

Medical Management of Metabolic Complications of Liver Transplant Recipients

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Abstract: Improved short- and long-term survival of liver transplant recipients has led to increased focus on complications of both the early and late posttransplant periods. A variety of metabolic complications have been observed in the post-orthotopic liver transplant population, including hypertension, hyperlipidemia, obesity, diabetes mellitus, nonalcoholic fatty liver disease, and nonalcoholic steatohepatitis. Although only a small proportion of patients experience metabolic complications prior to transplantation, the prevalence of these complications posttransplantation reaches or exceeds that of the general population. This is of particular concern, as cardiovascular disease is the second leading cause of death in the late transplant period. A number of mechanisms mediate these metabolic complications, including reversal of cirrhosis pathophysiology, patient lifestyle factors, and immunosuppressive medications. Titration and modification of immunosuppression have been demonstrated to improve and sometimes even eliminate these conditions. Therefore, given the multiple etiologies contributing to the metabolic derangements, an effective management approach must incorporate lifestyle modifications, immunosuppression titration, and medical management. Best practices and understanding of the mechanisms underlying these complications allow for discussion of initial therapies and strategies; however, further study is necessary to determine the optimal management of metabolic complications over time.

Liver transplantation is the most effective treatment for end-stage liver disease, resulting in increased survival and quality of life for the recipient. Developments and advancements in surgical techniques, as well as the implementation of tolerable and effective immunosuppressive regimens, have resulted in steady gains in post-liver transplant outcomes, with survival of recipients at 1 and 5 years reported to be 86.9% and 73.9%, respectively.¹ With improvements in short- and long-term survival following liver

Keywords

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transplantation, new dilemmas, particularly metabolic complications and their associated increased cardiovascular disease risk, have risen in the management of the liver transplant recipient.² Cardiovascular disease is the second leading cause of death in the late posttransplant period.³ Retrospective analysis has demonstrated that despite the low incidence of cardiovascular disease prior to liver transplantation, 10.6%, 20.7%, and 30.3% of transplant recipients developed cardiovascular disease at 1, 5, and 8 years posttransplant, respectively.⁴ A variety of metabolic factors contribute to increased cardiovascular disease risk, including hypertension, hyperlipidemia, diabetes mellitus, and obesity. Although these disorders affect the general population, their prevalence in transplant recipients, as well as their potentiation by the same immunosuppressive medications that lead to improved long-term graft function, is of particular concern.⁵ Additionally, the management of these complications in the post-liver transplant patient is poor. A 2009 survey of hepatologists found that only one-third of clinicians perceived that their transplant patients' hypertension was well controlled.⁶ Findings were similar regarding hyperlipidemia and diabetes mellitus.⁶ This review outlines the incidence and etiology of the aforementioned post-liver transplant metabolic complications and comments on the management strategies currently available.

Hypertension

Hypertension is both a common and significant condition in the post-liver transplant patient, with an established association of increased risk of cardiovascular events.⁷ End-stage liver disease is characterized by a state of high cardiac output accompanied by low systemic vascular resistance and low mean arterial pressure. This state is reversed by liver transplantation itself. Following transplantation, 45% to 75% of patients meet criteria for arterial hypertension, which is defined as a systolic blood pressure greater than 140 mm Hg and/or a diastolic blood pressure greater than 90 mm Hg.⁸ The onset of arterial hypertension occurs rapidly following transplantation; 50% of liver transplant recipients develop hypertension within 6 months postprocedure.⁹ The etiology of post-transplant hypertension is multifactorial and includes the change in hemodynamics noted previously and, perhaps more relevant, the immunosuppressive medications essential to maintaining the graft.

Standard immunosuppressive regimens currently employed, which typically include a calcineurin inhibitor and glucocorticoid, have been associated with exacerbation of existing arterial hypertension as well as de novo hypertension.¹⁰ Calcineurin inhibitors lead to increased blood pressure by a variety of mechanisms. The

primary mechanism is widespread arterial vasoconstriction leading to increased systemic vascular resistance, followed by induction of the renin angiotensin aldosterone system, reduction in prostacyclin and nitric oxide production, and increase in thromboxane and endothelin release.¹¹ However, not all calcineurin inhibitors are equal. The prevalence of hypertension in patients treated with cyclosporine is 58% to 82% compared with 31% to 38% in patients maintained on tacrolimus.¹² Glucocorticoids increase blood pressure through the renin angiotensin aldosterone system, a reduction in prostacyclin and nitric oxide production, or an increase in the quantity of angiotensin II receptors.^{13,14} Although it is widely accepted that both calcineurin inhibitors and corticosteroid therapy are essential for graft survival, it is important to consider their role in hypertension and their influence on the risk of cardiovascular disease in the patient in the late posttransplant period.

The control of hypertension is essential to the long-term survival of the graft recipient given its well-established role in the development of cardiovascular disease. Cardiovascular disease was cited as the cause of death in 21% of liver transplant recipients with good graft function who survived 3 or more years.¹⁵ Given this percentage, most transplant recipients are considered high risk by cardiovascular standards, and a goal blood pressure of lower than 130/80 mm Hg is targeted to minimize cardiovascular disease risk.¹⁶ At the initial recognition of hypertension, lifestyle modifications (eg, adoption of a low-sodium diet, cessation of smoking, avoidance of alcohol, and loss of weight, when appropriate) should be emphasized to the patient. However, if these measures are ineffective, calcium channel blockers (CCBs) are the preferred first-line agents in patients who do not exhibit proteinuria in order to directly counteract the vasoconstriction associated with calcineurin inhibitors. Of the CCBs available, the dihydropyridine class is preferred due to its relatively decreased medication interaction as compared with the nondihydropyridine CCBs.¹⁷ Patients with proteinuria and hypertension should take an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker as a first-line agent.¹⁷ However, due to low activity of plasma renin in the early posttransplant period, these agents are more effective in the late posttransplant period.¹⁸ If single-agent therapy in combination with appropriate lifestyle modifications is ineffective, the results of a 2008 study have demonstrated that combined CCB and ACE inhibitor therapy is more effective than ACE inhibitor and beta blocker therapy.¹⁹ Diuretic therapy is typically avoided, as the volume contraction in the face of renal vasoconstriction may lead to impaired renal function.¹⁸ It is also important to note that antihypertensive selection

can significantly impact levels of immunosuppressive medications, especially in the case of beta blockers. Levels should be monitored and adjusted accordingly following the initiation of therapy.

If the aforementioned strategies are unsuccessful, practitioners may need to down-titrate or modify the patient's immunosuppressive regimen. The rapid taper of glucocorticoids, when possible, can improve blood pressure.¹⁸ As previously mentioned, patients maintained on cyclosporine as opposed to tacrolimus have increased rates of hypertension.¹² Transition from cyclosporine to tacrolimus has been shown to improve blood pressure in liver and kidney transplant recipients.²⁰ Switching to mycophenolate mofetil or sirolimus in place of a calcineurin inhibitor is another option.¹⁷ However, this strategy presents a risk of insufficient immunosuppression. Ultimately, practitioners must find the balance between antihypertensive therapy and immunosuppressive modulation to appropriately control blood pressure and preserve the graft.

Hyperlipidemia

Hyperlipidemia is uncommon in the pre-liver transplant population due to impaired hepatic synthetic function in the setting of cirrhosis.²¹ However, this metabolic derangement is commonly reported in 45% to 71% of liver transplant recipients.^{18,22} Lower-density lipoprotein concentrations reduce the risk of cardiovascular disease, and because liver transplant recipients have an approximately 64% greater risk of cardiovascular events, appropriate management of hyperlipidemia is essential for long-term survival.^{23,24}

Hyperlipidemia in the posttransplant patient is multifactorial. Body weight, renal function, nutritional status, glycemic control, genetic predisposition, donor factors, and immunosuppressive medications all contribute to the degree of hyperlipidemia that is observed in a patient.^{18,21} Notably, early renal dysfunction posttransplant has been identified as an independent contributor to hyperlipidemia.²⁵ In regard to specific immunosuppressive drugs, cyclosporine increases serum lipid concentrations depending on dosage. Converting from a cyclosporine-based regimen to a tacrolimus-based regimen has been shown to improve posttransplant hyperlipidemia.²⁶ However, tacrolimus can induce hyperinsulinemia, which may ultimately lead to lipid derangements, especially hypertriglyceridemia. Mammalian target of rapamycin inhibitors are also known to increase the risk of hyperlipidemia, although they often do not exacerbate existing hyperlipidemia and, if their usage in lieu of calcineurin inhibitors leads to improved renal function, they may ultimately improve a patient's lipid profile.²⁷

Hyperlipidemia associated with immunosuppressive medications responds to traditional lipid management strategies such as weight loss, dietary modification, optimization of blood glucose control, and utilization of lipid-lowering agents.²⁸ As in the general population, lipid-lowering therapy primarily targets serum total cholesterol and low-density lipoprotein (LDL) in liver transplant recipients. Although no specific total cholesterol and LDL goals have been identified for the post-liver transplant patient, the general guidelines of the American Heart Association are often used to guide therapy.² In the absence of other significant risk factors, the goal of LDL should be at least 130 mg/dL for most patients.²¹ As with all patients, dietary and lifestyle modifications are first-line treatments for hyperlipidemia in liver transplant recipients. In addition, patients should be evaluated for secondary causes of hyperlipidemia, such as hypothyroidism, diabetes mellitus, and nephrotic syndrome.

Statin therapy is considered safe in the liver transplant patient, with pravastatin and fluvastatin being the preferred agents for patients on calcineurin inhibitors given the lack of interaction with cytochrome P450 3A4.²⁹ Importantly, concurrent use of nicotinic acid and/or fibrates with statin therapy increases the risk of myopathies and, thus, should be avoided.³⁰ Following initiation of statin therapy, close monitoring of creatine kinase levels and liver function tests are recommended. Additionally, patients should be counseled regarding myalgias as a potential early warning of rhabdomyolysis or myositis.

Obesity

Obesity is a national epidemic, with the average body mass index (BMI) increasing across all cohorts. The Centers for Disease Control and Prevention defines obesity as a BMI of greater than 30 and morbid obesity as a BMI of greater than 35.³¹ It is estimated that 15% to 30% of pretransplant patients meet the criteria for obesity.³² When considering the pretransplant patient with end-stage liver disease, it is important to note that assessments of pretransplant BMI may be skewed by the quantity of ascites. Therefore, total body dry weight is a more reflective measurement for risk stratification. However, these data are not always available.¹⁸ The United Network for Organ Sharing (UNOS) database reports that 54% of liver transplant recipients worldwide are considered overweight or obese.³³ BMI increases progressively with time; at 1 year postprocedure, 33.7% of patients meet the criteria for obesity, and by 5 years, 40.3% of patients meet the criteria.⁴ This is particularly concerning, as there is a higher prevalence of cardiovascular events in the severely and morbidly obese cohorts in the posttransplant period that lead to a significant increase in 5-year mortality.³³

A variety of factors lead to an increased propensity for weight gain following transplant, such as corticosteroid usage and reversal of cirrhosis.¹⁸ Most patients who are overweight or obese prior to transplantation remain so following the procedure. Furthermore, one-third of patients of normal weight prior to transplant become obese following the procedure.³² Overweight posttransplant patients are more likely to have a family history of diabetes mellitus, atherosclerosis, and hypertension.³⁴ Risk factors for posttransplant obesity include age greater than 50 years, obesity prior to transplant, and higher cumulative corticosteroid dose.^{18,35} Pretransplant diabetes mellitus, diabetes mellitus at 1 year posttransplant, and nonalcoholic fatty liver disease (NAFLD) are also predictive of obesity following transplant.⁴ In addition, patients undergoing transplantation for chronic liver disease are at a higher risk of obesity compared with patients undergoing transplantation for fulminant hepatic failure.³⁶

Patients should be advised to achieve a healthy body weight prior to undergoing transplantation, as obesity is associated with numerous negative postoperative outcomes such as prolonged stays in an intensive care unit and poor wound healing.³⁷ Sawyer and colleagues demonstrated that elevated BMI is associated with multisystem organ failure and early postoperative death.³⁸ Furthermore, weight gain places transplant recipients at risk of complications, including diabetes mellitus, metabolic syndrome, and nonalcoholic steatohepatitis (NASH) in the allograft.

Lifestyle modifications (eg, exercise and healthy diet) are essential for management of obesity. However, it is important to acknowledge the role that transplant medications play in the propensity for weight gain. For example, patients treated for acute rejection ultimately receive greater exposure to high-dose corticosteroids and, in turn, gain more weight.³⁹ Rapid tapering of high-dose corticosteroids can assist in weight loss. Data for calcineurin inhibitors are less definitive. Compared with tacrolimus, cyclosporine is associated with more weight gain in the first year following transplant. However, data demonstrate that this difference does not persist 2 years posttransplant.³⁶ Therefore, limitation of glucocorticoid exposure and standard counseling regarding a low-calorie diet and regular exercise remain the current methods of posttransplant obesity management.

Diabetes Mellitus

In 2012, the American Diabetes Association estimated the annual cost of diabetes mellitus at \$245 billion.⁴⁰ Diabetes is defined by a hemoglobin A1c level of 6.5% in both the general and liver transplant populations. The prevalence of diabetes ranges from 31% to 38% in

post-liver transplant patients,³² and the new onset of diabetes in the posttransplant period has a prevalence of 13% to 28% in the first year following transplantation.^{8,41} This complication can develop rapidly; some patients experience acute-onset hyperglycemia immediately following transplant and require management with an insulin drip postoperatively.⁴²

Diabetes has been found to have significant consequences in both the early and late posttransplant periods. Patients with diabetes have an increased risk of cardiovascular events, graft complications, and death.⁴³ This population also experiences a higher number of acute rejection episodes compared with nondiabetic patients.⁴⁴ Furthermore, complications of diabetes that develop in the general population, such as nephropathy and increased rates of infection, carry additional weight in the transplant population.² Currently, the relationship between early posttransplant mortality in the first year and new-onset posttransplant diabetes is not well defined. Studies have demonstrated conflicting results; however, it is clear that the diagnosis of diabetes can carry significant clinical consequences.^{41,45,46}

Numerous risk factors for diabetes in the transplant population have been identified both in regard to inherent patient characteristics and treatment effects. For example, male sex increases the risk of new-onset diabetes following transplantation.⁴⁷ Hepatitis C virus (HCV) infection also leads to an increased risk of diabetes in the transplant population via increased insulin resistance secondary to the virus itself.⁴⁸ Cytomegalovirus infection in the first year following transplantation increases the risk of new-onset diabetes as well.⁴⁹ Immunosuppressive medications also significantly contribute to the risk of de novo posttransplant diabetes, and corticosteroids have been shown to increase the risk of new-onset diabetes in a dose-dependent manner.⁵⁰ Calcineurin inhibitors predispose patients to diabetes through direct damage to islet cells. Tacrolimus has been demonstrated to have a more profound effect vs cyclosporine, resulting in a greater association with diabetes.⁵¹

It is recommended that patients are screened for diabetes at weekly intervals during the first month following transplantation and subsequently at 3, 6, and 12 months.⁵² The goal for transplant patients with identified diabetes is a hemoglobin A1c level of less than 7%.¹¹ Strict glycemic control is known to reduce the incidence of microvascular complications of diabetes in the nontransplant patient, as well as reduce the risk of myocardial infarction.⁵³ In practice, it is assumed that this likely translates to the posttransplant population as well. During the subacute and late posttransplant periods, diabetic care mirrors that of the nontransplant patient (ie, a diet low in calories and carbohydrates, moderate exercise,

Table 1. Frequency of NAFLD in LT Recipients

Histology	NASH LT Recipients	Non-NASH LT Recipients
NAFLD	31%-100%	10%-43%
NASH	11%-38%	0%-3%
Cirrhosis	0%-10%	6%-7%

LT, liver transplant; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

oral hypoglycemic agents, and insulin as needed).¹¹ Clinicians should consider that many commonly used oral diabetic medications are metabolized via the liver and, therefore, can only be utilized in patients with normal graft function.⁴² Combination therapy with rosiglitazone and sulfonylureas has been studied in the posttransplant population and has been shown to minimize and often eliminate insulin requirements.⁵⁴ Pioglitazone has demonstrated similar success in lowering hemoglobin A1c levels and decreasing insulin requirements.⁵⁵ Adjustments to immunosuppressive regimens can also help reduce the risk of posttransplant diabetes and improve glycemic control. Minimization of corticosteroids can reduce hyperglycemia, and the use of cyclosporine, rather than the more diabetogenic tacrolimus, can also improve glycemic control.⁵⁶ Mycophenolate mofetil is less diabetogenic than calcineurin inhibitors; however, complete elimination of calcineurin inhibitors risks insufficient immunosuppression and increases the chance of rejection.⁵⁷ Therefore, diabetes in the transplant patient necessitates a careful balance between lifestyle modifications, medical therapy, and immunosuppression titration.

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

The spectrum of NAFLD and NASH represents a chronic liver disease that ranges from indolent and asymptomatic to end-stage liver disease necessitating transplantation. NASH is currently projected to overtake HCV cirrhosis as the leading indication for liver transplantation in the United States.⁵⁸ A review of the UNOS database demonstrated a 4-fold increase in NASH as the etiology of end-stage liver disease requiring transplantation between 2002 and 2012.⁵⁹ NASH is observed in patients with metabolic syndrome, a condition defined by the presence of truncal obesity, dyslipidemia, impaired fasting glucose, and hypertension.⁶⁰ In addition to its emergence as a leading indication for liver transplantation, NASH is also of great concern in the posttransplant period with regard to both recurrence and de novo

Table 2. Immunosuppressant Adverse Effects

Cyclosporine	Nephrotoxicity, neurotoxicity, hypertension, hyperlipidemia, hirsutism
Tacrolimus	Nephrotoxicity, neurotoxicity, hypertension, hyperglycemia, gastrointestinal toxicity
Sirolimus	Hyperlipidemia, cytopenias, gastrointestinal toxicity
Corticosteroids	Osteoporosis, weight gain, hyperglycemia, body changes, other adverse effects
Mycophenolate Mofetil	Cytopenias, gastrointestinal toxicity

disease. Unsurprisingly, the rates of NAFLD and NASH are notably higher in recipients undergoing transplantation for NASH. However, a significant proportion (up to 43%) of the non-NASH transplant population has been observed to develop de novo NAFLD (Table 1).⁵⁸⁻⁶⁹ Independent risk factors for de novo NAFLD include obesity, tacrolimus-based immunosuppression, hyperlipidemia, diabetes, hypertension, and pretransplant liver steatosis.⁶⁰ In regard to NAFLD recurrence, it was found that the average corticosteroid dose at 6 months following transplantation was significantly higher in patients in whom recurrence was documented.⁷⁰ Additionally, an association with elevated pre- and posttransplant BMI and elevated triglyceride levels following transplantation was observed.⁷⁰ While long-term post-liver transplant survival is not significantly different in patients with recurrent NASH, there is a notable increased risk of cardiovascular disease.⁷⁰ Currently, no concrete guidelines have been established for the monitoring or treatment of NASH development or recurrence. However, expert opinion generally encourages more frequent liver biopsy and aggressive risk factor modification in patients undergoing transplantation for NASH.⁵⁸

Analysis

The prevention and treatment of metabolic complications in the liver transplant recipient is a dynamic challenge that requires management and understanding of host factors as well as the impact of the posttransplant immunosuppressive regimen (Table 2). Appropriate immunosuppression is essential for both short- and long-term graft survival and positive patient outcomes. However, as outlined above, these medications carry with them the capacity to both initiate and exacerbate significant metabolic complications (Table 3).¹¹ The ideal

Table 3. Enhanced Metabolic Risk by Maintenance Immunosuppressants

	Cyclosporine	Tacrolimus	Sirolimus	Corticosteroids	Mycophenolate Mofetil
Hypertension	Moderate	Mild	None	Moderate	None
Diabetes Mellitus	Mild	Moderate	None	Severe	None
Renal Insufficiency	Moderate	Moderate	None	None	None
Hyperlipidemia	Moderate	Mild	Severe	Moderate	None

Table 4. Rationale for Individualizing Immunosuppression^a

Over-immunosuppression	Cardiovascular disease, infection, neoplasia, nephrotoxicity, neurotoxicity, noncompliance
Under-immunosuppression	Allograft rejection, allograft loss

^aIndividualization of immunosuppression is based on the balance between under-immunosuppression leading to graft rejection and over-immunosuppression leading to cardiovascular disease, infection, malignancy, and/or nephrotoxicity.

management and prevention of metabolic complications requires multiple modalities, such as lifestyle modifications (before and after transplantation), early screening and identification of complications, and careful medication selection and titration (Table 4).²⁻⁶ To successfully employ these individual strategies, a multidisciplinary approach requires coordination and collaboration by various members of the medical team, including those specializing in nutrition and pharmacy in addition to hepatology and internal medicine. As transplant recipients progress to the late transplant period, it is important to develop systems that optimize communication between transplant hepatologists and primary care providers to ensure the recognition and aggressive management of metabolic complications.⁶

Many of the management recommendations outlined above are based on current best practices and expert opinion. There still remains a need for high-quality studies to confirm the efficacy of these strategies and affirm current guidelines. However, even in the absence of these rigorous studies, early recognition and aggressive management of metabolic complications are advised to reduce morbidity and mortality in the later transplant period.

Conclusion

As survival time following liver transplant increases, the management of metabolic complications demands

increased attention. Cardiovascular disease is the second leading cause of death in the late posttransplant period, and its association with hypertension, hyperlipidemia, obesity, and diabetes has been well established. The incidences of these metabolic complications in the early and late posttransplant periods are driven by a variety of factors, including the immunosuppressive regimens essential for graft function. Early recognition of metabolic complications, lifestyle modifications, immunosuppression titration, and medical management are all essential to minimize the impact of metabolic disorders. Further study is necessary to refine the optimal management of the aforementioned complications.

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References

- Pondrom S. The AJT Report. News and issues that affect organ and tissue transplantation. *Am J Transplant.* 2008;8(5):909-910.
- Watt KD. Keys to long-term care of the liver transplant recipient. *Nat Rev Gastroenterol Hepatol.* 2015;12(11):639-648.
- Bostom AD, Brown RS Jr, Chavers BM, et al. Prevention of post-transplant cardiovascular disease—report and recommendations of an ad hoc group. *Am J Transplant.* 2002;2(6):491-500.
- Fussner LA, Heimbach JK, Fan C, et al. Cardiovascular disease after liver transplantation: when, what, and who is at risk. *Liver Transpl.* 2015;21(7):889-896.
- Benten D, Staufer K, Sterneck M. Orthotopic liver transplantation and what to do during follow-up: recommendations for the practitioner. *Nat Clin Pract Gastroenterol Hepatol.* 2009;6(1):23-36.
- Heller JC, Prochazka AV, Everson GT, Forman LM. Long-term management after liver transplantation: primary care physician versus hepatologist. *Liver Transpl.* 2009;15(10):1330-1335.
- Nwankwo T, Yoon SS, Burt V, Gu Q. Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011-2012. *NCHS Data Brief.* 2013;133:1-8.
- Fernández-Miranda C, Sanz M, dela Calle A, et al. Cardiovascular risk factors in 116 patients 5 years or more after liver transplantation. *Transpl Int.* 2002;15(11):556-562.
- Rabkin JM, Corless CL, Rosen HR, Olyaei AJ. Immunosuppression impact on long-term cardiovascular complications after liver transplantation. *Am J Surg.* 2002;183(5):595-599.
- Hong JC, Kahan BD. Immunosuppressive agents in organ transplantation: past, present, and future. *Semin Nephrol.* 2000;20(2):108-125.
- Desai S, Hong JC, Saab S. Cardiovascular risk factors following orthotopic liver transplantation: predisposing factors, incidence and management. *Liver Int.* 2010;30(7):948-957.
- Rabkin JM, Rosen HR, Corless CL, Olyaei AJ. Tacrolimus is associated with a lower incidence of cardiovascular complications in liver transplant recipients. *Transplant Proc.* 2002;34(5):1557-1558.

13. Saruta T. Mechanism of glucocorticoid-induced hypertension. *Hypertens Res.* 1996;19(1):1-8.
14. Mitchell BM, Webb RC. Impaired vasodilation and nitric oxide synthase activity in glucocorticoid-induced hypertension. *Biol Res Nurs.* 2002;4(1):16-21.
15. Pruthi J, Medkiff KA, Esrason KT, et al. Analysis of causes of death in liver transplant recipients who survived more than 3 years. *Liver Transpl.* 2001;7(9):811-815.
16. Issa DH, Alkhoury N. Long-term management of liver transplant recipients: a review for the internist. *Cleve Clin J Med.* 2015;82(6):361-372.
17. Guckelberger O. Long-term medical comorbidities and their management: hypertension/cardiovascular disease. *Liver Transpl.* 2009;15(2)(suppl 2):S75-S78.
18. Luca L, Westbrook R, Tsochatzis EA. Metabolic and cardiovascular complications in the liver transplant recipient. *Ann Gastroenterol.* 2015;28(2):183-192.
19. Galioto A, Semplicini A, Zanus G, et al. Nifedipine versus carvedilol in the treatment of de novo arterial hypertension after liver transplantation: results of a controlled clinical trial. *Liver Transpl.* 2008;14(7):1020-1028.
20. Neal DA, Gimson AE, Gibbs P, Alexander GJ. Beneficial effects of converting liver transplant recipients from cyclosporine to tacrolimus on blood pressure, serum lipids, and weight. *Liver Transpl.* 2001;7(6):533-539.
21. Singh S, Watt KD. Long-term medical management of the liver transplant recipient: what the primary care physician needs to know. *Mayo Clin Proc.* 2012;87(8):779-790.
22. Mells G, Neuberger J. Reducing the risks of cardiovascular disease in liver allograft recipients. *Transplantation.* 2007;83(9):1141-1150.
23. Baigent C, Blackwell L, Emberson J, et al; Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet.* 2010;376(9753):1670-1681.
24. Madhwal S, Atreja A, Albelldawi M, Lopez R, Post A, Costa MA. Is liver transplantation a risk factor for cardiovascular disease? A meta-analysis of observational studies. *Liver Transpl.* 2012;18(10):1140-1146.
25. Ling Q, Wang K, Lu D, et al. Major influence of renal function on hyperlipidemia after living donor liver transplantation. *World J Gastroenterol.* 2012;18(47):7033-7039.
26. Artz MA, Boots JM, Ligtenberg G, et al. Improved cardiovascular risk profile and renal function in renal transplant patients after randomized conversion from cyclosporine to tacrolimus. *J Am Soc Nephrol.* 2003;14(7):1880-1888.
27. Morrisett JD, Abdel-Fattah G, Kahan BD. Sirolimus changes lipid concentrations and lipoprotein metabolism in kidney transplant recipients. *Transplant Proc.* 2003;35(3)(suppl):143S-150S.
28. Hüsing A, Kabar I, Schmidt HH. Lipids in liver transplant recipients. *World J Gastroenterol.* 2016;22(12):3315-3324.
29. Watt KD, Charlton MR. Metabolic syndrome and liver transplantation: a review and guide to management. *J Hepatol.* 2010;53(1):199-206.
30. Bays H, Cohen DE, Chalasani N, Harrison SA; The National Lipid Association's Statin Safety Task Force. An assessment by the Statin Liver Safety Task Force: 2014 update. *J Clin Lipidol.* 2014;8(3)(suppl):S47-S57.
31. Disability and obesity. Centers for Disease Control and Prevention. <http://www.cdc.gov/ncbddd/disabilityandhealth/obesity.html>. Published March 30, 2016. Accessed July 5, 2016.
32. Nair S, Verma S, Thuluvath PJ. Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States. *Hepatology.* 2002;35(1):105-109.
33. Bianchi G, Marchesini G, Marzocchi R, Pinna AD, Zoli M. Metabolic syndrome in liver transplantation: relation to etiology and immunosuppression. *Liver Transpl.* 2008;14(11):1648-1654.
34. Palmer M, Schaffner F, Thung SN. Excessive weight gain after liver transplantation. *Transplantation.* 1991;51(4):797-800.
35. Everhart JE, Lombardero M, Lake JR, Wiesner RH, Zetterman RK, Hoofnagle JH. Weight change and obesity after liver transplantation: incidence and risk factors. *Liver Transpl Surg.* 1998;4(4):285-296.
36. Richards J, Gunson B, Johnson J, Neuberger J. Weight gain and obesity after liver transplantation. *Transpl Int.* 2005;18(4):461-466.
37. Choban PS, Flancbaum L. The impact of obesity on surgical outcomes: a review. *J Am Coll Surg.* 1997;185(6):593-603.
38. Sawyer RG, Pelletier SJ, Pruett TL. Increased early morbidity and mortality with acceptable long-term function in severely obese patients undergoing liver transplantation. *Clin Transplant.* 1999;13(1 pt 2):126-130.
39. T D Correia MI, Rego LO, Lima AS. Post-liver transplant obesity and diabetes. *Curr Opin Clin Nutr Metab Care.* 2003;6(4):457-460.
40. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care.* 2013;36(4):1033-1046.
41. Baid S, Cosimi AB, Farrell ML, et al. Posttransplant diabetes mellitus in liver transplant recipients: risk factors, temporal relationship with hepatitis C virus allograft hepatitis, and impact on mortality. *Transplantation.* 2001;72(6):1066-1072.
42. Marchetti P. New-onset diabetes after liver transplantation: from pathogenesis to management. *Liver Transpl.* 2005;11(6):612-620.
43. Bodziak KA, Hricik DE. New-onset diabetes mellitus after solid organ transplantation. *Transpl Int.* 2009;22(5):519-530.
44. John PR, Thuluvath PJ. Outcome of patients with new-onset diabetes mellitus after liver transplantation compared with those without diabetes mellitus. *Liver Transpl.* 2002;8(8):708-713.
45. Trail KC, McCashland TM, Larsen JL, et al. Morbidity in patients with posttransplant diabetes mellitus following orthotopic liver transplantation. *Liver Transpl Surg.* 1996;2(4):276-283.
46. Navasa M, Bustamante J, Marroni C, et al. Diabetes mellitus after liver transplantation: prevalence and predictive factors. *J Hepatol.* 1996;25(1):64-71.
47. Saab S, Shpaner A, Zhao Y, et al. Prevalence and risk factors for diabetes mellitus in moderate term survivors of liver transplantation. *Am J Transplant.* 2006;6(8):1890-1895.
48. Delgado-Borrego A, Casson D, Schoenfeld D, et al. Hepatitis C virus is independently associated with increased insulin resistance after liver transplantation. *Transplantation.* 2004;77(5):703-710.
49. Driscoll CJ, Cashion AK, Hathaway DK, et al. Posttransplant diabetes mellitus in liver transplant recipients. *Prog Transplant.* 2006;16(2):110-116.
50. Hjeltneseth J, Hartmann A, Kofstad J, et al. Glucose intolerance after renal transplantation depends upon prednisolone dose and recipient age. *Transplantation.* 1997;64(7):979-983.
51. Drachenberg CB, Klassen DK, Weir MR, et al. Islet cell damage associated with tacrolimus and cyclosporine: morphological features in pancreas allograft biopsies and clinical correlation. *Transplantation.* 1999;68(3):396-402.
52. Davidson J, Wilkinson A, Dantal J, et al; International Expert Panel. New-onset diabetes after transplantation: 2003 international consensus guidelines. Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003. *Transplantation.* 2003;75(10)(suppl):SS3-SS24.
53. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med.* 2008;359(15):1577-1589.
54. Villanueva G, Baldwin D. Rosiglitazone therapy of posttransplant diabetes mellitus. *Transplantation.* 2005;80(10):1402-1405.
55. Luther P, Baldwin D Jr. Pioglitazone in the management of diabetes mellitus after transplantation. *Am J Transplant.* 2004;4(12):2135-2138.
56. Emre S, Genyk Y, Schluger LK, et al. Treatment of tacrolimus-related adverse effects by conversion to cyclosporine in liver transplant recipients. *Transpl Int.* 2000;13(1):73-78.
57. Herrero JI, Quiroga J, Sangro B, et al. Conversion from calcineurin inhibitors to mycophenolate mofetil in liver transplant recipients with diabetes mellitus. *Transplant Proc.* 2003;35(5):1877-1879.
58. Hejlova I, Honsova E, Sticova E, et al. Prevalence and risk factors of steatosis after liver transplantation and patient outcomes. *Liver Transpl.* 2016;22(5):644-655.
59. Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. *Hepatology.* 2014;59(6):2188-2195.
60. Dumortier J, Giostra E, Belbouab S, et al. Non-alcoholic fatty liver disease in liver transplant recipients: another story of "seed and soil". *Am J Gastroenterol.* 2010;105(3):613-620.
61. Ong J, Younossi ZM, Reddy V, et al. Cryptogenic cirrhosis and post-transplantation nonalcoholic fatty liver disease. *Liver Transpl.* 2001;7(9):797-801.
62. Malik SM, Devera ME, Fontes P, Shaikh O, Sasatomi E, Ahmad J. Recurrent disease following liver transplantation for nonalcoholic steatohepatitis cirrhosis. *Liver Transpl.* 2009;15(12):1843-1851.
63. Kim WR, Poterucha JJ, Porayko MK, Dickson ER, Steers JL, Wiesner RH. Recurrence of nonalcoholic steatohepatitis following liver transplantation. *Transplantation.* 1996;62(12):1802-1805.
64. Lim LG, Cheng CL, Wee A, et al. Prevalence and clinical associations of posttransplant fatty liver disease. *Liver Int.* 2007;27(1):76-80.
65. Contos MJ, Cales W, Sterling RK, et al. Development of nonalcoholic fatty liver disease after orthotopic liver transplantation for cryptogenic cirrhosis. *Liver Transpl.* 2001;7(4):363-373.

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66. Kim H, Lee K, Lee KW, et al. Histologically proven non-alcoholic fatty liver disease and clinically related factors in recipients after liver transplantation. *Clin Transplant*. 2014;28(5):521-529.
67. El Atrache MM, Abouljoud MS, Divine G, et al. Recurrence of non-alcoholic steatohepatitis and cryptogenic cirrhosis following orthotopic liver transplantation in the context of the metabolic syndrome. *Clin Transplant*. 2012;26(5):E505-E512.
68. Bhagat V, Mindikoglu AL, Nudo CG, Schiff ER, Tzakis A, Regev A. Outcomes of liver transplantation in patients with cirrhosis due to nonalcoholic steatohepatitis versus patients with cirrhosis due to alcoholic liver disease. *Liver Transpl*. 2009;15(12):1814-1820.
69. Yalamanchili K, Saadeh S, Klintmalm GB, Jennings LW, Davis GL. Nonalcoholic fatty liver disease after liver transplantation for cryptogenic cirrhosis or nonalcoholic fatty liver disease. *Liver Transpl*. 2010;16(4):431-439.
70. Dureja P, Mellinger J, Agni R, et al. NAFLD recurrence in liver transplant recipients. *Transplantation*. 2011;91(6):684-689.