

Gastric Bypass After Liver Transplantation

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Few data are available for assessing the outcomes of bariatric surgery for patients who have undergone orthotopic liver transplantation (OLT). The University of Minnesota bariatric surgery database and transplant registry were retrospectively reviewed to identify patients who had undergone OLT and then open Roux-en-Y gastric bypass (RYGB) surgery between 2001 and 2009. Comorbidity-appropriate laboratory values, body mass indices (BMIs), histopathology reports, and immunosuppressive regimens were collected. Seven patients were identified with a mean age of 55.4 ± 8.64 years and a mean follow-up of 59.14 ± 41.49 months from the time of RYGB. The mean time between OLT and RYGB was 26.57 ± 8.12 months. The liver disease etiologies were hepatitis C ($n = 4$), jejunoileal bypass surgery ($n = 1$), hemangioendothelioma ($n = 1$), and alcoholic cirrhosis ($n = 1$). There were 2 deaths for patients with hepatitis C 6 and 9 months after bariatric surgery due to multiple-organ dysfunction syndrome and metastatic esophageal squamous carcinoma, respectively. One patient with hepatitis C required a reversal of the RYGB because of malnutrition and an inability to tolerate oral intake. Four of the 7 patients had type 2 diabetes mellitus (T2DM), 4 had hypertension, and 6 patients had dyslipidemia. All patients were on immunosuppressive medications, but only 4 were on corticosteroids. Glycemic control was improved in all surviving patients with T2DM. The mean BMI was 34.27 ± 5.51 kg/m² before OLT and 44.34 ± 6.08 kg/m² before RYGB; it declined to 26.47 ± 5.53 kg/m² after RYGB. In conclusion, in this case series of patients undergoing RYGB after OLT, we observed therapeutic weight loss, improved glycemic control, and improved high-density lipoprotein levels in the presence of continued dyslipidemia. RYGB may have contributed to the death of 1 patient due to multiple-organ dysfunction syndrome. *Liver Transpl* 19:1324–1329, 2013. © 2013 AASLD.

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Obesity is an established risk factor for nonalcoholic fatty liver disease (NAFLD),^{1–6} and obese patients undergoing liver transplantation may be at increased risk for NAFLD recurrence.^{7–9} The best protocol for weight-loss surgery and liver transplantation has not yet been elucidated. There is much uncertainty about the optimal timing of bariatric surgery, the type of

procedure, and the evolution of liver disease. Some authors have proposed bariatric surgery before liver transplantation, whereas others prefer to do the liver transplant first. There are a number of case studies and series reporting various practices,^{10–14,22} but only one has reported on the particular experience of patients undergoing orthotopic liver transplantation

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; OLT, orthotopic liver transplantation; RYGB, Roux-en-Y gastric bypass; T2DM, type 2 diabetes mellitus.

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(OLT) and then open Roux-en-Y gastric bypass (RYGB surgery). Bariatric surgery is known to improve metabolic profiles in nontransplant patients, but with the addition of metabolism-altering immunosuppressive medications, it is unclear how much an OLT recipient would benefit from a bariatric operation.^{15,16} This case series describes the experience of the Division of Gastrointestinal and Bariatric Surgery at the University of Minnesota with post-liver transplant patients who have subsequently undergone open RYGB.

PATIENTS AND METHODS

We conducted a retrospective chart review of all patients between 2001 and 2009 who underwent RYGB after OLT. Patients were considered candidates for RYGB after OLT if they had a body mass index (BMI) of 35 kg/m² or greater with weight-related comorbidities. The selection of patients was not based on adipose deposits in allograft tissue. The choice of RYGB was based on the preference of the surgeon in consultation with the patient. The decision regarding the technique of open surgery was related to the anticipated pattern of extensive adhesions in the upper abdomen due to each patient's prior large incisions for liver transplantation. All patients underwent both transplantation and RYGB at the University of Minnesota Medical Center. In preparation for bariatric surgery, all patients attended a standard, comprehensive weight-loss seminar with specially trained dietitians and nurse practitioners and received counseling from a bariatric surgeon at a later appointment.

The open RYGB procedure at our institution has been described previously.¹⁷ Briefly, a 15- to 30-mL gastric pouch is created with a 10- to 12-mm gastrojejunal anastomosis. The length of the Roux limb is 75 to 150 cm, whereas the biliopancreatic limb measures 75 to 100 cm.¹⁷ In accordance with our standard post-bariatric surgery protocol, these patients were seen 1 week after RYGB, again at 1, 3, 6, 9, and 12 months, and then every 6 months at the bariatric surgery clinic. At these visits, patients were weighed, their blood pressure was measured, and the following labs were performed: fasting high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, total cholesterol, very low-density lipoprotein, sodium, potassium, chloride, blood urea nitrogen, glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, albumin, and partial thromboplastin time. These patients were also seen separately in the gastroenterology clinic every 6 months, and the following labs were performed every 2 months after OLT: fasting HDL, LDL, triglycerides, total cholesterol, very low-density lipoprotein, sodium, potassium, chloride, blood urea nitrogen, glucose, ALT, AST, alkaline phosphatase, albumin, partial thromboplastin time, and blood drug levels.

Patient data were collected from the bariatric surgery database of the University of Minnesota, which includes operative notes as well as inpatient and out-

patient records. We collected pretransplant data, including BMIs and past medical, surgical, and medication histories. We also collected laboratory values, including albumin, ALT, AST, and total cholesterol levels and international normalized ratios. The same data were collected before RYGB and during follow-up visits along with HDL, LDL, and triglyceride levels as well as immunosuppressive medication doses. In addition, we reviewed post-RYGB complications and liver histopathology reports. This study was approved by the institutional review board of the University of Minnesota (0510M76107).

RESULTS

Between 2001 and 2009, our bariatric surgery group performed 2631 RYGB procedures; 632 of these procedures were performed with an open approach. Among these patients, 7 (4 men and 3 women) with a mean age of 55.4 ± 8.64 years underwent OLT before RYGB. The mean time interval between OLT and RYGB was 26.57 ± 8.64 months. Five patients were alive at the latest follow-up after bariatric surgery.

Patients in this series required liver transplantation because of hepatitis C ($n = 4$), alcohol-induced cirrhosis ($n = 1$), jejunoileal bypass surgery ($n = 1$), or hemangioendothelioma ($n = 1$). Three patients had a history of alcohol abuse; 2 of these patients were infected with hepatitis C. Complications of liver failure included hepatorenal syndrome, encephalopathy, and bleeding esophageal varices. The mean number of intra-abdominal procedures for these patients was 1.86. According to intraoperative RYGB liver biopsy samples from 6 of the 7 patients, there was no gross or microscopic evidence of rejection. Four patients were, however, found to have fatty liver disease on biopsy at the time of RYGB (3 with steatosis and 1 with nonalcoholic steatohepatitis). The etiologies of liver failure, the liver biopsy results at the time of RYGB, and the immunosuppressant medications are shown in Table 1.

Before OLT, 5 patients were obese, and 2 were overweight, whereas all the patients became obese after OLT. The mean BMI increased in the period between liver transplantation and RYGB from 34.27 to 44.34 kg/mg². Conversely, the mean BMI declined to 26.47 kg/mg² after RYGB during the mean follow-up duration of 59 ± 41.41 months. The BMIs for each patient in this series are indicated in Table 2.

Laboratory results before RYGB and at the latest follow-up after RYGB are shown in Tables 3 and 4. The albumin level decreased in the patients who died in the post-RYGB period; however, the mean albumin level improved for the surviving patients. The mean AST, ALT, and total bilirubin levels declined postoperatively. Triglycerides decreased for all patients except for the patient who required a reversal of the RYGB, whereas the mean HDL level increased. Patient comorbidities before RYGB are listed in Table 5. Four patients suffered from type 2 diabetes mellitus

TABLE 1. Causes of Liver Failure, Histopathology, and Immunosuppression Regimens

Patient	Etiology of Liver Failure	Liver Biopsy Histopathology at Time of RYGB	Immunosuppressant and Dosage Before RYGB	Immunosuppressant and Dosage After RYGB
1	Hepatitis C	Steatosis, grade 1, stage 0	Tacrolimus, 4 mg/day	Tacrolimus, 4 mg/day
2	Hepatitis C	Nonalcoholic steatohepatitis, grade 4, stage 3	Tacrolimus, 2 mg/day	Tacrolimus, 3 mg/day Mycophenolic acid, 2000 mg/day
3	Hepatitis C	Grade 2, stage 0	Tacrolimus, 6 mg/day	Tacrolimus, 4 mg/day Prednisone, 5 mg/day
4	Alcoholic cirrhosis	Grade 0, stage 0	Mycophenolic acid, 2000 mg/day	Sirolimus 6 mg/day Prednisone, 5 mg/day
5	Jejunioileal bypass	Steatosis, grade 3, stage 0	Cyclosporine, 200 mg/day	Cyclosporine, 225 mg/day Prednisone, 5 mg/day
6	Hepatitis C	Steatosis, grade 1, stage 1	Tacrolimus, 3.5 mg/day	Tacrolimus, 2 mg/day Prednisone, 5 mg/day
7	Hemangioendothelioma	Not done	Tacrolimus, 4 mg/day	Tacrolimus, 9 mg/day

TABLE 2. BMI Values Before OLT and RYGB and at the Latest Follow-Up

Patient	Sex	Pretransplant BMI (kg/m ²)	Pre-RYGB BMI (kg/m ²)	OLT-RYGB		Follow-Up Duration After RYGB (Months)
				Interval (Months)	Post-RYGB BMI (kg/m ²)	
1	Female	32.6	38	38	18.7	103
2	Male	35.7	46	26	32.5	6
3	Male	39.4	46	19	24.3	9
4	Male	38.7	39.5	31	24.5	48
5	Female	26.3	55.9	32	28	98
6	Male	27.8	45	26	34.4	96
7	Female	39.4	40	14	22.9	55
Mean		34.27	44.34	26.57	26.47	59.14
Standard deviation		5.51	6.08	8.12	5.53	41.59

TABLE 3. Albumin, Total Bilirubin, ALT, and AST Levels Before and After RYGB

Patient	Albumin (g/L)		Total Bilirubin (mg/dL)		ALT (U/L)		AST (U/L)		Follow-Up Duration (Months)
	Before	After	Before	After	Before	After	Before	After	
1	4	4.1	0.4	0.5	50	43	34	47	100
2	4.1	1.5	3.9	1.5	100	94	153	171	6 (deceased)
3	3.6	2.1	0.9	1.5	80	30	78	29	9 (deceased)
4	3.5	4.3	0.7	0.5	69	28	93	32	48 (reversed)
5	4.5	4.1	0.5	0.6	20	22	20	44	99
6	2.8	3.5	2.4	0.5	163	39	147	36	46
7	4.2	4.4	0.4	1.1	21	39	24	36	55
Mean	3.81	3.43	1.31	0.89	71.86	42.14	78.43	56.43	
Standard deviation	0.56	1.16	1.34	0.47	49.88	24.02	56.01	50.91	

(T2DM). Two of those patients achieved normal glyce-
mic control after RYGB, whereas the other 2 patients
died within 1 year of RYGB.

Patients' adverse events varied considerably. One
patient had persistent wound complications from his
OLT procedure before RYGB, and this continued in

TABLE 4. Triglyceride, LDL, and HDL Levels Before and After RYGB

Patient	Triglycerides (mg/dL)		LDL (mg/dL)		HDL (mg/dL)		Follow-Up Duration (Months)
	Before	After	Before	After	Before	After	
1	569	178	117	91	34	60	94
2	227	146	35	38	83	14	6 (deceased)
3	314	81	102	46	25	37	9 (deceased)
4	126	180	42	141	42	54	48 (reversed)
5	209	116	38	127	25	74	99
6	405	206	52	75	19	49	28
7	196	62	106	98	42	62	55
Mean	292.29	138.43	70.29	88.00	38.57	50.00	
Standard deviation	151.58	54.10	36.25	38.45	21.49	19.59	

TABLE 5. Presurgical Comorbidities for Which Patients Were Being Treated

Patient	Hypertension	Diabetes	Hyperlipidemia	Vascular Disease	OSA	GERD
1	No	Yes	Yes	No	No	Yes
2	Yes	Yes	Yes	Yes	No	Yes
3	No	Yes	Yes	No	Yes	Yes
4	Yes	Yes	Yes	Yes	Yes	No
5	Yes	No	Yes	No	No	No
6	Yes	No	Yes	Yes	No	No
7	No	No	No	No	Yes	Yes

the post-RYGB period. Two patients developed transient wound infections after RYGB. Two patients developed incisional hernias, 1 of which was a recurrence after a previous repair. There were no deaths in the first 90 days after the bariatric procedure in this case series. Two of the 4 patients with hepatitis C died within the first year after bariatric surgery; no other patients died. The first death was due to sepsis secondary to Fournier's gangrene 6 months after RYGB, whereas the other death was secondary to metastatic esophageal squamous carcinoma 9 months after bariatric surgery. Lastly, 1 patient required a reversal of the RYGB 22 months after the surgery because of malnutrition and a recalcitrant gastrojejunal ulcer.

DISCUSSION

The effects of obesity on short- and long-term morbidity and mortality among patients who have previously undergone liver transplantation have been reported in the literature.^{18,19} Several studies have compared the outcomes of obese and nonobese transplant patients. In 1999, Sawyer et al.²⁰ studied the effects of BMI on morbidity, mortality, and long-term function in 277 patients who underwent OLT. They found that the outcomes of liver transplantation for patients with

BMIs between 30 and 34 kg/m² were not different from the outcomes for nonobese patients. However, patients with BMIs greater than 35 kg/m² had more complications in the short term but similar graft survival and mortality rates in comparison with nonobese patients. Conversely, Nair et al.¹⁸ found different results in the United Network for Organ Sharing database with 23,675 records. Nair et al. concluded that in comparison with nonobese patients, obese patients had increased long-term mortality after liver transplantation, and they recommended weight loss for all obese patients awaiting liver transplantation. These findings led the American Association for the Study of Liver Diseases to make morbid obesity (BMI > 40 kg/m²) a contraindication to liver transplantation in its guidelines.²¹

Among the many case series and reports providing evidence supporting weight-loss surgery after liver transplantation, only one has reported experience with open RYGB.^{10,12-14,22} Duchini and Brunson²² reported 2 cases of RYGB after OLT due to nonalcoholic steatohepatitis; the only complication was minor dumping syndrome in 1 patient. Our case series contributes to and extends this literature.

Among the patients in our case series, the mean BMI increased during the period between liver transplantation and bariatric surgery from 34.27 to 44.34

kg/mg². Several other studies have shown that weight gain commonly occurs after solid organ transplantation as a result of exercise intolerance, immobility, and immunosuppressive regimens.²³ The occurrence of metabolic syndrome after liver transplantation has been well established in several studies.^{23,24} Patients receiving OLT may be at risk for NAFLD recurrence in the transplanted liver if their obesity is not managed.⁷⁻⁹ In our series, after RYGB, the BMI declined to 26.47 kg/mg² during the mean follow-up duration of 59.14 months. These last values ranged from 18.7 to 34.4 kg/mg² 6 to 103 months after bariatric surgery and reflected apparently good weight-loss efficacy for these patients.

All OLT recipients at the University of Minnesota Medical Center undergo immunosuppression induction with basiliximab, tacrolimus, mycophenolate mofetil, and a corticosteroid for 3 days, and then a steroid-avoidance protocol is adopted. Despite this general principle, 4 patients in this series required immunosuppressive regimens that included corticosteroids. One patient was on prednisone before death because of an episode of acute rejection in the setting of metastatic esophageal squamous carcinoma. Two patients were on prednisone because tacrolimus was contraindicated on account of poor renal function. One patient was on prednisone because he had undergone OLT before the implementation of the steroid-avoidance regimen. It is well established that immunosuppressive drugs worsen lipid and glucose metabolism.²⁵⁻²⁷ We believe that those side effects are mitigated by the beneficial metabolic effects of weight-loss surgery.²⁸⁻³¹ Six patients in this series had dyslipidemia, and 4 of them had diabetes before RYGB. All the patients continued to have dyslipidemia throughout their follow-up despite improvements in HDL and triglyceride levels in most patients. Two patients with T2DM were alive 1 year after RYGB, achieved normalized glycemic control (hemoglobin A1c < 6%), and were off their antihyperglycemic medications, although 1 of the patients required corticosteroids. Four patients had hypertension and were taking antihypertensive medications before bariatric surgery. One of these patients died within 1 year of the operation, whereas 2 of the remaining 3 patients required no antihypertensive drugs. Although the metabolic profiles of our patients improved in the post-RYGB period, it is unclear how these results might vary with different immunosuppressive regimes.

Three of the 7 patients had serious adverse outcomes after RYGB. The first patient died at 6 months after the discovery of a new metastatic, poorly differentiated esophageal squamous carcinoma with lung metastasis. Intraoperative esophagogastroduodenoscopy was performed for this patient, and no abnormalities were noted at the time. The patient who succumbed to Fournier's gangrene had T2DM, received a concomitant liver and kidney transplant 2 years before RYGB, and had a penile prosthesis a year before the weight-loss procedure. Although this patient was adequately nourished before RYGB, his albumin levels declined immediately after bariatric surgery and did

not return to the normal range. Furthermore, this patient had watery diarrhea, and this may have been due to the effect of the postsurgical antibiotic course on intestinal flora. These conditions in the context of T2DM, an immunocompromised state, and a penile implant likely contributed to the progression of Fournier's gangrene and death. The patient who underwent a reversal of the RYGB suffered from a gastrojejunal (marginal) ulcer, which is an established complication of the bariatric procedure. His weight before the RYGB reversal was 143 lb, and it was relatively stable at the 1-year follow-up (133 lb). For both the death and the reversal, it was not clear whether or how much of the poor outcome was due to an antagonistic interaction between the OLT and RYGB procedures. In the remaining 4 OLT patients in this series, RYGB did not appear to cause unusual complications. We found that open RYGB in these OLT patients provided adequate weight loss despite equivocal effects on lipid profiles. This important weight reduction could potentially prevent the recurrence of NAFLD.

Weight loss is difficult. However, for many liver transplant candidates, the choice is not between being obese or not being obese but rather between waiting or not waiting. In 2007, Pelletier et al.¹⁹ recognized that a more useful comparison was between obese patients who were waiting for a transplant and obese patients who underwent transplantation. That group compared survival between obese patients awaiting liver transplantation and obese patients who had undergone transplantation. They found that liver transplantation improved survival in comparison with remaining on the transplant waiting list for all BMI categories.¹⁹ Although we have examined only our experience with OLT patients undergoing open RYGB, there is some literature on post-OLT patients undergoing laparoscopic RYGB, sleeve gastrectomy, and adjustable gastric banding. Tichansky and Madan¹² reported 1 case of laparoscopic RYGB in a post-OLT patient with hepatitis C without any complications for 2 years. Lin et al.¹⁰ described the outcomes of sleeve gastrectomy after OLT for 9 patients, including 3 complications in 3 patients: the recurrence of an incisional hernia after a repair during surgery, a bile leak, and dysphagia. The last was converted to RYGB. Lastly, there is a case series by Campsen et al.¹⁴ describing gastric band placement at the time of liver transplantation. They reported good outcomes 6 months after the combined procedure.

In conclusion, these patients are more complex than typical bariatric patients. In addition to obesity-related comorbidities, they face the added burden of liver transplantation and the complications of immunosuppressive medications. Appropriate care provision requires the collaboration of a multidisciplinary team at a tertiary care center and intensive postoperative care and follow-up. This work provides new evidence for metabolic and weight-loss outcomes among patients undergoing RYGB after OLT. Importantly, it appears that RYGB improves metabolic profiles (lipids, glycemic control, hypertension, and BMI) in post-OLT

patients. Although 2 patients died and 1 patient underwent a reversal of the RYGB, future studies are indicated to determine the role of particular bariatric surgeries in these adverse outcomes. Major limitations of this work include the small number of patients, the retrospective nature of the study, and the paucity of comparable literature. Further studies with more patients are indicated to assess the outcomes of bariatric surgery for OLT patients and to evaluate the effect of RYGB on lipid and glucose metabolism in post-OLT patients taking immunosuppressive medications. Future studies should also focus on the effects of various types of bariatric surgeries on the absorption of immunosuppressive medications.

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