. Once developing cirrhosis, approximately 25% will experience complications of portal hypertension within 3 years [9].

This review article provides an update on the diagnosis and management of NASH with the focus on the role of bariatric surgery on NASH therapy. Evidence for each treatment option is discussed, along with the most updated guidelines from the major societies. Additionally, a brief discussion on the potential role of emerging endoscopic therapies for NASH treatment is also reviewed.

Nonalcoholic Steatohepatitis (NASH)

NASH is a spectrum of NAFLD. It is defined as the presence of at least 5% of fat within hepatocytes with inflammation and hepatocyte injury with or without fibrosis [10]. Unlike NAFL,

This article is part of the Topical Collection on *Stomach and Duodenum*

✉ Christopher C. Thompson
cthompson@hms.harvard.edu

[1] Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA

[2] Harvard Medical School, Boston, MA, USA

NASH is more aggressive and is associated with a risk of approximately 10 to 29% of progression to cirrhosis within 10 years [9]. It is approximated that about one third of patients with NASH will progress to stage 3 or 4 fibrosis (cirrhosis) over 5 to 10 years [9]. Therefore, early-stage NASH represents a group of patients that is most likely to benefit from treatments in order to prevent progression to cirrhosis and its complications.

Diagnosis of NASH

Liver Biopsy

Liver biopsy remains the gold standard for diagnosing and grading NASH. Specifically, the criteria for the histological diagnosis of NASH include steatosis and hepatocyte injury, usually in the form of ballooning and/or lobular inflammation. Fibrosis is not required to histologically diagnose NASH. Steatosis in NASH is usually macrovesicular, which refers to hepatocytes with a single large intracytoplastic fat droplet displacing the nucleus to the cell periphery. Generally, the extent of steatosis is assessed using percentage involvement by steatotic hepatocytes in liver parenchyma and reported as mild (5–33%), moderate (33–66%), and severe (> 66%) [11, 12]. In addition to steatosis, NASH histological diagnosis requires evidence of hepatocyte injury, which usually takes the form of ballooning or lobular inflammation. Ballooned hepatocytes are enlarged with swollen pale cytoplasm and a large hyperchromatic nucleus often with a prominent nucleolus (Fig. 1a). The presence of ballooning has been shown to be associated with more aggressive disease and high incidence of cirrhosis [14]. Lobular inflammation usually consists of mixed inflammatory cells including lymphocytes, some eosinophils, and occasionally a few neutrophils (Fig. 1a). In addition to ballooning and lobular inflammation, other forms of hepatocyte injury may be seen such as apoptosis and lytic necrosis. When fibrosis occurs in NASH, it usually starts in acinar zone 3 (around central veins), which may later progress to bridging fibrosis and cirrhosis (Fig. 1b).

Currently, there are three main histological scoring systems to grade and stage NASH. For all systems, grading generally refers to the amount of necroinflammatory activity, which include the degree of steatosis, ballooning, and lobular inflammation. Staging, on the other hand, is used to categorize the extent and location of fibrosis.

The Brunt System was developed in 1999 by Dr. Elizabeth Brunt and colleagues at Saint Louis University from systematic review of liver biopsies of 51 patients with clinically diagnosed NASH. The grading system divides NASH into mild (grade 1), moderate (grade 2), and severe (grade 3) based on the amount of steatosis, ballooning, and lobular and portal inflammation. Fibrosis stage ranges from 0 to 4 (0: no fibrosis, 1: perisinusoidal/pericellular fibrosis, 2: periportal fibrosis, 3: bridging fibrosis, 4: cirrhosis) (Table 1). This method of grading and staging is to be used once the diagnosis of NASH has been made. In this system, ballooning is the major determinant of severity (i.e., increasing severity of ballooning with increased severity of grade), and the amount of steatosis is the least determinant. While the system has been used widely, it has never been validated [11].

The NAFLD Activity Score (NAS) was developed in 2005 by the Pathology Committee of the NASH Clinical Research Network (NASH CRN) for the purpose of clinical trials [12]. The NAS score represents the sum of scores for steatosis (0–3), ballooning (0–2), and lobular inflammation (0–3) (Table 1). The score ranges from 0 to 8 with the NAS score of 5–8 considered diagnostic of NASH, the NAS score of 3–4 considered borderline NASH, and the NAS score of 0–2 considered not diagnostic of NASH. Additionally, there is a separate fibrosis stage ranging from 0 to 4 (0: no fibrosis, 1: perisinusoidal or periportal, 2: perisinusoidal and portal/periportal, 3: bridging fibrosis, 4: cirrhosis).

The Steatosis, Activity and Fibrosis Score (SAF) was developed in 2012 by the European Fatty Liver Inhibition of Progression Consortium [16]. It was originally intended for grading and staging NAFLD in patients with morbid obesity about to undergo bariatric surgery. The SAF score consists of the steatosis score (S_0–S_3), the activity grade (A_0–A_3), which combines hepatocyte ballooning (0–2) and lobular inflammation (0–2), and the fibrosis stage (F_0–F_4) (Table 1). The activity grade of the SAF score enables the discrimination of NASH from NAFL as all patients with NASH have $A \geq 2$, whereas no patients with $A < 2$ have NASH [16].

Noninvasive Tools for Diagnosing NASH

Given the cost, sampling error, and possible adverse events that are associated with liver biopsy, there has been a significant interest in developing clinical prediction tools and noninvasive methods at diagnosing NASH in patients with NAFLD. These noninvasive tools may be divided into (1) those that quantify the amount of hepatic steatosis in patients with NAFLD, (2) those that predict steatohepatitis in patients with NAFLD, and (3) those that assess advanced fibrosis in patients with NAFLD.

Steatosis Some studies have shown a correlation between the degree of steatosis and severity of NASH. Specifically, Chalasani and colleagues from the NASH-CRN group demonstrated that increasing levels of steatosis severity were associated with lobular inflammation, fibrosis, and definite steatohepatitis [17]. Therefore, noninvasive methods to assess the amount of steatosis may be used as a surrogate for diagnosing NASH. To date, there have been no clinical predictors for the amount of steatosis. However, there are a few emerging radiologic techniques to quantify the amount of fat. These include magnetic resonance spectroscopy (MRS), which

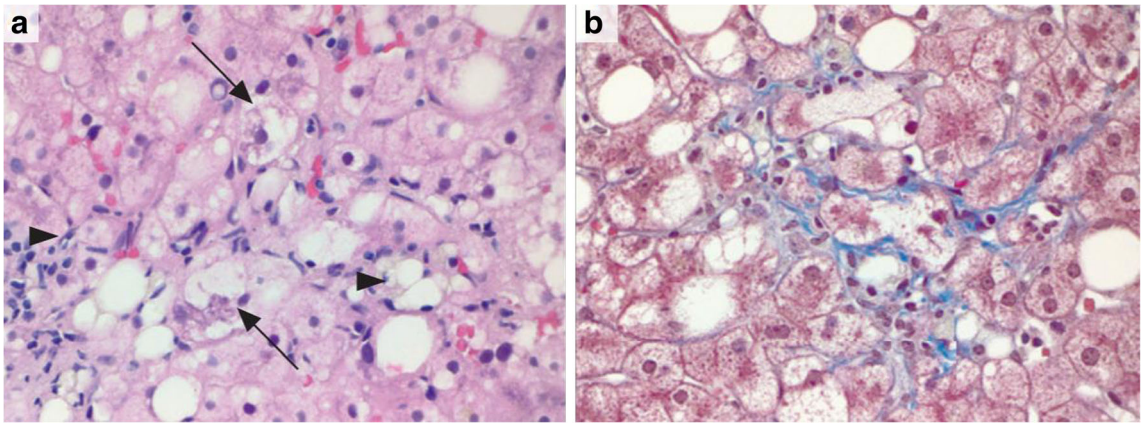

Fig. 1 Histologic features of nonalcoholic steatohepatitis (**a**) ballooned hepatocytes (arrow) and inflammatory infiltrate (arrowheads) (**b**) fibrosis. From Diehl and Day [13]. Used with permission from the Massachusetts Medical Society

separates the liver signal into its water and fat components and calculates a signal fat-fraction [18], and magnetic resonance imaging-based proton density fat fraction (MRI-PDFF), which is a more recent MRI technique that eliminates biases like T1 bias, T2 decay, spectral complexity of fat and noise bias to allow a more accurate estimation of PDFF [19, 20]. Additionally, transient elastography (TE) with controlled attenuation parameter (CAP) may be used to quantify the degree of liver steatosis (Fig. 2). The CAP score ranges from 100 to 400 dB/m with a higher number representing a more severe degree of steatosis [21].

Steatohepatitis The presence of metabolic syndrome is a strong predictor of steatohepatitis in patients with NAFLD. Specifically, studies have shown that an increase in the number of metabolic diseases, such as visceral obesity, dyslipidemia, hypertension, insulin resistance, and type 2 diabetes, is associated with an increased risk of progressive liver disease [22–24]. Additionally, recent studies have proposed the use of the biomarker caspase-generated cytokeratin-18 (CK-18) fragments for the diagnosis and staging of NASH. Specifically, an increase in hepatocyte cell apoptosis is typically present in NASH and not NAFL. When apoptosis occurs, activation of the effector caspases follows to cleave a number of substrates inside the cell including CK-18, the major intermediate filament protein in the liver. While many studies have shown a correlation between CK-18 fragments and the presence of NASH, this test is currently not available for clinical use [25, 26].

Fibrosis Noninvasive tools to assess the presence of advanced fibrosis may be divided into clinical risk scores, serum biomarkers, and imaging. To date, there are several clinical decision aids developed to predict advanced fibrosis, such as NAFLD fibrosis score (NFS), FIB-4 index, aspartate aminotransferase (AST) to platelet ratio index (APRI), BARD score, and AST/ALT ratio. The NFS is calculated based on six readily available parameters (age, BMI, hyperglycemia, platelet count, albumin, and AST/ALT ratio) [27]. The NFS is then divided into three groups: less than − 1.455, between − 1.455 and 0.675, and greater than 0.675, which represent F0–F2, indeterminate and F3–F4, respectively. A meta-analysis of 13 studies with 3064 patients demonstrated that the NFS had an area under the receiver operating curve (AUROC) of 0.85 for predicting advanced fibrosis, i.e., bridging fibrosis (F3) and cirrhosis (F4) [28]. FIB-4 uses a combination of age, AST, ALT, and platelet count and offers dual cut-off values (score < 1.45 and score > 3.25 representing unlikely and likely advanced fibrosis, respectively) [29]. A recent study demonstrated that NFS and FIB-4 were better than other risk scores and were as good as magnetic resonance elastograpy (MRE) at predicting advanced fibrosis [30]. Regarding serum biomarkers, there are a few that have been shown to correlate with the level of liver fibrosis. The enhanced liver fibrosis (ELF) panel combines three serum markers including hyaluronic acid, amino-terminal propeptide of type III procollagen, and tissue inhibitor of metalloproteinase 1. The panel had an AUROC of 0.90 for detecting advanced fibrosis and was recently approved for clinical use in Europe but not in the USA [27]. Imaging modalities that measure liver stiffness noninvasively include transient elastography (TE) and magnetic resonance elastography (MRE), which were both approved by the Food and Drug Administration (FDA) for use in patients with liver diseases. In the study by Imajo et al., AUROC for TE and MRE at diagnosing advanced fibrosis were 0.88 and 0.89, respectively. Compared to TE, MRE performed better at identifying fibrosis stage 2 and above, while both performed equally well at identifying fibrosis stage 3 and above [30].

Medical Management of NASH

To date, weight loss achieved via lifestyle intervention remains the mainstay of treatment of NASH. A meta-analysis of 8 randomized controlled trials (RCTs) including 373 patients, with 4 studies including post-treatment histology, showed that although ≥ 5% total weight loss

Table 1 Histologic scoring systems for grading and staging nonalcoholic fatty liver disease (NAFLD). Modified from Brunt [15]

System/ characteristics	Brunt system	NASH CRN	*SAP/**FLIP algorithm
Patient population	Adults only	Adults + children	Adults
Applicable to	NASH	All NAFLD	All NAFLD
Grade	Mild, moderate, severe; S + LI, PI + B; unweighted but steatosis does not affect score; LI + PI, ballooning increase incrementally with score	NAFLD Activity Score (NAS): S + LI + B = 0–8; unweighted scores for each lesion	Steatosis is not a component of activity Activity: LI + B; *SAF: steatosis + activity + fibrosis = S_xA-$_xF_x$; **FLIP: fatty liver inhibition of progression algorithm for diagnosis
Details of scoring	Steatosis	Steatosis	Steatosis
	0: 0	0: < 5%	0: < 5%
	1: 0–33%	1: 5–33%	1: 5–33%
	2: 34–66%	2: 34–66%	2: 34–66%
	3: > 66%	3: > 67%	3: > 67%
	LI	LI	LI
	0:0	0:0	0: 0
	1: 1–2/20×	1: < 2120×	1: < 2/20×
	2: 2–4/20X	2: 2–4/20X	2: 2/20×
	3: > 4/20X	3: > 4/20X	–
	PI:	Ballooning:	Ballooning: 0–2
	0: none	0: None	0: 0
	1: mild	1: Few	1: clusters, reticulated cytoplasm
	2: moderate	2: Many	2: enlarged hepatocytes
	3: severe	–	–
	Ballooning	Prominent	–
	Acinar location	–	–
	Mild	–	–
	Marked	–	–
	Fibrosis stage	Fibrosis stage	Fibrosis stage
	0: none	0: none	FO: 0
	1: zone 3 perisinusoidal	1a: zone 3 perisinusiodal, dense 1b: zone 3 perisinusiodal, dense 1c: portal only	
	2: 1 + periportal	2: 1a or 1b + periportal	F2: zone 3 + periportal
	3: bridging	3: bridging	F3: bridging
	4: cirrhosis	4: cirrhosis	F4: cirrhosis

Table 1 (continued)

System/ characteristics	Brunt system	NASH CRN	*SAP/**FLIP algorithm
Fibrosis stages	0–4	0–4; # 1a, 1b, 1c	0–4; # 1a, 1b, 1c
Scoring method used for diagnosis	Minimal criteria for dx	Correlates but does not replace; used in clinical trials for feature comparisons	Yes, for diagnosis
Clinical associations	Grade: AST	ALT, AST	AST, ALT

S steatosis amount, *LI* lobular inflammation, *PI* portal inflammation, *B* ballooning, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *WC* waist circumference, *MetSynd* metabolic syndrome, *TG* triglyceride levels

(TWL) improved hepatic steatosis, a ≥ 7% TWL was required to improve NAS [31]. These data have been supported by a recent prospective study, which included 261 paired liver biopsies obtained before and at 12 months after lifestyle intervention in patients with biopsy-proven NASH. The study demonstrated that at 12 months, 25% of patients achieved the primary outcome—NASH resolution—which was defined as the absence of histologic features of steatohepatitis. Additionally, 47% of patients had reductions in NAS (a decrease of at least 2 points in the NAS in more than one category), and 19% had regression of fibrosis (a decrease of at least 1 point in the fibrosis score). Moreover, the study showed a dose response curve between the amount of weight loss and the degree of NASH histological improvement such that ≥ 10% TWL was associated with improvement of all NASH features, including portal inflammation and fibrosis. Additionally, all patients with ≥ 10% TWL had at least a 2-point reduction in NAS, while only 82 and 32% of those who achieved 5–10% TBWL and < 5% TBWL experienced NAS improvement, respectively [32].

Despite the evidence supporting the benefit of weight loss via lifestyle intervention on NASH, less than one third was able to achieve significant weight loss of ≥ 5% and less than 10% was able to achieve weight loss of ≥ 10% in this trial [32].

Other potential medical therapies to treat NASH include vitamin E, thiazolidinediones, glucagon-like peptide-1 (GLP-1) agonist, and obeticholic acid. Thus far, the best evidence is for vitamin E in nondiabetic adults with biopsy-proven NASH and thiazolidinediones in patients with and without diabetes with biopsy-proven NASH with other modalities currently undergoing ongoing studies [10]. However, their detailed discussion is beyond the scope of this review.

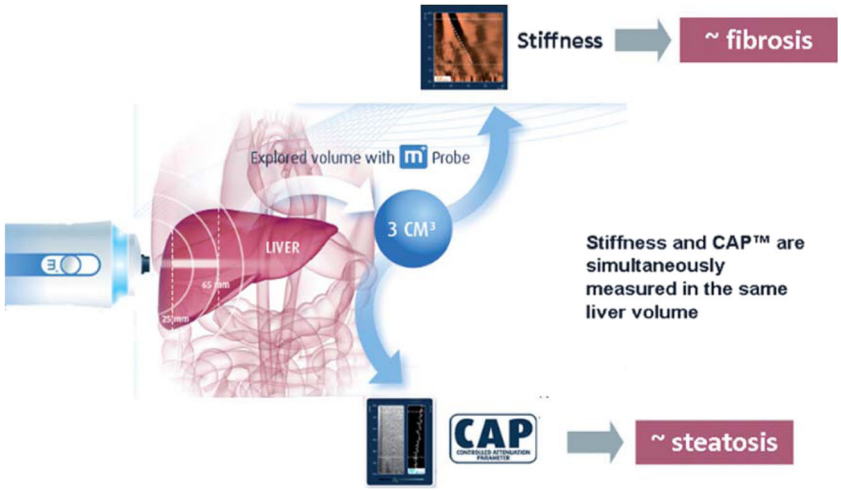

Fig. 2 Controlled attenuation parameter (CAP) assessment using transient elastrography. From Sasso et al. [21]

Treatment of NASH with Gastric Bypass

Given the known beneficial consequence of weight loss on NASH and the known effect of bariatric surgery on weight loss, several studies have explored the potential role of bariatric surgery on the treatment of NASH. To date, RYGB remains the most extensively studied bariatric surgery as a potential NASH therapy.

A pioneering study conducted by Silverman et al. in 1995 retrospectively evaluated liver histology in 91 patients before and at 2 to 61 months after RYGB. Of the 91 patients, 18 had no steatosis at baseline. Among the 73 remaining patients, 65 experienced reduction in steatosis in follow-up biopsies, 5 with minimal steatosis at baseline showed no change, and 3 had increased steatosis. Thirteen of the 91 patients had perisinusoidal fibrosis (PSF) at baseline—3 with bridging fibrosis, 1 with moderate fibrosis, and 9 with slight fibrosis. Following RYGB, PSF resolved in 10 patients, decreased in 1 patient and remained the same in 2 patients. One patient developed PSF after RYGB [33].

Subsequently, there are several retrospective and prospective observational studies evaluating the effect of RYGB on NASH histologic features, including the two large, single-center studies with follow-up liver biopsies. In 2009, Mathurin et al. conducted a 5-year prospective cohort study on 381 patients with severe obesity, defined as body mass index (BMI) of >40 kg/m^2 or >35 kg/m^2 with at least one obesity-related comorbidity. Liver biopsies were performed prior to and at 1 and 5 years after bariatric surgery. In this study, gastric banding, biliointestinal bypass, and RYGB were performed in 214 (56.2%), 87 (22.8%), and 80 (21%) patients, respectively. Compared to baseline, there was a significant improvement in the prevalence and severity of steatosis (frequency 82 to 37.7%; extent 37.4 to 16%) and ballooning (NAS ballooning score 0.2 to 0.1) and a significant reduction in NAS (total NAS 1.9 to 1). Inflammation remained unchanged, while levels of fibrosis statistically significantly increased at 5 years (fibrosis stage 0.27 to 0.36). Despite this increase, 96% of patients had fibrosis score ≤ 1 at 5 years suggesting that there was no clinically significant worsening in fibrosis. Additionally, the study demonstrated that the percentage of patients with probable or definite NASH, defined as NAS ≥ 3, significantly decreased from 27.4% at the time of bariatric surgery to 14.2% at 5 years. In this study, refractory insulin resistance (IR), defined by homeostatic model assessment for insulin resistance (HOMA-IR) at 1 year of >3.13, independently predicted the persistence of steatosis and ballooning at 5 years, suggesting a possible parallel between the kinetics of insulin resistance and that of steatosis and ballooning [34].

A follow-up study in 2015 focused on patients with baseline NASH prior to bariatric surgery. Lassailly et al. conducted a 1-year prospective cohort study on 109 patients with biopsy-proven NASH and severe obesity, defined as body mass index (BMI) of >40 or >35 kg/m^2 with at least one obesity-related comorbidity. Liver biopsies were performed prior to and at 1 year after bariatric surgery. Out of 109 patients, 70 (64.2%), 32 (29.4%), 6 (5.5%), and 1 (0.9%) underwent RYGB, gastric banding, sleeve gastrectomy, and biliointestinal bypass, respectively. At 1 year, 85% of patients had NASH resolution. Compared to baseline, there was a significant reduction in the prevalence of steatosis from 60 to 10%. Ballooning improved in 84% of cases, and lobular inflammation in 67%. More importantly, in contrast to the data from the previous study, fibrosis improved in 34% of the cohort at 1 year after RYGB [35••]. The authors therefore proposed that bariatric surgery may be considered as a therapeutic option for appropriately morbidly obese patients with NASH who did not respond to lifestyle intervention.

To date, there have been no randomized controlled trials (RCTs) evaluating the effect of RYGB or other bariatric surgeries on NASH. A meta-analysis in 2008 including 15 studies and 766 paired liver biopsies evaluated the effect of bariatric surgery on NAFLD histology. RYGB was the most

common bariatric surgery performed, i.e., in 9 out of 15 included studies. The duration between the pre- and post-bariatric surgery biopsies ranged from 2 to 111 months. At follow-up, the pooled proportion of patients with improvement or resolution in steatosis, steatohepatitis, and fibrosis was 91.6% (15 studies), 81.3% (9 studies), and 65.5% (5 studies), respectively (Fig. 3a–c). In 69.5%, there was complete resolution of NASH, defined as complete disappearance of all NASH histopathologic components of interest (nine studies) (Fig. 3d) [36].

A follow-up meta-analysis in 2015 assessed the effect of bariatric surgery on NAFLD liver histology and/or liver biochemistry. Specifically, the analysis pooled 29 studies and demonstrated a significant reduction in the incidence of all NAFLD histologic features following bariatric surgery: steatosis (16 studies: reduction in the incidence by 50.2%), ballooning (8 studies: 67.7%), lobular inflammation (7 studies: 50.7%), portal inflammation (4 studies: 13.1%), and fibrosis (12 studies: 11.9%) (Fig. 4a) [37••]. Additionally, there were statistically significant reductions in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT) after bariatric surgery (Fig. 4b). Nevertheless, due to the lack of RCTs and quasi-randomized clinical studies, the Cochrane review concluded that no definite benefits or harms could be made regarding the role of bariatric surgery as a therapeutic approach for NASH. The review suggested that the current studies were too heterogenous with a small number of patients, which limited any unbiased conclusion on bariatric surgery for treatment of NASH [38].

Comparison of Gastric Bypass to Other Bariatric Surgeries as a Therapy for NASH

In addition to RYGB, there have been a few studies assessing the effect of other bariatric surgeries on NASH therapy. Caiazzo et al. conducted a 5-year prospective, non-randomized longitudinal study comparing the effect of RYGB and adjustable gastric banding (AGB) on NASH. The study included 1236 patients with obesity who underwent RYGB ($n = 681$) or AGB ($n = 555$). Liver biopsies were available on 1201 patients (97.2% of those at risk) at baseline, 578 patients (47.2%) at 1 year, and 413 patients (68.9%) at 5 years. At baseline, NAFLD was present in 86% of patients (defined as steatosis ≥ 5%) and categorized as severe in 22% of patients (defined as NAS ≥ 3). RYGB was associated with significantly greater improvement in the amount of steatosis and NAS at 1 and 5 years compared to AGB (steatosis (%): 1 year: 17.9 versus 7.9/ 5 years: 14.5 versus 8.7; NAS: 1 year: 1.1 versus 0.7/ 5 years: 1.0 versus 0.7). At baseline, the proportion of

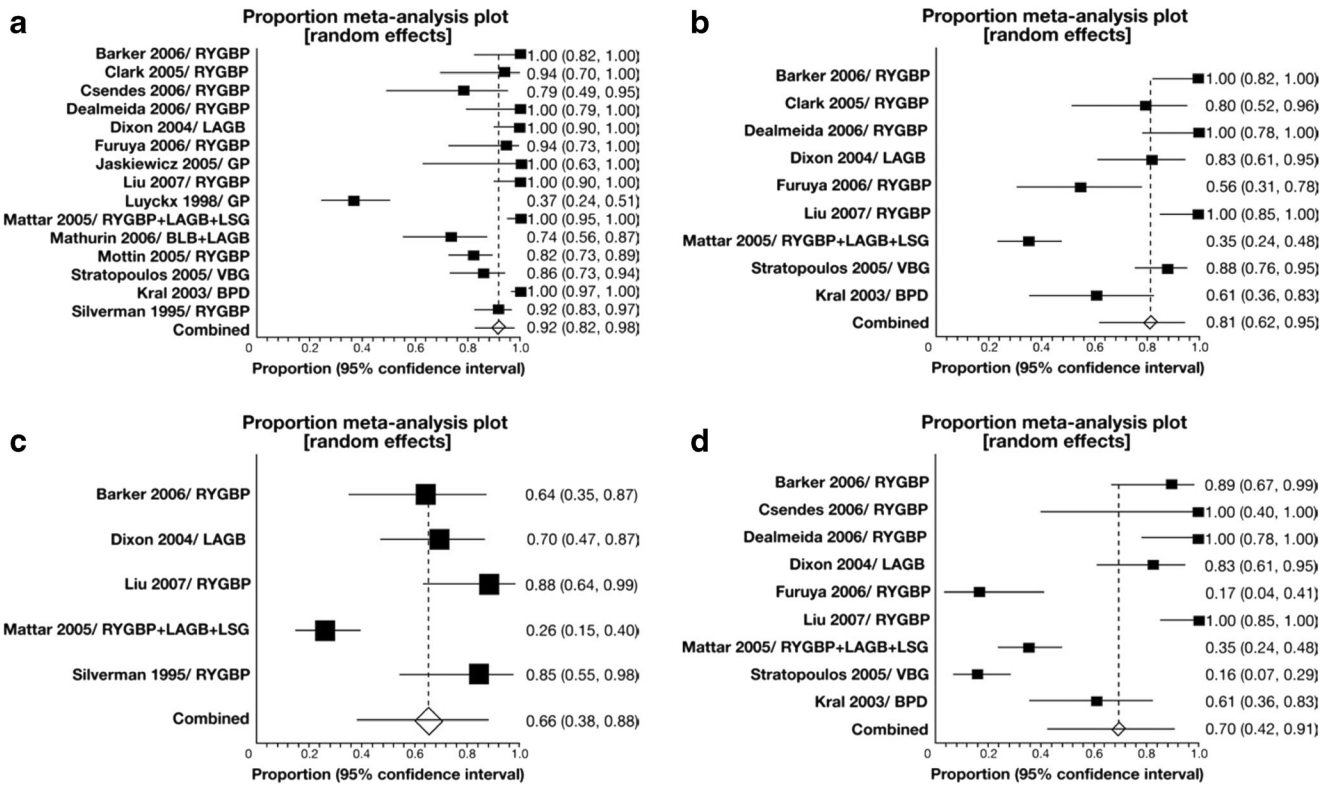

Fig. 3 Forest plots demonstrating the effect of bariatric surgery on the improvement of **a** steatosis, **b** steatohepatitis, **c** fibrosis, and on **d** complete resolution of steatohepatitis. Taken from Mummadi et al. [36]. Used with permission from Elsevier

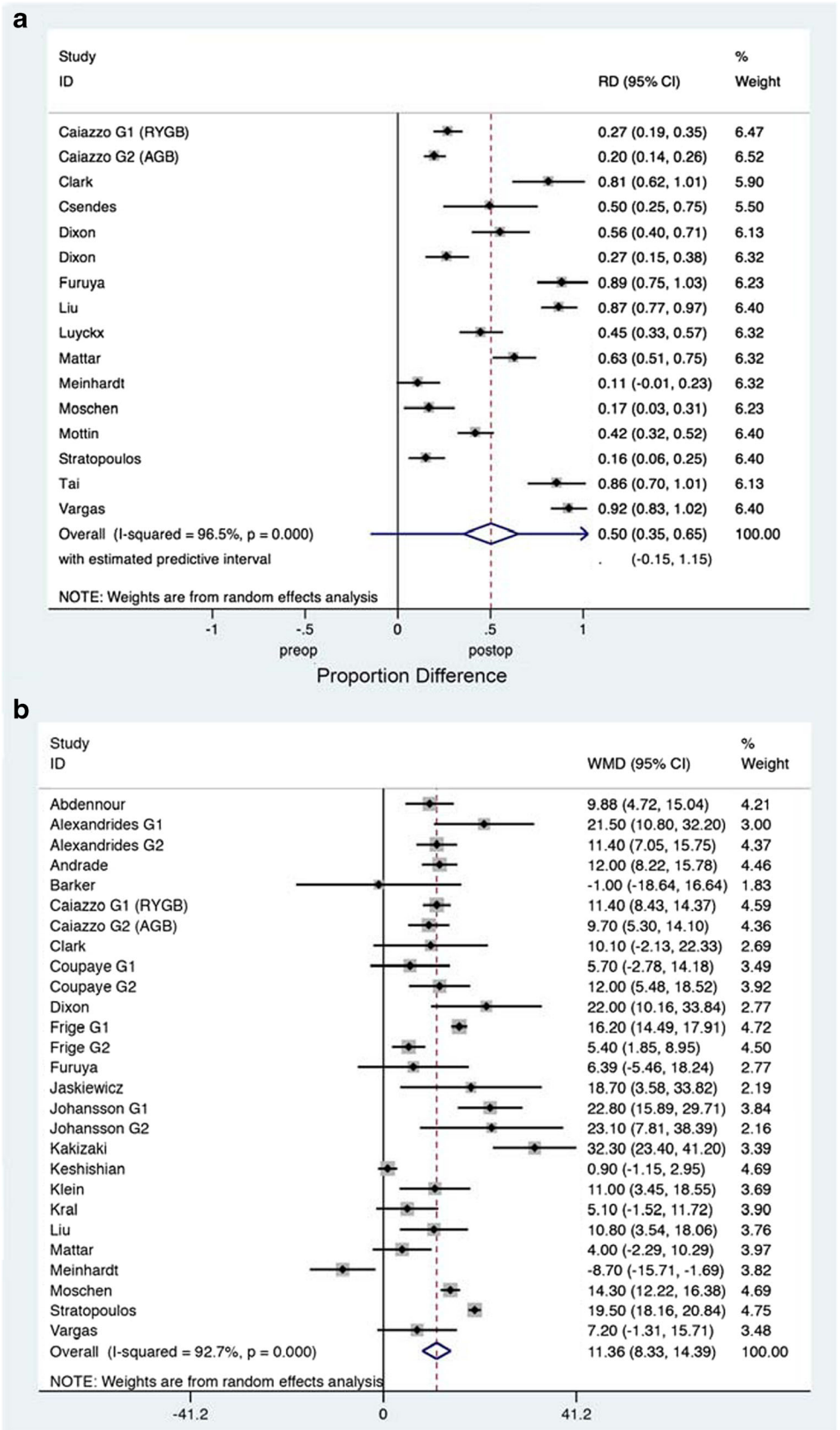

Fig. 4 Forest plots demonstrating the effect of bariatric surgery on the improvement of **a** liver histology for steatosis and **b** liver biochemistry for alanine aminotransferase (ALT). Taken from Bower et al. [37]. Used with permission from Springer Nature

patients with severe NAFLD was similar in both groups. However, at 1 and 5 years, a significantly lower proportion of patients in the RYGB remained in the severe NAFLD category compared to AGB. The study therefore concluded that the improvement of NAFLD was superior after RYGB when compared to AGB [39].

To date, there have been no studies that evaluate the effect of sleeve gastrectomy (SG) on the changes in histologic features of NASH. Nevertheless, a recent study conducted by Kalinowski et al. in 2017 attempted to answer this question by using liver function tests as a primary outcome. Specifically, the study was an analysis of prospectively selected endpoints of a randomized trial comparing outcomes of RYGB and SG [40, 41]. The study randomized 66 patients with morbid obesity to RYGB ($n = 33$) or SG ($n = 33$). Intraoperative liver biopsy was performed at the time of the bariatric surgery, and liver function tests were measured prior to and at 1, 6, and 12 months after surgery. At baseline, the proportions of patients who had NASH (defined as NAS ≥ 5) were similar between the two groups (54.5% in RYGB and 51.5% in SG groups, respectively). Similarly, there was no difference in baseline liver function tests between the two surgical groups, including ALT, AST, GGT, and lactate dehydrogenase (LDH). At 12 months, significant improvement in liver function tests was observed only in NASH patients who underwent SG (ALT 23.8 vs. 39.9, AST 21.5 vs. 32.4, GGT 24.5 vs. 34.3, LDH 292.4 vs. 510.8). In contrast to the findings of some of the previous studies, liver function tests did not significantly change after RYGB [42].

Future long-term head-to-head controlled trials focusing on analysis of liver pathology in patients with biopsy proven NASH are needed before any conclusion can be made regarding which bariatric surgery should be offered to patients with NASH with or without obesity.

Emerging Endoscopic Therapies for NASH

Endoscopic bariatric and metabolic therapies (EBMTs) are emerging therapies for obesity and its related comorbidities. To date, there are three types of EBMTs that are approved by the U.S. Food and Drug Administration (FDA) for the treatment of obesity. These include intragastric balloons (IGBs), endoscopic sleeve gastroplasty (ESG), and aspiration therapy (AT) [43, 44]. Data on the efficacy of EBMTs at treating NASH remain limited. In 2012, Lee et al. conducted a randomized controlled pilot study to evaluate the effect of the Bioenterics intragastric balloon (BIB) at improving histology of NASH in patients with obesity and biopsy-proven NASH. The study randomized 18 patients to receive BIB placement plus the American Heart Association (AHA) diet and exercise ($n = 8$) versus sham BIB placement plus the AHA diet and exercise ($n = 10$). At 6 months, total NAS was significantly lower in the BIB group compared to the sham group (2 vs. 4). There was a trend towards improvement in the median steatosis scores in the BIB group. However, there was no change in the median ballooning, lobular inflammation or fibrosis scores in either group [45]. A recent meta-analysis was conducted to assess the effect of IGB on obesity-related comorbidities. While there were not enough studies to pool the effect of IGB on changes in NASH histologic features, the study showed a significant decrease in ALT (−9 U/l, 10 studies) and AST (−3 U/l, 7 studies) [46]. Data on the effect of other EBMTs, including ESG or AT, are lacking and eagerly awaited.

Current Guidelines

According to The American Association for the Study of Liver Diseases (AASLD), bariatric surgery can be considered in otherwise eligible patients with obesity and concomitant NAFLD or NASH. However, the 2018 AASLD guidance states that "it is premature to consider bariatric surgery as an established option to specifically treat NASH" [10]. The European Association for the Study of the Liver (EASL), along with the European Association for the Study of Diabetes (EASD) and the European Association for the Study of Obesity (EASO), provides level B1 grading (strong recommendation with moderate quality of evidence) for bariatric surgery as a treatment for NASH. Specifically, the 2016 EASL-EASD-EASO guideline states that "by improving obesity and diabetes, bariatric (metabolic) surgery reduces liver fat and is likely to reduce NASH progression; prospective data have shown an improvement in all histologic lesions of NASH, including fibrosis" [47].

Summary

There is emerging evidence that bariatric surgery, in particular RYGB, is effective at treating NASH with improvement in histological features in the short term. Current guidelines suggest that it is premature for bariatric surgery to be considered an established treatment specifically for NASH alone, without concomitant obesity. Randomized controlled trials and long-term studies are underway to better clarify the role of these procedures specifically for NASH therapy.

Compliance with Ethical Standards

Conflict of Interest Christopher Thompson reports receiving consulting fees from Boston Scientific, Covidien, USGI Medical, Valentx, and Apollo Endosurgery; has served as an advisory board member for USGI Medical; has served as an advisory board member for Fractyl; has received research/grant support from USGI Medical and Apollo Endosurgery, laboratory supplies and equipment from Olympus, trial funding from Aspire bariatrics and Spatz; and served as a consultant for

Olympus and Fractyl; as an expert reviewer for GI Dynamics, and has an ownership interest in GI Windows.
Pichamol Jirapinyo declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major Importance

1. Younossi ZM, Stepanova M, Afendy M, Fang Y, Younossi Y, Mir H, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. Clin Gastroenterol Hepatol. 2011;9(6):524–30.e1. quiz e60
2. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34(3):274–85.
3. Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. Gastroenterology. 2011;141(4):1249–53.
4. Sayiner M, Otgonsuren M, Cable R, Younossi I, Afendy M, Golabi P, et al. Variables associated with inpatient and outpatient resource utilization among Medicare beneficiaries with nonalcoholic fatty liver disease with or without cirrhosis. J Clin Gastroenterol. 2017;51(3):254–60.
5. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology. 2005;129(1):113–21.
6. Younossi Z, Henry L. Contribution of alcoholic and nonalcoholic fatty liver disease to the burden of liver-related morbidity and mortality. Gastroenterology. 2016;150(8):1778–85.
7. Younossi ZM, Blissett D, Blissett R, Henry L, Stepanova M, Younossi Y, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology. 2016;64(5):1577–86.
8. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2018;15(1):11–20.
9. Argo CK, Caldwell SH. Epidemiology and natural history of nonalcoholic steatohepatitis. Clin Liver Dis. 2009;13(4):511–31.
10. Chalasani N, Younossi Z. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. 2018;67(1):328–57.
11. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. Am J Gastroenterol. 1999;94(9):2467–74.
12. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005;41(6):1313–21.
13. Diehl AM, Day C. Cause, pathogenesis, and treatment of nonalcoholic steatohepatitis. N Engl J Med. 2017;377(21):2063–72.
14. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology. 1999;116(6):1413–9.
15. Brunt EM. Nonalcoholic fatty liver disease: pros and cons of histologic systems of evaluation. Int J Mol Sci. 2016;17(1).
16. Bedossa P, Poitou C, Veyrie N, Bouillot JL, Basdevant A, Paradis V, et al. Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients. Hepatology. 2012;56(5):1751–9.
17. Chalasani N, Wilson L, Kleiner DE, Cummings OW, Brunt EM, Unalp A. Relationship of steatosis grade and zonal location to histological features of steatohepatitis in adult patients with nonalcoholic fatty liver disease. J Hepatol. 2008;48(5):829–34.
18. Reeder SB, Cruite I, Hamilton G, Sirlin CB. Quantitative assessment of liver fat with magnetic resonance imaging and spectroscopy. J Magn Reson Imaging. 2011;34(4):spcone.
19. Idilman IS, Keskin O, Celik A, Savas B, Elhan AH, Idilman R, et al. A comparison of liver fat content as determined by magnetic resonance imaging-proton density fat fraction and MRS versus liver histology in non-alcoholic fatty liver disease. Acta Radiol (Stockholm, Sweden: 1987). 2016;57(3):271–8.
20. Heba ER, Desai A, Zand KA, Hamilton G, Wolfson T, Schlein AN, et al. Accuracy and the effect of possible subject-based confounders of magnitude-based MRI for estimating hepatic proton density fat fraction in adults, using MR spectroscopy as reference. J Magn Reson Imaging. 2016;43(2):398–406.
21. Sasso M, Miette V, Sandrin L, Beaugrand M. The controlled attenuation parameter (CAP): a novel tool for the non-invasive evaluation of steatosis using Fibroscan. Clin Res Hepatol Gastroenterol. 2012;36(1):13–20.
22. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73–84.
23. Byrne CD, Targher G. NAFLD: a multisystem disease. J Hepatol. 2015;62(1 Suppl):S47–64.
24. Caldwell S, Argo C. The natural history of non-alcoholic fatty liver disease. Dig Dis (Basel, Switzerland). 2010;28(1):162–8.
25. Cusi K, Chang Z, Harrison S, Lomonaco R, Bril F, Orsak B, et al. Limited value of plasma cytokeratin-18 as a biomarker for NASH and fibrosis in patients with non-alcoholic fatty liver disease. J Hepatol. 2014;60(1):167–74.
26. Chen J, Zhu Y, Zheng Q, Jiang J. Serum cytokeratin-18 in the diagnosis of non-alcoholic steatohepatitis: a meta-analysis. Hepatol Res. 2014;44(8):854–62.
27. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007;45(4):846–54.
28. Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann Med. 2011;43(8):617–49.
29. Kaswala DH, Lai M, Afdhal NH. Fibrosis assessment in nonalcoholic fatty liver disease (NAFLD) in 2016. Dig Dis Sci. 2016;61(5):1356–64.
30. Imajo K, Kessoku T, Honda Y, Tomeno W, Ogawa Y, Mawatari H, et al. Magnetic resonance imaging more accurately classifies steatosis and fibrosis in patients with nonalcoholic fatty liver disease than transient elastography. Gastroenterology. 2016;150(3):626–37.e7.
31. Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. Diabetologia. 2012;55(4):885–904.
32. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of

nonalcoholic steatohepatitis. Gastroenterology. 2015;149(2):367–78.e5. quiz e14–5

33. Silverman EM, Sapala JA, Appelman HD. Regression of hepatic steatosis in morbidly obese persons after gastric bypass. Am J Clin Pathol. 1995;104(1):23–31.
34. Mathurin P, Hollebecque A, Arnalsteen L, Buob D, Leteurtre E, Caiazzo R, et al. Prospective study of the long-term effects of bariatric surgery on liver injury in patients without advanced disease. Gastroenterology. 2009;137(2):532–40.
35.•• Lassailly G, Caiazzo R, Buob D, Pigeyre M, Verkindt H, Labreuche J, et al. Bariatric surgery reduces features of nonalcoholic steatohepatitis in morbidly obese patients. Gastroenterology. 2015;149(2):379–88. quiz e15–6. **This study assessed the effect of bariatric surgery on NASH histologic features in patients with biopsy proven NASH and severe obesity. The study showed that there was a significant reduction in the prevalence of steatosis, ballooning, lobular inflammation and fibrosis on a follow-up liver biopsy at one year after bariatric surgery.**
36. Mummadi RR, Kasturi KS, Chennareddygari S, Sood GK. Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2008;6(12):1396–402.
37.•• Bower G, Toma T, Harling L, Jiao LR, Efthimiou E, Darzi A, et al. Bariatric surgery and non-alcoholic fatty liver disease: a systematic review of liver biochemistry and histology. Obes Surg. 2015;25(12):2280–9. **This systematic review and meta-analysis pooled the data from the studies that assessed the effect of bariatric surgery on NAFLD liver histology and/or liver biochemistry. The study demonstrated a significant reduction in the incidence of all NAFLD histologic features and a significant improvement in liver enzymes following bariatric surgery.**
38. Chavez-Tapia NC, Tellez-Avila FI, Barrientos-Gutierrez T, Mendez-Sanchez N, Lizardi-Cervera J, Uribe M. Bariatric surgery for non-alcoholic steatohepatitis in obese patients. Cochrane Database Syst Rev. 2010;1:Cd007340.
39. Caiazzo R, Lassailly G, Leteurtre E, Baud G, Verkindt H, Raverdy V, et al. Roux-en-Y gastric bypass versus adjustable gastric banding to reduce nonalcoholic fatty liver disease: a 5-year controlled longitudinal study. Ann Surg. 2014;260(5):893–8. **discussion 8-9**
40. Kalinowski P, Paluszkiewicz R, Wroblewski T, Remiszewski P, Grodzicki M, Bartoszewicz Z, et al. Ghrelin, leptin, and glycemic control after sleeve gastrectomy versus roux-en-Y gastric bypass-results of a randomized clinical trial. Surg Obes Relat Dis. 2017;13(2):181–8.
41. Paluszkiewicz R, Kalinowski P, Wroblewski T, Bartoszewicz Z, Bialobrzeska-Paluszkiewicz J, Ziarkiewicz-Wroblewska B, et al. Prospective randomized clinical trial of laparoscopic sleeve gastrectomy versus open Roux-en-Y gastric bypass for the management of patients with morbid obesity. Wideochir Inne Tech Maloinwazyjne. 2012;7(4):225–32.
42. Kalinowski P, Paluszkiewicz R, Ziarkiewicz-Wroblewska B, Wroblewski T, Remiszewski P, Grodzicki M, 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(5):738–45.
43. Jirapinyo P, Thompson CC. Endoscopic bariatric and metabolic therapies: surgical analogues and mechanisms of action. Clin Gastroenterol Hepatol. 2017;15(5):619–30.
44. Sullivan S, Edmundowicz SA, Thompson CC. Endoscopic bariatric and metabolic therapies: new and emerging technologies. Gastroenterology. 2017;152(7):1791–801.
45. Lee YM, Low HC, Lim LG, Dan YY, Aung MO, Cheng CL, et al. Intragastric balloon significantly improves nonalcoholic fatty liver disease activity score in obese patients with nonalcoholic steatohepatitis: a pilot study. Gastrointest Endosc. 2012;76(4):756–60.
46. Popov VB, Ou A, Schulman AR, Thompson CC. The impact of Intragastric balloons on obesity-related co-morbidities: a systematic review and meta-analysis. Am J Gastroenterol. 2017;112(3):429–39.
47. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Journal of hepatology. 2016;64(6):1388–402.