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Review

Non-Alcoholic Fatty Liver Disease in Living Liver Transplantation: Defatting Strategies

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Abstract

Liver transplantation (LT) is the only treatment option saving lives of the patients who have end-stage liver failure. The disparity between the number of patients waiting for transplantation and that of available cadaveric donors is increasingly being bridged through living donors. However, considering the post-transplantation process, graft selection remains a critical determinant of post-transplant outcomes. Despite the high demand and mortality on waiting lists, numerous donors are rejected due to non-alcoholic fatty liver disease (NAFLD). Consequently, defatting strategies are vital and promising for addressing organ shortage. NAFLD might recur following the transplantation or develop de novo in patients who underwent transplantation operation for other liver diseases. The development of de novo or recurrent NAFLD is closely related with metabolic risk factors and use of immunosuppressive medications by recipients. However, no pharmacological treatment specifically approved for NAFLD exists. Therefore, a multidisciplinary approach is necessary both before and after LT. This review aims to evaluate strategies for preventing NAFLD and implementing defatting techniques in living liver transplant donors and recipients.

Keywords: Living liver transplantation, NAFLD, defatting strategy

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Non-alcoholic fatty liver disease (NAFLD) encompasses a wide clinical spectrum, ranging from steatohepatitis, characterized by fat accumulation in over 5% of hepatocytes, independent of excessive alcohol consumption (≥30 g/day for males, ≥20 g/day for females), to liver cirrhosis and hepatocellular carcinoma (HCC).[1,2] NAFLD, the "hepatic epidemic of the 21st century," affects approximately 25% of the global population.[3] Liver cirrhosis and/or HCC secondary to NAFLD is the second most common etiology among liver transplant candidates on the waiting list.[4]

LT is the only treatment option saving the lives of patients who have end-stage liver failure. Successful outcomes after transplantation depend heavily on graft selection. Steatotic grafts are more vulnerable to cold ischemic injury, which results in an increase in the risks of graft dysfunction, loss, and retransplantation.[5] Fat infiltration is considered treatable for living donors. Defatting strategies, aiming to reduce lipid content in steatotic grafts, have the potential to alleviate organ shortages by significantly expanding the donor pool.[6]

NAFLD can recur after LT or develop de novo in recipients who underwent transplantation due to other liver diseases.[7] Post-transplant steatosis is significantly related with metabolic syndrome, diabetes mellitus (DM), hypertension, and dyslipidemia.[7,8] Immunosuppressive drugs exacerbate

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these metabolic risk factors, further contributing to the development of post-transplant steatosis.[9] This review focuses on strategies for preventing NAFLD and exploring defatting interventions in living donor liver transplantation (LDLT).

1. NAFLD

1.1. Histopathology of NAFLD

Steatosis, which is characterized by triacylglycerol accumulation within hepatocytes, is commonly seen in many liver biopsies. Lipids are estimated to constitute up to 5% of liver parenchyma. Thus, levels of lipid content higher than 5% of liver mass can be seen as "pathological".[10] Macrovesicular steatosis is defined as lipid droplet accumulation within hepatocytes, causing peripheral displacement of the cell nucleus (Fig. 1).[11]

In contrast, microvesicular steatosis involves centrally located nuclei within hepatocytes exhibiting a characteristic "foamy" appearance (Fig. 2).[10,12] The etiologies of macrovesicular and microvesicular steatosis are presented in Table 1.[13]

Drug-induced hepatic steatosis is a rare condition caused by the direct toxic impacts of a medication on the liver. It is estimated that approximately 2% of steatosis cases are drug-induced. Medications can lead to both microvesicular and macrovesicular steatosis. Drug-induced hepatic steatosis is closely related to the duration and dosage of medication use. The medications associated with macrovesicular and/or microvesicular steatosis are illustrated in Figure 3.[2,14]

1.2. Clinical Course of NAFLD

NAFLD encompasses a wide clinical spectrum, ranging between simple steatosis, steatohepatitis, liver cirrhosis, and HCC.[1,2] Non-alcoholic steatohepatitis (NASH), observed in 20% of NAFLD patients, is characterized by hepatic steatosis (>5%) with inflammation and ballooning degeneration. NASH is related to a higher risk of fibrosis.[22,13] Approximately 15–25% of NASH cases progress to cirrhosis, which is related with the development of HCC and increased mortality. The progression of NAFLD from a healthy liver to HCC is illustrated in Figure 4.[16]

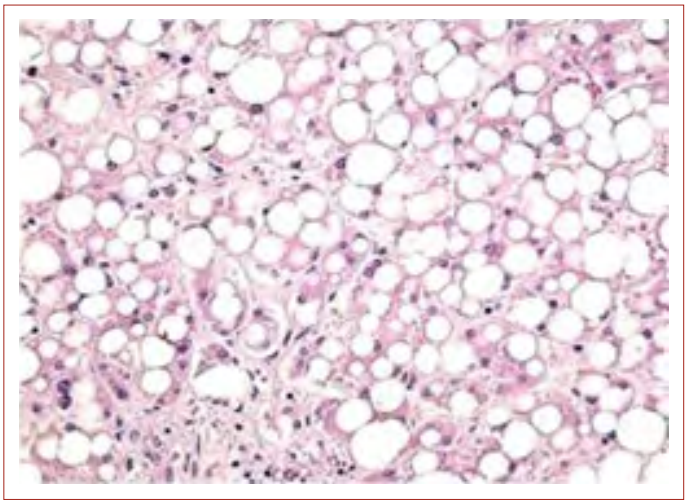

Figure 1. Macrovesicular steatosis.

2. Donor Steatosis in LDLT

2.1. Pre-Donation Steatosis and Defatting Strategies

LT is widely considered a treatment modality for end-stage liver diseases. In countries with limited availability of cadaveric donations, LDLT mitigates organ shortages and reduces mortality rates among transplant candidates.[17] Graft selection is a critical factor for achieving favorable post-transplant outcomes. Donor liver steatosis is considered a risk factor for poor outcomes after transplantation, as it increases the risk of primary non-function (PNF).[14] Macrosteatosis exceeding 30% in donors is an independent risk factor for graft failure.[15,16] The use of liver grafts with mild steatosis (<30% macro- and microsteatosis) is generally accepted to not be related with an elevated risk of PNF.

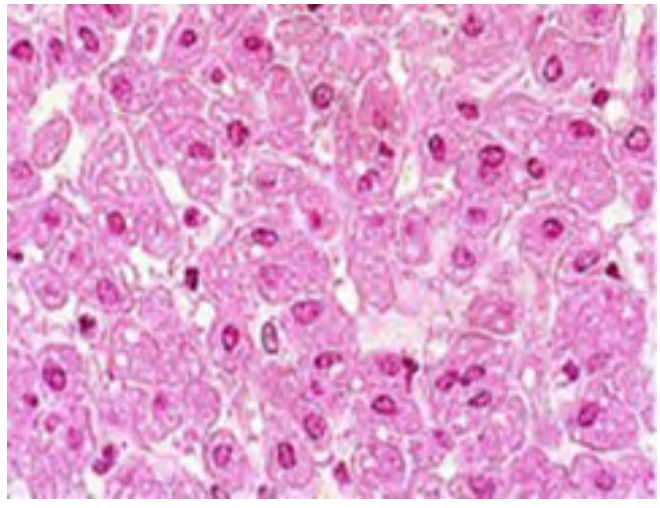

Figure 2. Microvesicular steatosis.

Table 1. Etiology of Macro- and Microvesicular Steatosis

Macrovesicular Steatosis	Microvesicular Steatosis
Obesity	Reye's syndrome
Malnutrition	Viral infections
Metabolic Disorder (Wilson's disease)	Acute Fatty Liver of Pregnancy
Infectious Diseases (e.g., Hepatitis C)	

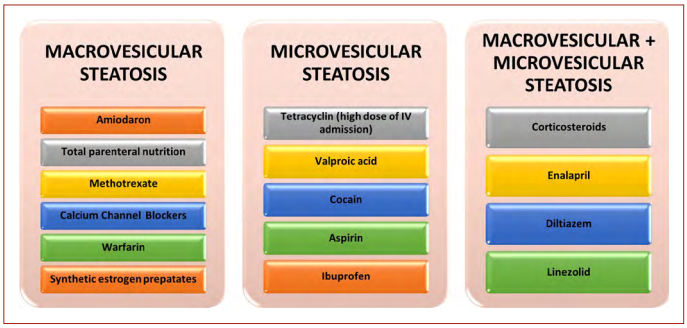

Figure 3. Drugs Causing Macrovesicular and/or Microvesicular Steatosis.

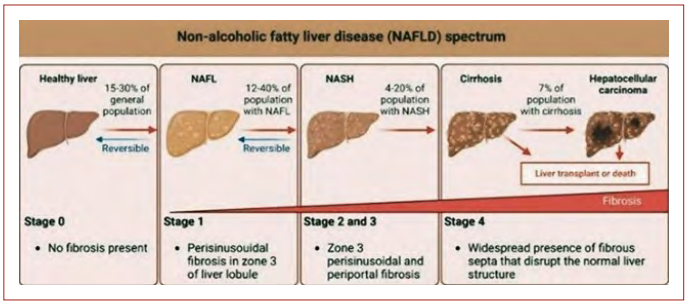

Figure 4. Stages of NAFLD progression from a healthy liver to HCC. *NAFL: Non-alcoholic fatty liver; NASH: Non-alcoholic steatohepatitis.*

Contrary to the livers with mild steatosis, the use of grafts with moderate macrosteatosis (30–60%) is still debated and often regarded as a relative contraindication.[17] Severe macrosteatosis (>60%) is considered an absolute contraindication for LT and is strongly associated with renal and hepatic failure in graft recipients.[18–20] Currently, there are no definitive guidelines on the use of steatotic donor livers, and decisions largely rely on the judgment of the transplant physician or surgeon.[17]

The reduction of lipid content in steatotic grafts, known as defatting, increases access to a larger donor pool and has the potential to alleviate organ shortages. There is growing interest in developing defatting strategies to rapidly reduce graft steatosis before LT and improve results in transplants involving steatotic grafts. Dietary interventions, exercise, and pharmacological treatments are utilized to address steatosis in living donors. Strategies for reducing liver fat in potential donors are summarized in Table 2.[6]

At İnönü University's Liver Transplantation Institute, a defatting protocol is applied to patients exhibiting predonation steatosis. This protocol includes an 8-week protein-rich diet (1000 kcal/day), 4 weeks of fenofibrate (267 mg/day), 8 weeks of exercise (600 kcal/day), 8 weeks of L-Carnitine (300 mg/kg/day), 8 weeks of essential phospholipid therapy (phosphatidylcholine 1500 mg/day), 8 weeks of Vitamin E supplementation (800 IU/day), and 8 weeks of Omega-3 supplementation 1000 mg/day, consisting of 500 mg docosahexaenoic acid (DHA) and 150 mg eicosapentaenoic acid (EPA).

Table 2. Defatting Strategies in Living Liver Donors

First Author	Year	Number of Donors Treated	Number of Transplantations Performed	Applied Strategy	Treatment Duration	Outcome
Nakamuta et al.[21]	2015	11	7	High-protein diet (1000 kcal/day) + exercise (600 kcal/day) + bezafibrate (400 mg/day)	2-8 weeks	Significant improvement in macrovesicular steatosis and a remarkable decrease in body weight and BMI
Clavien et al.[22]	2010	42	3	Omega-3 fatty acids (1 g/day)	12 months	Improvements in biochemical, ultrasonographic, and hemodynamic features of liver steatosis with n-3 PUFA supplementation
Fujii et al.[23]	2015-2019	8	8	Daily caloric intake < 1600 kcal/day + exercise (20 minutes, three times per week) + statin therapy for patients with hyperlipidemia +/- essential phospholipid therapy (1500 mg/day) for patients unresponsive to treatment	5-16 weeks	No major complications observed post-donor hepatectomy; 100% graft and patient survival at three months
Doyle et al.[24]	2016	16	14	OptiFast administered to 16 donors (53 donors received no intervention); patients were provided with OptiFast 900 meal-replacement shakes containing 225 kcal, 22.5 g protein, 7.5 g fat, and 16.8 g carbohydrates per portion. Four shakes were consumed daily.	4 weeks	Reduction in the prevalence of <10% macrosteatosis among OptiFast-treated patients; greater BMI reduction in the OptiFast group compared to untreated individuals

2.2. Post-Hepatectomy Steatosis and Defatting Strategies

It is widely recognized that the regenerating liver temporarily accumulates lipids. Numerous experimental reports demonstrated that acute hepatic steatosis is necessary for normal liver regeneration.[29]

Glucocorticoid levels increase because of preoperative and postoperative fasting and surgical stress after liver resection, leading to a reduced rate of glucose utilization. Therefore, the primary energy source for liver regeneration - an energy-intensive process - is derived from fatty acids released into the bloodstream through lipolysis. Increased fatty acid uptake by hepatocytes results in transient steatosis, a critical event during liver regeneration.[25,26] Hepatic lipid accumulation during liver regeneration peaks within 12–24 hours after liver hepatectomy, and triglyceride content increases three- to fourfold when compared to preoperative levels. Lipid levels gradually return to baseline by 72 hours postoperatively.[27,28]

While large lipid reserves can provide massive energy for liver regeneration, excessive lipid accumulation and lipid peroxidation may induce hepatocyte apoptosis, trigger aseptic inflammation, and impair liver function.[34]

In a study carried out in 2023, Xi et al. examined the role of L-carnitine in liver regeneration, highlighting its ability to support lipid metabolism. The authors reported that L-carnitine promotes cellular regeneration in the liver by enhancing lipid metabolism and reducing aseptic inflammation due to excessive lipid accumulation.[29]

Oral administration of omega-3 fatty acids is related with improvements in steatosis and liver regeneration in rats subjected to a methionine-choline-deficient diet, as well as enhanced functional recovery following partial hepatectomy.[30]

For healthy individuals, the recommended dose of L-carnitine is 15 g/day for healthy individuals and ranges between 100 and 400 mg/kg/day for patients with carnitine deficiency.[31,32] Studies indicated that high doses of L-carnitine supplementation may cause certain side effects, including gastrointestinal issues, diarrhea, and the production of trimethylamine, which leads to a fishy odor.[33] In a meta-analysis investigating the efficacy and safety of carnitine supplementation in patients with NAFLD, it was found that high therapeutic doses (>1000 mg/day) and prolonged treatment durations (>24 weeks) could provide benefits without causing significant adverse effects.[34]

The three most clinically significant omega-3 polyunsaturated fatty acids (PUFAs) are α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Deciding which omega-3 PUFA to use in the treatment of NAFLD is an important point. Preclinical and clinical studies revealed that EPA and DHA do not have equivalent effects on NAFLD, with DHA being superior to EPA in controlling steatosis, inflammation, and fibrosis.[35] When examining four meta-analyses of randomized controlled trials on omega-3 PUFA treatment in NAFLD patients, the administered omega-3 PUFA doses varied between 0.83 and 6.4 g/day among 561 patients, with treatment durations spanning 2 to 18 months.[36–39]

3. Steatosis and Its Management in Recipients After LDLT

There are two forms of liver steatosis with distinct histological features and prognoses after LT. The recurrent or de novo steatosis forms observed post-transplantation are becoming an increasing concern among LT recipients. De novo steatosis refers to the development of steatosis after LT in patients with no prior diagnosis of steatosis. Recurrent steatosis, on the other hand, occurs when steatosis reappears post-transplantation in patients who had been diagnosed with steatosis before LT.[40] In a study carried out in 2014 by Melanie et al. comparing the clinical, biological, and histological characteristics of recurrent and de novo steatosis post-transplantation, recurrent steatosis was found to have an earlier onset, greater severity, and to be an irreversible condition.[41]

It is very important to understand and evaluate the risk factors for post-LT steatosis. Risk factors for de novo and recurrent steatosis are summarized in Table 3.[40,42]

3.1 Management of NAFLD Following LT

At this moment, there is no pharmacological therapy approved by any health authority for NAFLD treatment. NAFLD management after LT is extrapolated from the management of non-LT NAFLD. It largely relies on lifestyle modifications and optimization of metabolic and medical comorbidities.[43] The management strategy for post-LT NAFLD is summarized in Figure 5.[43] Given the data obtained from non-transplanted patients, the medications used in NAFLD/NASH treatment are summarized in Figure 6.[42]

At Inonu University's Liver Transplantation Institute, a defatting protocol is applied for post-transplant patients exhibiting steatosis. This protocol consists of an 8-week high-protein diet (1000 kcal/day), L-Carnitine (300 mg/kg/day), comorbidity management, immunosuppression management, 8 weeks of essential phospholipid therapy (phosphatidylcholine 1500 mg/day), 8 weeks of Vitamin E supplementation (800 IU/day), and 8 weeks of Omega-3 supplementation (1000 mg/day, consisting of 500 mg DHA and 150 mg EPA).

Table 3. Risk Factors for De Novo and Recurrent Steatosis

Pre-transplantation Risk Factors	Post-transplantation Risk Factors
Presence of cardiometabolic comorbidities	Weight gain
Pre-transplant obesity	Sarcopenic obesity
PNPLA3 and TM6SF2 gene polymorphisms	Use of immunosuppressive medications (extended steroid therapy, calcineurin inhibitors, sirolimus)
Pre-existing NASH and/or alcoholic liver disease and/or hepatitis C virus infection	Advanced age
	Renal dysfunction
	Sleep apnea
	Donor steatosis
	Metabolic syndrome (diabetes, hypertension, dyslipidemia)

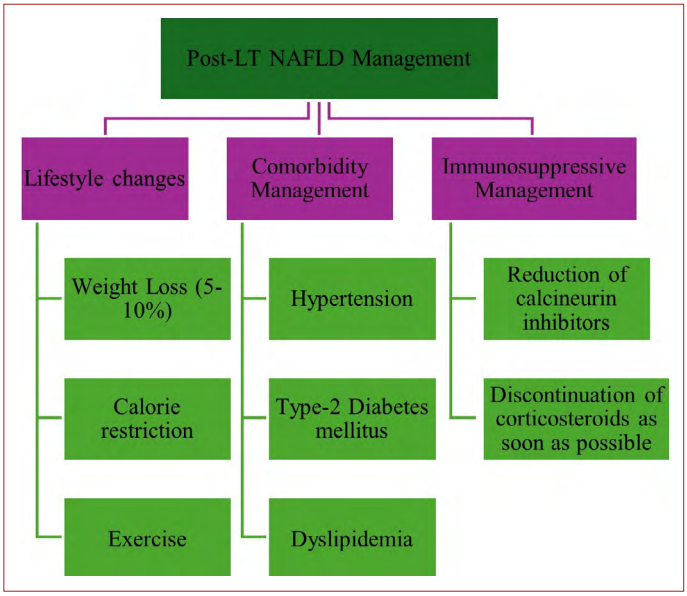

Figure 5. Management of NAFLD After LT.

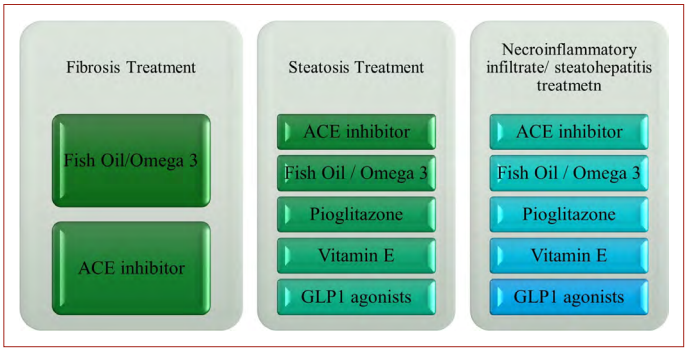

Figure 6. Medications Used in NAFLD/NASH Treatment.

3.1.1 Post-Transplant Immunosuppression Management

Immunosuppressive therapy is very important for improving allograft survival and outcomes but is associated with numerous side effects, including altered metabolic homeostasis.[43] The development of metabolic risk factors related with immunosuppressive regimens can jeopardize long-term graft function and survival.[44] In patients with recurrent or de novo NAFLD/NASH after LT, modifications in the immunosuppressive regimen are necessary to optimize the management of metabolic comorbidities.

Steroid use poses a significant risk for the development of post-transplant diabetes mellitus (PTDM) and other features of metabolic syndrome. Therefore, it should be minimized and/or discontinued approximately three months post-transplant, whenever feasible. Calcineurin inhibitors (CNIs) are closely associated with hypertension, diabetes, and hyperlipidemia. For patients who fail to achieve adequate control of these comorbidities despite medical treatment, dose reduction should be considered. Mammalian target of rapamycin (mTOR) inhibitors are significantly associated with hyperlipidemia. For patients in whom hyperlipidemia remains uncontrolled, transitioning to an alternative immunosuppressive agent is recommended.[43]

3.1.2. Post-Transplant Hypertension Management

Arterial hypertension is seen in 30–50% of transplant recipients and has a prevalence of approximately 70% during long-term follow-up.[45] Hypertension is multifactorial in origin but is closely associated with the use of CNIs and glucocorticoids. For liver transplant recipients, the target blood pressure should be <130/80 mmHg to decrease the risk of cardiovascular disease.[46] Achieving this blood pressure target often requires specific pharmacological therapy. In patients without proteinuria, dihydropyridine calcium channel blockers (DCCBs) are the first-line option. Amlodipine, felodipine, and nicardipine are preferred as first-line agents due to their long half-life, minimal interactions with CNIs, and limited side effects.[47]

Approximately 30% of patients necessitate multiple agents for effective BP control. If CCBs are ineffective or poorly tolerated, adding or substituting a cardioselective beta-blocker, such as metoprolol or atenolol, is recommended. Non-selective beta-blockers are avoided due to their impact on portal blood flow. In patients with difficult-to-control hypertension and/or diabetes, angiotensin-converting

enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are preferred.[47] In their study carried out in 2023, Ahad et al. investigated the impact of ARB use on liver steatosis in transplant recipients, reporting a significant association between ARB use and reduced incidence of hepatic steatosis.[48]

3.1.3. Post-Transplant Diabetes Mellitus Management

The prevalence of PTDM ranges between 31% and 38%, with a new-onset diabetes prevalence of 13% to 28% during the first three years after surgery.[49] PTDM severely impacts the prognosis of transplant recipients, increasing 10-year mortality, infection rates, and cardiovascular events. Considering these adverse effects on post-transplant outcomes, maintaining euglycemia is a primary goal in the management of transplant recipients. Male gender, ethnicity, family history, and hepatitis C are well-established risk factors for the development of PTDM. Once diagnosed, PTDM requires the evaluation of specific therapeutic strategies. Lifestyle modifications, representing the first-line approach, have generally been insufficient for achieving adequate glycemic control.[50]

Among oral antidiabetic agents, administration of metformin, pioglitazone, and sulfonylureas after solid organ transplantation (SOT) was studied and demonstrated to be safe when used alone or in combination with insulin.[51,52] Recently, dipeptidyl peptidase-4 (DPP-4) inhibitors started to be routinely administered to SOT recipients due to their beneficial effects on weight loss. However, the potential impact of DPP-4 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists on the bioavailability of immunosuppressive drugs remains unclear. Specific drug-drug interactions, such as those between sitagliptin and cyclosporine or vildagliptin and tacrolimus, warrant further investigation.[53] While data on sodium-glucose cotransporter-2 (SGLT2) inhibitors in transplant recipients are currently lacking, recent studies suggest that empagliflozin decreases liver steatosis and improves alanine aminotransferase levels in patients with type 2 diabetes and NAFLD.[53] Insulin continues to be the preferred therapy when therapeutic targets are not achieved, or metabolic homeostasis cannot be maintained.[54]

3.1.4. Post-Transplantation Management of Dyslipidemia

The prevalence of dyslipidemia after LT ranges between 45% and 71%. Immunosuppressive therapy, DM, obesity, and the genetic characteristics of the recipient represent the primary risk factors for post-LT dyslipidemia.[50,55] Compared to the pre-transplant period, dyslipidemia developing after LT is often resistant to dietary interventions, necessitating pharmacological treatment. The European Society of Cardiology recently proposed stringent targets for the management of dyslipidemia in solid organ transplant (SOT) recipients, aligned with those recommended for patients at high and very high cardiovascular risk.[56] Statins are considered the first-line therapy in LT recipients, but potential interactions with immunosuppressive medications should be closely monitored.[57] Statins such as fluvastatin, pravastatin, pitavastatin, and rosuvastatin, which are metabolized via different cytochrome P450 enzymes, are associated with fewer pharmacological interactions.[58] In LT recipients who cannot tolerate statins, ezetimibe may be considered as an alternative.[59]

Conclusion

The efficacy of defatting strategies has been demonstrated in only a limited number of studies, underscoring the need for more comprehensive research evaluating defatting agents and protocols. To date, there is no approved pharmacological treatment for NAFLD. Managing NAFLD in LT recipients requires a multidisciplinary and holistic approach, heavily reliant on lifestyle modifications, optimization of metabolic and medical comorbidities, and the individualization of immunosuppressive therapy.

Disclosures

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