**Lipid parameters in post renal transplants**

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**ABSTRACT**

Organ transplantation is a relatively novel field of medicine and has made significant progress in the recent years. Renal transplantation is the preferred treatment for most patients with end-stage renal disease. Despite the improvement after renal transplantation, cardiovascular disease still is the prime cause of death. Dyslipidemia may develop de novo after transplantation, as well as a complication of a chronic kidney disease. The correlation between high lipid levels and cardiovascular mortality is well established in the general population. Dyslipidemia treatment should be considered an important intervention to improve overall patient post-transplant survival.

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

**I. INTRODUCTION**

Organ transplantation is a relatively novel field of medicine that has made significant progress since the second half of the 20th century. It is now well established as an effective treatment for selected patients with end-stage organ failure. The first successful kidney transplant was a living-donor transplant performed between identical twins. However, organ transplantation when the donor and recipient were not genetically identical, pose a problem due to graft rejection. With the invention of different immunosuppressive agents, allograft transplantation has become easier.

Renal transplantation is the preferred treatment for many patients with end-stage renal disease because it provides a better quality of life for them than dialysis. It releases patients from the dietary and fluid restrictions of dialysis and the physical constraints imposed by the need to dialysis. For renal transplant, careful patient selection is essential as a significant number of patients are likely to be considered unsuitable for renal transplantation because of major comorbid disease, especially cardiovascular disease. A careful assessment of comorbid disease that might significantly reduce the chances of successful outcome after transplantation is essential. Rigorous evaluation of the cardiovascular system is particularly important. Cardiovascular disease is very common in the dialysis population, especially those with diabetes, and is the major cause of death after transplantation.

The two major problems in organ transplantation are: chronic graft rejection and the side effects of non-specific immunosuppression; and the shortage of organs for transplantation. There is continuing research into the development of non-invasive biomarkers (in urine or blood) that will allow early diagnosis of graft rejection.

Despite the improvement after renal transplantation, in the overall survival of patients and renal grafts, cardiovascular disease still is the prime cause of death accounting for almost 50% of mortality in renal transplant recipient. About 60% of renal transplant recipients have post-transplant lipid abnormalities and almost 40% have a cardiovascular-related event within 36 months after transplantation. Reported changes in serum lipid levels include elevation of levels of both triglycerides (TG) and total cholesterol (TC). Dyslipidemia may develop de novo after transplantation, as well as a complication of a chronic kidney disease. The correlation between high lipid levels and cardiovascular mortality is well established in the general population. Accelerated atherosclerosis accounts for a major proportion of morbidity and mortality in renal transplant recipients. Dyslipidemia treatment should be considered an important intervention to improve overall patient post-transplant survival. Proper diet and physical activity are the main general measures to manage dyslipidemia and should be introduced initially in every patient after kidney transplant. In the case of an insufficient correction of lipemia, statins are the basis for hypolipidemic treatment.

**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 summarized in the table given 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. FFA synthetase and acetyl-CoA carboxylase are also increased by steroids and so hepatic synthesis of VLDL is increased. Insulin resistance also leads to a reduction in lipoprotein lipase, which leads to reduced triglyceride clearance. There is an increased conversion of VLDL to LDL (low density lipoprotein) cholesterol, leading to increase in LDL cholesterol levels. Another contributory mechanism is down-regulation of LDL receptor expression. Finally, corticosteroids increase the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), which is the rate-limiting step in the pathway of cholesterol biosynthesis.

Cyclosporine interferes with the binding of LDL cholesterol to the LDL receptor. As a result, there is a decline in LDL clearance, leading to a rise in LDL cholesterol levels. In this respect, there may be an additive effect of cyclosporine with corticosteroids. Cyclosporine also interferes with bile acid synthesis by interfering with the enzyme 26 hydroxylase. Decreased bile acid synthesis in turn leads to LDL receptor down-regulation, further reducing the clearance of cholesterol. Cyclosporine, by virtue of being highly lipophilic, is transported within the core of LDL cholesterol particles. In the process, it may change the molecular configuration of LDL and alter the normal feedback regulation of cholesterol synthesis. Glucose intolerance may even potentiate the effect of cyclosporine on lipid levels. The effects of tacrolimus on lipid metabolism are generally similar to those of cyclosporine, so it remains unclear why tacrolimus is associated with less hyperlipidemia. Sirolimus provides a strong connection between pharmacotherapy and dyslipidemia on the one hand, and yet its cardiovascular effects both harmful and protective on the other. It may inhibit lipoprotein lipase and decrease lipolysis. There may also be hepatic over-production of lipoprotein in general. Other effects include a decrease in apolipoprotein B100 catabolism. Finally, sirolimus alters insulin signaling, increases the activity of tissue lipase, and increases the secretion of VLDL cholesterol. Sirolimus is almost never used as monotherapy for transplant-related immunosuppression and so likely acts in a synergistic manner with other immunosuppressive agents in promoting dyslipidemia. It is also used as an anti-proliferative agent in endovascular stents, but the amount of exposure is unlikely to promote lipid abnormalities in that instance.

**IV. MEASURES TO PREVENT DYSLIPIDEMIA**

Physical activity and a proper diet are vital determinants of the lower incidence of CVD in patients of all ages. Physical activity before kidney transplantation (KT) predicts all-cause mortality in renal transplant recipients (RTRs) and is associated with better graft function after KT. Regular physical performance positively correlates with elevated high density lipoprotein-cholesterol (HDL-C), lower levels of TG (in overweight and obese adults), and positive qualitative changes in lipoproteins. RTRs exhibit decreased physical activity compared to the general population, yet were higher than the dialysis population. A healthy diet has been proven to lower cardiovascular risk. Obesity is frequent amongst RTRs, although weight loss should not be considered the main nutritional goal. National Kidney Foundation Guidelines from 2020 recommend 25–35 kcal/kg/d intake for RTRs. The average transplanted patient may have difficulties understanding and implementing isolated nutrients references. Hence, patients should be educated and provided with dietary patterns.

**V. Pharmacological Treatment of Dyslipidemia**

Reduction of cardiovascular risk by lowering LDL-C is the main target of hypolipidemic treatment in RTRs. Statins are considered first-line drugs with ezetimibe being the second-line treatment. Management of dyslipidemia depends on whether the patient has established atherosclerotic cardiovascular disease (ASCVD) or not. A lipid profile measurement should be carried out before, and 4 to 12 weeks after, the introduction of pharmacological treatment of dyslipidemia to determine medication adherence, and then repeated every 3 to 12 months. Some of the commonly used drugs are discussed briefly.

**A. Statins:**

Statins are HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase inhibitors and they are potent hypolipidemic drugs that markedly reduce LDL serum concentration. Reduction in intra-hepatocyte cholesterol levels causes enhanced LDL-R expression and increased uptake of LDL and, among others, TG rich ApoB particles. Statins are suggested to have a pleiotropic effect, as they inhibit the rate control enzyme of the mevalonate pathway, a precursor for non-steroid compounds. Some experimental studies suggest statins may have anti-inflammatory and antioxidative effects, important in cardiovascular disease prevention. Statins are generally well-tolerated, nonetheless, some adverse events like nausea, vomiting, and muscle and joint pain cannot be overlooked, thus this may contribute to poor medication adherence.

**B. Ezetimibe:**

Ezetimibe inhibits the uptake of cholesterol in the intestines by interacting with Niemann-Pick C1 (NPC1) protein. It lowers both TC and TG levels, yet has no influence on HDL-C. Ezetimibe is considered to be a second-line drug due to its lower hypolipidemic potential (lowers LDL-C by 13–20%). Ezetimibe may be prescribed as an alternative in the case of statin intolerance on the inability to reach a therapeutic dose. Ezetimibe combined with maximal doses of statins may reduce hypercholesterolemia and triglyceridemia in RTRs, with no significant influence on creatine kinase concentration and kidney function.

**C. Bile Sequestrants:**

Bile acid sequestrants like cholestyramine prevent bile reabsorption in the intestines and lower serum cholesterol levels. Cholestyramine insignificantly affects renal function in the general population. Due to side effects like constipation, the elevation of triglycerides, and interfering with the absorption of other drugs, bile sequestrants are rarely used.

**D.Fibrates:**

Fibrates are agonists of PPAR-α (Peroxisome Proliferator-Activated Receptor Alpha), regulating the lipid and lipoprotein metabolism. They are efficient in lowering fasting TG serum levels and slightly elevating HDL concentration. Their TG lowering effect is highly dependent on the initial TG level. Fibrates modestly reduce CV events in primary prevention. However, a combination of statins with fibrates raises the risk of myopathy, thus the concomitant use of these drugs must be avoided. In the case of the coexistence of triglyceridemia and hypercholesterolemia, the use of fenofibrate rather than gemfibrozil is recommended because of the lower risk of severe myopathy.

**VI. CONCLUSION**

Post-transplant dyslipidemia is highly prevalent and presents unique management challenges to the clinician. There are two major outcomes when considering post-transplant therapies: preserving or improving allograft function and reducing cardiovascular risk. 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 synonymous with hyperlipidemia. Numerous mechanisms exist for the occurrence of post-transplant dyslipidemia, including those mediated by immunosuppressive drug therapy. Statin therapy has received the most attention in all renal transplantation recipient populations, although the effect of proper dietary advice and adjuvant pharmacological or nonpharmacological agents should not be dismissed. At all stages of treatment appropriate monitoring for side effects should be implemented so that the benefits from these therapies can be achieved.

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