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ABOUT COVER

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MINIREVIEWS

Growing challenge of post-liver transplantation non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is one of the leading causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma worldwide, with an estimated prevalence of 25%. Post-liver transplantation (LT) recurrent or *de novo* hepatic steatosis is a common complication in recipients, irrespective of transplantation indication. Risk factors for graft steatosis mainly include obesity, immunosuppression, donor steatosis, and genetic factors. Liver transplant recipients are at high risk of developing insulin resistance, new-onset diabetes, and post-transplantation metabolic syndrome that is highly associated with immunosuppressive treatment. Post-LT NAFLD is often underdiagnosed due to the poor sensitivity of most routine imaging methods. The gold standard for the diagnosis of hepatic steatosis is liver biopsy, which is, however, limited to more complex cases due to its invasive nature. There is no approved pharmacotherapy in NAFLD. Lifestyle modification remains the cornerstone in NAFLD treatment. Other treatment strategies in post-LT NAFLD include lifestyle modifications, pharmacotherapy, bariatric surgery, and tailored immunosuppression. However, these approaches originate from recommendations in the general population, as there is scarce data regarding the safety and efficacy of current management strategies for NAFLD in liver transplant patients. Future prospective studies are required to achieve tailored treatment for these patients.

Key Words: Non-alcoholic fatty liver disease; Steatohepatitis; Hepatic steatosis; Liver transplantation; Cirrhosis; Metabolic syndrome

Core Tip: Non-alcoholic fatty liver disease (NAFLD) is a common complication in liver transplant recipients. Despite the rising prevalence and potentially progressive nature of this entity, there are currently no recommendations regarding NAFLD diagnosis and management in the post-transplant setting. Future studies are urgently needed to fill this knowledge gap and define optimal diagnostic and treatment approaches in this patient population.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is characterized by the presence of steatosis in at least 5% of hepatocytes in the absence of any secondary causes, such as excessive alcohol consumption or other chronic liver diseases[1]. NAFLD encompasses a wide spectrum of histological findings, ranging from simple steatosis (non-alcoholic fatty liver, NAFL) to non-alcoholic steatohepatitis (NASH), the latter of which is additionally characterized by lobular inflammation and hepatocyte ballooning[2]. NAFL is generally considered a slowly progressive or non-progressive condition, while NASH is associated with an increased risk of disease progression to cirrhosis and hepatocellular carcinoma[3].

EPIDEMIOLOGY

NAFLD has become the leading cause of chronic liver disease worldwide, with an estimated prevalence of 25%, which is constantly rising in parallel to the worldwide obesity pandemic[4]. NAFLD is often considered the hepatic component of the metabolic syndrome and is associated with other metabolic disorders, such as obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and insulin resistance (IR)[5]. Due to the increasing prevalence and high risk of progression, NASH has become the second most common indication for liver transplantation (LT) in the United States, reporting a 170% increase from 2004 to 2013[6,7]. LT leads to the resolution of NASH-related complications; however, the underlying metabolic risk factors remain, and are even exacerbated following LT, resulting in a high rate of post-LT NAFLD recurrence[8]. In addition, many recipients are prone to develop a post-LT metabolic syndrome (PTMS), mainly due to the reversal of the cirrhosis-related catabolic state and immunosuppression side effects, leading to *de novo* NAFLD[9].

Recurrent NAFLD

Recurrence of steatosis and steatohepatitis in recipients with a pre-transplant diagnosis of NASH is more common compared to *de novo* NAFLD, with a prevalence ranging between 8% and 100% in a follow-up period of 1-10 years[10]. Yalamanchili *et al*[11] studied 257 patients transplanted for NASH or cryptogenic cirrhosis. Post-LT steatosis was reported in 31% of patients; however, bridging fibrosis or cirrhosis was only found in 5% and 10% of recipients after 5 years and 10 years, respectively[11]. In a recent retrospective study of 275 NASH recipients, the prevalence of NAFLD and NASH recurrence was 22% and 11%, respectively[12]. However, it should be underlined that most studies have important heterogeneity regarding NAFLD diagnosis and patient selection. Recipients with cryptogenic cirrhosis as an indication for LT were included in most of these studies, resulting in a possible NAFLD recurrence overdiagnosis[11,13,14].

De novo NAFLD

De novo NAFLD is defined as the presence of steatosis or steatohepatitis in patients who underwent LT for indications other than NASH[15]. Up to one-third of liver transplant recipients develop *de novo* NAFLD depending on a combination of host and graft factors[16,17]. Dumortier *et al*[16] studied 599 non-NASH liver transplant recipients and reported a prevalence of *de novo* NAFLD of 31%[16]. The authors demonstrated several independent risk factors for the occurrence of post-LT *de novo* steatosis, such as post-LT obesity, tacrolimus-based immunosuppression therapy, diabetes mellitus, and pre-transplant liver graft steatosis, demonstrating a dose-dependent relationship between the number of these risk factors and the risk of developing *de novo* NAFLD. In a recent meta-analysis by Losurdo *et al*[15] the pooled prevalence of *de novo* NAFLD and NASH was 26% and 2%, respectively, at a follow-up period of 6 mo to 10 years[15]. The highest prevalences were observed in patients transplanted for either alcoholic (37%) or cryptogenic cirrhosis (35%), or those receiving tacrolimus (26%). Data remain,

however, scarce regarding these entities, while the retrospective design and small sample size of most studies represent important limitations.

RISK FACTORS

Several risk factors have been associated with post-LT NAFLD occurrence (Table 1). As mentioned above, the pre-transplant metabolic risk factors persist following LT, despite the resolution of liver disease. In addition, the commonly used maintenance immunosuppressive regimens, namely corticosteroids, calcineurin inhibitors (CNIs), and mammalian targets of rapamycin (mTOR) inhibitors are directly linked to obesity, hypertension, dyslipidemia, and hyperglycemia, exacerbating the existing metabolic profile of transplanted patients or leading to a new-onset PTMS. Recipients are at high risk of developing PTMS, irrespective of LT indication, with an estimated prevalence ranging from 44%-58% at 6 mo following LT[17]. The presence of PTMS has been associated with both recurrent and *de novo* NAFLD[16,18,19]. Pre-transplant graft-steatosis, genetics, and other recipient-related risk factors appear to contribute to the development of both recurrent and *de novo* NAFLD in the transplanted population [20]. In a recent observational study of 108 recipients, it was concluded that recipient-related factors are more important than donor-related factors in the development of NAFLD, following LT[21].

Genetic factors

Several studies have attempted to reveal the role of genetic predisposition in the development of post-LT NAFLD. Both recipient and donor genetics have been associated with an increased risk of graft steatosis. The role of patatin-like phospholipase domain-containing protein 3 (PNPLA3) in the development of NAFLD is well established. Finkenstedt *et al*[22] showed that LT recipients who carry rs738409-GG in PNPLA3 are at increased risk of post-LT NAFLD[22]. In another study of 176 liver transplant patients, Trunečka *et al*[23] demonstrated that the expression of PNPLA3 p.148M variant in donors represents an independent risk factor for graft steatosis[23]. The donor transmembrane 6 superfamily member 2 c.499A allele was also associated with a higher risk of steatosis in recipients[24]. John *et al*[25] found that recipient, but not donor, adiponectin polymorphisms rs1501299 G/G and rs17300539 G/G were related to a higher prevalence of post-LT graft steatosis[25].

Immunosuppression

The maintenance immunosuppressive agents used after LT can exacerbate a preexisting metabolic syndrome in recipients, or lead to a new-onset PTMS, thereby contributing to the development of recurrent and *de novo* NAFLD[26]. Corticosteroids are widely used in the immediate post-operative period against allograft rejection. They increase the hepatic output of glucose and decrease insulin production and peripheral glucose uptake, inducing IR. Corticosteroid use has been associated with an increased risk of T2DM, dyslipidemia, hypertension, and rapid weight gain in recipients following LT [27]. CNI therapy (cyclosporine and tacrolimus) is also recognized as a risk factor for metabolic syndrome and consequent post-LT NAFLD. They are linked to hypertension, dyslipidemia, new-onset T2DM, and chronic renal disease, with tacrolimus having a more prominent diabetogenic effect compared to cyclosporine, which is mainly associated with post-transplant hypertension[26,28,29]. However, studies investigating the direct association between CNI therapy and post-LT NAFLD seem to provide conflicting results[16,30,31]. Another commonly used class of immunosuppressive drugs, mTOR inhibitors, appear to have metabolic adverse effects, being associated with significant dyslipidemia and IR[26]. Sirolimus increases adipose tissue lipase activity and decreases lipoprotein lipase activity, resulting in hypertriglyceridemia, especially with concomitant cyclosporine therapy[32,33]. In a retrospective study of 430 post-LT biopsies, Galvin *et al*[31] reported that sirolimus use was predictive of *de novo* NAFLD following LT[31].

Donor graft steatosis

Donor steatosis has also been suggested as a potential risk factor for post-LT *de novo* and recurrent NAFLD. While microvesicular steatosis does not affect graft function or survival, donor livers with severe macrovesicular steatosis have been associated with an increased risk of primary graft dysfunction, inferior graft survival, and requirement for retransplantation[34]. However, there is not enough evidence to support the predictive role of donor steatosis in the development of post-LT NAFLD. Three studies have indicated an association between pre-existing donor graft steatosis and post-LT NAFLD, whereas findings in a meta-analysis by Saeed *et al*[35] did not support this association [16,35-37].

Pre-transplant liver disease

Aside from NASH, specific other LT indications have been associated with an increased risk of *de novo* NAFLD. Recipients with a pre-transplant diagnosis of alcoholic liver disease (ALD) are at higher risk of developing *de novo* post-LT steatosis[16,30]. Hepatitis C virus infection was also reported as a risk factor for post-LT NAFLD[31,38]. In a meta-analysis by Losurdo *et al*[15], the authors reported the highest

Table 1 Risk factors associated with post-transplantation non-alcoholic fatty liver disease

Recipient factors	Donor factors
Obesity/post-LT weight gain	Macrovesicular graft steatosis
T2DM	Genetics
Dyslipidemia	
Genetics	
Immunosuppression	
LT indication: NASH, HCV, ALD	

ALD: Alcoholic liver disease; HCV: Hepatitis C virus; LT: Liver transplantation; NASH: Non-alcoholic steatohepatitis; T2DM: Type 2 diabetes mellitus.

prevalence of *de novo* NAFLD in patients that underwent an LT for ALD and cryptogenic cirrhosis (37% and 35%, respectively)[15].

PROGNOSIS

Despite the high prevalence of recurrent and *de novo* NAFLD following LT, progression to NASH and advanced fibrosis is less frequent in these patients. Dumortier *et al*[16] reported recurrent steatosis in 31% of recipients; however, NASH and advanced fibrosis/cirrhosis were only observed in 3.8% and 2.25% of patients[16]. Yalamanchili *et al*[11] confirmed these findings, reporting similarly low incidence rates of NASH and cirrhosis in patients with post-LT NAFLD (4% and 10%, respectively)[11]. However, in the meta-analysis by Saeed *et al*[35], the authors reported significantly higher rates of recurrent and *de novo* NASH (38% and 17%, respectively)[35]. Overall survival of patients transplanted for NASH-related cirrhosis is comparable to those with non-NASH indications in most studies[39-41]. In a recent retrospective analysis of 68950 patients that underwent LT for end-stage liver disease of various indications, Haldar *et al*[42] confirmed the aforementioned findings and demonstrated a patient survival at 1, 5, and 10 years post-LT of 84.1%, 73.4%, and 62.1%, respectively, for NASH patients that underwent LT[42]. Overall graft survival was also reported similar between NASH recipients *vs* those with non-NASH LT indications. Mortality in patients transplanted for NASH was mainly attributed to cardio/cerebrovascular disease and infection rather than liver-related complications. However, the true impact of recurrent or *de novo* NAFLD on overall and graft survival has not been largely investigated. Dureja *et al*[43] studied 88 liver transplant recipients and found no difference in post-LT survival between patients with NAFLD recurrence and those without in a follow-up period of 5 years[43]. More relevant studies with longer follow-up time are necessary to clarify whether post-LT NAFLD *per se* is associated with increased mortality in the post-transplant setting.

MANAGEMENT

There are scarce data regarding the treatment of NAFLD in liver transplant patients. Main treatment strategies include lifestyle modifications, pharmacotherapy, bariatric surgery, and alteration in immunosuppression therapy[44]. The first approach in the management of post-LT NAFLD is lifestyle modification including adequate physical activity, weight loss, and calorie restriction. No drugs have been approved for the treatment of NAFLD and none of the proposed pharmacotherapies has been studied in the post-transplant population. In the latest American Association for the Study of Liver Diseases and European Association for the Study of the Liver guidelines, pioglitazone, and vitamin E, either as monotherapy or as combination therapy, have been proposed as a potential treatment approach in biopsy-proven NASH patients[45]. However, there are concerns about the safety of long-term use of vitamin E, as it has been associated with an increased risk of prostate cancer and hemorrhagic stroke[46,47]. Pioglitazone has been associated with weight gain and should be, therefore, cautiously recommended in transplanted patients, for fear of exacerbating post-LT obesity and PTMS [48]. Bariatric surgery is recommended in cases where obese patients cannot achieve weight reduction following LT; however, there are concerns regarding the potential malabsorption and altered pharmacokinetics of immunosuppressive drugs[49,50]. Optimization of immunosuppression is of vital importance to reduce drug-induced metabolic risks and subsequent NAFLD in the post-LT period. Early steroid withdrawal, minimization, and alterations of immunosuppressive regimens based on patient's metabolic complications are common approaches in the management of PTMS. More specifically, in cases where hypertension is the major metabolic complication, conversion from

cyclosporine to tacrolimus has been shown to have a beneficial effect on blood pressure[51]. Similarly, reducing tacrolimus dosage or switching to another immunosuppression regimen has been associated with better glycemic control in recipients with new-onset T2DM[52]. mTOR inhibitors, on the other hand, should be avoided in cases of severe uncontrolled dyslipidemia[32,33].

CONCLUSION

Post-LT NAFLD remains a great challenge for hepatologists and transplant surgeons. Early detection of modifiable risk factors plays a crucial role in preventing disease occurrence. There is an unmet need for specific recommendations regarding both NAFLD screening and management in the post-transplant setting. Post-LT diagnosis tends to be underdiagnosed due to poor sensitivity of routine imaging modalities, whereas liver biopsy is not routinely used for NAFLD diagnosis, due to its invasive nature and possible complications. Regarding disease management, while numerous studies have investigated potential treatment approaches for NAFLD in non-transplant patients, there are scarce data on liver-transplant recipients, with most treatment strategies being extrapolated from recommendations in the general population. However, certain limitations in transplanted patients, such as reduced physical activity, immunosuppressive therapy, and drug-drug interactions with NAFLD treatment regimens, as well as treatment dilemmas regarding minimization or alteration of immunosuppression therapy in the setting of PTMS remain major problems for hepatologists. Prospective, longitudinal studies in liver transplant recipients are necessary to optimize screening, disease monitoring, and treatment in this special patient population.

FOOTNOTES

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