

Liver transplantation for nontransplant physicians

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Many of the nontransplant physicians who manage hepatic patients (internists and hepatologists) keep asking about liver transplantation. The purpose of this article is to highlight important topics a nontransplant colleague may require in his practice. There are many topics in this respect; however, three most important topics need to be highlighted; those are; the time of referral to transplantation, the indications and contraindications and the metabolic issues regarding a transplanted patient. Still, there are no clear guidelines for the management of many of the metabolic issues regarding liver transplanted patients. And this why, collaborative efforts of transplant and nontransplant physicians are needed to conduct multicenter, long term randomized controlled trials and proper follow up programs.

Keywords:

calcineurin inhibitors, liver transplantation, new-onset diabetes mellitus after transplantation, post-transplantation metabolic complications, post-transplant diabetes mellitus

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Introduction

Liver transplantation (LT) has become the only curable treatment for liver cell failure, fulminant liver failure, and hepatocellular carcinoma (HCC).

Liver diseases (specially chronic HCV) are national health problems in Egypt. They have a great impact on health insurance programs, national human and financial resources. Hence, the remarkable continuous growth of liver transplantation programs and the escalation of the number of transplanted patients.

Besides, LT generally has a 5-year survival rate of 70–80%. Given the increasing lifespan of those patients, the recognition and prevention of long-term complications after transplantation have become ever more important.

Among the many post-liver-transplantation complications, metabolic complications are very common. In the era of LT, physicians may encounter such patients in the ER or in their clinic; therefore, they should be acquainted with such complications in a way that will help them manage those patients in cooperation with the transplant team.

The purpose of this review is to highlight the important issues regarding LT that an internist should know.

This article highlights the following issues:

(1) Indications and timing for referring a hepatic patient for LT.

- (2) Contraindication for LT.
- (3) Late post-transplantation complications.

Timing of referral of a hepatic patient to a liver transplantation center

The timing should aim at:

- (1) improving the quality of the patient's life, or
- (2) saving the patient's life.

Therefore, a patient who has a liver disease that is incapacitating him or will result in a life-threatening situation should be referred to a liver transplantation center for evaluation.

Indications for liver transplantation

- (1) Decompensated cirrhosis (due to any etiology – e.g. chronic viral hepatitis, steatosis, AIH, PBC, or vascular, metabolic, and inherited diseases).
- (2) Fulminant liver failure (e.g. Wilson's and drug-induced liver injury).
- (3) Compensated cirrhosis in cases of life-threatening complications, as in HCC, or when complications incapacitate the patient's life, as in HPS, and in chronic encephalopathy.
- (4) Malignant liver diseases.

Contraindications to liver transplantation

Absolute

- (1) Extrahepatic malignancy.
- (2) HCC (advanced stage).
- (3) Advanced cardiopulmonary disease.
- (4) Uncontrolled sepsis/active infection.
- (5) AIDS.

(6) Persistent noncompliance and/or lack of adequate social support.

Relative

- (1) Age more than 60 years (variable among centers).
- (2) Intrahepatic cholangiocarcinoma.
- (3) Hepatopulmonary syndrome (if pulmonary pressure is > 40 mmHg).
- (4) Previous major abdominal surgery.

It should be noted that these contraindications may differ from country to country and from center to center.

Late post-transplant metabolic complications

With the availability of LT and the increasing longevity of liver-transplanted patients, metabolic complications, mainly metabolic syndrome (or its components), are expected to commune into an epidemic waiting to happen [1].

A study of 252 liver transplant patients found that 52% had metabolic syndrome following transplantation compared with only 5% before transplantation [2].

The clinical features of metabolic syndrome, either alone or in combination, contribute to post- LT morbidity and mortality. The clinical factors related to LT that exacerbate metabolic syndrome are shown in Table 1 [3].

It should be noted that studies in this field have been few until now, and that the definition and diagnosis of metabolic syndrome or of any of its components have been the same for nontransplanted patients until now.

The development of metabolic complications is mainly due to the side effects of the immunosuppressives used, as shown in Table 1 [3].

Diabetes mellitus

New-onset diabetes mellitus after transplantation (NODAT), or post-transplant diabetes mellitus, is common. In LT recipients followed up beyond 1 year, estimates of the prevalence of NODAT vary from 5 to 26% [3]. In a retrospective study involving 40 liver transplant patients in KA Cairo University Hospital, 25% developed NODAT [4].

Risk factors include

- (1) Immunosuppressive drugs: glucocorticoids and calcineurin inhibitors (CNI) (cyclosporine and tacrolimus) (Table 2) [5].
- (2) Weight gain (discussed later).
- (3) Chronic viral C hepatitis (HCV).

The mechanism of action is mainly through the development of an insulin-resistant state .

Both tacrolimus and cyclosporine (first-line immunosuppressive drugs used in LT) exert direct cytotoxic effects on pancreatic B islet cells (tacrolimus more than cyclosporine). Moreover, the development of weight gain and obesity after Tx also leads to a state of insulin resistance [6].

Chronic HCV also leads to a state of hyperinsulinemia, resulting in glucose intolerance and/or diabetes mellitus [7].

Mortality and morbidity are mainly related to graft survival, infections, and cardiovascular complications.

The development of diabetes does not adversely affect survival in the first year of transplantation, but it is associated with decreased survival after the first year. This is mainly because of increased prevalence of infection [8].

Table 1 Factors associated with the clinical features of metabolic syndrome [3]

Factor	Corticosteroids	Tacrolimus	Cyclosporine	Sirolimus	Chronic HCV
Abdominal obesity	+	-	-	-	-
Dyslipidemia	+	+	+	+++	-
Systemic hypertension	+	++	++	+	-
Insulin-resistant DM	+++	++	+	-	++

DM, diabetes mellitus; HCV, hepatitis C virus.

Table 2 Drug-induced new-onset diabetes mellitus after transplantation; potential mechanisms [5]

Immunosuppressive agent	Pathogenic mechanism(s)	Comments
Corticosteroids	<ul style="list-style-type: none"> • ↓ Peripheral insulin sensitivity • Inhibit pancreatic insulin production and secretion • ↑ Hepatic gluconeogenesis • Promote protein degradation to free amino acids in muscle, lipolysis 	<ul style="list-style-type: none"> • Dose-dependent • Impact of complete withdrawal of chronic low-dose steroids unclear • Potential ↓ NODAT risk in steroid-free regimens
Cyclosporine	<ul style="list-style-type: none"> • ↓ insulin secretion (CsA < Tac) • ↓ insulin synthesis • ↓ β-cell density 	<ul style="list-style-type: none"> • Dose-dependent. • Diabetogenic effect ↑ with ↑ steroid dose*
Tacrolimus	<ul style="list-style-type: none"> • ↓ insulin secretion (Tac > CsA) • ↓ insulin synthesis 	<ul style="list-style-type: none"> • Dose-dependent. • Diabetogenic effect ↑ with ↑ steroid dose*
Sirolimus	<ul style="list-style-type: none"> • ↑ Peripheral insulin resistance • Impair pancreatic β-cell response 	<ul style="list-style-type: none"> • ↑ Diabetogenicity when use with CNIs

CNI, calcineurin inhibitors; NODAT, new-onset diabetes mellitus after transplantation; *Demonstrated in some but not all studies; Arrow up=increased; Arrow down=decreased.

NODAT tends to remit over time, especially as corticosteroids are withdrawn and the tacrolimus dosage is reduced, and patients may go from insulin therapy to oral hypoglycemic agents to diet control only over the years [3].

Management

- (1) Diabetes should be screened for by evaluating fasting plasma glucose levels or hemoglobin A1C every 6 months.
- (2) Annual eye examinations to identify cataract or diabetic changes should be carried out every 6 months.
- (3) The goals of the long-term management of diabetes after LT are not substantially different from the goals for nontransplant patients (Table 3) [3].
- (4) Insulin is generally used in the perioperative and postoperative period and until stabilization of graft function. Patients may be switched to oral antidiabetics later.
- (5) Doses of immunosuppressive drugs should be modified or patients should be shifted to other forms of therapy (in cooperation with the transplant physician).

Treatment of new-onset diabetes mellitus after transplantation

This includes standard medical and nutritional therapy in the form of lifestyle changes, by limiting caloric intake and through appropriate diet, weight control, and initiation of pharmacologic agents for treatment of diabetes (Table 3) [9].

In the perioperative and early postoperative period, insulin is generally required. A combination of NPH and regular insulin should be used to cover postprandial increases in blood glucose.

When insulin requirements are low, oral agents may be substituted if graft function is normal. Metformin or a sulfonylurea may be used in LT recipients with normal renal function, whereas sulfonylureas such as glipizide and glimepiride are preferable if there is any deterioration in renal function. The safety of thiazolidinediones in LT recipients is unproven. Retrospective data and a small prospective study suggest that the conversion of immunosuppressive from tacrolimus to cyclosporine improves glycemic control in patients with established DM and NODM [10]. This is because tacrolimus is more diabetogenic than cyclosporine [11].

In addition, modulating immunosuppression, including lowering or cessation of glucocorticoids, may be of benefit (Table 4).

The goal of therapy

There is controversy regarding the appropriate target level of hemoglobin A1c; consequently, the recommendation of a threshold less than 7.0% rather than a threshold less than 6.0% reflects the view that the more demanding standard may confer no additional advantage [3].

Hypertension

Cirrhotic patients have a hyperdynamic state. Reversal begins immediately after LT and is complete in 6 months. Approximately 65–70% of liver transplant recipients develop hypertension after transplantation [12].

Causes and risk factors

The main contributors to hypertension after LT are immunosuppressives: CNI (cyclosporine or tacrolimus) and steroids.

CNIs cause vasoconstriction of afferent renal arterioles, triggering the RA system and leading to salt and water retention. Steroids further potentiate the condition [13].

By comparison, steroids are usually not a major risk factor for chronic hypertension in transplant recipients because of rapid dose reduction. However, they may

Table 3 Long-term management of diabetes mellitus (new-onset or pre-existing) after liver transplantation [3]

	Intervention	Frequency
Diagnosis Monitoring	Fasting plasma glucose	Every 3 months in the first year and then annually
	Self-monitoring of blood glucose	Review every 3 months
	HbA1c	Every 3 months (intervention at $\geq 7.0\%$)
	Diabetic complications	Annual screening (retinopathy)
Treatment	Microalbuminuria	Annual screening
	Tailoring of immunosuppression (especially if there is poor control): discontinuation of steroids and change from tacrolimus to cyclosporine	
	Lipid levels	Annual evaluation
	For all patients	
	Dietary and lifestyle modification: exercise and weight loss (if the patient is obese)	
	Control of hypertension and dyslipidemia	
	Depending on glycemic control	
	Insulin*	
	Oral agent or agents	
	Insulin ± oral agent (if there is poor control)	

*This should be interpreted with care for patients with anemia or renal impairment. Refer patients to an endocrinologist once insulin is started.

Table 4 Showing the stepwise approach for treating dyslipidemia in liver transplant patients [3]

<p>Elevated low-density lipoprotein cholesterol level > 100 mg/dL (with or without elevated triglycerides)</p> <ol style="list-style-type: none"> 1. Therapeutic lifestyle and dietary changes 2. Statins 3. Addition of ezetimibe <p>Hypertriglyceridemia with normal cholesterol</p> <ol style="list-style-type: none"> 1. Fish oil at 1000 mg twice daily to 4 g daily if tolerated 2. Fibric acid derivatives <p>Refractory hyperlipidemia: consider changes in immunosuppression</p>
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play a contributory role, and a gradual withdrawal of steroid therapy results in a fall in blood pressure in most patients.

Management

Because hypertension is common after transplantation, it is suggested that for the first 6 months following transplantation the patient's blood pressure be assessed at home by self-monitoring every week and by a healthcare provider every month.

In patients without hypertension after 6 months, blood pressure monitoring should be performed by a healthcare provider every 6 months.

The goal of therapy

A target blood pressure of less than 130/80 mmHg is reasonable for liver transplant recipients as most have multiple risk factors for cardiovascular disease (e.g., diabetes, obesity, dyslipidemia) [3,14].

Most transplant centers approach hypertension with a stepwise approach, including the following:

- (1) Limiting salt intake.
- (2) Assessing CNI serum levels.
- (3) Modulating CNI dose if the level is inappropriately elevated.
- (4) Drug therapy if all else fails.

Drug therapy

If antihypertensive medications are required, calcium channel blockers are recommended, as a part of the mechanism of hypertension is thought to be due to renal arteriolar vasoconstriction. Amlodipine, felodipine, and nifedipine are preferred as first-line agents as they are long-acting, minimally interact with CNIs, and have limited side effects. First-generation calcium channel blockers (e.g. nifedipine or verapamil) may inhibit cytochrome P450, increasing CNI levels, and should be avoided.

Up to 30% of patients will require more than one agent to control their blood pressure. If calcium channel blockers are not effective or are not tolerated, the addition or substitution of a cardioselective β blocker, such as metoprolol or atenolol, is suggested. Nonselective beta blockers may decrease portal blood flow, compromising graft function. An angiotensin-converting enzyme (ACE) inhibitor or angiotensin-2 receptor blocker (ARB) can also be used in patients with difficult-to-control hypertension and may have additional benefits in diabetic patients with microalbuminuria. However, ACE inhibitors and

ARBs may have untoward effects on renal function in patients taking CNI inhibitors and may induce hyperkalemia; they should therefore be used with caution [15].

Diuretics are not used as primary therapy for hypertension because of concerns related to the potential to exacerbate electrolyte disturbances and dyslipidemias induced by CNIs [16].

Dyslipidemia

Dyslipidemia is common after LT, and patients should have a fasting lipid profile obtained annually. Hypercholesterolemia develops in 16–43% of patients and hypertriglyceridemia in 40–47%; reduced serum high-density lipoprotein cholesterol is also common [17].

Hypertriglyceridemia usually develops within the first month after transplantation and then remains stable throughout the first year. By comparison, serum cholesterol increases gradually and plateaus at 6 months.

Dyslipidemia after Tx is a major risk factor for CV morbidity and mortality.

Risk factors include the following:

- (1) Pretransplantation dyslipidemia.
- (2) Drugs (steroids, CNI).
- (3) NODAT.
- (4) Obesity.

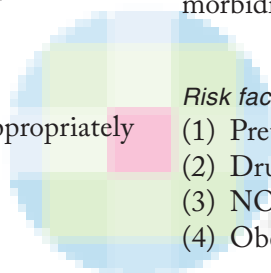
Glucocorticoids increase activity of acetyl-CoA carboxylase, free fatty acid synthetase and HMG CoA reductase, leading to elevated VLDL, total cholesterol, and triglycerides and reduced high-density lipoprotein (HDL).

CNI induces hypercholesterolemia through inhibition of sterol 27-hydroxylase, a key enzyme in the bile acid biosynthetic pathway, as well as through binding of the drug to the low-density lipoprotein (LDL) receptor [18].

Management

- (1) Screening by biannual assessment of the lipid profile.
- (2) Lifestyle and dietary recommendations as in nontransplanted patients.
- (3) Revision of the type and dose of CNI and withdrawal of steroid therapy.
- (4) Drug therapy.

Most patients are treated with a statin. Pravastatin and fluvastatin are preferred because of decreased interactions with immunosuppressants.



The goals of treatment depend upon whether the patient has a history of cardiovascular disease and other risk factors for cardiovascular disease.

Ezetimibe has also been studied alone or as an adjunct to a statin in liver and kidney transplant recipients. It has been shown to reduce low-density lipoprotein levels with generally stable levels of immunosuppression and a low risk for serious side effects. However, there have been reports of myalgia, rhabdomyolysis, hepatitis, acute pancreatitis, and thrombocytopenia. In addition, studies in patients outside of the transplant setting have failed to show convincing evidence for clinical benefits from ezetimibe [19].

Dyslipidemia improves in many patients over time if the maintenance dose of tacrolimus or cyclosporine is low, and after withdrawal of steroids.

Obesity

Weight gain is common after LT. In American and European cohorts, ~20% of lean patients become obese (BMI >30 kg/m²) in the first 2–3 years after LT; this phenomenon is driven by the restoration of health and by the stimulation of appetite by medicines such as corticosteroids [20].

Approximately one-third of patients who are of normal weight at the time of transplantation will become obese after transplantation. Body weight tends to increase during the first 2 years after transplantation and then stabilizes [21].

Risk factors

- (1) Pretransplantation overweight.
- (2) Cumulative dose of steroids used during the post-transplantation period.

Management

Overweight liver transplant recipients may have great difficulty losing weight. Excessive weight gain often leads to reduced physical activity, which predisposes to further weight gain and a sedentary lifestyle. Thus, prevention of excessive weight gain through patient education, nutritional counseling, and an exercise program is important for reducing post-transplantation morbidity [22].

The treatment for obesity includes caloric restriction, encouraging exercise, and tapering steroids, with an initial goal of losing one to two pounds per week. If these measures fail to result in adequate weight loss, additional treatment options include switching from cyclosporine to tacrolimus and possibly bariatric surgery [23].

Cardiovascular risk

It should be mentioned that, although the hemodynamic state typical of advanced liver disease results in a low prevalence of systemic hypertension and although impaired hepatic production of lipids may reduce serum cholesterol levels, coronary artery disease is at least as frequent in LT candidates as in the general population and is influenced by typical cardiovascular risk factors [24].

Because of the high rates of hypertension, diabetes, obesity, and dyslipidemia following LT, it is not surprising that coronary heart disease is also common.

After excluding infection, recurrent disease, graft loss due to technical complications, and de novo malignancy, coronary heart disease is the most common cause of death after LT [25].

As in any patient with cardiovascular disease, modification of risk factors both before and after LT is essential for maximizing outcomes. Thus, treatment and prevention of obesity, hyperlipidemia, diabetes, and hypertension is priority. At present, no clear guidelines exist for invasive modalities (coronary angiography) and noninvasive modalities (cardiac stress testing) for assessing cardiac function and coronary artery patency after LT. Our approach is to perform adenosine or dobutamine stress testing every 3–5 years in patients with risk factors for coronary artery disease and more frequently in patients with pre-existing coronary artery disease [26].

Suggested long-term follow-up plan in liver transplant recipients

- (1) General assessment: annual history and physical examination, as well as annual dental evaluation in addition to routine (twice yearly) cleaning.
- (2) Hypertension: for the first 6 months following transplantation, self-monitoring every week and blood pressure monitoring by a healthcare provider every month. In patients without hypertension after 6 months, blood pressure monitoring by a healthcare provider every 6 months.
- (3) Diabetes mellitus: screening every 6 months (typically with fasting plasma glucose or a hemoglobin A1C) and an annual eye examination to check for cataract or diabetic changes.
- (4) Dyslipidemia: annual fasting lipid profile.
- (5) Cardiovascular disease: stress testing every 3–5 years in patients with risk factors for coronary artery disease and more frequently in patients with pre-existing coronary artery disease. Exercise stress testing is preferred for those who are able to perform the test. For those unable to perform exercise stress testing, adenosine and dobutamine stress tests are alternatives.

Other post-liver transplantation metabolic complications

- (1) Osteopenia.
- (2) Renal complications.

Conclusion

As the outcome of patients is improving and the number of transplanted patients is increasing, and because metabolic complications are common after LT, the role of the internist is crucial in follow-up and management of these patients. Cooperation between internists and the transplant team is essential.

Liver transplant recipients have a higher risk for cardiovascular death and ischemic events compared with an age-matched and sex-matched population who have not undergone LT. The clinician must be diligent at administering efficacious and prompt treatment for these modifiable risk factors, in the form of lifestyle changes, pharmacological therapy, and immunosuppressive regimen alterations, to prevent serious complications.

Guidelines specifically considering PTMS (rather than adopting those for nontransplanted patients) are strongly needed, for which multicenter trials and RCTs are of paramount importance (Table 4).

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Conflicts of interest

There are no conflicts of interest.

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