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Metabolic Syndrome After Liver Transplantation

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1. Introduction

The survival of patients who undergo liver transplantation has improved over recent years, due to the perfectioning of the surgical technique, the optimization of immunosuppressive therapy and the prevention of infection, and is estimated to be 90% at one year and 70% at five years (Pagadala et al., 2009). However, at the same time the incidence of metabolic complications has increased, and they now constitute one of the main causes of mortality unrelated to the graft (Muñoz & ElGenaidi, 2005; Watt et al., 2010). The metabolic syndrome (MS), which associates overweight, dyslipidaemia, hyperglycaemia and hypertension, has a greater prevalence in patients who have a liver transplant as compared with the general population (Francioso et al., 2008; Sorice et al., 2011). Though the impact of the MS on post-transplant mortality is controversial, its diagnosis or the presence of certain of its components increases the risk of cardiovascular complications, renal failure or fatty liver disease in the graft, and it has also been related with a greater risk for infections and rejection. The MS has special relevance in patients with hepatitis C, as the development of the MS in general, and diabetes in particular, can affect the natural history of the hepatitis C in the graft (Vedt et al., 2009). The identification of modifiable predisposing factors and early treatment of hypertension, hyperglycaemia and dyslipidaemia, together with the prevention of overweight during the peri-transplant period, can all help to reduce the morbidity and mortality in this population.

2. Diagnosis and prevalence of the metabolic syndrome in liver transplant patients

Many definitions for the MS can be found in the literature. The criteria defined by the National Cholesterol Education Program, Adult Treatment Panel III (NCEP/ATPIII) adapted by the National Heart, Lung and Blood Institute/American Heart Association (NHLBI/AHA) and International Diabetes Federation (IDF) are detailed in Table 1(Grundy et al., 2004; Alberti et al., 2006).

These criteria all have in common insulin resistance (IR) as the physiological basis of the MS. IR is defined as the reduction of sensitivity of tissues to the action of insulin, which implies a compensating hyperinsulinaemia that in the end exhausts the capacity of the pancreatic beta cells to produce insulin. Secondary to this is produced hyperglycaemia and diabetes. IR is

measured using the HOMA (Homeostatic Model Assessment) index, though its measurement is not necessary for the diagnosis of the MS (Matthews et al., 1985).

$$HOMA= \text{fasting insulin (mU/ml)} \times \text{fasting glucose (mmol/L)}/22.5$$

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> 130mmHg and/or diastolic blood pressure >85 mmHg or on antihypertensive treatment in a patient with history of hypertension • HDL <50 mg/dl for women and <40 mg/dl for men • Triglycerides >150 mg/dl or on drug treatment for elevated TG	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 or on antihypertensive treatment • HDL <50 mg/dl for women and <40 mg/dl for men • Triglycerides >150 mg/dl

Table 1. Definition of the metabolic syndrome by NHLBI/AHA and IDF 2005

The prevalence of the MS in the general population is approximately 30% (Ford et al., 2004). However, in liver transplant patients it is considerably higher, approximately 40-50% (Laryea et al., 2007; Bianchi et al, 2008), though these percentages can vary according to geographical area, and are slightly lower, for example, in the Spanish population, both transplanted and non-transplanted (Ruiz-Rebollo et al., 2010).

Independent analysis of each of the components of the MS also shows a greater incidence in the transplanted population; 40-85% develop hypertension, 13-61% diabetes, 40-66% dyslipidaemia, mainly hypertriglyceridaemia, and up to 40% obesity, which can reach 70% three years post-transplant (Laish et al., 2011).

3. Risk factors for post-transplant metabolic syndrome

Different studies have evaluated possible risk factors for the development of post-transplant metabolic syndrome (PTMS) in an attempt to identify them early and treat them as far as possible.

In general, considering that IR triggers the MS, the situations that predispose to this condition are applicable, in addition to the underlying aetiology of the liver disease and the use of immunosuppressive drugs.

Of the causes leading to the liver transplant, HCV infection (Bigam et al., 2000) and cryptogenic cirrhosis are significantly associated with PTMS (Ong et al., 2001), versus other

factors such as autoimmune disorders or hepatitis B. Biliary diseases are not related with PTMS, perhaps because of the later hepatocyte involvement, which is, after all, responsible for glucose metabolism (Laryea et al., 2007). Review of all the publications available confirms the two-way relation of the hepatitis C virus, insulin-resistance and the development of diabetes (Hanouneh et al., 2008).

Immunosuppressive drugs, particularly steroids and calcineurin inhibitors, are associated with the appearance of cardiovascular risk factors, though tacrolimus is more diabetogenic and cyclosporine predisposes more to hypertension and dyslipidaemia (Marchetti & Navalesi, 2000). In fact, most of the metabolic complications appear during the first months after the transplant, when the immunosuppressive treatment is greater. Nevertheless, no clear relation exists between the MS and a particular immunosuppressive regimen, probably because of its multifactorial origin (Bianchi et al., 2008).

The characteristics of the donor and the recipient also influence the development of PTMS; mainly the age of both, the presence of any of the components of the MS prior to the transplant, and the existence and degree of graft steatosis are considered risk factors.

4. Components of PTMS

4.1 Obesity

Overweight is defined as a body mass index (BMI) of 25-30 and obesity as a BMI >30, with the latter being classified into class I (BMI of 30-35), class II (BMI of 35-40) and class III (BMI>40). Obesity can also be differentiated between peripheral or central obesity, with the latter having more implication in the metabolism (Watt, 2010).

Pre-transplant obesity is associated with greater peri-operative morbidity and mortality, with a longer hospital stay and reduced patient and graft survival. An analysis by the Scientific Registry of Transplant Recipients showed that five-year post-transplant mortality was greater in recipients with class II and III obesity (Nair et al., 2002), though no consideration was given to the influence of ascites on overweight. Studies that corrected obesity for ascites found no significant differences regarding morbidity or survival between obese and non-obese recipients, though ascites was found to be indicative of a worse postoperative course (Leonard et al., 2008). These studies could, however, be influenced by the fact that the obese patients were studied more closely from the cardiological aspect, with more exhaustive screening for pre-transplant cardiovascular risk.

Post-transplant obesity is very usual. Patients who are overweight prior to the transplant usually remain so, and up to one third develop de novo obesity (Wawrzynonowicz-Syczewska et al., 2009). The main triggering factor is the return to dietary habits but not to physical activity (Painter et al., 2001), which leads to a progressive weight gain, generally greater during the first post-transplant months. The immunosuppressive medication has traditionally been considered a trigger of overweight, though the association is in fact controversial and it has only been shown with the long-term use of steroids (Everhart et al., 1998).

Whilst not associated with greater mortality, post-transplant obesity, particularly central obesity, causes an imbalance in the production of adipokines, favouring those that produce

peripheral insulin resistance, and thus PTMS (Fox et al., 2007). In addition, obesity is related with osteoarthritis, sleep apnoea syndrome, and alterations in the distribution volume of drugs. The toxicity of non-lipophylic drugs that are adjusted to weight may be increased, and the blood levels of lipophylic drugs reduced (Watt & Charlton, 2010). Obesity can also affect the activity of the cytochrome P450 (Kotlyar & Carson, 1999).

The management of pre-transplant overweight is mainly based on dietary measures and lifestyle recommendations. Though there is currently no BMI that is an absolute contraindication for liver transplantation, obesity is considered a surgical and post-operative risk factor. The recommendations after the transplant are similar to those for the general population. Weight should be controlled, and the patient instructed about the prevention of obesity, with a suitable diet and physical exercise. Immunosuppression, especially corticosteroids, should be minimized as far as possible.

Bariatric surgery has been considered as a treatment option in patients with morbid obesity (Takata et al., 2008). However, performing it before the transplant operation is associated with technical difficulties, and after transplantation it may affect the absorption of the immunosuppressive medication, with repercussions on graft viability, and may also make treatment of any biliary problems more difficult (Butte et al., 2007).

Concerning pharmacological measures, pancreatic lipase inhibitors like tetrahydrolipstatin (orlistat), which can be used in the general population with morbid obesity, present important interactions with the immunosuppressive agents, and thus have to be limited in the transplant population (Desai et al., 2010).

4.2 Diabetes

Candidate patients for a liver transplant may have diabetes or, more likely, glucose intolerance due to the IR present in many patients with hepatic cirrhosis. In this context, IR can be related with the hyperglucagonaemia found in many cirrhotic patients, as well as with the lower insulin degradation by a diseased liver or by the leakage phenomena from a portosystemic shunt. After the transplant, the insulin levels and glucose metabolism become normal in up to 6% of these patients (Watt & Charlton, 2010). However, from 20% to 60% remain diabetic or develop post-transplant diabetes mellitus (PTDM). The main risk factors for the development of PTDM are prior diabetes, obesity, hepatitis C and a family history of diabetes (Anastáscio et al., 2010).

After the transplant, the immunosuppressive drugs are the main trigger for de novo DM. Steroids induce IR in a dose-dependent manner, by reducing the pancreatic production of insulin and increasing hepatic gluconeogenesis (Schake et al., 2002). Calcineurin inhibitors can also reduce insulin production via a direct toxic effect and/or reduction in the peripheral use of insulin. Tacrolimus seems to have a greater diabetogenic effect than cyclosporine (Haddad et al., 2006). The effect of mTOR inhibitors on the development of IR is unclear; on one hand they may favour the response to insulin and thus reduce the risk of diabetes, though on the other hand they can also block the proliferation of pancreatic beta cells, thereby predisposing to PTDM (Vodenik et al., 2009).

PTDM is associated with cardiovascular complications, increased and accelerated progression of fibrosis in patients with hepatitis C, and a reduction in the response to

antiviral therapy (Veldt et al., 2009). It is also associated with a greater incidence of chronic rejection and late hepatic artery thrombosis. The survival of transplant patients who develop diabetes is lower than that for those without diabetes. In addition, these patients can present the same microvascular complications as in the general population, including retinopathy, nephropathy and infections (Desai et al., 2010).

The aims of treatment in the transplant patient with diabetes are similar to those in the general population: fasting blood glucose levels of 80-130 mg/dl, post-prandial levels of 140-180 mg/dl and glycosylated haemoglobin <6.5-7% (Bilbao et al., 2010)..

The treatment of PTDM includes dietary measures, limiting the intake of carbohydrates, and physical activity. A reduction in steroids or their complete withdrawal, plus dose optimization of calcineurin inhibitors or their minimization, adding other immunosuppressive drugs (mycophenolate or mTOR inhibitors) may suffice, thereby avoiding pharmacological therapy (Dumortier et al., 2006; Herrero el at., 2006).

Hyperglycaemia during the early post-transplant period requires treatment with insulin, which can later be reduced or even stopped. The drugs of choice for maintenance therapy are oral antidiabetic agents (Marchetti, 2005). The choice of oral antidiabetic agent to be used should be based on the advantages and possible side effects of each drug group in general or each drug in particular. The sulphonylureas can favour overweight and hypoglycaemia and should be avoided in patients with advanced kidney failure; the alpha glucosidase inhibitors can produce adverse side effects in the digestive system; the thiazolidinediones, which have a greater glucose lowering action, have been shown to increase the cardiovascular risk in the general population and are not therefore advised (Watt & Charlton, 2010). Metformin may be the most suitable oral antidiabetic agent because it lacks hepatic metabolism and is the recommended first line drug of choice, though it should be remembered that it can produce lactic acidosis in patients with kidney failure (Sharif, 2011).

4.3 Dyslipidaemia

Prior to the transplant, most cirrhotic patients do not have dyslipidaemia, due to the lower liver production of lipids and the malnutrition experienced by most of them. An exception, though, is patients with cholestatic liver disease, but in these cases the pattern of dyslipidaemia is not associated with a greater risk of arteriosclerosis (Muñoz & ElGenaidi, 2005).

After the transplant, however, dyslipidaemia, both hypertriglyceridaemia and hypercholesterolaemia, is very frequent, occurring in up to 70% of transplant patients within one year (Bianchi et al., 2008). Some authors consider dyslipidaemia to be the main cardiovascular risk factor (Reuben, 2001).

As with the other components of the PTMS, the aetiology of dyslipidaemia involves many factors, though the immunosuppressive agents are the main triggering factor. Steroids are associated with hyperlipidaemia as they stimulate the activity of acetyl-CoA carboxylase and the synthesis of fatty acids, thus raising concentrations of total cholesterol and triglycerides (Ballantyne et al., 1992). M-TOR inhibitors increase lipoprotein-lipase activity, increasing the hepatic synthesis of triglycerides (Morrisett et al., 2003). Calcineurin

inhibitors reduce the excretion of cholesterol to the bile and the peripheral LDL-cholesterol receptors, thereby raising circulating levels of cholesterol (Chan et al., 1998).

Treatment of the hypercholesterolaemia starts with dietary measures, including supplements of omega 3 fatty acid. In most cases, though, this is insufficient and it is necessary to initiate pharmacological treatment. The recommendations for this are the same as for the general population. In patients with no cardiovascular events, the LDL cholesterol should be maintained <130 mg/dl, though for secondary prevention this level should be <100 mg/dl. Statins are the drugs of choice in both the general and the transplant populations, reducing cardiovascular disease as well as having a certain immunosuppressive effect that has been related with a lower incidence of rejection (Martin et al., 2008). Most statins use the same metabolic pathways as calcineurin inhibitors (P450 cytochrome), which explains the pharmacological interactions and the greater risk for myositis and rhabdomyolysis (Desai et al., 2010). It is therefore recommended to start with low doses and gradually increase them according to needs. In particular, pravastatin is eliminated via the kidneys and fluvastatin uses a different cytochrome, so that these two may be the statins of choice (Watt & Charlton, 2010). Treatment with ion exchange resins, whilst it may help normalize cholesterol levels, interrupts the enterohepatic circulation and may, secondarily, alter levels of calcineurin inhibitors, particularly cyclosporine.

Hypertriglyceridaemia is better treated with dietary restriction, with drugs generally being reserved for patients with severe hypertriglyceridaemia. Fibrates, such as gemfibrozil, are indicated in these cases, but with caution if associated with statins due to the greater muscular toxicity.

Ezetimibe, an inhibitor of the enterohepatic recirculation of lipids, has been show to be well-tolerated and effective when used in combination with statin, but interacts with immunosuppressive drugs and can produce hepatotoxicity (Almutairi et al., 2009).

In all cases the use of steroids should be kept to a minimum and calcineurin inhibitors optimized.

4.4 Hypertension

The incidence of hypertension before transplant is very low. However, after transplantation, the hyperdynamic circulation of the cirrhotic patient is reverted, with an increase in blood pressure that can reach values considered normal. Once again, the immunosuppressive drugs, whether or not in the presence of other risk factors, are related with the onset of hypertension, considered as a systolic pressure ≥140 mmHg and a diastolic pressure ≥90 mmHg; this occurs in around 60-70% of all patients (Watt et al., 2010). The pathophysiology of post-transplant hypertension does not reside in alterations of the renin-angiotensin-aldosterone system, as occurs in the non-transplanted population. The fundamental mechanism is related to the systemic and renal haemodynamic changes produced by the immunosuppressive drug. Calcineurin inhibitors, particularly cyclosporine, produce renal vasoconstriction of the afferent arteriole, with secondary renal hypoperfusion leading to reabsorption of sodium and water (Textor et al., 2000). Steroids potentiate this latter situation through their mineralocorticoid effect and mTOR inhibitors can produce hypertension if associated with calcineurin inhibitors.

The aims of treatment are to maintain blood pressure figures <140/90 mmHg (or lower in the presence of other risk factors), and the first step is restriction of dietary salt, coupled with control of other risk factors and the undertaking of physical activity.

As far as drugs are concerned, calcium antagonists are considered the first choice as they can reverse renal vasoconstriction. Within this group of drugs, diltiazem, verapamil or nicardipine interfere in the hepatic metabolism of calcineurin whilst amlodipine does not, and this latter is thus the most used (Watt, 2010). Angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) produce vasodilation of the efferent arteriole, reducing glomerular pressure and hyperfiltration (Desai et al., 2010). They are the choice group for patients with proteinuria and renal failure because they slow its progress.

Beta blockers are not first-line drugs, but they can be used in selected cases. Finally, diuretics in association with other antihypertensive drugs are beneficial in cases that are difficult to control, but should not be used as a single therapy and also require strict electrolyte control. The reduction of calcineurin inhibitors favours blood pressure control.

5. Consequences of the metabolic syndrome

5.1 Major cardiovascular complications

Major cardiovascular complications or events mainly include ischaemic heart disease, stroke or peripheral ischaemia phenomena. Transplant patients who develop PTMS have an accumulated incidence of cardiovascular disease around twice that of transplant patients without PTMS (12.9% vs. 4.9%, respectively; Figure 1, Laish et al 2011). Cardiovascular mortality can reach 40% (Laish et al., 2011; Laryea et al., 2007; Anastáscio et al., 2010).

5.2 Fatty liver graft disease

Up to 60% of patients transplanted due to nonalcoholic steatohepatitis (NASH) relapse at one year and 100% at five years. In cases of cryptogenic cirrhosis, the presence of different degrees of steatosis in the graft is 50% at two years post-transplant. Although no exact study has been undertaken on the repercussion of steatosis on graft function, between 2.5% and 15% of relapses of NASH are estimated to end in cirrhosis. The main independent risk factor for fatty liver graft disease is a 10% increase in body mass index (Charlton, 2009; Dureja et al., 2011).

5.3 Influence of HCV recurrence

A bidirectional relation exists between HCV and IR, with 21% of HCV-positive patients being diabetic, and the presence of HCV multiplies the long-term risk of developing diabetes by 2-3 times. A recent analysis of cardiovascular risk after liver transplantation according to HCV status showed higher incidence of DM among HCV-positive patients (Pérez et al., 2011). Inversely, IR or the presence of established diabetes is associated with greater viral replication, a higher degree of steatosis and fibrosis and worse response to antiviral therapy (Arase et al., 2009). The main reason for this association is that not only

does HCV block the intracellular signals that trigger insulin after binding to the receptor, but also IR stimulates hepatic lipogenesis and stellate cells, thus increasing steatosis and fibrosis. IR and hyperinsulinaemia induce resistance to interferon, such that patients with a HOMA >2 have a lower percentage of sustained viral response (SVR). In parallel, those patients who achieve a SVR have a lower risk of developing diabetes because, in the absence of viral replication, the IR almost disappears (Romero et al., 2009)

5.4 Renal failure

In both the general population and in persons who have a transplant, patients with the MS present a greater incidence of renal failure. The reduction in glomerular filtration and the presence of microalbuminuria are associated with the number of components of the MS present. IR, and secondary hyperinsulinaemia and hyperglycaemia, cause an imbalance between vasodilatating and vasoconstricting substances, in favour of the latter; they favour oxidative stress and endothelial damage; stimulate the renin-angiotensin-aldosterone axis and release of growth factors. This all leads to structural damage in the kidney, mainly tubular atrophy, glomerulosclerosis and tubulointerstitial fibrosis, damage that eventually produces a reduction in glomerular filtration, proteinuria and a rise in creatinine. If added to this there is renal damage caused by the immunosuppressive drugs, transplant patients with PTMS thus have a greater incidence of chronic transplant nephropathy (Morales et al., 2006).

6. Prevention and treatment of PTMS

It is necessary to identify patients with risk factors for PTMS as obesity, pretransplant diabetes, older age, and transplantation due to HCV infection or cryptogenic cirrhosis, which in many cases is in fact an unrecognized steatohepatitis. Usual check-ups should include a search for the early detection of components of PTMS and, if found, they should be treated as per the recommendations above. In all cases good dietary advice is recommended as well as the promotion of physical activity. Concerning immunosuppression, the use of steroids and calcineurin inhibitors should be reduced as much as is possible. This generally means the early introduction of other immunosuppressive drugs, mainly mycophenolate and mTOR inhibitors, which permits calcineurin inhibitors to be spared. In patients presenting with several cardiovascular risk factors or in those who have had a cardiovascular event, antiaggregation therapy should be considered.

7. Conclusions

The MS and each of its individual components are more prevalent in transplant patients than in the general population. The presence of PTMS is associated with a grater incidence of cardiovascular diseases and chronic transplant nephropathy. It is related with a worse course of HCV recurrence and favours the onset of fatty liver graft disease. Immunosuppressive drugs are the main factor related with PTMS. Strict vigilance should be exercised at the regular clinic visits for the appearance of any of the components of MS and treatment started accordingly. The immunosuppression should be individualised, recommending the early introduction of calcineurin inhibitor sparing drugs, with fewer metabolic and renal side effects.
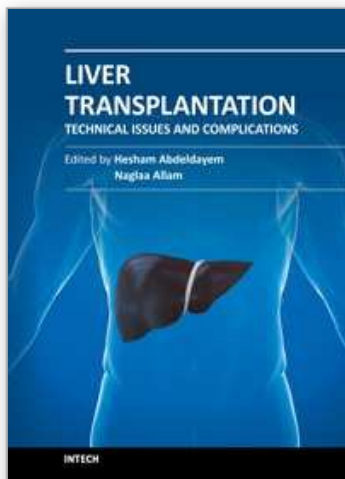
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This book covers a wide spectrum of topics including, but not limited to, the technical issues in living and deceased donor liver transplant procedures, cell and experimental liver transplantation, and the complications of liver transplantation. Some of the very important topics, such as the arterial reconstruction in living donor liver transplantation, biliary complications, and the post-transplant-lymphoprolifrative disorders (PTLD), have been covered in more than one chapter.

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