Dyslipidemia in Chronic Kidney Disease: An Approach to Pathogenesis and Treatment

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Lipids  •  Chronic kidney disease  •  Erythropoietin  •  Hypolipidemic drugs

Abstract
Background/Aims: Cardiovascular disease (CVD) is a major cause of mortality in patients with mild to moderate chronic kidney disease (CKD) and end-stage renal disease (ESRD). Dyslipidemia has been established as a well-known traditional risk factor for CVD in the general population and it is well known that patients with CKD exhibit significant alterations in lipoprotein metabolism. In this review the pathogenesis and treatment of renal dyslipidemia are discussed. Methods: Studies on lipid abnormalities in CKD stages 1–4, in nephrotic syndrome, and in hemodialysis and peritoneal dialysis patients are analyzed, as well as the lipid profile of kidney graft recipients. Also, the results of the effects of erythropoietin treatment and hypolipidemic drugs in CKD patients are reported. Results: Disturbances in lipoprotein metabolism are evident even at the early stages of CKD and usually follow a downhill course that parallels the decline of renal function. However, several intrinsic or exogenous factors can influence the phenotypic expression of these alterations. According to the literature, current evidence suggests that unlike dialysis patients, mild to moderate CKD patients could benefit from the use of statins. Conclusion: The use of statins is indicated in patients with mild to moderate CKD, while in subjects with ESRD lipid-lowering therapy should be individualized.

Background

The incidence and prevalence of chronic kidney disease (CKD) are increasing worldwide and are associated with poor outcomes. According to the 1999–2004 National Health and Nutrition Examination Survey (NHANES), the prevalence of CKD among the USA population is 15.3% [1]. Although there is still some controversy whether CKD represents an independent causal risk factor for incident cardiovascular disease (CVD), accumulating evidence over the last decade marks out CVD as the major cause of mortality in patients with mild to moderate CKD and end-stage renal disease (ESRD) [2, 3]. It becomes apparent that the severity of CKD along with CVD severity in any population makes a 'devastated' combination for both patients and healthcare systems. Approximately 50% of patients with ESRD die from a cardiovascular event [4], which indicates a cardiovascular mortality that is 30 times higher in dialysis patients and 500 times higher in 25- to 34-year-old ESRD patients than in individuals from the general population of the
Premature CVD extends from mild to moderate stages of CKD. A pooled analysis of four community-based studies showed that moderate renal insufficiency carries a 19% excess risk of cardiovascular complications [5]. In a retrospective cohort study only a tiny minority of patients (0.5–1%) with mild to moderate CKD developed ESRD over a 5-year follow-up, while as many as 19 and 24% of these patients with mild and moderate renal insufficiency, respectively, died mostly of cardiovascular complications in the same period [6].

In the general population as much as 75% of the excess risk of coronary heart disease could be explained by traditional Framingham risk factors [7]. However, use of traditional risk factors underestimates the CVD risk in patients with CKD [8], while the Framingham predictive instrument demonstrates poor overall accuracy in predicting cardiac events in patients with mild to moderate CKD [9]. Moreover, traditional CVD risk factors were found often to relate to outcome in ESRD dialysis patients in an opposite direction, a phenomenon termed ‘reverse epidemiology’ [10]. The introduction of uremia-related, non-traditional CVD risk factors and evaluation of their corresponding biomarkers were thought to enhance the clinical ability to predict cardiovascular events in patients with all stages of CKD. However, studies investigating the usefulness of current CVD biomarkers have concluded that they only add moderately to traditional risk factors for risk assessment of individuals both with almost normal renal function [11] as well as with mild to moderate CKD [12, 13].

Dyslipidemia has been established as a well-known traditional risk factor for CVD in the general population and large-scale observational studies have shown that total and low-density lipoprotein (LDL)-cholesterol values are two of the most important independent predictors of cardiovascular morbidity and mortality [14]. Also, it is well known that patients with impaired renal function exhibit significant alterations in lipoprotein metabolism, which in their most advanced form may result in the development of severe dyslipidemia. In this review studies on the pathogenesis of renal dyslipidemia and the results of drug therapy are discussed.

**Lipids in CKD Stages 1–4**

The process of exogenous and endogenous pathways of lipid metabolism is a complicated phenomenon in both normal and abnormal conditions. A schematic presentation of both pathways is shown in figure 1.

Although lipid abnormalities were originally considered as complications of ESRD, these changes can be present in early stages of CKD and may actively participate in the pathogenesis of serious complications such as atherosclerotic vascular disease. Although the nature of
Dyslipidemia can be significantly influenced by several intrinsic (nephrotic range proteinuria, concomitant diseases such as diabetes mellitus, hereditary disorders of lipid metabolism) or exogenous (epoietin administration, drugs such as steroids, calcineurin inhibitors, etc.) factors, the most common quantitative lipid abnormalities in predialysis CKD patients are hypertriglyceridemia, increased concentrations of triglyceride-rich lipoprotein remnants, reduced high-density lipoprotein (HDL)-cholesterol levels as well as increased concentrations of lipoprotein(a) (Lp(a)) [15]. Notably, total and LDL-cholesterol levels are usually within normal limits or slightly reduced in these individuals (table 1) [16].

Hypertriglyceridemia represents an early feature of renal failure. Indeed, previous studies have shown that patients with impaired renal function exhibit increased concentrations of triglycerides even though serum creatinine levels are within normal limits [17, 18]. In addition, individuals with renal insufficiency usually display abnormal increases in serum triglyceride levels after a fat meal (postprandial lipemia) [19]. Experimental studies revealed that the accumulation of triglyceride-rich lipoproteins (very-low-density lipoprotein (VLDL), chylomicrons and their remnants) in individuals with predialysis CKD is mainly due to their decreased catabolism [20]. The downregulation of the expression of several genes [21–23] along with the changes in the composition of lipoprotein particles [24] and the direct inhibitory effect of various uremic ‘toxins’ on the enzymes involved in lipid metabolism [25], represent the most important pathophysiological mechanisms underlying the development of hypertriglyceridemia in renal failure. Interestingly, it has been proposed that secondary hyperparathyroidism may also contribute to the impaired catabolism of triglyceride-rich lipoproteins [26, 27] and that parathyroidec- tomy or the administration of the calcium channel blocker verapamil [28] may partially ameliorate the hypertriglyceridemia of CKD. It is well known that impaired insulin sensitivity represents an early feature of CKD [17–19]. Thus, it could be hypothesized that the insulin resistance-driven overproduction of VLDL may significantly contribute to the development of hypertriglyceridemia in CKD patients. However, the role of the increased hepatic production of triglyceride-rich lipoproteins in the pathogenesis of renal dyslipidemia remains a subject of debate [20].

Epidemiological studies have shown that HDL-cholesterol levels are inversely related to the future cardiovascular risk [29]. HDL particles possess multiple antiatherogenic activities including reverse cholesterol transport (transport of surplus cholesterol from the arterial wall to the liver for excretion) as well as antioxidative, anti-inflammatory and antithrombotic functions, which are attributed to HDL-associated apolipoproteins (mainly apolipoprotein AI) and enzymes (paraoxonase-1, platelet-activating factor acetylhydrolase and lecithin-cholesterol acyltransferase (LCAT)) [30]. A schematic presentation of the normal reverse cholesterol transport pathway is shown in figure 2. Studies in patients or laboratory animals with predialysis renal failure consistently reveal decreased concentrations of HDL-cholesterol compared to individuals with normal renal function [31, 32]. Several mechanisms, working in concert, may underlie this reduction in HDL-cholesterol levels, which is usually indicative of impaired reverse cholesterol transport. Thus, uremic patients usually exhibit decreased levels of apolipoproteins AI and AII (the main protein constituents of HDL) [32], diminished activity of LCAT (the enzyme re-
sponsible for the esterification of free cholesterol in HDL particles [22, 33] as well as increased activity of cholesteryl ester transfer protein [34] that facilitates the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins thus reducing the serum concentrations of HDL-cholesterol. In addition to their reduced efficiency as cholesterol acceptors, HDL particles from individuals with renal failure may also possess impaired antioxidative and anti-inflammatory function. This impairment can, at least in part, be attributed to the reduction in the activities of HDL-associated enzymes [35, 36].

Lp(a) represents an LDL-like particle distinguished from LDL by the presence of apolipoprotein(a) (apo(a)), which is attached to the apolipoprotein B-100 molecule through disulfide linkage [37]. Apo(a) is highly homologous to the plasma protease zymogen plasminogen and thus it has been suggested that Lp(a) may promote thrombogenesis by inhibiting fibrinolysis [37]. Studies in healthy individuals and in patients with CKD have shown that serum Lp(a) levels are strongly and negatively associated with apo(a) isoform size. Indeed, subjects who have low-molecular-weight apo(a) isoforms show on average higher Lp(a) concentrations compared to those who have high-molecular-weight isoforms [38]. The large concentration gradient of Lp(a) between the aorta and renal vein [39] as well as the identification of apo(a) fragments in urine [40] suggest that the kidney may actively participate in the degradation of Lp(a). Thus, it is not surprising that patients with primary kidney diseases (even those with normal GFR values) usually exhibit markedly elevated concentrations of Lp(a) [41, 42] as well as increased concentrations of LDL-unbound apo(a) [43]. However, recently published studies indicate that the negative association between renal function and Lp(a) levels is phenotype-specific. Thus, predialysis renal failure patients with high-molecular-weight apo(a) isoforms tend to have much higher Lp(a) values than apo(a) phenotype-matched healthy controls, whereas patients with kidney diseases who exhibit low-molecular-weight apo(a) isoforms have similar Lp(a) concentrations with phenotype-matched healthy individuals, who already have high Lp(a) levels [37, 44]. It is worth mentioning that prospective studies identified small apo(a) isoform size and not Lp(a) level as an independent predictor of total and cardiovascular mortality in CKD patients [45, 46].

In addition to the aforementioned quantitative changes in serum lipoprotein concentrations, patients with CKD display important qualitative alterations in lipid metabolism that cannot be easily assessed with conventional laboratory techniques [16]. Thus, it has been shown that VLDLs from individuals with impaired renal function have increased cholesterol content, while their triglyceride content is usually reduced. In contrast, chronic renal failure usually results in decreased cholesterol content of LDLs and HDLs, whereas the triglyceride content of these particles is relatively increased. Finally, although uremic patients usually have a normal or slightly reduced LDL-cholesterol concentration, they exhibit important disturbances in the density distribution of LDL subfractions that is characterized by a predominance of small, dense LDL particles [47, 48]. These particles are more atherogenic than the large, buoyant ones and can substantially contribute to the pathogenesis of atherosclerotic vascular disease [49].

**Lipids in Nephrotic Syndrome**

Disturbed lipoprotein metabolism is a consistent feature of the nephrotic syndrome (NS) [50, 51]. The development of this form of secondary dyslipidemia appears to be independent of the underlying renal disease and may substantially contribute to the increased cardiovascular risk that has been observed in these individuals [52] as well as to the progression of renal failure [53]. The most common lipid abnormalities in patients with NS are elevated concentrations of total and LDL-cholesterol as well
as a predominance of cholesterol-depleted small, dense LDL particles (table 1) [51, 54]. However, in a considerable number of cases, elevated concentrations of triglycerides (due to accumulation of VLDL and remnant lipoproteins such as intermediate-density lipoprotein (IDL)) can also be observed [51]. In addition, individuals with nephrotic-range proteinuria exhibit increased concentrations of Lp(a) that, in contrast to what is usually noticed in CKD patients without proteinuria, is not phenotype-specific [55]. This means that most patients with the NS have Lp(a) concentrations that are substantially elevated compared with controls of the same apo(a) isoform [55]. Finally, HDL-cholesterol levels have variously been reported to be increased, decreased, or normal in subjects with nephrosis [50, 56].

The pathophysiological mechanisms that are responsible for the development of nephrotic dyslipidemia remain ill defined. In addition, the reasons for the occurrence of two different patterns of dyslipidemia (namely hypercholesterolemia and combined dyslipidemia) have not been fully explained. Nevertheless, it has been proposed that two of the most important determinants of triglyceride levels in patients with NS could be the degree of proteinuria and the deterioration in renal function [31, 57].

Early studies that tried to elucidate the mechanisms behind nephrotic dyslipidemia concluded that increased hepatic production and secretion of apolipoprotein B-containing lipoproteins (VLDL and LDL) is the major cause of the lipid abnormalities observed in this patient population [58–60]. According to this hypothesis, the reduced serum albumin levels and/or the decreased plasma oncotic pressure may lead to a coordinated increase in the synthesis of albumin and other proteins by the liver, including lipoproteins [58, 61, 62]. In this context, experimental studies showed that albumin, dextran and other oncotically active macromolecules are equally effective in correcting this abnormality [61, 63, 64]. In contrast to this assumption, the vast majority of the subsequent kinetic studies revealed that the dyslipidemia of NS is primarily a result of defective lipoprotein catabolism, whereas the increased hepatic lipoprotein production is not associated with albumin metabolism and possibly plays a secondary role [57, 65–67]. In line with this theory are the findings of several research groups who showed impaired intravascular lipolysis of triglyceride-rich lipoproteins and reduced fractional catabolic rates of LDL in individuals with NS. It is well known that the progressive delipidation of triglyceride-rich lipoproteins is facilitated by the action of two different enzymes namely endothelial-bound lipoprotein lipase and hepatic lipase. The expression of the genes of these enzymes has been found to be downregulated in patients with NS [68]. In addition, other factors such as hypoalbuminemia and proteinuria may further decrease the efficiency of lipoprotein lipase-induced lipolysis of triglyceride-rich lipoproteins by interfering with the endothelial binding of the enzyme and by changing the composition of VLDLs in a way that reduces their suitability as lipoprotein lipase substrates, respectively [69].

Recently published studies indicate that individuals with NS exhibit an acquired LDL-receptor deficiency [70]. Although the nature of this deficiency has not been fully characterized, studies in experimental animals have shown that the inefficient translation and/or the increased LDL-receptor protein turnover may represent the most important causes for its development [71, 72]. In addition to these mechanisms, conformational changes in the apolipoprotein B moiety of LDLs may further reduce the affinity of LDL particles for LDL receptor thus contributing to the elevated LDL-cholesterol levels that represent the prominent feature of nephrotic dyslipidemia [54]. The reduced receptor-mediated catabolism of LDL particles along with the upregulation of acyl-coenzyme A:cholesterol acyltransferase (ACAT) gene (the enzyme responsible for cholesterol esterification in hepatocytes) that has been observed in individuals with NS [73] may reduce the free cholesterol content of hepatocytes and thus may lead to the dysregulation of the key enzymes that are involved in cholesterol homeostasis. Indeed, studies in animals with experimental nephrosis revealed an upregulation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (the rate-limiting enzyme in cholesterol biosynthesis) [74] as well as a relative reduction in cholesterol 7α-hydroxylase (an enzyme that plays an important role in cholesterol catabolism through the formation of bile acids) [75]. All the aforementioned mechanisms in concert may result in the increased concentration of LDL-cholesterol in individuals with NS. In addition to the elevated LDL-cholesterol levels, patients with heavy proteinuria usually exhibit increased concentrations of Lp(a) independent of the genetically determined apo(a) isoform. Kinetic studies revealed that this increase is mainly due to the increased hepatic production of this lipoprotein whereas the rate of Lp(a) catabolism was not significantly affected by the presence of the NS [76].

Finally, although HDL-cholesterol levels are usually well preserved in individuals with NS, the reverse cholesterol transport (i.e. the transport of excessive cholesterol...
from the peripheral tissues to the liver for excretion) is usually impaired. This impairment is mainly related to the acquired defect in LCAT activity [77], to the increased cholesteryl ester transfer protein activity [78] as well as to the downregulation of scavenger receptor B-1 (hepatic HDL receptor) that has been observed in patients with NS [79]. In addition to its deleterious effects on the reverse cholesteryl transport, the dysregulation of these key enzymes and receptors can also significantly affect the efficiency of the catabolism of triglyceride-rich lipoproteins. Indeed, it is well known that the HDLs, during their maturation from cholesterol-depleted HDL₃ to cholesterol-enriched HDL₂ particles, donate sufficient amounts of apolipoproteins E and C-II to VLDL and chylomicrons. These apolipoproteins play significant roles in the catabolism of triglyceride-rich lipoproteins since they facilitate their interaction with endothelial-bound lipoprotein lipase and hepatic receptors. As a consequence, the disturbed maturation of HDL particles in individuals with NS further impairs the intravascular delipidation and hepatic removal of VLDLs thus contributing to the development of hypertriglyceridaemia [70].

It is noteworthy that the treatment of nephrotic dyslipidemia with the application of LDL-apheresis [80, 81] or with the use of medications such as statins [82] and direct ACAT inhibitors [83] has a favorable effect on some NS-related parameters such as hypoalbuminemia and albuminuria. These observations clearly demonstrate the existence of a vicious circle involving proteinuria and dyslipidemia.

**Lipids in Hemodialysis and Peritoneal Dialysis**

Dialysis is very effective for the amelioration of uremic symptoms and certain features of uremic toxicity. The initiation of renal replacement therapy as well as the choice of dialysis modality may also influence the phenotypic characteristics of uremic dyslipidemia in patients with ESRD (table 1). However, the lipid and apolipoprotein profile that characterizes predialytic renal failure remains essentially unchanged during long-term hemodialysis (HD) [31, 84]. Thus, HD patients usually display increased concentrations of intact or partially metabolized triglyceride-rich lipoproteins, reduced serum levels of HDL-cholesterol and elevated concentrations of Lp(a). Total and LDL-cholesterol values are within normal limits or reduced in this patient population, whereas the subtraction of apolipoprotein B-containing lipoproteins usually reveals a predominance of small, dense LDL particles [48]. The pathophysiological mechanisms that underlie the alterations in lipoprotein metabolism in HD patients are generally similar with those described in predialysis renal failure individuals. However, the dialysis procedure may result in additional defects in lipid homeostasis (such as increased catabolic rate of apolipoprotein AI) [85] that reinforce the clinical expression of these mechanisms.

Despite the neutral effect of dialysis on serum lipid profile, certain dialysis-related parameters may significantly affect lipoprotein metabolism and modify the features of dyslipidemia in HD patients. Thus, it has been shown that the use of high-flux polysulfone or cellulose triacetate membranes instead of low-flux membranes is accompanied by a significant reduction in serum triglyceride levels as well as by an increase in apolipoprotein AI and HDL-cholesterol levels [86, 87]. This improvement could, at least in part, be attributed to an increase in the apolipoprotein C-II/C-III ratio which increases the activity of lipoprotein lipase and facilitates the intravascular lipolysis of triglyceride-rich lipoproteins [88]. In addition, the type of dialysate may also significantly affect the serum levels of lipoproteins in HD patients. Indeed, it has been shown that the use of bicarbonate dialysate may result in higher HDL-cholesterol concentrations than the use of acetate dialysate [89]. Another factor that can potentially affect lipoprotein metabolism in HD patients is the repeated use of heparin as an anticoagulant. Heparin releases lipoprotein lipase from the endothelial surface and thus its chronic use may result in lipoprotein lipase depletion and defective catabolism of triglyceride-rich lipoproteins. However, the studies that tested the role of heparin in the pathogenesis of HD-induced dyslipidemia revealed contradictory results [90–92]. In addition, controversy exists as to whether low-molecular weight heparins have a more favorable effect on the lipid profile of HD patients compared to standard unfractionated heparins [93, 94]. Finally, recent studies indicate that the use of the phosphate-binder sevelamer hydrochloride significantly reduces the concentrations of total cholesterol and apolipoprotein B in HD patients [95]. Obviously, the cholesterol-lowering properties of this compound are irrelevant to phosphate reduction and can be mainly attributed to its bile acid sequestrating properties.

In contrast to HD patients whose serum lipoprotein concentrations resemble those of predialysis renal failure subjects, continuous ambulatory peritoneal dialysis (CAPD) patients usually exhibit a more atherogenic lipid profile that is characterized by higher total and LDL-cholesterol values, increased apolipoprotein B concentra-
tions, and more pronounced hypertriglyceridemia [84, 96]. In addition, CAPD patients have increased concentrations of small, dense LDL, higher Lp(a) values and reduced HDL-cholesterol concentrations compared to healthy age- and sex-matched individuals [48, 96]. The pathophysiological mechanisms that exacerbate dyslipidemia in CAPD individuals are not well characterized. However, a number of factors have been proposed to play contributory roles in this exacerbation. It is well known that CAPD patients lose substantial amount of proteins into the peritoneal dialysate, resembling the protein losses observed in NS. This protein loss may, in turn, stimulate the hepatic production of albumin and cholesterol-enriched lipoproteins thus leading to elevated concentrations of LDL-cholesterol and Lp(a) [97–101]. In addition, the absorption of glucose from the dialysis fluid and the resultant increase in insulin levels may enhance the hepatic synthesis and secretion of VLDL and possibly that of other lipoproteins such as Lp(a) [102]. Although no direct correlation has been observed between peritoneal glucose absorption and serum lipid levels in peritoneal dialysis patients, recent studies indicate that the reduction in glucose load with the use of less absorbed icodextrin-containing dialysis solution instead of glucose for the overnight dwell sufficiently reduces the serum levels of total and LDL-cholesterol as well as the concentrations of triglycerides and small, dense LDL particles [103, 104]. It should be noted that even though substantial amounts of apolipoproteins and intact lipoproteins (especially HDL) are lost via the peritoneal cavity in CAPD patients, the pathophysiological significance of these losses as well as their impact on lipoprotein metabolism remain indeterminate [105, 106].

In a recent study we investigated the efficiency of the phosphate-binder sevelamer hydrochloride in the treatment of hyperphosphatemia and its influence on serum lipid parameters in patients on CAPD. The data from this prospective, randomized, cross-over study indicate that, over a period of 8 weeks, the drug effectively lowered serum phosphorus and also had a significant beneficial effect on both total and LDL-cholesterol serum levels [107].

**Lipids in Kidney Graft Recipients**

The number of kidney transplant recipients has increased considerably during the latter years [1]. As a consequence, knowledge of the impact of renal transplantation on various metabolic pathways is of paramount importance. Theoretically it could be expected that the restoration of normal (or near-normal) renal function after a successful renal transplantation might favorably affect the metabolism of lipoproteins in a way opposite to that observed during the development of uremia. However, the various metabolic changes that take place after renal transplantation cannot be evaluated outside the context of immunosuppressive therapy. In addition, since immunosuppressive regimens usually include more than one medication, the individual contribution of either drug to the observed metabolic disturbances cannot be easily interpreted.

Although the results of the trials that evaluated the lipid profile in renal graft recipients are contradictory, numerous studies revealed deterioration in the metabolism of apolipoprotein B-containing lipoproteins after successful renal transplantation [108–111]. This is characterized by elevated values of total, VLDL and LDL-cholesterol as well as increased concentrations of triglycerides and apolipoprotein B (table 1) [108–111]. In addition, determination of the LDL subfraction profile in these subjects usually discloses a preponderance of small, dense LDL particles [112, 113]. HDL-cholesterol levels tend to increase in the post-transplant period and this change has been mainly attributed to the effects of corticosteroids [114]. Finally, Kerschdorfer et al. [115] clearly demonstrated a significant decrease in the concentrations of Lp(a) after renal transplantation (table 1). The magnitude of this reduction was significantly influenced by the mode of dialysis before transplantation (greater reductions were observed in CAPD patients), the apo(a) isoform size (patients with high-molecular-weight isoforms exhibited greater reductions) and the type of immunosuppressive therapy (azathioprine was the only drug that had a positive dose-related effect on the relative decreases of Lp(a) concentrations) [115]. Finally, the deterioration of renal function after transplantation (as indicated by a decreasing GFR or increasing proteinuria) significantly limited or even reversed the observed decreases in Lp(a) values [115]. There is little doubt that among the immunosuppressive drugs usually used in kidney graft recipients cyclosporine has the most detrimental effects on lipoprotein metabolism. It has been shown that cyclosporine administration significantly increases the concentrations of LDL-cholesterol and triglycerides while it reduces the serum values of HDL-cholesterol [116–118]. On the other hand tacrolimus, azathioprine and mycophenolate mofetil usually induce only minor changes in serum lipid levels. In this context, previous studies have shown that the conversion of cyclosporine to one of these
drugs is followed by a significant decrease in the levels of total and LDL-cholesterol [118–120]. In addition, the substitution of cyclosporine for tacrolimus also reduces the concentrations of triglycerides [120] while the conversion of cyclosporine to mycophenolate mofetil is followed by a further reduction in HDL-cholesterol levels [118].

It has been proposed that in addition to its potential involvement in the pathogenesis of cardiovascular disease in kidney graft recipients, dyslipidemia may also contribute to the chronic allograft dysfunction that is commonly observed in this patient population [121]. These assumptions, along with the differential impact of the various immunosuppressive medications on lipoprotein metabolism, underlie the need for individually adjusted immunosuppressive therapy and possibly necessitate the use of hypolipidemic drugs in dyslipidemic kidney graft recipients.

### Lipids in CKD Patients Receiving Epoietin Treatment

Recombinant human erythropoietin (rhEPO) represents the cornerstone of the treatment of renal anemia in patients with ESRD. However, a considerable number of studies revealed that rhEPO not only affects erythropoiesis but also may have important metabolic actions in maintenance dialysis patients [122–124]. Early studies attempting to investigate the effect of rhEPO administration on lipoprotein metabolism revealed contradictory results [125–127]. However, most of these studies had insufficient power to detect small changes in serum lipid values. In their pioneer study Pollock et al. [128] showed that the administration of rhEPO for 1 year significantly reduces the serum levels of total cholesterol and triglycerides as well as the concentrations of apolipoprotein B in maintenance HD patients. These observations were partially confirmed by a subsequent study showing that the beneficial effect of rhEPO on lipid homeostasis is confined to individuals who do not increase their energy intake during the study period [129]. In contrast, patients who increase their food intake during rhEPO administration display an important deterioration in serum lipid profile that is characterized by significant increases in the concentrations of total and LDL-cholesterol, triglycerides and apolipoprotein B [129]. On the other hand, studies with longer follow-up periods (2 years) failed to detect any significant effect of rhEPO on apolipoprotein B-containing lipoprotein metabolism and concluded that the only effect of long-term rhEPO administration is an increase in the concentrations of apolipoprotein AI [126].

The effects of rhEPO on serum lipid levels in patients with predialysis CKD were recently investigated. In these studies the administration of rhEPO alone or in combination with keto acids and a low-protein diet significantly decreased the concentrations of total and LDL-cholesterol as well as the serum values of triglycerides and apolipoprotein B [130, 131]. In addition, rhEPO also significantly increased the concentrations of HDL-cholesterol and this increase was positively correlated with that in hemoglobin levels [131]. This finding, along with the rhEPO-induced increase in HDL-associated platelet-activating factor acetylhydrolase activity that has been observed by our group [132], clearly demonstrates that the administration of rhEPO in patients with predialysis CKD improves the antiatherogenic function of HDLs in a number of different ways.

The mechanisms that underlie the rhEPO-induced changes in lipid metabolism remain ill defined. However, it is well known that rhEPO increases the exercise capacity [133], improves the insulin sensitivity [122, 134] and increases the activities of both lipoprotein and hepatic lipase [135] in individuals with ESRD. These actions, along with the increased tissue oxygenation resulting from the correction of anemia may favorably affect lipoprotein metabolism. Finally, the antioxidative and anti-inflammatory properties of erythropoietin as well as the preservation of renal function that follows its administration in individuals with CKD may also play contributory roles [131, 136].

### Drug Therapy of Dyslipidemia in CKD Patients

Interventional studies have shown that the pharmacological reduction of total and LDL-cholesterol values is followed by an impressive decrease in the risk of the development of ischemic events. Thus, based on the extremely high cardiovascular mortality that characterizes the individuals with CKD [2, 3], the Work Group for Kidney Disease Outcomes Quality Initiative (K/DOQI) published the Clinical Practice Guidelines for Managing Dyslipidemias in CKD [137] and proposed the adoption of Adult Treatment Panel (ATP) III LDL-cholesterol targets [138] for individuals with stage 5 CKD. In other words, these guidelines suggested that in individuals with ESRD an LDL-cholesterol value lower that 100 mg/dl should be achieved. However, the utilization of LDL-cholesterol as a target for preventive therapy in patients with CKD has several important limitations. It is well known that LDL-cholesterol is commonly determined by
the Friedewald calculation in specimens from fasting subjects and with triglyceride concentrations of <400 mg/dl. However, the equation is considerably inaccurate even at triglyceride concentrations of 200–400 mg/dl [139]. Thus, since uremic dyslipidemia is mainly characterized by increased concentrations of triglycerides, the use of Friedewald equation for the determination of LDL-cholesterol values in this patient population may result in important measurement errors. As a consequence, it has been proposed that a number of different equations that take into consideration the serum levels of apolipoprotein B may be more appropriate in individuals with impaired renal function [140]. An alternative approach to this problem is the calculation of non-HDL-cholesterol (total cholesterol – HDL cholesterol) values. The calculation of this parameter (which represents the sum of the concentrations of all apolipoprotein B-containing particles) overcomes the methodological limitations of LDL-cholesterol determination, does not require fasting specimens [141] and, most importantly, in addition to LDL particles takes into account the concentrations of all apolipoprotein B-containing particles such as VLDL, Lp(a), IDL and chylomicron remnants [142]. Several studies have shown that the concentrations of these particles (that are not captured by conventional LDL measurement) are elevated in patients with renal failure and may independently contribute to the determination of future cardiovascular risk [143, 144]. The National Kidney Foundation guidelines suggest non-HDL-cholesterol values of <130 mg/dl as a secondary target of therapy in individuals with triglyceride values of >200 mg/dl [137]. However, since observational studies have proved the predictive value of the non-HDL-cholesterol concentration in HD patients [145], other investigators suggest its use as a therapeutic target regardless of the serum triglyceride levels [146].

Another set of data that questions the role of cholesterol concentration as a target for preventive or therapeutically interventions in individuals with ESRD comes from studies attempting to determine the impact of plasma lipoprotein concentrations on total and cardiovascular mortality in this patient population. Indeed, although high total and LDL-cholesterol values can predict cardiovascular events in HD patients [147], the large observational studies that tested the impact of hypercholesterolemia on total and cardiovascular mortality revealed contradictory results. Thus, in contrast to what is observed in the general population, the initial studies showed an inverse relationship between cholesterol values and mortality rates in individuals with ESRD (so-called reverse epidemiology) [148, 149]. In contrast, other studies demonstrated that reverse epidemiology is, in fact, the result of the confounding effect of malnutrition and/or inflammation that are commonly observed in the advanced stages of renal failure [150, 151]. Thus, although in the absence of malnutrition/inflammation high cholesterol values are associated with higher mortality rates, in the presence of these ‘disturbances’ the association of cholesterol with mortality risk can be modified or even reversed [150, 151]. However, it must be mentioned that the aforesaid assumptions were not confirmed by the results of recent studies. Indeed, Kilpatrick et al. [152] in a cohort of 15,859 HD patients showed that the positive relationship between cholesterol values and cardiovascular death risk may be confined to certain racial subgroups such as black HD patients. These discrepancies clearly show that further studies are needed to delineate the impact of lipoprotein concentrations on total and cardiovascular risk in individuals with ESRD.

It is possible that the most important factor that limits the use of hypolipidemic drugs in individuals with CKD is the contradictory results of the studies that tried to delineate the effects of statins on total and cardiovascular mortality in this patient population. It is well known that statins are by far the most commonly prescribed hypolipidemic drugs in the general population, and numerous large, randomized, prospective studies have shown that their use is accompanied by an impressive reduction in the incidence of cardiovascular events [153]. On the other hand, data from studies conducted in individuals with CKD suggest that the effect of these drugs on cardiovascular morbidity and mortality in this patient population is significantly influenced by the severity of renal dysfunction. Thus, in several large, prospective, placebo-controlled trials of statins, post hoc analyses of subgroups with mild to moderate renal failure revealed a significant reduction in cardiovascular morbidity and mortality [154–157]. The same results were also obtained by studying prespecified subgroups of individuals with impaired renal function in the HPS [158] and ASCOT-LLA [159] studies that utilized simvastatin and atorvastatin, respectively. In addition, the recently published ALERT study revealed that although the administration of fluvastatin in renal transplant recipients did not significantly reduce the risk of the composite primary end point (cardiac death, nonfatal myocardial infarction, or coronary intervention procedure), it resulted in a significant decrease in the risk of cardiac death and nonfatal myocardial infarction [160]. It must be mentioned that the adverse event rates in these statin trials

were similar to those observed in the placebo arms. As a consequence, the use of statins as a first-line therapy for the prevention of ischemic events in dyslipidemic individuals with CKD (stages 1–3) seems to be a safe, reasonable, and evidence-based approach.

Although several observational studies showed that the administration of statins in individuals with ESRD is associated with a significant decrease in cardiovascular and all-cause mortality [161–163], these observations were not confirmed in the subsequent prospective, placebo-controlled trials. In the 4D (Die Deutsche Diabetes Dialyse) trial 1,255 diabetic subjects who had been on maintenance HD for less than 2 years were randomized to receive either placebo or 20 mg/day of atorvastatin [164]. Overall, after a mean follow-up period of 2.4 years, atorvastatin did not significantly reduce the risk of the composite primary end point (cardiovascular death, non-fatal myocardial infarction and stroke), despite a significant 42% reduction in LDL-cholesterol concentration [165]. However, this study had several methodological limitations. Thus, it must be noted that the majority of cardiovascular events in the 4D study were possibly non-ischemic in nature (mainly congestive heart failure and sudden deaths), although the ischemic origin of sudden deaths cannot be definitely excluded. In addition, another confounding factor could be that a significant proportion of individuals in the placebo arm (about 15%) also received a non-study statin. Nevertheless, similar findings were also reported in a recent small Scandinavian study that showed a significant decrease in cardiovascular end points after atorvastatin administration in patients with predialysis renal failure but no effect in individuals who were on maintenance HD [166]. Several mechanisms have been proposed for the explanation of the failure of statins to improve cardiovascular outcomes in individuals with advanced renal failure. Thus, it has been suggested that the development of atherosclerosis in this population may have a different pathophysiological basis (arterial wall calcification, inflammation, etc.), whereas other investigators emphasized that lipoproteins other than LDL (such as Lp(a), IDL, etc.) may play a significant role in the initiation and progression of coronary atherosclerosis [146, 167, 168]. Finally, it has been proposed that the beneficial effect of statins may be confounded by the presence of micro-inflammation and/or malnutrition in individuals with ESRD [169]. Whatever the cause, and while awaiting the results of ongoing statin trials [170, 171] in this patient population, we believe that the decision for the administration of statins in HD patients should be individualized.

It is well known that fibrates reduce the concentrations of triglycerides, increase the serum concentrations of HDL-cholesterol and induce a shift in the LDL subfraction distribution towards larger and more buoyant particles [172]. Thus, these drugs could represent an ideal option for the treatment of uremic dyslipidemia. However, it has been shown that the administration of fibrates (possibly with the exception of gemfibrozil) in individuals with impaired renal function is associated with an extremely high risk of muscular toxicity [173, 174]. In addition, these drugs also significantly increase serum creatinine values. Although it has been proposed that this increase does not represent a true deterioration in renal function but rather is due to increased metabolic production of creatinine, other investigators have reported cases of nonreversible renal failure after fibrate administration [173]. In addition, the impact of fibrates on cardiovascular end points in individuals with impaired renal function has not been extensively studied. Thus, although an observational study suggested that the use of fibrates in patients with renal failure does not reduce total mortality [161], a post hoc analysis of the secondary prevention VA-HIT study revealed that the administration of gemfibrozil in individuals with moderate renal failure reduced the risk of the primary end point (coronary death or nonfatal myocardial infarction) by 27% [175]. In our opinion fibrates should be used only in the subpopulation of patients with CKD who exhibit extremely elevated triglycerides values (>500 mg/dl). In these cases the risk of acute pancreatitis justifies the use of gemfibrozil as the fibrate of choice in individuals with impaired renal function [173], although previous studies have shown that its administration in CKD patients may, in some cases, be followed by muscle aches and a significant rise in serum creatine phosphokinase values [176]. The administration of ω–3 polyunsaturated fatty acids may also play a role in the management of this extremely rare condition [177].

A number of other hypolipidemic drugs that are increasingly used in the general population (such as niacin, ω–3 polyunsaturated fatty acids and ezetimibe) may also play important roles in the management of uremic dyslipidemia. However, although small studies have documented the efficiency and the tolerability of these substances in patients with chronic kidney disease, there is a lack of evidence concerning their impact on the cardiovascular risk in this patient population. Further prospective, placebo-controlled studies are needed to delineate the role of these drugs in the treatment of dyslipidemia in individuals with CKD.
Conclusions

Dyslipidemia represents an integral component of CKD. Disturbances in lipoprotein metabolism (mainly accumulation of intact or partially metabolized apolipoprotein B-containing particles as well as reduced concentrations of HDL-cholesterol) are evident even at the early stages of CKD and usually follow a downhill course that parallels the deterioration in renal function. Since several intrinsic (genetic, primary kidney disease) or exogenous (drugs, method of renal replacement) factors can influence the phenotypic expression of these alterations, the precise knowledge of the pathophysiological mechanisms that underlie their development is of paramount importance. Recently published studies indicate that dyslipidemia in these patients may actively participate in the pathogenesis of CVD as well as in the deterioration of renal function. Thus, we believe that the current evidence dictates the use of statins in patients with mild to moderate CKD. On the other hand, in subjects with established CVD as well as in those who run a high risk for acute pancreatitis due to severe hypertriglyceridemia, the administration of hypolipidemic drugs (statins and gemfibrozil, respectively) is a safe and reasonable approach. However, it should be kept in mind that further studies are needed to delineate the clinical efficacy of these interventions.

References


Dyslipidemia in CKD


Dyslipidemia in CKD


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