Can Nonalcoholic Steatohepatitis Be Surgically Cured?

Liver Histologic Comparison After Metabolic Surgery Versus Usual Care

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Objective: To compare histologic outcomes in patients with fibrotic nonalcoholic steatohepatitis (NASH) and obesity after metabolic surgery versus nonsurgical care.

Background: There are no published data comparing the effects of metabolic surgery versus nonsurgical care on histologic progression of NASH.

Methods: Repeat liver biopsies were performed in patients with body mass index > 30 kg/m^2 at a US health system whose baseline liver biopsy between 2004 and 2016 confirmed a histologic diagnosis of NASH including the presence of liver fibrosis, but without cirrhosis. Baseline characteristics of liver histology for patients who underwent simultaneous liver biopsy at the time of metabolic surgery were balanced with a nonsurgical control group using overlap weighting methods. The primary composite endpoint required both resolution of NASH and improvement of at least 1 fibrosis stage in the repeat liver biopsy.

Results: A total of 133 patients (42 metabolic surgery and 91 nonsurgical controls) had a repeat liver biopsy with a median interval of 2 years. Overlap weighting provided balance for baseline histologic disease activity, fibrosis stage, and time interval between liver biopsies. In overlap-weighted patients, 50.1% in the surgical and 12.1% in the nonsurgical group met the primary endpoint (odds ratio = 7.3; 95% CI, 2.8–19.2, $P < 0.001$). NASH resolution and fibrosis improvement occurred in 68.5% and 64.1% of surgical patients, respectively. Surgical and nonsurgical patients who met the primary endpoint lost more weight than their counterparts who did not meet the primary endpoint [mean weight loss difference in the surgical group: 12.2% (95% CI, 7.3%–17.2%) and in the nonsurgical group: 11.6% (95% CI, 6.2%–16.9%)].

Conclusions: Among patients with fibrotic noncirrhotic NASH, metabolic surgery resulted in simultaneous NASH resolution and fibrosis improvement in half of patients.

Keywords: bariatric surgery, fatty liver, gastric bypass, liver biopsy, metabolic surgery, NAFLD, NASH, sleeve gastrectomy, steatohepatitis

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Obesity is a major pathophysiological culprit of metabolic disease including nonalcoholic steatohepatitis (NASH). In recent years, in parallel to the rising worldwide epidemic of obesity, NASH has become the most common cause of cirrhosis. There is currently no licensed pharmacotherapy for NASH approved by regulatory authorities.[1–3]

Metabolic surgery (defined as procedures that influence metabolism by inducing weight loss and altering gastrointestinal physiology) is currently the most effective treatment for obesity and type 2 diabetes.[4–7] Recently, the SPLENDOR (Surgical Procedures and Long-term Effectiveness in NASH Disease and Obesity Risk) study showed that among patients with NASH and obesity, metabolic surgery compared with nonsurgical management was associated with a significantly reduced risk of incident major adverse liver outcomes (MALO) and major adverse cardiovascular events (MACE) during long-term follow-up.[1]

Small single-arm observational studies utilizing liver biopsy before and after surgery suggest that metabolic surgery may improve some histologic features of NASH.[8–10] However, there are no published data comparing the effects of metabolic surgery with nonsurgical care on the histologic progression of NASH. To address the current knowledge gap, hepatic histologic outcomes were compared between the metabolic surgery and the nonsurgical control group in the subset of SPLENDOR study patients who had a repeat liver biopsy in follow-up using overlap weighting statistical methods to precisely balance baseline histologic severity of liver injury among the study groups.

METHODS

Study Cohorts

Details of the SPLENDOR study including enrollment criteria, study cohorts, and exposures were published previously.[1] In brief, the study included adults (age between 18 and 80 years) with body mass index ≥ 30 kg/m^2 at the Cleveland Clinic Health System in the United States whose baseline liver biopsy between 2004 and 2016 confirmed a histologic diagnosis of NASH including the presence of liver fibrosis but without cirrhosis. Patients with causes of chronic liver disease other than NASH, history of excessive alcohol use, and history of

hepatocellular carcinoma were excluded. The study compared outcomes in metabolic surgery patients who underwent either a Roux-en-Y gastric bypass or sleeve gastrectomy with a nonsurgical control group.[1] Only fibrotic noncirrhotic NASH patients who had a repeat liver biopsy after the index date were included on this analysis.

The nonalcoholic fatty liver disease (NAFLD) Activity Score was calculated for each patient based on the cumulative scores of liver steatosis (graded 0–3), hepatocyte ballooning (graded 0–2), and lobular inflammation (graded 0–3). To meet the diagnostic criteria for NASH, having at least 1 point for each of steatosis, hepatocellular ballooning, and lobular inflammation was required. Liver fibrosis was staged as F0 (lack of fibrosis), F1 (perisinusoidal or periportal fibrosis), F2 (perisinusoidal and periportal fibrosis), F3 (bridging fibrosis), or F4 (cirrhosis). Grading and staging of biopsies were based on the NASH Clinical Research Network (NASH CRN) definitions.[11]

Simultaneous core needle biopsy from the left lobe of the liver under direct laparoscopic visualization was performed for all patients who underwent Roux-en-Y gastric bypass or sleeve gastrectomy. The date of surgery was considered the index date for surgical patients. Liver biopsy was obtained through a percutaneous or transjugular approach in the nonsurgical control group. The date of the first liver biopsy for which all selection criteria were met served as the index date for nonsurgical control patients.[1] Patients in the control group were advised on lifestyle modifications.

Primary Endpoint

The primary endpoint was a composite of simultaneous NASH resolution and fibrosis improvement.

Other Endpoints

NASH resolution was defined as no hepatocyte ballooning (grade 0), no more than mild residual inflammatory cells (grade 0 or 1), without worsening of liver fibrosis stage in the repeat liver biopsy.

Fibrosis improvement was defined as an improvement of at least 1 fibrosis stage of the Kleiner fibrosis classification[11] and no worsening of NASH (with worsening defined as an increase of at least 1 point in either the lobular inflammation grade or the hepatocyte ballooning grade) in the repeat liver biopsy.

Fibrosis progression was defined as the worsening of at least 1 fibrosis stage of the Kleiner fibrosis classification in the repeat liver biopsy.[11] Histologic progression to cirrhosis (F4) in the repeat liver biopsy was also considered an endpoint.

Other outcomes included change in the NAFLD Activity Score between the repeat and baseline liver biopsies (a continuous variable) and improvement of the NAFLD Activity Score by at least 2 points in the repeat liver biopsy (a binary outcome).

Changes from baseline to repeat liver biopsy in body weight and glycated hemoglobin (only for patients with diabetes at baseline) were compared between the 2 groups.

Statistical Analysis

Continuous variables were presented as median [interquartile range (IQR)]. Categorical variables were reported as frequency and percentage for crude samples and as percentage only for the weighted samples.

To balance surgical and nonsurgical patients who had a repeat liver biopsy, weighted samples were created using overlap weighting. Overlap weighting assigns weights to each patient that are proportional to the probability of that patient belonging to the opposite treatment group resulting in rigorous balance on the mean of all covariates included in the model. This approach can reproduce key aspects of randomized clinical trials and avoids some of the limitations associated with classic propensity score matching.[12,13] Histologic NAFLD Activity Score, liver fibrosis stage, and the time interval between liver biopsies were used for overlap weighting before comparing histologic changes among the study groups.

To compare groups after overlap weighting, logistic regression models with robust SEs were used when estimating effects for 6 binary outcomes. Linear models with similar robust errors were used for change in the NAFLD Activity Score. Odds ratios (ORs) or mean difference with 95% CIs were presented for all models.

Change in body weight and glycated hemoglobin between the metabolic surgery group and the nonsurgical control group was assessed with a linear mixed effect model using a 4-knot restricted cubic spline for time that was interacted with treatment.

A significance level of $\alpha = 0.05$ for 2-sided comparisons was considered to be statistically significant. All analyses were performed using the SAS software (version 9.4).

RESULTS

A total of 133 patients including 42 metabolic surgery and 91 nonsurgical control patients were studied (Table 1). Metabolic surgical procedures included Roux-en-Y gastric bypass (n = 35, 83%) and sleeve gastrectomy (n = 7, 17%). Among the overlap-weighted patients, the frequency of a histologic NAFLD Activity Score of 3 was 16.0%, 4 (25.3%), 5 (27.6%), 6 (21.5%), 7 (6.5%), and 8 (3.1%), and histologic fibrosis stage 1 (37.0%), stage 2 (32.9%), and stage 3 (30.2%) which were precisely similar between the metabolic surgery and nonsurgical control groups (Table 2). For clinical covariates, surgical patients had a higher risk profile at baseline including higher frequency comorbidities including diabetes, hypertension, and a greater Charlson Comorbidity Index than nonsurgical control patients (Table 1).

Among the overlap-weighted patients, the median time interval between the liver biopsies was 23.0 months (IQR: 15.0–46.0) for surgical patients and 28.0 months (IQR: 18.0–45.0) for nonsurgical control patients.

Primary Endpoint

At the end of the study period in the unweighted dataset, 23 patients in the surgical group and 10 patients in the nonsurgical group had simultaneous NASH resolution and fibrosis improvement.

Among the overlap-weighted patients, 50.1% in the surgical group and 12.1% in the nonsurgical group had simultaneous NASH resolution and fibrosis improvement (OR = 7.3; 95% CI, 2.8–19.2, $P < 0.001$) (Fig. 1, Table 3).

Other Histologic Endpoints

In the weighted samples, compared with nonsurgical patients, patients who underwent metabolic surgery had a greater reduction in the NAFLD Activity Score (3 vs 1 point, mean difference −1.9; 95% CI, −2.6 to −1.2), higher rates of improvement of NAFLD Activity Score ≥ 2 points (85.8% vs 37.8%, OR = 9.9; 95% CI, 3.8–26.3), NASH resolution (68.5% vs 22.7%, OR = 7.4; 95% CI, 3.0–18.3), fibrosis improvement (64.1% vs 21.7%, OR = 6.4; 95% CI, 2.6–15.7), and lower rate of fibrosis progression (5.6% vs 25.2%, OR = 0.2; 95% CI, 0.04–0.8) (Fig. 1, Table 3). Histologic progression to cirrhosis occurred in

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TABLE 1. Characteristics of Metabolic Surgery Patients and Nonsurgical Control Patients at the Index Date Before and After Overlap Weighting

	Crude (unweighted)			After overlap weighting		
Variables	**Metabolic surgery (N = 42)**	**Nonsurgical controls (N = 91)**	**Standardized difference***	**Metabolic surgery**	**Nonsurgical controls**	**Standardized difference***
Demographic data						
Sex			0.16			0.25
Male	10 (23.8)	28 (30.8)		24.0%	35.5%	
Female	32 (76.2)	63 (69.2)		76.0%	64.5%	
Age (yr)	48.4 (42.1–53.1)	50.3 (41.3–58.2)	−0.07	48.0 (42.1–53.1)	49.8 (41.3–57.8)	−0.12
BMI (kg/m^2)	46.6 (40.8–55.2)	35.5 (33.1–40.1)	1.34	45.4 (41.4–55.2)	36.3 (33.2–40.6)	1.81
Weight (kg)	127.2 (111.0–151.0)	104.3 (92.5–114.8)	1.18	126.5 (110.8–146.5)	107.6 (95.3–114.8)	1.49
Race			0.25			0.22
White	38 (90.5)	85 (93.4)		89.2%	92.6%	
Black	3 (7.1)	6 (6.6)		8.6%	7.4%	
Other	1 (2.4)	0		2.2%	0	
Annual zip code income ($)	55,002 (47,606–67,451)	59,722 (46,110–78,924)	−0.38	55,182 (46,110–67,451)	59,722 (46,110–84,910)	−0.76
Smoking status			0.05			0.04
Never	21 (50.0)	47 (51.6)		51.1%	52.5%	
Former	18 (42.9)	38 (41.8)		40.9%	39.0%	
Current	3 (7.1)	6 (6.6)		7.9%	8.5%	
Location			0.26			0.33
Florida	0	3 (3.3)		0	5.3%	
Ohio	42 (100.0)	88 (96.7)		100%	94.7%	
Medical history						
Charlson Comorbidity Index	3.0 (2.0–5.0)	3.0 (2.0–4.0)	0.35	4.0 (2.0–5.0)	3.0 (2.0–4.0)	0.58
Type 2 diabetes	21 (50.0)	40 (44.0)	0.12	49.7%	38.4%	0.23
Hypertension	33 (78.6)	33 (36.3)	0.95	78.5%	38.7%	0.88
Dyslipidemia	31 (73.8)	37 (40.7)	0.71	73.6%	47.8%	0.55
Heart failure	1 (2.4)	1 (1.10)	0.10	2.2%	1.9%	0.02
Coronary artery disease	0	2 (2.2)	−0.21	0	1.3%	−0.17
Cerebrovascular disease	0	1 (1.10)	−0.15	0	0.5%	−0.10
Clinical and laboratory data						
Systolic blood pressure (mm Hg)	135.0 (119.0–142.0)	133.0 (123.0–144.0)	−0.01	135.0 (119.0–141.0)	131.0 (124.0–141.0)	−0.06
Diastolic blood pressure (mm Hg)	73.0 (64.0–81.0)	77.5 (70.0–85.5)	−0.39	73.0 (64.0–82.0)	77.0 (71.0–86.0)	−0.60
HbA1c (%)†	6.9 (6.0–7.2)	6.7 (6.1–7.4)	−0.15	6.9 (6.0–7.1)	6.6 (6.0–7.2)	−0.16
Bilirubin (mg/dL)	0.5 (0.4–0.6)	0.4 (0.3–0.6)	0.27	0.5 (0.4–0.6)	0.4 (0.3–0.6)	0.49
ALT (IU/L)	40.0 (30.0–85.0)	77.0 (50.0–125.0)	−0.59	42.0 (30.0–90.0)	76.0 (49.0–124.0)	−0.83
AST (IU/L)	42.0 (31.0–63.0)	59.0 (41.0–88.0)	−0.43	43.0 (31.0–66.0)	56.0 (37.0–87.0)	−0.54
Albumin (g/dL)	4.4 (4.1–4.6)	4.4 (4.1–4.6)	−0.01	4.4 (4.1–4.6)	4.4 (4.0–4.7)	0.09
INR	1.0 (1.0–1.1)	1.0 (0.9–1.0)	0.07	1.0 (1.0–1.0)	1.0 (0.9–1.0)	0.37
Creatinine (mg/dL)	0.8 (0.6–1.0)	0.8 (0.7–0.9)	0.16	0.8 (0.6–1.0)	0.9 (0.7–0.9)	0.15
Platelet counts (k/μL)	246.0 (198.0–324.0)	243.5 (211.0–310.0)	0.10	243.0 (198.0–334.0)	239.0 (199.0–304.0)	0.19
HDL (mg/dL)	43.0 (38.0–49.0)	44.0 (37.0–50.0)	−0.06	42.0 (38.0–49.0)	45.0 (38.0–50.0)	−0.19
LDL (mg/dL)	106.5 (84.0–129.0)	112.5 (92.0–151.0)	−0.43	108.0 (87.0–130.0)	116.0 (93.0–149.0)	−0.61
Triglycerides (mg/dL)	152.0 (120.0–238.0)	165.0 (124.5–233.0)	0.22	140.0 (120.0–238.0)	163.0 (127.0–233.0)	0.36
Medication history						
Noninsulin diabetes medications	20 (47.6)	28 (30.8)	0.35	47.3%	27.4%	0.42
Insulin	10 (23.8)	2 (2.2)	0.68	24.6%	3.4%	0.64
Lipid-lowering medications	22 (52.4)	26 (28.6)	0.50	49.3%	27.3%	0.46
Antihypertensive medications	31 (73.8)	48 (52.7)	0.45	73.9%	52.6%	0.45
Vitamin E	2 (4.8)	3 (3.3)	0.07	4.4%	4.0%	0.02

Statistics reflect medians (IQR) or n (%). After overlap weighting, a single individual no longer represents a single data entity and thus raw counts are not reported after overlap weighting.

*Standardized differences are the absolute value of the difference in means or proportions between the groups (metabolic surgery−nonsurgical control group) divided by pooled standard deviation.

†Only in patients with type 2 diabetes at baseline.

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; INR, international normalized ratio; LDL, low-density lipoprotein cholesterol.

TABLE 2. Liver Biopsy Characteristics of Metabolic Surgery Patients and Nonsurgical Control Patients at the Index Date Before and After Overlap Weighting

	Crude (unweighted)			After overlap weighting		
Variables	Metabolic surgery (N = 42)	Nonsurgical controls (N = 91)	Standardized difference*	Metabolic surgery	Nonsurgical controls	Standardized difference*
First liver biopsy date	9/25/2009 (12/10/2008–8/19/2011)	3/17/2009 (3/13/2008–12/28/2011)	0.03	10/06/2009 (12/10/2008–8/19/2011)	5/29/2009 (3/21/2008–3/16/2012)	0.03
Interval between first and last liver biopsies (mo)	19.0 (14.0–38.0)	37.0 (20.0–67.0)	−0.60	23.0 (15.0–46.0)	28.0 (18.0,45.0)	0 †
Steatosis Score			0.15			0.21
1	14 (33.3)	24 (26.4)		25.6%	33.2%	
2	17 (40.5)	40 (44.0)		40.0%	41.6%	
3	11 (26.2)	27 (29.7)		34.4%	25.2%	
Lobular Inflammation Score			0.35			0.08
1	26 (61.9)	41 (45.1)		54.4%	51.8%	
2	14 (33.3)	42 (46.2)		39.9%	40.5%	
3	2 (4.8)	8 (8.8)		5.7%	7.8%	
Hepatocyte Ballooning Score			0.52			0.26
1	33 (78.6)	50 (54.9)		73.5%	61.5%	
2	9 (21.4)	41 (45.1)		26.5%	38.5%	
NAFLD Activity Score			0.53			0 †
3	10 (23.8)	9 (9.9)		16.0%	16.0%	
4	12 (28.6)	18 (19.8)		25.3%	25.3%	
5	10 (23.8)	30 (33.0)		27.6%	27.6%	
6	7 (16.7)	22 (24.2)		21.5%	21.5%	
7	2 (4.8)	11 (12.1)		6.5%	6.5%	
8	1 (2.4)	1 (1.10)		3.1%	3.1%	
Fibrosis stage			0.23			0 †
1	18 (42.9)	29 (31.9)		37.0%	37.0%	
2	13 (31.0)	32 (35.2)		32.9%	32.9%	
3	11 (26.2)	30 (33.0)		30.2%	30.2%	

Statistics reflect median (IQR) or n (%). After overlap weighting, a single individual no longer represents a single data entity and thus raw counts are not reported after overlap weighting.

*Standardized differences are the absolute value of the difference in means or proportions between the groups (metabolic surgery−nonsurgical control group) divided by pooled standard deviation.

†Overlap weighting provided exact balance for these important variables.

3.1% of surgical patients versus 13.8% of nonsurgical control group (OR = 0.2; 95% CI, 0.03–1.6).

Status of Obesity and Diabetes Over Time

In the nonsurgical control group, 17 (18.6%) patients were prescribed pharmacotherapies with weight loss effects between the 2 liver biopsies including liraglutide (n = 12), lorcaserin (n = 2), naltrexone-bupropion (n = 2), phentermine or phentermine-topiramate (n = 2), and orlistat (n = 1).

The mean body weight at 3 years in patients in the surgical and nonsurgical groups was reduced by 24.3% (95% CI, 21.6%–26.9%) and 2.8% (95% CI, 0.9%–4.6%), respectively (mean difference: 21.5%; 95% CI, 18.3%–24.7%, $P < 0.001$) (Fig. 2A).

Among the metabolic surgery group, patients who met the primary endpoint lost more weight (28.4%; 95% CI, 25.1%–31.7%) compared with patients who did not meet the primary endpoint (16.3%; 95% CI, 12.7%–19.8%) with a mean difference of 12.2% (95% CI, 7.3%–17.2%, $P < 0.001$). Similarly, in the nonsurgical control group, a subgroup who met the histologic primary endpoint lost more weight (13.0%; 95% CI, 8.0%–18.1%) compared with patients who did not meet the primary endpoint (1.5%; 95% CI, −0.3% to 3.3%) with a mean difference of 11.6% (95% CI, 6.2%–16.9%, $P < 0.001$) (Fig. 2B).

Among patients with type 2 diabetes at baseline, mean changes in glycated hemoglobin at 3 years compared with baseline were −1.3% (95% CI, −1.7% to −0.9%) in the metabolic surgery group and 0.2% (95% CI, −0.2 to 0.5) in the nonsurgical control group [mean difference in changes from baseline at 3 years between groups: 1.4% (95% CI, 0.9–2.0), $P < 0.001$] (Fig. 3).

DISCUSSION

In this observational comparative study among patients with fibrotic noncirrhotic NASH, metabolic surgery resulted in simultaneous NASH resolution and fibrosis improvement in half of the patients with 7 times greater odds of meeting the primary endpoint compared with nonsurgical care. Separate analyses in the surgical and nonsurgical groups also suggest a dose-response relationship; greater weight loss leads to a higher rate of histologic improvement of fibrotic NASH.

Successful management of NASH requires a therapy to minimize the risk of major clinical adverse events including MALO and MACE and, at the same time, reverse or decrease the severity of liver damage.[1–3] The SPLENDOR study showed that surgically induced weight loss could reduce the risk of MALO by 88% and MACE by 70% in patients with NASH.[1] That was the first study showing a therapy that could reduce the risk of major clinical adverse events in patients with NASH. Findings from the subset of SPLENDOR study participants who

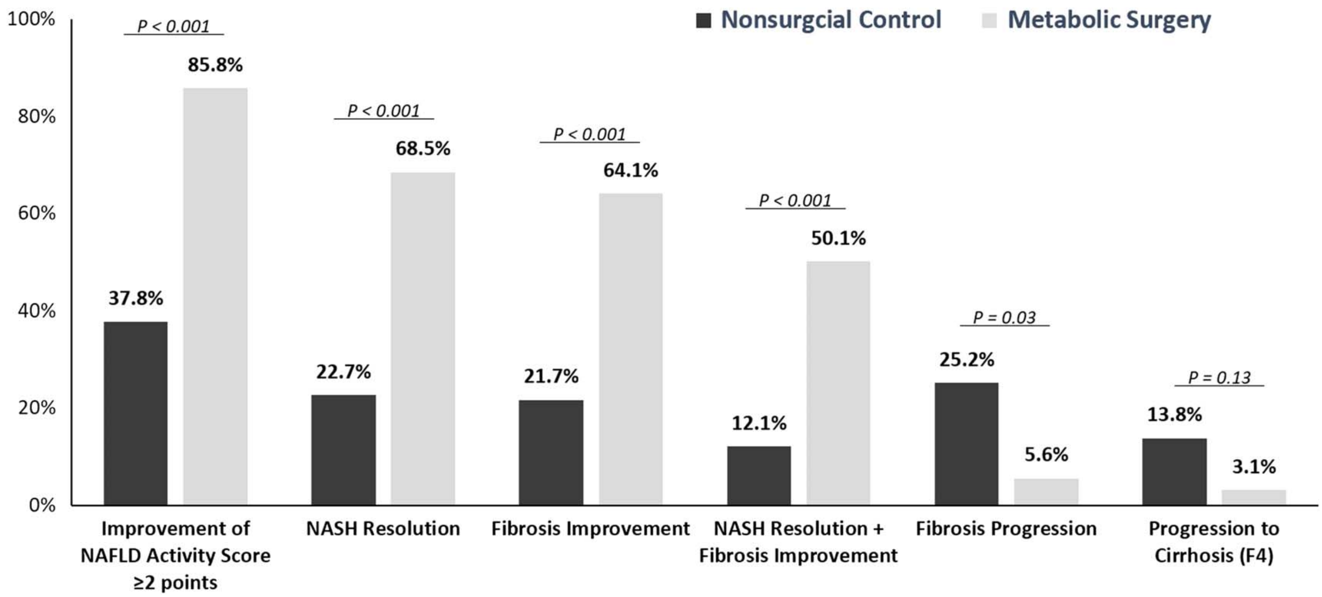

FIGURE 1. Changes in liver histology of metabolic surgery patients and nonsurgical control patients after overlap weighting (N = 133). Overlap weighting provided precise balance for baseline NAFLD Activity Score, fibrosis stage, and time interval between liver biopsies. NASH resolution was defined as no hepatocyte ballooning (score of 0), no more than mild residual inflammatory cells (score of 0 or 1), without worsening of liver fibrosis stage in the repeat liver biopsy. Fibrosis improvement was defined as an improvement of at least 1 fibrosis stage of the Kleiner fibrosis classification and no worsening of NASH (with worsening defined as an increase of ≥ 1 point in either the lobular inflammation score or the hepatocyte ballooning score according to the NASH Clinical Research Network criteria) in the repeat liver biopsy. Fibrosis progression was defined as the worsening of at least 1 fibrosis stage of the Kleiner fibrosis classification in the repeat liver biopsy.

had repeat liver biopsy suggest that metabolic surgery is also associated with improvement of all histologic outcomes of NASH examined in the current study. Nearly two third of patients experienced NASH resolution or fibrosis improvement after metabolic surgery, while half the patients had both outcomes simultaneously. In only 2 surgical patients, repeat liver biopsy showed progression of fibrosis with only 1 case of cirrhosis.

TABLE 3. Changes in Liver Histology of Metabolic Surgery Patients and Nonsurgical Control Patients Before and After Overlap Weighting

	Crude (unweighted)		After overlap weighting*			
Histologic outcome	Metabolic surgery (N = 42)	Nonsurgical controls (N = 91)	Metabolic surgery	Nonsurgical controls	Odds ratio or mean difference (95% CI)†	*P*
Change in NAFLD Activity Score	−3.0 (−4.0, −2.0)	−1.00 (−2.0, 0)	−3.0 (−4.0, −2.0)	−1.0 (−2.0, 0)	−1.9 (−2.6, −1.2)	< 0.001
Improvement of NAFLD Activity Score ≥ 2 points	35 (83.3)	38 (41.8)	85.8%	37.8%	9.9 (3.8–26.3)	< 0.001
NASH resolution‡	30 (71.4)	17 (18.7)	68.5%	22.7%	7.4 (3.0–18.3)	< 0.001
Fibrosis improvement§	29 (69.0)	19 (20.9)	64.1%	21.7%	6.4 (2.6–15.7)	< 0.001
NASH Resolution+Fibrosis Improvement‖	23 (54.8)	10 (11.0)	50.1%	12.1%	7.3 (2.8–19.2)	< 0.001
Fibrosis progression¶	2 (4.8)	29 (31.9)	5.6%	25.2%	0.2 (0.04–0.8)	0.03
Cirrhosis#	1 (2.4)	16 (17.6)	3.1%	13.8%	0.2 (0.03–1.6)	0.13

Statistics reflect median (IQR) or n (%). After overlap weighting, a single individual no longer represents a single data entity and thus raw counts are not reported after overlap weighting.

*Overlap weighting provided exact balance for baseline NAFLD Activity Score, fibrosis stage, and the time interval between liver biopsies.

†Odds ratios reflect metabolic surgery versus nonsurgical controls (values > 1 reflect greater prevalence after metabolic surgery). The mean difference in the NAFLD Activity Score reflects metabolic surgery versus nonsurgical controls (a value <0 reflects a greater decrease after metabolic surgery).

‡Defined by the NASH Clinical Research Network as no hepatocyte ballooning (score of 0), no more than mild residual inflammatory cells (score of 0 or 1), without worsening of liver fibrosis stage in the repeat liver biopsy.

§An improvement of at least 1 fibrosis stage of the Kleiner fibrosis classification and no worsening of NASH (with worsening defined as an increase of ≥ 1 point in either the lobular inflammation score or the hepatocyte ballooning score according to the NASH Clinical Research Network criteria) in the repeat liver biopsy.

‖Presence of both NASH resolution ‡ and fibrosis improvement §.

¶Worsening of at least 1 fibrosis stage of the Kleiner fibrosis classification in the repeat liver biopsy.

#Progression of fibrosis stage to F4 (cirrhosis) in the repeat liver biopsy.

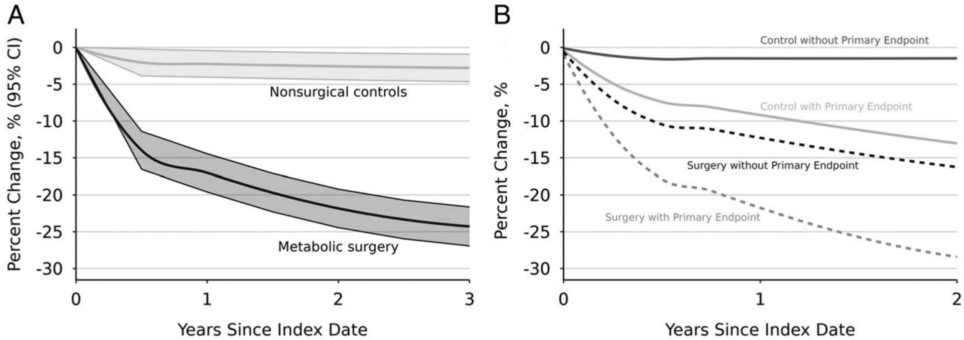

FIGURE 2. Mean trend curves of weight changes over 3 years of follow-up among overlap-weighted patients. A, Percent changes in body weight from baseline until the repeat liver biopsy in surgical and nonsurgical patients. Shaded areas indicate 95% CIs. The mean difference in weight changes between groups at 3 years from baseline was 21.5% (95% CI, 18.3%–24.7%) which was estimated from a flexible regression model with a 4-knot spline on time that was interacted with treatment. B, Percent changes in body weight in surgical and nonsurgical patients stratified by meeting versus not meeting the primary histologic endpoint (simultaneous NASH resolution and fibrosis improvement). Among the metabolic surgery group, patients who met the primary endpoint lost more weight compared with patients who did not meet the primary endpoint with a mean difference of 12.2% (95% CI, 7.3%–17.2%) at 2 years. Similarly, in the nonsurgical control group, a subgroup who met the histologic primary endpoint lost more weight compared with patients who did not meet the primary endpoint with a mean difference of 11.6% (95% CI, 6.2%–16.9%) at 2 years.

A few small randomized clinical trials utilizing repeat liver biopsy have reported some histologic benefits for a small number of medications including vitamin E (NASH resolution in 36% and fibrosis improvement in 41%),[14] pioglitazone (NASH resolution in 47% and fibrosis improvement in 44%),[14] obeticholic acid (NASH resolution in 22% and fibrosis improvement in 35%),[15] liraglutide (NASH resolution in 39% and fibrosis improvement in 26%),[16] and semaglutide (NASH resolution in 59% and fibrosis improvement in 43%).[17] Compared with pharmacotherapy, the magnitude of histologic benefits is larger after metabolic surgery. In the current study, both in the crude data and in the weighted sample, approximately 70% of patients experienced NASH resolution or fibrosis improvement after metabolic surgery. A prospective study from France in 64 patients with NASH who had baseline fibrosis stage of 0 to 4 and a mean baseline body mass index of 48 kg/m^2 reported histologic changes 5 years after metabolic surgery. Postsurgical liver biopsy showed NASH resolution in 84% (95% CI, 73%–92%) and fibrosis improvement in 70% (95% CI, 57%–82%) of patients. Compared with gastric banding, Roux-en-Y gastric bypass was associated with a significantly greater rate of NASH resolution (68% vs 90%).[8] Similar findings have been reported in meta-analyses of small single-arm case series utilizing paired liver biopsy before and after metabolic surgery.[18,19] These findings are not surprising because obesity is the main pathophysiologic driver for the development and progression of NASH[1–3,20] and metabolic surgery is the most effective treatment for obesity and associated type 2 diabetes.[4–7] In the current study, surgical patients who met the primary endpoint lost 28% of their body weight, which could reverse histopathological changes and prevent progressive liver injury.

FIGURE 3. Mean trend curves of glycated hemoglobin changes over 3 years of follow-up among overlap-weighted patients. The figure displays absolute changes in glycated hemoglobin values (%) for patients with type 2 diabetes from baseline until the repeat liver biopsy in surgical and nonsurgical patients. Shaded areas indicate 95% CIs. The mean difference in absolute changes in glycated hemoglobin values between groups at 3 years from baseline was 1.4% (95% CI, 0.9–2.0) which was estimated from a flexible regression model with a 4-knot spline on time that was interacted with treatment.

In patients with obesity and NASH, the current guidelines recommend weight loss.[21,22] Our findings support these recommendations. However, instead of focusing on lifestyle modification alone, treating obesity with effective and durable medications and interventions is likely required. Metabolic surgery and, to a lesser extent, glucagon-like peptide-1 analogs (eg, semaglutide) can provide global metabolic benefits including weight loss, glycemic control, decreased risk of cardiovascular disease, and histologic improvement of NASH which would be reasonable choices in the holistic approach to obesity and metabolic disease. Given the growing epidemic of obesity and NASH globally, the current findings have considerable public health implications.

This observational study has several limitations. First, of 1158 patients included in the SPLENDOR study, only 11% had a repeat liver biopsy in the follow-up and were included in this analysis. Clinical reasons for repeat liver biopsy in this subset of

patients are not known, but we would not expect the reasons to obtain the repeat liver biopsy to be different between the surgical and nonsurgical control groups. Second, sampling bias and interobserver inconsistency are recognized challenges in histologic assessments of liver biopsies.[2,3] Third, while overlap weighting created a detailed balance for histologic NAFLD Activity Score, fibrosis stage, and time interval to repeat liver biopsy between the 2 groups, there was an imbalance in some baseline clinical variables. Therefore, unmeasured and residual measured confounders could have influenced the findings. Nonetheless, most existing imbalances favored the nonsurgical control group (eg, lower frequency of diabetes in the control group). Fourth, the small sample size generated wide CIs for study outcomes and limited our ability to precisely estimate the magnitude of effects. Fifth, misclassification bias can occur in studies based on electronic medical records. Sixth, the small sample size of surgical patients precluded comparative analysis of gastric bypass versus sleeve gastrectomy on study outcomes. Seventh, although all patients in the nonsurgical control group were advised on lifestyle modifications, <20% of them were prescribed pharmacotherapies with weight loss effects.

CONCLUSION

Among patients with fibrotic noncirrhotic NASH, metabolic surgery resulted in simultaneous NASH resolution and fibrosis improvement in half of the patients with 7 times greater odds to meet this endpoint than nonsurgical care.

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