Bariatric surgery post-liver transplantation: a Belgian nationwide study

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ABBREVIATIONS

Abbreviation	Definition
AHT	Arterial hypertension
ARLD	Alcohol-related liver disease
BMI	Body mass index
BS	Bariatric surgery
DM	Diabetes mellitus
ESLD	End-stage liver disease
HCC	Hepatocellular carcinoma
LT	Liver transplantation
MASH	Metabolic dysfunction-associated steatotic hepatitis
MASLD	Metabolic dysfunction-associated steatotic liver disease
metALD	Metabolic and alcohol-related liver disease
MELD	Model for end-stage liver disease
OAGB	One-anastomosis gastric bypass
RYGB	Roux-en-Y gastric bypass
SD	Standard deviation
SG	Sleeve gastrectomy

ABSTRACT

Background

Weight gain poses a rising concern post-liver transplantation (LT), and metabolic dysfunction-associated steatotic liver disease (MASLD) might impair graft health. The timing is crucial when considering BS in a population with liver disease or transplantation. Bariatric surgery (BS) can be considered for post-LT weight gain, although the literature is limited and the long-term outcome still uncertain.

Methods

We conducted a national retrospective analysis in 5 Belgian transplant centres and included 25 patients with a liver transplantation followed by a bariatric procedure. 187 LT patients without BS were included for comparison. Clinical, biochemical and outcome data were retrospectively retrieved.

Results

In our nationwide sample, 25 patients had undergone BS post-LT, at a median 3.5 years after LT. Twenty-one (84.0%) patients received a sleeve gastrectomy (SG). Patients were predominantly male (72.0%), with a lower age at time of transplantation compared to non-BS population (54.5 vs 60.6, $p<0.0001$). Transient acute kidney failure (20.0%) was the only short-term complication occurring in more than one patient, all after SG. Weight loss was significant and sustained, with a decrease in BMI from 41.0 ± 4.5 pre-BS to 32.6 ± 5.8 ($p<0.0001$) 1 to 3 years post-BS and 31.1 ± 5.8 ($p<0.0001$) 3 to 5 years post-BS. Post-LT pre-BS three (12.0%) patients presented with recurrent and one (4.0%) de novo MASLD, with 100% resolution post-BS ($p=0.016$). Notable reductions were observed in ALT levels (40.5 ± 28.5 U/L to 27.1 ± 25.1 U/L post-BS, $p=0.051$) and HbA1c levels (6.9 ± 1.6 to 6.0 ± 1.4 post-BS, $p<0.0001$). Three patients were re-transplanted, and eight patients died, of which five (20.0%) due to a non-hepatic malignancy and one (4.0%) due to liver failure. Given the small sample size and relatively high mortality due to competing risks, a statistical analysis of patient or transplant-free survival was not feasible.

Conclusions

SG is the favored BS post-LT and has proven to be safe and feasible in a post-LT setting. SG post-LT is a valid treatment for de novo and recurrent MASLD post-LT. Although we report on the largest cohort to date, there is still a need for larger cohorts to examine the effect of BS on patient and graft survival.

Lay Summary

We examined the clinical significance of bariatric surgery in patients with a history of liver transplantation in a national multicentre retrospective study in 25 patients, with transplantation between 2000 and 2018 and subsequent optional bariatric surgery between 2005 and 2020. We selected 187 control patients who received transplantation between 2000 and 2018.

Sleeve gastrectomy was the most performed procedure, with negligible long-term complications. De novo MASLD post-liver transplantation is resolved in all cases with bariatric surgery. Contrary to Tacrolimus, Cyclosporine dosage lowered post-BS, with higher blood levels.

Highlights

- Bariatric procedures post-LT are mainly sleeve gastrectomies with low complication rate and deemed feasible and safe.
- MASLD post-LT was resolved in all patients undergoing BS.
- Contrary to Tacrolimus, Cyclosporine dosage lowered post-BS, with higher blood levels.

Introduction

Thirteen percent of the world's population suffers from obesity[1], proving to be a global issue with steadily growing prevalence, associated with lower life expectancy[2]. Bariatric surgery (BS) is currently the most efficacious long-term treatment for obesity[3–6] and it has been shown to ameliorate metabolic disease-associated liver disease (MASLD), cardiovascular disease, insulin resistance, and dyslipidemia[4,7–9]. In contrast, conservative treatments often fall short of achieving comparable long-term outcomes[10]. Multiple bariatric procedures are standard of care, of which the Roux-en-Y gastric bypass (RYGB) and the sleeve gastrectomy (SG) are the most performed procedures today[4,6,11].

The spectrum of metabolic liver injury, now termed MASLD, in patients with obesity ranges from fatty liver to cirrhosis and end-stage liver disease (ESLD)[12,13]. The prevalence of MASLD reaches 70% in patients with obesity and 85 – 95% in patients with severe obesity[14,15]. MASLD is predicted to become the most frequent indication of liver transplantation (LT) by 2030 [16], the only curative treatment for ESLD[17,18]. Weight gain and the associated emergence or recurrence of MASLD, hypertension and diabetes mellitus (DM) post-LT pose a rising concern[19] and have been attributed to the initiation of immunosuppressive agents, donor steatosis, genetic predisposition, and a lack of post-LT physical well-being[20–25]. Thus, weight evolution post-LT presents challenges, considering the reduced physical activity as well[25]. MASLD can shorten graft survival post-liver transplantation[26]. BMI is less of risk factor for post-LT mortality compared to DM[27]. Recurrence of MASLD can reach up to 60%, and is often more severe than primary MASLD, due to faster development of fibrosis, possibly requiring re-transplantation and is linked to DM[21]. For these reasons, BS might be an attractive therapeutic option for patients with a prior LT, although the risk of complications will be higher[22,23,27]. Case reports have described death and severe comorbidities regarding gastric bypass procedures post-LT[28,29]. Surgery in the upper abdomen post-LT can cause stress in the surgical team, however, malignant adhesions are infrequent, partially due to the use of immunosuppressive drugs. There is a paucity of data in this field[22], with uncertainty regarding the optimal timing of BS post-LT and selection of the appropriate type of BS.

In this study, we aimed to extend and validate these findings in a national multicenter cohort of LT patients and compare patients who underwent postoperative BS in the post-LT period with those who did not. The main outcomes of our study were the occurrence of post-operative complications, metabolic comorbidities and (re-)transplant-free survival.

Patients and methods

Cohort

We conducted a multicentric study in five Belgian liver transplant centers, namely the University Hospital of Leuven, University Hospital Saint-Luc Brussels, University Hospital of Antwerp, University Hospital of Liege and University Hospital of Ghent. We included patients who underwent a liver transplantation between 1/1/2000 and 31/12/2018 followed by a potential bariatric procedure between 1/1/2005 and 31/12/2020. This time frame allowed for at least five years of follow-up in weight evolution and survival for all transplanted patients. Control patients without BS, but otherwise fulfilling the inclusion criteria, were selected to represent the spectrum of pre-surgery BMI. Patients were ≥ 18 years of age at the time of liver transplantation. We excluded patients with recurrent liver failure post-LT due to chronic or acute rejection, patients with more than one transplantation in the medical history, BS before or during LT. Data were retrieved retrospectively from the electronic medical records and included biometry, lab results, and baseline characteristics, survival data and complication rates.

Our study was approved by the University Hospital of Ghent Ethics Committee (study reference ONZ-2022-0128) and is conform the Helsinki Declaration. Approvals and data transfer agreements were completed and received in all participating centers. Patients were followed up until death, lost to follow-up, or until 31/07/2023. Given the retrospective nature of data collection, no informed consent was deemed necessary by the ethics committee.

Statistics and data analysis

Continuous variables are presented as mean ± SD or median (interquartile range (IQR)) and were analysed using the unpaired student's t-test or Mann-Whitney U test, depending on the normality of distribution. Categorical variables are represented as n (%) and were analysed by the Chi^2 or Fisher's exact test. Repeated measures were analysed using the paired-samples t-test.

For survival analysis, several matching methods were tried until balance did not improve any further. The best balance was achieved with 5:1 matching, combining a nearest neighbour algorithm and a calliper of 0.45 with age, ALT and BMI as predictors for the propensity score model, with exact matching on sex. For the propensity score model, values for BMI less than 30 were set to 0 because it was assumed that there would only be a linear trend starting from there. Balance was assessed by graphical (love, empirical quartile-quartile, estimator of the cumulative distribution function, and density plots) and numerical (standardized mean difference, variance ratio and estimator of the cumulative distribution function statistics) inspection of variables, as well as their interactions and second order polynomials. After matching, an extended Cox model with BS as time-varying treatment variable was fitted with matching subclass as cluster. Robust variance estimates were requested, and the analysis was weighted according to the number of subjects per subclass so that each BS patient was receiving a weight equal 1, and the sum of the weights of its within subclass matches was also equal to 1. Because perfect balance was not achieved, several sensitivity analyses were performed: 1:1 matching, full optimal matching, propensity score adjustment (with and without spline terms for the propensity score), propensity score + covariate adjustment (with and without spline terms for the propensity score).

A two-tailed P value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS 28.0 (SPSS Software, IBM Corp., NY, US), GraphPad Prism 9 (GraphPad Software Inc., Boston, US) and R 4.3.1 (R studio).

Results

Transplanted patient characteristics

Twenty-five patients with BS post-LT were retrieved from 5 transplant centers in Belgium. 178 control patients were provided by random selection in the transplanted population. University Hospital of Ghent provided 75 patients, University Hospital of Leuven 50 patients, University Hospital Saint-Luc Brussels 45 patients, University Hospital of Antwerp 25 patients and University Hospital of Liège 17 patients. All patients underwent transplantation between January 1st, 2000, and December 31st, 2020. Control and BS patients were divided by BMI for patient description, into normal weight BMI 18.5 – 24.9 kg/m^2 (n = 66), overweight 25 – 29.9 kg/m^2 (n = 63), obese 30 – 34.9 kg/m^2 (n = 53) and severely obese > 35 kg/m^2 (n = 30) (p<0.0001) (Supplementary Tables 1 and 2). The prevalence of obesity after LT increased slightly over time (38.1% obesity pre-LT, 35.0% one year post-LT, 38.3% two years post-LT and 42.2% five years post-LT).

Perioperative condition and bariatric surgery

In our nationwide sample, 25 post-LT patients underwent BS, comprising 21 individuals (84.0%) who underwent SG, three (12.0%) RYGB, and one (4.0%) one anastomosis gastric bypass (OAGB) (Table 1). All but one procedure was conducted laparoscopically. For comparative analysis, we included 187 LT patients who did not undergo BS during the same period. The demographic profile of BS patients revealed a predominance of males (72.0%), comparable to the control group (69.6%, p=0.501), and their age at the time of transplantation was significantly lower than that of the non-BS population (54.5 vs 61.6, p<0.0001). Alcohol-related liver disease was the cause of cirrhosis in most patients (56% vs 39%, p=0.105), while 20% suffered from metabolic and alcohol-related liver disease (metALD), which was significantly higher compared to the control group (7.5%, p=0.040) (Table2). HCC was present in the explant liver of 8 patients (32%). Almost half of the BS group presented with a BMI > 35 during transplant work-up, and 14% were obese. Conversely, 43.8% and 14.0% of patients with a pre-LT BMI > 35 and BMI 30 – 35, respectively, were subsequently treated with BS.

The complication rate post-BS was generally low, with one open RYGB resulting in an anastomotic leak, requiring revisional surgery and an extended hospital stay (19 days). Notably, no instances of dysphagia or liver failure were seen post-BS and only one (4.0%) patient had wound complications. Transient acute kidney failure occurred in five (20.0%) patients, all following SG. Weight loss was significant and sustained, with a decrease in BMI from 41.0 ± 4.5 pre-BS to 32.6 ± 5.8 (p<0.0001) 1 to 3 years post-BS and 31.1 ± 5.8 (p<0.0001) 3 to 5 years post-BS.

Survival

Survival was similar in the BS group and the control population (68.0% vs 78.6%, p=0.083). No significant differences were present in the frequency of re-transplantations (12.0% vs 6.7%, p=0.347) (Table 2). Unfortunately, while we explored multiple statistical analysis methodologies a conclusive analysis of transplant-free survival was precluded due to the small sample size, variable timing of BS, and the occurrence of non-liver-related oncological mortality post-BS. The BS group displayed a 20% mortality due to non-hepatic malignancy, vs 5.1% (p=0.006). Other causes of death showed no significant differences.

Evolution of metabolic comorbidities and immunosuppressive drugs

Before undergoing BS, 4 patients (16.0%) exhibited MASLD, with complete resolution observed in all cases post-BS (p=0.037). Notably, one patient developed de novo MASLD following BS, possibly attributed to gradual weight regain post-surgery. The prevalence of DM and AHT remained constant. Pre-BS, 4 patients (16.0%) reported orthopedic complaints, all of which completely resolved post-BS (p=0.037). Notable reductions were observed in ALT levels (40.5 ± 28.5 U/L to 27.1 ± 25.1 U/L post-BS, p=0.051) and HbA1c levels (6.9 ± 1.6 to 6.0 ± 1.4 post-BS, p<0.0001).

Although the specific immunosuppressive treatment did not change after BS, tacrolimus serum levels decreased from 8.5 ± 3.4 ng/ml to 5.1 ± 2.4 ng/ml (p=0.415), despite dose increases from 4.0 ± 2.6 mg/day to 7.5 ± 11.7 (p=0.374). Daily mycophenolic acid intake rose from 1187.5 ± 530.3 mg/day to 1281 ± 1532.0 mg/day (p = 0.390). Unexpectedly, cyclosporin serum levels rose from 118.5 ± 19.1 ng/ml to 152.5 ± 31.8 ng/ml (p<0.001), while the daily dose was lowered from 300.0 ± 141.4 mg/day to 250.0 ± 70.7 mg/day (p<0.001). Details of the metabolic comorbidities and immunosuppressive drugs are displayed in Table 3.

Discussion

In this study, we examined the population that underwent a bariatric procedure in the post-LT course. We included 25 patients from five Belgian transplant centres in this nationwide survey[30]. Our post-LT BS patients shared similarities with other BS post-LT cohorts, including a male predominance, younger age, and higher pre-LT obesity rates compared to the overall transplanted population.

The largest studies to date consist of matched case-control studies by Tsamalaidze et al. and Chierici et al., who compared 12 and 20 SG patients after LT to a general BS population without LT or liver disease[19,23]. These studies reported higher complication and mortality rates and a lower excess body weight loss in transplanted patients. Reports of serious complications vary between 25 and 40%[27,31] in a post-LT setting, due to the possibility of acute graft rejection, which has been described in some case reports. RYGB post-transplantation may necessitate a higher immunosuppressive medication dosage. After RYGB, severe malnutrition is also conceivable[32], which could have a detrimental effect on patient and graft survival. We argue that RYGB is an inferior option compared to SG in the post-transplant setting, with higher complication rates, technical challenges related to the hepaticojejunostomy anatomical construction and potential adhesions, and impaired post-operative access to the biliary tree[22,33]. This view was reflected in the Belgian practice, with 84.0% of the procedures being SG. Dziodzio et al. reported 26.7% major complications after post-LT SG as well[33], which we did not see in our cohort, with only one patient with a major complication, resulting in longer hospital stay, but not death. A meta-analysis by Lee et. al comprising 64 patients undergoing BS post-LT, found that no patient had died at postoperative day 30[34], fitting our results without short-term mortality and low post-BS complication rate. Kidney failure associated with obesity is mostly prevented with SG after 3 months to 1 year[35,36]. As a short-term complication post-SG, it is relatively rare[37]. The possible malabsorption of immunosuppressive drugs remains unclear in BS post-LT[27], although SG was reported to have minimal impact[19]. However, we report a relatively higher daily dosage of tacrolimus, with lower blood levels and significantly lower daily dosage of cyclosporin post-BS with higher blood levels, without clear explanation. We hypothesize that tacrolimus clearance is accelerated after BS, requiring a higher dosage[38]. No data is available on cyclosporin dosage and clearance post-SG.

Post-LT, 15 – 30% of transplanted patients develop new-onset obesity in the first 1 – 3 years[23], which we confirmed with new-onset obesity of 15.6% one year, 17.6% two years and 19.0% five years post-LT, whereas we show a total level of obesity of 38.3 – 42.2% between 2 – 5 years post-LT. In our BS cohort, 4 (16.0%) presented with new-onset obesity, requiring surgery.

MASLD develops in up to 40% of the liver grafts[39], with higher percentages in those transplanted for MASLD. The time to BS was 3.5 years median, which is shorter than in other cohorts[27,30]. Whereas we hypothesized that graft as well as patient survival would be improved by BS, we could not substantiate this statement due to high mortality because of non-hepatological malignancies. A lower BMI will result in an overall better health and a lower cardiovascular risk profile. SG is deemed to be a cardio- and hepatoprotective measure in selected post-LT patients, at risk for de novo and recurrent MASLD. This notion is supported by the previously demonstrated protective effect of RYGB and SG on MASLD resolution[8,9,27,30,40,41]. Combined with the safety and feasibility of SG in a post-LT setting, it can be considered an established treatment option in selected post-LT patients. We need to keep in mind that failed weight loss is described after SG, which was the case in one patient in our BS cohort who developed MASLD in the post-BS course.

Our study is constrained by its retrospective design, necessitating the need to match our patients for survival analysis. While this design feature does confer certain advantages, such as the ability to discern patterns over time, the overall cohort is composed of a modest 25 patients. This sample size is deemed insufficient for conducting extensive comparative analyses, particularly in rendering conclusive statements regarding graft survival. Nevertheless, it is noteworthy as the most extensive cohort to date examining BS post-LT, representing a collaborative effort among Belgian transplant centers.

The efficacy of BS as a treatment modality for obesity in a post-transplant setting is evident, imparting protective effects on both patient and graft, with notable benefits concerning body weight and associated metabolic comorbidities mirroring those associated with MASLD. Key elements in the success of this therapeutic approach include the proficiency of the surgical team, coupled with vigilant multidisciplinary care and thorough follow-up protocol.

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