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Review

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Liver transplantation and nonalcoholic steatohepatitis: the state of the art

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Abstract

Nonalcoholic fatty liver disease (NAFLD) represents one of the most diffuse liver diseases worldwide. It is a condition ranging from liver steatosis to non-alcoholic steatohepatitis (NASH) and NASH-related cirrhosis. Recently, the term metabolic dysfunction-associated fatty liver disease has been proposed in place of NAFLD, accenting the metabolic and cardiovascular risks that accompany hepatic disease. In the last decades, NASH and NASH-related cirrhosis have been the fastest growing indications for liver transplantation (LT), and they will probably overcome the other indications in next future. After LT, recipients show an important increase in body weight due to a greater caloric intake, partially because of the metabolic influence of immunosuppressant drugs, favoring the development of diabetes mellitus, dyslipidemias, and arterial hypertension. These metabolic complications will, in turn, elevate cardiovascular risk in this population. In this review, we analyze the main metabolic challenges of both pre-and post-LT periods.

Keywords: Non-alcoholic steatohepatitis, liver transplantation, diabetes, metabolic syndrome, cardiovascular risk, graft survival

INTRODUCTION

Liver transplantation (LT) represents a consolidated therapy for acute liver failure, decompensated cirrhosis, and hepatocellular carcinoma (HCC)[1].

The transplantation scenario has deeply changed over time. In industrialized countries, hepatitis B- or C-related cirrhosis is constantly decreasing thanks to the development of vaccine campaigns or new direct-acting antivirals, respectively[2,3]. Conversely, non-alcoholic steatohepatitis (NASH), alcoholic liver disease, and HCC are becoming leading indications for LT[4].

NAFLD is a condition ranging from "simple" steatosis (NAFL) to a necro-inflammatory variant, named NASH, that may eventually progress to NASH-related cirrhosis and HCC (also in pre-cirrhotic stage). Notably, NAFLD and NASH are hepatic expressions of a systemic disorder[5,6].

The term metabolic dysfunction-associated fatty liver disease has been recently proposed in place of NAFLD, indicating the metabolic and cardiovascular (CV) risks that accompany the hepatic disorder[7].

Singh *et al.*[8] analyzed 11 cohort studies including 411 subjects with biopsy-proven NAFL (n = 150) and NASH (n = 261). Among 2145.5 person-years of follow-up evaluation, 33.6% of subjects showed a fibrosis increase, 43.1% displayed stable fibrosis, and 22.3% had a decrease in fibrosis. The annual fibrosis progression rate in patients with NAFL was 0.07 stages, while patients with NASH had 0.14 stages. In other words, patients with NAFL showed one stage of progression over 14.3 years and those with NASH one stage of progression over 7.1 years.

Remarkably, the increasing incidence of both obesity and type 2 diabetes mellitus (DM2) well explains the growing occurrence of NASH-related cirrhosis itself[9].

Available data clearly indicate that in future decades NASH will be the main clinical issue for both hepatologists and transplantologists. Coherently, the United Network for Organ Sharing (UNOS) and the European Liver Transplant Registry reported that NASH has been the fastest growing indication for LT in the last 20 years in North America and Europe[10,11].

In 2018, NASH was the second main indication for adult LTs in North America (1321, 21.5%)[10], and NASH-related cirrhosis accounted for 8.4% of European LTs in 2016 (*vs.* 1.2% in 2002)[11].

Remarkably, NAFLD is a chief cause of cirrhosis and HCC (also in the pre-cirrhotic stage), and it represents the fastest growing cause of HCC in both Europe and the United States[12,13].

In the European context, NASH represents 4% of indications for LT, and among whom, one-third showed a liver disease complicated by HCC[14]. In the United States, NASH is the most rapidly increasing cause of HCC among patients waiting for LT. In particular, NASH-related HCC accounted for 0/472 in 2002, 41/1013 (4.0%) in 2007, and 81/1336 (6.0%) in 2012, reaching 16.2% in 2016[13,15].

Interestingly, NASH-related cirrhosis is also the fastest rising LT indication for acute-on-chronic liver failure (ACLF)-related hospitalization and use of hospital resources[16]. From 2006 to 2014, ACLF as LT indication increased by 24% with a 63% growth in NASH (from 3.5% to 5.7%)[16].

Patients with NASH-cirrhosis, NASH-related HCC, and NASH-related ACLF increasingly require LT[17]. In fact, Parikh *et al.*[18] predicted an increase in NASH as an indication for LT in the United States of 55.4% by 2030.

After LT, recipients frequently experience a noteworthy surge in body weight due to an increase in caloric intake[19,20].

Diabetes mellitus, hyperlipidemia, and arterial hypertension are usual complications after LT, all negatively affecting the quality of life, morbidity, and patient and graft survival[19].

In the context of metabolic impairment, CV disorders are the chief causes of death unrelated to liver illness, being the third most usual cause of mortality in LT recipients (12%-16% of deaths)[19].

Notably, the role of immunosuppressant drugs is relevant. Considering that all immunosuppressant drugs negatively influence both glycemic and lipid metabolism, it is not surprising that transplanted subjects develop metabolic disorders with major prevalence and incidence with respect to the general population[21].

In this setting, both recurrent and *de novo* NAFLD/NASH are common post-transplant complications[22].

Here, we analyze the main challenges of NAFLD/NASH in both pre-and post-LT periods.

METHODS

We prepared a non-systematic review article with the following electronic sources: PubMed, MEDLINE, Google Scholar, Ovid, Scopus, and Web of Science. We used the following search words: "non-alcoholic steatohepatitis", "liver transplant", "diabetes", "metabolic syndrome", and "cardiovascular risk" alone or in combination with "outcome", "epidemiology", and "graft survival". We considered all papers reporting human-related data (inclusion criteria), excluding articles with unavailable full text, not in the English language, abstracts, book chapters, and articles published before 1990 (exclusion criteria). Finally, we analyzed supplementary references/articles among manuscripts considered in the first research.

PRE- AND POST-TRANSPLANT METABOLIC DISORDERS

Obesity

Obesity is commonly associated with NASH in its progressive form[9]. However, the role of obesity as an outcome predictor for LT candidates is debated. Nair *et al.*[23] clearly reported that severe obesity (BMI ≥ 40 kg/m^2) represents a strong independent predictor of post-LT mortality. Conversely, Leonard *et al.*[24] stated that adjusting the body mass index (BMI) for ascites does not correlate with post-LT outcomes. In any case, several authors suggested that obesity can be related to an increased percentage of early graft dysfunction, longer hospital stays and increased infection risk[23,25,26]. Furthermore, Segev *et al.*[27] reported that candidates with obesity were more likely to be excluded from the organ allocation than leaner ones.

Since the prognosis of obese patients seems to be significantly affected by the concomitant presence of diabetes[28], the International Liver Transplantation Consensus Statement recommends an accurate selection of NASH candidates, especially if more than one comorbidity is diagnosed[29].

Van Son *et al.*[30] reported that one year from transplant, 44% of patients became obese. Obesity registered one year after OLT determined a two-fold risk of mortality, representing a strong predictor of in the very

long-term follow-up. In fact, BMI was contrariwise related to 15-year patient survival (HR 1.08, 95% CI 1.03-1.14, $P = 0.001$ per kg/m^2, independently of many patterns such as age, gender, and CV risk profile.

Obesity represents one major negative issue for transplanted patients since subjects with BMI > 30 show poorer patient and graft survival than normal-weight recipients (72.6% *vs.* 69.8% and 75.8% *vs.* 85.4%, respectively)[31]. Obesity and type 2 diabetes together increased the 30-day risk of post-surgery complications, the extent of hospital stay, and reduced graft survival[32]. Post-LT diabetes alone increases the risk of graft rejection and patient mortality[33]. Nair *et al.*[23] confirmed the above-reported data by revising the UNOS data from 1988 to 1996. They described a rise in primary graft non-function and an increase of one-month, one-year, and two-year mortality in morbidly obese LT recipients.

The greater mortality risk and the higher early postoperative complications, mostly due to cardiopulmonary complications in obese patients, were definitively confirmed by a meta-analysis (on 132,162 subjects)[34].

Starting from these clear data, both the American Association for the Study of Liver Disease and European Association for the Study of the Liver stated that severely obese patients should be carefully studied before LT and that high-degree obesity (BMI > 40 kg/m^2 for North America and BMI > 35 kg/m^2 for Europe) can represent a relative contraindication for LT itself[1,35].

Further developing primary and secondary prevention strategies (i.e., early diet, lifestyle modification, and in selected cases, the bariatric surgery approach) against obesity should be mandatory.

Diabetes

The prevalence of diabetes amongst subjects awaiting LT for NASH ranges from 46% to 55%[35,36]. Considering the pre-LT context, diabetes is associated with early postoperative complications, such as infection and adverse CV events[37]. Moreover, we recently demonstrated that pre-LT diabetes represents an independent predictor of post-transplant atherosclerotic events and CV-related mortality[38].

Pre-transplant diabetes, frequently associated with NASH, is related to worse post-LT outcomes since it increases the risk of portal venous thrombosis and consequently the three-month post-LT mortality[32,39].

Notably, diabetes, together with recipient age, Model for End-Stage Liver Disease score (MELD), BMI, and dialysis before LT, is a chief predictor for 90-day post-LT mortality[40].

Insulin resistance and diabetes, which are often diagnosed in the pre-LT period, tend to improve the following LT, but the high incidence of post-LT metabolic syndrome and the use of immunosuppressive drugs favor diabetes recurrence or new-onset diabetes after transplant (NODAT)[41,42]. Notably, calcineurin inhibitors (CNIs) (tacrolimus and cyclosporine) are the main risk factors for post-LT diabetes[41,42]. Markedly, the incidence of NODAT at 12 and 60 months is about 25% and 18%, respectively[41,42]. The incidence becomes higher and higher the closer we get to the transplant, reaching 44% at three months[41,42].

Advanced age, ethnicity, family history, body mass index, hepatitis C virus infection, and immunosuppressive drugs such as corticosteroids and tacrolimus all are main risk factors for post-LT diabetes[41,42]. A BMI ≥ 30 kg/m^2 is related to an augmented risk for diabetes[41,42].

NODAT negatively impacts the recipient's long-term survival, similarly to pre-LT disease. Notably, LT recipients developing NODAT show a worse overall survival and a major incidence of both infection and chronic renal failure[41,42].

KIDNEY DISEASE BEFORE AND AFTER TRANSPLANT

Patients with NASH usually show several risk factors for chronic kidney disease (CKD)[35,43,44]. Indeed, it is not surprising that CKD prevalence among these patients is high, ranging from 20% to 55%[35,43,44].

Interestingly, NASH can also lead to an increased risk of CKD after adjusting for the presence of diabetes[45]. Additionally, in patients with diabetes-related kidney disease, NASH represents a strong risk factor for CV events[46]. Remarkably, in patients with NASH, CKD was associated with decreased global survival[47].

The existence of CKD before LT represents a consolidated risk factor for post-LT renal damage, being associated with a decrease in both graft and patient survival[48,49]. Candidates for NASH-related cirrhosis, particularly if in end-stage liver disease, are more prone to require renal replacement therapy before LT in comparison with other main indications, and this leads to a significant increase in pre-LT mortality risk (+150%)[50,51].

Female sex, pre-transplant CKD, and NASH are strong and independent predictors of post-LT CKD (stage ≥ III)[48]. Considering patients transplanted for NASH, subjects with normal pre-LT renal function show a lower risk of death and increased graft survival than those with pre-LT severe renal dysfunction[52]. NASH patients undergoing LT develop a significant reduction of glomerular filtration rate after three months from LT in comparison with non-NASH candidates. Interestingly, the renal impairment tends to persist also after adjustments for body weight, diabetes, tacrolimus, hypertension, and HCC[53].

The renal condition is a very important point in the management of LT recipients since the main immunosuppressant drug category (calcineurin inhibitors) shows well-known nephrotoxicity[1]. Indeed, patients with NASH deserve particular attention, and newly defined protocols to minimize the calcineurin inhibitor dosages in this specific subgroup of recipients should be implemented.

CARDIOVASCULAR RISK AND PRE-TRANSPLANT SCREENING

Patients with NASH awaiting LT require specific clinical attention[54]. In fact, candidates with NASH often show a clinical phenotype of metabolic syndrome and a noteworthy prevalence of CV events[55].

The pathogenesis of CV disease in patients with NASH is multifactorial. Besides the "classic" risk factors such as hypertension, hyperlipidemia, and impaired glucose tolerance, a typical NASH-related endothelial dysfunction has been described[56,57].

Considering the metabolic, CV, and renal impairment of patients with NASH awaiting LT, an accurate CV risk stratification is mandatory[30].

Before LT, all patients are subjected to a transthoracic echocardiogram to evaluate both structural and functional heart capacity. In the absence of consolidated protocols, some authors proposed that subjects who show more than two CV risk factors (age > 50 years, hypertension, hyperlipidemia, and obesity) should also receive stress testing[51]. Obviously, coronary angiography should be a further step in patients with

altered stress tests[58].

Furthermore, pre-transplant percutaneous coronary intervention and revascularization are needed in obstructive coronary artery disease (> 50% reduction in luminal diameter of major coronaries). On the contrary, medical management with beta-blockers and statins might be enough in candidates with non-obstructive diseases[59].

The relevance of pre-LT CV assessment is determined by the great transplant-related cardiac stress. In fact, during LT, acute CV changes, including the reduced venous return and an abrupt upsurge in peripheral vascular resistance, can be registered. Moreover, hemorrhage and reperfusion syndrome can complicate the hemodynamic situation[60].

POST-TRANSPLANT OUTCOMES

Survival

According to the European Liver Transplant Registry, patients with NASH show a post-LT survival comparable to other aetiologies[14]. In particular, there was no substantial variance between NASH and non-NASH recipients, nor for subjects with or without evidence of HCC[14]. Among patients without HCC, NASH showed equivalent post-LT survival in comparison with alcohol-related disease and higher survival with respect to hepatitis C virus (HCV)[14]. Considering patients with a diagnosis of HCC, survival in recipients with NASH was slightly poorer than alcohol-related liver disease, but it was comparable to HCV[14]. Despite the overall data, factors typically associated with NASH, such as age > 60 years, BMI ≥ 30 kg/m^2, and diabetes, are well-consolidated risk factors for both 1- and 12-month mortality after LT[55].

Post-transplant cardiovascular risk

CV disease is the foremost reason for death among LT recipients since it accounts for 19-42% of non-graft-related mortality[61]. Rubín *et al.*[62] analyzed the outcome of LT recipients surviving at least 10 years from LT. Among 323 LT recipients, 52% were alive > 10 years post-LT. Twenty-seven CV events occurred in 27 patients (17%), between 0.18 and 8.1 years post-LT (median 3.1 years), with 1-, 3-, 5-, and 10-year cumulative rates from baseline of 2%, 5%, 10%, and 17%, respectively.

Diabetes, hypertension, renal dysfunction, and NASH represent consolidated risk factor for post-LT CV disorders[61,63,64]. In particular, patients with pre-LT NASH show a higher risk of CV- and cerebrovascular-related mortality, especially in the first year after LT, if compared to candidates with other indications[65,66].

Pre-LT diabetes and kidney disease are other important predictors of post-LT CV mortality[50]. Notably, we recently demonstrated through a multicenter cohort study that pre-transplant diabetes represents the major risk factor for both post-LT atherosclerotic vascular events and CV mortality[38].

Immunosuppressive regimes show a key role in influencing the CV risk of LT recipients[1].

Fussner *et al.*[67] analyzed the CV risk factors with a retrospective study involving 455 transplanted patients with a considerable follow-up period (8-12 years). Notably, CV disease was diagnosed in 10.6%, 20.7%, and 30.3% of patients at one, five, and eight years from transplant, respectively. In the multivariate analysis, age, diabetes, history of CV disorder, pre-LT troponin level (> 0.07 ng/mL), and tacrolimus use *vs.* "other" (hazard ratio, 0.26; 95%CI: 0.14-0.49; $P < 0.001$) emerged as independent predictors of CV risk in the post-LT phase. The authors underlined that the potential CV benefit of tacrolimus should be confirmed with further prospective studies.

The role of steroids, widely used in the first period after transplant, is important. In fact, considering the general population, high-dose steroids are consolidated risk factors for both steatosis and metabolic impairment. However, in the post-LT, most specialists taper steroids over 1-6 months, and consequently, their effects on the long-term outcome might be marginal. However, the total daily dose of steroid treatment seems to be strongly correlated with the risk of post-LT metabolic syndrome[68]. Interestingly, in the last years, steroid-free protocols have been proposed to achieve a relevant decrease in diabetes and hyperlipidemia incidence[69].

Gilad *et al.*[70] developed a retrospective study involving 52 LT recipients who received mTOR inhibitors. They demonstrated that a kidney function improvement was observed without a significant weight gain or new-onset diabetes mellitus. However, they reported a few upsurges in total cholesterol (+7 mg/dL) and blood pressure. In general, treatment with mTOR inhibitors does not seem to lead to a noteworthy metabolic impairment, representing a good option, especially if a metabolic risk profile is present (i.e., NASH as transplant indication).

Among CNIs, tacrolimus is better than cyclosporine in terms of metabolic impact. In fact, post-transplant deaths and re-transplantation rates are higher in patients treated with cyclosporine compared to subjects on tacrolimus therapy. Moreover, patients on cyclosporine more often developed hypertension and hyperlipidemia than those in the tacrolimus group[71,72].

It is important to act on modifiable CV risk factors, such as hypertension, diabetes, dyslipidemia, and smoking. Hyperlipidemia, in particular, is very common after LT, affecting up to 71% of subjects. The best approach for the treatment of hyperlipidemia might be starting with lifestyle modification, then optimization of the dose and/or type of immunosuppressive drugs, and finally, the use of lipid-lowering agents (with particular attention to the possible drug interactions)[73].

Post-transplant NAFLD/NASH

Considering the high prevalence of metabolic disorders after LT, it is not surprising that both recurrent and *de novo* NAFLD/NASH can often be diagnosed.

De novo NAFLD and NASH can be detected in 26% and 2% of patients, respectively[74], while NASH recurrence ranges from 20% to 40% of cases[75].

Diabetes, hypertension, hyperlipidemia, renal dysfunction, and weight gain represent the major adjustable risk factors for the development of *de novo* and recurrent NAFLD, while age, genetics (i.e., PNPLA3), sex, and pre-existing CV disease are the most relevant non-modifiable ones[76-82].

Vallin *et al.*[83], in a biopsy-based study, and Narayanan *et al.*[84], in an ultrasound study, demonstrated that recurrent NAFLD and *de novo* NAFLD are different conditions with different prognoses. Recurrent NAFLD seems to be more severe and clinically aggressive and with earlier onset in comparison with *de novo* NAFLD. Narayanan *et al.*[84] described allograft steatosis in 78% of subjects transplanted for NASH and in 44% of patients with other indications. Patients with a recurrent form showed a more rapid fibrosis progression to cirrhosis within five years, and liver disease is more often associated with CV events.

CONCLUSION

As summarized in Table 1, metabolic impairment of both pre- and post-LT periods represents a very complex matter.

Table 1. Main key messages about the metabolic disorders of both pre- and post-transplant period

	Key message	Ref.
Pre-LT	Increased risk of developing HCC	[12,13]
	High prevalence of diabetes mellitus	[35,36]
	CKD is a frequent comorbidity and is associated with poor outcome	[35,43,44,46,47,50,51]
	Increased prevalence of CVE	[55]
Post-LT	Obesity is a strong predictor of mortality, graft dysfunction, longer hospital stay, infection	[23,25,26,30]
	Diabetes mellitus increases the risk of portal vein thrombosis and mortality	[32,39,40]
	NODAT negatively impacts the overall survival, increasing infection and CKD risk	[41,42]
	CKD is associated with post-LT renal damage, decreasing both graft and patient survival	[48,49,52]
	Significant reduction of renal function after 3 months from LT	[53]
	CVE accounts for most of the non-graft related mortality	[61,62,67]
	Optimization of immunosuppression is a chief part of therapy against metabolic impairment	[69,70,73]

HCC: Hepatocellular carcinoma; CKD: chronic kidney disease; CVE: cardiovascular events; NODAT: new-onset diabetes after transplant; LT: liver transplantation; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis

Patients undergoing LT for NASH represent a substantial challenge for transplant specialists due to the simultaneous presence of liver disease and systemic metabolic disorders. Before LT, a multidisciplinary team including cardiologists, nephrologists, diabetologists, nutritionists, and anesthesiologists should act to decrease the metabolic impairment as much as possible and to stratify the intra- and perioperative risks of patients to confirm the transplant feasibility. Interestingly, Moura *et al.*[85] proposed a similar team concept for transplanted patients with nutritionists and diabetologists who might work together with surgeons.

Early after LT, recipients should be thoroughly informed and educated to avoid uncontrolled weight gain.

Supervised diet and exercise programs should be recommended to all patients after LT, especially those with major metabolic risk factors and/or poor functional capacity. Furthermore, early adaptation of an immunosuppressive regimen should be implemented to decrease the cardio-metabolic risk as well as to reduce the risk of CKD.

Further studies should clarify the impact of CV events on the recipients' survival. In fact, patients with pre-LT NASH show a higher risk of those events and a long-term survival comparable to or better than other aetiologies.

DECLARATIONS

Authors' Contributions

Made a substantial contribution in writing-original draft preparation, to the design of the work, the acquisition, analysis, and interpretation of data: Gitto S, Mannelli N

Made a substantial contribution in critically review and editing the work: Andreone P, Nascimbeni F, Tassi A, Gabrielli F

Supervisor: Andreone P

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Not applicable.

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