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REVIEW ARTICLE

Current Controversies in Metabolic Surgery for Nonalcoholic Fatty Liver Disease

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Abstract
Nonalcoholic fatty liver disease (NAFLD) represents the most common liver disease, and it is expected to become the leading cause of end-stage liver disease in the near future. Bariatric operations have beneficial effects on NAFLD, inducing histological resolution of liver damage through weight loss-dependent and weight loss-independent mechanisms. Due to lack of randomized controlled trials, no specific guidelines have been established so far. Yet there is growing evidence that NAFLD will eventually become a formal indication for metabolic surgery. Data regarding the choice of procedure are conflicting, although gastric bypass seems to be slightly superior to sleeve gastrectomy. The purpose of this review is to provide an update on the ongoing research regarding the role of metabolic surgery in NAFLD management.

Keywords Nonalcoholic fatty liver disease · Liver steatosis · Steatohepatitis · Bariatric surgery · Metabolic surgery · Gastric bypass · Sleeve gastrectomy

Introduction

The term nonalcoholic fatty liver disease (NAFLD) refers to a broad spectrum of disease characterized of excessive fat deposition in the liver, in the absence of alcohol abuse, or any other secondary cause. NAFLD varies from simple steatosis to steatohepatitis (nonalcoholic steatohepatitis (NASH)) and liver fibrosis, with possible progression to cirrhosis and/or hepatocellular carcinoma [1]. Having a prevalence of more than 20% as well as an incidence of more than 30 new cases per 1000 persons per year, NAFLD has become a worldwide pandemic [2, 3]. Not only does NAFLD represent the most common liver disease in the western world but, most importantly, its prevalence continues to rise steadily over time [4, 5]. Even higher prevalence is reported in obese and diabetic patients, reflecting the close pathogenetic correlation between NAFLD, obesity, and metabolic syndrome. Indeed, NAFLD can be regarded as the hepatic manifestation of metabolic syndrome. More than 80% of morbidly obese patients have some sort of NAFLD, while the more severe forms (NASH, fibrosis) affect nearly 15% of obese patients [5]. For the time being, NAFLD represents the third most common cause of hepatocellular carcinoma and the second most common cause of end-stage liver disease and need for liver transplantation, after hepatitis C. Given the upward trend in its frequency as well as the production of more effective drugs against hepatitis C virus, it is estimated that during the following decade, NAFLD is going to emerge as the leading cause of end-stage liver disease [1, 6].

The primary hormonal derangement in most NAFLD patients is insulin resistance. Furthermore, several other fat-derived hormones, including leptin, adiponectin, and resistin, contribute to the development of steatosis and fibrosis mainly rendering hepatocytes more insulin-resistant. Insulin resistance leads to increased lipolysis and increased hepatic uptake of free fatty acids (FFAs). Through this process, hepatic fat gradually replaces normal liver tissue but without hepatic function impairment up to this point. In some patients,

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NAFLD presents with a progressive manner, leading to NASH, fibrosis, and even cirrhosis. The key in understanding this progressive biology is systemic inflammatory response, which is caused by the production of inflammatory cytokines in excess adipose tissue, the production of hepatotoxic free oxygen radical species (induced by FFAs), and hepatic release of inflammatory proteins (induced by oxidative stress). Specific composition of gut microbiota may also play a role in both the inflammatory and fibrosis responses in patients with NAFLD. Suggested mechanisms include the production of endogenous alcohol and acetaldehyde, endotoxin production, deconjugation of bile salts, and inactivation of hepatic lipotropes such as choline [5].

Apart of environmental etiologic factors, several genetic factors contribute as well to the pathogenesis of NAFLD. Multiple genome-wide association and large candidate gene studies have recently shed light on the genetic basis of NAFLD. At least four gene loci are associated with NAFLD susceptibility. The I148M PNPLA3 variant has been identified as the major common genetic determinant of NAFLD, while variants with moderate effect size in TM6SF2, MBOAT7, and GCKR have also been shown to have a significant contribution. Other gene loci are responsible for NAFLD progression through mechanisms including regulation of lipid metabolism, inflammation, insulin signaling, oxidative stress, and fibrogenesis [7].

Weight loss achieved by lifestyle interventions represents the primary therapy for most patients with NAFLD. Nevertheless, it is uniformly agreed that bariatric surgery is the most consistently effective method of sustained weight reduction [8]. Additionally, bariatric procedures have been shown to induce biochemical and histologic remission of NAFLD, through mechanisms of action that are both weight loss-dependent and weight loss-independent. The latter include changes in gut hormones, gastrointestinal motility, bile acids, gut microbiota as well as incomplete nutrient ingestion and absorption [9]. Taking all these factors into consideration, bariatric surgery represents a promising option for morbidly obese patients with NAFLD [5].

Although the aforementioned data stress the need for optimizing treatment strategies against NAFLD, bibliography lacks high-quality randomized controlled trials (RCTs) which will provide concrete evidence and support the establishment of specific guidelines. Main areas of controversy are the optimal procedure and the indications for surgical treatment. The purpose of this review is to provide an update on the ongoing research regarding these two questions.

Materials and Methods

A comprehensive literature search was conducted using the PubMed-NCBI database (MEDLINE) for reports published until October 1, 2018. English articles containing the terms "nonalcoholic fatty liver disease" OR "steatosis" OR "steatohepatitis" AND "surgical treatment" OR "bariatric surgery" OR "metabolic surgery" OR "gastric bypass" OR "sleeve gastrectomy" were retrieved for inclusion in this review article. Research was focused on studies dealing with the effectiveness of metabolic surgery on adults with NAFLD as well as with the choice of procedure.

Quality of Existing Data

The latest guidelines regarding surgical treatment of NAFLD were published by the American Association for the Study of Liver Disease in 2018, the Asia-Pacific Working Party on Nonalcoholic Liver Disease in 2017, and the European Association for the Study of the Liver in 2016 [1, 2, 10]. All three expert panels state that surgical treatment is clearly indicated in patients with NAFLD who also meet the criteria for bariatric surgery. Moreover, it is suggested that, for the time being, there is not enough evidence to consider surgical treatment in mildly obese patients with NAFLD and that such patients should be dealt with in a case-by-case basis.

Indeed, there are no high-quality RCTs available so far, and the existing studies are characterized by significant heterogeneity in terms of study design, patient selection criteria, scoring systems, and primary endpoints. Furthermore, intraobserver and interobserver variability between expert pathologists explains the wide range of rates reported in literature. These discrepancies among studies render data combining rather challenging.

One of the most principal differences is the use of various diagnostic methods, either for the initial diagnosis or for follow-up. The gold standard diagnostic test for NAFLD as well as the only method capable of distinguishing steatosis from NASH is liver biopsy [11]. Nevertheless, liver biopsy, either surgical or percutaneous, represents a costly and invasive procedure that carries hemorrhagic risks for the patient, especially an obese one. Obesity after all represents a relative contraindication for percutaneous liver biopsy [12]. Obtaining a liver biopsy during another operation (e.g., bariatric surgery) is relatively easy and does not increase the operative risk significantly. On the other hand, the morbidity of postoperative percutaneous biopsies during follow-up is non-negligible [13]. Another limitation of biopsy is that it does not provide information for the whole parenchyma, which is important in cases of inhomogeneous fat distribution [14]. Furthermore, wedge liver resection, which is the most familiar biopsy technique to most surgeons, may be misinterpreted by pathologists as it may contain subcapsular fibrosis not indicative of NAFLD [15]. Therefore, utilizing noninvasive modalities to diagnose NAFLD and follow-up patients is quite tempting, especially in the context of studies.

There are two general categories of noninvasive methods used to detect NAFLD and related liver fibrosis: radiologic and serologic tests. Imaging methods include ultrasound-based transient elastography, acoustic radiation force impulse imaging, controlled attenuation parameter (CAP), and cross-sectional imaging (CT, MRI, MRS/magnetic resonance spectroscopy, MRE/magnetic resonance elastography). Among them, ultrasound-based transient elastography (Fibroscan) is the most widely used. Elastography estimates liver stiffness by applying mechanical waves and measuring their propagation speed through tissue. Furthermore, a variety of serologic markers have been evaluated, and panels have been developed that combine assays of multiple markers to improve predictive ability. The best-validated scores are the fatty liver index (FLI), SteatoTest, NAFLD liver fat score, NAFLD fibrosis score, fibrosis 4 calculator (FIB-4), the aspartate aminotransferase (AST) to platelet ratio (APRI), FibroTest/FibroSure, Hepascore, and FibroSpect. The former three are steatosis scores, whereas the latter six are fibrosis scores. The NAFLD fibrosis score is based on six readily available variables (age, BMI, hyperglycemia, platelet count, albumin, APRI) and is calculated using the published formula (http://gihep.com/calculators/hepatology/nafld-fibrosis-score/). FIB-4 index (http://gihep.com/calculators/hepatology/fibrosis-4-score/) is an algorithm based on platelet count, age, AST, and ALT that offers dual cutoff values. Combining serologic panels with radiographic imaging may improve the ability to correctly assess the degree of a patient's fibrosis [1, 2, 16].

However, the use of noninvasive methods is subject to several limitations. First of all, all noninvasive tests do not diagnose NASH. Among imaging methods, ultrasound-based transient elastography (Fibroscan) has limited sensitivity and does not reliably detect steatosis when it is less than 20% or in individuals with BMI > 40 kg/m^2. Last but not least like all US techniques, it is observer dependent. Cross-sectional imaging techniques (MRI/CT) are more expensive and less widely available than Fibroscan. Moreover, serologic tests do not predict the severity of steatosis and do not reliably distinguish nonsignificant (F2/F1) fibrosis from no fibrosis [1, 2, 16].

Despite the aforementioned arguments of the proponents of noninvasive modalities, the employment of diagnostic methods other than biopsy is constantly reported as a major limitation of these studies. Therefore, studies regarding the efficacy of metabolic surgery on NAFLD have been classified in this review paper into two categories, depending on whether paired biopsies have been performed or not.

Safety and Efficacy of Metabolic Surgery in NAFLD Management

Despite the lack of RCTs, the undoubtedly promising results that have been reported regarding the beneficial effects of both gastric bypass and sleeve gastrectomy (SG) on NAFLD have prompted several authors to suggest that metabolic surgery should be regarded as an option to treat NAFLD alone, much like diabetes [4, 5, 17]. Metabolic surgery is nowadays indicated for the treatment of uncontrolled type 2 diabetes mellitus even in patients with BMI as low as 30 kg/m^2 (i.e., not eligible for bariatric surgery) [18]. Similarly, surgery could be offered to mildly obese patients with NAFLD, who do not fulfill the criteria for bariatric surgery. Indeed, this is the objective of a prospective RCT which started recently in Lille, France, organized by Philippe Mathurin, and that is estimated to be completed in 2023 (NASHSURG, ClinicalTrials.gov Identifier NCT03472157). Only patients with NASH-related advanced fibrosis and BMI = 30–35 kg/m^2 will be included in this study. Patients in the bariatric surgery arm will undergo either RYGB or SG. The aim of the study is to demonstrate the superiority of bariatric surgery on the disappearance of NASH without worsening of fibrosis in comparison to medical standard treatment in these patients.

Initial concerns about the safety of bariatric surgery in patients with advanced NAFLD seem to have been disproved. Singh et al. reported the results of bariatric surgery in 297 patients with NAFLD and liver fibrosis, concluding that surgery was safe even in patients with advanced fibrosis [19]. Kalinowski et al. have conducted the only RCT so far which was designed to compare the effect of RYGB and SG on liver function tests, utilizing liver biopsy only for the initial diagnosis. The authors reported early transient negative influence of RYGB on liver function (↑INR, ↓Alb) without clinical sequelae. Similar disturbances in liver biochemistry were not found after SG [20]. Even patients with compensated NASH cirrhosis (Child-Pugh class A) may represent candidates for bariatric surgery with slightly higher but acceptable morbidity and mortality, although this is not a well-established statement due to lack of relevant data [10, 21]. Rebibo et al. found that SG can be performed with the same safety in patients with NASH-related Child A cirrhosis and noncirrhotic patients [22]. However, a review of 11 studies on bariatric surgery in cirrhotic patients by Jan et al. indicated that no clear recommendations can be made, despite the fact that several authors reported encouraging results [21].

Postoperative worsening of liver fibrosis used to be a major concern after primarily malabsorptive procedures such as jejunoileal bypass that are no longer performed. In these procedures, liver fibrosis was possibly related to excessive bacterial overgrowth in the defunctionalized limb which led to liver damage through portal circulation and not to weight loss [23]. In 2009, Mathurin et al. published a prospective cohort study of 381 patients who were followed for 5 years. The authors concluded that postoperative weight loss is associated with worsening of liver fibrosis although the latter was not clinically significant. Specifically, 19.8% of patients showed fibrosis progression at 5 years and 80.2% regressed or remained unchanged. Yet, 95.7% of patients at the end of follow-up had a fibrosis score ≤ F1, and > 90% of patients with fibrosis worsening increased from F0 to F1. It has to be stressed though that 56% of patients underwent AGB, 23% biliointestinal bypass, which was later abandoned, and only 21% gastric bypass [24]. Recently, Schwenger et al. and Garg et al. also reported approximately 9.5% worsening of fibrosis after bariatric surgery in NAFLD patients, without clinical implications [15]. Yet, most relevant studies discussed in this review suggest that not only metabolic surgery does not worsen liver fibrosis but it leads to fibrosis resolution as well.

From an economic point of view, the only clinical and cost-effectiveness analysis by Klebanoff et al. suggested that metabolic surgery is cost-effective for both obese patients with NASH and for overweight patients with NASH-related advanced fibrosis. According to the authors, metabolic surgery should be offered as treatment for NASH without the need for further clinical trials. Patients with simple steatosis were not included in this study [17].

Several studies have reported significant improvement of NAFLD after gastric bypass and SG. Biopsy-proven resolution of NAFLD has been reported in high percentages by many authors [4, 15, 24–46]. Schwenger et al. found significant improvement in NAFLD 12 months after RYGB, including steatosis, lobular inflammation, hepatocyte ballooning, and fibrosis [15]. Esquivel et al. also reported improvement in steatosis and steatohepatitis, whereas fibrosis group was not amenable to statistical analysis due to its small size [4]. Aldoheyan et al. reported the phase 1 results of their trial, according to which significant improvement was noticed following bariatric surgery in steatosis and fibrosis. Lobular inflammation and hepatocyte ballooning did not change significantly during follow-up, which was only 3 months [26]. Garg et al. found biopsy-proven improvement in steatosis, lobular inflammation, hepatocyte ballooning, and fibrosis in 76 patients with NAFLD after bariatric surgery [25]. A large retrospective study with paired biopsies by Taitano et al. found 75% resolution of steatosis, 90% resolution of NASH, and 50% resolution of fibrosis [29]. Parker et al. also reported that RYGB reversed NASH and fibrosis histologically in a large cohort of 105 patients [28]. Similar results were reported by Lassailly et al. according to which NASH disappeared in 85% of the patients and fibrosis was reduced in 34% of patients [27]. Moretto et al. focused on the effect of RYGB on hepatic fibrosis, and concluded that weight loss is associated with reduction in the prevalence of fibrosis [33]. A summary of studies with results based on paired liver biopsies is presented in Table 1.

Other studies have shown even greater percentages of NAFLD resolution following surgery, but in these studies, the results were not histologically proven as liver biopsy was not part of their protocol for the initial diagnosis, for follow-up, or even both. Researchers have utilized instead several different noninvasive methods, including serologic panels, radiographic tests, and liver function tests [14, 47–56]. The results of these studies are summarized in Table 2.

More recently, research interests shifted towards a more targeted approach to NAFLD treatment, based on the patients' genetic predisposition. Literature indicates a close association between NAFLD and PNPLA3 polymorphism, with each allele demonstrating different response to various therapies. Patients with the C allele (148M variant) seem to benefit more from metabolic surgery, although this genotype is associated with more severe NAFLD [57, 58]. Consequently, genotype stratification could further assist patient selection for surgical treatment of NAFLD.

Given the multifactorial pathogenetic model of NAFLD, the efficacy of surgery in treating NAFLD could be lessened by the continued presence of risk factors postoperatively, some of which are modifiable. All patients should be strongly advised to refrain from excessive alcohol consumption because it is associated with disease progression. Vaccination against hepatitis A and hepatitis B should be undertaken to patients without serologic evidence of immunity. Continuance of lifestyle interventions such as dietary therapy and exercise in the postoperative period is of paramount importance in order to achieve sustainable results. Finally, risk factors for cardiovascular disease such as diabetes, hypertension, and hyperlipidemia should be identified preoperatively. If present, these conditions should be treated appropriately as they can adversely affect the overall outcome. Consequently, any modifiable risk factor should be identified and modified preoperatively in order to maximize the efficacy of bariatric surgery in NAFLD management [59, 60].

Comparison Between Bypass and Nonbypass Procedures for NAFLD

The optimal metabolic procedure for the treatment of NAFLD has not been yet elucidated. Several studies have addressed this question comparing the effectiveness of different procedures on NAFLD resolution, with conflicting results (Table 3). Consequently, no specific statement regarding the choice of procedure has been made in the latest guidelines for the management of NAFLD [1, 2, 10].

Theoretically, the effectiveness of each procedure in improving weight-related comorbidities mainly depends on its metabolic actions. Hormonal effects of RYGB are nowadays recognized as far more important in correcting metabolic disorders than restriction and malabsorption, which were previously considered as the only mechanisms of action. These hormonal effects are mediated by changes in the expression of signaling peptides. The "foregut hypothesis" suggests that these changes are caused by the bypass of the duodenum, whereas the "hindgut hypothesis" focuses on the rapid entry

Table 1 Summary of studies dealing with the impact of metabolic surgery on NAFLD, based on paired biopsies

Author	Year	Number of patients	Type of operation	Outcome
Schwenger et al. [15]	2018	42	RYGB	78% resolution of NAFLD
				9.5% worsening of fibrosis
Garg et al. [25]	2018	32	RYGB	Improvement of steatosis, inflammation, and fibrosis
			SG OAGB	FibroScan is accurate at diagnosing steatosis and fibrosis in obese patients
Esquivel et al. [4]	2018	43	SG	100% improvement of NAFLD
Parker et al. [28]	2017	37	RYGB	RYGB reverses NASH and fibrosis (70% normalization, stable or reduced severity in the remaining patients)
Aldoheyan et al. [26]	2017	27	BPD-DS RYGB	Improvement of steatosis and fibrosis (not inflammation and hepatocyte ballooning)
			AGB SG	Phase 1 report—short follow-up (3 months)
Schneck et al. [46]	2016	9	RYGB	Improvement of steatosis and NASH
Lassailly et al. [27]	2015	109	BIB	NASH disappeared in 85% of patients
			AGB RYGB	Fibrosis was reduced in 34% of patients
			SG	
Taitano et al. [29]	2014	160	RYGB	75% resolution of steatosis
			AGB	90% resolution of NASH
				50% resolution of fibrosis
Vargas et al. [30]	2012	26	RYGB	Improvement of steatosis, NASH, and fibrosis
Tai et al. [39]	2012	21	RYGB	Improvement of steatosis, NASH, and fibrosis
Moretto et al. [33]	2012	78	RYGB	Improvement of fibrosis (44.8% → 30.8%)
				11.6% new-onset fibrosis at follow-up biopsy
Weiner et al. [38]	2010	116	RYGB AGB	Complete regression of NAFLD in 82.8%
			BPD-DS	
Mathurin et al. [24]	2009	381	BIB	19.8% worsening of fibrosis
			AGB	Improvement of NASH (27.4% → 14.2%)
			RYGB	Improvement of steatosis (37.4% → 16%)
Furuya et al. [41]	2007	18	RYGB	Improvement of steatosis, NASH, and fibrosis
Liu et al. [40]	2007	39	RYGB	Improvement of steatosis and NASH
				Fibrosis unchanged
de Almeida et al. [42]	2006	16	RYGB	Improvement of steatosis, NASH, and fibrosis
Barker et al. [43]	2006	19	RYGB	Improvement of steatosis, NASH, and fibrosis
Csendes et al. [45]	2006	16	RYGB	Improvement of steatosis and NASH
Keshishian et al. [34]	2005	78	BPD-DS	60% improvement of steatosis
				Improvement of NASH
Mattar et al. [35]	2005	70	RYGB SG	Improvement of steatosis (88% → 8%), NASH (23% → 2%), and fibrosis (31% → 13%)
			AGB	Overall improvement of 82% in grade and 39% in stage of liver disease
Mottin et al. [36]	2005	90	RYGB	82% improvement of steatosis
Clark et al. [44]	2005	16	RYGB	Improvement of steatosis, NASH and fibrosis
Stratopoulos et al. [37]	2005	51	VBG	84% improvement of NASH and 47% improvement of fibrosis
Kral et al. [32]	2004	104	BPD	Severe fibrosis decreased in 27%
				Mild fibrosis appeared in 40%
Silverman et al. [31]	1995	91	RYGB	Steatosis improvement in 91%

AGB adjustable gastric band, *BIB* biliointestinal bypass, *BPD* biliary-pancreatic diversion, *DS* duodenal switch, *GP* gastroplasty, *SG* sleeve gastrectomy, *RYGB* Roux-en-Y gastric bypass, *VBG* (Mason's) vertical banded gastroplasty, *OAGB* one anastomosis gastric bypass

Table 2 Summary of studies dealing with the impact of metabolic surgery on NAFLD, utilizing noninvasive diagnostic methods, instead of paired biopsies

Author	Year	Number of patients	Type of operation	Comments—outcome
Jimenez et al. [49]	2018	90	RYGB	No biopsy at all (NAFLD fibrosis score)
				Significant decrease in NAFLD fibrosis score
				Beneficial effect attenuated by weight regain
Luo et al. [56]	2018	49	RYGB	No biopsy for follow-up (MRI)
			SG	83.7% resolution of steatosis
				Decrease in liver volume
				No difference between the two procedures
Motamedi et al. [55]	2018	809	SG	No biopsy at all (ultrasonography, liver biochemistry)
			RYGB	Improvement in liver function parameters
			OAGB	Superiority of SG
Ruiz-Tovar et al. [48]	2017	50	SG	No biopsy at all (ultrasonography)
				90% resolution of steatosis
Ooi et al. [47]	2017	84	AGB	No biopsy for follow-up (liver function tests)
				Decrease in ALT levels precedes metabolic improvement
Hedderich et al. [14]	2017	19	RYGB	No biopsy at all (MRI).
			SG	Significant decrease in liver fat fraction and liver volume
Algooneh et al. [50]	2015	84	SG	No biopsy at all (ultrasonography)
				56% complete resolution of NAFLD
Alizai et al. [51]	2015	34	RYGB	No biopsy for follow-up (LiMAx test)
			SG	Significant functional recovery of the liver
Cazzo et al. [52]	2014	63	RYGB	No biopsy at all (NAFLD fibrosis score)
				55% resolution of advanced fibrosis
Burza et al. [53]	2013	3570	Non-AGB	No biopsy at all (AST, ALT)
			AGB	Comparison of surgery with usual care (Swedish Obese Subjects (SOS) Study)
			VBG GB	Bariatric surgery results in sustained reduction in transaminase levels
Karcz et al. [54]	2011	236	SG	No biopsy for follow-up (liver biochemistry) Improvement of NASH

AGB adjustable gastric banding, *OAGB* one anastomosis gastric bypass, *SG* sleeve gastrectomy, *RYGB* Roux-en-Y gastric bypass, *VBG* vertical-banded gastroplasty, *GB* gastric bypass, *non-AGB* nonadjustable gastric banding

of food in the distal small bowel. Implicated signaling peptides include glucagon-like peptide-1 (GLP-1), gastric inhibitory peptide (GIP), peptide YY, cholecystokinin (CCK), and oxyntomodulin. On the other hand, endocrine actions of SG include suppression of appetite secondary to decrease in ghrelin levels and increase in GLP-1 levels [23]. Therefore, metabolic comorbidity correction rates should be expected to be higher after RYGB than after SG, although the findings of several trials come in disagreement with this hypothesis.

In most of these trials, the comparison is made between "bypass" and "nonbypass" procedures. Although the majority of them deals with strictly metabolic procedures, some studies have included patients with adjustable gastric banding (AGB) in the nonbypass group, which being a purely restrictive operation that cannot be regarded as metabolic procedure [35, 56, 61, 67]. A study by Tan et al. for example suggested that one anastomosis gastric bypass (OAGB) is superior in NASH resolution than nonbypass procedures. Yet, the comparison was practically made between OAGB and AGB as the nonbypass group was comprised of 19 patients with AGB and only 3 patients with SG [61]. Of course weight reduction induced by AGB is likely to have beneficial effects in NAFLD through weight loss-dependent mechanisms, as shown by Dixon et al. [68]. However, the aforementioned comparisons disregard the weight loss-independent mechanisms of action that characterize metabolic surgery, thus underestimating the efficacy of nonbypass procedures.

Several reports have failed to show any difference between gastric bypass and SG in terms of NAFLD resolution. Luo et al. also included patients with AGB in the nonbypass group, but these patients represented only 6.1% of the total study population. The authors found no difference in NAFLD improvement between RYGB and SG [56]. Similar results have been reported by other authors as well [56, 62, 66].

Table 3 Summary of studies comparing the effectiveness of different metabolic procedures in NAFLD improvement

Author	Year	Number of patients	Type of operation	Outcome
Tan et al. [61]	2018	135	OAGB	No biopsy for follow-up (highly sensitive CRP)
			AGB	Superiority of OAGB in NASH resolution
			SG	Comparison practically made with AGB (very few SG)
Luo et al. [56]	2018	49	RYGB	No biopsy for follow-up (MRI)
			SG	83.7% resolution of steatosis
			AGB	Decrease in liver volume
				No difference between RYGB and SG (92.3% vs 80% resolution of steatosis, $p = 0.215$)
von Schonfels et al. [62]	2018	53	RYGB	Significant improvement of NAFLD
			SG	No difference between the two procedures
Motamedi et al. [55]	2018	809	SG	No biopsy at all (ultrasonography, liver biochemistry)
			RYGB	Improvement of liver function parameters
			OAGB	Superiority of SG
Nickel et al. [63]	2017	100	RYGB	No biopsy at all (transient elastography and laboratory-based fibrosis scores)
			SG	Superiority of RYGB in reducing liver stiffness
Kalinowski et al. [20]	2017	66	RYGB	RCT. No biopsy for follow-up
			SG	Early transient negative influence of RYGB only on liver function in patients with NASH (↑INR, ↓Alb) without clinical sequelae
Froylich et al. [64]	2016	23	RYGB	Total NAS improved after both
			SG	Only RYGB improved all baseline characteristics
Billeter et al. [65]	2016	34	RYGB	No biopsy at all. NAFLD was defined as ALT > 35 IU/L
			SG	SG better than in NAFLD improvement, based on liver function tests
Praveen Raj et al. [66]	2015	30	RYGB	Improvement of steatosis, inflammation, and fibrosis
			SG	No difference between the two procedures
Caiazzo et al. [67]	2014	1236	RYGB	578 pts. with paired biopsies at 1 year
			AGB	413 pts. with paired biopsies at 5 years
				RYGB superior to AGB in NAFLD improvement
				The superiority of RYGB was not entirely explained by weight loss
Mattar et al. [35]	2005	70	RYGB SG	Improvement of 82% in grade and 39% in stage of liver disease
			AGB	Better results with RYGB in liver disease (due to more weight loss)

AGB adjustable gastric banding, *SG* sleeve gastrectomy, *RYGB* Roux-en-Y gastric bypass, *OAGB* one anastomosis gastric bypass, *RCT* randomized controlled trial, *NAS* NAFLD activity score

Nickel et al. on the other hand included 100 patients that underwent RYGB or SG in their study and reported superiority of RYGB in reducing liver stiffness. Nevertheless, liver biopsy was not utilized in any stage of their protocol [63]. Froylich et al. also compared 23 patients with NAFLD who were submitted to RYGB or SG. Although total NAFLD activity score (NAS) improved after both procedures, only RYGB significantly improved all baseline characteristics [64]. Billeter et al. compared SG and RYGB in 34 obese patients with NAFLD and T2DM. The authors suggested that SG may have a better effect on NAFLD than RYGB in metabolically sick obese patients. However, the diagnosis of NAFLD was made based on elevated transaminase levels instead of biopsy [65]. Similarly, Motamedi et al. recently found advantage of SG over bypass procedures in improving liver function parameters, based on ultrasound and blood tests [55].

Conclusion

In 2010, a Cochrane Database systematic review regarding the effect of bariatric surgery on NASH in obese patients was unable to draw any unbiased conclusion due to lack of randomized clinical trials [69]. Eight years later, it is still premature to consider metabolic surgery as an established treatment for NAFLD. However, there is growing evidence from prospective and retrospective observational cohort studies regarding the beneficial effects of metabolic operations on NAFLD. According to literature, gastric bypass seems to be slightly superior to sleeve gastrectomy in improving NAFLD. Moreover, studies have shown that the mortality and morbidity of laparoscopic RYGB are similar to that of common operations such as laparoscopic cholecystectomy, laparoscopic appendectomy, and knee arthroplasty [70]. It is the authors' opinion that the combination of this data cannot be disregarded, although there is still a need for RCTs. In morbidly obese patients with any stage of NAFLD, the benefit from metabolic/bariatric surgery is clear. The unanswered question is whether the presence of advanced NAFLD in class I obese patients, that are not candidates for bariatric surgery, should lower the BMI threshold for metabolic surgery. The NASHSURG trial which will be completed in 2023 is expected to shed light on this question. Until then, the decision for surgical treatment in these patients should be taken in a case-by-case basis, as specific guidelines are not available.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Statement This article does not contain any studies with human participants or animals performed by authors.

Consent Statement For this type of study, formal consent is not required.

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