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Concise Review

Post-liver transplantation medical complications

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Abstract

Liver transplantation (LT) is widely accepted as an effective therapeutic modality for a variety of irreversible acute and chronic liver disease. The success of liver transplantation has increased steadily over the last two decades and several advances have been made since the first human liver transplant. This procedure has become routine with an excellent outcome in terms of both quality and length of survival. The results of liver transplantation have improved due to advances in perioperative technique, a better understanding of the course and prognosis of several liver disease, improved immunosuppressive therapy and more effective postoperative care. Nevertheless, improved tools detecting under immunosuppression, new strategies against viral infections (i.e. cytomegalovirus), and new immunosuppressive drugs will probably even prevent further graft dysfunction in the future. However, complications are common in the early and long term period and contribute to significant morbidity and mortality. One of the major challenges facing the transplant community is the increasing metabolic complications that are now affecting quality of life and long-term survival. Thus, knowledge of complications that emerge during follow up period, early and accurate establishment of diagnosis, and prompt institution of appropriate interventions are essential for optimal patient and graft outcome.

This review summarizes available data about medical complications of the early and long term follow up.

Key words: Liver transplantation, immunosuppression, infections, graft dysfunction, complications.

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Introduction

Liver transplantation has become an effective therapy for patients with acute or chronic end-stage liver disease. Initially, transplantation was considered the last therapeutic option for patients who were in a very serious clinical condition at the time of surgery, and therefore premature mortality was very high. Currently though, survival rates of over 90-95% and 70% at one year and five years post-transplantation, respectively are expected.[1-3] The main barriers to overcome in the first period were immediate post-surgical survival together with prevention of acute rejection. With greater survival of patients, new problems have arose that basically affect transplant recipients with long-term follow-up. Indeed, despite substantial technological, medical and surgical advances, liver transplantation remains a complex procedure that is accompanied by significant morbidity-mortality.[2-5]

The liver is an organ that actively interacts with all body systems, so that the patient who receives a liver graft faces a huge set of physiological changes. During and in the immediate postoperative period, the liver is subjected to a wide variety of potentially damaging factors, including hypotension, hypoxia, ischaemia and hepatotoxic drugs; in addition, donor-related factors (hepatic steatosis, use of vasoactive drugs, hemodynamic changes), surgical-related aspects (intra- or postoperative hemorrhage, vascular or biliary complications) or immune responses (rejection) might lead to a very different outcome. In summary, the postoperative outcome of each patient varies greatly depending on the patient's preoperative state, the quality of the donated organ, and the complexity of the surgery.[6,7]

The complications occur both immediately post-transplantation and in the long-term. The main complications in the immediate postoperative period are related to the function of the graft (dysfunction and rejection), the surgical technique, infections (bacterial, fungal, and viral), and systemic problems (pulmonary, renal, or neurological). In the long term, the complications are typically a consequence of the prolonged immunosuppressive therapy, and include diabetes mellitus, systemic arterial hypertension, de novo neoplasia, and organ toxicities, particularly nephrotoxicity.[8] Although recurrence of the original disease is one of the main problems that can threaten long-term survival and graft loss, it is not con-

sidered a transplantation-derived complication. Indeed, in most cases, the transplant procedure does not eliminate the underlying illness that caused the failure of the native liver.[9]

Establishing the correct diagnosis is essential for all the complications given the potential implications of different therapies on the graft function and patient outcome. The differential diagnosis is difficult though due to the similarities of clinical manifestations and laboratory abnormalities of most liver transplant complications. This review describes the most frequent complications following liver transplantation divided into two groups, immediate complications and long-term complications.

Immediate complications

Postoperative technical and organic medical complications, primary dysfunction, graft rejection and infections are the major short-term complications[10] *(Table I)*.

1. Technical complications

The prevalence of technical complications is on average 26%. **Arterial complications**, particularly the **thrombosis of the hepatic artery** (prevalence ranging from 1.5 to 25%) are the most frequent ones. Hepatic artery thrombosis is a complication that develops more frequently in the pediatric population. It has been attributed to multiple causes including poor arterial flow, increased sinusoidal resistance, preservation injury, stenosis of the anastomosis and a state of hypercoagulability. Symptoms are highly variable and depend on the timing of development and diagnosis. When the thrombosis occurs at an early stage, it typically leads to ischemia/necrosis of the graft; in contrast, when it occurs at a later time point, it generally leads to biliary complications (intrahepatic biliomas and biliary stenosis) but with preservation of the graft function. The diagnosis is confirmed by Doppler ultrasonography, selective arteriogram or helicoidal CT scan. The treatment is highly dependent on the timing of occurrence and the clinical consequences. In the acute form, thrombolysis can be accomplished by surgical radiology. Arterial thrombectomy may be an alternative that can be done either by interventional radiology or surgical intervention. In patients where these options fail, urgent re-transplantation may be required. In the late form, treatment is mainly focused to prevent/treat biliary complications derived from the thrombosis. Antibiotic therapy, percutaneous drainage, bilio-enteric bypass or elective re-transplantation are potential approaches. Overall, 50-70% of patients diagnosed with arterial thrombosis require retransplantation.

Table I. Allograft dysfunction and surgical complications occurring in the immediate postoperative period.

Allograft dysfunction
• Primary non function
• Primary poor function
• Acute cellular rejection
• Recurrent viral hepatitis
• Drug hepatotoxicity
Surgical complications
• Postoperative hemorrhage
• Vascular complications
Hepatic artery thrombosis
Portal vein thrombosis
Hepatic venous obstruction
Other
• Biliary tract complications
Bile leak or fistula
Biliary stricture

Portal vein thrombosis is an infrequent complication with an overall prevalence of 2-3%. It is related to pretransplantation portal thrombosis, splenectomy, and prior portal hypertension surgery. In the acute form, the clinical picture is dominated by symptoms/signs of hepatic failure; in contrast, portal hypertension is the typical presentation in the late form. In some occasions, there is only a stenosis of the venous anastomosis. In these cases, percutaneous dilation by angiography may solve the problem. Additional options include surgical resection followed by direct anastomosis with/without a venous graft.[11,12]

Biliary complications are considered the Achilles' heel of liver transplantation, particularly in the setting of live donor liver transplantation. While interventional radiology and/or endoscopy may solve many cases, up to 10-20% will require surgical intervention for a definitive resolution. *Biliary fistula* can occur initially in the first month in relation to anastomotic dehiscence secondary to technical errors or biliary tract ischaemia. It is also a common complication in the third month when the T-tube is withdrawn. The clinical picture is variable and depends on the time of development, lead time to diagnosis, and existence of a T-tube. The lack of bile formation through a drainage, the formation of a bilioma evidenced radiologically, and the increase of cholestatic enzymes together with discrete leukocytosis are indicative of a biliary problem. As with the thrombosis of the hepatic artery, the treatment of the biliary complications mainly depends on the patient's condition and the postoperative moment; indeed, while in some occasions it can be conservatively solved by opening the T-tube together with antibiotic coverage, endoscopic papillotomy and/or percutaneous drainage of the bilioma is still required in some cases. If all measures fail or there is overt peritonitis, open surgery has to be considered. *Biliary obstruction* can occur in the setting of anastomotic stenosis, intrahepatic stenosis and coledolithiasis. The clinical picture is variable from elevation of the cholestatic enzymes in an asymptomatic patient to a septic shock due to bacterial cholangitis.[13]

A **hemorrhage** in the immediate postoperative period is another potential complication with a variable prevalence that, in some series, has reached 20%. Preexisting coagulopathy, significant hemorrhage during surgery, and/or immediate poor synthetic function are some of the factors associated with this complication. It is typically diagnosed within the first 48 hours post-transplantation (hemorrhagic abdominal drainages, hemodynamic instability, serial determination of the hematocrit/hemoglobin) and will subside in most instances with a conservative approach. A re-operation is needed in 10-15% of cases, and the cause of the hemorrhage is found in only 50% of these.[14,15]

2. Medical complications

When the transplant evolves favorably, the patient is awake, hemodynamically stable, with spontaneous respiration, preserved renal function, and with progressively improving liver activity. When complications develop, the stay in the intensive care unit is prolonged and mortality increases. The global mortality in this early post-transplantation period is approximately 5-10%. The most frequent medical complications that can be expected during this early post-transplant period are hemodynamic alterations, and respiratory, renal and neurological complications.

Hemodynamic complications are frequent during the early post-transplant period. Of these, the most common is arterial hypertension, mainly caused by the effect of immunosuppressive drugs, the presence of intense pain, or due to hypervolemia secondary to excessive hydrous replacement. It is usually controlled with the addition of calcium inhibitors and/or diuretics. **Electrolytic alterations**, particularly of sodium, potassium, calcium, and magnesium, due to hepatic reperfusion and to the transplant itself, can cause cardiac arrhythmia and, hence, need to be quickly treated; if they persist, additional factors such as acidosis, renal or liver failure, must be excluded. The most frequent arrhythmia is bradycardia, a complication that is rarely symptomatic. In contrast, supraventricular arrhythmias (particularly atrial fibrillation) have greater clinical repercussion but are less frequent.

It is increasingly frequent to include patients in the waiting list with a history of ischemic, hypertensive or valvular cardiopathy. In these cases, a complete cardiologic evaluation needs to be performed prior to transplantation. Once transplantation has taken place though and despite a careful pre-transplant cardiologic evaluation, the cardiopathy may destabilize.[10]

Respiratory changes are those inherent to any abdominal surgery that causes reduced ventilation capacity, together with the reduction in diaphragm motility and/or the presence of ascitis. Pleural leakage, predominantly on the right, is the most frequent complication with a prevalence reported to be as high as 100% in some series. Determinant factors are prior hypoproteinemia, fluid replacement in large amounts during surgery and the development of renal insufficiency. These circumstances can also set the stage for interstitial edema and acute pulmonary edema. Early removal of mechanical ventilation is an indirect marker of favorable outcome; primary graft failure, hemorrhage, respiratory infection, respiratory distress syndrome or emboligenic problems secondary to surgery may complicate removal of the mechanical ventilation.[16] Atelectasias, pneumo- or hemothorax are less frequent and are typically controlled in the usual manner.

There are multiple reasons potentially associated with changes in **renal function** during this period: prior existence of renal dysfunction, peri-operative hemorrhage, vascular clamping with hypotension, the use of nephrotoxic drugs, sepsis, a state of shock, and possibly dysfunction of the graft. Renal dysfunction is defined by a creatinine level above 2-3 mg/dL and/or an increase in the basal seric creatinine greater than 50%. The clinical manifestations are oliguria, diuresis of less than 0.5 mL/kg/h, electrolytic changes, ascitis, edema and acid/base disorders with increases in the levels of creatinine between the second and fourth days postoperatively. Since a state of euvolemia has to be maintained with adequate renal perfusion pressures, colloid-based hydrous replacement should be aggressive. The use of diuretics and the employment of dopamine and even noradrenalin are justified. Early dialysis must be considered at all times if necessary.[17]

The patient's **neurological state** can be altered as a response to both the surgery and the drugs used. Potential complications include intracranial hemorrhage due to coagulopathy and hypertension, anoxic ischemic encephalopathy due to hemorrhage or hypoxia, and convulsions due to the effect of the cyclosporine, tacrolimus or antibiotics. Myopathies or neuropathies can also develop due to drug-toxicity and/or pre-existing conditions (alcohol, diabetes…). The most frequent neurological alterations are disorientation with episodes of agitation and confusion;[18] they typically respond to a conservative approach.

3. Liver graft dysfunction

The transplanted liver can have a normal postoperative course, manifested by progressive decrease of transaminases, increase of factor V, prothrombin and platelets, control of acidosis, normalization of ammonium, good biliary production, and absence of encephalopathy. Dysfunction of the graft may occur in the immediate postoperative period (early dysfunction) or late during the follow-up of the patient {typically related to the recurrence of the original disease (viral hepatitis, primary biliary disease, sclerosing cholangitis, alcohol or autoimmune liver disease) or chronic rejection}.

The **early dysfunction of the graft** can be due to: 1) problems of the graft itself (primary dysfunction/malfunction, nonspecific cholestatic syndrome, rejection), 2) complications of the surgical technique {vascular (arterial, portal thrombosis, poor drainage of the suprahepatic veins), or biliary}, and 3) other causes such as drug-related liver toxicity (e.g., cyclosporine) or infections (CMV, bacterial). The problem in many of these cases is the differential diagnosis, since although from a clinical and biological point of view, they share many manifestations, the therapeutic approach is completely different. *Primary graft failure* is defined as the clinical situation in which there is poor liver function to maintain the individual's life leading to death of the patient or retransplantation during the first seven postoperative days. It is one of the most serious situations in the early post-transplant setting; it is characterized by immediate non-function of the liver, with elevated hepatic enzymes, scant or no elimination of bile, encephalopathy and coagulopathy. Its incidence is estimated at 5-10%; although there is a series of predisposing conditions (advanced age, hemodynamic instability, suboptimal donors, cold ischemia time, reperfusion damage, release of intestinal endotoxins, drug-related liver toxicity), the exact cause of this severe complication is unknown. The diagnosis may be suspected from the time of the surgical procedure, when coagulopathy is seen after reperfusion, scant bile production, poor liver appearance, etc. From a biological and clinical point of view, it is characterized by an increase of AST > 5,000 I.U., Factor V < 20%, prothrombin time < 60% despite administration of plasma, scant biliary production, hepatic encephalopathy (the patient does not wake up and cannot be extubated), elevated ammonium values and lactic acidosis that cannot be corrected. Histopathology findings are those of ischemic hepatic necrosis. Prostaglandins can be used in the first hours of implementation of the procedure, in an attempt to improve microcirculation of the liver. However, if regression of the clinical situation is not observed after 24-48 hours, retransplantation must be considered as soon as possible to avoid the development of multi-organ failure, in which case the mortality associated with retransplantation is very high.[19,20]

4. Rejection

In the absence of immunosuppression, a transplanted organ invariably experiences progressive immune-mediated aggression. In recent years, immunosuppression protocols have evolved considerably, making solid organ transplantation a routine clinical procedure with excellent short-, medium- and long-term results. Several studies have demonstrated that acute rejection is a risk factor for graft survival, particularly in patients transplanted for HCV-related liver disease.

Rejection can be divided into hyperacute, acute, and chronic. Hyperacute responses occur within minutes to hours, are antibody and complement mediated, and are generally irreversible. Acute rejection is cell mediated, occurs over a period of days to months, and can be reversed using a variety of currently available drugs. Chronic rejection generally occurs over a span of months, can be unresponsive to current therapy, and continues to be a source of graft loss.[19,20] During episodes of acute rejection, patients may be asymptomatic, or may describe general malaise or discomfort in the upper quadrant. The diagnosis should be considered in liver transplant recipients patient with rising serum transaminase levels, particularly if this is accompanied by sub-therapeutic blood levels of immunosuppressive agents. A liver biopsy is mandatory to confirm the diagnosis. The treatment is based on increases in baseline immunosuppressive doses, switching to a more potent agent (for instance, from cyclosporine to tacrolimus) introduction of an additional agent (i.e. mycophenolate mofetil) and pulse boluses of intravenous corticosteroids. Repeated episodes of acute rejection may indicate the need for introduction of a second line immunosuppressive agent.[21,22]

5. Infections

Infections continue to be one of the main complications that can contribute to the patient's death. More than half of transplanted patients have at least one infections complication and an infection is responsible of more than half of the deaths in liver transplant recipients. The source of the infecting organism can be: a) the donor organ and transfused blood products (especially viral infections, such as cytomegalovirus, Epstein-Barr virus, hepatitis-B and hepatitis-C virus), b) the reactivation of previous infection, c) invasion by exogenous micro-organisms or by endogenous flora. Predisposing factors include the need for repeat surgical intervention,[23] the reduction in defense mechanisms such as breakage of the muco-cutaneous defense barriers, excessive exposure to pathogenic micro-organisms due to prolonged hospitalization, decreased defense immune response due the patient's poor condition prior to transplantation (presence of cytopenias, other illnesses, malnutrition, etc.) as well as by the immunosuppression used to avoid rejection. The infecting organism and type of infection is closely related to the time post-transplantation. During the first month, infections are typically of nosocomial origin. Depending on the circumstances of each case, surgical technique-related infection is located fundamentally in the abdomen, liver and biliary tract, and includes superficial and deep infection of the surgical bed (surgical wound, intra-hepatic and extra-hepatic abscess, peritonitis and cholangitis). All these infections are associated with surgical problems. Thus, intra-hepatic abscess is associated with the existence of hepatic ischaemia zones secondary to thrombosis or stenosis of the hepatic artery. Extra-hepatic abscess is produced by infection of perisurgical

bloody collections or infection of biliomas secondary to biliary fistula. Cholangitis is a consequence of stenosis or obstruction (due to microlithiasis or lithiasis) of the biliary tract. The incidence of each one of these infections complications has a close connection to the incidence of complications and experience of each surgical group. Prolonged hospitalization leads frequently to nosocomial infection and includes pneumonia, bacteremia and urinary infection. This type of infection is related, to a greater or lesser degree, to invasive procedures. Thus, pneumonia is related to prolonged intubation and to re-intubation; urinary infection, to bladder catheterization, and bacteremia, to intra-vascular catheterization.

In the intermediate period, from the second to the sixth months, the higher immunosuppression period, bacterial infections (opportunistic bacteria) are less common than viral infections (especially cytomegalovirus, recurrence of HCV, Epstein-Barr and adeno-viruses). Viral infections are followed in decreasing order of frequency, by fungi (*Pneumocystis carinii, Candida, Aspergyllus, Cryptococcus*), bacteria (*Mycobacteria, Nocardia* and *Listeria*)and parasites.[24-26]

Regardless of the cause of the liver disease, cytomegalovirus (CMV) is the most frequently isolated micro-organism liver transplantation. The graft from a seropositive donor implanted in a seronegative recipient, polytransfusion and the use of anti-lymphocyte antibodies are considered risk factors for this complication. In the absence of prophylaxis, between 23 and 85% of patients will present cytomegalic infection, but only 10-40% develop the disease. Infection by cytomegalovirus is associated with increased post-transplantation mortality and loss of the graft.

After the sixth month, with the transplanted organ functioning normally and minimum immunosuppressive doses, the frequency of bacterial infections is reduced to figures similar to those of the general population and the causes are pathogenic bacteria of the community. Infections in this period affect mainly the respiratory tract and are caused principally by *Pneumococcus* and *Haemophilus influenzae*.[24,25]

Infection in the liver transplant patient is diagnosed in the same way as in the non-transplanted population. However, it tends to be laborious work-up due to the wide differential diagnosis and the attenuation of clinical manifestations because of the immunosuppressive medication. For initial assessment, if non-focalized fever or bacteremia is present, urgent chest x-ray (to discard pneumonia), Doppler abdominal ultrasound and CT scan of the abdomen (intra-abdominal collections) are indicated. Other explorations, such as cholangiography (through the Kehr or trans-hepatic tube), endoscopic cholangiography, or cholangio-MRI are indicated to discard the existence respectively, of fistulae or stenoses of the biliary tract. All intra-abdominal collections must be aspirated in order to confirm infection and identify the microorganism. Methods for early detection of viral infection, in the case of cytomegalovirus, are periodic determination of CMV antigenemia in peripheral blood leukocytes and PCR techniques to detect the blood viral genome.

When a bacterial etiology is probable, or the patient's situation deteriorates, empirical treatment is recommended with prior blood sample cultured for microbiological diagnosis. The choice of empirical treatment should be based on the type of infection, and the antibiotic sensitivity of the causative micro-organisms.[27] When choosing an antibiotic, it is important to be aware of drug-drug interactions between any antimicrobials and immunosuppressive drugs. Drug interaction occurs with antimicrobial agents that use the P450-3A hepatic cytochrome system, the main metabolic route of cyclosporine and tacrolimus. Antimicrobial agents that inhibit this system increase serum concentrations of immunosuppressive drugs, nephrotoxicity and neurotoxicity. In contrast, antimicrobials that induce P450 cytochrome, increase the metabolism of cyclosporine/tacrolimus, decrease their serum concentrations, and increase the risk of acute rejection.

The prophylaxis of bacterial infection includes the following strategies: a) selective intestinal decontamination; b) administration of systemic antibiotics peri-operatively, c) antibiotic prophylaxis before invasive explorations of the biliary tract, and d) personnel hand washing together with strict asepsis in all invasive procedures.[28,29]

Another form of prevention, mainly targeted to avoiding the development of clinically manifest CMV disease, is the treatment of infection in the pre-symptomatic stage. Universal prophylaxis is useful mainly in high-risk patients (donor+/recipient- CMV, high transfusion requirements, rejection episodes, treatment with steroids, acute renal and liver failure, etc.) and can be done effectively and safely with oral drugs (e.g., oral ganciclovir 3 g/day or oral valganciclovir 900 mg/day for 100 days). Anticipated treatment is also an effective and probably most cost-effective strategy.[30,31]

Long-term complications

In the early era of transplant activity, liver transplantation was considered an experimental procedure and the last therapeutic option for patients who were in a very critical condition; in these circumstances, the long-term complications were not a great concern. Today, with improved survival in most transplant centers, increasing attention is being given to complications that develop in the long-term, and that are highly related to the immunosuppressive treatment. The most frequent complications are chronic renal failure, systemic arterial hypertension, diabetes mellitus, dyslipidemia, obesity, bone or neurological complications and the development of *de novo* tumors[32] *(Table II)*.

1. Chronic rejection

Chronic rejection is usually not evident until at least 6 months after transplant. The pathogenesis is still unclear.

Table II. Medical complications during follow up period.

Immediate complications
- Medical complications
  - Hemodynamic complications
  - Respiratory changes
  - Renal dysfunction
  - Neurological complications
- Technical complications
  - Postoperative hemorrhage
  - Vascular complications
  - Biliary tract complications
- Liver graft dysfunction
  - Primary poor function
  - Acute cellular rejection
  - Recurrent viral hepatitis
- Infections
  - Bacterial
  - Viral
  - Fungal

Long-term complications
- Chronic rejection
- Renal failure
- Arterial hypertension
- Diabetes mellitus
- Dyslipidemia
- Obesity
- Bone complications
- Neurological complications
- Malignancy

Clinical and biochemical cholestasis is the predominant form of presentation. The confirmation of chronic rejection requires a liver biopsy, where loss of small bile ducts and obliterative angiopathy are evidenced. In the early stages, the changes may mimic acute rejection, with a dense portal tract infiltration and bile duct endothelitis. The presence of foamy macrophage infiltration of arterial branches supports the diagnosis.[33,34] The treatment is based on the same principles than acute rejection. Response though is infrequent. Once bilirubin is greater than 10 mg/dl, a response to immunosuppressive therapy is uncommon and liver retransplantation should be considered.

2. Renal failure

Post-transplantation chronic renal failure is closely related to the use of calcineurin inhibitors (CNI) (cyclosporine and tacrolimus). The prevalence is variable, depending on the criterion used to define it and to the method used to assess renal function. Indeed, serum creatinine measurement may underestimate the presence of renal failure. Significant renal failure is defined by a serum creatinine level above 2.3 mg/dl or a glomerular filtrate rate below 50 ml/min. Chronic nephrotoxicity due to calcineurin inhibitors includes vascular damage (arteriopathy), tubular atrophy and interstitial fibrosis.

Risk factors implicated in the development of significant renal failure in the first post-transplantation year are advanced age of the recipient, post-transplantation infection due to cytomegalovirus, the need for dialysis during surgery or in the immediate postoperative stage and retransplantation. The need for renal support and advanced age probably indicate previously deteriorated renal function, while cytomegalovirus infection and retransplantation reflect greater deterioration of the general condition and more powerful immunosuppression.

The treatment of chronic renal dysfunction related to CNI's is not well established; other causes have to be discarded first, in particular other potentially reversible conditions such as neuropathy due to non-steroid anti-inflammatory agents. In patients with mild renal dysfunction, the reduction of the CNI dose may be sufficient to normalize the renal function. While most patients tolerate this decrease with any complications, some need the addition of/or increase of another immunosuppressive agent without renal toxicity (such as azathioprine, mycophenolate mofetil, sirolimus). Another strategy, particularly in patients with severe damage, is the progressive withdrawal of the CNI drug and its replacement by a non-nephrotoxic immunosuppressive drug.[35,36]

3. Arterial hypertension

Arterial hypertension (AHT) is a frequent complication in liver transplant recipients. Its prevalence varies between 50-70% in the first post-transplantation months but decreases thereafter probably due to the reduction of the immunosuppressive doses. AHT seems to be less frequent and late in those immunosuppression protocols that are based on tacrolimus than in those based on cyclosporine. The pathogeny is not well defined but possibly involves the vasoconstriction of the afferent renal arterioles leading to changes in glomerular filtration and sodium excretion. Steroids also play an important role and their withdrawal is associated with improved blood pressure. The general principles of AHT treatment are similar to those used in the general population, including low sodium diet and weight loss. Specific measures include the reduction in CNI doses and early steroid withdrawal within the first 3-6 months post-transplantation. Care must be taken in relation to possible drug interactions between immunosuppressive agents and anti-hypertensive drugs. The drugs of first choice are those that induce vasodilatation as calcium antagonists. Inhibitors of the angiotensin converter enzyme and the loop diuretics are also used.[35-38]

4. Diabetes mellitus

A variable percentage of patients, 4-20% according to the series, will develop diabetes mellitus following transplantation (*de novo* DM). The prevalence depends on the time elapsed since transplantation and particularly on the immunosuppressive drugs. In the initial post-transplantation period, DM is very frequent, probably due to the use

of high CNI and steroid doses. The use of long-term steroids predisposes a state of insulin resistance. In addition, cyclosporine and tacrolimus can cause altered insulin synthesis and secretion. Additional risk factors are a recipient advanced age, a family history of diabetes, obesity and the number of rejection episodes. Finally, diabetes mellitus prior to transplantation is a frequent finding in liver transplant recipients, particularly those with alcoholic cirrhosis or cirrhosis secondary to chronic infection by the hepatitis C virus.[39,40]

5. Dyslipidemia

With the exception of patients with cholestatic disease, who frequently present hypercholesterolemia tied to bile secretion alteration, most cirrhotic patients have synthesis-reduction related hypocholesterolemia. In the post-transplantation sertting 17-66% develop serum lipids changes that can require dietary and/or pharmacological treatment. The etiology of post-transplantation hyperlipidemia involves many factors, such as the diet, genetic predisposition, *de novo* DM, post-transplantation kidney dysfunction, and immunosuppressive treatment. In particular, steroids play a significant role in hyperlipidemia onset mediated by increased hepatic secretion of VLDL and of its conversion to LDL. The use of CNI is also related with the development of hypercholesterolemia and hypertriglyceridemia. Sirolimus is a relatively new immunosuppressive drug that has as a major side effect the development of hyperlipemia. Treatment is focused on patients with persistent dyslipidemia, particularly if they have concurrent cardiovascular risk factors. Appropriate diet, weight reduction, strict control of DM and arterial hypertension along with smoking or drinking cessation are initial measures. Secondarily, HMG-CoA reductase inhibitor drugs such as pravastatin can be used as second line alternatives.

6. Obesity

Obesity is a very frequent complication in transplanted patients with a prevalence that ranges between 15 and 40% one year after transplantation, the period when the greatest weight gain is seen. Many factors are involved in this complication, including pre-transplantation obesity, post-transplantation sedentary life style, and greater food intake following transplantation. Drugs also play a significant role; the frequency of obesity seems to be higher with cyclosporine than with tacrolimus. Withdrawal of steroids within the first 6 months can be useful in these patients. The treatment of obesity is focused to its prevention since the treatment of morbid obesity is frustrating and has few effective results. The initial steps must include ongoing dietary advice and progressive introduction of physical exercise.[39,40]

7. Bone complications

Osteopenia is a frequent finding in patients with advanced, chronic liver disease, particularly in those with cholestatic disease. Globally, 20-40% of liver transplant recipients present atraumatic bone fractures; this prevalence rises to 65% in patients transplanted due to cholestatic disease and in retransplant patients. The most frequent locations are the vertebrae and the ribs. Multiple factors have been implicated, such as hormonal changes associated with the pathogenesis of the liver disease, prolonged immobilization, and immunosuppressive treatment, particularly steroids. Indeed, immunosuppression by itself affects bone density through its influence on the cytokines that intervene in bone metabolism. In addition, some of the drugs directly suppress osteoblast function, inhibit intestinal absorption of calcium, and stimulate its secretion through the kidneys. Calcium, vitamin D, calcitonine and biphosphonates have been used to avoid post-transplantation osteoporosis, but no consensus has been reached yet as to the best approach.[41,42]

8. Neurological complications

A large proportion of liver transplant recipients develop some degree of neurotoxicity secondary to CNI. The prevalence seems to be slightly higher with tacrolimus than with cyclosporine. Tremor, the most frequent symptom, usually responds to calcineurin inhibitors dose reduction. Headache, paraesthesia or insomnia are other complaints that can actually become very disabling. Chronic headache may improve with reduction of the CNI doses; if no other cause is identified, beta blockers, tricyclic anti-depressants and calcium antagonists may be useful.[18]

9. Malignancy

De novo malignancy developing after transplantation constitutes a well-known complication of organ transplantation; indeed, 5-15% of patients who receive a solid organ transplant develop a *de novo* tumor, with a prevalence of cancer doubling that seen in the normal population. The duration and intensity of immunosuppression, the type of transplant and the disease that motivated the transplantation are known factors associated with this complication. Although malignant tumors can appear at any time after transplantation, Kaposi's sarcoma followed by lymphoproliferative disorders are the earliest that usually develop. The later ones are skin tumors and carcinomas of the vulva and perineum. A higher frequency of oropharyngeal cancer has been described in transplanted patients for alcoholic cirrhosis, as well as increased presentation of lymphoproliferative syndromes in those transplanted for HCV-cirrhosis. The natural history of malignant tumors in the transplant patient tends

to be different from that of the normal population; they appear at an earlier age, tend to be in a more advanced stage when diagnosed, and their evolution is more aggressive, causing high mortality directly related to the tumor. Some data suggest that in patients undergoing liver transplantation in recent years, there is a higher incidence of hematological neoplasms with *de novo* internal neoplasms developing at earlier time-points than in those transplanted years ago. Risk factors for tumor development include alcohol, HCV and possibly strong immunosuppression.[43,44]

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