Management of metabolic syndrome and cardiovascular risk post-liver transplantation

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Abstract

Cardiovascular events are the second most prevalent cause of non-hepatic mortality in liver transplant (LT) candidates. Their incidence is projected to rise further due to the growing prevalence of NASH as a transplant indication and the ageing LT population. Recipients with metabolic syndrome are up to 4 times more likely to have a cardiovascular event than recipients without, therefore prevention and optimal treatment of its components is key in reducing risk. Although treatment data specifically for the LT population are scarce, there is detailed guidance from learned societies that mostly mirrors the guidance for patients in the general population at increased cardiovascular risk. In this review article, we discuss in detail the management of such comorbidities and provide practical step-by-step guidance. We also emphasize the need for adequately powered studies for the treatment of metabolic comorbidities in the post-LT population.

Introduction

Liver transplantation (LT) is the standard therapy for acute and chronic liver failure not amenable to conservative management [1]. Over the recent years the improvement of surgical techniques, patient selection and the optimization of immunosuppressive therapies have led to markedly improved survival rates following LT, with average 1- and 5-year survival of 85-90% and 75-80% respectively[2,3]. As a consequence, the prevalence of non-hepatic causes of morbidity and mortality has increased. Cardiovascular events are the second cause of non-hepatic mortality post-LT with an estimated prevalence of 11% [2]. Metabolic syndrome and its components are a common predisposing factor for cardiovascular morbidity and have an increasing prevalence in the general and post-LT population[4].

The metabolic syndrome is defined by the Adult Treatment Panel III criteria as the combination of any three of the following: elevated blood pressure (≥130/85 mmHg), increased abdominal circumference (>102 cm for men and >90 cm in women), blood glucose levels ≥110 mg/dl, increased values for plasma triglycerides (≥150 mg/dl) and low plasma levels of HDL cholesterol (<40 mg/dl for men and <50 mg/dl for women) [5]. Non-alcoholic fatty liver disease (NAFLD) is considered the hepatic manifestation of metabolic syndrome; it is an increasing indication for LT in Europe and the US but also an important co-factor in patients with other etiologies of cirrhosis[6,7].

The aim of this review is to summarize the management of metabolic syndrome and cardiovascular risk post LT. We look separately at each component of the metabolic syndrome and provide stepwise practical guidance for their management. We further discuss de novo and recurrent NAFLD in view of the growing prevalence and the associated increased cardiovascular risk.

Search strategy and selection criteria

We searched MEDLINE (January 2005- February 2019) using the search term «liver transplantation» combined with the terms «metabolic syndrome» or «diabetes» or «hypertension» or «dyslipidaemia» or «NAFLD» or «obesity» without language restrictions. We selected further relevant publications from the reference lists of articles identified by this search strategy. Relevant articles were selected based on the subheadings used in this Review. We largely selected publications in the past 5 years (until February 2019), but did not exclude highly relevant older publications. Review articles are cited to provide more details and references than this Seminar has room for.

Cardiovascular events post LT

Cardiovascular events post LT are a leading cause of morbidity and mortality and can be divided in those occuring during the peri-operative or early postoperative period and those that occur later on. The former are mainly due to pre-transplant risk factors and/or perioperative complications, while the latter are related to post LT metabolic syndrome and its components and are the focus of this review. Thorough pre-LT cardiovascular assessment of the LT candidates is key in reducing the perioperative risk. This has been covered extensively in review articles[8] and guidelines[9] and is beyond the scope of this article. A point-based risk score was recently developed (available at www.carolt.us), which can quantify and stratify patients' risk for major cardiovascular events in the first year following LT[10].

It is still unclear if LT recipients are at higher cardiovascular risk compared to age-matched non-LT population[11,12]. This uncertainty is partly due to a lack of consensus regarding outcome definition and poor data quality in LT recipients, as exposed in a systematic review of 29 studies that included 57,493 patients[13]. The same review reported that older age and pre-exisitng cardiac disease were the most consistent risk factors for the development of cardiovascular events post LT[13]. In the largest single centre cohort to date, which reported on 775 patients over a 22 year period, the cumulative risk of cardiovascular events at 5 years post LT was calculated at 13.5%[14]. Metabolic syndrome was twice more prevalent in patients who developed such events (61% versus 34%)[14]. Another meta-analysis that included 12 studies and 4,792 LT recipients, calculated that the 10-year risk for developing a cardiovascular event was 13.6% in unselected recipients, which is consistent with a moderate to high Framingham risk score category [15]. Data on cardiovascular mortality post-LT are summarized in Table 1.

A recent US study based on hospital records from 153 facilities, reported a 115% increase of hospitalizations due to cardiovascular disease in LT recipients over the last decade[16]. This most likely reflects a combination of improved short-term LT outcomes but also the increasing age of LT candidates and the growing prevalence of NAFLD as an indication for LT. Surprisingly, transplant hospitals had higher total costs and patient mortality, but due to the nature of the study the reason for this could not be ascertained[16]. This does emphasize the need for improvement in the quality and consistency of cardiovascular care delivered.

Therefore, the significant burden of morbidity and mortality of cardiovascular events and the projected further rise in their incidence underlines the need for a coordinated strategy to minimize risk factors.

Post LT metabolic syndrome

Metabolic syndrome is prevalent in 40-60% of patients post LT [17,18]. Not surprisingly, its prevalence increases over the years post-LT as demonstrated in a prospective study of 117 LT recipients [18]. Patients with metabolic syndrome were 4 times more likely to have a cardiovascular event than recipients without MS, however there was no increase in all-cause mortality, as demonstrated in a meta-analysis of 12 studies [15]. Immunosuppressive medication is associated with all components of the metabolic syndrome as shown in Figure 1 and discussed in detail below. Each component of the metabolic syndrome is analyzed separately with treatment recommendations.

Obesity post LT

The growing prevalence of obesity is reflected in the patients assessed for LT, with up to 30% estimated to be obese [19]. Some transplant centers have an upper limit of BMI beyond which there is a relative contraindication to transplantation. This approach is a reflection of a study by Nair [20] that included over 23,000 recipients and showed increased 5-year mortality in patients with class II and III obesity compared to non-obese recipients. However, this study overestimated obesity in the presence of ascites, in which case the reported increased mortality and morbidity might reflect the impact of ascites and advanced liver disease on LT outcomes. In a prospective multicenter study [21] which included 1,300 patients and where BMI was calculated after paracentesis, obesity was not associated with neither patient nor graft survival and no difference was observed regarding postoperative care and hospital stay. In a recent meta-analysis which included 24 studies, only candidates with a BMI>40 kg/m^2 had a significantly higher mortality risk and post-operative complications compared to normal/overweight patients at 1, 2 and 5 years after LT[22]. However, only three of the

included studies have taken into account the presence of ascites by calculating a corrected BMI, which hugely affects the validity of this meta-analysis[22]. A registry study of 57,255 LT based on the UNOS database (2003-2012) showed that patients in all categories of obesity had similar survival rates and interestingly overweight and class I obese patients had better survival than patients with normal BMI, even after adjusting for ascites and albumin levels. [23] Presence of diabetes at the time of LT but not obesity was an independent predictor of post-LT survival (HR1.29; 95%CI 1.21-1.36) [23].

The International Liver Transplantation Society (ILTS) Consensus Statement on NASH and LT recommend that class I-III obesity alone in not a contraindication for LT. However, strict patient selection is recommended in the context of concurrent diabetes mellitus (DM) or other medical comorbidities[24].

It is estimated that 30-70% of patients become obese or overweight after LT, with the most rapid weight gain occurring within the first year post LT [25]. On average, patients gain approximately 5 kg within the first year and 10kg within 3 years following LT. Older patients (age>50 years) and obese prior to LT are shown to be at greater risk of post LT obesity [4,25].

Post-transplant weight gain is considered to be multifactorial; reversal of catabolic state of cirrhosis and increased appetite due to the absence of chronic liver disease and the effect of steroids, are some of the reasons that can explain this. In addition, physicians often overlook weight gain as the main focus remains on managing post-operative complications, rejection, sepsis and renal dysfunction. Weight distribution rather than absolute BMI may be more important in estimating cardiovascular risk post-LT.

Management

Lifestyle changes with diet and exercise should be discussed with all LT recipients, however the long-term efficacy of this approach is limited. A randomized trial including 151 patients compared a combined intervention of exercise and diet counseling to standard care early post LT [26]. The adherence to the intervention was low at 37% and there was no difference in body weight between the two groups, however there was significantly better exercise capacity in the intervention group [26].

Limited data exist on the use of pharmacotherapy for weight loss in LT recipients. In a pilot study of 15 patients, orlistat (a reversible inhibitor of pancreatic lipase) administered for a six-month period was well tolerated. Results showed that orlistat can significantly reduce waist circumference and is safe provided that immunosuppression levels are closely monitored, as 50% of the patients required does adjustment in the tacrolimus levels [27]. Glucagon-like peptide-1 analogues are licensed for the management of type II diabetes, however they might have an anti-obesity effect. In a phase II of obese non-diabetic patients, semagutide administered for 52 weeks achieved a weight loss of 6-13.8% across different doses [28]. There are no potential interactions of this class of drugs with immunosuppressive medication, so they represent an attractive therapeutic option for obese patients with diabetes or in the treatment for obesity if licensed for this indication.

Bariatric surgery is feasible in the setting of liver transplantation although data regarding optimal timing and type of procedure are still lacking. Sleeve gastrectomy seems to be the preferred approach, as it preserves access to gastric fundus and the biliary tree to manage post LT biliary complications, preserves the absorption and maintains adequate levels of immunosuppression and is associated with fewer adhesions in the transplant field[24]. As far as timing is concerned, patients with low MELD score can be considered for pre-LT surgery, although this is associated with

increased mortality risk up to 16.7%[29]. In patients with an acceptable risk profile, history of bariatric surgery prior to LT is not associated with worse graft survival rates or increased risk for post-LT complications as shown in a single centre study[30], although this need to be confirmed in larger patient cohorts. Concomitant LT and bariatric surgery is an option only for selected patients with high MELD score who cannot be considered for pre-LT surgery [31]. In a case-control study of 29 patients who underwent simultaneous LT and sleeve gastrectomy, 100% of the patients in the intervention group maintained >10% of weight loss post LT compared to 30% in the control group of non-invasive weight loss program[32]. Moreover, they had a lower prevalence of hypertension and insulin resistance and required less anti-hypertensive and lipid-lowering medications. Bariatric surgery following LT is a less preferred option as it is technically more challenging and has been associated with high post-operative mortality and re-operation rates at 5.3% and 12.2% respectively [33].

Diabetes post LT

Diabetes mellitus is relatively common in cirrhosis due to impaired glucose homeostasis and is more prevalent in specific aetiologies, namely alcohol-related, NAFLD, haemochromatosis and HCV. Most of these patients will remain diabetic post-LT. Moreover, the incidence of post-LT diabetes (PLTDM) is as high as 30%, depending on the diagnostic criteria used and pre- and post- LT risk factors[34]. Transient hyperglycaemia is common in the first month post LT and is associated with infections, high dose steroid treatment and the stress response of the immediate post-operative period. A formal diagnosis of PLTDM can only be made if hyperglycemia persists 45 days post LT[35].

Risk factors for PLTDM can be classified as risk factors associated with the development of DM in the general population and those particularly associated with LT recipients[36]. The former include older age, male sex, pre-transplant impaired fasting glucose, obesity, family history of diabetes and African-American or Hispanic ethnicity. Among the predisposing factors associated with LT are hepatitis C virus (HCV) and cytomegalovirus (CMV) infection, high dose steroids and CNI inhibitors. The risk of PLTDM is significantly higher with tacrolimus compared to cyclosporine and is dose-dependent[4]. Other factors associated with PLTDM are central obesity prior to LT, hyperglycaemia in the first post-LT month and ITU stay >15days. Donor characteristics such as age>60, deceased liver donor grafts, steatotic allografts and cold ischaemia time>9 hours are also associated with increased risk of PLTDM.

Most studies have reported reduced overall survival in patients with PLTDM and only few have reported comparable outcome regardless of the presence of PLTDM[37]. A retrospective analysis of 798 LT patients from the U.S. National Institute of Diabetes and Digestive and Kidney Diseases registry showed that both pre-LT (hazard ratio [HR] 1.94, 95%CI 1.40–2.68) and post-LT diabetes (HR 1.87, 95%CI 1.41–2.48) were associated with reduced 1-year survival [2]. Persistent PLTDM has also been shown to be associated with significantly worse 5-year survival compared to transient hyperglycaemia (36.5% vs.13.9%) in deceased-donor recipients [38]. Similarly in a study of 438 LT recipients without DM prior to transplantation, PLTDM was associated with a mean survival of 4.2 years compared to 6.1 years in those without[39]. A study of 35,870 LT patients from the U.S. Scientific Registry of Transplant Recipients showed that both pre-LT DM (HR=1.21, 95%CI 1.12-1.30) and PLTDM (HR=1.06, 95%CI 1.02-1.19) were independently associated with reduced survival. Additionally, donor's

history of DM was also independently associated with an increased risk of graft failure and mortality [40].

Studies have consistently shown that PLTDM is an independent predictor of cardiovascular events. A retrospective analysis of the UNOS database (2003-2013) aimed to compare different diabetes states and the risk for cardiovascular events and showed that although pre LT diabetes has traditionally been associated with cardiovascular disease, cardiovascular risk is greatest in LT recipients with sustained PLTDM[41]. The presence of PLTDM has also been associated with renal dysfunction and higher incidence of post-operative bacterial infections, which is attributed to the lower chemotactic, migratory and phagocytic functions of neutrophil granulocytes in diabetic patients compared to healthy individuals[39].

PLTDM also has a significant impact on graft survival. Historically, in patients with hepatitis C, DM and insulin resistance were associated with higher risk of HCV recurrence and progression of fibrosis [42] but in the era of direct acting antivirals this risk no longer exists. Interestingly, recent data suggest that eradication of HCV prior to LT is independently associated with a reduced incidence of PLTDM in patients without previous history of DM, and the risk is significantly lower compared to patients that achieved sustained virology response (SVR) immediately post LT. Moreover, PLTDM has been associated with late onset hepatic artery thrombosis and acute and chronic rejection[38,43]. Data on the impact of diabetes on post-LT mortality are summarized in Table 2.

Management

Several studies have shown that in the intraoperative period strict glycemic control results in significantly less infection rated, ITU stay and 1 year survival[44-46]. In the

immediate post LT period, glycemic control can be difficult due to pain, surgical stress, introduction of immunosuppression and administration of steroids. Sliding scale intravenous insulin therapy is the standard of care until regular eating is established when a basal subcutaneous bolus regimen can be safely administered. Treatment goals remain the same as per any hospitalized patient.

Few data exist on the management of diabetes in the post-LT setting. In the outpatient setting, the ILTS consensus statement on LT suggests that all LT recipients should undergo fasting glucose and HbA1c measurement at least 3, 6 and 12 months after LT and annually thereafter [47]. Although there is no data on the impact of glycaemic control on cardiovascular events post LT, it is reasonable to assume that a tight control will have a beneficial effect similarly to the general population. Therefore the treatment target is an HbA1c <7.0% for most patients [47]. Annual screening for retinopathy and proteinuria in patients with diabetes is also advisable. A stepwise approach that consists of lifestyle modification followed by oral anti-diabetic medication and then insulin is recommended by the International Consensus Guidelines on PLTDM[35]. The choice of immunosuppression should be based on the best outcome for graft and patient survival irrespective of the risk or presence of PLTDM[35]. Having said that, steroids should be tapered and stopped within 3 months post LT in the majority of patients. Our own data suggest that CNI minimization improves long-term outcomes with no adverse effects to graft survival[48,49].

Most oral hypoglycaemic agents have not been studied in the post-transplant setting and no comparative studies exist. Metformin is a reasonable first choice given its beneficial effect on cardiovascular events; the perceived risk of lactic acidosis in LT recipients has not been confirmed in existing studies[3]. Sulfonylureas are also considered safe, although there is a potential risk for drug interactions due to their

hepatic metabolism and are potentially associated with hypoglycaemia and weight gain [3]. Meglitinides are less likely to cause hypoglycaemic events but are also metabolized in the liver therefore caution is warranted. Thiazolidinediones are considered safe and there is some evidence on their use in the renal transplant setting; moreover, pioglitazone might have a beneficial effect in patients with NASH [3]. Similarly, there is some encouraging data in post renal transplant patients for the use dipeptidyl-peptidase -4 inhibitors (linagliptin, sitagliptin), which appear to be both safe and effective, although data from LT patients are lacking. GLP-1 agonists are not metabolized in the liver, therefore the risk of drug interactions is low. They do cause however delayed gastric emptying, which could theoretically impact on the absorption of immunosuppressive drugs. SGLT-2 inhibitors could lead to volume depletion and importantly increase the risk of genitourinary infections, therefore their use should be avoided [47].

Overall, in the absence of comparative data, we advocate a tailored approach based on individual patient characteristics. Treatment choices should follow the recommendations in the general population, with the exception of SGLT-2 inhibitors. Data from Spain suggest that diabetic control is suboptimal in up to a third of patients with PLTDM, therefore potential improvement and progress can have a significant impact on cardiovascular outcomes[50]. Management principles are summarized in Figure 2.

Dyslipidaemia

Hyperlipidaemia is not common in patients with cirrhosis due to impaired synthetic function and esterification. However, patients with cholestatic liver disease may have increased serum cholesterol if their synthetic function is reasonably preserved.

Nonetheless, patients with end-stage liver disease might have dyslipidemia based on the definition criteria due to low HDL-C levels secondary to liver synthetic failure. Dyslipidaemia appears to be highly prevalent post-LT, affecting 40-66% of the LT recipients [1]. The presence of dyslipidaemia has been associated with increased cardiovascular risk and associated morbidity and mortality [51].

Immunosuppression plays a fundamental role in the development of post-LT hyperlipidemia. Although steroids are associated with dyslipidemia, steroid-free immunosuppression has not shown to reduce post-LT hyperlipidemia. CNI inhibitors are also associated with hyperlipidemia, with cyclopsorin having a more pronounced effect compared to tacrolimus [52]. This is because cyclosporin may inhibit hepatic bile acid-26 hydroxylase which results in decreased bile acid synthesis from cholesterol and reduced cholesterol transport into the bile and intestine [52]. In addition, it can increase the circulating LDL-C levels by binding to the LDL-C receptor. MTOR inhibitors (sirolimus) are also potent hyperlipidaemic agents particularly in combination with cyclosporine [47].

Management

There is robust guidance for the treatment of dyslipidaemia from learned societies, however data specifically on the post-LT population are scarce. The Atherosclerotic Cardiovascular Disease calculator, as suggested by the American Cardiology Association/American Heart Association, helps to assess cardiovascular risk and the instigation of appropriate therapy according to the risk category (https://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/). The UK National Institute for Clinical Excellence guidelines suggest the use of a different risk assessment tool (QRISK2) to identify and stratify people with high risk for developing

CVD and point out that standard CVD risk scores underestimate risk in people who have additional risk because of underlying medical conditions or treatment (autoimmune diseases, corticosteroids or immunosuppressant drugs) [53].

Specifically for LT, the ILTS consensus suggests that a fasting lipid panel should be obtained at 3-6 months, 1 year and annually thereafter post-LT with a recommended target LDL-C <100mg/dL and triglyceride levels <250mg/dl [47]. Statin therapy should be started on all patients with hypercholesterolemia who have failed dietary/lifestyle measures. Although statins are considered to be safe in the post LT setting, most of them are metabolized by cytochrome P450-3A4, with a potential reduction in CNI levels and/or increase in statin concentrations. Therefore a low initial dose of lipophilic statins should be started (Simvastatin 20mg/day, Atorvastatin 10mg/day), with careful titration and follow up. Hydrophilic statins, such as fluvastatin and pravastatin, are not metabolized by the cytochrome P450 and should be used preferentially[1,54]. Ezetimibe is safe in LT recipients and can be used in addition to statins if the LDL target levels are not achieved on monotherapy[55].

In the setting of persistent hypercholesterolemia, a switch from cyclosporine to tacrolimus is recommended, as this can result in reduction of LDL levels [56]. CNI minimization strategies with introduction or increase in the dose of mycophenolate or azathioprine could also help. Finally, if hyperlipidemia develops while receiving mTOR inhibitors and initial treatment with lipid lowering agent has failed, then mTOR dose reduction or switch to other immunosuppression is recommended.

Hypertriglyceridemia with normal cholesterol levels which has failed dietary and lifestyle changes responds to fish oil (omega 3) at a starting dose of 1000mg twice daily titrated up to 4000mg if tolerated [47,57]. Some patients may experience increase

in LDL on fish oil and careful monitoring is advised. Finally, fibric acid derivatives (gemfibrozil, clofibrate, fenofibrate) are well tolerated but should be used in caution due to the potential risk of rhabdomyolysis when administered with statins. The above is summarized in Figure 3.

Hypertension

Systemic arterial hypertension is an established risk factor for cardiovascular morbidity and mortality but affects only a small minority of cirrhotic patients due to peripheral vasodilatation. On the contrary, post LT hypertension is very common and affects up to 70% of liver transplant recipients, with blood pressure being particularly labile in the early postoperative period[17,58,59]. This is largely related to systemic and renal vasoconstriction caused by CNI immunosuppression and the mineralocorticoid effect of steroids. Among CNI inhibitors, tacrolimus is less likely to cause hypertension compared to cyclosporine within the first year post LT[60].

Management

Hypertension is suboptimally controlled in a third of LT recipients[61], therefore further education of healthcare providers on this aspect is required. All transplant patients should have regular blood pressure (BP) monitoring (daily for the first month, at 3 to 6 months and annually thereafter) and the goal should be a BP<130/80mmHg [47]. These targets mirror those in the general population for those who are at high risk of cardiovascular events. The SPRINT randomized controlled trial further reduced these targets to a systolic blood pressure of 120 mmHg or lower in patients at high cardiovascular risk, however such intensive treatment targets are not yet endorsed in LT recipients [62].

Hypertension management mirrors the general population with sodium restriction, smoking cessation, alcohol avoidance and exercise being the first line interventions. Immunosuppression minimization with early tapering of steroids and optimization of CNI dose should be aimed in the immediate post-transplant period.

As far as pharmacotherapy is concerned, calcium channel blockers (amlodipine or felodipine) are preferred as first line treatment due to their inhibition of CNI induced renal vasoconstriction, their safety profile and minimum interaction with CNI immunosuppression [47]. Nifedipine inhibits the intestinal cytochrome P450 and therefore increases CNI levels [25]. Diltiazem and verapamil are not recommended due to the potential drug interaction that can increase CNI levels [25]. Cardioselective b-blockers are thought to be effective and are safe second line agents in the management of post LT hypertension [25].

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are of limited use in the early post-transplant period due to low plasma renin activity and can also exacerbate the CNI induced hyperkalaemia. In the late post-transplant period these agents are recommended as first line agents in patients with chronic kidney disease with or without proteinuria and diabetes. Thiazides and loop diuretics should be used with caution as they can lead to electrolyte imbalance and renal dysfunction and require frequent monitoring. Finally, up to 30% of the patients may require more than one agent in order to achieve adequate BP control[12]. The above is summarized in Figure 4. It should be noted that good quality data to support this approach are scarce and these recommendations are based on low level evidence.

De Novo and recurrent NAFLD

NAFLD can cause a wide spectrum of disease, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), progressive fibrosis and ultimately cirrhosis[63]. As highlighted by the recently published OPTN/SRTR report [64], NAFLD has now become the leading cause of liver transplantation in the U.S with 35% of all adult recipients being obese by body mass index (BMI) criteria, including 14% of recipients with a BMI ≥35 Kg/m^2. Over the past 10 years, the prevalence of NAFLD as an indication for LT has increased by 170% and is likely to increase further due to the worldwide increasing incidence of MS, the lack of screening tools for early diagnosis and the absence of widely established therapies [64]. Patients transplanted for NAFLD/NASH have an increased risk of both early and late cardiovascular events compared to other aetiologies[65,66].

Patients transplanted for NAFLD-related cirrhosis are at higher risk of developing NAFLD recurrence compared to patients that have been transplanted for other aetiologies[25]. It is estimated that 30-60% of patients transplanted for NAFLD will have disease recurrence within 1-5 years following LT, where 10-33% of those will develop NASH and 5-10% will develop advanced fibrosis[67]. De novo NAFLD post LT, occurs in 20-35% of patients of which 5-10% will develop NASH and 2-4% will develop advanced fibrosis [68-70]. The rate of graft failure due to de novo or recurrent NAFLD is low.

Risk factors that have been associated with increased risk of de novo NAFLD include obesity, tacrolimus-based immunosuppression, diabetes, hyperlipidaemia, arterial hypertension, alcoholic cirrhosis as an indication for LT and pre-transplant graft steatosis[70,71]. As shown by Dumortier, there is a “dose-dependent” relationship between the number of MS components and the risk of developing de novo NAFLD[70].

Despite the obvious similarities between de novo and recurrent NAFLD in terms of risk factors, the natural history of these two entities can differ significantly. Recurrent NAFLD has an earlier onset, is more severe and irreversible compared to de novo NAFLD as shown in a study of 91 patients with available histology [72]. Progression of fibrosis was higher in patients with recurrent compared to de novo NAFLD (bridging fibrosis at 5 years 71% vs. 12.5%) possibly due to the longer exposure to metabolic risk factors. It is noteworthy that steatosis resolved in 22% of patients with de novo vs. none with recurrent NAFLD [72]. In a retrospective cohort study of 588 LT recipients, allograft steatosis developed in 43% of recipients and was more common in those with pre-existing NAFLD (78% vs. 45% at 10 years) [73]. Importantly, NASH but not NAFLD was associated with CVS events. Similarly, in a retrospective study of 194 patients, histologically proven NASH was an independent predictor of long-term mortality [74].

Management

There is no licensed pharmacological treatment for NAFLD or NASH at the moment [75], however there are several ongoing phase II and III randomized controlled trials, with expected results within the next two years [76]. Vitamin E and pioglitazone that might have a role in the NASH population, have not been tested in the post-LT setting and cannot be recommended [77]. Weight loss through diet and lifestyle changes is associated with resolution of NASH and improvement in fibrosis and should be pursued in overweigh LT recipients, with a target of 7-10% reduction [78]. Tight control of the metabolic comorbidities reduces the CVS risk and might improve NAFLD [76].

Conclusions

Cardiovascular events are an important cause of morbidity and mortality post LT, and their incidence is projected to rise further due to the growing prevalence of NASH as

a transplant indication and the ageing LT population. There is a lack of studies and data in the management of metabolic comorbidities specifically in the LT population and it is still unclear if aggressive management of such comorbidities in the post-LT setting improves outcomes. Transplant physicians often overlook the treatment of metabolic comorbidities as they mainly focus on liver function and immunosuppression issues. Primary care physicians are often unfamiliar with drug-to-drug interactions and not confident to manage metabolic comorbidities in LT recipients. Therefore, the management of such conditions is often suboptimal [66] and this can impact on the mid- and long-term outcome of these patients. Although treatment data specifically for the LT population are scarce, there is detailed guidance from learned societies that mostly mirrors the guidance for patients in the general population at increased cardiovascular risk [1,47,54]. The routine use of cardiovascular comorbidity checklists could potentially help in the management of post LT patients as well as the establishment of multidisciplinary or nurse-led clinics to implement them, however their utility would need to be prospectively tested. Ultimately, there needs to be a paradigm shift in the quality measures of transplant programs, which should also incorporate five and even ten-year survival post LT alongside the existing one-year survival.

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Table 1. Overview of studies reporting late cardiovascular mortality (>12 months) in liver-transplant recipients.

Author	Country	Patients, n	Follow-up, years	Year of LT	Overall Mortality	CVS Mortality	Predictors of CVS events
Albeldawi[14]	US	775	3.3	1996-2008	NR	10.7% at maximum follow-up	Age, diabetes, hypertension, MMF, male sex
Borg[79]	Netherlands	311	6.2	1979-2001	17%	21% at maximum follow-up (excluding deaths up to 1 year post LT)	Renal failure and age associated with CVS mortality
Di Maira[80]	Spain	250	5.6	2006-2008	1-year: 15.2% 3-year: 22% 5-year: 26%	8% at maximum follow-up	eGFR, Framingham risk score
Gerson[81]	UK	4,483	9.6	1994-2007	14.8%	8.7% at maximum follow-up (excluding deaths up to 1 year post LT)	NR
Nicolau-Raducu[82]	US	389	3.4	2008-2011	27%	21% at maximum follow-up (excluding deaths up to 1 year post LT)	NR

Rabkin[83]	US	459	8.6	1991-2000	24.6%	10% at maximum follow-up (excluding deaths up to 1 year post LT)	NR
Vogt[84]	US	433	5.6	1984-2001	5-year mortality: 24% 10-year mortality: 35% for those who survived 1-year post LT	20% at maximum follow-up (excluding deaths up to 1 year post LT)	NR
Watt[2]	US	798	12.6	1990-1994	40.9%	11% at maximum follow-up (excluding deaths up to 1 year post LT)	Age, cryptogenic cirrhosis pre-LT, alcoholic liver disease pre-LT

Abbreviations: NR: not reported, eGFR: glomerular filtration rate, MMF: mycophenolate mofetil, [2] LT: liver transplantation

Table 2. Overview of studies reporting on the impact of diabetes on post liver transplantation mortality.

Author	Country	Patients, n	Year of LT	Diabetes, n (%)	Predictors of PLTDM	Mortality in diabetic vs. non-diabetic patients
Aravinthan[85]	Canada	2,209	1990-2015	Pre-LT 298 (13%) New onset 362 (16%)	NASH, use of Tacrolimus or Sirolimus	Overall mortality 35% No impaired survival in patients with pre-LT or new onset diabetes.
Liu[37]	Taiwan	2248	1998-2012	New onset 189 (8.4%)	Alcoholic hepatitis, severity of pre-LT liver disease	12.7% vs. 14.6% at maximum follow-up (P=NS)
Lv[39]	China	438	2001-2008	New onset 140 (32%)	Pre-operative blood glucose, donor liver	Mean survival 4.2 vs. 6.1 years (P<0.001)

					steatosis, no IL-2R antagonist	
Moon[38]	US	778	1996-2004	Pre-LT 159 (20.4%) New onset 284 (36.5%)	NR	31% vs. 22% at 10 years (P=0.012)
Roccaro[41]	US	994	2003-2013	Pre-LT 243 (24%) New onset 224 (23%)	African-America race, HCV, NASH, MELD pre-LT, year of LT	Overall mortality 27% Pre-LT diabetes and new onset diabetes independently associated with mortality (HR 1.61 for both)
Younossi[40]	US	85,194	1994-2013	Pre-LT 8,238 (11.2%) New onset 21,274 (29.7%)		Overall mortality 29.4% Pre-LT diabetes and new onset diabetes

						independently associated with mortality (aHR 1.21 and 1.06 respectively)

Abbreviations: LT: liver transplantation, PLTDM: post liver-transplant diabetes mellitus. IL-2R: interleukin-2 receptor, aHR: adjusted hazards ratio, MELD: Model for End Stage Liver Disease, NASH: Non-alcoholic steatohepatitis.

Figure 1. Effects of immunosuppressive medication on metabolic syndrome components.

Figure 2. Management principles of type II diabetes in liver transplant recipients

Abbreviations: LT: liver transplant, PLTDM: post liver transplant diabetes mellitus, SLGT2: sodium-glucose co-transporter 2 inhibitors

Figure 3. Stepwise management of dyslipidemia in liver transplant recipients

Abbreviations: IS: immunosuppression, CYA: cyclosporine, TAC: tacrolimus, MTORi: mammalian target of rapamycin inhibitors

Figure 4. Stepwise management of arterial hypertension in liver transplant recipients

Abbreviations: ACE: angiotensin converting enzyme, ARB: angiotensin II receptor blockers, CKD: chronic kidney disease, DM: diabetes mellitus