World Journal of Transplantation

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DOI: 10.5500/wjt.v6.i1.125

World J Transplant 2016 March 24; 6(1): 125-134
ISSN 2220-3230 (online)

REVIEW

Post-transplant dyslipidemia: Mechanisms, diagnosis and management

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Author contributions: Agarwal A and Prasad GVR conducted the research and wrote the paper.

Conflict-of-interest statement: No potential conflict of interest. No financial support.

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Received: July 29, 2015
Peer-review started: July 31, 2015
First decision: October 27, 2015
Revised: November 26, 2015
Accepted: February 16, 2016
Article in press: February 17, 2016
Published online: March 24, 2016

Abstract

Post-transplant dyslipidemia is highly prevalent and presents unique management challenges to the clinician. The two major outcomes to consider with post-transplant therapies for dyslipidemia are preserving or improving allograft function, and reducing cardiovascular risk. Although there are other cardiovascular risk factors such as graft dysfunction, hypertension, and diabetes, 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 solid organ transplant recipient populations, although the effect of proper dietary advice and adjuvant pharmacological and non-pharmacological agents should not be dismissed. At all stages of treatment appropriate monitoring strategies for side effects should be implemented so that the benefits from these therapies can be achieved. Clinicians have a choice when there is a conflict between various transplant society and lipid society guidelines for therapy and targets.

Key words: Cholesterol; Dyslipidemia; Triglycerides; Statins; Immunosuppression

Core tip: Post-transplant dyslipidemia is highly prevalent in all solid organ transplant recipient populations. Guidelines for therapy are derived mostly from general population experiences, although the mechanisms for dyslipidemia due to immunosuppression are distinct and known. Statin therapy has understandably received the most attention in transplant populations but the potential efficacy of other therapeutic strategies should not be ignored.

Agarwal A, Prasad GVR. Post-transplant dyslipidemia: Mechanisms, diagnosis and management. *World J Transplant* 2016; 6(1):

125-134 Available from: URL: http://www.wjgnet.com/2220-3230/full/v6/i1/125.htm DOI: http://dx.doi.org/10.5500/wjt.v6.i1.125

INTRODUCTION

The great success of solid organ transplantation (SOT) over the past 50 years is demonstrated by the fact that both excellent short-term allograft survival and adequate long-term allograft function without the development of overwhelming comorbidity are routinely expected. Immunosuppressive medication regimens have advanced to the point that acute rejection has declined significantly, and even chronic forms of rejection are being delayed and their effects mitigated. As a result, increased clinician attention is being focused on the general well-being of transplant recipients, apart from allograft health *per se*, towards which cardiovascular (CV) health is an important component. In turn, each of the traditional CV disease (CVD) risk factors has received a share of the thrust on management strategies in transplant populations[1], including dyslipidemia[2]. However, most interventions are typically mapped to transplant recipients on the basis of evidence garnered from the general population. While the mechanisms for post-transplant dyslipidemia have largely been worked out, it is still not sufficiently known whether there is value to measuring isolated cholesterol subfractions, designing interventions for specific subfractions, or altering immunosuppressive medication regimens towards the goal of improving lipid profiles and CV health.

This review article provides a comprehensive overview of dyslipidemia in SOT recipients, based on the currently available literature. The prevalence and types of post-transplant dyslipidemia are first described, followed by the factors associated with lipid abnormalities, mechanisms of dyslipidemia after transplantation, the consequences of dyslipidemia, and finally its clinical diagnosis, monitoring, and treatment.

PREVALENCE AND TYPES OF DYSLIPIDEMIA

At one time, the prevalence of hyperlipidemia, which is the most common form of dyslipidemia, was estimated to be as high as 80% in kidney transplant recipients (KTR)[3]. Reports of the high prevalence of hyperlipidemia go back as far as 1973[4]. In the azathioprine-corticosteroid era of post-transplant immunosuppression, the prevalence rate was estimated at 50%-78%[5-7]. Hypertriglyceridemia was just as common as hypercholesterolemia. However, with the introduction of cyclosporine, hypercholesterolemia has become the predominant abnormality[8], particularly low density lipoprotein (LDL) cholesterol elevation[9]. An early prevalence estimate of hyperlipidemia of over 50% has been reported in heart transplant recipients (HTR)[10]. Lung transplantation has been associated with a prevalence of hypercholesterolemia and hypertriglyceridemia of 32% and 41% respectively[11]. Estimates of dyslipidemia in liver transplant recipients (LTR) include 43%[12] and 31%-51%[13]. The point prevalence of hyperlipidemia is unlikely to vary over time post-transplant. In KTR, hyperlipidemia is persistent if untreated. It is also possible that the prevalence is higher with time, due to inadequate surveillance in long-term patients. Cumulative factors such as advancing age, immunosuppression, weight gain, and the development of diabetes may all contribute to developing hyperlipidemia over time. Hyperlipidemia has also been documented in children after kidney transplantation[14].

Dyslipidemia is not synonymous with hyperlipidemia, so it is conceivable that dyslipidemia may still be present despite normal lipid levels. Increased levels of very low-density lipoprotein (VLDL) cholesterol and decreased high-density lipoprotein (HDL) cholesterol levels despite normal "total" cholesterol levels are well-described[15]. A low HDL has been noted in lung transplant recipients[16] but not necessarily in HTR[17]. In particular, a low level of the HDL2 sub-fraction has been reported after kidney transplantation[18]. There is also a higher amount of oxidized LDL cholesterol[19,20]. The lipid profile of LTR has also recently been elaborated. Compared to controls with no chronic medical disease, LTR had higher apolipoprotein B, small dense LDL cholesterol, and VLDL cholesterol concentrations[21]. VLDL cholesterol concentration was also related to cyclosporine levels[21]. Despite the initial excitement surrounding HDL sub-fractions and oxidized LDL cholesterol[18-20], measurement of these lipid forms has yet to reach clinical practice almost thirty years after their description. The prevalence of small dense LDL cholesterol has been estimated at 26%-33% in KTR[22]. Elevations in serum apolipoprotein B and lipoprotein (a)[23], as well as decreased apolipoprotein A-I[24], and decreased ratios of apolipoproteins C-Ⅱ to C-Ⅲ[25,26] also generated significant interest, but at the present time none of these are routinely measured in a clinical setting. More recently, "non-HDL cholesterol", which is simply the total cholesterol minus HDL cholesterol level, has received attention in transplant patients[27]. However, the importance of this particular measure has not yet been placed in full context.

FACTORS ASSOCIATED WITH LIPID ABNORMALITIES

Given the variety of lipid abnormalities seen, it is useful to divide factors contributing to dyslipidemia into those that contribute primarily to hypercholesterolemia and those that contribute primarily to hypertriglyceridemia, notwithstanding their qualitative impact that cannot be routinely assessed in the clinic. These risk factors are summarized in Table 1 (partially adapted from[8]).

Table 1 Factors associated with lipid abnormalities after transplantation

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

Hypercholesterolemia is considered more prevalent based on the available literature, although the literature is dominated by North American and Western European publications. Genetic predisposition may be based on the prevalence of various polymorphisms of the lipoprotein system. For example, the GA genotype of the apo A-1 promoter region has been associated with a greater rise in LDL cholesterol after heart transplantation[28]. Conversely, some genes such as the TP-binding cassette subfamily B member 1 (*ABCB1*) lose their association with LDL cholesterol after heart transplantation[29]. Advanced age is another non-modifiable risk factor. However, modifiable risk factors such as a diet high in saturated fat may be just as important as a contributor to hypercholesterolemia. Obesity, proteinuria either as a result of native or transplant kidney disease, or the use of thiazide diuretics or beta-blockers for hypertension and heart disease may also contribute. Corticosteroids, cyclosporine, and sirolimus may all cause elevations in cholesterol levels[8]. Although tacrolimus is generally believed to cause less elevation in LDL cholesterol than cyclosporine, this may not always be the case, particularly in LTR in whom lipid levels may correlate with tacrolimus levels[30]. The association with sirolimus is particularly strong. LDL cholesterol levels were higher in the sirolimus arm of the Symphony study[31].

In the case of post-transplant hypertriglyceridemia, as with hypercholesterolemia, genetic predisposition plays an important role. The apolipoprotein E 2/2 and 2/3 genotypes are associated with elevated triglycerides after kidney transplantation[32]. The apo A-1 promoter region[28] also correlates with elevated triglycerides. The development of hypertriglyceridemia in response to sirolimus has been subject to genetic analysis, with positive associations demonstrated with the ABCB1 1236 TT homozygote and the interleukin-10 1082AA homozygote in the case of KTR[33]. Age, however, seems to be less important as a risk factor for hypertriglyceridemia. A diet rich in simple sugars predisposes to hypertriglyceridemia, and although obesity and proteinuria are also associated with hypertriglyceridemia, poor renal function *per se* appears to be an additional risk factor[8]. Sirolimus is more strongly associated with hypertriglyceridemia than hypercholesterolemia, with even a lower drug exposure leading to this abnormality[31], although the contribution of other immunosuppressive drugs is less clear. More common is the association of hypertriglyceridemia with other metabolic syndrome components[1].

MECHANISMS OF POST-TRANSPLANT DYSLIPIDEMIA

Immunosuppressive agents contribute significantly and specifically to lipid abnormalities after SOT.

Corticosteroids induce insulin resistance. The resultant hyperinsulinemia leads to increased hepatic uptake of free fatty acids (FFA)[34]. FFA constitutes the main substrate for VLDL cholesterol synthesis. FFA synthetase and acetyl-CoA carboxylase are also increased by steroids[35] and so hepatic synthesis of VLDL is increased. Insulin resistance also leads to a reduction in lipoprotein lipase, which leads to reduced triglyceride clearance[36]. There is an increased conversion of VLDL to LDL cholesterol, leading to a rise in LDL cholesterol levels. Yet another contributory mechanism is down-regulation of LDL receptor expression[37]. Finally, corticosteroids increase the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), which is the rate-limiting step in the cholesterol biosynthetic pathway[37].

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[38] by interfering with the enzyme 26 hydroxylase[15]. 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[39] and alter the normal feedback regulation of cholesterol synthesis[8]. 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 fascinating instance of a strong connection between pharmacotherapy and dyslipidemia on the one hand, yet ongoing debate about its cardiovascular effects both harmful and protective on the other. Sirolimus may inhibit lipoprotein lipase[40]

and decrease lipolysis. There may also be hepatic over-production of lipoprotein in general[41]. Other effects include a decrease in apolipoprotein B100 catabolism[42]. Finally, sirolimus alters insulin signaling, increases the activity of tissue lipase, and increases the secretion of VLDL cholesterol[40]. 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. Sirolimus 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.

CONSEQUENCES OF DYSLIPIDEMIA POST-TRANSPLANTATION

SOT recipients, especially KTR, are at high risk for the development of post-transplant CVD. The link between dyslipidemia and CVD may not be as strong as, for instance, diabetes[1], but there is no reason to believe that the association does not hold in transplant populations as it does in the general population. The underlying assumptions, however, are not so straightforward. Atherosclerosis is accelerated after transplantation[8], and this can be linked at least retrospectively to cardiovascular events[43]. The association of elevations in cholesterol to cardiovascular events may be stronger with cholesterol than with triglycerides, and likewise, more associated with ischemic heart disease than other forms of CVD such as cerebrovascular disease or peripheral vascular disease[44]. It has been estimated that an increase in LDL cholesterol concentration by 2 mmol/L doubles the risk for major adverse cardiac events (MACE), comparable to an age increase by 23 years[45]. A low level of HDL cholesterol has been associated with a threefold increase in post-transplant MACE[46] and also an increase in all-cause mortality[46]. Non-HDL cholesterol has been found to be as powerful a predictor of MACE as diabetes in KTR[47].

Despite some correlative success between various lipid level abnormalities and MACE, consistent demonstration of the association remains quite difficult, since a large proportion of MACE is explained by unmeasured risk factors outside of the traditional Framingham risk factors, including dyslipidemia[48]. Moreover, hyperlipidemia has not been found to be an independent risk factor for MACE in non-Caucasian populations in whom non-traditional risk factors may be more important[49]. The Assessment of Lescol in Renal Transplantation (ALERT) study database[50] has formed the basis for significant understanding of the link of dyslipidemia to human pathology, but all links remain associative. Data from another large database, the Patient Outcomes in Renal Transplantation study, however, indicate that dyslipidemia adds little predictive value to more transplant-specific and graft-related variables in predicting acute myocardial infarction (MI), coronary artery revascularization or sudden death[51]. Nonetheless, hypertriglyceridemia in particular has been associated with the progression of coronary artery calcification (CAC) in KTR[52], although it must be understood that CAC is only a surrogate marker for CVD and is itself controversial in that respect at best. Information regarding dyslipidemia and CVD risk in SOT outside of kidney transplantation is limited. In HTR, hypercholesterolemia has been associated with non-fatal MACE in a retrospective analysis[53]. Although LTR display a higher CVD risk and CVD is the leading cause of non-graft related deaths[54], demonstration of dyslipidemia as a CVD risk factor lags behind other risk factors such as diabetes and hypertension[54]. While other studies in liver transplantation have also either not addressed or failed to demonstrate a relationship of dyslipidemia to CVD[55], a link with CVD has been found with metabolic syndrome and hypertriglyceridemia[56].

Dyslipidemia, or at least one aspect of it (hypertriglyceridemia and low HDL cholesterol), is one among five components constituting the metabolic syndrome. Therefore, it is helpful to understand the contribution of dyslipidemia to post-transplant morbidity relative to its sister CVD risk factors such as hypertension, microalbuminuria, obesity and dysglycemia. As one example, in a cohort study of 1182 stable KTR with close to 7500 patient-years of follow-up, dyslipidemia did not attain statistical significance as a stand-alone CVD risk factor, but provided additive value to dysglycemia and microalbuminuria in predicting MACE ahead of hypertension and obesity[1]. Interventions for dyslipidemia have an impact on reducing cardiac deaths and non-fatal MI in clinical trials specific to the transplant population[2]. Therefore, attention to dyslipidemia is indeed warranted.

In contrast to other populations, SOT permits the assessment of the relationship of dyslipidemia to the performance of the allograft itself. It is possible, at least theoretically, that an allograft is predisposed differently to metabolic injury compared to a native organ due to its intersection with injury from the actions of the immune system. Hyperlipidemia is a paradigmatic contributor to chronic kidney allograft injury as a "non-immune" risk factor[57]. Atherosclerosis is believed to be an integral part of the rejection process, by virtue of the accumulation of oxidized LDL cholesterol in the kidney interstitium leading to fibrosis[58]. However, this may be a bidirectional relationship, with lipid abnormalities perpetuated by allograft dysfunction. Hypercholesterolemia has been associated with kidney allograft loss in the context of prior acute rejection[59]. Hypercholesterolemia itself may predispose to acute rejection, by altering cyclosporine pharmacokinetics and increased binding with less tissue release[60]. At a clinical level, overall there has been little progress in understanding beyond earlier studies that demonstrate associations between early post-kidney transplant lipid

levels and subsequent graft function or death-censored graft loss[61,62]. A demonstrable effect of lipid levels on graft function may be blunted by more aggressive lipid lowering in transplant recipients for cardiovascular protection with the advent of other potent medical therapies, as well as due to data on safety and efficacy of lipid-lowering therapies from studies such as ALERT. Effective immunosuppressive therapy, and other graft-related variables such as donor organ quality may also be too overpowering to allow for demonstrating any effects of lipid profiles on graft function.

DIAGNOSIS AND MONITORING

The diagnosis of dyslipidemia in SOT recipients typically starts with a lipid profile obtained after 8 to 12 h of fasting. Although non-fasting lipid level measurement has been occasionally recommended for the general population, transplant recipients should be considered a high-risk group for CVD and should therefore be subject to fasting measurements. Normal "cut-offs" for hyperlipidemia are typically the same as those used for the general population[15], in the absence of any evidence to the contrary. Measurements of lipid parameters beyond total, HDL and LDL cholesterol, or triglycerides are rarely performed outside of research studies. All recipients require at least one such fasting lipid profile, with the first profile obtained at some point during the first year. An initial evaluation as soon as three months post-transplant has been recommended[8]. A Canadian commentary on the 2009 KDIGO Clinical Practice Guideline[63] advises initial measurement 2-3 mo post-transplant, 2-3 mo after a change in treatment, and annually thereafter[63]. Annual monitoring is corroborated by older European guidelines[64]. More recently, the need for repeat lipid level measurement in many forms of chronic kidney disease has been questioned[65], mostly on the basis of lack of evidence for utility and the absence of clinical trial data. A useful approach might be to gauge the transplant recipient's overall cardiac risk profile, and reserve lipid monitoring to those at a perceived higher CV risk, understanding that chronic graft dysfunction may itself be a high-risk equivalent.

TREATMENT

All transplant recipients require consultation with a dietician on a regular, if infrequent basis. A diet low in total fat, saturated fatty acids, and cholesterol can be prescribed as an initial measure, particularly in KTR who by definition have chronic kidney disease (CKD). Hypertriglyceridemia may be controlled with the help of a diet low in simple sugars and alcohol. The American Heart Association Step Ⅰ diet can be considered as a starting point for those with an elevated LDL cholesterol level. Limiting dietary cholesterol intake to under 300 mg/d and caloric intake from fat to under 30% of the total caloric intake may be helpful. A further Step Ⅱ approach would be to limit these further to under 200 mg/d and 10% respectively. However, evidence of the efficacy of such diets in transplant recipients is lacking. Balance of the saturated to polyunsaturated fat intake should be sought. Losing excess body weight is important, and control of total caloric intake is likely to have the biggest impact[3]. Improved glycemic control will also help to improve hyperlipidemia. Adherence to prescribed diets can be highly variable, and so culture-specific dietary interventions may be needed to improve adherence. Incorporation of soy protein into the diet[15] has not been tested in SOT recipients. The success of dietary intervention alone at improving dyslipidemia has been estimated at under 20% in KTR[66].

Non-conventional pharmacological therapies have received some attention, particularly in KTR. There may be attempts by SOT recipients to reduce their lipid levels through herbal supplements. Obviously, this can be quite dangerous in the context of immunosuppressive medication. For example, red yeast rice (Monascus purpureus) is a remedy designed to lower cholesterol levels. Red yeast rice contains varieties of mevinic acid, a naturally occurring statin, that has been associated with rhabdomyolysis[67]. Since statin concentrations show batch variability and production is unregulated, herbal remedies should be discouraged. Fish oil is rich in omega-3 polyunsaturated fatty acids and can lower serum triglycerides[68] by reducing its hepatic synthesis. Fish oil may even have a beneficial effect on graft function[69], although further studies are clearly needed before this therapy can be endorsed. Finally, the use of antioxidants particularly antioxidant vitamins has also been considered based on the rationale that oxidized LDL cholesterol is particularly atherogenic. However, antioxidants are not considered efficacious at preventing CVD in the general population[70]. The administration of homocysteine-lowering therapies is also not recommended[68].

HMG-CoA reductase inhibitors, or statins, are widely used in KTR, LTR and HTR. They are potent reducers of LDL cholesterol levels, and are generally considered safe as long as patients are appropriately monitored. Some statins may have modest beneficial effects in lowering serum triglycerides and raising HDL cholesterol levels[15]. There are also claims that statins have pleiotropic effects, involving a favorable modulation of endothelial function that translates into improved CV health[71]. Since CKD may be a high-risk equivalent for CVD, this paradigm seems appealing. Perhaps the most commonly used statin is atorvastatin, despite the fact that the single prospective randomized trial of statins *vs* placebo in KTR, the ALERT study, utilized a different but older statin, namely fluvastatin[2]. This large trial was successful in demonstrating benefit for secondary CVD endpoints, but not the primary composite

endpoint. Since a greater reduction in LDL cholesterol is believed to translate into greater cardiovascular advantage, atorvastatin or another more potent statin such as rosuvastatin may be preferred by clinicians. Atorvastatin and rosuvastatin are not as dependent on time of day for administration as the other statins[15]. Maximum doses used are generally less than those for the general population, although the rationale for this practice in SOT recipients is based more on the known interaction of calcineurin-inhibitors through the CYP3A4 isoenzyme system[72] than clinical evidence. Transplant recipients are also prescribed multiple other medications that can interact through this busy enzyme system, and so regular monitoring for the major statin-induced side effects, namely myositis or rhabdomyolysis, as well as hepatitis, is warranted. Simvastatin has recently been singled out as an offender with regards to rhabdomyolysis[15]. However, statins remain appealing agents to use, being once-daily drugs and especially since they have also been shown to improve patient survival[73]. Detailed guidelines on the use of specific statins in KTR are available[15]. The recommended target for LDL cholesterol is a level under 2.0 mmol/L[63] although this may be based more on extrapolation from the general population. A non-HDL cholesterol target of under 3.36 mmol/L in adults and 4.14 mmol/L in adolescents is a recommendation that serves as a surrogate for forms of cholesterol besides LDL cholesterol[63]. It might be easier to initiate statin therapy early after the transplant, when other medications are being adjusted and patients are more receptive to new suggestions for optimizing their overall health. As more time elapses post-transplant, longer-term risks such as CVD may become less appreciated and the introduction of new medications may be perceived as an unnecessary risk or potential threat to allograft health.

Statins are also used in other SOT recipients besides KTR. Statins are generally considered safe in LTR with no severe complications[74], although pravastatin in particular has been recommended[75]. Statins also reduce accelerated graft atherosclerosis and mortality in HTR, especially pravastatin and simvastatin[76], although atorvastatin has also been studied[77]. The benefit of statins has also been extended to pediatric and adolescent HTR[78]. Although the literature with other solid organs is not as expansive as that for KTR, there is no reason to believe that safety and efficacy concerns are substantially different among them.

If a maximal dose of statin proves to be insufficient at bringing the LDL cholesterol level to target, then consideration can be given to adding a second agent. Ezetimibe inhibits cholesterol absorption at the level of the intestinal brush border. Ezetimibe is generally safe in KTR[79] although consultation at this point with a lipid metabolism specialist could be considered, particularly when increased transaminase levels have previously been noted with statin therapy. There are no time-of-day restrictions with ezetimibe. Ezetimibe can be considered for use in LTR[75,80] and in HTR[81] in whom it has also been tested as monotherapy[82]. Ezetimibe also increases HDL cholesterol levels in some HTR[83].

Fibrates reduce hepatic VLDL cholesterol synthesis and increase lipoprotein lipase activity, decreasing triglyceride levels and increasing HDL cholesterol levels to some extent. LDL cholesterol levels may also decline, but not to the same extent as triglycerides. Among fibrates, fenofibrate is generally preferred over gemfibrozil due to less myotoxicity when added to a statin, as a result of less drug interaction. A concern regarding fibrate use is the potential for decline in kidney function in the presence of existing renal insufficiency[84]. The use of fibrates should be avoided in advanced CKD since fibrates are metabolized by the kidneys[15]. Their efficacy at preventing cardiac events in other population groups such as type 2 diabetes has also been seriously questioned[85] and they are rarely, if ever used in combination with statins. Fibrates are believed to be generally well tolerated in LTR[86]. Severe hypertriglyceridemia however may require plasma exchange in order to manage the associated pancreatitis[87].

Niacin and bile acid sequestrants have both been explored for use in SOT recipients. Niacin could be considered as an option for montherapy to reduce LDL cholesterol levels in those intolerant to statins[15]. Niacin has been studied favorably in combination with simvastatin in the general population at preventing coronary disease[70], although this has also been questioned[88]. If used, a gradual dose escalation is required, and liver enzyme monitoring is warranted. Bile acid sequestrants are not popular in transplant recipients due to their gastrointestinal side effects including nausea and bloating, which patients are often already prone to as a result of immunosuppressive drug therapy. They can also interfere with the absorption of immunosuppressive drugs and should be separately administered from them by at least two hours.

Table 2 provides one suggested summary approach to post-transplant hyperlipidemia that can be tailored to individual clinic circumstances. However, relevant national society guidelines should preferably be followed. Clinicians have a choice when there is a conflict between various transplant society and lipid society guidelines for therapy and targets. There are few, if any clinical trials where modification of immunosuppressive therapy has been pursued with the intention of addressing dyslipidemia or reducing CVD risk and similarly, large database reviews are not sufficiently informative in this respect.

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

Table 2 A suggested approach to managing post-transplant dyslipidemia

Initial post-transplant period	Manage acute graft-related concerns Optimize immunosuppressive medication to graft function
2-3 mo post-transplant	Measure 8-12 h fasting lipid profile
If LDL cholesterol and/or triglyceride level above target[1]	Dietician consult
2-3 mo post-dietary intervention	Measure 8-12 h fasting lipid profile
If LDL cholesterol and/or triglyceride level still above target[1]	Initiate statin therapy, *e.g.*, atorvastatin 10 mg/d or rosuvastatin 5 mg/d Assess for potential drug interactions Monitor creatine kinase and liver transaminase levels
2-3 mo post-statin initiation	Measure 8-12 h fasting lipid profile
If LDL cholesterol and/or triglyceride level still above target[1]	Repeat all of the above until targets are achieved. Increase statin dose as tolerated to a maximum acceptable dose with each measurement not at target. If targets are not achieved then consider adding a supplemental agent, *e.g.*, ezetimibe 10 mg/d
If LDL cholesterol and/or triglyceride level still above target[1]	Consider consultation with lipid specialist
LDL and triglyceride target levels achieved	Annual monitoring of lipid levels. Consider more frequent monitoring for side effects
At all times post-transplant	Gauge overall cardiovascular risk

[1]See text for relevant targets but also consult relevant local transplant and lipid society guidelines. LDL: Low density lipoprotein.

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 SOT recipient populations, although the effect of proper dietary advice and adjuvant pharmacological or non-pharmacological 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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P- Reviewer: Vlachopanos G **S- Editor**: Gong XM **L- Editor**: A **E- Editor**: Wang CH

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