Dyslipidemia in Chronic Kidney Disease and Nephrotic Syndrome

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Nosratola D. Vaziri

Introduction

The association of kidney disease with lipid abnormalities has been known for many decades [1–3]. More recent studies employing experimental animals and cultured cells have helped to expand the understanding of the molecular mechanisms by which kidney disease alters lipid metabolism and plasma lipid profile. In addition, much has been learned about the role of the associated lipid disorders in progression of kidney disease and its cardiovascular, metabolic, and other complications. The nature of lipid abnormalities in patients with kidney disease varies depending on the presence and severity of proteinuria, reduction in glomerular filtration rate (GFR), renal replacement modalities (hemodialysis, peritoneal dialysis, and renal transplantation), dietary and drug regimens, and coexistent genetic disorders of lipid metabolism. An overview of the features, mechanisms, consequences, and treatment of kidney disease-associated lipid disorders is provided in this chapter.

Historical Perspective The association of kidney disease with changes in serum lipids has been known for many decades. For instance, hyperlipidemia has long been considered as one of the cardinal manifestations of nephrotic syndrome [1, 4]. In addition, numerous studies conducted in the 1960s and 1970s demonstrated the association of chronic renal failure with elevated serum triglyceride and triglyceride-rich lipoproteins [5–9]. Building upon these pioneering investigations, during the past two decades, considerable progress has been made in elucidation of the nature, mechanisms, consequences, and potential treatment of lipid disorders caused by renal disease.

Part I: Lipid Disorders in Nephrotic Syndrome

A variety of primary and secondary kidney diseases impair the glomerular filtration barrier which leads to proteinuria (Table 8.1). Glomerular proteinuria exceeding 3.5 g/day in adults or urine protein/creatinine ratio of 2–3 or greater in children results in nephrotic syndrome which is characterized by the tetrad of proteinuria, hypoalbuminemia, edema, and hyperlipidemia. The magnitude of hyperlipidemia and the associated alteration in lipoprotein metabolism in nephrotic syndrome parallels the severity of proteinuria. Plasma concentrations of cholesterol, triglycerides, apoB-containing lipoproteins (very-low-density lipoprotein, VLDL; intermediate-density lipoprotein, IDL; and low-density lipoprotein, LDL), and lipoprotein(a)(Lp(a)) are elevated in nephrotic syndrome [10, 11]. However, high-density lipoprotein (HDL) cholesterol concentration is usually unchanged or

N. D. Vaziri (✉)
Division of Nephrology and Hypertension, University of California Irvine Medical Center, Medicine, Suite 400 City Tower, 101 City Drive, Orange, CA 92868, USA
e-mail: ndvaziri@uci.edu

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Table 8.1 Common causes of nephrotic syndrome in children and adults are listed in this table. The most common cause of nephrotic syndrome in children is minimal change disease (77%) followed by membranoproliferative glomerulonephritis (8%) and focal segmental glomerulosclerosis (7%) with the remainder of listed conditions representing approximately 2% of the cases each. Causes of nephrotic syndrome in adults are listed according to their prevalence

Children
Minimal change disease
Membranoproliferative glomerulonephritis
Focal segmental glomerulosclerosis
Proliferative glomerulonephritis
Mesangial proliferation
Membranous glomerulonephropathy
Focal and global glomerulosclerosis
Adults
Focal segmental glomerulosclerosis
Membranous nephropathy (including lupus)
Minimal change disease
Diabetic nephropathy
IgA nephropathy
Preeclampsia
Post-infectious glomerulonephritis
Primary amyloidosis or the related disorder light-chain deposition disease
Benign nephrosclerosis

IgA immunoglobulin A

reduced and occasionally elevated and the total cholesterol/HDL cholesterol ratio and triglyceride content of HDL are generally increased in the patients with nephrotic syndrome [10, 11]. In addition to these quantitative changes, nephrotic syndrome markedly alters the composition of lipoproteins. In this context, the cholesterol to triglyceride, free cholesterol to cholesterol ester, and phospholipid to protein ratios in the lipoproteins are altered in nephrotic syndrome [11]. This is accompanied by significant increase in apolipoproteins—A-I, A-IV, B, C, and E levels—and the apoC-III/apoC-II ratio.

Pathogenesis of Nephrotic Dyslipidemia

The abnormalities of serum lipids and lipoproteins in nephrotic syndrome are largely due to their impaired clearance and to a lesser extent their altered biosynthesis. The underlying mechanisms by which nephrotic syndrome alters lipid and lipoprotein metabolism are summarized below.

Impaired Triglyceride-Rich Lipoprotein Metabolism in Nephrotic Syndrome

Fasting serum triglyceride, VLDL, and IDL levels are elevated, triglyceride contents of apoB-containing lipoproteins is increased, and postprandial lipemia is prolonged in nephrotic syndrome [12–16]. These abnormalities are primarily due to impaired clearance of VLDL and chylomicrons [14–18]. Nephrotic syndrome results in lipoprotein lipase (LPL), hepatic lipase, and VLDL receptor deficiencies. In addition, by changing the structure and composition of the lipoproteins, nephrotic syndrome impairs effective binding of the triglyceride-rich lipoproteins to the key receptors, their ability to activate lipolytic enzymes, and engage in a proper lipid and apoprotein exchange with HDL. The effects of nephrotic syndrome on the key steps in metabolism of triglyceride-rich lipoproteins are briefly described here.

Several studies have shown marked reduction of post-heparin lipolytic activity in the nephrotic humans [12, 13] and animals [11, 14, 16, 19] pointing to depletion of endothelium-bound LPL pool. In addition, a series of studies conducted in the author's laboratory have shown marked reductions of heparin-releasable and intracellular LPL, along with a significant reduction of LPL protein abundance despite normal LPL messenger RNA (mRNA) abundance in the adipose tissue, skeletal muscle, and myocardium of Imai rats with spontaneous focal glomerulosclerosis [20] and Sprague–Dawley rats with puromycin-induced nephrotic syndrome [21]. These findings point to the posttranscriptional/posttranslational nature of LPL deficiency and dysfunction in nephrotic syndrome. Marked downregulation of hepatic lipase expression and activity, and of VLDL receptor mRNA and protein in the skeletal muscle and myocardium, is also seen in these animals [22–24].

Diminished apoE and apoC-II contents and increased apoC-III/apoC-II ratio in VLDL and chylomicrons further contribute to impaired LPL-mediated lipolysis of triglyceride-rich lipoproteins [25, 26]. This is, in part, due to the HDL dysfunction in nephrotic syndrome [27, 28]. In fact, in vivo studies have shown impaired endothelial binding and LPL-mediated lipolysis of VLDL in nephrotic rats and their correction by infusion of HDL from normal animals. Likewise, in vitro studies using cultured rat aortic endothelial cells have shown impaired binding and LPL-mediated lipolysis of VLDL and chylomicron particles from nephrotic rats and their restoration by addition of HDL from normal rats [18, 28]. In vitro studies have shown a 50% lower heparin-releasable lipase activity in the livers of nephrotic rats compared with the normal rats [14]. Nephrotic syndrome results in increased expression of the key enzymes involved in fatty acid, phospholipid, and triglyceride biosynthesis and downregulation of genes-encoding proteins involved in fatty acid catabolism in the liver [29–31]. These abnormalities suggest that increased production of fatty acids, triglycerides, and phospholipids may contribute to the pathogenesis of hyperlipidemia in nephrotic syndrome.

LDL and Cholesterol Metabolism in Nephrotic Syndrome

Serum total cholesterol and LDL cholesterol are markedly elevated in nephrotic syndrome. This is due to increased production of cholesterol and LDL and impaired catabolism/clearance of apoB and LDL [15, 32]. Data from animal models of nephrotic syndrome reveal that several factors contribute to the defective LDL clearance and increased cholesterol biosynthesis. These include posttranscriptional or posttranslational reduction in LDL receptor (LDLR) protein expression in the liver [33–35] upregulation of 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase [34, 36] and Acetyl-CoA acetyltransferase (ACAT-2) expressions [37] and activities as well as increased apoB-100 biosynthesis [10]. Recent studies conducted in the author's laboratories have revealed upregulation of hepatic proprotein convertase subtilisin/kexin type 9 (PCSK-9) inducible degrader of LDLR (IDOL) as the main cause of the posttranslational deficiency of the LDL receptor in nephrotic syndrome [38]

HDL Metabolism in Nephrotic Syndrome

Nephrotic syndrome results in Lecithin cholesterol acyltransferase (LCAT) deficiency which is caused by its heavy losses in the urine [39] and contributes to impaired cholesterol enrichment of HDL. This is not surprising since molecular weight of LCAT (63 kD) is close to that of albumin whose heavy urinary loss is the defining feature of nephrotic syndrome. HDL receives a significant amount of its cholesterol content from albumin, which serves as a carrier of free cholesterol from the peripheral tissues to the freely floating HDL-3 [40]. Consequently, hypoalbuminemia, which is a cardinal feature of nephrotic syndrome can potentially contribute to the prevalence of cholesterol ester-poor HDL in nephrotic syndrome.

Several studies have shown significant elevation of serum cholesterol ester transfer protein (CETP) in humans with nephrotic syndrome [41–43] which can deplete cholesterol esters and raise triglyceride content of HDL in nephrotic patients. Cholesterol-rich HDL particles serve as the apoE and C donors to the nascent VLDL

and chylomicrons, and thus the impaired maturation of HDL can contribute to the dysregulation of triglyceride-rich lipoproteins in the nephrotic individuals [28]. In addition, a marked reduction in scavenger receptor class B type 1 (SR-B1) protein abundance and significant downregulation of PDZ-containing kidney protein 1 (PDZK1) mRNA and protein expressions are seen in animals with nephrotic syndrome [44, 45]. By compromising the reverse cholesterol transport, the observed SR-B1 deficiency may contribute to the associated atherogenic diathesis.

Increased Plasma Lipoprotein(a) in Nephrotic Syndrome

Nephrotic syndrome results in marked elevations of serum Lp(a) [46–48] which is due to its increased production by the liver [49]. Plasma Lp(a) falls in response to spontaneous remission or anti-proteinuric therapies. Elevation of Lp(a) in nephrotic syndrome contributes to the prothrombotic and atherogenic diathesis in this population.

Part II: Lipid and Lipoprotein Metabolism in Chronic Renal Failure

The serum lipid profile evolves during the course of progression of chronic kidney disease (CKD). Patients with mild-to-moderate CKD and nephrotic proteinuria commonly exhibit hypercholesterolemia and elevated LDL levels [50]. In contrast, serum total cholesterol and LDL cholesterol concentrations are commonly within the normal limits or reduced in most patients with CKD and minimal proteinuria and in patients with end-stage renal disease (ESRD) maintained on hemodialysis. Serum triglycerides and VLDL levels are commonly increased and clearance of VLDL, chylomicrons, IDL, and chylomicron remnants is impaired in advanced CKD or ESRD patients. This is associated with presence of small dense LDL, accumulation of IDL, chylomicron remnants, and oxidized LDL [50–53], reduced serum apoA-1 and HDL cholesterol, impaired HDL maturation, and defective HDL antioxidant, and anti-inflammatory and reverse cholesterol transport properties [50, 51, 54–56].

In patients with ESRD, the renal replacement modality and kidney transplantation significantly affect lipid profile. For instance, serum total cholesterol and LDL cholesterol levels are commonly elevated in patients treated with chronic peritoneal dialysis [50, 52], contrasting normal or reduced values in most hemodialysis-treated patients. In addition, serum lipid profile in this population is affected by severity of inflammation, malnutrition, and lipid-altering drugs (e.g., statins, fibrates, steroids, rapamycin, calcineurin inhibitors, and sevelamer, etc.) as well as coexisting genetic disorders of lipid metabolism. Moreover, oxidative stress and inflammation, which are common features of CKD [57, 58], lower serum cholesterol and simultaneously may cause atherosclerosis by promoting LDL oxidation and monocyte adhesion, infiltration, and foam-cell formation in the artery wall [59]. The mechanisms by which CKD/ESRD alters lipid metabolism are briefly described here:

Abnormalities of Triglyceride-Rich Lipoprotein Metabolism in CKD

Accumulation of triglyceride-rich lipoproteins in CKD is exclusively due to impaired clearance of VLDL and chylomicrons and their remnants which is caused by downregulation of lipoprotein lipase and VLDL receptor in the skeletal muscle, adipose tissue, and myocardium and hepatic lipase and LDL receptor-related protein (LRP) in the liver as well as increased ratio of apoC-III to apoC-II. Several studies have demonstrated marked reduction of plasma post-heparin lipolytic activity in patients with chronic renal failure [60–62]. In addition, studies conducted in experimental animals have demonstrated marked reduction of LPL mRNA and protein expression [63] accompanied by downregulation of glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1 (GPIHBP1) in the adipose tissue, myocardium, and skeletal muscles of rats with CKD [64] and secondary hyperparathyroidism [65]. Indeed, Akmal et al. [60] showed improvement in post-heparin lipolytic activity with parathyroidectomy in patients

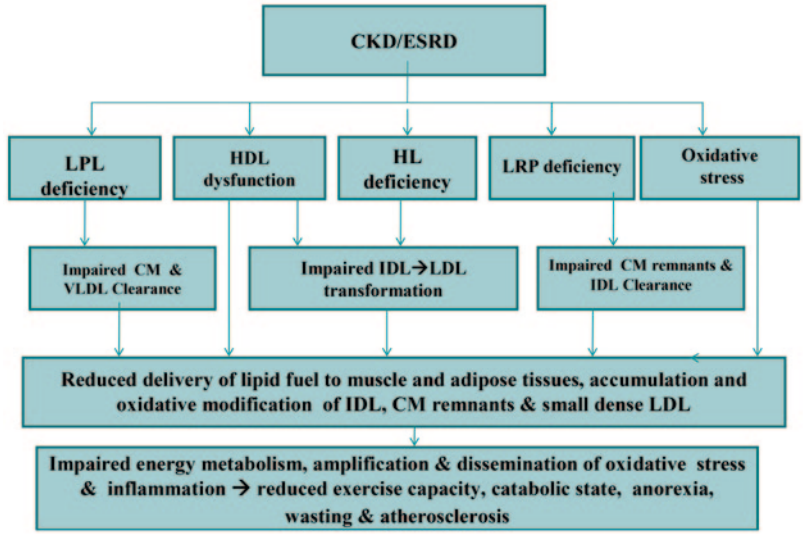

Fig. 8.1 CKD-induced downregulation of LPL, hepatic lipase (HL), and LRP and HDL deficiency and dysfunction lead to impaired delivery of lipid fuel to skeletal muscles and adipose tissue, accumulation and oxidative modification of LDL, IDL, and chylomicrons. Together, these abnormalities contribute to reduced exercise capacity, amplification of oxidative stress, inflammation, catabolic state, and atherosclerosis. CKD chronic kidney disease, LPL lipoprotein lipase, LRP LDL receptor-related protein, HDL high-density lipoprotein, IDL intermediate-density lipoprotein

with ESRD. In addition, a number of other factors, such as reductions of apoC-II and apoE may contribute to LPL deficiency and dysfunction in patients with advanced CKD. Other contributing factors include insulin resistance [66], reduced physical activity, and diminished thyroxin (T_4) to-triiodothyronin (T_3) conversion which are common consequences of advanced CKD and are known to downregulate expression and activity of LPL. Finally, by promoting the release and degradation of the endothelium-bound LPL, recurrent heparinization used with each hemodialysis procedure may contribute to LPL depletion in ESRD patients [67]. LPL deficiency and dysfunction plays a major part in the pathogenesis of the CKD-associated hypertriglyceridemia and impaired energy metabolism [68].

Patients and animals with CKD also have hepatic lipase deficiency, in part, caused by secondary hyperparathyroidism [69] which can result in accumulation of IDL particles. Reduced hepatic *LRP* gene expression and protein abundance is seen in rats with CKD [70] which can further contribute to accumulation of the highly atherogenic IDL and chylomicron remnants. In addition, CKD results in marked reduction of VLDL receptor abundance in skeletal muscle, adipose tissue, and myocardium [71], a phenomenon which can contribute to elevation of VLDL in this population.

Consequences of Triglyceride-Rich Lipoprotein Abnormalities in CKD (Fig. 8.1) The CKD-associated impairment of clearance of triglyceride-rich lipoproteins and accumulation of their remnants have numerous adverse consequences [68]. Accumulation of oxidation-prone IDL, chylomicron remnants, and triglyceride-containing small dense LDL may lead to accelerated atherosclerosis. In addition, binding of oxidized LDL and phospholipids to their receptors on the leukocytes, macrophages, and resident cells stimulates production and release of cytokines and chemokines which participate in the development and intensification of CKD-associated inflammation [72]. Finally, by initiating lipid peroxidation chain reaction, the circulating oxidized lipoproteins and their remnants facilitate

the dissemination and maintenance of oxidative stress throughout the body. Therefore, the presence of oxidized lipids and lipoproteins is both a cause and a consequence of oxidative stress.

Effect of CKD on Cholesterol and LDL Metabolism

Despite having normal or subnormal serum total cholesterol and LDL cholesterol levels, the risk of atherosclerosis and cardiovascular disease is greatly increased in CKD patients. It is likely that oxidative stress and inflammation as opposed to elevated plasma cholesterol or increased cholesterol biosynthesis play a more important role as the cause of atherosclerosis in CKD. It is, therefore, not surprising that clinical trials of statins have proven ineffective in lowering the incidence of cardiovascular disease in patients with ESRD maintained on hemodialysis [73]. As noted earlier, due to the constellation of LPL and hepatic lipase deficiencies and scarcity of cholesterol-rich HDL particles, conversion of IDL to triglyceride-depleted cholesterol-rich LDL is impaired in advanced CKD. Accumulation of these abnormal oxidation-prone LDL particles contributes to the atherogenic diathesis in this population.

When present, nephrotic proteinuria compounds the effect of renal insufficiency causing hypercholesterolemia [33, 36]. It is tempting to speculate that a similar phenomenon may be involved in the pathogenesis of hypercholesterolemia in peritoneal dialysis patients due to losses of proteins in the peritoneal dialysate effluent.

HDL Abnormalities in Chronic Renal Failure

Serum HDL cholesterol concentration is commonly reduced, triglyceride content of HDL is increased, maturation of pre-beta-migrating cholesterol ester-poor to alpha-migrating cholesterol ester-rich HDL is impaired, and proportion of cholesterol ester-poor HDL to cholesterol ester-rich HDL is increased in patients with advanced chronic renal failure [50, 51, 56, 74]. The chronic renal failure-induced structural and quantitative abnormalities of HDL are accompanied by its impaired antioxidant and anti-inflammatory activities and reverse cholesterol transport capacity [56]. Interestingly, HDL cholesterol is markedly elevated and is paradoxically associated with increased cardiovascular and overall mortality/morbidity in a sizeable minority of this population [75]. The HDL particles in these patients are highly oxidized and pro-inflammatory in nature and contain high levels of the acute phase protein, serum amyloid A1, albumin, lipoprotein-associated phospholipase A2, and apoC-III. In addition, the HDL particles from hemodialysis patients have reduced phospholipid and increased triglyceride content and impaired ability to promote cholesterol efflux from macrophages [76]. The following factors contribute to the abnormalities of HDL function and metabolism in CKD:

Serum apoA1 and apoA2 levels are significantly reduced in ESRD patients [56]. Studies in ESRD patients maintained on hemodialysis have shown increased catabolism of apoA1 as a major cause of its reduced serum concentration [77]. In addition, in vivo and in vitro studies have shown marked reduction in hepatic biosynthesis of apoA1 in uremic animals due to mRNA instability in cultured hepatocytes exposed to uremic milieu [78–80]. Interestingly, there is a high prevalence of anti-apoA1 autoantibodies in maintenance hemodialysis patients which is associated with dialysis vintage [81].

Deficiency and diminished hepatic production of LCAT [82–85] may impair maturation of cholesterol ester-poor pre-beta-HDL to mature cholesterol ester-rich HDL in chronic renal failure. In vitro studies have shown that the ability of HDL in removing cholesterol from lipid-laden macrophages is significantly lower in hemodialysis-dependent patients than healthy control individuals [86]. Chronic renal failure also results in marked upregulation of ACAT1 in the artery wall and the diseased kidney [87–90]. The combination of LCAT deficiency and upregulation of ACAT works in concert to impair HDL maturation and reverse cholesterol transport in chronic renal failure. In fact, oxidative modification of

HDL has been demonstrated in ESRD patients [54, 91, 92], which can also contribute to the defective HDL maturation, impaired reverse cholesterol transport, and accelerated atherosclerosis in chronic renal failure.

Serum CETP levels and activity are normal in hemodialysis patients [93, 94]. Elevated HDL triglyceride content in advanced CKD is primarily due to deficiency of hepatic triglyceride lipase [22, 69].

In a recent study, we found marked reductions of HDL antioxidant capacity in ESRD patients maintained on hemodialysis [54], in part, due to significant reduction of paraoxonase1, and glutathione peroxidase [54, 95]. In addition, we have found marked reduction of anti-inflammatory activity of HDL in ESRD patients [54, 55]. These observations were subsequently confirmed by Yamamoto et al. [86] who found that in contrast to the HDL from healthy individuals, the HDL from hemodialysis patients stimulated production of inflammatory cytokines (tumor necrosis factor (TNF)-α, interleukin (IL)6, and IL1 beta) in isolated macrophages in vitro. This was associated with significant reduction of the HDL antichemotactic activity. Likewise, Weichhart et al. [96] have shown that HDL from the majority of ESRD patients lacked anti-inflammatory property and in many cases promoted production of inflammatory cytokines by macrophages in vitro. They attributed the pro-inflammatory activity of HDL to the presence of serum amyloid A in this population.

Oxidative modification and reduced antioxidant and anti-inflammatory functions of HDL in this population are largely due to the prevailing oxidative stress and inflammation as seen in other conditions [97, 98] and can, in turn, intensify the inciting oxidative stress and inflammation and, thereby, participate in a vicious cycle. In fact, oxidative modification of HDL is associated with a high risk of cardiovascular and overall mortality [75].

The abnormalities cited above have serious consequences: The reduction in the antioxidant capacity of HDL and the oxidative milieu of CKD lead to accumulation of oxidized LDL and phospholipids, their avid uptake by macrophages, and resident cells leading to foam-cell formation and atherosclerosis. This is compounded by oxidative modification of HDL [54, 75] which limits its binding affinity for ATP-binding cassette transporter A1 (ABCA-1) transporter, increased ACAT1 activity which favors intracellular retention of cholesterol, and LCAT deficiency which limits uptake of cholesterol by HDL. Together, these abnormalities severely limit cholesterol efflux and can contribute to accelerated atherosclerosis and cardiovascular disease in CKD. In addition, HDL deficiency and dysfunction contribute to the prevailing oxidative stress and inflammation [72] which are the major cause of morbidity and mortality in this population. Finally, given the antithrombotic effect of normal HDL, its deficiency and dysfunction may contribute to blood-access thrombosis in the dialysis population.

Lp(a) in CKD

Plasma Lp(a) concentration is generally elevated in patients with chronic renal failure. Comparison of patients receiving continuous ambulatory peritoneal dialysis with patients receiving hemodialysis has shown significantly higher Lp(a) levels in former population in whom significant losses of proteins in the peritoneal dialysis fluid effluent simulates nephrotic syndrome in functionally anephric subjects [99]. Both free and LDL-bound Lp(a) fractions are elevated in the plasma of patients with ESRD. This is, in part, due to the lack of renal catabolism of this lipoprotein in this population [100].

Part III: Superimposing Factors that Modify Lipid Metabolism in CKD/ESRD

Effect of Chronic Peritoneal Dialysis on Lipid Metabolism in ESRD Patients Peritoneal dialysis results in significant losses of proteins in the dialysate effluent averaging 10 g/day. In addition, high glucose concentrations in peritoneal fluids used as an osmotic agent to facilitate

fluid removal leads to the unintended absorption of large amounts of glucose through peritoneal membrane. Loss of substantial amounts of protein in the peritoneal fluid can raise serum LDL and total cholesterol levels by simulating nephrotic syndrome. Moreover, influx of large amounts of glucose from the peritoneal fluid can further raise plasma triglyceride levels by activating Carbohydrate-responsive element-binding protein (chREBP) and thereby de novo fatty acid synthesis and lipogenesis in these patients. In fact, compared to the hemodialysis patients, LDL cholesterol, triglyceride and Lp(a) concentrations and LDL/HDL ratio are significantly higher in the majority of patients maintained on peritoneal dialysis [101–107]. The role of excess glucose load in the pathogenesis of peritoneal dialysis-associated dyslipidemia was demonstrated by Babazono et al. [108] who found significant reduction of serum LDL cholesterol, triglycerides, and small dense LDL particles using an icodextrin-containing instead of glucose-containing peritoneal dialysis solution. However, despite more atherogenic lipid profile in peritoneal dialysis patients, the risk of cardiovascular mortality in them is comparable to hemodialysis patients [109]. This is primarily due to lower incidence of dialysis-induced hypotension and cardiac arrhythmias caused by the rapid rise and fall in electrolytes as well as better control of fluid balance with peritoneal dialysis.

Effect of Kidney Transplantation on Lipid Profile The kidney transplant recipients frequently exhibit dyslipidemia which is typically marked by increased total cholesterol, LDL cholesterol, and triglyceride levels and normal or reduced HDL concentration [110–112]. The associated dyslipidemia plays an important part in the pathogenesis of cardiovascular disease in this population [113]. Dyslipidemia in transplant recipients is largely due to the use of immunosuppressive agents, particularly prednisone, cyclosporine, and sirolimus, which are commonly used in this population to prevent graft rejection. In this context, glucocorticosteroids promote insulin resistance and raise hepatic production and blood concentration of glucose which stimulates production of fatty acids and triglycerides and lowers HDL cholesterol [114]. In addition, cyclosporine-A increases serum triglyceride, cholesterol, and Lp(a) levels. Animal studies conducted in our laboratories to discern the mechanism by which cyclosporine-A raises serum cholesterol and triglycerides have identified downregulation of hepatic cholesterol 7-alpha-hydroxylase (which limits conversion of cholesterol to bile acids) and of LPL in the skeletal muscle and adipose tissue [115]. In fact, Artz et al. [116] have shown that the replacement of cyclosporine by tacrolimus, azathioprine, or mycophenolate mofetil results in a significant decrease in total cholesterol and LDL cholesterol concentrations and triglyceride levels in transplant patients. Likewise, rapamycin can cause hypertriglyceridemia and hypercholesterolemia by as-yet unknown mechanism(s). Among the commonly used immunosuppressants, azathioprine and tacrolimus have little or no impact on lipid metabolism.

Part IV: Treatment of Dyslipidemia in Patients with Kidney Disease

It is critical to tailor and modify the treatment on an individualized basis and make the necessary changes as the kidney disease evolves over time. This viewpoint is supported by the results of several clinical trials which have shown the futility of the application of uniform therapeutic strategies in this population. The available data concerning the efficacy or lack thereof of various classes of lipid-modulating therapies are briefly described below.

Statins

Statins are generally effective in attenuating hypercholesterolemia and reducing the risk of adverse outcomes in patients with nephrotic syndrome. However, as described below, the efficacy of these products in reducing the risk of cardiovascular and overall morbidity and mortality in patients with CKD varies depending on the nature and severity of renal disease, the renal

Table 8.2 Results of statin trials in patients with chronic renal failure undergoing dialysis. The primary end points of these trials was fatal and nonfatal cardiovascular events

	n	Duration (year)	Baseline LDL-C	LDL-C ↓ (%)	Statins (dose)	Primary end point (95% CI)
4D	1255	4	125 mg/dl	42	Atorvastatin (20 mg/d)	0.77–1.10
AURORA	2276	2.4	100 mg/dL	43	Rosuvastatin (10 mg/d)	Not significant 0.84–1.11
SHARP	2527	4.9	100 mg/dL	30–43	Simvastatin (20 mg/d) ± Ezetimibe (10 mg/d)	Not significant 0.78–1.15 (hemodialysis patients)

LDL-C low-density lipoprotein cholesterol, *SHARP* study of heart and renal protection, *4D* Die Deutsche Diabetes Dialyse, *AROURA* an assessment of survival and cardiovascular events

replacement modalities, and presence or absence of hypercholesterolemia. A brief description of the available data is provided below.

Statins for Prevention of Cardiovascular Disease in Patients with Mild-to-Moderate CKD Post hoc analyses of several, large, randomized, placebo-controlled statin trials evaluating the effect of statins on cardiovascular (CV) outcomes have shown that statin therapy results in a similar risk reduction and medication-related toxicity in patients with mild CKD and those with normal kidney function [117–119]. (Table 8.2) However, since the event rates in people with CKD are higher, the absolute risk reduction conferred by statin therapy was greater in the presence of impaired kidney function. It should be noted, however, that less than 1% of the patients enrolled in these studies had stage 4 CKD, and none had end-stage renal disease requiring dialysis. Therefore, these conclusions cannot be extended to patients with advanced CKD. The subgroup analysis of the secondary prevention trials suggest that statins may reduce CV morbidity and mortality and all cause mortality in patients with stage I-IV CKD [119–121]. These findings were supported by the results of the Study of Heart and Renal Protection (SHARP) Trial which showed significant reductions in major atherosclerotic events, nonhemorrhagic stroke, and coronary revascularization, and a trend toward reduction of the nonfatal myocardial infarction with a combination of simvastatin and ezetimibe in patients with mild-to-moderate CKD as compared to their placebo-treated counterpart [122]. In contrast, the Prevention of Renal and Vascular End-Stage Disease Intervention Trial (PREVENT IT) study, a prospective randomized trial designed to examine the efficacy of pravastatin in patients with very mild CKD yielded inconclusive results [123]. This trial, which had randomized patients with microalbuminuria to receive fosinopril, pravastatin, or matching placebos for 4 years, showed only an insignificant reduction in the cardiovascular mortality and hospitalization for cardiovascular events in the pravastatin-treated group. The reason for discrepancy between the latter study and the abovementioned studies is not clear. However, it may be due to the difference in severity of proteinuria among the patients enrolled in these trials. As noted earlier, heavy proteinuria results in downregulation of hepatic LDL receptor and HDL docking receptor which leads to hypercholesterolemia by increasing hepatic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity and cholesterol synthesis [11, 33, 36, 44]. Consequently, HMG-CoA reductase inhibitor can have salutary effect in such individuals. The PREVENT IT trial had enrolled patients with microalbuminuria, whereas patients enrolled in the former trials had stage I-IV CKD, a significant subset of whom exhibited significant proteinuria.

Effect of Statins on Progression of CKD The available data on this topic are derived from secondary or post hoc analyses of secondary prevention studies and a few randomized clinical trials. For instance, compared to placebo-treated patients, the simvastatin-treated patients

experienced a significantly lower rate of decline in GFR in the Heart Protection Trial [124]. Likewise, the post hoc analysis of data from the Greek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study showed an approximately 5% fall in the estimated GFR in the untreated but not in the statin-treated patients with dyslipidemia, coronary disease, and normal baseline renal function during the 3-year study period [125]. These findings were confirmed by subanalysis of data from the "Treatment to New Targets" (TNT) study [126] which revealed a significant improvement in estimated GFR in patients with coronary heart disease over the 5-year study period. The subgroup analysis of the Cholesterol and Recurrent Events (CARE) trial revealed that pravastatin slowed the annual rate of decline in GFR (2.5 mL/min/year) in individuals with GFR below 40 mL/min/1.73 m^2, but not in the entire study population [127]. The meta-analysis of 12 small randomized controlled trials (RCTs) which directly explored the impact of statins on renal function including 362 participants revealed that statins may retard progression of renal disease and reduce proteinuria [128]. These findings were confirmed by meta-analysis of data from 27 published or unpublished randomized, controlled trials or crossover trials of statins (encompassing nearly 40,000 participants) which showed a significant reduction in the annual rate of decline in estimated GFR (1.22 mL/min per year) in the statin-treated individuals [129]. Interestingly, the subgroup analysis of the data revealed a statistically significant favorable effect of statin therapy in the participants with cardiovascular disease but not in patients with preexisting kidney disease, i.e., glomerulonephritis, diabetic nephropathy, or hypertensive nephrosclerosis.

There is evidence that statin therapy can modestly reduce proteinuria in patients with kidney disease. This assumption is supported by the meta-analyses of data derived from 50 trials including large numbers of CKD and transplant patients [130]. It should be noted, however, that in contrast to most statins, rosuvastatin does not have an anti-proteinuric effect and instead it can cause or intensify proteinuria. This phenomenon was confirmed in the Prospective Evaluation of Proteinuria and Renal Function in diabetic and non-Diabetic Patients with Progressive Renal Disease Trials (PLANET I and II studies, respectively) [131]. The PLANET I and II studies were undertaken to determine the efficacy of rosuvastatin (10 or 40 mg/day) and atorvastatin (80 mg/day) on progression of renal disease in CKD patients with and without diabetes. The studies showed significant reductions in proteinuria and the rate of decline in estimated GFR in atorvastatin-treated patients but significant increase in proteinuria and faster decline in GFR in rosuvastatin-treated group. The likely mechanism for this phenomenon is accumulation of rosuvastatin and its metabolites in the renal tissue where it can cause injury, especially at high doses.

Thus, except for rosuvastatin which can worsen proteinuria, most statins can be beneficial in slowing progression of CKD, particularly in patients who have significant proteinuria and hypercholesterolemia. Nonetheless, statins should be prescribed with caution since high doses of these agents can lead to renal and extrarenal complications. For instance, proteinuria can occur in some patients when treated with a high dose of simvastatin (40 mg/day), regress following discontinuation, and recur with the resumption of the drug [132]. The mechanism by which rosuvastatin and occasionally other statins cause proteinuria is not entirely clear. However, it appears to be, in part, due to impaired reabsorption of filtered proteins in proximal tubules. This supposition is supported by in vitro experiments which showed concentration-dependent inhibition of protein uptake by simvastatin, pravastatin, and rosuvastatin in cultured human renal proximal tubular epithelial cells [133].

Statins in ESRD Patients Maintained on Hemodialysis Randomized prospective clinical trials of different statins have consistently shown no reduction in the risk of cardiovascular events and cardiovascular or overall mortality in ESRD patients maintained on hemodialysis. The first among these studies was the Die Deutsche Diabetes Dialyse (4D) trial [134] which had enrolled 1255 hemodialysis patients with type 2 diabetes randomized to receive atorvastatin, 20 mg/day or

placebo for 4 years. The trial showed no significant reduction in mortality from cardiac causes or nonfatal myocardial infarction and stroke (95% CI 0.77–1.10) despite about 42% reduction in LDL cholesterol in patients receiving atorvastatin. While atorvastatin reduced the rate of all cardiac events combined (95% CI.68–99), the deaths from stroke were increased (95% CI 1.05–3.93). The second trial, an assessment of survival and cardiovascular events (AURORA), was a double-blind, randomized, placebo-controlled trial designed to compare the effect of rosuvastatin 10 mg/day versus placebo on cardiovascular morbidity and mortality in hemodialysis patients [135]. The study had enrolled 2776 patients with identical mean baseline LDL cholesterol values of 100 mg/dL in the rosuvastatin-treated group and 99 mg/dL in the placebo-treated group. The mean length of the treatment was 2.4 years and the mean length of follow-up was 3.2 years. The rosuvastatin-treated group showed an approximately 43% reduction in LDL cholesterol concentration within the first year of trial. Despite the dramatic reduction in serum cholesterol level in the rosuvastatin-treated group, no significant difference was found in the incidence of nonfatal myocardial infarction, cardiovascular, or overall mortality between the rosuvastatin- and placebo-treated groups. In fact, the rosuvastatin-treated patients with diabetes experienced a significant increase in the incidence of fatal hemorrhagic stroke as was seen in the 4D study.

The latest and the largest primary prevention trial in this series was the Study of Heart and Renal Protection (SHARP) Trial [122] which was different from the former trials as in addition to dialysis patients it included a large cohort of CKD patients who did not require dialysis. The estimated glomerular filtration rate (eGFR) in the CKD groups averaged 27 mL/min/1.73 m^2. The study was designed to determine the effectiveness of LDL cholesterol reduction on major vascular events and the rate of progression of CKD in as-yet dialysis-independent patients. Patients were randomized to receive either simvastatin 20 mg/day with or without ezetimibe 10 mg/day or placebo. The median duration of follow-up was 4.9 years. Mean baseline LDL cholesterol levels (108 mg/dL in the entire group and 100 mg/dL in the dialysis subgroup) were reduced by 30 mg/dL with simvastatin alone and by 43 mg/dL with simvastatin plus ezetimibe at 1 year. Patients on simvastatin alone were re-randomized to simvastatin and ezetimibe after 1 year. Compared to the placebo-treated arm, the simvastatin and ezetimibe-treated arm showed a 17% reduction in major atherosclerotic events, a 25% reduction in nonhemorrhagic stroke, a 21% reduction in coronary revascularization, and trend toward a reduction in nonfatal myocardial infarction. It is of note, however, that cholesterol-lowering therapy failed to reduce either mortality rates or cardiovascular events in the dialysis-dependent ESRD patients in this trial thus recapitulated the results of the earlier studies. The reason for the favorable results of this trial was inclusion of a large cohort of patients with less advanced CKD in whom the underlying mechanisms of cardiovascular disease resembles that in the general population.

The failure of statins to confer protection against cardiovascular disease in hemodialysis patients observed in the above clinical trials contrasts their favorable effects in the general population [136] and the majority of CKD patients who do not require dialysis. Several factors account for the ineffectiveness of statins in the majority of hemodialysis population. As mentioned above, accelerated atherosclerosis and cardiovascular disease in the majority of hemodialysis patients are associated with normal or subnormal serum cholesterol level. This observation excludes elevated cholesterol production or concentration as the central player in the pathogenesis of the associated cardiovascular disease in the majority of these patients. Instead, cardiovascular disease in this population may be primarily driven by systemic inflammation, oxidative stress, accumulation of atherogenic VLDL and chylomicron remnants, formation of small dense LDL, and HDL deficiency and dysfunction, hypertension, vascular calcification, and arrhythmogenic electrolyte disorders which are not amenable to statin therapy. It should be noted, however, that due to preexisting genetic or other unrelated mechanisms a minority of hemodialysis patients exhibit

hypercholesterolemia which can contribute to the cardiovascular disease. Statin therapy can have salutary effects in such patients as demonstrated by the post hoc analysis of the 4D study [137]. In this study, the authors demonstrated that atorvastatin significantly reduced the rates of adverse cardiovascular and overall outcomes in hemodialysis patients with the highest quartile of baseline LDL cholesterol (≥145 mg/dL, 3.76 mmol/L) but not in patients with the other quartiles of LDL cholesterol at baseline.

Statin in Peritoneal Dialysis Population Statins may lower the risk of cardiovascular complications in peritoneal dialysis patients primarily by lowering serum cholesterol, but may be by improving endothelial function, reducing neointima formation, and inhibiting vascular smooth muscle cell proliferation, platelet activation, and aggregation [138]. In addition, statins may help to protect peritoneal membrane by limiting deposition of fibrin and development of adhesion in these patients [139].

Statins in Kidney Transplant Population In a long-term randomized clinical trial comparing fluvastatin XL 80 mg/day with placebo including over 1600 kidney transplant recipients, the fluvastatin-treated group showed a significant reduction in mean LDL cholesterol (from 159 mg/dL at baseline to 98 mg/dL at last follow-up) [140]. This was associated with a significant reduction in the risk of major adverse cardiac events ($p=0.036$), and a 29% reduction in cardiac death or nonfatal myocardial infarction ($p=0.014$). However, the treatment did not significantly impact total mortality or graft loss in the study population.

Importance of Individualized Care Approach in Prescribing Statins in CKD Population Patients with advanced CKD generally suffer from uremic myopathy, mitochondrial dysfunction, and type 2 diabetes and insulin resistance; events that can make them more vulnerable to the unintended actions of statins. Thus, the author believes that the use of statins in CKD and ESRD patients should be restricted to those with hypercholesterolemia and should be avoided in those with normal serum cholesterol levels. In addition, given the vulnerability of this population, the lowest effective dose should be prescribed. Finally, statins which are metabolized/excreted by the kidney such as rosuvastatin should be avoided in patients with kidney disease.

Fibrates

In view of the prevalence of hypertriglyceridemia and HDL deficiency in CKD patients, PPAR-α agonists (fibrates) which can lower triglyceride and raise HDL cholesterol levels can be useful in the management of CKD-induced dyslipidemia. The trial of PPAR-α agonist, gemfibrozil, has shown significant reduction in serum triglyceride, increase in serum HDL cholesterol, and reduced incidence of coronary death and nonfatal myocardial infarction in patients with mild-to-moderate CKD who had coronary disease and low HDL cholesterol level [141–143]. However, the treatment did not attenuate progression of renal disease in the study population. On the contrary, the drug tended to increase the risk of persistent elevations of serum creatinine in participants with or without CKD. These concerns have greatly curtailed the use of fibrates in the management of dyslipidemia in the CKD population. However, according to a recently published meta-analysis [144], the initial spike in serum creatinine following the onset of therapy with fibrates reverses over time. The authors further found reduction in proteinuria in the fibrate-treated groups and suggested that the drug might have renal protective effect. It should be noted that the safety and efficacy of fibrates in patients with advanced CKD have not been definitively established. The National Kidney Foundation Clinical Practice Guidelines (K/DOQI; 2003) recommend gemfibrozil as the fibrate of choice for use in patients with CKD. This was based on its dual biliary- and urinary-excretion pathways which require less intense dose adjustment in patients with mild CKD. The National Lipid Association recommended a 50% reduction in the dose of gemfibrozil for patients with GFR below 60 mL/min/1.73 m^2 and avoidance of all

fibrates in patients with GFR less than 30 mL/min/1.73 m^2. Caution should be exercised to avoid or minimize interaction of gemfibrozil and other fibrates with other drugs, specially statins and Coumadin, that can lead to serious consequences. Among statins, fluvastatin is the only product whose plasma level does not increase when co-administered with gemfibrozil; therefore, this combination may be preferred in CKD patients with mixed dyslipidemia [145]. With the exception of fenofibrate, all other fibrates can elevate serum level of statins and predispose the patients to rhabdomyolysis and liver injury [146]. However, the dose of fenofibrate should be markedly reduced in patients with diminished GFR and the drug should be avoided when the GFR is below 15 mL/min/1.73 m^2 [146].

Niacin

Low doses of niacin can increase serum HDL cholesterol and high doses of niacin can raise HDL cholesterol and lower LDL, triglyceride, and Lp(a) concentrations. Moreover, the antioxidant and anti-inflammatory properties of niacin may further help to slow progression of atherosclerosis and kidney disease. However, due to its poor tolerability, use of niacin in CKD population has been limited. The dose-dependent hyperglycemic effect of niacin on serum glucose is of particular concern in patients with diabetes which is the most common cause of CKD.

Experimental Lipid-Modulating Agents (ACAT Inhibitors)

In a series of studies, we found significant improvements in proteinuria, renal function, and plasma lipid profile with administration of the ACAT inhibitor, avasimibe, in animal models of nephrotic syndrome and chronic renal failure [147, 148]. These findings in experimental animals suggest that ACAT inhibitors may be effective in ameliorating kidney disease and preventing atherosclerosis in selected patients with CKD or chronic nephrotic proteinuria. However, clinical trial of avasimibe was prematurely halted due to acute cardiovascular events [149].

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