Multidisciplinary Approach for Liver Transplantation in Patients with Nonalcoholic Steatohepatitis: It Takes a Village

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Abstract

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Nonalcoholic fatty liver disease (NAFLD) is the leading cause of liver disease in Western countries, and its aggressive form, nonalcoholic steatohepatitis (NASH), is a leading cause of cirrhosis and end-stage liver disease. The total number of new liver transplantation waitlist registrants with NASH continues to increase rapidly, making NASH the second most common indication for liver transplantation. Compared with recipients for other etiologies, patients with NASH often have higher rates of obesity, diabetes, dyslipidemia, hypertension, kidney disease, and cardiac disease. Many of these medical comorbidities are independently associated with increased preoperative risk and both short- and long-term complications. The presence of these particular risk factors necessitates the need for early detection, medical optimization, and careful preoperative care. Bariatric surgery is an effective strategy for weight loss and ultimately reducing obesity-related medical complications. In select patients, bariatric surgery—before, during, or after liver transplantation—may be useful to help improve posttransplant outcomes. NAFLD/NASH can present after liver transplantation and occurs as either recurrent or de novo disease. Posttransplant NAFLD occurs in the setting of metabolic syndrome, immunosuppression use, and genetic determinants. Future studies and efforts should focus on optimizing medical management strategies to further improve transplant outcomes in patients with NAFLD.

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of liver disease in North America. NAFLD is an umbrella term, encompassing a wide histological spectrum of disease severity, for which definitive diagnosis requires histology.[1] The disease spectrum ranges from simple steatosis, which is defined by the presence of steatosis in at least 5% of hepatocytes in the absence of other causes (e.g., alcohol or medications), to nonalcoholic steatohepatitis (NASH), which is defined by the presence of hepatic fat accumulation, inflammation, and ballooning of hepatocytes, to fibrosis and ultimately cirrhosis. In a small proportion of patients, NASH cirrhosis can lead to complications including end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC).

Without any U.S. Food and Drug Administration (FDA) approved pharmacological treatments for NAFLD, the disease spectrum is quickly emerging as a top indication for liver transplant (LT).[2] In the 2015 United Network for Organ Sharing (UNOS) registry, NASH surpassed hepatitis C virus (HCV) infection as the leading indication for LT in patients

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under the age of 50 years.[3] It is predicted to become the leading cause of LT by 2030.[4]

Unfortunately, the increase in obesity and insulin resistance that leads to NAFLD also means that the potential donor pool of livers available for transplant will only continue to decrease in the future. In addition, once these patients undergo an LT, due to their medical comorbidities, they are at an increased risk of cardiac events, sepsis, and renal failure. Pre- and posttransplant management needs to be specialized for patients with NASH.[5]

NAFLD/NASH Pathophysiology and Epidemiology

Pathophysiology

The exact pathophysiological mechanisms of NAFLD still remain incompletely understood; however, the disease process is affected by insulin resistance, lipids, nutritional factors, physical activity, intestinal microbiota, and genetic determinants.[6]

The *two-hit* hypothesis postulates that the first hit is the intrahepatic accumulation of fatty acids, which then increases the susceptibility of the hepatocytes to a "second hit," which includes oxidative stress, mitochondrial dysfunction, proinflammatory cytokines, and gut dysbiosis).[7,8] The two-hit hypothesis is now considered outdated and has been replaced by the *multiple parallel-hit* hypothesis to explain the natural history and pathogenesis of NAFLD. The multiple-hit pathogenesis suggests that multiple insults act together in genetically predisposed patients.[9,10]

Epidemiology

Historically, chronic HCV infection was the most common cause of hepatic decompensation leading to HCC and LT.[11] However, in recent years, due to the advent of curative direct antiviral agents (DAA), there has been a sharp decrease in the proportion of candidates with HCV. In contrast, the proportion of candidates with NASH has demonstrated a tremendous increase over the last decade.[12] This increase parallels the rising prevalence of type 2 diabetes mellitus (T2DM) and obesity.

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities that is a precursor to cardiovascular disease (CVD) and is a significant risk factor for NAFLD/NASH. In 2005, the American Heart Association and the National Heart, Lung, and Blood Institute updated the previous 2001 National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) definition of MetS. According to the NCEP ATP III definition, MetS is present if any three of the following five criteria are present: (1) obesity (waist circumference > 40 inches in males or >35 inches in females; (2) hyperglycemia (fasting glucose ≥ 100 mg/dL or on medication); (3) dyslipidemia (triglyceride ≥ 150 mg/dL or on medication); (4) dyslipidemia (second, separate criteria) (high-density lipoprotein cholesterol < 40 mg/dL in males or < 50 mg/dL in females or on medication; (5) hypertension (>130 mm Hg systolic or >85 mm Hg diastolic or on medication).[13]

The prevalence of NAFLD worldwide is estimated at 9 to 50% in the adult population, whereas the prevalence of NAFLD in the United States is reported at 10 to 35%.[14] The majority of patients with NAFLD have just simple steatosis; however, analysis of NAFLD cohorts using paired liver biopsies suggest that one-third of patients with NAFL/NASH have progressive fibrosis, whereas one-fifth of patients will have some regression.[15] One global meta-analysis demonstrated fibrosis progression in NASH to be as high as 41%.[16] NASH progression to cirrhosis and HCC has an estimated prevalence of 3 to 5% in the adult population, whereas cirrhosis is observed in up to 20% of patients with NASH in a 10-year period.[17] It is projected that by 2030, the incidence of decompensated NASH cirrhosis and HCC in the setting of NAFLD/NASH to increase by 168 and 137%, respectively.[18] In patients with cirrhosis due to NASH, the 10-year mortality from liver failure occurs in 30 to 40% of patients.[19]

NAFLD-associated HCC occurs in patients with cirrhosis as a potential complication of the disease. In developed countries, the rising incidence of HCC is thought to directly parallel the increasing prevalence of MetS.[20] In a study of 4,929 cases of HCC between 2004 and 2009, 14.1% of HCC were due to NAFLD, with an annual increase of 9%.[21]

Diabetes and obesity are associated risk factors for HCC in patients.[22] While most cases of HCC are associated with cirrhosis, HCC can occur in the absence of cirrhosis in patients with NAFLD, thus leading to a later diagnosis. NAFLD-HCC is more often diagnosed at a later stage with larger tumors when compared with those with cirrhosis and HCC.[23]

Nonalcoholic Steatohepatitis and Transplant

Based on national registries, the greatest increase in new LT waitlist registrations from 2004 to 2013 was in candidates with NASH; the increase, by 170%, far exceeded registrants with alcohol-related liver disease (increased by 45%) and HCV (increased by 14%).[24]

In 2015, 10,630 new candidates were added to the LT waitlist, and NASH was the second leading cause of liver disease among the candidates.[11] This rising incidence is seen in various subgroups. NASH has become the leading indication for LT in women; from 2004 to 2016, there has been a 91% increase in female transplant recipients with NASH.[25] Even in the baby boomer generation (persons born between 1945 and 1965), which was considered the hepatitis C generation, the proportion of patients with NASH added to LT waitlist has demonstrated incremental growth, up to 83.2% in 2015, compared with 60.6% in 2004 (p < 0.01).[26] The proportion of baby boomer LT recipients with NASH also increased incrementally, coming in second after recipients with HCV.[27]

While the number of waitlist registrants with NASH is rapidly increasing, earlier studies demonstrated that patients with NASH are less likely to receive an LT when compared with patients with HCV; the NASH patients were ultimately more likely to be delisted or die before receiving an LT.[28] However, in an analysis of the UNOS data from 2002 to 2016, Thuluvath et al demonstrated that patients with

NASH are not disadvantaged by higher waitlist removal or lower transplant rates when compared with their counterparts with other liver disease etiologies. The cumulative incidence of death or deterioration was similar for patients with NASH cirrhosis, cryptogenic cirrhosis, alcohol-related cirrhosis, and autoimmune hepatitis (29, 28, 28, and 24%, respectively) along with similar rates of transplantation (48–54%) across all groups.[29]

Pretransplant Considerations

There is growing evidence that NAFLD is a multisystem disease and therefore the clinical burden extends beyond the liver alone. NAFLD is closely related to T2DM, CVD, and chronic kidney disease (CKD), and many patients with NAFLD have the aforementioned comorbidities. Recognition of these medical conditions is important to help medically optimize patients in the pretransplant setting.

Obesity

The prevalence of obesity in the United States is currently estimated to be approximately 35%.[30] In patients with obesity, the prevalence of NAFLD is approximately 70 to 80%, whereas the prevalence of NASH is estimated at around 15 to 20%.[31] The current epidemic of obesity has impacted patients with ESLD and may be either the primary cause of liver disease or at least a contributing factor in the patient's disease. As the rates of obesity continue to rise, the prevalence of NAFLD increases in parallel.

Obesity is strongly associated with diabetes, heart disease, and cancer, which are leading causes of morbidity and mortality post-LT.[32] Studies on the impact of obesity on posttransplant outcomes have been inconsistent. In an early study, Leonard et al. demonstrated that obese patients require greater operative time and blood product usage and had a higher risk of complications including increased intensive care unit length of stay, wound and intra-abdominal infections, and biliary complications.[33] Later studies have demonstrated that obese and morbidly obese patients may be transplanted with short-term outcomes similar to nonobese patients.[34,35] While the short-term outcomes of LT may be similar in those who are obese and nonobese, the long-term impact of obesity on post-LT outcomes including recurrence of NASH is becoming increasingly evident.[36]

Despite the technical surgical challenges and potential medical complications, obesity alone should not be an absolute contraindication to LT. Many programs aim to optimize recipients' body mass index (BMI) to allow for the best outcomes. Bariatric surgery has long been proven to be an effective weight loss strategy that can also reduce obesity-related complications.

Bariatric Surgery and NAFLD/NASH

The role of bariatric surgery in patients with liver disease continues to evolve. Weight loss induced by bariatric surgery has demonstrated some promise as a treatment option for NAFLD. Studies have demonstrated dramatic improvement in, even resolution of, NASH in obese patients who undergo bariatric surgery.[37–39] In a recent, large propensity-matched cohort study, results supported older studies stating that bariatric surgery in obese patients significantly reduce the incidence of NASH.[40] Various bariatric surgeries are available, and in comparative studies on Roux-en-Y gastric bypass (RYGB) and laparoscopic sleeve gastrectomy (LSG), there were no significant differences in improvement in liver histology of NASH between the two surgical methods.[41,42]

In a patient with cirrhosis, particularly decompensated cirrhosis, bariatric surgery is associated with a higher mortality.[43] However, in posttransplant patients, it may be associated with technical difficulty due to adhesions and issues of long-term immunosuppression use.[44]

Bariatric Surgery and Liver Transplantation

RYGB provides more effective weight loss than LSG.[45] In the study by Nickel et al, there was a significant improvement of NAFLD 12.5 months after bariatric surgery, with the median fibrosis stage in transient elastography (TE) decreasing from F3 to F1.[45] The high preoperative fibrosis stages are in line with findings in the study by Luger et al, which showed a prevalence, confirmed by liver biopsy, of NASH in 72%, simple steatosis in 11%, and a normal liver in 17% of bariatric surgery patients.[46]

However, since LSG results in fewer complications, it is increasingly the preferred choice in complex patients such as LT recipients.[47] Concerns with altered drug absorption and the need for higher doses of immunosuppression along with hypovitaminosis associated with RYGB also support the use of LSG.[44,48] Another benefit of LSG compared with RYGB is preserved access to the biliary tree for a potential future need for endoscopic evaluation of the allograft liver. Hence, most studies have focused on the LSG before or after LT.

The optimal time for bariatric surgery in this population remains undefined. Bariatric surgery has been described in patients before, during, and after LT.

In 2013, Heimbach et al presented data on a small, randomized, single-center study demonstrating that LT combined with LSG for patients with ESLD and obesity (BMI > 35 kg/m^2) was effective for weight loss', with significant decrease in post-LT metabolic complications including posttransplant hepatic steatosis or diabetes when compared with LT with medically managed weight loss.[49] 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, although one patient did develop early graft dysfunction and a subsequent leak from the gastric staple line, necessitating multiple reoperations. Notably, the noninvasive management of obesity, with dedicated obesity programs centered on dietary education, was effective in reducing patient weight and BMI at the time of transplant, indicating that weight loss is achievable without surgery and with medical management through intensive education and counseling.

The largest series on simultaneous LT with LSG is by Zamora-Valdes et al. In their study, out of Mayo Clinic, the group demonstrated a total body weight loss percentage of 36% in 12 months, but an overall complication rate nearing

50% and two postoperative deaths.[50] However, morbidity and mortality were likely associated with LT and not LSG. The complications ranged from infection to hepatic artery thrombosis (HAT) and allograft failure.

Obesity confers an increase in the prothrombotic state and is known as a predisposing factor for thromboembolic events. In obese individuals, there is an up to fivefold increased risk of deep venous thrombosis and pulmonary embolisms with increasing BMI.[51] HAT is the most feared and common vascular complication in LTs, affecting 2 to 12% of transplants, and the leading cause of graft failure and mortality.[52] Risk factors for HAT are related to surgical technique, ABO blood group incompatibility, prolonged cold ischemia time of the allograft, and rejection. Pediatric LTs are also more susceptible to HAT, likely due to small vessel caliber.[53] In the study by Zamora-Valdes et al, 2 of 29 patients developed postoperative HAT, which corresponds with the published percent of LT patients that develop HAT.[50] Hence, it is difficult to say if the increased hypercoagulability risk in bariatric patients contributed to HAT or if it was the innate risk of patients undergoing LT.

Studies in patients with LSG after LT have been promising. In a retrospective case–control study of patients undergoing LSG after LT, there was no significant difference in mean operative time or morbidity when compared with the non-LT LSG group. There were no conversions to open procedures, suggesting that prior LT did not increase complications as it relates to the surgical field. In patients with long-term follow-up, change in BMI after LSG was similar between LT and non-LT groups, although non-LT patients had significantly more excess body weight loss at 2 years. Importantly, LSG did not lead to changes in dosage of immunosuppressive mediations nor did it lead to liver complications.[54]

In the largest series to date, Morris et al demonstrated the safety, weight loss efficacy, and pronounced effect on the resolution of diabetes mellitus of LSG in post-LT recipients.[55] Following LSG, there was a significant decrease in BMI (42.7 to 35.9 kg/m^2; $p < 0.01$), with up to a 20.6% total body weight loss at 1-year follow-up. There was significant improvement in diabetes following LSG, as demonstrated by a significant decrease in the median daily insulin requirements (from 98 to 0 units/day; $p = 0.02$), with 60% of patients able to discontinue insulin. A total of 15 patients underwent LSG following LT at a median time of 2.2 years between the two surgeries and a median follow-up period of 2.6 years. Most importantly, there was no liver allograft rejection after LSG and only one postoperative complication (surgical site infection). For patients undergoing LSG, post-LT patients had a similar decrease in BMI and reduction in comorbidities at 1 year compared with the matched non-LT patient cohort. This extended study experience highlights the relatively low morbidity and mortality in the delayed approach for LSG after transplant.

Diabetes

The relationship between NAFLD and T2DM is bidirectional; patients with NAFLD are at an increased risk of developing T2DM and those with T2DM are at an increased risk of developing NAFLD.[56] In a cross-sectional study of 180 T2DM patients, the prevalence of steatosis found on ultrasound was 69.4%.[57] NAFLD and T2DM are both strongly associated with features of MetS, which include insulin resistance, dyslipidemia, and obesity. There is growing evidence to support NAFLD and MetS sharing common genetic pathogenic mechanisms.[58,59]

Along with having higher prevalence of NALFD, patients with T2DM are at an increased risk of progression of NAFLD/NASH and development of fibrosis, cirrhosis, and HCC.[60,61] Therefore, it is not surprising that in patients with NASH who undergo LT, up to 70% also carry a diagnosis of diabetes.[62,63]

Diabetes prior to LT is a strong predictor of early posttransplant complications, cardiovascular mortality, and overall decreased patient survival.[64,65] In a retrospective cohort study of 12,442 patients who underwent LT, Hoehn et al reported longer hospital length of stay; higher peritransplant mortality, 30-day mortality, and 30-day readmission rates; and inferior graft and patient survival in those who had diabetes when compared with those without diabetes.[66]

There is currently no evidence to suggest that tightly controlled diabetes will improve survival rates. However preoperative hemoglobin A1c (HbA1C) has been shown to be predictive of posttransplant complications. In a small retrospective study with 173 patients, HbA1c > 7.3% was associated with a fourfold increased risk of biliary stricture formation.[67]

In pretransplant patients with diabetes, close monitoring and careful management of diabetes are crucial to minimize posttransplant complications and improve graft and patient survival.

Renal Disease

The burden of CKD still remains uncertain, with estimates of prevalence ranging widely from 4 to 42%.[68] Despite the uncertainty, a continued increase in burden is expected, paralleling the rising prevalence of its risk factors including diabetes, obesity, MetS, hypertension, and aging.[69] Patients with ESLD from cirrhosis and liver failure are at a risk of developing kidney injury.[70] Patients who have ESLD from NAFLD are at even a higher risk of kidney injury. Given that NAFLD and CKD share many underlying risk factors, it is unsurprising that the two conditions are closely associated with one another. Experimental studies have suggested interlinked pathogenic mechanisms including serum proteins fetuin-A, adiponectin, and the energy sensor 5′-AMP-activated protein kinase (AMPK).[71,72]

There have been limited studies on NAFLD and CKD risk, but in the studies available, prevalence of CKD is increased in patients with NAFLD independent of age, sex, BMI, and other confounders such as diabetes, hypertension, and obesity.[73–75] In a meta-analysis by Musso et al, patients with simple steatosis had increased incidence (hazard ratio: 1.79; 95% confidence interval [CI]: 1.65–1.95) and prevalence (odds ratio: 2.12; 95% CI: 1.69–2.66) of CKD risk. NAFLD disease progression was associated with even higher incidence and prevalence of CKD. NASH with advanced fibrosis

was associated with higher incidence and prevalence of CKD than simple steatosis and nonadvanced fibrosis.[76] A few years later, Mantovani et al also reported the association of NAFLD and CKD, finding nearly a 40% increase in the long-term risk of incident CKD in patients with NAFLD.[77]

CKD is prevalent in 46.8% of patients with cirrhosis admitted to the hospital.[78] Patients with cirrhosis who have CKD have significantly higher rates of acute kidney injury (AKI), eventual need for dialysis, and reduced 30- and 90-day overall survival.[78] Dependence on hemodialysis is a significant independent predictor of posttransplant survival.[79] Patients who are dialysis-dependent and are obese have a decreased 3-year posttransplant survival rate.[63] In patients with both liver and kidney injuries, simultaneous liver/kidney (SLK) transplantation is often required. With the rising prevalence of NAFLD and CKD, NASH cirrhosis is the most rapidly growing indication for SLK transplantation.[56] Unfortunately, patients with NASH have generally poor renal outcomes after SLK.[2]

Cardiovascular Disease/Perioperative Risk

CVD is the leading cause of nongraft-related mortality, accounting for up to 42% of nongraft-related deaths.[80–83] LT imposes stresses on the cardiovascular system, such as increased blood pressure and peripheral vascular resistance after transplantation, which can unmask latent or clinically mild cirrhotic myocardial dysfunction, known as "cirrhotic cardiomyopathy."[84] MetS is associated with an increased risk of CVD and accounts for up to one-third of CVD in men.[85] The prevalence of MetS in patients after LT has been reported to be between 44 and 58%, conferring an increased risk of cardiovascular complications.[86,87]

NAFLD is recognized as an independent risk factor of CVD. Vanwagner et al found that patients undergoing LT for NASH had higher rates of cardiovascular events within the first year after transplant compared with alcoholic cirrhosis patients even after controlling for comorbidities and a pretransplant history of cardiac disease. The majority of the events occurred in the perioperative period, but it was also found that cardiovascular complications do not appear to alter the overall survival of patients undergoing LT for cirrhosis resulting from NASH compared with alcohol.[88]

In a 2012 study, the cumulative risk of cardiovascular events post-LT was reported to be 4.5 and 10.1% at 1 and 3 years, respectively. The 1- and 3-year risk was significantly higher in patients undergoing transplantation for NASH (15.3 and 19.3%, respectively) as compared with all other etiologies.[89]

Interestingly, coronary artery disease (CAD) does not seem to confer an increased risk of CVD mortality in transplant patients.[90] Patel et al recently reported that pre-LT CAD presence and severity did not impact survival after LT. This could be partly related to the fact that these patients were already being managed for CAD prior to LT and may have received more intensive monitoring after LT. The same group showed that diabetes was associated with an increased risk of having a cardiovascular event, and statin use demonstrated a survival benefit in patients who have undergone LT.[90,91] This supports earlier studies demonstrating the association of MetS with CV complications, thus necessitating early identification and aggressive modification of MetS to improve outcomes.

Perioperative cardiac assessment of pretransplant patients with NASH is crucial to identify high-risk candidates who require medical optimization. There are currently no specific guidelines for the identification of CAD and CVD in pretransplant patients.[92] The initial approach includes a clinical history to determine cardiovascular risk factors that include age, cigarette smoking, diabetes, dyslipidemia, and hypertension (►Table 1).[93,94]

All patients should undergo noninvasive pharmacological stress testing; dobutamine stress echocardiography is often preferred due to its high negative predictive value. In those who have equivocal or positive results on stress testing, coronary angiography is then recommended. Revascularization procedures should be considered in patients with significant stenosis, although there are no clear guidelines or recommendations in ESLD patients.

Transplant Outcomes in NAFLD

Patient and graft survival for patients who undergo LT for NASH cirrhosis are comparable with those of patients who undergo transplant for other etiologies.[95] The 1-, 3- and 6-month survival for LT in NASH recipients are 94, 91, and 88%, respectively.[96] Posttransplant survival in patients with NASH at 1, 3, and 5 years was superior to the survival of patients with HCC, HCV, and alcohol-related liver disease, with rates reported at 87.6, 82.2, and 76.7%, respectively.[97]

Post-LT NAFLD is a potential long-term complication that can occur as a recurrent disease in patients undergoing LT for

Table 1 Cardiovascular risk factor assessment

Traditional cardiovascular risk factors	Coronary heart disease risk equivalents
Age	Clinical coronary heart disease
Sex	Symptomatic coronary artery disease
Dyslipidemia	Peripheral artery disease
Systolic blood pressure and the use of antihypertensive medications	Diabetes mellitus
Current cigarette smoking	Chronic kidney disease
Diabetes mellitus	Abdominal aortic aneurysm
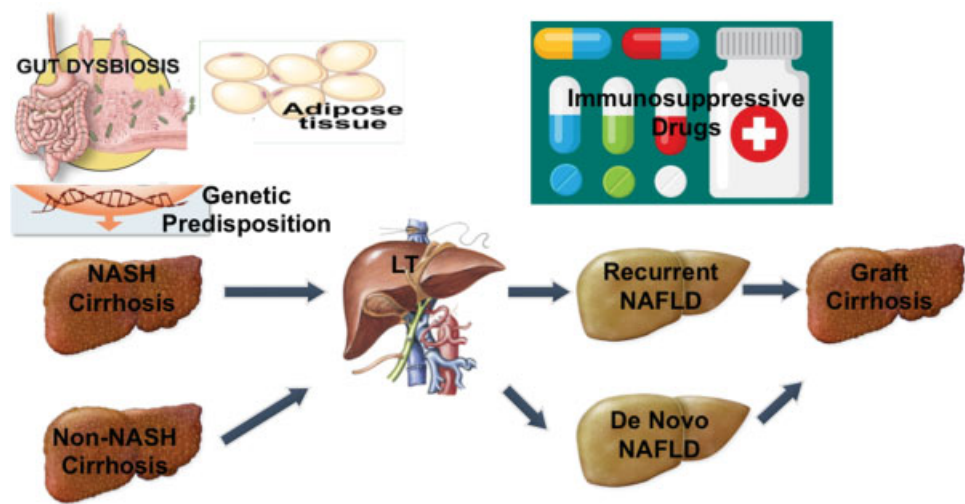
Fig. 1 NAFLD and liver transplantation (LT). NAFLD develops in genetically predisposed individuals due to multiple factors including obesity, insulin resistance, and gut dysbiosis. The disease may progress to cirrhosis requiring LT. NAFLD may recur after LT or may develop de novo in patients who were transplanted for other indications. Immunosuppressive drugs may contribute to the development of post-LT NAFLD. The natural history of post-LT NAFLD is not fully understood but the disease may eventually lead to graft cirrhosis. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

NAFLD (recurrent post-LT NAFLD) or as a de novo complication in patients undergoing LT for indications other than NAFLD (de novo post-LT NAFLD) (►**Fig. 1**).[98]

Recurrent Post-LT NAFLD

A rising number of cases of recurrent NAFLD and NASH after LT have been reported.[36] In a study of more than 200 transplant patients, Yalamanchili et al found that at 10 years, 33% developed NAFLD. At 20 years, approximately 6% of patients developed NASH.[99] Recurrence of NASH seems to demonstrate a distinctly different clinical evolution when compared with de novo NAFLD, exhibiting greater severity, more irreversibility, and an earlier onset.[98] At 1-year post-LT, individuals transplanted for NASH cirrhosis have the highest risk of developing steatosis when compared with other etiologies including alcoholic cirrhosis, HCV, and cholestatic diseases (5%).[95,100] In a retrospective review of 588 adult LT recipients, Narayanan et al demonstrated that allograft steatosis at 10 years occurred in 77.6% of NASH recipients compared with 44.7% of non-

Table 2 Risk factors for recurrent NAFLD/NASH after liver transplantation

Modifiable	Nonmodifiable
Diabetes	Age
Hypertension	Genetics (e.g., genetic polymorphisms PNPLA3)
Hyperlipidemia	Sex
Increased BMI or weight gain	Preexisting cardiovascular disease
Renal dysfunction	

Abbreviations: BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PNPLA3, patatin-like phospholipase domain-containing protein 3.

NASH recipients, supporting the distinct difference between recurrent and de novo NAFLD post-LT.[101]

Factors that predict the presence of NAFLD in the pretransplant setting include older age, increased BMI and weight gain, and the presence of diabetes mellitus.[102] Risk factors for the development of recurrent post-LT NAFLD can be categorized into modifiable versus nonmodifiable risk factors (►**Table 2**).[103] Modifiable risk factors include diabetes, hypertension, hyperlipidemia, and renal dysfunction, whereas nonmodifiable risk factors include age, genetics, sex, and preexisting CVD.

Recent studies have shown that genetics play an important role in NAFLD, with special attention to patatin-like phospholipase domain-containing protein 3 (PNPLA3) polymorphism and interleukin 28B.[104–106] In a recent study assessing the frequency of steatosis recurrence in the transplanted graft over a 5-year period, Finkenstedt et al demonstrated that the presence of PNPLA3 was associated with a greater prevalence of graft steatosis and increased risk of hepatic triglyceride accumulation.[106]

De Novo Post-LT NAFLD

Up to 56% of non-NASH transplant recipients develop post-transplant hepatic steatosis.[107] In an early retrospective analysis by Seo et al, development of de novo NAFLD and de novo NASH occurred in 18 and 9% of post-LT patients, respectively.[108] Dumortier et al., reported a higher prevalence of post-LT NAFLD of 31%, however the prevalence of steatohepatitis and severe fibrosis was low (5.3% and 2.3%, respectively).[109] In a later study, Vallin et al reported the prevalence of steatohepatitis and severe fibrosis 5 years post-LT as 12.5 and 17.2%, respectively.[98]

Weight gain and obesity are significantly associated with de novo post-LT NAFLD.[108,109] In later studies, additional risk factors were identified, which can be broadly characterized into recipient pre- and posttransplant risk factors.

Table 3 Risk factors for de novo NAFLD/NASH after liver transplantation

Pretransplant risk factors	Posttransplant risk factors
Liver graft steatosis	Obesity
Alcoholic cirrhosis as an indication for LT	Tacrolimus-based regimen
	Diabetes mellitus
	Hyperlipidemia
	Hypertension

Abbreviations: LT, liver transplantation; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Posttransplant risk factors mirror the ones in recurrent post-LT NAFLD: higher BMI, weight gain from time of transplant, the presence of diabetes, and higher HbA1c. Galvin et al conducted a retrospective single-center analysis in LT recipients, separately identifying pretransplant recipient risk factors to include older age, male sex, and HCV as indications for transplantation.[110] Donor risk factors include older donor age and higher donor BMI (►Table 3). On multivariate analysis, BMI and tacrolimus were risk factors for the development of de novo post-LT NALFD.[110]

The use of donor livers with severe hepatic steatosis (>60%) is associated with primary graft nonfunction. The use of donor livers with moderate-to-severe hepatic steatosis (>30%) is associated with diminished outcomes including a significant decrease in 4-month graft survival (76 vs. 89%; $p < 0.05$) and in 2-year patient survival (77 vs. 91%; $p < 0.05$).[111] Risk factors for donor liver steatosis include older age and the presence of MetS. Steatosis in donor livers may ultimately further exacerbate the donor shortage for LT.[112]

Immunosuppression and Post-LT NAFLD

Following transplant, the routine use of immunosuppressant drugs is known to enhance metabolic risk. Corticosteroids, calcineurin inhibitors, and mTOR (mammalian target of rapamycin) inhibitors all, to varying degrees, are involved in the development of insulin resistance (IR), diabetes, hypertension, obesity, and hyperlipidemia (►Table 4).[113]

Intuitively, the development of MetS could lead to NAFLD in the posttransplant setting.

Steroids are associated with hypertension, hyperglycemia, dyslipidemia, and obesity; thus, steroid-free regimens are favored. Increased levels of cholesterol and triglycerides

are more frequently associated with cyclosporine. Posttransplant diabetes is more common with tacrolimus, probably due to more marked effects on the pancreatic β-cells. Sirolimus, a nonnephrotoxic drug, can also contribute independently to dyslipidemia.[113] Thus, the general management rationale is to provide minimal immunosuppression to limit the possible side effects on the development of MetS, without risking graft rejection.

Management of Recurrent/De Novo Post-LT NAFLD

Currently, there are no established guidelines for the monitoring or treatment of NAFLD/NASH development or recurrence posttransplant. The prevention of recurrent NAFLD and NASH relies on the identification and management of risk factors such as obesity, diabetes, dyslipidemia, and hypertension. Aggressive risk factor modification in patients undergoing transplantation for NASH and in the pre- and posttransplant setting is crucial. Lifestyle modification, including prevention of weight gain and promotion of weight loss in those who are overweight or obese, is the first-line therapy for post-LT recurrent/de novo NAFLD.[103]

Assessment of posttransplant metabolic comorbidities and MetS should be routinely performed in transplant recipients as progression of graft fibrosis is significantly accelerated in immunosuppressed patients.[114] General recommendations should include maintaining a healthy lifestyle and aggressive management of weight, diabetes, hypertension, dyslipidemia, and CVD (►Table 5).

No specific guidelines exist for follow-up for transplant recipients; thus, interval follow-up can be based on guidelines for the general population. However, clinicians must be cognizant of the increased risk of posttransplant metabolic complications so that early detection can ultimately lead to decreased incidences of recurrent and de novo NAFLD post-LT.

Evaluation of fibrosis and progression over time is important to ensure early identification of complications. The "gold standard" test, liver biopsy, has many limitations including cost, patient unwillingness, and risk of complications. This has led to the development of numerous noninvasive tools to detect and stage fibrosis. Serum markers (e.g., fibrosis-4 [FIB-4] and aspartate aminotransferase-to-platelet ratio index [APRI]) as well as imaging studies (e.g., TE and magnetic resonance elastography) have been validated as clinical tools in pretransplant NAFLD.[115–119] TE is a noninvasive method that is useful in detecting the degree of liver stiffness in patients with chronic liver disease.[120] The

Table 4 Summary of immunosuppression and potential side effects

	CS	Mycophenolate	Tacrolimus	Cyclosporine	Sirolimus	Everolimus
Diabetes	a	b	c	d	d	d
Hypertension	a	b	c	a	d	d
Dyslipidemia	c	b	d	c	a	a
Renal dysfunction	b	b	a	a	d	d

Abbreviation: CS, corticosteroids.
[a]High risk, [b]No known association. [c]Moderate risk. [d]Least risk.

Table 5 Recommendation and treatment aims in the posttransplant patient

Maintain a healthy lifestyle
Smoking cessation
Routine physical activity
Weight control
Good control of blood pressure
Tight control of glucose levels and diabetes
Tight control of LDL cholesterol

Abbreviation: LDL, low-density lipoprotein.

accuracy of TE in diagnosing NAFLD and staging fibrosis in nontransplant patients has been extensively studied and validated.[121]

There have been few published studies of these noninvasive tools in posttransplant recipients, and even fewer with posttransplant NAFLD patients. Many studies evaluating fibrosis in the post-LT setting have focused on HCV-related disease and thus different proposed cutoff values when compared with NAFLD. Liver graft steatosis detection has been demonstrated with TE and controlled attenuation parameter (CAP), although the results were not validated against the "gold standard" of liver biopsy, and only 2% of the patients underwent transplant for the indication of NASH.[122] In a meta-analysis by Bhat et al, the authors found that the APRI and FIB-4 can be used as estimates of significant fibrosis where TE is not available; however, TE is best to diagnose recurrent fibrosis in LT patients.[123] However, the meta-analysis included studies where the etiology for transplant was primarily HCV. In a recent study, Galvin et al evaluated the diagnostic utility of noninvasive fibrosis scores such as FIB-4 and found limited utility of these scores in posttransplant NAFLD fibrosis evaluation.[110]

Unfortunately, there are no studies to date that compare the accuracy of TE for the diagnosis of NAFLD and fibrosis assessment with that for liver biopsy. Additionally, it is important to underscore the limitations of TE and how it impacts clinical practice, including liver position in instances of hemidiaphragmatic elevation or geometric mismatch of graft and abdominal cavity, and the lack of established cutoff values for the prediction of fibrosis or cirrhosis in the post-LT setting.[124]

Although there are no FDA-approved medications for NAFLD/ NASH, several agents are being developed with some advancing to phase 3 trials. Obeticholic acid (OCA), which is an agonist for the farnesoid X receptor (FXR), a nuclear receptor that senses bile acids and regulates their synthesis, is the most advanced drug in development. OCA showed consistent efficacy on fibrosis regression in phase 2 and 3 trials[125,126] in patients with NASH and significant fibrosis, paving the way for potential FDA approval by 2020. In the phase 3 REGENERATE trial (NCT02548351), patients who received OCA 25 mg daily had significant improvement in fibrosis by 1 stage at 18 months compared with those in the placebo arm (23.1 vs. 11.9%; $p = 0.0002$). Other drugs

with different mechanisms of action have advanced to phase 3 as well, including elafibranor, cenicriviroc, resmetirom, aramchol, and saroglitazar. Although none of these drugs are being currently tested in the post-LT settings, these trials are likely to be conducted once the drugs are approved by the FDA in the general NASH population.

Summary

The prevalence of NAFLD has risen in parallel with the increasing prevalence of major risk factors including obesity, hypertension, T2DM, and hypertension. Unfortunately, with no FDA-approved medical treatments, NASH is rapidly becoming the leading indication for LT. Patients with NASH generally have medical comorbidities that require special consideration in the pretransplant setting. Medical optimization of risk factors such as obesity, CKD, and MetS will ultimately allow for improved LT outcomes. The presence of certain pretransplant risk factors such as obesity and diabetes increase the risk of posttransplant complications including recurrent NAFLD. De novo NAFLD is increasingly becoming an issue as donor organs are affected by the epidemic of obesity, diabetes, and NAFLD. Management of NAFLD posttransplant is similar to the management pretransplant. Early detection and intervention can prevent significant progression of disease.

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