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Bariatric surgery and liver transplantation, here we are now: a French nationwide

retrospective study

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Abbreviations:

BS: bariatric surgery

HCC: hepatocellular carcinoma

LT: Liver transplantation,

MS: metabolic syndrome

NAFLD: non-alcohol-related fatty liver disease

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Jérôme Dumortier and Tarek Debs had the idea for the project and analysed the data.

François Villeret and Domitille Erard performed statistical analysis.

Jérôme Dumortier and Tarek Debs wrote the manuscript.

All authors were involved in the medical care of the patients, collected the data, and approved the final version of the manuscript.

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Abstract

At the time of the growing obesity epidemic worldwide, liver transplantation (LT) and metabolic syndrome are closely linked: non-alcohol-related fatty liver disease (NAFLD) is one of the leading indications for liver transplantation, and metabolic syndrome can also appear after liver transplantation, in relation to immunosuppressive medications and weight gain, whatever was the initial liver disease leading to the indication of LT. Therefore, the role of bariatric surgery (BS) is important due to its longer-lasting effect and efficacy. We performed a retrospective review of all 50 adult French liver transplant recipients who had a history of bariatric surgery, including 37 procedures before transplantation, and 14 after. There were three significantly different characteristics when comparing pre-and post-LT BS: patients were older (at the time of BS), presented more frequently arterial hypertension (at the time of LT), and the proportion of NAFLD as initial liver disease leading to LT was lower, in the post-LT group. Regarding pre-LT BS, in one case BS was complicated by liver failure leading to the rapid indication of LT; it was the single patient for whom the delay between BS and LT was less than 1 year; there was no patient who specifically underwent BS for the purpose of LT listing.

Introduction

At the time of the growing obesity epidemic worldwide, especially in Western countries, liver transplantation (LT) and metabolic syndrome (MS) are closely linked. First, non-alcohol-related fatty liver disease (NAFLD) emerged as one of the leading indications for LT over the past decade, and disease recurrence after LT seems inevitable [1]. In this context, MS usually worsens after LT. In addition, MS can appear after LT, related to immunosuppressive medications and weight gain, whatever was the initial liver disease leading to the indication for LT. Even if lifestyle modification and/or medications (such as antidiabetics) remain first-line in managing obesity, bariatric surgery (BS) is of great relevance due to its longer-lasting effect and efficacy. Therefore, the role of BS in the LT context has been explored more recently. In a recent review of the literature, Ahmed and coll. emphasized that the role of BS in LT patients remains an arena to be fully explored: the impact of BS and long-term outcomes are well understood in the non-transplant population however less is known for LT patients [2]. Sleeve gastrectomy has shown to be more promising when compared to other procedures with regard to long-term weight loss without issues with malabsorption. Regarding BS in cirrhotic patients, there is a need for evidence-based management of hepatic failure post-BS. Finally, the optimal timing of BS in the setting of LT remains controversial. These authors concluded that large multicenter randomized studies are needed to devise an optimal management plan and strategy for this patient population. Such studies will probably be difficult to implement. The aim of the present study was to describe all LT recipients who have a history of BS, before or after LT, in France.

Patients

We performed a retrospective review of all adult LT recipients before 2022, in all active and past adult LT French centers (n=21), with a history of BS. Were retrospectively collected data about pre-transplant, transplant, and post-transplant characteristics. All data were analysed using SPSS version

23.0 (IBM, Armonk, NY). Data were described using a median with a range for continuous variables and a number with a percentage for categorical variables. Categorical variables were compared with the Chi-square test and quantitative variables were compared using Mann-Whitney non-parametric test. A p value less than 0.05 was considered statistically significant.

The study population comprised 51 cases (50 patients), including 37 cases of BS before LT, and 14 after (Table 1). Eight patients had 2 successive BS procedures; 1 patient had both pre- and post-LT BS. There were three significantly different characteristics when comparing pre- and post-LT BS: patients were older (at the time of BS), presented more frequently arterial hypertension (at the time of LT), and the proportion of NAFLD as initial liver disease leading to LT was lower, in the post-LT group. Regarding pre-LT BS, in one case BS was complicated by liver failure leading to the rapid indication of LT; it was the single patient for whom the delay between BS and LT was less than 1 year; there was no patient who specifically underwent BS for the purpose of LT listing. Two patients (5.4%) died from surgical complications after LT in the group of pre-LT BS.

Discussion

The main result of the present nationwide study is that only a very small proportion of French LT patients have a history of BS; considering that 13,913 patients were alive after having undergone a LT in France by December 31, 2021, this represents 0.37% (data from the French Agence de la Biomédecine [3]). In addition, it consisted of pre-LT BS in the majority of the cases, which was performed without any relation to the subsequent LT (median delay 6.4 years). One explanation is the relatively low proportion of patients listed (first LT) for complications of NAFLD (with or without hepatocellular carcinoma (HCC)) in France, which is very recently increasing (13.6% in 2021, data from the French Agence de la Biomédecine [3]). Indeed, there is a rapidly growing literature on BS and LT, for patients with NAFLD. Timing for BS in LT patients and type of surgery (sleeve gastrectomy, Roux-en-Y gastric bypass, adjustable gastric banding) have to be better defined.

Theoretically, LT candidates can undergo BS while waiting for LT, if the waiting period is expected to be long (this is the case when the indication is HCC, in France, and more generally) and when liver function is preserved (it is also usually the case for HCC patients). A rare but potentially deadly complication after BS in the presence of cirrhosis is liver failure, with the need for an LT (we have one such patient in our cohort). A literature review described 14 studies, including 36 patients who underwent BS and had severe complications leading to liver failure (32 had an LT, while 4 died while on the waiting list for LT) [4]. Interestingly, liver failure developed a median of 20 months after BS, which can be considered a long delay. Another open question is the impact of previous BS on the outcome of LT surgery. Ianelli and coll. compared 39 French LT patients with a history of BS, to 1798 obese LT patients without previous BS [5]. No significant difference was detected between the 2 groups regarding the rates of mortality, re-LT, re-hospitalization after LT, and costs of hospitalization and re-hospitalizations. Because patients with decompensated cirrhosis and obesity are considered at greater risk of accessing BS before LT, this situation makes a simultaneous (or with a short interval) sleeve gastrectomy and LT attractive. Interestingly, Safavi and coll. recently performed a systemic review examining the role of BS in LT patients; primary outcomes included patient and graft survival and secondary outcomes were post-operative morbidities after LT, length of hospital stay after LT, change in BMI and recurrence of steatosis [6]. This analysis included 162 patients who underwent both BS and LT and 1426 who had a LT alone. Four studies looked at patients with BS before LT (n=133) and one study looked at BS and LT being done simultaneously (n=26). The percentage of female patients in the BS + LT cohort was higher than in the LT alone cohort: 75% vs. 35% respectively. The most common indications for LT (when available) in the BS + LT cohort were NAFLD (n=76), viral hepatitis (n=39) and alcoholic liver disease (n=36), confirming that NAFLD is not exclusive, as observed in our population. Patients undergoing BS had comparable outcomes in terms of overall patient survival, graft survival, and postoperative morbidity compared to LT alone. When comparing BMI change in patients with prior vs. simultaneous BS+LT, no significant difference was

found. Only the study with simultaneous BS + LT reported NAFLD recurrence, in which the BS + LT cohort showed a lower recurrence rate in the graft when compared to the LT-only cohort: 23.1% vs. 66.7%.

When conducting a dual (bariatric and transplantation surgery) psychosocial assessment, it seems prudent to understand the overlap and differentiation of specific psychosocial components that influence outcomes in these procedures [7]. In addition, a history of alcohol use disorders makes this assessment even more complex. While it has long been known that alcohol withdrawal can lead to massive weight gain, it has been reported more recently that patients with prior BS are at risk for developing alcohol use disorder, more frequently in females [8]. It can be hypothesized that psychosocial concerns could explain in part the very low number of LT recipients who underwent bariatric surgery in our experience. Specific data on the psychosocial comorbidities were not available in our population; this is a limitation of your study, due to its retrospective nature.

In our cohort, none of the patients had planned BS before LT, or simultaneous BS+LT; 14 patients had BS after LT (median delay 5.1 years). BS after LT is a challenging task; as it can be technically difficult due to adhesions, the patient will be under immunosuppression, and the operation itself may alter the absorption of immunosuppressive medications, placing the graft at risk of rejection. Nevertheless, BS can be performed after LT once the early postoperative period is over and the patient's clinical condition is stabilized, after 6 or 12 months for instance. In a comprehensive study, Rogers and coll. evaluated the pharmacokinetics of immunosuppressant drugs (tacrolimus, sirolimus, mycophenolic acid) in patients submitted to BS. They reported that people undergoing a transplant and who have BS should need a higher immunosuppressant medicine dose than non-BS patients, especially those who undergo bypass interventions [9]. As illustrated in our cohort, sleeve gastrectomy is therefore probably the first choice for surgery type, rather than other techniques such as Roux-en-Y gastric bypass, because of a lower risk of immunosuppressive drugs malabsorption, persistent accessibility of the gastric remnant and biliary tract, and its simplicity,

without digestive anastomosis, and therefore a reduced risk of anastomosis-related complications [10]. In a single-center experience, Yemini and coll. reported 34 solid organ transplant recipients who underwent laparoscopic sleeve gastrectomy or laparoscopic Roux-en-Y gastric bypass. A successful weight loss occurred in the vast majority of patients (82%), comorbidities improved significantly but the surgical risk was found higher than in the regular BS population, and tacrolimus blood trough levels declined slightly but remained within the therapeutic range [11].

Finally, an open question is about the selection of obese patients who will benefit from BS. Regarding the risk of severe NAFLD recurrence, we recently identified that independent significant risk factors for post-LT NAFLD-related advanced graft fibrosis were MS before LT, long-term use of cyclosporine, and grade ≥ 2 steatosis at 1 year [1]. Of note, it must be emphasized that the majority of the patients reported here who underwent BS after LT was transplanted for an initial liver disease different than NAFLD, especially alcohol-related liver disease; this can be explained by a frequent massive weight gain and the development of *de novo* NAFLD in this particular population [12].

In conclusion, the present French retrospective multicenter cohort results show that a very small part of LT recipients has a history of BS, especially after LT. Recommendations can be proposed as soon as the level of knowledge of risk factors for severe hepatic and extra-hepatic disease related to metabolic syndrome has significantly increased. This requires long-term follow-up of large cohorts.

Table 1. Study population

	Bariatric surgery before LT (n=37)	Bariatric surgery after LT (n=14)	p
Sex (M/F)	14/23	9/5	>0.05
The time between bariatric surgery and LT, (years), median (min-max)	6.4 (0.6-14.2)	5.1 (3.0-25.7)	>0.05
Bariatric surgery			
Patient age, (years), median (min-max)	42.0 (21.8-63.2)	58.3 (43.0-65.5)	0.022
Co-morbidities (n, %)			
Diabetes	18 (48.7%)	4 (28.6%)	>0.05
Hypertension	19 (51.4%)	5 (35.7%)	>0.05
Cardiovascular event*	13 (35.1%)	2 (14.3%)	>0.05
Obstructive sleep apnea syndrome	8 (21.6%)	1 (7.1%)	>0.05
Tobacco consumption	12 (32.4%)	2 (14.3%)	>0.05
Hypercholesterolemia	9 (24.3%)	3 (21.4%)	>0.05
BMI, (kg/m ²), median (min-max)	43.9 (34.0-62.5)	45.1 (37.1-66.5)	>0.05
Bariatric surgery type**			
Roux-en-Y gastric bypass	19 (51.4%)	6 (42.9%)	
Sleeve gastrectomy	10 (27.0%)	8 (57.1%)	
Omega loop gastric bypass	3 (8.1%)	0	
Biliopancreatic diversion with duodenal switch	2 (5.4%)	0	
Adjustable gastric banding	3 (8.1%)	0	
Complications after bariatric surgery			
Total (patients, n, %)	10 (27.0%)	3 (21.4%)	>0.05
Liver failure	1 (2.7%)	0	
Leak	4 (10.8%)	1 (7.1%)	
Hemorrhage	0	2 (14.3%)	
Anastomotic stenosis	1 (2.7%)	0	
Surgical revision	4 (10.8%)	2 (14.3%)	
Weight loss (1 year), (kg), median (min-max)	48.2 (25.0-101.0)	31.3 (14.0-100.0)	>0.05
Liver transplantation			
Patient age, (years), median (min-max)	48.0 (28.0-66.7)	53.0 (21.0-62.2)	>0.05
Causes of initial liver disease*** (n, %)			
NAFLD	23 (62.2%)	4 (28.6%)	0.032
Alcohol	11 (29.7%)	7 (50.0%)	>0.05
HCV	3 (8.1%)	1 (7.1%)	>0.05
Fulminant hepatitis	3 (8.1%)	0	>0.05
Other	7 (18.9%)	3 (21.4%)	>0.05
Hepatocellular carcinoma (n, %)	7 (18.9%)	4 (28.6%)	>0.05
BMI, (kg/m ²), median (min-max)	32.3 (18.7-52.2)	34.4 (23.7-49.8)	>0.05
Co-morbidities (n, %)			
Diabetes	10 (27.0%)	7 (50.0%)	>0.05
Hypertension	14 (37.8%)	10 (71.4%)	0.032
Cardiovascular event*	13 (35.1%)	5 (37.5%)	>0.05
Obstructive sleep apnea syndrome	3 (8.1%)	3 (21.4%)	>0.05
Tobacco consumption	8 (21.6%)	1 (7.1%)	>0.05
Hypercholesterolemia	4 (10.8%)	3 (21.4%)	>0.05
Liver function			
Score Child-Pugh -Turcotte (class)(n, %)			>0.05
A	14 (37.8%)	6 (42.9%)	
B	12 (32.4%)	5 (37.5%)	
C	11 (29.7%)	3 (21.4%)	

MELD score, median (min-max)	23.6 (7-40)	16.6 (7-40)	>0.05
Complications after liver transplantation (within 3 months)			
Total (patients, n, %)	17 (46.0%)	4 (28.6%)	>0.05
Hemorrhage	6 (16.2%)	1 (7.1%)	
Hepatic or portal vein thrombosis	1 (2.7%)	0	
Biliary complication	5 (13.5%)	0	
Wound infection	3 (8.1%)	1 (7.1%)	
Pneumopathy	5 (13.5%)	1 (7.1%)	
Ascites infection	4 (10.8%)	1 (7.1%)	
Surgical revision	13 (35.1%)	0	
Mortality	2 (5.4%)	0	

*coronary artery disease, valvular heart disease, arrhythmia, stroke, obliterative arteriopathy

** last bariatric surgery type in cases of several successive procedures

***a single patient may have several causes of liver disease

Abbreviations: NAFLD, non-alcohol-related fatty liver disease; HCV, Hepatitis C virus.

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