





ORIGINAL ARTICLE

Bariatric surgery proves long-term benefit in patients with cirrhosis

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Abstract

Background: Obesity is commonly observed in patients with cirrhosis, especially with the increasing prevalence of non-alcoholic steatohepatitis (NASH). Bariatric surgery has been avoided in these patients given concerns about increased peri-operative risk; therefore, data are lacking regarding long-term outcomes. In this study, we aimed to evaluate the long-term outcomes of patients with cirrhosis who underwent bariatric surgery.

Methods: We reviewed the charts of adult patients with compensated cirrhosis who underwent bariatric surgery after they were prospectively enrolled between February 23, 2009 and November 9, 2011, and followed in a pilot study for evaluation of bariatric surgery outcomes. Only patients with more than 4 years of follow-up were included in the analysis. Data regarding their liver disease, metabolic status, and survival were collected. A descriptive analysis was performed.

Results: The cohort consisted of 10 patients, of whom 7 were females. The median post-surgical follow-up was 8.7 years (± 1.4 years). All patients had biopsy-proven NASH; two patients had concurrent, untreated hepatitis C infection. During the observation period, there was a mean weight loss of 24 kg (19.2% of total body weight pre surgery, $P < 0.001$) and only one patient regained weight to the baseline pre-surgical measurement. One patient who was not eligible for transplant developed hepatic encephalopathy 3 years after surgery and later died. The remainder of the patients did not have any hepatic decompensation, cardiovascular event, or mortality. Except for one patient with Gilbert syndrome, bilirubin was normal in all patients at last follow-up.

Conclusions: Bariatric surgery in patients with compensated cirrhosis can lead to sustained weight loss and stable hepatic function on long-term follow-up.

Key words: obesity; weight loss; bariatric surgery; cirrhosis; non-alcoholic steatohepatitis

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Introduction

Cirrhosis secondary to non-alcoholic steatohepatitis (NASH) has become the fastest-growing and the second most common indication for liver transplant in the USA [1]. In fact, NASH cirrhosis is currently the most common indication for liver transplant among women in the USA [2]. There are ~400,000 cases of NASH-related cirrhosis and 4 million cases of NASH-related advanced fibrosis in the US population [3]. At the global level, it is estimated that there are 671 million and 425 million patients with obesity and diabetes mellitus, respectively [4], which suggests that NASH can become the most common liver disease in the world in the near future. Preventing or slowing the progression to end-stage liver disease and undergoing transplantation is critically important for NASH patients, especially with the paucity of available organs for transplant. In the absence of approved pharmacologic therapy for NASH, bariatric surgery has been shown to improve the outcomes in these patients [5, 6], although it has not gained momentum in patients with cirrhotic-stage NASH. This likely reflects concerns regarding perioperative complications secondary to portal hypertension [7], as well as the decreased perceived value of this intervention when cirrhosis is established. Obesity, however, has been shown to independently increase the risk of decompensation in patients with cirrhosis [8]. Recent data suggest that weight loss can result in a significant decrease in hepatic vein–portal vein pressure gradient measurements [9], which is an important surrogate of portal-hypertension severity. With obesity affecting approximately one-third of patients with cirrhosis [8], investigating the efficacy and safety of potential therapeutic interventions becomes of paramount importance. We have previously reported safety and favorable short-term metabolic and liver-related outcomes for bariatric surgery in patients with compensated NASH-related cirrhosis with or without mild portal hypertension, in a prospective pilot study [10]. In this report, we present the long-term follow-up data for that cohort of patients [10].

Methods

Study population and design

This study is a retrospective analysis of records of obese patients with compensated cirrhosis who underwent bariatric surgery at the Mayo Clinic, Rochester (MN, USA) as part of a prospective pilot study (enrolled patients between February 23, 2009 and November 9, 2011, previously published by Pestana *et al.* [10]) and had documented long-term follow-up after surgery. All patients had cirrhosis with active NASH confirmed by liver biopsy that was performed perioperatively in eight patients, 3 months before surgery in one patient, and 2 years before surgery in another patient. Two patients had concurrent, untreated hepatitis C infection, which was not genotype 3. All patients were Child–Pugh class A. Six patients had evidence of clinically significant portal hypertension before surgery (one with esophageal varices, one with portal hypertensive gastropathy, and four with thrombocytopenia and/or splenomegaly). Patients with evidence of clinically significant portal hypertension underwent sleeve gastrectomy. Patients without evidence of clinically significant portal hypertension were offered either laparoscopic sleeve gastrectomy or Roux-en-Y gastric bypass, and the eventual choice between the two operations was the result of shared decision-making between the bariatric surgery

team and the patient. Long-term follow-up duration was defined as > 4 years after surgery.

Data collection

Variables relating to age, sex, body mass index, diabetes mellitus, hypertension, dyslipidemia, cardiovascular events (i.e. acute coronary syndrome, heart failure, and/or stroke), prescribed medications, hepatic function, hepatic decompensation manifestations, Model for End-stage Liver Disease–Sodium (MELD–Na), and patients' survival were manually collected, when available, until May 22, 2019. Hepatic decompensation was defined as current or prior development of ascites, hepatic encephalopathy, or variceal bleeding. This study was approved by the Mayo Clinic Institutional Review Board.

Data analysis

Continuous variables were expressed as means (\pm standard deviation). Weight measurements and glycosylated hemoglobin levels were analysed and compared using paired t-test. A value of $P < 0.05$ was considered statistically significant. The primary outcome was a sustained total body weight loss (TBWL) of > 20% compared with the pre-surgery baseline and the secondary outcomes were changes in metabolic co-morbidities (i.e. hypertension, dyslipidemia, or diabetes mellitus), hepatic decompensation, and all-cause mortality. Given the small sample size, only descriptive analysis was performed for the remainder of the variables. For quality control, we reported the adequacy of relevant domains of a recent tool for methodological quality of case series [11]: the exposure (liver cirrhosis) as well as intervention (bariatric surgery) and outcome (weight loss) were adequately ascertained. All relevant data are reported in the results.

Results

Baseline patient characteristics

Ten patients had long-term follow-up data determined over 8.7 years (\pm 1.4 years) after bariatric surgery (Table 1). The mean age at the time of surgery was 58.4 years (\pm 9.6 years). Seven patients were female. Nine patients underwent sleeve gastrectomy and one patient underwent Roux-en-Y gastric bypass. There was no perioperative or post-operative surgical complication and there was no perioperative mortality.

Weight-related outcomes

The mean weight for the cohort decreased from 125.2 kg (\pm 18.7 kg) before bariatric surgery to 94.4 kg (\pm 17.8 kg) after 1 year and 101.1 kg (\pm 20.2 kg) on the last follow-up ($P < 0.001$). The mean percentage of TBWL noted at the end of the observation period was 19.2%. One patient experienced weight gain and eventually returned close to the pre-surgery baseline (pre-surgery weight 141.4 kg, last follow-up weight 139 kg). The mean percentage of TBWL after excluding this patient is 21.4% of the pre-surgery weight. Seven patients achieved the primary outcome (sustained > 20% TBWL). Two patients had sustained TBWL of < 20% but > 10%.

Metabolic co-morbidities-related outcomes

As shown in Table 1, there were seven patients with diabetes mellitus at baseline. The glycemic control was evaluated using

Table 1. Baseline characteristics and changes following bariatric surgery

Characteristic	Patient #									
	1	2	3	4	5	6	7	8	9	10
Age at surgery (years)	47	69	57	58	63	69	66	44	65	46
Gender	F	M	F	M	F	F	F	M	M	F
Weight pre surgery (kg)	140	109	124	136	98.1	126	94.5	148	141	136
Weight at last F/U ^a (kg)	97	94.1	98.1	120	75.6	93	72.2	117	139	106
TBWL (%)	30	13.6	20.8	11.6	22.9	26	23.5	21.2	0.01	22.7
BMI pre surgery	49.5	49	45	45	39.3	47	39	44.9	45	53.1
BMI at last F/U	32.4	43	37.3	42	32.8	35	31.3	34.8	44.6	42.8
A1C pre surgery (%)	NA	NA	8.6	10.2	7.3	6.8	6.5	6.4	6.6	4.8
A1C at last F/U (%)	4.5	5.7	6	7.7	7.3	7.8	5.2	7.6	6.3	5.4
Insulin use pre surgery	N	N	Y	Y	Y	Y	N	Y	Y	N
Insulin use at last F/U	N	N	N	N	N	Y	Y	Y	Y	N
Oral hypoglycemic agents pre surgery (n)	0	0	1	1	0	0	0	2	0	0
Oral hypoglycemic agents at last F/U (n)	0	0	0	2	0	0	0	0	1	0
HTN pre surgery	N	Y	N	Y	N	Y	N	Y	Y	N
Anti-HTN medications pre surgery (n)	0	3	0	4	0	1	0	3	2	0
HTN at last F/U	N	Y	N	Y	N	Y	N	Y	Y	Y
Anti-HTN medications at last F/U (n)	0	2	0	2	0	2	0	1	3	2
Anti-lipid medications pre surgery (n)	0	1	1	1	0	0	0	2	0	0
Anti-lipid medications at last F/U (n)	0	1	0	1	0	0	0	1	1	0
INR pre surgery	1.2	1	1	NA	1.1	NA	1	1.7	1.9	1.1
INR at last follow-up	1.2	1.1	NA	1.1	1.2	1.1	1.4	1.4	1.1	0.9
Albumin pre surgery (g/dL)	NA	NA	NA	3.5	3.8	NA	3.4	NA	4.2	4.8
Albumin at last follow-up (g/dL)	4.3	4.7	NA	3.8	3.4	4.2	3.1	2.9	4.2	4.1
Total bilirubin pre surgery (mg/dL)	0.6	NA	NA	0.8	0.9	0.7	1.2 ^b	NA	0.7	0.6
Total bilirubin at last follow-up (mg/dL)	0.7	0.2	0.3	0.5	0.9	0.6	2.6 ^b	0.2	0.9	0.3

This table illustrates the sustained weight-loss benefit observed in most of the cohort and shows a trend towards metabolic benefit and stability in hepatic function.

F, female; M, male; F/U, follow-up; TBWL, total body weight loss; BMI, body mass index; A1C, glycated hemoglobin; N, no; Y, yes; n, number of agents; HTN, hypertension; NA, not available; INR, international standardized ratio.

^aMean weight loss on last follow-up remained significantly lower than pre-surgery mean weight ($P < 0.001$).

^bPatient with Gilbert syndrome.

the glycated hemoglobin measurement, which was 7.5% ($\pm 1.4\%$) before surgery and 6.8% ($\pm 1.6\%$) at 1 year and 6.8% ($\pm 1.0\%$) at the end of follow-up period ($P = 0.387$). One patient's diabetes mellitus resolved (i.e. HbA1c became 6.0% without further need for anti-diabetic treatment) on follow-up, two patients discontinued insulin, and one patient required the addition of insulin; notably, this was not the patient experiencing weight regain back to baseline.

Four patients were on anti-lipid medications before bariatric surgery, one of whom was able to discontinue these medications on the last follow-up, and one patient's regimen was de-escalated to one medication from two. The patient who experienced weight regain required initiation of an anti-lipid agent.

Hypertension was present in five patients before surgery; antihypertensives were de-escalated in three patients and two patients needed escalation on the last follow-up (one of whom experienced weight regain). Antihypertension medications were initiated in one patient post surgery. There were no cardiovascular events in this series.

Liver-related outcomes

One patient, with a pre-existing transjugular intrahepatic portosystemic shunt, developed mania and then hepatic encephalopathy 2 and 3 years post surgery, respectively. Of note, she self-discontinued all of her medications, became severely confused, and eventually died (6 years post-operatively). She was not a candidate for liver transplantation. There were no hepatic

decompensation events or deaths in the rest of the cohort. The mean preoperative platelet level was 131,000/mL and remained the same at the last follow-up. At the end of the observation period, the MELD-Na score was available for nine patients and it was 9 (± 6). Two patients had MELD-Na of 14 and 15 driven by Gilbert syndrome and chronic kidney disease, respectively. There were two patients with international normalized ratio (INR) > 1.5 preoperatively (1.7 and 1.9), which decreased on the last follow-up (1.4 and 1.1, respectively; [Table 1](#)). No patient required liver transplantation during the follow-up period. Of note, the two patients with hepatitis C were successfully treated and achieved sustained virologic response within 5 years of bariatric surgery.

Discussion

In this case series, a sustained and clinically significant long-term weight loss with metabolic benefits in obese patients with cirrhosis who underwent bariatric surgery (mainly with sleeve gastrectomy) was demonstrated. A systematic review has previously evaluated the role of bariatric surgery in cirrhosis and showed an acceptable overall risk profile for the procedure [12]. The majority of the included studies in that systematic review only assessed short-term follow-up. There is a dearth of literature regarding the long-term outcome for these patients. Rebibo et al. [13] showed a weight loss of 34.1% from baseline at 12 months in patients with cirrhosis who underwent bariatric

surgery. The cohort discussed in the current report demonstrated no significant perioperative events and weight loss of 25% at 24 months post-operatively [10]. In obese patients without identified liver disease, a study by Adams *et al.* [14] showed sustained benefits more than a decade after surgery, with 28% TBWL at 6 years post-operatively. This weight loss was in line with what is observed in our cohort ~9 years after bariatric surgery, where most patients maintained >20% TBWL. Additionally, this current study showed that metabolic comorbidities reflected a trend for improvement or stabilization following the intervention.

Non-alcoholic fatty liver disease (NAFLD) portends a high risk for cardiovascular mortality (eight times more than the general population). Even after adjusting for traditional cardiovascular risk factors, a large population-based study over 9 years confirmed and exemplified this risk [15]. Although none of our 10 patients experienced a cardiovascular event during the long follow-up period, this may be due to a small, underpowered sample size. However, bariatric surgery has been shown to impart a favorable impact on cardiovascular outcomes, with coronary artery disease-related mortality decreased by 56% approximately 7 years after bariatric surgery. Not surprisingly, the same study showed a decrease in diabetes-related complications as well [16].

With respect to the underlying liver disease, patients in this series demonstrated a lower risk of hepatic decompensation than what is typically expected based on natural-history data, which suggest a decompensation rate of 6% per year in one study and 50% over 10 years in another study [17, 18]. Only 1 out of the 10 patients developed hepatic decompensation on long-term follow-up after bariatric surgery. This patient was with pre-existing transjugular intra-hepatic portosystemic shunt and eventually developed a component of encephalopathy in the setting of difficult-to-control mania and medication non-compliance, which was felt unlikely to be related to the bariatric procedure 3 years prior. Overall, these outcomes may suggest a favorable impact of bariatric surgery-induced weight loss on the natural course of liver disease in this patient population. Weight loss has been shown to be associated with improvement in portal hypertension in a recent study in which lifestyle interventions leading to weight loss of $\geq 10\%$ were associated with significant changes in portosystemic gradients ($-23.7\% \pm 19.9\%$ in patients who lost $\geq 10\%$ of their total body weight vs $-8.2\% \pm 16.6\%$ in patients who lost $< 10\%$ of their total body weight; $P=0.024$) [9]. The stability of platelet counts and liver synthetic function observed throughout this study suggests possibly an advantageous impact of bariatric surgery on hepatic function and portal hypertension.

Our findings are consistent with a growing body of evidence that supports early consideration for bariatric surgery in patients with compensated cirrhosis [19]. Patients with decompensated cirrhosis are at higher risk for periprocedural mortality after undergoing bariatric surgery than those with compensated cirrhosis or patients without cirrhosis [20]. The increased prevalence of malnutrition in patients with decompensated cirrhosis, which can exceed 50%, further complicates consideration for bariatric surgery [21]. On the other hand, additional consideration of bariatric surgery in cirrhosis before the development of clinically significant portal hypertension would be to either delay the need for transplant or to potentially enhance the patient candidacy for transplant in the future.

Although bariatric endoscopic therapies are gaining traction and momentum [22–24], their application in cirrhotic patients remains limited, largely due to portal-hypertension and gastric-

varices concerns, especially for techniques that involve full-thickness suturing [25]. Endoscopic sleeve gastropasty mimics a surgical-sleeve gastrectomy and may be superior in terms of mitigating the development of gastroesophageal-reflux symptoms, which may be an advantage in cirrhotic patients [26, 27]. Other techniques such as duodenal mucosal resurfacing, which would not involve the transmural application of sutures or pliations, may also have a role in patients with cirrhosis, but more data are required [28]. Recent data have shown that a gastric-space-occupying device can reverse established liver fibrosis in NAFLD, although their effectiveness in established cirrhosis has yet to be determined [29].

In summary, this case series offers insight into the long-term benefits of bariatric surgery in patients with NASH-related compensated cirrhosis. It shows sustained weight-loss benefit and suggests metabolic and hepatic stability in these patients. With the increased prevalence of obesity in patients with cirrhosis [8], the clinical implications of these findings may extend beyond NASH patients and apply to obese patients with other cirrhosis etiologies. A therapeutic window may exist in obese patients with compensated cirrhosis, where the benefits of weight loss outweigh the surgical risk known to apply to cirrhotic patients. Therefore, a multidisciplinary approach involving hepatologists, nutritionists, and weight-loss specialists (medical and surgical) is warranted upon encountering every patient with cirrhosis and morbid obesity to determine the potential benefits (illustrated in our report) vs possible risks of bariatric surgery in these patients. Larger studies are warranted and these data suggest relative safety in performing those studies.

Authors' contributions

M.I. contributed to the study concept and design, acquisition and analysis of data, interpretation of data, as well as drafting of the manuscript. M.A. contributed to the acquisition and analysis of data. B.A. contributed to critical revision of the manuscript for important intellectual content. F.B. contributed to drafting of the manuscript and critical revision of the manuscript for important intellectual content. K.W. contributed to the study concept and design, critical revision of the manuscript for important intellectual content, drafting of the manuscript, and study supervision.

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Conflicts of interest

None declared.

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