Annals of Gastroenterology (2015) **28,** 182-192

Metabolic and cardiovascular complications in the liver transplant recipient

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Abstract

Metabolic syndrome (MS) is an established risk factor for atherosclerosis and cardiovascular disease that affects 20-30% of the adult population in the western world, correlating with increased incidence of cardiovascular disease. Survival following liver transplantation (LT) has been steadily improving over the last 2 decades, with graft loss becoming a relatively rare cause of morbidity and mortality post LT. The improvement in short-term survival following LT has resulted in an increased incidence of metabolic and cardiovascular complications, which affect the mid- and long term survival. Patients following LT typically gain weight and might develop diabetes, hypertension and dyslipidemia as a consequence of their immunosuppressive therapy and their lifestyle. In this paper we review the prevalence of metabolic and cardiovascular complications following LT, their impact on post-transplant morbidity and mortality and their optimal management.

Keywords Liver transplantation, metabolic syndrome, cardiovascular disease, epidemiology, risk factors, morbidity, mortality, NAFLD, NASH, hypertension, obesity, dyslipidemia, diabetes mellitus

Ann Gastroenterol 2015; 28 (2): 182-192

Introduction

Metabolic syndrome (MS) comprises several metabolic disorders including visceral obesity, diabetes mellitus (DM), dyslipidemia and hypertension (Table 1). It is an established risk factor for atherosclerosis and cardiovascular (CV) disease (CVD) [1-4] and is associated with nonalcoholic fatty liver disease (NAFLD), gallstones, obstructive sleep apnea, gout, depression, musculoskeletal diseases, and polycystic ovary syndrome [3].

MS has 3 potential etiologies, namely insulin resistance [5-7], obesity and disorders of adipose tissue [8], and a constellation of independent factors that mediate its specific components (e.g., molecules of hepatic, vascular, and immunologic origin) [9,10]. Additional factors such as aging, pro-inflammatory states and hormonal changes have also been implicated as contributors.

In the Western world dramatic changes in lifestyle and diet are fueling a persistent and sustained increase in the prevalence of MS. It is currently estimated to affect 20-30% of the adult population [11]. Its increasing prevalence correlates with an increasing incidence of CVD; the risk of atherosclerotic CVD accompanying MS is approximately double compared with the absence of the syndrome [3]. MS confers a risk independent of traditional CVD risk factors (relative risk [RR] 1.54) indicating that the associated CVD risk cannot be explained entirely by its individual components [12]. In a recent meta-analysis of 43 studies with 172,573 individuals, MS was shown to convey a RR for CVD events and death of 1.78 [2].

NAFLD is the hepatic manifestation of the MS and the leading cause of abnormal liver function tests in the Western world [13]. NAFLD occurs in subjects of all ages, even in patients with a normal body weight [14]. In MS, fatty liver infiltration causes a spectrum of disease ranging from simple steatosis, to nonalcoholic steatohepatitis (NASH), fibrosis and ultimately cirrhosis. Once cirrhosis is established, steatosis often disappears and many patients with NASH are labeled as having cryptogenic cirrhosis [15].

Liver transplantation (LT) is the most effective treatment for patients with decompensated chronic liver disease and significantly improves both quality of life and survival. In the pre-LT era, patients with advanced liver disease would die within months [16], whereas transplanted patients now have 1- and 5-year survival of 90% and 80% respectively [17,18]. Post-LT survival has been steadily improving over the last 2 decades. This is likely due to a combination of greater surgical expertise reducing technical complications, better selection of patients reducing peri-operative deaths, and perhaps most impressive improvement in the efficacy and tolerability of post-transplant immunosuppressive therapy (IS) reducing graft

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Conflict of Interest: None

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Received 15 September 2014; accepted 29 October 2014

loss from acute and chronic rejection [19]. These advances have resulted in graft loss becoming a relatively rare cause of morbidity and mortality 1 year after LT.

Non-liver causes of death following LT are increasing with malignancy (22%), CVD (11%), infection (9%), and renal failure (6%) becoming leading causes of mortality one year post LT (Fig. 1) [20]. MS is a common thread of risk for each of these making the prevalence, etiology, prevention, and management of post-transplant MS (PTMS) of increasing interest and importance to the transplant community.

LT does not have an impact on MS and patients transplanted for NAFLD with an underlying MS remain at risk of its sequalae [21,22]. Patients transplanted for etiologies other than NASH typically gain weight and often develop DM, hypertension and dyslipidemia as a consequence of IS therapy and a resultant MS. Therefore, all transplanted patients have an increased risk of non-liver-related morbidity and mortality owing to MS.

With the increasing prevalence of MS and its sequalae having an impact on morbidity and mortality post LT, physicians need to be aware of the syndrome and its management. In this paper, we review the prevalence of metabolic and CV complications following LT, their impact on post-transplant morbidity and mortality, and their optimal management.

Post-LT development of obesity

The World Health Organization (WHO) defines obesity as a body mass index (BMI) >30 kg/m^2 and morbid obesity as a BMI >35 kg/m^2. The increasing average BMI of the general population is reflected in patients being assessed for LT, as 15-30% of patients listed for LT have a BMI >30 kg/m^2 [23]. Moreover, cirrhosis secondary to NAFLD is rapidly becoming a leading indication for LT. In patients with cirrhosis and fluid retention, weight and subsequently BMI can be inaccurate; the estimation of dry weight by subtracting the amount of ascites from the total body weight is a more reliable estimate.

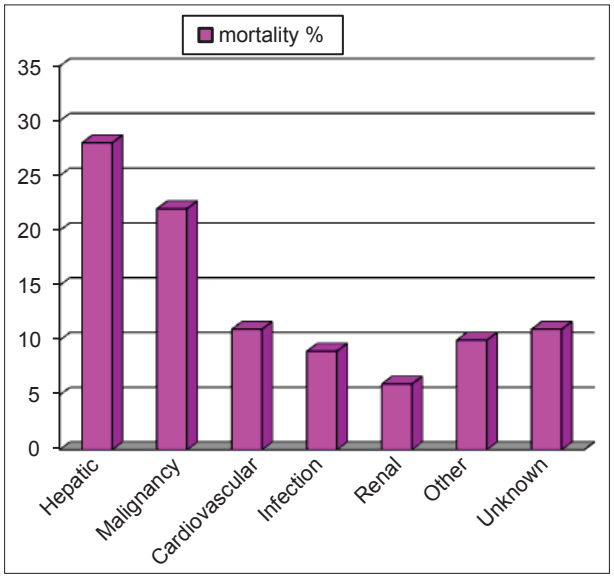

Figure 1 Etiology of death in liver transplant recipients 1 year post transplant [20]

Obese patients listed for LT should be advised and helped reduce their BMI, as this is associated with worse peri- and post-operative outcomes, including prolonged intensive therapy unit (ITU) and hospital stay, prolonged wound healing, and higher infection rates [24].

In the analysis of the UNOS database (1988-1996) by Nair *et al*, 7% of LT recipients were severely or morbidly obese (BMI ≥35 kg/m^2); this was associated with an increased prevalence of adverse CV events leading to a 5-year mortality significantly higher in the severely obese (51%) and morbidly obese (58%) groups compared with the non-obese group (44%) [25]. This effect is more striking in the presence of DM [26].

Following LT, weight gain is the norm and is due to multiple factors such as the reversal of cirrhosis and its associated catabolic state, increased appetite due to the absence of chronic disease, and the effect of steroids. With few exceptions, patients that are overweight or obese prior to transplant will remain so after, while one-third of patients of normal weight pre-LT become obese post-transplant [23,28]. Obesity rates post-LT are 20-68% and are highest in those patients who are transplanted over the age of 50, those who are obese prior to LT and those on high-dose steroids.

In the 1st post-LT year, weight gain is frequently overlooked due to the focus of physicians on issues such as graft function, infection risks and renal function. The potential impact of post-LT weight gain includes increased risk of DM, and MS and its associated complications, such as CVD, renal disease, and *de novo* NASH in the allograft. In light of the above, patient education regarding weight control via diet and exercise should begin during the LT assessment process and reinforced throughout the post-LT period along with rapid tapering of corticosteroids in obese patients, and consideration to pharmacotherapy where the above interventions are unsuccessful.

Post-transplant development of DM

New-onset DM (NODM) is increasingly recognized as a complication of organ transplantation. NODM results in increased susceptibility to infectious and CV complications, may lead to diminished long-term graft survival, and has a major impact on the quality of life and survival [29-32].

The development of NODM is multi-factorial, however studies have shown an increased incidence in patients transplanted for HCV (OR 5.8, 95%CI 1.9-17.9), presence of DM, pre LT (OR 24.4, 95%CI 8.2-73.2), male gender (OR 3.57, 95%CI 1.2-10) [33-36].

The choice and dose of immunosuppressive medications is the major modifiable risk factor for NODM post LT. Corticosteroids have a well-known diabetogenic effect. The main mechanism underlying this effect is development of insulin resistance along with increased gluconeogenesis [37]. Although steroids are required in high doses for the first few weeks after LT, they should be rapidly tapered and discontinued

unless otherwise needed to prevent disease recurrence or rejection. Calcineurin inhibitors (CNI) are also associated with NODM post-LT, as they directly damage pancreatic islet cells. The risk of NODM is significantly higher with tacrolimus (TAC) than cyclosporine A (CSA). Individualizing the immunosuppression regimen in the light of a patient's risk profile would seem a prudent, as opposed to a "one size fits all" strategy. There is strong evidence to support that CNI minimization improves long-term outcomes with no adverse effects to graft survival [38-40].

In a meta-analysis including 3043 transplant recipients [41], NODM was reported in 13.4% of patients after solid organ transplantation, with a higher incidence in patients receiving immunosuppressive regimen of TAC than CSA (16.6% vs. 9.8%). This trend was consistent across patients that received renal, liver, heart and lung transplants. Sixteen studies with 1106 patients have reported the incidence of NODM in patients undergoing LT. The mean incidence of NODM across the 14 TAC-based studies was 18.2%, compared with 7.7% across the 12 CSA-based studies, with no evident impact of concomitant therapy in the incidence of NODM in either treatment group. The average NODM rates in the 7 prospective randomized trials included in the meta-analysis (338 LT recipients) were 15.9% for TAC-treated patients and 4.9% for CSA-treated patients.

There is convincing evidence from the non-LT population that tight glycemic control significantly reduces morbidity and mortality in patients with either type 1 or type 2 DM [42,43]. Although this approach has not been specifically tested in the LT population, it is reasonable to assume that similar benefits would be derived from effective management of glucose levels [44]. Little information exists on the use of anti-diabetic compounds in patients who undergo transplantation, and no comparative trials have been conducted [45-48].

In view of the current absence of precise recommendations, clinical judgement should be used when selecting anti-diabetic therapy, based on the medical history, severity of glucose deregulation, and properties of the anti-diabetic agents [47].

Post-transplant development of systemic hypertension

Arterial hypertension is an established risk factor for CV-related morbidity and mortality in the general population [49]. Although it affects a minority of patients prior to LT, its prevalence increases to 70% post LT [50]. Immunosuppressive medication is largely responsible for the development of hypertension post LT, with CNI and corticosteroids being the most strongly implicated. The primary mechanism of CNI induced hypertension is through widespread arterial vasoconstriction that results in increased systemic vascular resistance. The effect of vasoconstriction in the kidney is to promote sodium reabsorption and volume expansion.

Several reports have suggested that the incidence of hypertension in patients treated with TAC is lower than in patients treated with CSA within the first 1-2 years after kidney transplantation [51-53], up to 3 years after heart transplantation [54], and during the first year after LT [55-57]. Canzanello *et al* demonstrated that at 24 months post-LT, the prevalence of hypertension in the CSA and TAC groups were 82% and 64%, respectively. For those patients who were hypertensive by 24 months, the onset of hypertension was significantly delayed in the TAC group compared with the CSA group: 40% versus 71% and 73% versus 93% at 1 and 12 months, respectively. Within the TAC group, hypertensive patients had significantly lower glomerular filtration rates compared with normotensive patients, 74±12 versus 47±6 mL/min respectively. These results indicate that, compared with CSA, the onset of hypertension after LT is delayed and less prevalent with TAC [58].

The general principles for treating non-LT patients with essential hypertension apply to transplant recipients as well, however the choice of antihypertensive drugs in patients treated with CNI must be undertaken with particular attention to drug interactions.

Dihydropyridine calcium channel blocking drugs, such as amlodipine or felodipine, are a good first line choice since part of the mechanism of hypertension is due to renal arteriolar vasoconstriction. They act most potently on vascular smooth muscle to reduce systemic vascular resistance, have minimal interactions with CNIs and limited side effects. They appear to improve renal blood flow, although this has not been apparent during long-term therapy in LT recipients [59]. β-Blockers are widely used and may facilitate the return of high cardiac outputs toward normal levels. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers, which block the renin-angiotensin system, are of limited value when used as monotherapy for hypertensive patients early after LT as plasma renin activity is low during this period. Furthermore, ACE inhibitors and angiotensin-2 blockers may magnify the collateral effects of the CNI treatment such as hyperkalemia and metabolic acidosis. They can be used effectively during later periods after transplantation when the activation of the renin-angiotensin system becomes more evident. The use of diuretic agents in post-transplantation hypertension is debatable. The tendency of diuretics to increase serum creatinine levels, primarily by augmenting volume contraction in the face of CNI-mediated vasoconstriction in the kidney, has led to concerns regarding the stability of renal function.

Post-transplant development of dyslipidemia

Dyslipidemia occurs in all solid organ transplantations, but prevalence rates vary with the organ, being greatest for heart transplant recipients (60-80%) and least for liver recipients (45-69%) [60,61].

Pre-transplant dyslipidemia usually persists post-transplant and requires continuation of medical treatment. Patients with end-stage liver disease (ESLD) often have low serum cholesterol levels because of impaired hepatic synthesis and esterification [60,62,63], however patients with cholestatic liver disease may have increased serum cholesterol if the liver synthetic function is reasonably preserved. Serum triglycerides

may be elevated both in obstructive jaundice and, less often, in parenchymal liver disease. Using the MS definition criteria (Table 1), the majority of ESLD patients have dyslipidemia based on low HDL-C levels due to the primary liver failure.

The recently published 2013 ACC/AHA Guideline changes the treatment paradigm for dyslipidemia. The new guideline no longer targets LDL-C levels but focuses on treating cholesterol to reduce atherosclerotic CVD (ASCVD) risk. Strong randomized control trial evidence supports a net benefit from statin therapy in individuals with clinical ASCVD (secondary prevention), and in three groups of individuals without clinical ASCVD (primary prevention), namely primary elevation of LDL-C >190 mg/dL; DM aged 40-75 years with LDL-C 70-189 mg/dL and without clinical ASCVD; without clinical ASCVD or DM with LDL-C 70-189 mg/dL and estimated 10-year ASCVD risk >7.5%. Statin therapy may be also considered in those who do not meet these criteria if other indications of increased ASCVD risk are present [64].

In post-transplant studies, the definition of hyperlipidemia varies widely and few use the NCEP-ATP III definitions [65]. Various individual patient risk factors along with the choice of immunosuppressive agents can influence the prevalence of post-transplant dyslipidemia. With regard to immunosuppression, CSA compared to TAC is associated with more frequent hyperlipidemia (14% versus 5%) [55,66-69] and hypertriglyceridemia (49% vs. 17%) [55]; in multiple series, changing from CSA to TAC improved hyperlipidemia [70-72]. The reason for this effect with CSA could be related to inhibition of bile salt synthesis [73]. Long-term corticosteroid use can also contribute to hyperlipidemia [74,75]. Steroid-free or sparing regimens were associated with improved lipid levels [76,77], including less hypertriglyceridemia in one [78] but not all series [79]. Sirolimus, an immunosuppressive agent used either in conjunction or instead of a CNI, is associated with high rates of dyslipidemia (up to 55%) [80]. This might result from changes in insulin signaling pathways resulting in excess triglyceride production and secretion [81]. Rates of dyslipidemia were lower when sirolimus was combined with TAC compared to CSA [82]. There is similar evidence of a synergistic hyperlipidemic effect between CSA and everolimus [83].

Table 1 Criteria for the clinical diagnosis of metabolic syndrome [65]

Measure (any 3 of 5 constitute diagnosis of metabolic syndrome)	Categorical cut-off points
Increased waist circumference	≥102 cm (≥40 inches) in men ≥ 88 cm (≥35 inches) in women
Elevated serum triglycerides	≥150 mg/dL (1.7 mmol/L) or On drug treatment for elevated triglycerides
Reduced serum HDL-C	<40 mg/dL (1.03 mmol/L) in men <50 mg/dL (1.3 mmol/L) in women or On drug treatment for reduced HDL-C
Elevated blood pressure	>130 mmHg systolic blood pressure or >85 mmHg diastolic blood pressure or On antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	>100 mg/dL or On drug treatment for elevated Glucose

The observation that TAC is less likely to cause hypercholesterolemia than CSA has led several groups to propose conversion of liver transplant recipients to TAC-based immunosuppressive therapy from CSA-based therapy in the setting of persistent hypercholesterolemia, with some evidence of efficacy [84].

Post-transplant dyslipidemia is generally resistant to dietary interventions. For hypercholesterolemia post-LT a good first-line approach is statin treatment. Statins have been extensively used in solid organ transplant recipients for decades and are safe, efficacious and well tolerated [85]. Pravastatin is the most studied and used statin in post-transplant patients. It is not metabolized via the P450 enzyme system so has no interaction with IS therapy; atorvastatin, simvastatin, lovastatin, cerivastatin and fluvastatin however have also been frequently used in transplanted patients with little documented ill effect.

Hypertriglyceridemia with normal cholesterol levels is also common post LT. Hypertriglyceridemia responds to fish oil (ω-3) and this could be the preferred regimen since very few side effects and drug interactions can be expected [86]. Fish oil does not significantly affect CSA (a highly lipophilic agent) levels [87], and is not known to affect TAC metabolism. It also has anti-inflammatory and anti-proliferative properties, and improves hepatic steatosis [88].

Alternative agents include the fibric acid derivatives (gemfibrozil, clofibrate, fenofibrate), which are generally well tolerated. Fibrates are highly protein bound and are metabolized by cytochrome P450, with some evidence of a mild effect of increasing CNI serum levels [87].

Post-transplant development of NAFLD

The development of *de novo* NAFLD post LT is due to the previously discussed high incidence of its risk factors post LT including obesity, hyperlipidemia, DM, hypertension, and MS. A single-center retrospective report of 68 transplant recipients without prior fatty liver described *de novo* NAFLD in 18% and *de novo* NASH in 9% post LT. The regression model indicated that the use of ACE inhibitors was associated with a reduced risk of post-LT NAFLD (OR 0.09, 95%CI 0.010-0.92), while >10% increase in BMI was associated with a higher risk of developing NAFLD (OR 19.38, 95%CI 3.50-107.40) [89]. Although fatty liver and steatohepatitis are widely accepted to re-occur after LT, Contos *et al* demonstrated that none of the 30 long-term survivors (up to 5 years) developed graft dysfunction or graft loss caused by recurrence of NAFLD, and the morbidity and mortality is usually due to non-liver related

causes, in particular CVD [90]. Further studies to define the long-term liver (>10 years) outcomes of such patients and methods to prevent recurrent fatty liver disease are needed.

Predictors of post-transplant MS

Higher age at transplantation, an increase in BMI post-LT, pre-LT DM, history of smoking, the immunosuppressant regimen used (CSA), and the indication for LT (hepatitis C, alcohol, or cryptogenic cirrhosis) are the risk factors most consistently associated with PTMS [23,91,92]. Anastácio *et al* assessed the prevalence and the predictors of PTMS in a cross-sectional study of 184 patients. MS was present in 39-50% post-LT depending on the criteria used. Predictors of PTMS were older age, shorter time since transplantation, alcohol abuse etiology, excessive weight at LT, physical activity reduction after LT and low intake of calcium, potassium, fiber and folic acid [93]. It could not be assessed if these factors were present before the onset of liver impairment or whether they were a consequence of it. Laryea *et al* [92] also found significantly higher pre-LT BMI, triglycerides, and abnormal HDL-C among patients with MS compared to those who did not develop PTMS.

The choice of immunosuppression has been implicated in the development of various components of MS as discussed above. However, given the superiority of TAC over CSA in terms of both graft and patient survival, no changes in the primary immunosuppressive regimen can be justified on this basis [94]. The predictors and risk factors of PTMS and for the individual components of the syndrome identified from the published data are shown in Table 2.

Post-transplant renal dysfunction

Both acute and chronic kidney disease occur frequently in liver transplant recipients. In its purest form, hepatorenal syndrome represents a functional form of renal dysfunction, theoretically reversible [95]. However, most patients with renal dysfunction at the time of transplant do not recover normal function after LT [96]. A significant proportion (5-50%) of recipients develop acute renal failure in the immediate postoperative period, with more frequent occurrence in those who have renal impairment at the time of LT [97-100].

In a retrospective study of 202 patients, pre-transplant renal impairment was an independent predictor of post-transplant cardiac events (HR 2.19) and reduced cardiac event-free survival (HR 2.27) [101]. In a study of 798 LT recipients, CV system (CVS)-related deaths >1 year post-LT were significantly associated with renal insufficiency pre- or post-LT (HR 3.59) [20]. About 10-20% of long-term survivors after LT develop permanent renal dysfunction or failure, attributed to a number of factors, including the use of CNIs [103,104]. In a retrospective study of 54 post-liver transplant patients, low eGFR predicted patients with high Framingham CV risk score, suggesting that liver recipients with low eGFR should undergo close management of CV risk factors [105]. DM, coronary artery disease, and primary graft non-function predicted the development of severe renal failure in a retrospective study of 172 patients [106]. A meta-analysis of randomized trials directly comparing TAC trough concentrations showed that "reduced" TAC trough concentrations (<10 ng/mL) within the first month after LT were associated with less severe renal impairment at 1 year (RR 0.51), with no significant influence on acute rejection (RR 0.92) compared to "conventional" TAC trough levels (>10 ng/mL) [38]. In a study that evaluated early TAC exposure (<15 days) in relation to long-term outcomes in 493 consecutive LT patients, mean TAC of 7-10 ng/mL were associated with reduced risk of graft loss (RR 0.46) compared to the recommended levels of 10-15 ng/mL. Lower TAC levels did not significantly influence chronic rejection or chronic renal impairment [39]. The relevance of renal failure among liver transplant recipients and the impact that this frequent complication has on subsequent management necessitates further studies on modifiable risk factors such as the dose and choice of immunosuppression.

Post-transplant development of CV events

CV risk of LT recipients differs substantially from kidney and heart recipients. The primary difference is related to hemodynamic and metabolic changes associated with chronic liver disease, which lead to peripheral vasodilatation, low arterial blood pressure, and reduced serum cholesterol levels [109,110]. A number of post-mortem studies in cirrhotic patients have shown little pathologic evidence of atherosclerosis and a decreased incidence of vascular diseases [111,112].

Nevertheless, CVD is one of the leading causes of morbidity and mortality in LT patients. It is the 3rd most common late (after 1 year) cause of death, accounting for 12–16% of deaths (primary or major contributing causes) in the USA [20], and the 6th cause of overall mortality in the UK [113].

It is estimated that 27% of patients considered for LT have unknown underlying coronary artery disease [114,115]. The purpose of cardiac evaluation pre-LT is to assess perioperative risk and to exclude concomitant cardiopulmonary disorders that would preclude a good long-term outcome. Severe cardiac disease with unacceptable perioperative risk is a contraindication to LT.

Patients routinely undergo pre-transplant CVS assessment for risk stratification which includes: full history and examination, witnessed climb of 2 flights of stairs with pre- and post-O_2 saturations, 12 lead ECG, and transthoracic echo with assessment of left ventricular, right ventricular and valvular function (with an estimation of systolic pulmonary artery pressure). Further investigation (right-side heart angiography, dobutamine stress echo, cardiac CT angiography) are based on medical history and findings from the initial screening tests [116]. Coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) should be considered in LT candidates

Table 2 Studies that evaluate independent predictors and risk factors of post-transplant metabolic syndrome and its individual components

Author	N. of patients	Post LT development of MS or individual component of PTMS	Prevalence	Independent predictors	Risk factors for PTMS
Bigam *et al* [34]	278	DM	DM 41% at 5-yrs in HCV group (110 pts)	Independent predictors of PTDM: HCV, pre-LT diabetes, male sex	
Baid *et al* [33]	176	DM	DM 64% in HCV+ vs. 28% HCV-	HCV infection (HR 2.5, 95%CI 1.45-4.36)	
Tueche *et al* [36]	143	DM	DM 31% (18% de novo DM)	Independent predictors of PTDM: pre-LT DM, alcoholic cirrhosis and male sex	
Bianchi *et al* [23]	296	MS, DM	44.5% MS, 41% DM	Independent predictors of PTMS: pre-LT BMI, BMI increase, and pre-LT DM	
Everhart *et al* [28]	774	Obesity	21.6%	Independent predictors of post LT obesity: higher cumulative prednisone dose in the 2nd year, high recipient BMI, high donor BMI, and being married	
Trail *et al* [35]	497	DM	5% (within 1 month of discharge)	Independent predictors of PTDM: higher pre-LT fasting blood glucose, lower BMI after LT, CSA rather than OKT3 induction	
Canzanello *et al* [55]	63	Hypertension, obesity, dyslipidemia		Independent predictor: CSA (compared to TAC)	
Gisbert *et al* [60]	85	Dyslipidemia	Hyperlipidemia 66%; isolated high TGL levels, 47%; both elevated CHOL and TGL levels 12%; isolated elevated CHOL levels 7%	Independent predictor of dyslipidemia: pre-LT total CHOL >141 mg/dL	Risk factors: pre-LT hepatocellular liver disease and post-LT renal dysfunction
Lim *et al* [128]	30	*De novo* NAFLD	40%	None	Risk factors: higher pre-LT BMI and higher BMI at last biopsy
Seo *et al* [89]	68	*De novo* NAFLD, *de novo* NASH	18% *de novo* NAFLD, 9% *de novo* NASH	Independent predictors of post-LT NAFLD: increase in BMI >10% after LT, use of ACE-I	
Laryea *et al* [92]	118	PTMS	58% PTMS, 61% DM, 48% dyslipidemia, 62% HT, 36% obesity	Independent predictors of PTMS: ETOH cirrhosis, cryptogenic cirrhosis, HCV infection	
Francioso *et al* [91]	75	PTMS	43% PTMS	Independent predictors: CSA, family history of CVD, age at LT time, history of smoking	
Bianchi *et al* [23]	296	PTMS	45% PTMS	Independent predictors: pre-LT BMI, BMI increase, and pre-LT DM	

DM, diabetes mellitus; PTDM, post-transplant diabetes mellitus; LT, liver transplant; HR, hazard ratio; HCV, hepatitis C virus; MS, metabolic syndrome; PTMS, post-transplant metabolic syndrome; BMI, body mass index; CSA, cyclosporine A; TAC, tacrolimus; TGL, triglycerides; CHOL, cholesterol; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; ACE-I, angiotensin-converting enzyme inhibitors; HT, hypertension; CVD, cardiovascular disease; ETOH, ethanol

with obstructive coronary heart disease (CHD) if the extent contraindicates LT [117].

It is unclear to what extent pre-transplant cardiac abnormalities affect long-term outcome after LT. In a case-control study of 42 LT recipients with known pre-LT CHD and 42 recipients without CHD, mortality rates were higher in the CHD than in the control group at 1 and 3 years although lower than previously reported in other series (at 3 years 26% vs. 50%) [118]. The overall improvement in the CVS outcomes from historical series is possibly due to better risk stratification

strategy and better management of the identified CHD (PCI, CABG). In a study of 1221 LT recipients divided in 3 sub-periods (reflecting the change in the risk stratification policy) the rate of cardiac catheterization during the pre-transplant assessment increased during the 3 time periods, as did the rate of PCI. All cause mortality decreased over time, as did the myocardial infarction (MI) rate [119].

LT recipients have a high prevalence of risk factors for CVD, exceeding that of the general population and thus have a higher predicted risk of developing CHD. Despite this, in a retrospective study of 181 consecutive adult liver transplant recipients, there were no deaths from CHD or stroke during the 54 months study period. The Framingham coronary risk equations provide an estimate of the 10-year risk of developing CHD. The 10-year probability for CHD (using the Framingham risk score) is higher in LT recipients (11%) than the general population (7%). Neal *et al* showed that the incidence ratios for MI and stroke were not significantly different in LT recipients compared with a matched non-transplant population [120]. Johnston *et al* assessed 110 consecutive liver recipients (median follow-up 3.9 years) for CV risk factors and reported a relative risk of ischemic cardiac events of 3.07 and a RR for CV deaths of 2.56 in allograft recipients compared to an age-matched population without transplants [121]. Vanwagner *et al* in a retrospective cohort study of 242 patients with >12 months follow up compared the incidence of CV events between patients transplanted for NASH and alcohol-induced cirrhosis. They demonstrated that patients with NASH have an increased risk of post-transplant CV events when compared to patients transplanted for alcohol-induced liver disease, even after controlling for traditional preoperative cardiac risk factors (26% vs. 8%; OR 4.12, 95%CI 1.91-8.90) [122]. In a cohort of 252 transplant recipients, MS was diagnosed in 5.4% of patients before and in 51.9% after transplantation. They split the cohort in 2 groups (with and without the PTMS): there was no difference between the groups in mortality or causes of death. The prevalence of major vascular events in the whole cohort increased from 2.3% before transplantation to 10.3% after but the difference was no statistically significant. The cumulative incidence of CV morbidity was statistically higher in patients with PTMS [123]. In 775 adult LT recipients, PTMS was significantly more prevalent in patients with CV events versus patients with no CV events (61.4% vs. 34.1%). The 1- and 3-year overall cumulative risks of CV events were 4.5% and 10.1% respectively [124]. These studies are summarized in Table 3.

Therefore, it is important to promptly identify and treat all the parameters of the MS that contribute to the development of CVD. The correct management and timely treatment may reduce significantly the risk of major CV events.

Predictors of CV events post LT

Albeldawi *et al* determined the cumulative risk of CV events after LT and analyzed the predictive risk factors. Independent predictors of CV events were older age at transplantation (OR 1.2, 95%CI 1.1-1.3), male sex (OR 2.0 95%CI=1.2-3.3) NODM (OR 2.0, 95%CI 1.3-3.3) post-transplant hypertension (OR 1.8, 95%CI=1.1-3.0), and use of mycophenolate mofetil (OR 2.0, 95%CI 1.3-3.2). They showed that patients with post-transplant hypertension and DM, i.e. with potentially modifiable risk factors, are approximately twice as likely to experience a CV event [124]. Regarding the etiology of the ESLD, compared with all other etiologies, patients undergoing transplantation for NASH had a significantly higher risk of a CV event 1 and 3 years after transplantation (15.3% and 19.3), whereas patients undergoing transplantation for primary biliary cirrhosis or primary sclerosing cholangitis had a significantly lower risk of a CV event 1 and 3 years after transplantation (0% and 4.5%) [124].

In the paper of Dec *et al*, pre-existing cardiac disease and older age at transplantation were the only independent predictors of major complications. Major cardiac events were significantly associated with a lower 5-year survival rate (event: 32% vs. event free: 52%). The frequency of major intraoperative (21% vs. 2%) and post operative (57% vs. 17%) cardiac complications was significantly higher for recipients with known heart disease compared to those without pre-existing heart disease [125]. Again the importance of recognizing and treating the risk factors is crucial to avoid CV complications [126]. It may therefore be important to identify and stratify high-risk patients for CVD prior to LT and offer targeted post-LT interventions.

Concluding remarks

At present, there are no established guidelines in the treatment and prevention of CV profile and metabolic complications in liver transplant recipients. We reviewed the prevalence and incidence of PTMS and its individual components in this population and the rate of CVS events affecting morbidity and mortality. We presented an overall view on the relationship between these and other modifiable factors such as immunosuppression and the current evidence for treating the individual components of the PTMS in this population. We further highlighted the need of high-quality studies to confirm these relationships and the need for practice guidelines to deal with this growing problem.

MS is a cluster of modifiable factors where early interventions can potentially prevent more deleterious consequences. The LT recipients should be considered as a high CV risk population independently of the cause of the liver disease, and the British Transplant Society recommendations on NASH-transplanted patients should be followed; these suggest an intensive control of glucose serum levels, early steroid withdrawal and low doses of CNI in the post-transplant period [127].

In conclusion, liver transplant recipients and especially those with PTMS are at high risk for CVS events. However, the literature is limited and lacks high-quality studies. Future prospective studies are necessary to accurately document the prevalence and incidence of these complications and determine whether aggressive risk reduction strategies can attenuate the increased CVS risk seen in this population.

Table 3 Studies that evaluate the post-transplant development of cardiovascular events

Author	N. patients	Follow up	Year of LT	Aim of the study	N. events	Main conclusions
Neal *et al* [120]	181	54 mths	1994-1999	10-year risk of CHD	7 (> 1 yr post LT)	Risk higher in LT recipients (11%) than the general population (7%)
Johnston *et al* [121]	110	3.9 yrs		Risk factors for IHD in LT recipients	56 fatal 18	Median 10-year risk of IHD: 7.9% ischemic cardiac events: RR 3.07; cardiovascular deaths: RR 2.56 (in allograft recipients compared to selected non-LT population)
Vanwagner *et al* [122]	242	>12 mths	1993-2010	Incidence of CVS events in NASH and ETOH cirrhosis	NASH 57 ETOH 65	NASH patients were more likely to have a CVS event <1 year after LT, compared to ETOH patients, (26% versus 8% OR 4.12)
Laish *et al* [123]	252	6.2 yrs		Prevalence and risk factors of PTMS	23	PTMS in 51.9% Independent predictors of PTMS: OR 1.04, 95%CI 1.01-1.07), pre-LT NAFLD (OR 3.4, 95%CI 1.17-9.95), BMI (OR 1.13, 95%CI 1.04-1.23), DM (OR 5.95, 95%CI 2.16-16.39), and TGL (OR 1.01, 95%CI 1.00-1.02)
Albeldawi *et al* [124]	775	40 mths	1996 -2008	Cumulative risk of CVS events after LT and predictive risk factors for CVS events	83	Independent predictors of CVS events: older age at LT (OR 1.2), male sex (OR 2.0), PTDM (OR 2.0), post-LT HT (OR 1.8), and MMF (OR 2.0) Cumulative risk of CVD 1-yr 4.5 %; 3-yrs 10.1%

CHD, chronic heart disease; IHD, ischemic heart disease; LT, liver transplant; RR, relative risk; CVS, cardiovascular system; NASH, non-alcoholic steatohepatitis; ETOH, ethanol; PTMS, post-transplant metabolic syndrome; BMI, body mass index; DM, diabetes mellitus; TGL, triglycerides; OR, odds ratio; NAFLD, non-alcoholic fatty liver disease; HT, hypertension; PTDM, post-transplant diabetes mellitus; CVD, cardiovascular disease; MMF, mycophenolate mofetil

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