LIPID PARAMETERS IN POST RENAL TRANSPLANTS

Abstract

Organ transplantation is a new field of medicine and has progressed significantly in the recent years. The treatment preferred for patients with end-stage renal disease (ESRD) is mostly renal transplantation (RT). Despite the improvement after RT, cardiovascular disease (CVD) is still the main cause of death. Following transplantation, dyslipidemia can develop de novo, and also as a complication of CKD (Chronic Kidney Disease). The correlation between cardiovascular mortality and high lipid levels is well established among the general population. Treatment of dyslipidemia is considered as an important measure to improve survival after transplantation.

Keywords: renal; transplantation; dyslipidemia; cardiovascular

Authors

Dr. Oinam Prabita Devi
Assistant Professor
Biochemistry Department
Shija Academy of Health Sciences
Imphal, India
prabitaoinam@gmail.com

Dr. Wahengbam Diana Devi
Senior Resident Doctor
Biochemistry Department
Shija Academy of Health Sciences
Imphal, India
wdd.rainbow@gmail.com

I. INTRODUCTION

Organ transplantation is a new field of medicine and has progressed significantly since the later half of the 20th century. Now, it is well known as an effective treatment for some patients with ESRD. Kidney transplant was successfully performed for the first time between identical twins which was a living-donor transplant. However, when the recipient and donor were not identical (genetically), organ transplantation posed a problem due to graft rejection. With the invention of different immunosuppressive agents, allograft transplantation has become easier.

The treatment preferred for most patients with ESRD is RT as it gives a better quality of life compared to dialysis. Patients are released from the physical constraints as well as the dietary and fluid restrictions due to dialysis. For renal transplant, careful patient selection is required as many patients may be unsuitable for RT because of associated comorbid conditions, especially CVD. It is essential to carefully assess the comorbidities that may significantly decrease the chances of success post transplantation. It is important to carefully evaluate the cardiovascular system since CVD usually occurs in dialysis patients (especially those with diabetes) and is the main cause of death post RT.

The main problems in RT are: chronic graft rejection, the adverse effects of immunosuppression and the lack of donors for RT. Continuing research is done to develop biomarkers (in blood or urine) that can permit early detection of graft rejection.

In the post transplant survival and renal grafts, despite the improvement after RT, CVD is the major cause of death (contributing half of the mortality) in renal transplant recipients (RTR). Nearly 60% of RTR have post-transplant dyslipidemia and most of them have a CVD-related event within 3years after RT. Changes in serum lipid levels include elevated levels of triglycerides (TG) and total cholesterol (TC). Following transplantation, dyslipidemia can develop de novo, and also as a complication of CKD. The correlation between cardiovascular mortality and high lipid levels is well established among the general population. Atherosclerosis accounts for a main proportion of morbidity and mortality in RTR. Treatment of dyslipidemia is considered as an important measure to improve survival after transplantation. General measures to control dyslipidemia are proper diet and physical activity and should be started early in all patients after RT. Statins are the basic hypolipidemic treatment in case of an insufficient correction of lipemia,.

II. FACTORS ASSOCIATED WITH DYSLIPIDEMIA

Since many types of dyslipidemia are found, factors contributing to dyslipidemia can be divided into those primarily contributing to hypercholesterolemia and hypertriglyceridemia. The risk factors are given in the table below.

Table 1: Factors associated with dyslipidemia after transplantation

Hypercholesterolemia	Hypertriglyceridemia
• Age • Genetic susceptibility • Excessive intake of saturated fats and cholesterol • Proteinuria • Obesity • Anti-hypertensive agents, e.g., diuretics, beta-blockers • Calcineurin-inhibitors (cyclosporine) • Corticosteroids • Mammalian target-of-rapamycin inhibitors (sirolimus, etc)	• Genetic susceptibility • Excessive intake of carbohydrates, cholesterol & saturated fat • Proteinuria • Obesity • Corticosteroids • Renal insufficiency • Mammalian target-of-rapamycin inhibitors (sirolimus)

III. MECHANISMS OF DYSLIPIDEMIA IN POST-TRANSPLANT PATIENTS

Dyslipidemia after RT is greatly contributed by immunosuppressants. Insulin resistance induced by corticosteroids results in hyperinsulinemia which leads to raised hepatic uptake of free fatty acids (FFA). FFA is the primary substrate for VLDL (very low density lipoprotein) cholesterol synthesis. Steroids increase FFA synthetase and acetyl-CoA carboxylase and thus increasing hepatic synthesis of VLDL. Reduced TG clearance due to reduction in lipoprotein lipase results from insulin resistance. There is increase in LDL cholesterol (LDL-C) levels due to an increase in conversion of VLDL to LDL (low density lipoprotein) cholesterol. Down-regulation of the expression of LDL receptor may also contribute to the mechanism. Finally, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) activity (rate-limiting step in cholesterol synthesis) is increased by corticosteroids.

LDL receptor binding to cholesterol is interfered by cyclosporine. Therefore, there is an increase in LDL cholesterol levels due to a decline in LDL clearance. Hence, cyclosporine may act as a confounder to corticosteroids. This drug also inhibits the synthesis of bile acid by affecting 26 hydroxylase enzyme. There is further decline in cholesterol clearance due to LDL receptor down-regulation (caused by decreased bile acid synthesis). Since cyclosporine is lipophilic, its transportation is done in the core region of LDL cholesterol. During this process, the LDL molecule configuration and the feedback regulation of synthesis of cholesterol may be changed. Intolerance to glucose also increases the impact of cyclosporine on lipid parameters. Tacrolimus has almost similar effects on lipid metabolism as cyclosporine. Sirolimus provides a strong connection between dyslipidemia and pharmacotherapy, and yet has both harmful and protective cardiovascular effects. Lipoprotein lipase may be inhibited by it, thereby decreasing lipolysis. Lipoprotein over-production by liver can also be there. A reduction in apolipoprotein B100 catabolism is another effect. Ultimately, tissue lipase activity is increased by sirolimus, it also alters insulin signaling and raises VLDL cholesterol production.

IV. MEASURES TO PREVENT DYSLIPIDEMIA

Proper diet and physical activity are important factors associated with decreased incidence of CVD in most cases. Physical activity before RT is associated with better graft function and predicts the mortality in RTRs. Regular physical performance positively correlates with reduced TG levels (in obese and overweight adults), elevated high density lipoprotein-cholesterol (HDL-C), and positive changes in lipoproteins. Compared to the general population, RTRs show decreased physical activity, but were higher than the dialysis patients. Cardiovascular risk is reduced by a healthy diet. Obesity is common among RTRs, but weight loss is not taken as the primary goal of nutrition. National Kidney Foundation Guidelines (2020) recommends an intake of 25–35 kcal/kg/d for RTRs. The average RTR patients should be educated about isolated nutrient references and provided with dietary patterns as they may have difficulties understanding and implementing it.

V. OUTCOMES OF DYSLIPIDEMIA AFTER RENAL TRANSPLANT

Recipients of renal transplant, are at increased risk for cardiovascular events post-RT. The association between CVD and dyslipidemia should not be ignored in transplant populations though the association is not that strong. Accelerated atherosclerosis post RT is responsible for cardiovascular events. There is more association of cardiovascular events with elevated cholesterol than with increased TG. Moreover among the CVDs, ischemic heart disease is the most common among RTRs. With every 2 mmol/L increase in LDL cholesterol concentration, risk for post RT major adverse cardiac events (MACE) doubles. When HDL-C level lowers, post-RT MACE increases three times. However, a concrete association between dyslipidemia and MACE is difficult to establish. Also, hyperlipidemia is not the sole risk factor for MACE where uncommon risk factors may play an important role. Some studies have shown that dyslipidemia can rarely predict post-transplant consequences like myocardial infarction or even death. Even so, elevated TG is associated with the developmemt of coronary artery calcification in RTRs. There is limited information about dyslipidemia and risk for CVD in transplant outside of RT. At least one component of dyslipidemia (eg. decreased HDL-C and elevated TG), is one of the criteria for diagnosis of metabolic syndrome. It is, therefore, useful to have a knowledge that dyslipidemia contributes to post-RT adverse events as compared to other risk factors of CVD (eg. hyperglycemia, microalbuminuria, obesity and hypertension). Dyslipidemia management can contribute in reducing deaths due to cardiovascular events and myocardial infarctions in some studies in transplant patients. Thus, attention should be given to dyslipidemia in post-RT follow-up. Unlike other cases, RT allows the evaluation of the association between dyslipidemia and the success of allograft. Because of the interaction of the immune system with the allograft, it is variably exposed to metabolic injury as compared to recipient’s organ. Hyperlipidemia is regarded as a “non-immune” risk factor to renal allograft injury. It is considered that atherosclerosis is an important part of the process of rejection, since fibrosis may result from oxidized LDL-C accumulation in the renal interstitium. Also, acute graft rejection is preceded by hypercholesterolemia prior to transplant. This occurs by change in the pharmacokinetics of cyclosporine, leading to reduced tissue bioavailability. Therefore, management of dyslipidemia in pre and post-transplant period is vital for lowering post-RT morbidities,

VI. PHARMACOLOGICAL TREATMENT OF DYSLIPIDEMIA

In RTRs, the main aim of hypolipidemic treatment is to lower LDL-C to reduce the cardiovascular risk. The first-line drugs are statins and ezetimibe is the second-line treatment. If the patient had atherosclerotic CVD or not, determines the management of dyslipidemia. To determine the adherence of medication, lipid profile measurement should be done before and 4-12 weeks after starting the treatment of dyslipidemia, and then repeated every 3-12 months. Some of the commonly used drugs are discussed briefly.

1. **Statins:** Statins are HMG-CoA reductase inhibitors and strong hypolipidemic agents that significantly lower serum LDL level. Decrease in cholesterol levels in the hepatocyte causes increased LDL-Receptor expression and accelerated uptake of LDL and ApoB particles (TG rich). As statins inhibit the rate limiting enzyme of mevalonate pathway (precursor for non-steroid compounds), they are considered to have a pleiotropic effect. Statins are considered to have antioxidant and anti-inflammatory effects, which is helpful in preventing CVD. Statins are mostly well-tolerated, but some side effects include nausea, vomiting, joint and muscle pain. Hence, this may lead to poor adherence to medication.

2. **Ezetimibe:** Ezetimibe is an inhibitor of intestinal cholesterol uptake by its interaction with Niemann-Pick C1 protein. This drug reduces TG and TC concentrations, but does not influence HDL-C levels. Because of its lesser hypolipidemic property (reduces LDL-Cholesterol by 13 to 20%), it is regarded as a second-line drug. In case of statin intolerance, ezetimibe may be used as an alternative. In RTRs, maximal doses of statins combined with ezetimibe can alleviate triglyceridemia and hypercholesterolemia, without influencing kidney function and creatine kinase concentration.

3. **Bile Sequestrants:** Bile sequestrants such as cholestyramine prevent intestinal reabsorption of bile and reduce cholesterol concentration. Renal function is affected by cholestyramine in the population, generally. Bile sequestrants are seldom used because of its adverse effects such as constipation, increase of TG and affecting other drugs' absorption.

4. **D.Fibrates:** Fibrates are Peroxisome Proliferator-Activated Receptor Alpha (PPAR-α) agonists, which regulates the metabolism of lipoprotein and lipid. They effectively reduce TG level and mildly raises the HDL level. Their effect of lowering TG strongly depends on the previous TG concentration. They also slightly decrease cardiovascular events by primary prevention. The combined use of fibrates and statins must, however, be avoided since it raises the risk of myopathy. If there is coexistence of hypercholesterolemia and triglyceridemia, fenofibrate is recommended rather than gemfibrozil due to lower risk of severe myopathy.

VII. CONCLUSION

Dyslipidemia after RT is very much prevalent and poses challenges of management to the doctors. During post RT therapies, there are two main consequences: reducing cardiovascular risk and preserving or improving allograft function. It is essential to give attention to dyslipidemia as correction of dyslipidemia contributes to reduce cardiac events in

post-RT patients. Dyslipidemia should not be considered same as hyperlipidemia. Several mechanisms are there for the existence of post-RT dyslipidemia, these include the effects of immunosuppressive agents. Therapy with statins is the most recognised in all RTR patients, although adjuvant pharmacological / nonpharmacological agents and proper diet also play a role. To achieve the benefits from these therapies, proper monitoring for adverse effects should be done at all stages of treatment.

REFERENCES

[1] Bailey & Love's short practice of surgery, 27th ed., vol. 2. chapter 82, pp. 1549.
[2] Geerlings W, Tufveson G, Ehrich JH, Jones EH, Landais P, Loirat C, et al., Report on management of renal failure in Europe, XXIII. Nephrol dial Transplant 1994;9 (Suppl 1):6-25.
[3] United State Renal Data System. 1998 annual data report. Causes of death, Am J Kidney Dis 1998;32(Suppl):81-8.
[4] S. Badiou, JP. Cristol and G. Mourad, Dyslipidemia following kidney transplantation: Diagnosis and treatment, Curr. Diabetes Rep. 2009, 9, 305-311.
[5] AC. Shirali and MJ. Bia, Management of cardiovascular disease in renal transplant recipients, Clin. J. Am. Soc. Nephrol. 2008, 3, 491-504.
[6] T. Kosugi, M. Eriguchi, H. Yoshida, H. Tasaki, F. Fukata, M. Nishimoto, et al., Association between chronic kidney disease and new-onset dyslipidemia: The Japan specific health checkups (J-SHC) study, Atherosclerosis 2021,332, 24-32.
[7] K. Chmielnicka, Z. Heleniak and A. Debska-Slizien, Dyslipidemia in renal transplant recipients, Transplantology. 2022, 3, 188-199.
[8] DE. Hricik, Hyperlipidemia in renal transplant recipients, Graft 2000; 3: 177-184
[9] G. Pagano, A. Bruno, P. Cavallo-Perin, L. Cesco and B. Imbimbo, Glucose intolerance after short-term administration of corticosteroids in healthy subjects. Prednisone, deflazacort, and betamethasone, Arch Intern Med 1989; 149: 1098-1101 [PMID: 2655543 DOI: 10.1001/ archinte.1989.00390050082016]
[10] AP. Hays and RB. Hill, Enzymes of lipid synthesis in the liver of the cortisone-treated rat, Biochim Biophys Acta 1965; 98: 646-648 [PMID: 5837463 DOI: 10.1016/0005-2760(65)90164-5]
[11] SL. Ibels, MF. Reardon and PJ. Nestel, Plasma post-heparin lipolytic activity and triglyceride clearance in uremic and hemodialysis patients and renal allograft recipients, J Lab Clin Med 1976; 87: 648-658 [PMID: 775004]
[12] JA. Kobashigawa and BL. Kasiske, Hyperlipidemia in solid organ transplantation, Transplantation 1997; 63: 331-338 [PMID: 9039919 DOI: 10.1097/00007890-199702150-00001]
[13] HM. Princen, P. Meijer, BG. Wolthers, RJ. Vonk RJ and F. Kuipers, Cyclosporin A blocks bile acid synthesis in cultured hepatocytes by specific inhibition of chenodeoxycholic acid synthesis, Biochem J 1991; 275 (Pt 2): 501-505 [PMID: 2025228 DOI: 10.1042/bj2750501]
[14] LV. Riella, S. Gabardi and A. Chandraker, Dyslipidemia and its therapeutic challenges in renal transplantation, Am J Transplant 2012; 12: 1975-1982 [PMID: 22578270 DOI: 10.1111/j.1600-6143.2012.04084.x]
[15] PC. de Groen, Cyclosporine, low-density lipoprotein, and cholesterol, Mayo Clin Proc 1988; 63: 1012-1021 [PMID: 3172850 DOI: 10.1016/S0025-6196(12)64916-7]
[16] JD. Morrisett, G. Abdel-Fattah, R. Hoogeveen, E. Mitchell, CM. Ballantyne, HJ. Pownall, et al., Effects of sirolimus on plasma lipids, lipoprotein levels, and fatty acid metabolism in renal transplant patients, J Lipid Res 2002; 43: 1170-1180 [PMID: 12177161]
[17] ZA. Massy, JP. De Bandt, E. Morelon, M. Thevenin, B. Lacour B and H. Kreis, Hyperlipidaemia and post-heparin lipase activities in renal transplant recipients treated with sirolimus or cyclosporin A, Nephrol Dial Transplant 2000; 15: 928 [PMID: 10831671 DOI: 10.1093/ ndt/15.6.928]

[18] BL. Kasiske, A. de Mattos, SM. Flechner, L. Gallon, HU. Meier-Kriesche, MR. Weir, et al., Mammalian target of rapamycin inhibitor dyslipidemia in kidney transplant recipients, Am J Transplant 2008; 8: 1384-1392 [PMID: 18510633 DOI: 10.1111/ j.1600-6143.2008.02272.x]
[19] F. Mach, C. Baigent, AL. Catapano, KC. Koskinas, M. Casula, L. Badimon, et al., 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk; The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS), Eur. Heart J. 2020, 41, 111–188.
[20] SE. Rosas, PP. Reese, Y. Huan, C. Doria, PT. Cochetti and A. Doyle, Pretransplant physical activity predicts all-cause mortality in kidney transplant recipients, Am. J. Nephrol. 2012, 35, 17–23.
[21] EJ. Gordon, TR. Prohaska, MP. Gallant, AR. Sehgal, D. Strogatz, R. Yucel, et al., Longitudinal analysis of physical activity, fluid intake, and graft function among kidney transplant recipients, Transpl. Int. 2009, 22, 990.
[22] F. Landi, A. Russo, M. Cesari, M. Pahor, R. Bernabei and G. Onder, HDL-Cholesterol and physical performance: results from the ageing and longevity study in the Sirente geographic area (ilsirente study), Age Ageing 2007, 36, 514–520.
[23] GA. Kelley, KS. Kelley and Z. Vu Tran, Aerobic exercise, lipids and lipoproteins in overweight and obese adults: a meta-analysis of randomized controlled trials, Int. J. Obes. 2005, 29, 881.
[24] S. de Smet and AH. van Craenenbroeck, Exercise training in patients after kidney transplantation, Clin. Kidney J. 2021, 14, ii15–ii24.
[25] DC. Goff, DM. Lloyd-Jones, G. Bennett, S. Coady, RB. D'Agostino, R. Gibbons, et al., 2013 ACC/AHA Guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines, Circulation 2014, 129, 49–73.
[26] G. Akbulut and F. Gencer-Bingol, Medical nutritional therapy for renal transplantation in the COVID-19 pandemic, World J. Transplant. 2021, 11, 212–219.
[27] NJ. Stone, JG. Robinson, AH. Lichtenstein, CN. Bairey Merz, CB. Blum, RH. Eckel, et al., 2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines, Circulation 2014, 129, 2889–2934.
[28] HN. Ginsberg, REVIEW: Efficacy and mechanisms of action of statins in the treatment of diabetic dyslipidemia, J. Clin. Endocrinol. Metab. 2006, 91, 383–392.
[29] MJ. Chapman and F. McTaggart, Optimizing the pharmacology of statins: characteristics of rosuvastatin, Atheroscler. Suppl. 2002, 2, 33–37.
[30] J. Davignon, Beneficial cardiovascular pleiotropic effects of statins, Circulation 2004, 109, III-39–III-43. [CrossRef]
[31] X. Li, J. Wang, E. Coutavas, H. Shi, Q. Hao and G. Blobel, Structure of human Niemann-Pick C1 protein, Proc. Natl. Acad. Sci. USA 2016, 113, 8212–8217.
[32] C. Wanner and M. Tonelli, KDIGO Clinical practice guideline for lipid management in CKD: Summary of recommendation statements and clinical approach to the patient, Kidney Int. 2014, 85, 1303–1309.
[33] Kohnle, M.; Pietruck, F.; Kribben, A.; Philipp, T.; Heemann, U.; Witzke, O. Ezetimibe for the Treatment of Uncontrolled Hypercholesterolemia in Patients with High-Dose Statin Therapy after Renal Transplantation. Am. J. Transplant. 2006, 6, 205–208. [CrossRef] [PubMed]
[34] Baigent, C.; Landray, M.J.; Reith, C.; Emberson, J.; Wheeler, D.C.; Tomson, C.; Wanner, C.; Krane, V.; Cass, A.; Craig, J.; et al. The Effects of Lowering LDL Cholesterol with Simvastatin plus Ezetimibe in Patients with Chronic Kidney Disease (Study of Heart and Renal Protection): A Randomised Placebo-Controlled Trial. Lancet 2011, 377, 2181. [CrossRef]
[35] Pontremoli, R.; Bellizzi, V.; Bianchi, S.; Bigazzi, R.; Cernaro, V.; del Vecchio, L.; de Nicola, L.; Leoncini, G.; Mallamaci, F.; Zoccali, C.; et al. Management of Dyslipidaemia in Patients with Chronic Kidney Disease: A Position Paper Endorsed by the Italian Society of Nephrology. J. Nephrol. 2020, 33, 417–430. [CrossRef]

[36] Kshirsagar, A.V.; Shoham, D.A.; Bang, H.; Hogan, S.L.; Simpson, R.J.; Colindres, R.E. The Effect of Cholesterol Reduction with Cholestyramine on Renal Function. Am. J. Kidney Dis. 2005, 46, 812–819. [CrossRef]
[37] Jakob, T.; Nordmann, A.J.; Schandelmaier, S.; Ferreira-González, I.; Briel, M. Fibrates for Primary Prevention of Cardiovascular Disease Events. Cochrane Database Syst. Rev. 2016, 11, CD009753. [CrossRef]
[38] Grundy, S.M.; Stone, N.J.; Bailey, A.L.; Beam, C.; Birtcher, K.K.; Blumenthal, R.S.; Braun, L.T.; de Ferranti, S.; Faiella-Tommasino, J.; Forman, D.E.; et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019, 139, E1082–E1143. [CrossRef]

