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Review

# Dyslipidemia and Kidney: An Updated View

**Author(s)** [1]Özgür Can

**Affiliation(s)** University of Health Sciences, Istanbul Haydarpaşa Numune Training and Research Hospital, Department of Nephrology, Istanbul, Turkey

**Corresponding Author** SBÜ Haydarpaşa Numune Eğitim ve Araştırma Hastanesi, Selimiye, Tıbbiye Cd No:23, 34668 Üsküdar/İstanbul
**E-mail:** canozgur62@hotmail.com



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## Abstract

Dyslipidemia is a common concern in various kidney-related conditions, including chronic kidney disease, nephrotic syndrome, kidney transplant patients, and those undergoing dialysis. Dyslipidemia is a significant risk factor for atherosclerosis and cardiovascular diseases in these patient groups. Understanding the unique challenges and factors associated with dyslipidemia in these kidney-related conditions is essential for providing effective patient care and reducing cardiovascular risk. This review explores the relationship between dyslipidemia and kidney diseases, highlighting the key recommendations and considerations for managing lipid profiles in each population.

**Keywords:** Chronic kidney disease, dialysis, dyslipidemia, nephrotic syndrome, statins, transplantation

## INTRODUCTION

The elevated plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides and high-density lipoprotein cholesterol (HDL-C) levels define dyslipidemia and having dyslipidemia is associated to the development of atherosclerosis and cardiovascular diseases (CVD). Patients with chronic kidney disease (CKD) shows significant changes in their lipid profiles and lipoprotein structure and function (1). They have also increased risk for atherosclerosis development from dyslipidemia.

Secondary causes of dyslipidemia include the nephrotic syndrome (NS), hypothyroidism, diabetes mellitus, excessive alcohol intake, obesity and chronic liver disease. 13-cis-retinoic acid, androgens, anticonvulsants, oral contraceptives, highly active anti-retroviral therapy, corticosteroids, diuretics, cyclosporine, beta-blockers, sirolimus are the drugs that are associated with secondary dyslipidemia. Genetic predisposition and low daily exercise also contribute to dyslipidemia. The major determinants of dyslipidemia in CKD patients are glomerular filtration rate (GFR), the presence of diabetes mellitus, severity of proteinuria, use of immunosuppressive agents, modality of renal replacement therapy, comorbidities and nutritional status (2).

In this chapter the association of dyslipidemia with kidney diseases is discussed.

### Triglyceride-rich Lipoproteins

Concentrations of triglyceride-rich lipoproteins [very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), chylomicrons and their residues] begin to increase in the early stages of CKD and are highest in NS and in dialysis patients, especially in peritoneal dialysis (PD) patients. Approximately half of the CKD patients have triglyceride levels >200 mg/dl. The increased production and decreased catabolism of triglyceride- rich lipoproteins are the causes of high triglyceride levels in patients with renal dysfunction. Increased Apo C3 level is an important cause of decreased catabolism of triglyceride- rich lipoproteins. Secondary hyperparathyroidism also causes calcium deposition in the liver and other tissues. As a result, lipoprotein lipase deficiency may develop in these tissues and decreased catabolism of triglyceride- rich lipoproteins may ensue. Repetitive use of low molecular weight heparin in hemodialysis (HD) patients results in the release of the endothelial lipoprotein lipase enzyme and leads to decreased catabolism of triglyceride-rich lipoproteins. Glucose absorption from PD solutions induce hyperinsulinemia (hyperinsulinemia is also

frequently detected in CKD patients) and increased hepatic lipoprotein lipase synthesis and thereby to increased VLDL production.

**Low-density Lipoprotein Rich Cholesterol**

Approximately 20 to 30 % of the CKD patients have LDL-C >130 mg/dl. Different concentrations of plasma cholesterol levels are observed in CKD patients. In contrast to normal or low concentrations in HD patients, PD and NS patients have higher concentrations of plasma cholesterol levels. Lipid profiles in various kidney-related conditions is shown in Table 1. In non-dialysis dependent CKD patients with NS, increased production and decreased catabolism of LDL-C are responsible for hypercholesterolemia. One of the most important factors that determine cholesterol-rich lipoprotein level is proteinuria. 3-hydroxy-3-methylglutaryl coenzyme A reductase and cholesterol 7 alpha-hydroxylase enzymes are rate-limiting enzymes in cholesterol biosynthesis and catabolism, respectively. Gene expression of these enzymes is not seen in CKD patients without proteinuria. Decreased function of hepatic LDL receptors is also associated with slower LDL clearance. Acquired LDL receptor deficiency develops in patients with nephrotic proteinuria. Atherogenic small dense LDL particles are increased in CKD patients. Higher electronegative LDL-C levels increase the differentiation of monocytes into proinflammatory M1 macrophages. As a result, increased inflammation and accelerated atherosclerosis develops. In PD patients, the protein passing into the peritoneal fluid is high and therefore hepatic albumin synthesis is increased, as well as the synthesis of other proteins and cholesterol-rich lipoproteins by the liver. There is also the escape of apolipoproteins and intact lipoproteins into the peritoneal cavity, but its significance is not yet clear.

**High-density Lipoprotein Cholesterol**

Transport of excess cholesterol from the artery wall to the liver for removal (reverse cholesterol transport) is the main function of HDL-C. Reverse cholesterol transport is important for cellular cholesterol homeostasis and protect against atherosclerosis. HDL-related apolipoproteins (mainly apolipoprotein AI-II) and enzymes [paroxonase-1, platelet-activating factor acetyl-hydrolase, and lecithin-cholesterol acyltransferase (LCAT)] takes part in important roles for endogenous inhibition of inflammation, platelet adhesion and LDL oxidation. HDL-C exhibits antioxidative properties by increasing endothelial nitric oxide synthase activity and by reducing the formation of reactive oxygen particles. Patients with impaired renal function generally have decreased levels of HDL-related apolipoproteins, decreased activity of LCAT and increased activity of the cholesteryl ester transfer protein (CETP) which are responsible for decreased serum concentrations of HDL-C. The antioxidant and anti-inflammatory function of HDL particles and the quality of reverse cholesterol transport decreased in patients with kidney dysfunction. These data explain the association between HDL-c and increased mortality in CKD patients. HDL carbonylation caused by CKD has been found to be responsible for impaired platelet aggregation and is thought to contribute to the etiology of cardiovascular events.

**Lipoprotein (a)**

High Lipoprotein (a)(Lp(a)) concentrations are associated with increased risk of CVD in the general population. Lp(a) plays important roles in thrombosis, inflammation and atherosclerosis. Lp(a) is a LDL-C like lipoprotein and is separated from LDL-C by covalently bound apolipoprotein (a). A large gradient of Lp(a) concentration between the aorta and renal vein and increased apolipoprotein (a) fragments in the urine shows the role of the kidneys in degradation of Lpa(a). There is an inverse relation between plasma Lp(a) concentrations and GFR. Highest plasma Lp(a) concentrations especially the large apolipoprotein(a) isoforms are seen in NS and PD patients. PD patients have increased protein loss into the peritoneal cavity which leads to increased hepatic production of Lp(a). Lp(a) levels are also high in HD patients due to inflammation, malnutrition and decreased clearance.

**Dyslipidemia in Chronic Kidney Disease**

The kidney disease: Improving Global Outcomes guideline (KDIGO-2013) recommends measuring lipid panel that includes TC, LDL-C, HDL-C and triglycerides (3). Fasting does not affect HDL-C but affect mainly triglyceride values and to a lesser extent LDL-C. Annual measurement of lipid panel is also advised regardless of the patients are treated with statins or not. More frequently monitoring of lipids may be necessary for patients with markedly abnormal values.

**Table 1.** Lipid profiles in various kidney-related conditions

| Parameters | Stage 1-5 CKD | Hemodialysis | Peritonealdialysis | Nephrotic syndrome |
|---|---|---|---|---|
| **Total cholesterol** | High* | Normal, low | High | High |
| **LDL cholesterol** | High* | Normal, low | High | High |
| **HDL cholesterol** | Low | Low | Low | Low |
| **Triglycerides** | High* | High | High | High |
| **Lipoporotein (a)** | High* | High | High | High |

LDL: low density lipoprotein; HDL: high density lipoprotein; CKD: chronic kidney disease. The asterisks (*) indicate increasing plasma levels with decreasing glomerular filtration rate

Annual measurement allows assessment of compliance, optimal dosing of medications, consideration of additional antihyperlipidemic therapy including ezetimibe or consideration of additional diet or lifestyle modifications. Change in renal replacement therapy modality, occurrence of other causes of dyslipidemia, need for reassessment of 10-year cardiovascular risk or not already taking a statin are reasons to measure the lipid profile after the initial measurement. Substantial random within-patient variation in serum cholesterol levels can be observed. So, the compliance of patients to treatment is unprovable in some instances. Measurement of Lp (a) is essential part of cardiovascular risk evaluation and should be measured at least once in patients' lifetime (4). Lp(a) can also be checked when changes in the CKD stage occur. Specialist referral is essential for triglyceride levels >1000 mg/dl or LDL-C levels>190 mg/dl.

Diet should be prioritized in the treatment of dyslipidemia before drug therapy. Only a small amount of change develops in serum cholesterol, but no clinical benefit is observed with therapeutic lifestyle measures. Mediterranean-type diet is beneficial in CKD and kidney transplant patients; low protein diet has positive effects on lipid profile. It is known that a diet with an increased fiber content is associated with an improvement in quality of life and lipid profile. The nonpharmacologic management of hypertriglyceridemia among CKD patients include dietary modification, weight reduction, increased physical activity and reduced alcohol intake. A low-fat diet (less than 15 percent of total calories), reduction of monosaccharides and disaccharides and use of fish oils are essential part of this diet.

As discussed previously, the structure and function of HDL-C is changed in CKD patients. A study included patients with CKD stage G3-G4 found that HDL-C ≤40 mg/dl was related to a higher risk of mortality in both genders and HDL-C >60 mg/dl was related to a lower risk of mortality in women but not in men (5). Compared to individuals with HDL-C ≥40 mg/dl, those with HDL-C <30 mg/dl had higher risk for CKD development or progression. However, genetic studies revealed nonsignificant results between HDL-C and CKD, regarding causality.

Rare CKD patients who have serum total triglycerides >1000 mg/dl despite nonpharmacologic interventions may require fibrates in order to prevent pancreatitis. The effect of gemfibrozil in CKD patients with established coronary heart disease and HDL-C <40 mg/dl was evaluated with the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT). Gemfibrozil lowered the risk of coronary death and nonfatal myocardial infarction. However, gemfibrozil therapy had no effect on total mortality (6).

Management of LDL-C to reduce cardiovascular risk is not different from the general population. The increased relative risk for CVD in patients with CKD (including albuminuria with a normal GFR) make essential to prescribe statins. Data also showed that treatment with statins reduce cardiovascular risks. However, the relation between LDL-C and CVD disappears as the GFR decreases and some studies show no association which should be because of the inflammation and malnutrition those are usually seen at advanced stages of CKD.

Statins can be used either for primary or secondary prevention of CVD in non-dialysis CKD patients as patients without CKD. For primary prevention, the predicted 10-year absolute risk of having a major cardiovascular event can be used. Cardiovascular risk can be annually assessed in CKD patients with validated risk prediction tools. Statins can be used if the predicted risk is ≥7.5 to 10% but not if the risk is <5%. Statins can be offered to patients with predictive risk of 5-7.5%. Patients who have atherosclerotic vascular diseases should receive maximum statin dose, similar to patients from general population with atherosclerotic vascular diseases. Patients with estimated GFR <60 mL/min/1.73 $m^2$ or patients with an estimated GFR ≥60 mL/min/1.73 $m^2$ with other cardiovascular risk factors (diabetes, hypertension, smoking, low levels of HDL-C, high levels Lp(a)) and older than a ≥50 years of age are suitable for secondary prevention. Recent myocardial infarction or greater life expectancy favors patient's decision to receive statin, but more severe comorbidity or higher current pill burden does not. The frequently prescribed statin is atorvastatin for patients with CKD because it undergoes hepatic clearance. Atorvastatin may also have positive effects on renal function and proteinuria.

Because Lp(a) may be measured as part of the TC or LDL-C fraction; patients who do not achieve target LDL- C levels should be checked for high plasma Lp(a) concentration. There are no drugs that specifically lower Lp(a) levels. However, protein convertase subtilisin/kexin type 9 inhibitors (PCSK9) can reduce Lp(a) by 25 to 30%. PCSK9 is a proprotein convertase involved in the degradation of LDL receptors in the liver. PCSK9 inhibitors are human monoclonal antibodies that inhibit the binding of PCSK9 to the LDL receptors. Two large randomized placebo-controlled trials involving high cardiovascular risk patients demonstrated that the PCSK9 inhibitors evolocumab (FOURIER trial, n= 27,564) and alirocumab (ODYSSEY trial, n= 18,924) reduce LDL-C levels significantly more than statins and significantly decrease cardiovascular morbidity and mortality independent of baseline LDL-C levels. Post-hoc analysis of these trials demonstrated that the efficacy and safety of alirocumab and evolocumab were comparable among subjects with and those without estimated GFR

**Table 2.** Summary of 4D, AURORA, SHARP studies

| | Die Deutsche Diabetes Dialyse Studie(4D) | A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) | Study of Heart and Renal Protection (SHARP) |
|---|---|---|---|
| **Study Design** | Germany, 178 centers median follow up: 4 years, aged: 18-80 years old, 1255 diabetic hemodialysis patients, randomized controlled trial: atorvastatin 20 mg versus placebo | 280 centers in 25 countries, median follow-up: 3.8 years, aged: 50-80 years old, 2776 patients on hemodialysis, randomized controlled trial: rosuvastatin 10 mg versus placebo | Median follow-up 4.9 years, aged ≥40 years old, 9270 patients (3023 on dialysis and 6247 not) no history of coronary intervention or myocardial infarction |
| **Primary End Points** | Composite of death from cardiac causes, nonfatal myocardial infarction and stroke | Death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke | Major vascular events, such as non-fatal myocardial infarction, non-fatal stroke, arterial revascularization and vascular death, doubling of baseline serum creatinine, the development of end-stage renal disease |
| **Secondary End Points** | Death from all causes and all cardiac and cerebrovascular events | Death from all causes and individual cardiac and vascular events | Fatal vascular events, non- vascular mortality, Hospitalization for heart failure, coronary revascularization procedures |
| **Results** | Primary end point: No significant effect<br>Secondary end point: The risk of all cardiac events combined was reduced by 18 % increased incidence of stroke, although the numbers were small | Primary end point: No significant effect<br>Secondary end point: No significant effect | Reduces the risk of major atherosclerotic events in a wide range of patients with chronic kidney disease. No significant impact on all-cause mortality |

<60 mL/min/1.73 m²(7). The role of PCSK9 inhibitors in the treatment of dyslipidemia or cardiovascular risk reduction in CKD patients remains to be studied. Novel antisense oligonucleotides against apolipoprotein(a) and lipoprotein apheresis are other options to reduce Lp(a). Nearly 90% of the Lp(a) concentrations can be lowered with antisense oligonucleotides. However, it is not known whether this treatment decreases cardiovascular events or not. Dramatic lowering of cardiovascular events is observed with lipoprotein apheresis.

**Dyslipidemia in Dialysis Patients**

The lipid profile in HD patients is similar to patients with non-dialysis CKD. LDL-C is not suitable to assess cardiovascular risk in dialysis patients. Regardless of LDL-C levels, an increased risk of CVD is seen in majority of dialysis patients. Therefore, interventions to reduce LDL-C and cardiovascular events in the general population are not mostly beneficial in dialysis patients. Because a subgroup of dialysis patients can benefit from statin therapy, patients should be periodically evaluated for statin therapy. The issue of whether statins are effective in lowering the risk of a cardiovascular event in dialysis patients was addressed in the 4-D, AURORA and SHARP trials. Summary of 4D, AURORA, SHARP Studies is shown in **Table 2**.

The 4D Study (Die Deutsche Diabetes Dialyse Studie) was the first placebo-controlled randomized conrolled trial (8). Compared to 1.3% decline of LDL-C with plasebo, atorvostatin decreased the median LDL-C level by 42% over 4 weeks. Over a median follow-up of 4 years, there was only an 8% non-significant decrease in the primary composite endpoint in the atorvastatin treated group. Despite no effect on overall mortality, the rate of all cardiac events reduced by 18%. The rate of fatal and non-fatal cardiac events and death from any cause was significantly reduced in subgroup of patients with pre-treatment LDL-C>145 mg/dl. Therefore, diabetic HD patients with high LDL-C may be target for statin therapy.

A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA), is the other placebo-controlled RCT (9). LDL- C levels reduced significantly with rosuvastatin versus no change with placebo after 3 months. At a median follow-up period of 3.8 years, the incidence of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke was similar in two groups. All-cause mortality was also not significantly different between the groups. Therapy with statins did not provide benefit in patients with diabetes or elevated C-reactive protein levels.

The Study of Heart and Renal Protection (SHARP) trial evaluated the efficacy of simvastatin plus ezetimibe compared with placebo in lowering cardiovascular morbidity in patients with CKD of whom 3023 were dialysis patients (10). They have no history of coronary intervention or myocardial infarction. A trend toward

benefit for lowering the incidence of the atherosclerotic cardiovascular events in the antihyperlipidemic therapy arm was observed during a median follow-up of 4.9 years. However, the SHARP trial was not powered to detect an effect on subgroups and there was no evidence that the effect differed according to the presence of end stage renal disease (ESRD) at baseline. Thus, the SHARP trial may be interpreted as showing efficacy for LDL cholesterol lowering and cardiovascular benefit in dialysis patients.

In addition, one meta-analysis showed a modest benefit in atherosclerotic-related events, while another found no benefit of statin treatment in all-cause mortality, cardiovascular mortality, and major cardiovascular events (11-12).

Unfortunately, as discussed above, lipid-lowering treatments are not as effective in reducing cardiovascular risk in dialysis patients as they are in the general population or in non-dialysis CKD patients. This should be because, compared to the general population, the pathophysiology and spectrum of CVD begin to differ from early to advanced stages of CKD, and the difference is more pronounced in dialysis patients. The process of atherosclerosis differs in dialysis patients compared to general population. Uremia-related risk factors including hyperphosphatemia, anemia, hyperhomocysteinemia, oxidative stress, malnutrition, inflammation and many of the traditional Framingham risk factors for atherosclerosis are frequently seen in dialysis patients and they contribute to atherosclerotic process. Accumulation of asymmetric dimethylarginine, Lp(a) and IDL also play important roles in the initiation and progression of coronary atherosclerosis. In addition to atherosclerosis; arterial stiffness, vascular calcification, left ventricular hypertrophy, left ventricular diastolic dysfunction, congestive cardiomyopathy and sudden cardiac death from arrhythmias are commonly seen in dialysis patients. Most deaths in dialysis patients are not associated with coronary artery disease and therefore cannot be replaced by statins or other lipid-lowering therapies.

The KDIGO guideline work group agree that statin therapy is not routinely initiated in dialysis patients including PD patients. Statin therapy should also be continued in patients who are already receiving statins or a statin/ezetimibe combination at the time of initiation of dialysis. It is stated that statins may be beneficial in a subgroup of HD patients with significant atherosclerotic disease and hyperlipidemia. Liu et al. reported that hypercholesterolemia was an independent risk factor for all-cause and CVD mortality in a subset of ESRD patients without serological evidence of inflammation or malnutrition. Patients with very high LDL cholesterol (>190 mg/dl) may also benefit from treatment. It is mostly unnecessary to include ezetimibe in the regimen as long as the LDL-C and the non-HDL C targets can be achieved with statin and/or other measures alone.

Since the PD patient group was small in number in the SHARP study, cardiovascular benefit could not be achieved in this group of patients despite lowering the cholesterol level. Data from a retrospective cohort study using propensity score matching showed reduced mortality in the statin arm in PD patients.

Hypertriglyceridemia is not usually treated with pharmacologic therapy in dialysis patients, partly because the relationship between serum triglyceride levels and clinical outcome is uncertain, the propensity of dialysis patients to develop side effects from drugs and the prevalence of polypharmacy in this population. Therapeutic lifestyle changes should be advised with avoiding malnutrition.

Effects of PCSK9 inhibitors on cardiovascular outcomes in patients with ESRD is unknown.

**Dyslipidemia in Kidney Transplant Patients**

Dyslipidemia is a frequent complication after kidney transplantation, even when allograft function is normal or near normal. Increases in TC and LDL-C levels are the most common abnormalities and elevated triglyceride levels are also frequently noted. A recent study showed that kidney transplantation by itself has beneficial effects on the lipid profile when compared to ESRD period. Improvement in HDL-C and triglyceride levels following kidney transplantation has been associated with successful engraftment and better graft function. Pre-transplant high-intensity statin therapy was also met with a survival benefit after transplantation. Given that allograft failure is the principal risk to a patient's health, dyslipidemia may be tolerated, even if it is related to immunosuppressive therapy and cannot be optimally treated. Because dyslipidemia have adverse effects on kidney graft function, use of antihyperlipidemic therapy is also reasonable.

Glucocorticoid withdrawal may lower TC and triglyceride levels in kidney transplanted patients (13). However, these benefits must be considered in the context of higher acute rejection risk, as well as a possible increased risk of allograft loss and recurrent glomerulonephritis. In addition, glucocorticoid elimination may not yield a net benefit in the overall lipid profile, since it may depress protective HDL-C levels to the same extent as TC as a result, the HDL-C to TC ratio remains unchanged. Nonetheless, reducing glucocorticoids may have other cardioprotective benefits, including improved blood pressure and glucose tolerance. There is also dose dependent effects of cyclosporin with elevations in TC and LDL-C concentrations and with reductions in HDL-C levels (14). Use of tacrolimus instead of

cyclosporine may have beneficial effects on serum lipid levels. The mammalian target of rapamycin (mTOR) inhibitors are frequently associated with dyslipidemia, particularly associated to hypertriglyceridemia. Studies comparing patients receiving sirolimus to patients receiving calcineurin inhibitors (CNI) showed that those on sirolimus had higher levels of triglycerides, LDL-C and TC in the first few months after transplantation, but these differences decreased at later timepoints. Sirolimus-treated patients were also more likely to be on lipid-lowering drugs in these studies (15). The antiproliferative and cardioprotective effects of mTOR inhibitors and the reduction in CNI-related risk factors may offset the adverse effects of mTOR inhibitor–associated hyperlipidemia. If dyslipidemia occurs cyclosporine can be converted to tacrolimus, sirolimus can be discontinued and low dose prednisone can be continued considering the risk of rejection.

There are no definitive data of statin-related improvement in atherosclerotic CVD outcomes in patients with kidney transplant patients, although there is suggestive evidence of benefits. The ALERT trial found beneficial effect of early initiation of statin therapy on posttransplant cardiovascular outcomes. Compared to patients who used statin therapy within the first 4 years after transplantation had risk reduction of 64% compared to 19% reduction in patients who had started therapy after ten years (16). Kidney transplant recipients with established atherosclerotic CVD, should receive maximum doses of statins, similar to nontransplant patients with established atherosclerotic CVD. Statin therapy is appropriate for patients> 40 years old without established atherosclerotic CVD if their estimated 10-year atherosclerotic CVD risk is >10%. Statin therapy is also suggested to patients>30 years old without established atherosclerotic CVD. For adult kidney transplant recipients between 8 to 29 years old without established atherosclerotic CVD, the decision to treat with statin therapy should be individualized, considering patient preferences and a relatively small expected atherosclerotic CVD reduction over 10 years versus the risks of polypharmacy and drug toxicity. Data evaluating the use of ezetimibe or statin and ezetimibe combination in the transplant population are limited. Ezetimibe and statins block intestinal absorption of dietary cholesterol and inhibits hepatic cholesterol synthesis; respectively. Ezetimibe can be used by transplant recipients who are refractory to the highest tolerated statin dose or as a second-line agent in those who are intolerant to statin.

PCSK9 inhibitors are not recommended given the lack of data on efficacy and safety in kidney transplanted patients.

**Dyslipidemia in Nephrotic Syndrome**

Patients with the NS frequently have marked elevations in serum TC and LDL-C. This is due to a combination of increased biosynthesis and impaired catabolism of lipoproteins. They also have marked elevations in the plasma triglycerides and Lp(a) concentrations. Total HDL-C levels are usually normal or reduced in the NS and there is often a pronounced decline in the cardioprotective HDL2 fraction. The severity of the hyperlipidemia is inversely related to the fall in plasma oncotic pressure. Some nephrotic patients diagnosed with renal amyloidosis and lupus nephritis may have no lipid abnormalities.

Patients with the NS have been shown to have elevated plasma PCSK9 levels that correlate with the degree of proteinuria, levels of TC, non-HDL-C and LDL-C. Hyperlipidemia results from altered expression of PCSK9. In one series of nephrotic patients who went into remission, a decrease in plasma cholesterol was accompanied by a reduction in plasma PCSK9. The impairment of reverse cholesterol transport is also observed in patients with NS and may contribute to proteinuria and disease progression in a number of glomerular disorders. Fatty acid uptake and accumulation of triglycerides in the kidney cortex have been shown to cause glomerular damage in experimental models of NS (17). CKD can also develop due to podocyte damage and mesangial cell proliferation. In addition, serum free fatty acid elevation may predict the development of acute kidney injury in NS.

It seems likely that patients with persistent NS and hyperlipidemia are at increased risk for atherosclerotic CVD, particularly if other cardiovascular risk factors are present. Spontaneous or drug-induced resolution of the NS reverses the hyperlipidemia (18). Because the nephrotic state is transient in minimal change disease with corticosteroid treatment and do not subject the patient to prolonged hyperlipidemia, there is no increased risk of coronary death as in other patients diagnosed with NS. Thus, intensive lipid-lowering therapy to prevent CVD may be warranted in patients with chronic NS who do not achieve disease remission.

A lipid panel at the time of diagnosis and repeat lipid panel every three months as long as the patient remains nephrotic can be obtained. It is important to note that most commonly used CVD risk calculators have not been validated in patients <40 years old and do not include NS as a potential factor in the estimation of the risk. So, nephrotic patients who do not have preexisting CVD risk factors could not be accurately assessed with CVD risk calculators.

The reduction in protein excretion with angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) may be associated with a 10 to 20%decline in the plasma levels of TC and LDL-C and Lp(a). The magnitude of these changes appears

to be related to the degree of fall in protein excretion, but they can occur with little or no elevation in the plasma albumin concentration. Evidence for the effect of low protein diets on the lipid profile in patients with nephrotic level proteinuria is also lacking. Decreased protein intake was also reported with decreasing serum TC and LDL levels.

In patients with the NS, the management of hyperlipidemia focuses primarily on treatment of the NS (Immunosuppressive therapy as well as supportive measures, such as treatment with an ACE inhibitor or ARB). Lifestyle modifications and lipid-lowering therapy may be indicated for selected patients, such as those with persistent NS and hyperlipidemia despite treatment of the underlying kidney disorder. However, evidence to guide the optimal therapy of hyperlipidemia in this patient population is limited. Although these lifestyle modifications have not been well studied in patients with the NS, these have been shown to have beneficial effects on preventing cardiovascular morbidity and mortality in the general population.

All patients with the NS should receive lipid-lowering therapies for primary or secondary prevention of CVD as appropriate based upon their assessed CVD risk. In patients with NS who do not have an indication for primary or secondary CVD preventive therapies, the optimal approach to pharmacologic lipid-lowering therapy is uncertain. Thus, the pharmacologic lipid-lowering therapy should be considered by weighing the potential benefits and risks of treatment. If the NS resolves within three to six months, pharmacologic lipid-lowering therapy is not initiated unless indicated for primary or secondary CVD prevention based upon the patient's CVD risk and GFR. If the NS does not resolve within three to six months, a lipid profile is repeated and pharmacologic lipid-lowering therapy with a statin is initiated if the LDL-C is >100 mg/dl or if indicated for primary or secondary CVD prevention based upon the patient's estimated CVD risk and GFR. In rare patients with an LDL-C ≤100 mg/dl who have isolated severe hypertriglyceridemia (>400 mg/dl), treatment with omega-3 fatty acids or a fibrate is required.

Statins are the preferred first-line agents for treatment of hyperlipidemia in patients with the NS. The optimal LDL-C target in patients with the NS is not known. Titration of the statin dose to target an LDL-C goal of <100 mg/dl in view of the increased CVD risk in patients with the NS is recommended. Antiproliferative and anti-inflammatory properties of statins and their ability to reduce systolic or diastolic blood pressure, C-reactive protein, endothelin-1 levels are features of statins that protect patients against CVD besides their lipid-lowering effects.

If the target LDL-C value is not achieved with maximally tolerated statin therapy, or if the drug is not tolerated, additional second-line agents may be required. Second-line therapies including ezetimibe, PCSK9 inhibitors, fibrates, bile acid sequestrants, nicotinic acid, omega-3 fatty acids and LDL apheresis can be used for patients who may not be able to tolerate a statin or may not be able to achieve the target LDL-C despite treatment with a maximally tolerated statin. These second-line therapies can also be used in patients who have concomitant hypertriglyceridemia that is not responsive to statin therapy. The efficacy of these second-line therapies is variable and use of these agents is often limited by side effects.

**Adverse Effects with Statins and Fibrates**

Reduced renal excretion of medications, polypharmacy and high prevalence of comorbidity makes CKD patients vulnerable to medication-related adverse events. So, reduced doses of statins are generally recommended in patients with advanced CKD. Statins are contraindicated in lactation, pregnancy and active liver disease or states when the transaminase levels are three times or more than the upper limit of normal. KDIGO guidelines recommend measuring transaminase levels before starting statin therapy. However, further measurements of transaminase levels are not necessary if the patient has no related symptoms. Statins are also associated with adverse muscle events and it is shown that routine monitoring of creatine kinase levels in the absence of symptoms of myopathy is not essential. In SHARP trial, despite no evidence of increased risk of rhabdomyolysis or liver dysfunction, some patients receiving simvastatin plus ezetimibe were significantly more likely to discontinue the drug.

Atorvastatin, lovastatin and simvastatin are all metabolized by CYP-3A4 and drug-drug interactions of statins with macrolides, azole antifungals, non-dihydropyridine calcium channel blockers, cyclosporine, tacrolimus, and sirolimus should be taken into account when statins are started. Coadministration of a statin with cyclosporine (cyclosporin inhibits CYP450 3A4) can increase statin levels and the risk of myotoxicity. In addition, cyclosporin inhibits OATP1B1/SLCO1B1-mediated hepatic uptake of statins, resulting in significant medication interaction. Therefore, in cyclosporin-treated patients, all statins should be introduced at low doses and up titrated. A nonsignificant but high risk of hemorrhagic and fatal stroke was also reported in the previously reported randomized controlled trials.

The risk of fibrate related myositis and rhabdomyolysis is higher in patients with CKD. Fenofibrate should not be used in patients with estimated GFR less than 30 mL/min/1.73 m². Fibrates when used with statins are also

more likely to produce muscle toxicity (17). Elevations in serum creatinine concentrations have been noted in patients taking fibrates, while such changes are often reversible and their relation to true alterations of GFR is unclear, such elevations may complicate the assessment of other conditions such as acute rejection. Acute kidney injury due to biopsy-verified proximal tubule dysfunction was also reported in three kidney transplant recipients treated with fenofibrate.

## CONCLUSION

The management of dyslipidemia in patients with CKD involves a multifaceted approach. Management of LDL-C to reduce cardiovascular risk is not different from the general population for non-dialysis dependent CKD patients. However, the relation between LDL-C and CVD disappears as the GFR decreases. The effectiveness of lipid-lowering treatments, particularly statins, in dialysis patients remains a topic of debate. While studies like 4D, AURORA, and SHARP offer insights, the diverse pathophysiology of CVD in dialysis patients challenges the applicability of general population guidelines. In kidney transplant recipients, dyslipidemia is a common concern post-transplantation. The dynamic nature of lipid profiles, influenced by immunosuppressive therapies and allograft function, underscores the need for personalized approaches. Nephrotic syndrome presents unique challenges, the transient nature of some cases necessitates cautious lipid-lowering therapy decisions. Management focuses on treating the underlying kidney disorder.

Throughout these diverse scenarios, the challenge lies in balancing the benefits and risks of pharmacological interventions, considering the specific needs of each patient. Adverse effects, drug interactions and individual response to treatment underscore the importance of close monitoring and a tailored approach to dyslipidemia management in the complex landscape of kidney-related disorders. The emergence of new therapeutic options, such as PCSK9 inhibitors, raises intriguing possibilities but requires further investigation in CKD populations.

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