

2016 Liver Transplantation: Global view

Metabolic complications in liver transplant recipients

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Abstract

The metabolic syndrome (MS), which includes obesity,

dyslipidaemia, hypertension and hyperglycaemia according to the most widely accepted definitions now used, is one of the most common post-transplant complications, with a prevalence of 44%-58%. The MS, together with the immunosuppression, is considered the main risk factor for the development of cardiovascular disease (CVD) in transplant recipients, which in turn accounts for 19%-42% of all deaths unrelated to the graft. The presence of MS represents a relative risk for the development of CVD and death of 1.78. On the other hand, non-alcoholic fatty liver disease (NAFLD), considered as the manifestation of the MS in the liver, is now the second leading reason for liver transplantation in the United States after hepatitis C and alcohol. NAFLD has a high rate of recurrence in the liver graft and a direct relation with the worsening of other metabolic disorders, such as insulin resistance or diabetes mellitus. Consequently, it is vitally important to identify and treat as soon as possible such modifiable factors as hypertension, overweight, hyperlipidaemia or diabetes in transplanted patients to thus minimise the impact on patient survival. Additionally, steroid-free regimens are favoured, with minimal immunosuppression to limit the possible effects on the development of the MS.

Key words: Metabolic syndrome; Liver transplantation; Immunosuppressions; Risk factors; Non-alcoholic fatty liver disease

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Core tip: The metabolic syndrome is a very frequent complication after liver transplantation; indeed, over half transplant patients will eventually develop it. It is also a risk factor for the development of cardiovascular disease, one of the main causes of long-term death after transplantation. The identification and early treatment of such factors as hypertension, dyslipidaemia, obesity and diabetes is crucial to

achieve a positive impact on long-term survival of liver transplant patients.

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INTRODUCTION

The optimization over recent years of the surgical technique and immunosuppressive therapy has led to excellent survival rates after liver transplantation, reaching 90% at one year and 80% at five years^[1-3]. This greater survival has, however, been accompanied by an increase in medical complications derived from the transplant, such as the development of de novo malignancies, recurrence of the underlying disease, metabolic complications and cardiovascular diseases, which today constitute the main causes of death unrelated to the graft^[4-6]. The metabolic syndrome (MS), which includes obesity, dyslipidaemia, hypertension and hyperglycaemia according to the most widely accepted definitions now used (Table 1)^[7,8], is one of the most common post-transplant complications, with a prevalence ranging from 44%-58% in different studies^[9-13]. The MS, together with the immunosuppression, is considered the main risk factor for the development of cardiovascular disease (CVD) in transplant recipients, which in turn accounts for 19%-42% of all deaths unrelated to the graft^[10,14]. The presence of the MS represents a relative risk for the development of CVD and death of 1.78^[15]. On the other hand, non-alcoholic fatty liver disease (NAFLD), considered as the manifestation of the MS in the liver, is now the second leading reason for liver transplantation in the US after hepatitis C and alcohol^[16,17]. NAFLD has a high rate of recurrence in the liver graft and a direct relation with the worsening of other metabolic disorders, such as insulin resistance or diabetes mellitus^[18]. Consequently, it is vitally important to identify and treat as soon as possible such modifiable factors as hypertension, overweight, hyperlipidaemia or diabetes in transplanted patients to thus minimise the impact on patient survival. Additionally, steroid-free regimens are preferred, with minimal immunosuppression to limit the possible effects on the development of the MS.

COMPONENTS OF POST-LIVER TRANSPLANT METABOLIC SYNDROME

Obesity

According to the World Health Organisation obesity

Table 1 Definition of the metabolic syndrome by the National Cholesterol Education Program, Adult Treatment Panel III adapted by the National Heart, Lung and Blood Institute/American Heart Association, and the International Diabetes Federation

American heart association	International diabetes federation
At least 3 of the following criteria: Waist circumference > 88 cm for women and > 102 cm for men Fasting glucose > 100 mg/dL Systolic blood pressure > 130 mmHg and/or diastolic blood pressure > 85 mmHg HDL < 50 mg/dL for women and < 40 mg/dL for men Triglycerides > 150 mg/dL	Abdominal obesity according to gender and ethnicity specific values (i.e., waist circumference > 80 cm for women and > 90 cm for men if they are American or European) and at least 2 the following criteria: Fasting glucose > 100 mg/dL Systolic blood pressure > 130 mmHg and/or diastolic blood pressure > 85 mmHg HDL < 50 mg/dL for women and < 40 mg/dL for men Triglycerides > 150 mg/dL

HDL: High density lipoprotein.

is determined from the body mass index (BMI) as: overweight BMI: 25-29.9 kg/m², class I : 30-34.9 kg/m², class II : 35-39.9 kg/m² and class III: > 40 kg/m². Central obesity seems to confer more risk of developing the MS and CVD than peripheral obesity^[19,20].

Two considerations concerning obesity and its impact on the results of liver transplantation should be considered; the presence of obesity at the time of transplantation and the development of obesity after transplantation.

Patients who are overweight or obese before the transplant remain overweight or obese after the transplant^[9]. Over 15% of patients who are of normal weight when they receive their liver transplant become obese within one year and over 25% within 3 years^[9,21]. This can be explained by the correction of the catabolic state induced by the cirrhosis and which disappears after transplantation, as well as the increased appetite due to the absence of chronic disease and the use of drugs like steroids. Weight gain after a transplant is associated with an increased risk for the MS and its complications, such as CVD, kidney disease or NAFLD/non-alcoholic steatohepatitis (NASH) on the liver graft^[22,23].

Another point is whether the presence of overweight at the time of transplantation impacts on the short- and long-term results post-transplant. One study found that at 5 years post-transplant there was greater mortality among patients who had a BMI > 35 (class I) and BMI > 40 (class II) when they received their transplant as compared with non-obese patients, though this study did not consider the possible influence of the presence of ascites^[24]. This may, therefore, be a confounding factor, as it could have been the presence of ascites at the time of transplantation that was associated with greater post-transplant mortality and not the greater BMI of the patients. Other studies, however,

that considered obesity but corrected for ascites found no differences in survival between obese and non-obese patients, probably due to the more exhaustive control of cardiovascular risk factors undergone by obese patients during the pre-transplant period. This, therefore, highlights the need to consider the presence of ascites at the time of transplantation and its association with worse results when interpreting the impact of the BMI on post-transplant results^[25]. Even in cases of morbid obesity excellent survival rates can be achieved, both for the graft and the patient, provided there is adequate selection^[25,26]. A study by the United Network of Organ Sharing found a lower survival rate among patients with a BMI > 40 and a high MELD score^[27]. Nevertheless, adoption of vigorous measures to prevent and correct overweight must be taken from before the time of transplant.

Hypertension

Although the incidence of hypertension before transplantation is low it can still reach 40%-85% afterwards^[28-30]. The immunosuppressive drugs, either alone or combined with other factors, are the main cause of the onset of hypertension, due mainly to the renal and systemic haemodynamic changes they induce. Steroids can also induce hypertension due to their mineralocorticoid effect as well as the increase in vascular resistance and cardiac contractility. Calcineurin inhibitors, mainly cyclosporine rather than tacrolimus^[31,32], produce hypertension due to vasoconstriction of the afferent renal arteriole, which in turn induces reabsorption of sodium and water and volume expansion, with the resulting increase in blood pressure^[33]. Mammalian target of rapamycin (mTOR) inhibitors, when combined with calcineurin inhibitors, can also cause hypertension^[34].

Salt-restriction diets and the correction of other associated risk factors accompanied by physical activity are determinant for the prevention and control of hypertension. If drugs are required to control the hypertension, calcium antagonists are considered the first choice as they act directly on the pathophysiological mechanism producing hypertension. In liver transplant patients the recommended drugs are amlodipine/felodipine because they do not interfere with the hepatic metabolism of calcineurin, unlike diltiazem, verapamil or nifedipine, which interfere with the cytochrome P450 and can increase the levels of calcineurin inhibitors and thus their possible toxicity. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers have a limited effect when used as single therapy during the early post-transplant period because the activity of the plasma renin system is low during this period, so that these drugs are more useful at later stages after the transplant in which plasma renin activity is greater^[33]. Specific beta blockers are considered second-line therapy. Although the ideal blood pressure level in transplant patients has not been established, the suggested levels are < 130/80; for which up to 30%

of patients would require at least two drugs^[35,36].

New-onset diabetes

In cirrhotic patients the prevalence of glucose intolerance is 60%-80% and that of diabetes is 10%-15%. The incidence of new-onset diabetes after liver transplant (NODALT) ranges from 14%-44%, similar to that seen after other solid-organ transplants (kidney, lung, heart)^[37-39]. Pre-transplant diabetes and the BMI have been found in one study to be factors predicting the development of NODALT^[9]. NODALT is associated with a high risk of developing CVD and post-transplant mortality^[38,40].

The predominant role played by the liver in the regulation of carbohydrate, protein, lipid and drug metabolism makes it the main organ responsible for the maintenance of glucose homeostasis. This has led some authors^[41,42] to suggest that it is the liver graft itself that causes the metabolic disorders that occur after the transplant. A high incidence of NODALT has been observed in patients who receive a graft with steatosis, which is associated with insulin resistance^[37]. Likewise, grafts from donors after circulatory death have a greater incidence of NODALT, probably in relation to the damage derived from the warm ischemia on the development of insulin resistance^[43]. However, in comparison to patients who receive a liver transplant from a deceased donor, patients who receive a liver transplant from a living donor (LDLT) have a lower incidence of NODALT, probably because LDLT livers have more favourable characteristics regarding such factors as age, BMI, or liver function state^[43].

Certain genotype characteristics of the graft are also considered to be determinant in the metabolic status after liver transplantation^[44]. Various gene polymorphisms have been associated with metabolic disorders and a particular response to immunosuppressive drugs. This would explain the inter-individual, and even the intra-individual variability of certain drugs like tacrolimus concerning their pharmacokinetic characteristics or dose individualisation^[45-47].

Recurrence of the underlying liver disease can also influence the appearance of NODALT. A strong association has been found between early recurrence of hepatitis C and NODALT^[48], probably related with the damage to the beta cells induced by the hepatitis C virus (HCV). The recurrence of steatosis/steatohepatitis, which can reach around 60% in patients who receive their transplants for this reason, has also been strongly associated with the development of the MS, as well as diabetes^[49]. The association between insulin resistance and beta-cell dysfunction is well known in cirrhosis caused by such agents as alcohol, HCV, or NASH, which all damage beta cells and alter glucose regulation. This results in over 90% of cirrhotic patients becoming intolerant to glucose during the final stages of the disease, with up to 30% developing diabetes^[50,51]. Various studies suggest that liver transplantation can

resolve up to 70% of cases of pre-transplant diabetes as a result of improving insulin resistance, with the other cases that fail to resolve possibly being due to the persistence of beta-cell injury^[52-54]. Nevertheless, these patients all remain exposed to factors associated with the development of diabetes after transplantation, such as immunosuppression, the presence of HCV, or age.

The use of immunosuppressive drugs after liver transplantation plays a crucial role in NODALT. Steroids cause increased insulin resistance and reduced beta-cell secretion. Likewise, calcineurin inhibitors, mainly tacrolimus, have been considered the inducers of NODALT, principally *via* reduction of insulin secretion by the beta cells through several pathways^[55,56]. The mTORs everolimus and sirolimus have not, however, been found to be more effective than tacrolimus in post-transplant blood glucose control^[57]; with one study even finding that mTORs reduce beta-cell mass and increase insulin resistance^[58]. This has all led to current immunosuppressive regimens tending to use steroid-free protocols and minimisation of the immunosuppression.

Recent studies have also shown the role of the intestinal microbiota in the regulation of carbohydrate metabolism, as well as its influence on the pathogenesis of glucose metabolism disorders. The intestinal microbiota could be affected by liver transplantation through multiple factors, including immunosuppression. Some authors have found an association between the dysbiosis produced by tacrolimus, insulin levels and the insulin resistance index^[44].

Dyslipidaemia

Although the prevalence of dyslipidaemia in cirrhotic patients is low, due to the alteration in hepatic synthesis, it can nevertheless reach 70% in liver transplant recipients^[59-62]. As with other components of the MS, immunosuppression also plays a fundamental role in dyslipidaemia. Steroids produce hypercholesterolaemia and hypertriglyceridaemia due to stimulation of the activity of acetyl-CoA carboxylase and fatty acid synthesis^[63,64]. Calcineurin inhibitors can also induce dyslipidaemia, more often cyclosporine than tacrolimus^[65-67]. Cyclosporine produces a reduction in biliary cholesterol excretion and blocks the LDL-cholesterol receptors, with the resulting increase in blood levels^[36]. mTOR inhibitors induce hypertriglyceridaemia by increasing the activity of adipose tissue lipase and reducing lipoprotein lipase, especially if combined with cyclosporine^[68,69].

The treatment of dyslipidaemia should be oriented towards dietary measures, steroid withdrawal and minimisation of immunosuppression. The treatment of post-transplant hypercholesterolaemia generally necessitates the use of drugs since dietary measures alone are not usually effective. Statins are the drugs of choice for the treatment of hypercholesterolaemia. Pravastatin is most recommended because it is not

metabolised by the P450 cytochrome and does not interact with the immunosuppression, unlike other statins like simvastatin, fluvastatin, atorvastatin or lovastatin, though these are widely used in transplant recipients with no great problems. Special care is required with the use of ion exchange resins given their effect on the enterohepatic circulation and their repercussion on the absorption of calcineurin inhibitors, particularly cyclosporine. Hypertriglyceridaemia with normal cholesterol concentrations is also usual in liver transplant recipients. It responds best to dietary treatment, particularly the use of omega 3 fatty acids. Drug therapy with fibrates (gemfibrozil) is reserved for severe cases, and is generally well tolerated^[33,36,70].

PREDICTORS OF POST-LIVER TRANSPLANT METABOLIC SYNDROME

The prevalence of the MS after liver transplantation is around 50%, depending on the criteria used^[9]. The factors most consistently related with the risk of developing post-liver transplant MS are a high recipient age at the time of transplant, the presence of diabetes mellitus before transplantation, an increase in BMI after transplantation, smoking and the indication for the transplant (hepatitis C, alcohol or cryptogenic cirrhosis)^[9,10,13,71,72]. Some studies have found the use of cyclosporine as an immunosuppressive agent to be a risk factor. In addition, recent studies provide increasing evidence for certain gene polymorphisms as independent risk factors for the development of the MS^[39,45,73].

REPERCUSSION OF THE METABOLIC SYNDROME AFTER LIVER TRANSPLANTATION

The MS after a liver transplant can have a significant negative impact on post-transplant morbidity and mortality due to its involvement in the development of different clinical aspects directly related with post-transplant survival.

Cardiovascular risk

All the components of the MS are considered cardiovascular risk factors. The higher prevalence of the MS in liver transplant recipients is associated with a higher incidence of cardiovascular events than in the general population^[74], though the risk is lower than in recipients of a kidney or heart transplant. This is because patients with chronic liver disease experience haemodynamic and metabolic changes resulting from peripheral vasodilation, as well as having low blood pressure and cholesterol levels, which all make these patients less liable to develop cardiovascular events, unlike the situation in kidney or heart transplant recipients. In addition, liver transplant recipients require

Table 2 Recommendations and treatment aims in patients with the metabolic syndrome

Maintain a healthy lifestyle
Stop smoking
Perform regular physical exercise
Weight control
Blood pressure
< 140/90 mmHg (if there are no other associated risk factors)
< 130/80 mmHg
(if diabetes, kidney failure or established cardiovascular disease)
Fasting blood glucose levels: 80-130 mg/dL
Post-prandial levels:140-180 mg/dL
Glycated haemoglobin < 6.5%-7.0%
LDL cholesterol level
< 130 mg/dL (if no cardiovascular risk)
< 115 mg/dL (if moderate cardiovascular risk)
< 110 mg/dL (if high cardiovascular risk)

HDL: High density lipoprotein.

lower immunosuppression than patients who receive a kidney or heart transplant^[75].

The incidence of cardiovascular events after liver transplantation is around 10% at 3 years^[30]. Diabetes mellitus, hypertension and having received the transplant due to NAFLD are the risk factors most associated with cardiovascular events^[76]. It is important to note that the risk of experiencing a cardiovascular event is 4 times greater in liver-transplant recipients who have the MS than those who do not have it^[75]. Around 20% of non-hepatic causes of death in liver transplant patients are due to CVD, which are one of the main causes of death unrelated with the graft^[14,77]. Factors predicting cardiovascular events are an older recipient age (OR = 1.2), male gender (OR = 2), NODALT (OR = 2), post-transplant hypertension (OR = 1.8) and the use of mycophenolate mofetil (OR = 2)^[30].

In general, prevention measures and treatment aims in CVD based on studies in the general population are also applicable to liver transplant patients, as no specific studies have yet been undertaken of the impact of these measures in transplant recipients. These recommendations are outlined in Table 2^[78].

Kidney failure

The presence of the MS in both the general population and in liver transplant recipients is associated with a higher incidence of kidney failure^[78]. The reduction in glomerular filtration and the microalbuminuria associated with hypertension or diabetes and the resulting structural damage in the kidney can be increased by the effect of immunosuppressive drugs, which in turn leads to the higher incidence of chronic kidney disease in transplant patients with the MS^[79].

Recurrence of hepatitis C

There is a bidirectional relationship between hepatitis C and insulin resistance and diabetes, these latter two being recognised as risk factors for the progression of

the fibrosis in patients with hepatitis C, whether or not they have received a transplant^[80,81]. Additionally, the recurrence of hepatitis C is also recognised as a risk factor for the development of NODALT^[60,82], which in turn is related with greater progression of the fibrosis.

Hepatitis C also affects lipid metabolism, producing a reduction in serum lipid concentrations. Though this could potentially be beneficial, reducing the cardiovascular risk, it has also been related with alterations in the intracellular lipid balance, which could increase the hepatic steatosis^[83].

The use of current direct-action antiviral agents against HCV and their high rate of efficacy has led to the recurrence of HCV becoming much less prevalent, with the resulting lower rate of possible effects on metabolic factors.

NAFLD and NASH

NAFLD and NASH can be considered hepatic events of the MS^[23]. Around 20% of patients with NASH can eventually develop cirrhosis and require liver transplantation. Over 60% of the patients who receive a transplant due to NASH experience a recurrence during the first year, with the main risk factor being the presence of the MS^[84]. One study found that around 20% of liver transplant patients who did not previously have fatty liver developed NAFLD afterwards and around 10% developed NASH post-transplant^[85]. On the other hand, various studies have identified a 10% increase in the BMI as the main risk factor for the development of NAFLD^[49,74,86]. Nonetheless, the true impact of the presence of NAFLD and NASH after transplantation still remains unclear.

CONCLUSION

The high prevalence of the MS after a liver transplant and its relation with the development of cardiovascular events, as well as its involvement in other clinical aspects after the transplant that can seriously influence morbidity and mortality, necessitates the early identification of these factors to achieve adequate management of the risks, thereby minimising their impact on patient survival. Other aspects in post-transplant MS, such as the role of gene polymorphisms or the gut microbiota require much greater study.

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