

Dyslipidemia in Renal Transplant Recipients

Subjects: Transplantation

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Dyslipidemia is a frequent complication after kidney transplantation (KT) and is an important risk factor for cardiovascular disease (CVD). Renal transplant recipients (RTRs) are considered at high, or very high, risk of CVD, which is a leading cause of death in patient group. Despite many factors of post-transplant dyslipidemia, the immunosuppressive treatment has the biggest influence on a lipid profile. There are no strict dyslipidemia treatment guidelines for RTRs, but the ones proposing an individual approach regarding CVD risk seem most suitable. Proper diet and physical activity are the main general measures to manage dyslipidemia and should be introduced initially in every patient after KT. In the case of an insufficient correction of lipemia, statins are the basis for hypolipidemic treatment. Statins should be introduced with caution to avoid serious side-effects (e.g., myopathy) or drug-drug interactions, especially with immunosuppressants. To lower the incidence of adverse effects, and improve medication adherence, ezetimibe in combination with statins is recommended.

Keywords: dyslipidemia ; kidney transplantation ; cardiovascular disease ; statin

1. Introduction

Dyslipidemia is frequent amongst renal transplant recipients (RTRs) and is considered an important cardiovascular disease (CVD) risk factor ^[1]. About 60% of RTRs have post-transplant lipid abnormalities ^[2] and almost 40% have a CV-related event within 36 months after transplantation ^[3]. CVD has emerged as the leading death cause in this patient group ^[4].

Post-transplant dyslipidemia is characterized by elevated plasma levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C) and triglycerides, (TG) but reduced high-density lipoprotein cholesterol (HDL-C) ^[5]. Dyslipidemia may develop de novo after transplantation, as well as a complication of a chronic kidney disease (CKD) (eGFR 15–59 mL/min/1.73 m²) ^[6]. Prolonged hemodialysis or peritoneal dialysis significantly alters the lipid profile (characterized by very high TG concentrations) ^[7], and worsens patients' post-transplant outcomes ^[8]. Dyslipidemia treatment should be considered an important intervention to improve overall patient post-transplant survival. Statins have become the mainstay of treatment for dyslipidemia, but other therapeutic methods should also be considered ^{[9][10][11]}.

2. Dyslipidemia Prevalence

Hyperlipidemia is the most common type of dyslipidemia in RTRs ^{[1][12][13]}. TC concentration rises by about 27% compared with results preceding KT ^[14]. Moreover, VLDL and LDL with higher concentrations of TG are observed ^[15]. Triglyceride-rich LDLs are prone to oxidation, and thus have a more atherogenic character ^[16]. HDL-C levels in RTRs are usually comparable or slightly reduced compared to the general population ^{[12][13]}.

3. Causes of Post-Transplant Dyslipidemia

The pathophysiology of post-transplant dyslipidemia is multicausal and includes modifiable and nonmodifiable risk factors^[2]. After transplantation, the sudden improvement of life quality can lead to an alleviation of dietary restrictions, previously dictated by impaired kidney function ^[17]. Following cholesterol- and fructose-rich diets is frequent amongst RTRs ^[18]. Obesity incidence rises by 34% after KT, and obesity is considered to be a factor of long-term graft dysfunction ^[19]. Weight gain may also contribute to the development of insulin resistance, and new-onset diabetes after transplantation (NODAT) thereafter ^[20]. Therefore, maintenance of a healthy weight should be an effective tool to reduce post-transplant complications.

A sedentary lifestyle is a frequently omitted factor leading to dyslipidemia ^[21]. Patients on prolonged hemodialysis prior to transplantation exhibit extremely low physical performance, caused by an underlying disease, sarcopenia, malnutrition,

and total body weakness [22]. After KT, many patients are also concerned about the safety of physical activity and its potentially detrimental effect on the graft [23].

Deficient doctor-patient communication could hinder patients' understanding of their illness; thus, comprehensive post-transplant health and lifestyle recommendations should be created and implemented [24]. Despite all this, immunosuppressive therapy is considered the main reason for the post-transplant lipid characteristics [13][25]. Widely used medications conducive to dyslipidemia include calcineurin inhibitors (CNI) (cyclosporine in particular), mTOR inhibitors, and glucocorticoids. Numerous studies indicate higher drug doses and the intensity of treatment in positive correlation with dyslipidemia [13][25].

4. Pharmacological Treatment of Dyslipidemia

Reduction of cardiovascular risk by lowering LDL-C is the main target of hypolipidemic treatment in RTRs, and dyslipidemia management is similar to that recommended for non-transplant patients with CKD. American 2018 [10] and European 2019 [9] guidelines both recommend identifying RTRs at high, or very high, risk of CVD, particularly those with LDL-C ≥ 1.8 mmol/L (70 mg/dL), and consider statins first-line drugs with ezetimibe being the second-line treatment. In order to estimate the patients' risk of CVD, physicians may use a calculator based on several readily-available pieces of information about the patient [26].

While European guidelines state a strict "treat-to-target" approach, the KDIGO 2013 guideline proposes a rather unrestricted approach, noting the polypharmacy problem and the potential adverse effects of lipid-lowering therapy in transplant patients. Hence, the American "fire and forget" [11][27] strategy will be discussed, owing to its holistic and patient-orientated character.

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 four to 12 weeks after, the introduction of pharmacological treatment of dyslipidemia to determine medication adherence, and then repeated every three to 12 months [28].

Due to the KDIGO 2013 guidelines, lower initial doses of statins are recommended and the dose may be increased, whether the patient receives cyclosporine or not, to avoid adverse effects like severe myopathy [11].

4.1. 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 CVD prevention [29][30][31].

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. Less frequent but serious side-effects of statin therapy include NODAT and hepatotoxicity [9]. In extreme cases, rhabdomyolysis may occur, a life-threatening condition that can lead to rapid kidney dysfunction [32].

Statins have no proven protective effect on graft rejection or patient post-transplant survival [33]. However, in the multicenter, double-blind study (ALERT) on 2102 RTRs treated with fluvastatin, the incidence of cardiac arrest deaths and non-fatal myocardial infarctions was reduced in favor of the research group, yet with no significant influence on the overall death rate [34]. The RTRs population is unique, taking into account the risk factors associated with transplantation itself. Therefore, even lacking outcomes in big controlled trials, RTRs with well-functioning grafts and increased risk of CVD may benefit from statin treatment [9][11][27].

Statins Drug-Drug Interactions

Drug-drug interactions may be frequent in the transplant population due to the high prevalence of polypharmacy [35]. Statins are extensively metabolized in the liver by cytochrome P450 complex, particularly CYP3A4. Fluvastatin, pravastatin, pitavastatin, and rosuvastatin are metabolized by different cytochromes and they rarely get into drug-drug interactions. Most statins are lipophilic except hydrophilic pravastatin and rosuvastatin, which underlies their high safety profile [36].

Concurrent treatment with statins and CNI, particularly cyclosporine, should be conducted with caution with lower doses of statins due to reported cases of rhabdomyolysis [9][37][38]. Tacrolimus drug-drug interactions are less severe and frequent in comparison with cyclosporine [39].

4.2. Ezetimibe

Ezetimibe inhibits the uptake of cholesterol in the intestines by interacting with NPC1 protein [40]. 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%) [11]. Both American and European guidelines recommend ezetimibe (10 mg) in combination with statins in patients at high, and very high, risk of CVD or in secondary prevention, in order to achieve target LDL concentrations [9][10]. 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 [41], with no significant influence on creatine kinase concentration and kidney function [42].

4.3. Bile Sequestrants

Bile acid sequestrants like cholestyramine prevent bile reabsorption in the intestines and lower serum cholesterol levels [43]. Cholestyramine insignificantly affects renal function in the general population [44]. Due to side effects like constipation, the elevation of triglycerides, and interfering with the absorption of other drugs, bile sequestrants are rarely used [9].

4.4. 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 [9]. 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 [45]. 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. Despite having a mild LDL-lowering potential, fibrates are not supported by RCTs as add-on drugs to statin therapy [10].

References

1. Agarwal, A.; Prasad, G.V.R. Post-Transplant Dyslipidemia: Mechanisms, Diagnosis and Management. *World J. Transplant.* 2016, 6, 125.
2. Badiou, S.; Cristol, J.P.; Mourad, G. Dyslipidemia Following Kidney Transplantation: Diagnosis and Treatment. *Curr. Diabetes Rep.* 2009, 9, 305–311.
3. Shirali, A.C.; Bia, M.J. Management of Cardiovascular Disease in Renal Transplant Recipients. *Clin. J. Am. Soc. Nephrol.* 2008, 3, 491–504.
4. Heleniak, Z.T.; Illersperger, S.; Brakemeier, S.; Dębska-Ślizień, A.; Bach, P.; Budde, K.; Halleck, F. Influence of Lipid Profile and Statin Administration on Arterial Stiffness in Renal Transplant Recipients. *Cardiol. J.* 2022, 29, 263–271.
5. Mikolasevic, I.; Žutelija, M.; Mavrinac, V.; Orlic, L. Dyslipidemia in Patients with Chronic Kidney Disease: Etiology and Management. *Int. J. Nephrol. Renov. Dis.* 2017, 10, 35–45.
6. Kosugi, T.; Eriguchi, M.; Yoshida, H.; Tasaki, H.; Fukata, F.; Nishimoto, M.; Matsui, M.; Samejima, K.I.; Iseki, K.; Fujimoto, S.; 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. Piecha, G.; Adamczak, M.; Ritz, E. Dyslipidemia in Chronic Kidney Disease: Pathogenesis and Intervention. *Pol. Arch. Med. Wewn.* 2009, 119, 487–492.
8. Dębska-Ślizień, A.; Bzoma, B.; Rutkowski, B. Wyprzedzające Przeszczepianie Nerek. *Forum Nefrol.* 2009, 2, 84–89.
9. Mach, F.; Baigent, C.; Catapano, A.L.; Koskinas, K.C.; Casula, M.; Badimon, L.; Chapman, M.J.; de Backer, G.G.; Delgado, V.; Ference, B.A.; 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.
10. 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 for the Management of Blood Cholesterol. *Circulation* 2019, 140, 516–548.

deline 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.

11. Wanner, C.; Tonelli, M. 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.
12. Pannu, H.S.; Singh, D.; Sandhu, J.S. Lipid Profile before and after Renal Transplantation—A Longitudinal Study. *Ren. Fail.* 2003, 25, 411–417.
13. Massy, Z.A.; Kasiske, B.L. Post-Transplant Hyperlipidemia: Mechanisms and Management. *J. Am. Soc. Nephrol.* 1996, 7, 971–977.
14. Corsini, A. The Safety of HMG-CoA Reductase Inhibitors in Special Populations at High Cardiovascular Risk. *Cardiovasc. Drugs Ther.* 2003, 17, 265–285.
15. Quaschnig, T.; Mainka, T.; Nauck, M.; Rump, L.C.; Wanner, C.; Krämer-Guth, A. Immunosuppression Enhances Atherogenicity of Lipid Profile after Transplantation. *Kidney Int. Suppl.* 1999, 56, S235–S237.
16. Van den Dorpel, M.A.; Ghanem, H.; Rischen-Vos, J.; Man In't Veld, A.J.; Jansen, H.; Weimar, W. Low-Density Lipoprotein in Oxidation Is Increased in Kidney Transplant Recipients. *Transplant. Int.* 1996, 9, S54–S57.
17. Sabbatini, M.; Ferreri, L.; Pisani, A.; Capuano, I.; Morgillo, M.; Memoli, A.; Riccio, E.; Guida, B. Nutritional Management in Renal Transplant Recipients: A Transplant Team Opportunity to Improve Graft Survival. *Nutr. Metab. Cardiovasc. Dis.* 2019, 29, 319–324.
18. Kluch, M.; Kurnatowska, I.; Matera, K.; Łokieć, K.; Puzio, T.; Czekwianianc, E.; Grzelak, P. Nutrition Trends in Patients over the Long Term after Kidney Transplantation. *Transplant. Proc.* 2020, 52, 2357–2362.
19. Nöhre, M.; Schieffer, E.; Hanke, A.; Pape, L.; Schiffer, L.; Schiffer, M.; de Zwaan, M. Obesity After Kidney Transplantation—Results of a KTx360° Substudy. *Front. Psychiatry* 2020, 11, 399.
20. Zielińska, K.; Kukulski, L.; Wróbel, M.; Przybyłowski, P.; Zakliczyński, M.; Strojek, K. Prevalence and Risk Factors of New-Onset Diabetes After Transplantation (NODAT). *Ann. Transplant.* 2021, 26, e926556-1.
21. Ponticelli, C.; Favi, E. Physical Inactivity: A Modifiable Risk Factor for Morbidity and Mortality in Kidney Transplantation. *J. Pers. Med.* 2021, 11, 927.
22. Moorthi, R.N.; Avin, K.G. Clinical Relevance of Sarcopenia in Chronic Kidney Disease. *Curr. Opin. Nephrol. Hypertens.* 2017, 26, 219.
23. Gordon, E.J.; Prohaska, T.R.; Gallant, M.; Siminoff, L.A. Self-Care Strategies and Barriers among Kidney Transplant Recipients: A Qualitative Study. *Chronic Illn.* 2009, 5, 75.
24. Ballesteros, F.; Allard, J.; Durand, C.; Cardinal, H.; Lalonde, L.; Fortin, M.-C. Kidney Transplant Recipients' Perspectives on Cardiovascular Disease and Related Risk Factors After Transplantation: A Qualitative Study. *Transplant. Direct* 2017, 3, e162.
25. Ponticelli, C.; Arnaboldi, L.; Moroni, G.; Corsini, A. Treatment of Dyslipidemia in Kidney Transplantation. *Expert Opin. Drug Saf.* 2020, 19, 257–267.
26. Goff, D.C.; Lloyd-Jones, D.M.; Bennett, G.; Coady, S.; D'Agostino, R.B.; Gibbons, R.; Greenland, P.; Lackland, D.T.; Levy, D.; O'Donnell, C.J.; 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.
27. Massy, Z.A.; Kolla, E.; Ferrières, J.; Bruckert, E.; Lambert, O.; Mansencal, N.; Laville, M.; Frimat, L.; Fouque, D.; Combès, C.; et al. Is a Treat-to-Target Approach to Lipid-Lowering Therapy Appropriate in Patients with Chronic Kidney Disease? A Prospective French Cohort Study. *J. Nephrol.* 2021, 34, 1467–1477.
28. Stone, N.J.; Robinson, J.G.; Lichtenstein, A.H.; Bairey Merz, C.N.; Blum, C.B.; Eckel, R.H.; Goldberg, A.C.; Gordon, D.; Levy, D.; Lloyd-Jones, D.M.; 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.
29. Ginsberg, H.N. REVIEW: Efficacy and Mechanisms of Action of Statins in the Treatment of Diabetic Dyslipidemia. *J. Clin. Endocrinol. Metab.* 2006, 91, 383–392.
30. Chapman, M.J.; McTaggart, F. Optimizing the Pharmacology of Statins: Characteristics of Rosuvastatin. *Atheroscler. Suppl.* 2002, 2, 33–37.
31. Davignon, J. Beneficial Cardiovascular Pleiotropic Effects of Statins. *Circulation* 2004, 109, III-39–III-43.
32. Stroes, E.S.; Thompson, P.D.; Corsini, A.; Vladutiu, G.D.; Raal, F.J.; Ray, K.K.; Roden, M.; Stein, E.; Tokgözoğlu, L.; Nordestgaard, B.G.; et al. Statin-Associated Muscle Symptoms: Impact on Statin Therapy-European Atherosclerosis Soci

33. Palmer, S.C.; Navaneethan, S.D.; Craig, J.C.; Perkovic, V.; Johnson, D.W.; Nigwekar, S.U.; Hegbrant, J.; Strippoli, G.F. M. HMG CoA Reductase Inhibitors (Statins) for Kidney Transplant Recipients. *Cochrane Database Syst. Rev.* 2014, 2014, CD005019.
34. Holdaas, H.; Fellström, B.; Jardine, A.G.; Holme, I.; Nyberg, G.; Fauchald, P.; Grönhagen-Riska, C.; Madsen, S.; Neumayer, H.H.; Cole, E.; et al. Effect of Fluvastatin on Cardiac Outcomes in Renal Transplant Recipients: A Multicentre, Randomised, Placebo-Controlled Trial. *Lancet* 2003, 361, 2024–2031.
35. Woron, J. Interactions of Immunosuppressive Drugs: Why They Are so Important in Clinical Practice? *Forum Nefrol.* 2019, 12, 106–113.
36. Oscanoa Espinoza, T.J.; Paredes-Pérez, N.; Lizaraso-Soto, F. Safety of Statins. *Indian J. Endocrinol. Metab.* 2013, 17, 636.
37. Scarfia, R.V.; Clementi, A.; Granata, A. Rhabdomyolysis and Acute Kidney Injury Secondary to Interaction between Simvastatin and Cyclosporine. *Ren. Fail.* 2013, 35, 1056–1057.
38. Monostory, K. Metabolic Drug Interactions with Immunosuppressants. In *Organ Donation and Transplantation—Current Status and Future Challenges*; IntechOpen: London, UK, 2018.
39. Akman, B.; Uyar, M.; Afsar, B.; Sezer, S.; Ozdemir, F.N.; Haberal, M. Lipid Profile during Azathioprine or Mycophenolate Mofetil Combinations with Cyclosporine and Steroids. *Transplant. Proc.* 2007, 39, 135–137.
40. Li, X.; Wang, J.; Coutavas, E.; Shi, H.; Hao, Q.; Blobel, G. Structure of Human Niemann-Pick C1 Protein. *Proc. Natl. Acad. Sci. USA* 2016, 113, 8212–8217.
41. 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.
42. 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.
43. 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.
44. 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.
45. 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.