Review Article

Liver transplantation for non-alcoholic fatty liver disease—a review

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Abstract: Non-alcoholic fatty liver disease (NAFLD) is the leading cause of liver disease in North America, and without any pharmacological treatments readily available for this disease, it is fast emerging as a top indication for liver transplant (LT). Since the main risk factors for the development of fatty liver are the various components of the metabolic syndrome, patients with fatty liver have high rates of cardiovascular (CV) disease and renal dysfunction, both pre- and post-LT. Obesity does not seem to affect transplant outcomes, once the body mass index (BMI) has been adjusted for ascites and edema. However, patients undergoing transplant for fatty liver are at increased risk for cardiac events and sepsis, and their care should be optimized pre-transplant in order to both screen for and optimize cardiac risk factors. The development of fatty liver post-transplant can be separated into two categories: recurrent disease and *de novo* disease. To date, there are few studies examining the long-term outcomes, but what data does exist suggests that these are two separate entities, with recurrent fatty liver resulting in poorer outcomes, both overall and graft related.

Keywords: Non-alcoholic fatty liver disease (NAFLD); non-alcoholic steatohepatitis (NASH); liver transplant (LT); recurrent NAFLD; *de novo* NAFLD; immunosuppression

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as the presence of steatosis in at least 5% of hepatocytes in the absence of other causes, such as alcohol or medications. It is an umbrella term, encompassing a wide spectrum of disease severity, from steatosis alone, to steatohepatitis [non-alcoholic steatohepatitis (NASH)] to cirrhosis. It is currently the leading cause of liver disease in North America, and is predicted to become the leading cause of liver transplant (LT) by 2030 (1-6). Uniquely among the various processes contributing to the cause of chronic liver disease (CLD) in North America, NAFLD is one that, as yet, has no approved treatment options, nor are there mechanisms in place to address risk of recurrence, such as those that exist for alcoholic liver disease (ALD). There are no definitive dietary guidelines that can be prescribed to patients, and not all patients are medically able to follow an exercise regimen strict enough to result in the desired 10% weight loss that has been associated with histological improvement (7), and to date, no pharmaceutical agents have been shown to result in histological or clinical improvement in the setting of cirrhosis, leaving LT as the only possible treatment option.

There are many factors to consider when addressing the issue of transplant for NASH—the prevalence of the disease, peri-operative cardiac and renal dysfunction, and risk of disease recurrence. The risk factors for the development of NASH are the various components of metabolic syndrome, all of which can be caused by the various immunosuppressants. In addition, both recipient obesity and donor steatosis have adverse effects on graft outcomes, thereby increasing morbidity and mortality in patients transplanted for NAFLD.

Epidemiology of NASH and LT

The hepatic manifestation of metabolic syndrome, the

rising incidence globally of NAFLD parallels the increase in the twin epidemics of obesity and insulin resistance (8-10). Although the mechanisms behind the development of steatosis and inflammation are manifold, insulin resistance is thought to play a significant role in both processes (11). Rates of NAFLD in North America and parts of Europe range around 20–30% (12), if not higher, and the prevalence of NASH is 2–5% in the general population. However, in certain populations, such as patients with diabetes mellitus type II (DM II) or morbid obesity, the rates of NAFLD are close to 50% and 90%, respectively, and rates of NASH range around 40% (13).

NASH was initially categorized by the United Network for Organ Sharing (UNOS) as a cause of cirrhosis requiring LT in 2001 (2); prior to this, most cases were likely classified as cryptogenic cirrhosis (CC), since lipid droplets are not seen in patients with NASH cirrhosis (14,15). A recent study examining the trends of LT for NASH in the USA using the United Network for Organ Sharing/Organ Procurement and Transplantation (UNOS/OPTN) database found that the incidence of NASH cirrhosis as an indication for LT increased exponentially, from 1.2% of all LTs in in the US in 2001 to 17.4% in 2014 (2,16). Since the authors presumed a diagnosis of NASH in patients with CC and a body mass index (BMI) >30 kg/m^2, one could argue that a rate of nearly one in five is an underestimate of the true prevalence of the disease, both because NASH is often seen in patients under a BMI of 30 kg/m^2, especially in different ethnicities, and because patients may have lost weight as their liver disease progressed. Another recent study found that the most common cause of liver disease in American teens and young adults is NAFLD, again reflecting the increase in obesity in that population group (1).

Additionally, NASH can coexist with other diseases, such as hepatitis C (HCV) or ALD. With other disease processes, the presence of multiple hepatic insults increases the rate of progression of fibrosis to cirrhosis (i.e., coinfection with HCV and HCB, alcohol abuse in the setting of viral hepatitis, etc.) (17). Therefore, it seems reasonable to consider that the presence of NASH superimposed upon another disease process may contribute to the severity of hepatic dysfunction than if the primary process existed alone.

Rates of HCC in NASH have increased significantly over the past two decades; it has increased by 9% between 2004 and 2009 in the US (4,18), while in Europe, 35% of all HCC cases were seen in patients with NASH (19). Interestingly, HCC has been reported to occur in non-cirrhotic NASH patients (20-22), thereby contributing to the increasing demand for LT through multiple mechanisms—CLD and HCC-related disease.

Patients with NASH awaiting LT tend to be older, overweight, and with a higher rate of metabolic syndrome and its constituent components (3,15). All of these are risk factors for diseases of other organ systems, such as ischemic cardiac disease. Indeed, patients with NASH cirrhosis are more likely to be removed from the transplant wait list for associated comorbidities than patients with viral hepatitis, ALD, or inherited causes of CLD (23), with a lower likelihood of receiving a transplant within 1 year of listing compared to either ALD or HCV infection (40.5% *vs.* 47%) (3).

Effect of obesity on LT outcomes

Recipient obesity

Early studies exploring the effect of obesity on LT outcomes were contradictory, with some studies demonstrating increased morbidity and mortality, while others found no association between BMI and transplant outcomes (24-26). Indeed, one study demonstrated a survival benefit in obese patients undergoing LT (27). However, the majority of these studies were limited by size, and the survival benefit of obesity may simply have been a reflection of a lack of sarcopenia or frailty, as opposed to any protective effect of obesity. Thus, it is difficult to draw any definitive conclusions from these studies.

Nair *et al.* (28) presented the first large scale study on the effects of obesity on transplant outcomes, noting that rates of primary non-function (PNF) and mortality were increased in both severely and morbidly obese patients. Using the UNOS database between 1988 and 1996, they found that of 18,172 LTs who fit their inclusion criteria, 46% were non-obese (BMI <25 kg/m^2), 33% were overweight, 14% were obese, 5% were severely obese (BMI: 35.1–40 kg/m^2) and 2% were morbidly obese (BMI >40.1 kg/m^2). Rates of PNF in the severely and morbidly obese group were 9% and 10%, respectively, whereas it was only 6% in those who were non-obese. Similarly, morbidly obese patients had a higher 1- and 2-year mortality (22% and 33%, respectively) compared to non-obese patients (16% and 25%, respectively, P=0.01), while both the severely and the morbidly obese categories had a significantly higher 5-year mortality. The morbidly obese group had a significantly lower survival on the Kaplan-Meier curve compared to the other categories (P=0.001), with morbid

obesity being an independent predictor of mortality at 2 years [odds ratio (OR) =1.52, 95% confidence interval (CI): 1.05–2.22; P=0.02). The main cause of mortality in these groups were related to cardiovascular (CV) events, which is similar to the leading cause of mortality in non-transplanted NASH patients. Other predictors of mortality in this study were recipient age at transplant, diabetes, serum creatinine, and UNOS status I or II at time of transplant. Of interest, other than increased rates of PNF, there was no decrease in graft survival in the three obese categories. Another study examining the UNOS database over a 20-year period found that, among 73,538 patients undergoing LT, a MELD score ≥22 in combination with a BMI ≥40 kg/m^2 was associated with an increase in post-transplant mortality of 40% (29). Another study suggested that the presence of both obesity and insulin resistance pre-transplant was associated with an increased rate of CV events, post-operative infections, and acute kidney injury (30).

In contrast, a study by Leonard *et al.* examined the combined databases from National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) liver transplantation records and from the Mayo Clinic. Of total of 1,313 patients undergoing LT, the authors found that once the BMI was corrected for the presence and amount of ascites at the time of transplant, there was no difference in either patient or graft mortality across the different categories of BMI. Indeed, they found that correcting for the volume of ascites resulted in reclassification of the BMI of 11–20% of patients initially classified as having a BMI >25 kg/m^2. Their conclusions were that it was the volume of ascites, not the BMI, which was an independent risk factor for mortality (HR =1.07, 95% CI: 1.03–1.11; P≤0.01) (31). This study also demonstrated that increased BMI was not associated with an increase in the infection, rates of cellular rejection, PNF, or length of stay. This is one of the few studies that was able to correct the BMI for the presence of ascites, and since most of the UNOS/OPTN/Scientific Registry for Transplant Recipient (SRTR) databases do not readily have this information available to be extracted from the data set, this is an important factor to be considered when assessing the effect of obesity on transplant outcomes.

Graft steatosis and outcomes

Just as the increasing rates of obesity and insulin resistance result in an increased number of patients who require transplants, so too will it affect the candidacy of potential donors who are declined because of their undiagnosed NAFLD. In 2010, 21% of livers offered were declined due to older age, increased BMI, and a high prevalence of diabetes (32), and anywhere from 3–21% of potential living donors were declined due to biopsy proven NAFLD (33). Thus, one can extrapolate that as time progresses, the demand for LT will increase while the available supply of potential organs will only decline.

Donor livers with increased degrees of steatosis have poorer post-transplant outcomes. Steatosis in excess of 60% within the donor liver usually results in increased rates of PNF, although this is also observed in livers with 30–60% steatosis, albeit a lower rate (34). It is thought that this may be due to lower levels of adenosine triphosphate (ATP) in steatotic livers, rendering them more susceptible to both ischemic injury and reperfusion injury (35). Due to this, donor livers with greater than 60% steatosis are generally not transplanted. An older study showed that greater than 30% macrovesicular steatosis in the donor liver was an independent risk factor for graft failure within the first year of transplant (36).

Visual examination has been shown to be unreliable as an assessment of hepatic steatosis, with a positive predictive value of <20% for predicting less than 30% hepatic steatosis, and 70% for predicting severe steatosis (greater than two-thirds of hepatocytes affected) (37). Unfortunately, there is no standardized practice across transplant centres for histological examination of donor livers for steatosis. While some centres routinely biopsy all donor livers, some centres only routinely biopsy livers in donors who are high risk for NAFLD (older age, increased BMI, associated comorbidities, or known abnormal liver enzymes).

Due to these concerns, centres performing living donor liver transplantation (LDLT) often exclude donors with significant macrovesicular steatosis (>20–30% steatosis). A study of almost 500 living liver donors with normal liver enzymes and imaging found that over 11% of donors had a minimum of ≥30% steatosis (38), suggesting that routine screening was not sufficient to determine moderate steatosis in donors.

In an effort to preserve the donor pool of livers, multiple options have been attempted to optimize a steatotic donor organ, such as intensive diet, dietary supplements, exercise measures, and medications in living donors (39,40), and ischemic preconditioning in the deceased donor organ (41,42). Unfortunately, the results of the studies in deceased donor livers are mixed, and there are no definitive measures that have been shown to decrease steatosis in a graft prior to transplant.

Increased rates of renal dysfunction in NASH

Like NAFLD, chronic kidney disease (CKD), defined as a glomerular filtration rate (GFR) ≤60 mL/min/1.73m^2, is also closely linked to obesity, diabetes and hypertension. Studies have shown that morbidly obese patients are at increased risk of developing proteinuria with histological abnormalities on renal biopsy, even in the absence of diabetes or hypertension (43-45).

In a community-based cohort of 2,000 patients with DM II, patients with a sonographic diagnosis of hepatic steatosis had a higher incidence of CKD than those without NAFLD (15% *vs.* 9%, P<0.0001), even after controlling for mitigating factors such as duration of diabetes, glycemic control, other components of metabolic syndrome, and use of medications such as anti-hypertensives, oral hypoglycemics, and anti-platelet agents (46). Another, similarly large-scale study of patients with an abnormal oral glucose tolerance test found that patients with NAFLD were more likely to have proteinuria than those without NAFLD, with a greater increase seen in those patients with diabetes and NAFLD (32.6% *vs.* 4.5%, P<0.0001) than in those with only pre-diabetes and NAFLD (19% *vs.* 6.3%) (47). The degree of fibrosis in NASH correlates with the degree of renal dysfunction, with a four-fold increased risk of CKD being seen in patients with a higher probability of fibrosis based on the NAFLD fibrosis score (48,49).

In a study comparing LT candidates, patients with NASH cirrhosis were found to have higher creatinine (1.26 *vs.* 0.98, P=0.0018) compared to patients listed for other causes of cirrhosis (50). In the post-LT setting, NASH cirrhosis as an indication for LT is a possible RF for the development of stage 3 CKD (or worse) 5 years after transplant (OR =2.95, 95% CI: 1.06–8.21; P=0.039) (51), although this was not seen in an earlier, larger, study (where only HCV status and pre-LT Cr were the only predictors of renal function 1-year post-LT) (52). However, the latter study was conducted in the era before direct acting antiviral therapy, and therefore may not be applicable going forward. Another study from the UK found that NASH patients had a significantly lower GFR than non-NASH patients, where at 2 years post-transplant, 31.2% of NASH patients had stage IIIb CKD, compared to 8.3% of non-NASH patients (P=0.009), even after controlling for BMI, tacrolimus levels, DM, hypertension, and the presence of HCC, indicating that NASH was an independent risk factor for developing renal failure post-transplant (53). Results of a retrospective analysis of the UNOS database for outcomes in patients undergoing SLK found that, although there was no difference in liver graft outcomes among groups, kidney graft outcomes were worst in patients being transplantation for NASH or CC compared to patients transplanted for ALD, biliary diseases (5), with a 1.5-fold increased risk of kidney graft loss compared to patients transplanted for ALD or PSC.

Outcomes of LT for NASH cirrhosis

Patients undergoing transplantation for NASH seem to have a lower survival (both 1 month and 1 year) than patients transplanted for alcoholic cirrhosis or viral hepatitis.

NASH cirrhosis was also associated with an increased rate of portal vein thrombosis than CLD due to other etiologies, based on one study examining the UNOS/OPTN database over a 9-year span (2003–2012) (54). This is thought to be due to a possible procoagulant factor seen in NASH cirrhosis (55). Portal vein thrombosis can cause more technically difficult surgeries, or may even result in removal of the patient from the transplant wait list (56).

Although initial data suggested that patients with NASH undergoing transplantation had poorer outcomes, these findings have not been borne out in subsequent studies. Initially, it seemed as though NASH patients had increased early mortality, with increased CV events. Malik *et al.*, in a study examining 2,021 patients undergoing LT (of which 143 had NASH cirrhosis), found increased 1-month mortality (6.1% 1-month mortality *vs.* 0.5% to 3.1% in non-NASH cirrhosis), and increased rates of sepsis in patients with NASH cirrhosis (57.1% in NASH patients *vs.* 21.6% to 33.3% in non-NAFLD patients) (57). However, Charlton *et al.* found that there was no difference in survival between patients transplanted for NASH cirrhosis and non-NASH cirrhosis, with a 1-year survival of 84% and a 3-year survival of 78% in patients with NASH cirrhosis (58). These findings were echoed in more recently published studies, with similar survival rates for patients transplanted for NASH cirrhosis as those for other causes of cirrhosis (59-62).

Vanwagner *et al.* found that patients undergoing LT for NASH cirrhosis had higher rates of CV events within the first year after transplant (26% *vs.* 8%, P<0.01), even after controlling for CV risk factors and a pre-transplant history of cardiac disease. The majority of the events occurring in the peri-operative period, but found that there was no difference in CV mortality between the NASH and non-

NASH groups (63). Interestingly, this study did find that there was a slight increase in rates of sepsis within the first 30 days in patients transplanted for NASH cirrhosis (17% *vs.* 6%, P=0.05).

In a meta-analysis of nine studies involving 4,237 patients (717 with NASH and 3,520 without), survival rates between the two groups at 1, 3 or 5 years were equivalent (1-year OR =0.77, 95% CI: 0.59–1.00, P=0.05; 3-year OR =0.97, 95% CI: 0.67–1.40, P=0.86; 5-year OR =1.07, 95% CI: 0.77–1.56, P=0.63). However, the study also found that patients with NASH had increased rates of mortality related to CV events (OR =1.65, 95% CI: 1.01–2.70, P=0.05) and sepsis (OR =1.71, 95% CI: 1.17–2.5, P=0.006) (59). The same meta-analysis found that patients transplanted for NASH cirrhosis had higher graft survival than compared to non-NASH transplants.

CV disease is the leading cause of non-transplant mortality among all LT recipients; the risk for CV death is increased in LT recipients compared to the general population (64). In fact, CV mortality accounts for 11% of all deaths at 1-year post-LT, making it the leading cause of non-graft related mortality (65). Given that the leading cause of death in NASH patients pre-transplant is CV (66), and that most immunosuppression medications are associated with development of hypertension, diabetes, or hyperlipidemia, the increased rates of cardiac disease are unsurprising. The current American Association for Study of Liver Diseases (AASLD) guidelines for management of NAFLD indicate that statins are recommended in patients with NAFLD and dyslipidemia. The Ekstedt study demonstrated that the risk of CV events increased as the degree of fibrosis increased, suggesting that patients with decompensated cirrhosis are at highest risk for a cardiac event.

Development of NAFLD post-transplant

NAFLD can occur post LT in one of two possible settings: recurrent NAFLD in patients transplanted for NASH or CC, or as *de novo* NAFLD, in patients who were transplanted for another form of CLD. *De novo* NAFLD can be seen in patients for a number of reasons, not the least of which are the metabolic effects of immunosuppressive medications such as steroids or calcineurin inhibitors.

Rates of *de novo* NAFLD post-transplant range from 8% to 31.1% over variable study periods (anywhere from 6 months to 20 years), whereas rates of recurrent NASH range from 13–100%, and advanced fibrosis is seen in 5–10% (67-73). As with pre-transplant NAFLD, rates of steatosis are higher in the post-transplant population than rates of steatohepatitis (8.2–62.5% *vs.* 4–33%) (68,70,74,75). The high variability in rates of steatosis and NASH in these studies is likely due to a large proportion of these patients who had concurrent HCV infection, as HCV can be associated with hepatic steatosis. Patients with post-transplant metabolic syndrome are at higher risk of developing post-transplant NAFLD, whether it be recurrent or *de novo* (73,76), with a non-linear increase in risk as the number of components of metabolic syndrome increases. Dumortier *et al.* found that the risk of *de novo* NAFLD was only 12% if the patient had one component of metabolic syndrome, compared to a 22% risk with two components, 29% with three, 65% with four, 81% with five, and a 100% risk of *de novo* NAFLD with all six components of metabolic syndrome (76).

Vallin *et al.* followed 532 LT recipients (of whom only 12 had NASH) over a 10-year period. The first study to examine the natural history of the two processes, the investigators found that recurrent and *de novo* NAFLD may be different clinical entities with different prognoses. A total of 91 patients developed NAFLD post-transplant, of which 11 were classified as recurrent NAFLD. At the 5-year mark, both NASH and advanced fibrosis (F3 and/or F4 disease) were seen at a higher rate in the recurrent NAFLD group compared to the *de novo* NAFLD group (NASH: 71.4% *vs.* 12.5%, P<0.01; advanced fibrosis 71.4% *vs.* 17.2%, P<0.01) (77). Thus, it would suggest that patients with recurrent NAFLD are at increased risk of progressing to NASH and advanced fibrosis, and at a faster rate, than patients with *de novo* NAFLD. At this time, there are few, if any, natural history studies on the rate of progression of post-transplant NAFLD as compared to pre-transplant NAFLD.

In Vallin's study, 100% of patients transplanted for NASH cirrhosis who had recurrent NASH had DM, compared to 37.5% of patients transplanted for other causes of liver disease (P<0.01). Although the ability to draw definitive conclusions from the study is limited by the small sample of NASH cirrhotics (n=12), it is the first study to demonstrate that recurrent NAFLD, and not *de novo* NAFLD, is a risk for the development of insulin resistance. These findings were echoed in a retrospective analysis of the SRTR database, comparing transplant outcomes in 2,916 NASH patients to 1,4268 patients with non-HCV related cirrhosis or HCC. In a multivariate analysis of the results, after adjusting for confounding factors such as the use of

different immunosuppressive medications, nearly 7.6% of the NASH cirrhotics developed long term DM, compared to 4.3% of the control group (P<0.0001), with an OR of 1.29 (95% CI: 1.18–1.42, P<0.0001) (78).

One of the possible risks for the development of both diabetes and NAFLD post-transplant may be recipient genetics, specifically mutations in the patatin-like phospholipase domain containing protein 3 (*PNPLA3*) gene (non-CC genotype) and *IL28B* (non-TT genotype) (79-81). Recipients who were homozygous for the mutation have a 63.2% risk of developing steatosis 5 years post-transplant, compared to 12.0% of those without the mutation (P=0.002), while donor genotypes were not associated with the development of steatosis. Similarly, the risk of post-transplant obesity was associated with the non-CC genotype in the recipient (HR =1.59, 95% CI: 1.38–4.66, P=0.003), while the presence of both the non-CC *PNPLA3* and the non-TT *IL28B* mutation conferred an increased risk of post-transplant diabetes (HR =2.64, 95% CI: 1.30–5.39, P=0.008) (80).

Bariatric surgery and LT

Given the increasing rates of obesity and NASH cirrhosis, as well as the increased morbidity and mortality associated with morbid obesity and LT, it is increasingly clear that new approaches are needed to cope with the impending onslaught of both disease processes. The role and timing of bariatric has been questionable: it would be contraindicated pre-transplant, in a patient with decompensated cirrhosis, whereas in the post-transplant patient, it may be associated with technical difficulty due to adhesions and issues of long term immunosuppression use.

Retrospective analyses of liver biopsies taken at the time of laparoscopic bariatric surgery in morbidly obese patients without a known history of liver disease revealed that a significant proportion (58%) of patients had evidence of NASH (82). Interestingly, this study found that 14% of patients had evidence of NASH with a ≥ F2 fibrosis, and that there was no difference in 30-day mortality or incidence of liver failure in this group compared to other NASH groups, indicating that these patients are able to tolerate a major surgery.

Although the weight loss surgical technique that is most associated with significant weight loss that is maintained over time is a Roux-en-Y bypass (83), this is not considered to a viable option in the setting of LT, both due to the complexity of the surgery as well as due to concerns regarding altered immunosuppressant absorption that may affect immunosuppression levels early on in the post-transplant course (84,85). Gastric banding has similarly been dismissed as a possible option for in the transplant setting, due to the infectious risks associated with a foreign body in an immunosuppressed patient (86).

In 2013, Heimbach *et al.* (87) were first to present data on the outcomes of combined LT and sleeve gastrectomy (LTSG) in patients with end stage liver disease and obesity. In this single centre study, all patients referred for transplant who had a BMI >35 kg/m^2 were enrolled in a study where they were randomized to a LT with medically managed weight loss (n=37), or to a LTSG (n=7), with a mean BMI in the former group of 40 kg/m^2 and in the latter group of 48 kg/m^2. In the control group, 21 patients regained weight (mean BMI =36 kg/m^2), 12 patients developed DM II, and 7 patients developed hepatic steatosis. Over a mean follow-up period of 35 months, there were three deaths and three graft losses in the control group, and no deaths or graft losses in the combined surgery arm (mean follow-up period of 17 months), although one patient did develop early graft dysfunction and a subsequent leak from the gastric staple line necessitating multiple re-operations. None of the patients in the treatment arm developed post-transplant diabetes or hepatic steatosis. Of key note, however, was that they demonstrated that noninvasive management of obesity, with dedicated obesity programs centered around dietary education, were effective in reducing patient weight and BMI from a mean BMI of 40 to 33 kg/m^2 at the time of transplant, indicating that weight loss is achievable with intensive education and counselling.

Although another controlled study has not been performed, Nesher *et al.* published their experience with LTSG in three patients who were unable to achieve a pre-transplant BMI <35 kg/m^2 prior to transplant (88). After a median follow-up of 13 months, all three patients were doing well, without any evidence of graft dysfunction, with two patients experiencing a remission of their hypertension and diabetes. Thus, although it is far too early to draw conclusions about the applicability of LTSG to the burgeoning NASH cirrhosis LT wait list, it is a fascinating area for future research.

Conclusions

NAFLD is poised to become the leading indication for LT in North America and areas of Europe. Unfortunately, the increase in obesity and insulin resistance that leads to

Table 1 Suggested management options for LT in NASH cirrhosis

Stage of management	Proposed interventions
Pre-transplant	Intensive cardiovascular risk stratification and investigation at outset and then on regular basis (every 2 years) until transplant; initiation of statin for cardiac risk reduction*; initiation of betablocker for cardiac risk reduction*; tight control of DM II, dyslipidemia, and hypertension; intensive education with dietician regarding dietary changes to maximize weight loss while ensuring no protein calorie malnutrition
Peri-operative	Avoidance of use of grafts with >30% steatosis in older patients, or if there is >5 hours CIT; consider concurrent bariatric surgery in patients with severe morbid obesity; aim for tight glucose control
Post-transplant	Adoption of renal sparing protocol; post-transplant monitoring for development of DM II with HbA1C every 3–6 months; patients with DM II should be optimized in accordance with national guidelines; nutritional counselling with dietary intervention to decrease risk of recurrence; target LDL of <2.6 mmol/L to decrease cardiac risk; consider annual ultrasound to assess for steatosis, especially in patients with metabolic syndrome; consider liver biopsy if evidence of steatosis on ultrasound

*, unless there is a contraindication to use. LT, liver transplant; NASH, non-alcoholic steatohepatitis; DM II, diabetes mellitus type II; HbA1C, glycated hemoglobin A1C; CIT, cold ischemic time; LDL, low density lipoprotein.

the development of NAFLD also means that the potential donor pool of livers available for transplant will only decrease in the future. In addition, once patients undergo a LT, they are still at increased risk of cardiac events, sepsis, and renal failure. Thus, both pre-transplant and post-transplant management needs to be specialized and optimized in patients with NASH cirrhosis (*Table 1*).

The data regarding BMI outcomes in LT are conflicting—although many studies seem to indicate that patients with a BMI >40 kg/m^2 do poorly, other studies have not shown that there is any difference in either graft or patient mortality. Further research is needed to address the issue of a true, dry-weight BMI (after having corrected for ascites and edema), as opposed to a random BMI. All patients awaiting transplant should undergo intensive education with a transplant dietician and a possibly bariatric surgery team, to optimize lifestyle measures and weight loss prior to transplant. Weight loss must be done with caution, in a monitored environment, as patients with decompensated cirrhosis are at high risk for developing protein-calorie malnutrition.

NASH is considered to be an independent risk factor for ischemic cardiac disease, and patients transplanted for NASH cirrhosis have higher rates of cardiac events post-transplant than their counterparts. Therefore, all patients with NASH on the transplant wait-list should have pre-operative cardiac risk stratification with non-invasive testing, regardless of age, to assess for structural heart disease, pulmonary hypertension, and coronary artery disease. Patients with NASH cirrhosis may also require further cardiac testing, and possibly invasive testing, then their non-NASH counterparts, especially if they are not able to achieve ≥ four METS on stress testing. Despite there being little data surrounding the frequency that cardiac testing should be repeated in asymptomatic patients awaiting LT, it would be sensible to routinely retest this patient population. In the renal transplant population, there is data to suggest that patients should be tested every 2 to 3 years (89,90)—given the increased incidence of cardiac disease both peri- and post-operatively in NASH cirrhosis, one could argue that retesting every 2 years is appropriate.

Patients with NASH cirrhosis may also benefit from being started on a beta-blocker prior to liver transplantation, if they can tolerate it. Similarly, all patients with NASH cirrhosis awaiting transplant should be on a statin, unless there is a contraindication, to decrease peri-operative and post-operative cardiac events. Although the AASLD guidelines only recommend the use of statins in patients with hyperlipidemia, given the increased rates of CV events peri- and post-operatively in patients with NASH cirrhosis, this would suggest that patients with NASH cirrhosis awaiting transplant should be on a statin prior to transplant for cardiac protection (66).

Given the documented poor outcomes with steatotic grafts, further testing should be undertaken to assess the possibility of hepatic steatosis in grafts. Studies of living donors have demonstrated that a noninvasive assessment with bloodwork and ultrasound miss over one-tenth of patients with moderate to severe steatosis, while studies of visual inspection of cadaveric organs has been shown to have a poor predictive value for steatosis. Therefore, we suggest that routine histological assessment with a biopsy

should be undertaken in all living donors, and in cadaveric donors with risk factors for NAFLD (obesity, known history of hyperlipidemia, diabetes, or use of medications associated with steatosis).

In organs with >30% steatosis, graft dysfunction is associated with a prolonged cold ischemic time (>5 hours) and circulatory cause of death. Therefore, use of steatotic organs should only be used if these factors can be controlled, and they should be avoided in older patients (>40 years), as these patients are at increased risk for PNF with a steatotic graft.

Further research is needed regarding the natural history of recurrent *vs. de novo* NAFLD, and whether the two entities progress at different rates and are associated with extra-hepatic complications (cardiac or cerebrovascular disease).

Patients transplanted for NASH cirrhosis have higher rates of renal failure post-transplant. This is a population in which induction should be considered for renal sparing effects, as well as implementing a renal sparing protocol of immunosuppression in these patients, with limitation of calcineurin inhibitor use and use of other medications, such as mycophenolate mofetil to permit lower tacrolimus levels. The British Transplant Society Guidelines suggest that immunosuppression target goals should be for a Tacrolimus trough of <10 ng/mL for the first 3 months post-transplant, and then 5–8 ng/mL thereafter.

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