

Dyslipidemia and transplantation

History:

An 8-year-old boy presented with generalized edema and hypertension. A renal biopsy confirmed a diagnosis of focal segmental glomerulosclerosis (FSGS). After his initial management, the boy underwent a successful renal transplant.

Physical examination:

During his most recent clinic visit:

- Height 131.3 cm
- Weight 39.9 kg (BMI 23.3)
- Blood pressure 108/68 mm Hg
- Appeared mildly cushingoid

Laboratory studies:

Lipid profile: Total cholesterol: 193 mg/dL

- Triglycerides: 64 mg/dL
- HDL-c cholesterol: 58 mg/dL
- LDL-c cholesterol: 124 mg/dL

Liver function studies:

- ALT: 16 mg/dL
- AST: 20 mg/dL

Renal function studies:

- BUN: 23 mg/dL
- Creatinine: .78 mg/dL

Questions:

1. Which of the following statements best describes the expected changes in this child's serum cholesterol?

- Levels of total cholesterol, but not LDL-c, are elevated after transplantation.
- Total cholesterol and LDL cholesterol levels are elevated, but they revert to normal levels 12 months after transplantation.
- Total cholesterol generally peaks approximately 3 to 6 months post-transplant and remains stable at an elevated level for 12 months.
- Total cholesterol levels are transiently elevated after transplantation, but with a persistent decrease in HDL-c.

Answer: c. Total cholesterol generally peaks approximately 3 to 6 months post transplant and remains stable at an elevated level for 12 months.

Discussion: Dyslipidemia is common in recipients of renal, heart or liver transplants. This dyslipidemia may result from the underlying disease process, organ malfunction or treatment interventions. Immunosuppressive agents in particular have an adverse effect on serum lipids in patients who have received transplants.

The following table lists the most common adverse effects of immunosuppressive drugs frequently used after transplantation.

Classification	Calcineurin inhibitors (CNI)		Glucocorticoids	Anti-proliferative		Proliferation–signal inhibitors (PSI)
	Cyclosporine	Tacrolimus		Azathioprine	Mycophenolate mofetil	
Immunosuppressive agents with potential adverse CVD effects			Prednisone Prednisolone			Sirolimus
Arterial hypertension	+++	++	++++	-	-	+
Gastrointestinal toxicity	+	+	+	+ ⁽¹⁾	+++	++
Hyperglycemia and diabetes mellitus	-(²)	+	+++	-	-	-
Hyperlipidemia	++	+	++	-	-	+++

It should be noted that each agent has other specific adverse effects in addition to those listed in the table.

(1) Pancreatitis; (2) relationship uncertain

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Probably the most experience with dyslipidemia after transplantation is in renal patients, in which it is well known that both total cholesterol and LDL-c levels are elevated. There is typically a 25 to 30 percent increase in total cholesterol, which peaks approximately 3 to 6 months post-transplant and remains stable at an elevated level for 12 months. From the literature, it is estimated that 60 percent of the renal transplant population has a total cholesterol level > 240 mg/dL and LDL-c level > 132 mg/dL. These, of course, are adult data, since there are fewer reports in the pediatric literature. Changes in HDL- c are more variable.

2. In considering changes to the patient’s anti-rejection therapy, which of the following statements is true?

- a. Azathioprine and mycophenolic acid (MPA) have more adverse effects on the lipid profile in transplant recipients than tacrolimus.
- b. Transplant recipients receiving tacrolimus appear to have fewer lipid anomalies than those receiving Cyclosporin.
- c. Sirolimus is not associated with hyperlipidemia.
- d. All anti-rejection therapy has similar effects on lipid levels.

Answer: b. Transplant recipients receiving tacrolimus appear to have fewer lipid anomalies than those receiving Cyclosporin.

Discussion: The prevailing view has been that the severity of hyperlipidemia from tacrolimus is less than that from Cyclosporin therapy. In general, Cyclosporin has a more detrimental effect on total cholesterol, LDL-cholesterol and triglycerides than tacrolimus. The 20 to 25 percent reduction in LDL-c has been reported after conversion from Cyclosporin to tacrolimus. The proliferation-signal inhibitors (PSIs), such as sirolimus are stronger inducers of hyperlipidemia than CNI agents. The mechanisms by which PSIs affect lipid levels may be related to changes in lipoprotein lipase and an increased production of triglycerides with increased secretion of VLDL. Interference with an insulin-dependent signaling pathway has also been suggested as a means by which PSI therapy may adversely affect lipid metabolism. In contrast, azathioprine and MPA are not associated with an adverse effect on lipid profile in transplant recipients.

In general:

Relative adverse effects on the lipid profile			
Highest			Lowest
Sirolimus	Prednisolone Cyclosporine Prednisone	Tacrolimus	Azathioprine Mycophenolic acid

Although dyslipidemia is present with the use of most of these medications, deciding factors for which agents to use may include analyzing the need for immunosuppressive agents, their availability through various formularies and their perceived or actual effectiveness in any given patient. Hyperlipidemia is also related to use of calcineurin inhibitor (CNI) therapy, such as the use of Cyclosporin and tacrolimus. In the literature, total cholesterol levels tend to be 30–60 mg/dL higher in renal transplant patients treated with Cyclosporin, prednisone and azathioprine than those who receive prednisolone and azathioprine alone. Cyclosporin interferes with lipid metabolism in several ways. Cholesterol clearance is reduced, probably via decreased LDL receptor synthesis and binding. Lipoprotein lipase activity is inhibited, which could explain the increase in triglycerides. Cyclosporin also interferes with the bile acid/biosynthetic pathway, leading to hypocholesterolemia.

3. This patient, like most, requires long-term use of corticosteroids. Which of the following statements best describes the effects of corticosteroids on serum lipoproteins?

- a. Corticosteroids promote insulin resistance leading to secondary hyperinsulinemia with a reduction in lipoprotein lipase activity, overproduction of triglycerides and secretion of VLDL.
- b. The dyslipidemia induced by corticosteroids is independent of the dose used.
- c. Steroid-induced dyslipidemia results primarily in marked elevation in serum triglycerides with little or no change in total and LDL-c.
- d. Steroid-induced dyslipidemia occurs with parenteral but not oral corticosteroids.

Answer: a. Corticosteroids promote insulin resistance leading to secondary hyperinsulinemia with a reduction in lipoprotein lipase activity, overproduction of triglycerides and secretion of VLDL.

Discussion: In addition to receiving other immune suppression and modulating therapy, individuals who have undergone transplantation are commonly treated with corticosteroids. Corticosteroids promote insulin resistance, leading to secondary hyperinsulinemia with a reduction in lipoprotein lipase activity, overproduction of triglycerides and secretion of VLDL. There is a significant correlation between the corticosteroid dose and hyperlipidemia.

4. In considering this child's long-term prognosis, which of the following statements is true?

- a. Cardiovascular disease resulting in acute MI or stroke is generally the cause of death in most adult renal transplant patients.
- b. Following renal transplantation, use of lipid-lowering agents in children has not been shown to be effective.
- c. Following renal transplant, the use of lipid-lowering agents has been associated with accelerated organ rejection in both children and adults.
- d. Following successful organ transplantation, current guidelines suggest the use of lipid-lowering agents in children only after the onset of puberty.

Answer: a. Cardiovascular disease resulting in acute MI or stroke is generally the cause of death in most adult renal transplant patients.

Discussion: Patients with cardiac transplants also have a unique cardiovascular condition called cardiac allograft vasculopathy (CAV). Cardiovascular risk factors in liver transplant recipients differ from those in heart or kidney transplant recipients, primarily because of the hemodynamic and metabolic changes associated with chronic liver disease. Nonetheless, cardiovascular disease is also an important factor restricting long-term survival following liver transplant. Current recommendations by the American Academy of Pediatrics for children and adolescents with kidney or heart transplants include: CKD/end-stage renal disease 1. Optimize renal failure management with dialysis or transplantation, and 2. Assess BMI, BP, lipids, FG: step 1 management for 6 months. If goals not achieved, proceed to step 2; statin prescription if the patient is more than 10 years old to achieve tier I treatment goals.

After heart transplantation: 1) Optimize anti-rejection therapy, treat for CMV, perform routine evaluation by angiography or perfusion imaging, and 2) Assess BMI, BP, lipids, FG; initiate step 2 therapy, including statins, immediately in all patients over 1 year old to achieve tier I treatment goals.

Key points:

The general approach to treating dyslipidemia in transplant patients, particularly those with renal transplants, can be summarized as follows:

- The most important contributor to lipid abnormalities after transplantation is the choice of immunosuppressive agents. Corticosteroids, cyclosporine, and sirolimus have all been shown to have profound adverse effects on serum lipid levels, while tacrolimus and mycophenolate mofetil (MMF) appear to have minimal to no dyslipidemic effects.
- When possible, use immunotherapy with the least adverse affect on lipid profile. This may not always be possible for a variety of reasons. For example, inadequate response or limitations imposed by medication formularies may prohibit immunotherapy choice.
- The first step is lowering LDL cholesterol. A reasonable goal for children is <130 mg/dL, although some would argue that it should be < 100 mg/dL.
- Once the LDL target of <100 to 130 mg/dl is reached, a secondary target would be non-HDL cholesterol <150 mg/dL. Statin therapy is important in managing hyperlipidemia in renal transplant recipients. Five of the 6 currently available statins have been widely used in recipients of solid organ transplants. Rosuvastatin, for which experience in organ transplantation is limited, is the sixth. The reported experience is primarily in adult populations.
- With adequate dosing, statins effectively lower total cholesterol and LDL- cholesterol in the renal transplant population.
- Ezetimibe, a cholesterol absorption inhibitor, may also be considered. Ten mg of ezetimibe daily typically reduces LDL cholesterol by approximately 20% and has little potential for drug interaction or toxicity. Although ezetimibe has not been used extensively in solid organ transplantation, studies of a small series of renal and heart transplant recipients have indicated that it may be effective and safe either as monotherapy or as a supplement to statin therapy in order to lower atherogenic lipids further.
- The omega-3 fatty acids (EPA, DHA) have been shown to reduce LDL, cholesterol and triglyceride levels; however, meta-analysis of randomized controlled trials in renal transplant patients have not disclosed any benefit except for modest decreases in triglyceride levels.
- Finally, one other consideration regarding statin therapy is the mode of metabolism. Atorvastatin, lovastatin, and simvastatin are primarily metabolized via the CYP3A4 pathway. Although pravastatin is partially metabolized by the CYP3A4 pathway, the drug is mainly subjected to a variety of conjugating reactions. Thus, unlike other statins, approximately 10% of an oral dose of pravastatin is excreted unchanged via the kidneys. Fluvastatin is also a CYP3A4 substrate, but it is metabolized mainly by the CYP2C9. Thus when possible, either pravastatin or fluvastatin should be considered in children. Currently, pravastatin is FDA approved to age 8 years for patients with heterogeneous FH.

References/suggested reading:

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