**Lipid parameters in post renal transplants**

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**ABSTRACT**

Organ transplantation is a relatively new field of medicine and significant progress has been made in the recent years. The preferred treatment 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. After transplantation, dyslipidemia may develop de novo, and also as a complication of chronic kidney disease. The correlation between cardiovascular mortality and high lipid levels is well established among the general population. Treatment of dyslipidemia should be considered as an important intervention to improve post-transplant survival of overall patient.

**Keywords –** renal; transplantation; dyslipidemia; cardiovascular

**I. INTRODUCTION**

Organ transplantation is a relatively new field of medicine and significant progress has been made since the later half of the 20th century. Now, it is well established as an effective treatment for some patients with end-stage organ disease. The first successful kidney transplant was performed between identical twins which was a living-donor transplant. However, when the donor and recipient 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 preferred treatment for most patients with ESRD is RT as it provides a better quality of life than dialysis. Patients are released from the dietary and fluid restrictions and the physical constraints imposed by the need for dialysis. For renal transplant, careful patient selection is required as many patients may be considered unsuitable for RT because of major comorbid conditions, especially CVD. It is essential to carefully assess the comorbid disease that might significantly reduce the chances of success after transplantation. Rigorous evaluation of the cardiovascular system is important. Cardiovascular disease is very common in the dialysis patients, especially those suffering from diabetes, and it is the main cause of death after RT.

The two main problems in RT are: chronic graft rejection and the adverse effects of non-specific immunosuppression; and the lack of organs for RT. Continuing research is done to develop non-invasive biomarkers (in blood or urine) that will permit early diagnosis of graft rejection.

In the overall survival of patients and renal grafts, despite the improvement after RT, CVD is the major cause of death accounting for about 50% of 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). After transplantation, dyslipidemia may develop de novo, and also as a complication of chronic kidney disease. 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 should be considered as an important intervention to improve post-transplant survival of overall patient. The main general measures to manage dyslipidemia are proper diet and physical activity and should be introduced early in all patients after RT. Statins are the basic hypolipidemic treatment in case of an insufficient correction of lipemia,.

**II. FACTORS ASSOCIATED WITH LIPID ABNORMALITIES**

Since a variety of lipid abnormalities are seen, 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 lipid abnormalities after transplantation**

|  |  |
| --- | --- |
| Hypercholesterolemia | Hypertriglyceridemia |
| Genetic predisposition  Age  Excessive dietary intake of cholesterol and saturated fats  Obesity  Proteinuria  Anti-hypertensive agents, e.g., diuretics, beta-blockers  Corticosteroids  Calcineurin-inhibitors (cyclosporine, possibly tacrolimus)  Mammalian target-of-rapamycin inhibitors (sirolimus, everolimus) | Genetic predisposition  Excessive dietary intake of carbohydrates, cholesterol, and saturated fat  Obesity  Proteinuria  Renal insufficiency  Corticosteroids  Mammalian target-of-rapamycin inhibitors (sirolimus) |

**III. MECHANISMS OF POST-TRANSPLANT DYSLIPIDEMIA**

Lipid abnormalities after renal transplant is significantly contributed by immunosuppressive agents. Corticosteroids induce insulin resistance and the resultant hyperinsulinemia leads to increased hepatic uptake of free fatty acids (FFA). FFA constitutes the main 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 LDL receptor expression may also contribute to the mechanism. Finally, the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), which is the rate-limiting step in the cholesterol biosynthesis, is increased by corticosteroids.

The binding of LDL cholesterol to the LDL receptor is interfered by cyclosporine. Therefore, there is a rise in LDL cholesterol levels due to a decline in LDL clearance. Hence, there may be an additional effect of cyclosporine with corticosteroids. This drug also interferes with bile acid synthesis by affecting the enzyme, 26 hydroxylase. There is further decline in cholesterol clearance due to LDL receptor down-regulation (caused by decreased bile acid synthesis). Since cyclosporine is lipophilic, it is transported in the core of LDL cholesterol. During the process, the molecular configuration of LDL and the normal feedback regulation of cholesterol synthesis may be changed. Glucose intolerance also potentiate the effect of cyclosporine on lipid parameters. The effects of tacrolimus on lipid metabolism are almost similar to those of cyclosporine. Sirolimus provides a strong connection between dyslipidemia and pharmacotherapy, and yet has cardiovascular effects both harmful and protective. It may inhibit lipoprotein lipase, decreasing lipolysis. There can also be hepatic over-production of lipoprotein. Other effects can be a decrease in apolipoprotein B100 catabolism. Finally, sirolimus increases the activity of tissue lipase, alters insulin signaling and increases VLDL cholesterol secretion.

**IV. MEASURES TO PREVENT DYSLIPIDEMIA**

Proper diet and physical activity are important determinants of the lower incidence of CVD in most patients. 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. A healthy diet has been proven to reduce cardiovascular risk. There is frequent obesity amongst RTRs, although weight loss should not be taken as the main nutritional goal. National Kidney Foundation Guidelines from 2020 recommends an intake of 25–35 kcal/kg/d for RTRs. The average RTR patients should be educated about isolated nutrients references and provided with dietary patterns as they may have difficulties understanding and implementing it.

**V. Pharmacological Treatment of Dyslipidemia**

The main target of hypolipidemic treatment in RTRs is to lower LDL-C to reduce the cardiovascular risk. The first-line drugs are statins and ezetimibe is the second-line treatment. Whether the patient has established atherosclerotic cardiovascular disease (ASCVD) 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.

**A. Statins:**

Statins are HMG-CoA reductase inhibitors and strong hypolipidemic drugs that significantly reduce LDL serum level. Decrease in intra-hepatocyte cholesterol levels causes enhanced LDL-Receptor expression and increased 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 antioxidative and anti-inflammatory effects, which is helpful in preventing CVD. Statins are mostly well-tolerated, but some side effects include nausea, vomiting, muscle and joint pain. Hence, this may lead to poor adherence to medication.

**B. Ezetimibe:**

Ezetimibe is an inhibitor of cholesterol uptake in the intestines by interacting with Niemann-Pick C1 (NPC1) protein. It reduces TG and TC levels, but does not influence HDL-C levels. Due to its lower hypolipidemic potential (reduces LDL-C by 13-20%), 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.

**C. Bile Sequestrants:**

Bile acid sequestrants such as cholestyramine prevent reabsorption of bile in the intestines and reduce serum cholesterol concentration. Renal function is insignificantly affected by cholestyramine in the general population. Bile sequestrants are seldom used because of its adverse effects like constipation, elevation of TG and interfering the absorption of other drugs.

**D.Fibrates:**

Fibrates are agonists of PPAR-α (Peroxisome Proliferator-Activated Receptor Alpha), which regulates the lipoprotein and lipid metabolism. They are efficient in reducing TG level and slightly raises the HDL level. Their TG lowering effect highly depends on the initial level of TG. Fibrates slightly reduce cardiovascular events (primary prevention). However, the combined use of fibrates with statins must 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.

**VI. CONCLUSION**

Post-transplant dyslipidemia is highly prevalent and presents management challenges to the clinician. There are two major outcomes while considering post-transplant therapies: reducing cardiovascular risk and preserving or improving allograft function. Attention to dyslipidemia is warranted because interventions for dyslipidemia have an impact on reducing cardiac events in clinical trials specific to the transplant population. Dyslipidemia is not the same with hyperlipidemia. Several mechanisms exist for the occurrence of post-transplant dyslipidemia, including the effects of immunosuppressive drug therapy. Statin therapy has received the most attention in all RTR patients, although adjuvant pharmacological / nonpharmacological agents and proper dietary advice also play a role. To achieve the benefits from these therapies, appropriate monitoring for adverse effects should be implemented at all stages of treatment.

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