Alterations of Lipid Metabolism in Chronic Nephropathies: Mechanisms, Diagnosis and Treatment

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Abstract

Nephropathic subjects show an increased tendency to develop cardiovascular diseases, mainly as the consequence of several risk factors including increased oxidative stress, inflammation, physical inactivity, anemia, vascular calcification, and endothelial dysfunction. The alterations in lipid metabolism represent a relatively lesser important cause of genesis and progression of atherosclerosis. Unfortunately, in these patients the atherogenic potential of dyslipidemia may depend more on apolipoproteins than on lipid abnormalities, and may not always be recognized by measurement of plasma lipids alone. The aim of this review was therefore to analyze the main lipid alterations that can occur in nephropathic patients, as well as their causes and their effects on the cardiovascular system. The clinical evidence and recommendations for the use of lipid-regulating drugs in patients with chronic kidney disease, nephrotic syndrome, in patients undergoing hemo- and peritoneal dialysis and in transplanted patients was also reviewed. Moreover, we analyzed the link between dyslipidemia and kidney disease onset and progression and the role of statins in preventing it.

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Introduction

Cardiovascular disease (CVD) represents the main cause of death in patients with end-stage renal disease. The risk for coronaropathy is higher in patients with renal impairment than in the general population and this evidence cannot be exclusively due to the 'traditional' risk factors.

The link between dyslipidemia and increased CVD risk in patients with chronic kidney disease (CKD) has been difficult to define, mainly due to the coexistence of several cardiovascular risk factors in patients with CKD, including increased oxidative stress, inflammation, physical inactivity, anemia, vascular calcification, endothelial dysfunction, and reduced nitric oxide availability.

The atherogenic potential of dyslipidemia in kidney disease may depend more on apolipoproteins than on lipid abnormalities, and may not always be recognized by measurement of plasma lipids alone [1, 2].

This review focuses on dyslipidemias as they occur in patients with chronic nephropathy, describing their causes and their effects on the cardiovascular system. We also reviewed the clinical evidence and recommendations for the use of lipid-regulating drugs in patients with CKD, nephrotic syndrome (NS), those undergoing hemo- and peritoneal dialysis, and in transplanted patients.
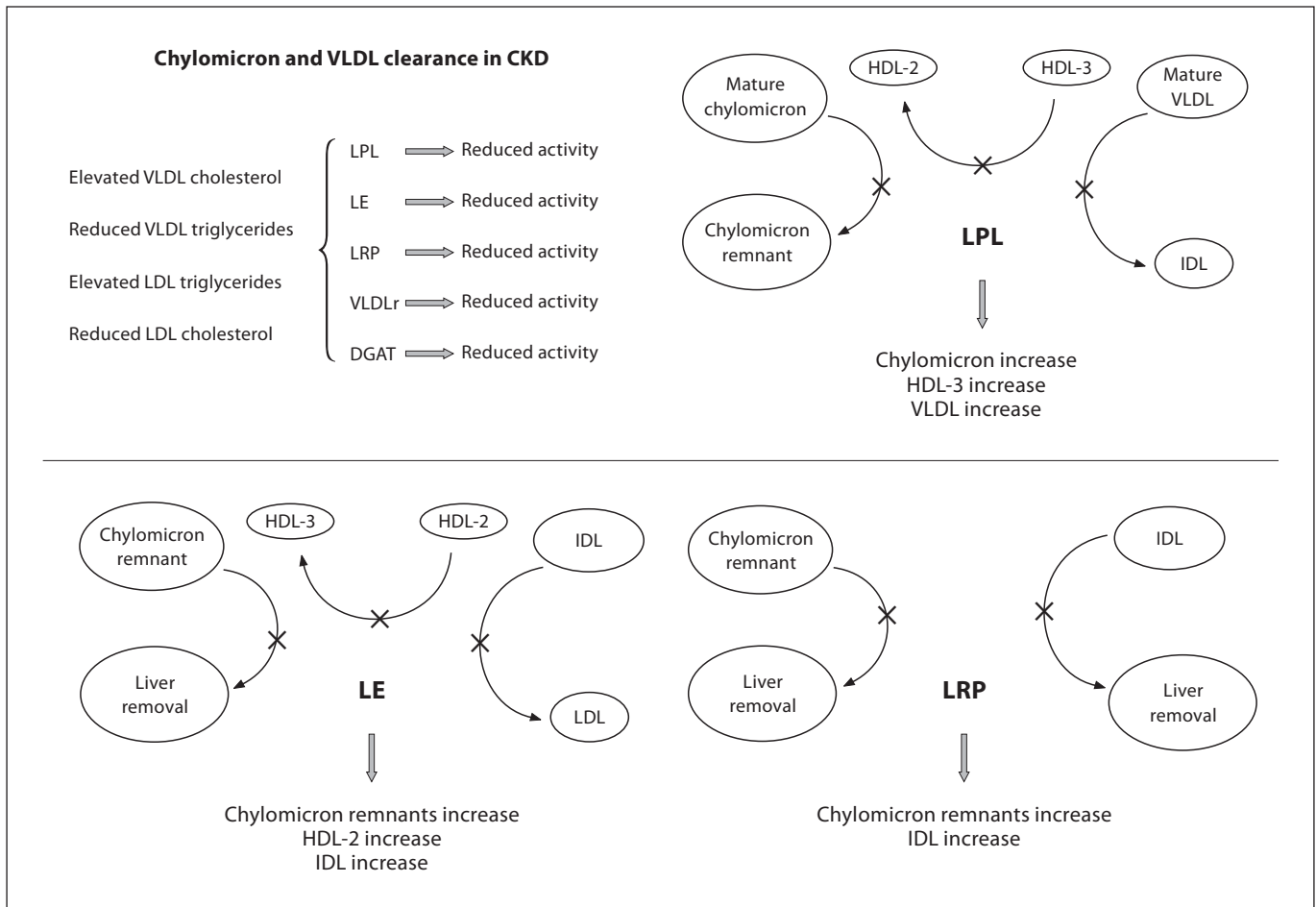
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Fig. 1. Hypertriglyceridaemia in CKD patients: impaired clearance of chylomicrons and VLDL. The impaired clearance of the major lipoprotein involved in the metabolism of triglycerides, which characterizes chronic renal failure, is due to a reduced function of enzymes involved in their catabolism. CKD = Chronic kidney disease; VLDL = very-low-density lipoprotein; LDL = low-density lipoprotein; LPL = lipoprotein lipase; LE = hepatic lipase; LRP = LDL receptor protein; VLDLr = VLDL receptor; DGAT = acyl-CoA diaglycerol acyltransferase; HDL = high-density lipoprotein; IDL = intermediate density lipoprotein.

Moreover, we analyzed the link between dyslipidemia, kidney disease onset and progression, and the role of statins in preventing it.

Chronic Kidney Disease

CKD is associated with an early atherosclerotic process and with an increased cardiovascular morbidity and mortality [3].

Although the nature of dyslipidemia can be significantly influenced by several intrinsic (nephrotic proteinuria, concomitant diseases such as diabetes mellitus, hereditar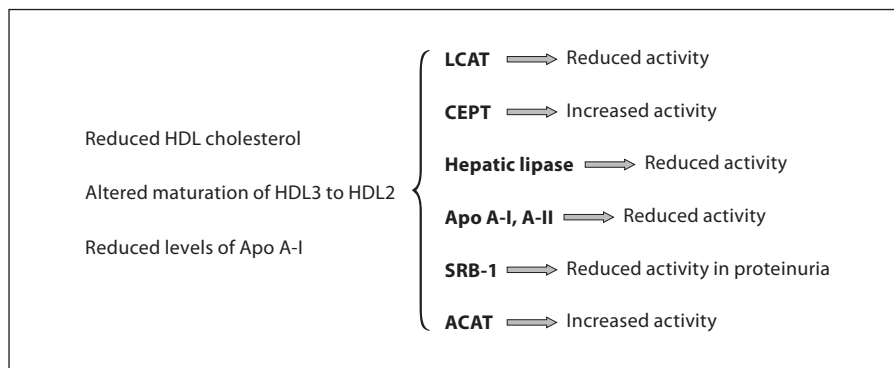y disorders of lipid metabolism) or exogenous (erythropoietin, steroids, calcineurin inhibitors, etc.) factors, the most common quantitative lipid abnormalities in predialysis CKD patients are hypertriglyceridemia, reduced high-density lipoprotein (HDL) cholesterol levels as well as increased concentrations of lipoprotein(a) (Lp(a)) [4].

Total and LDL cholesterol levels are usually within normal limits or slightly reduced in these patients [5].

VLDL and Triglyceride Levels
Hypertriglyceridemia is partially due to a downregulation of lipoprotein lipase (LPL), hepatic lipase, very-low-density lipoprotein (VLDL) and low-density lipoprotein receptor (LDL-r) expression (fig. 1).

Fig. 2. Impaired clearance of LDL and HDL in CKD. CKD = Chronic kidney disease; LDL = low-density lipoprotein; HDL = high-density lipoprotein; LCAT = lecithin-cholesterol acyltransferase; CEPT = cholesterol ester transfer protein; Apo = apolipoprotein; SRB-1 = scavenger receptor B1; ACAT = acyl-coenzyme A:cholesterol acyltransferase.

Reduced HDL cholesterol

Altered maturation of HDL3 to HDL2

Reduced levels of Apo A-I

- **LCAT** ⟹ Reduced activity
- **CEPT** ⟹ Increased activity
- **Hepatic lipase** ⟹ Reduced activity
- **Apo A-I, A-II** ⟹ Reduced activity
- **SRB-1** ⟹ Reduced activity in proteinuria
- **ACAT** ⟹ Increased activity

The increased plasma triglyceride levels can also be explained by significant increases in plasma levels of ApoC-III which is a potent inhibitor of LPL and is responsible for the degradation of triglyceride-rich particles.

Experimental studies revealed that the accumulation of triglyceride-rich lipoproteins such as VLDL, chylomicrons and their remnants in individuals with CKD is mainly due to their decreased catabolism [6].

In fact the downregulation of several genes, along with the changes in the composition of lipoprotein particles and the direct inhibitory effect of various uremic 'toxins' on the enzymes involved in lipid metabolism, represents the most important pathophysiological mechanisms underlying the development of hypertriglyceridemia in renal failure [7].

High-Density Lipoprotein

Reductions in plasma concentrations of apolipoprotein (ApoA) I and II, which are mandatory components of the HDL particle, are thought to play a large role in determining the low-HDL cholesterol levels. Patients with CKD have been shown to have reduced genetic expression of these apoproteins in the sites of HDL production in the liver [8].

Another factor contributing to low HDL levels is the profound inflammatory state of these patients. Chronic inflammation results in decreased albumin levels. Albumin is a carrier of free cholesterol from the peripheral tissues to HDL, and a reduction in albumin may contribute to reduce HDL levels [4].

The diminished activity of lecithin-cholesterol acyltransferase (which is the enzyme responsible for the esterification of free cholesterol in HDL particles) as well as increased activity of cholesteryl ester transfer protein (which facilitates the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins) reduce the HDL cholesterol serum concentration [9, 10] (fig. 2).

Low-Density Lipoprotein

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 are characterized by a predominance of small, dense LDL particles. These particles are more atherogenic than the large ones and can substantially contribute to the pathogenesis of atherosclerotic vascular disease [11].

Lipoprotein(a)

Lp(a) is similar in structure to LDL but is characterized by the presence of an additional protein called apolipoprotein(a), which is linked by a single disulfide bond to ApoB.

Numerous studies in the general population have demonstrated that Lp(a) represents a risk factor for CVD [12].

In kidney disease, plasma Lp(a) levels are significantly influenced by the glomerular filtration rate (GFR). In patients with large apo(a) isoforms, but not in those with small apo(a) isoforms, plasma Lp(a) levels begin to increase already in the earliest stages of renal impairment before GFR starts to decrease [13].

Then Lp(a) levels are elevated in CKD secondary to loss of functional renal tissue.

Therapeutic Measures

If therapeutic lifestyle changes (TLCs) are not sufficient to reduce triglycerides to <500 mg/dl, then treatment with a fibrate or nicotinic acid should be considered [14].

Studies from the general population suggest that fibrates and nicotinic acid lower triglycerides by 20–50% [15].

Fig. 3. Main pathogenetic mechanisms responsible of hyperlipidemia in nephrotic syndrome. The ability of the liver to capture circulating LDL is reduced because of low expression of the LDL receptor, due to its loss in the urine. This implies a low concentration of intrahepatic free cholesterol that determines the activation of compensatory pathways. An increased activity of HMG-CoA reductase and ACAT leads to an increased endogenous synthesis of cholesterol, while a reduced activity of the enzyme 7α-hydroxylase results in lower use of cholesterol in the bile synthesis. The final result is an increased hepatic production of cholesterol that is poured into the circulation causing hypercholesterolemia. HMG-CoA reductase = 3-Hydroxy-3-methylglutaryl CoA reductase; ACAT = acyl-coenzyme A:cholesterol acyltransferase; LDL = low-density lipoprotein.
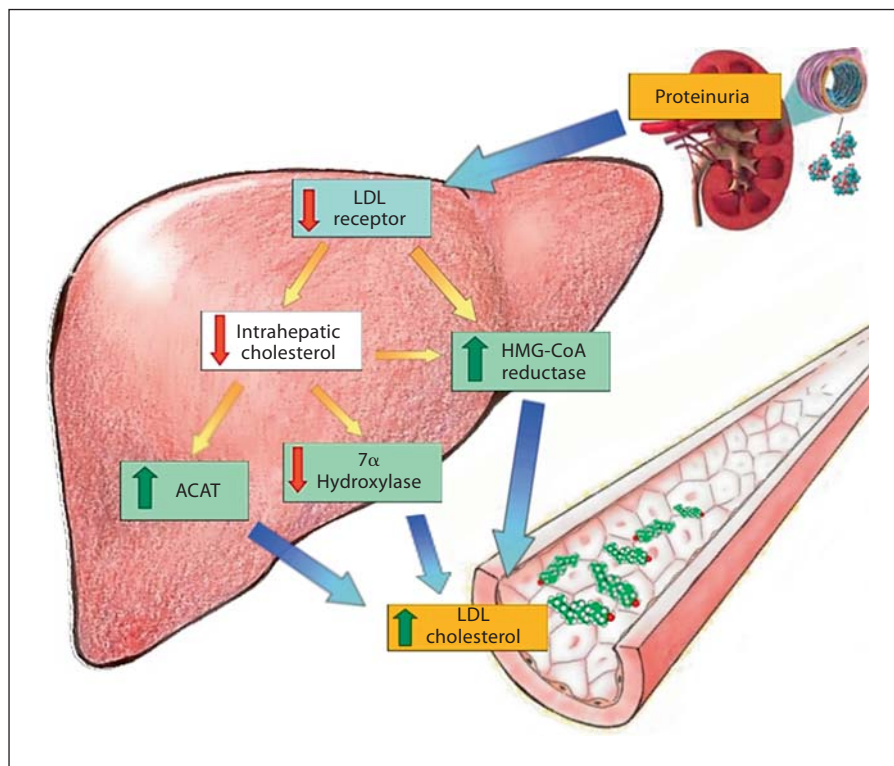
In any case, the benefits of drug therapy for hypertriglyceridemia should be weighed against the risks, and the risk of complications (particularly myositis and rhabdomyolysis) is increased in CKD.

In the VA-HIT study [16] that analyzed patients with established coronary heart disease, gemfibrozil increased HDL cholesterol levels by 5% and lowered triglyceride levels by 20% with no change in LDL cholesterol levels, and there was a 32% risk reduction in cardiac events.

The reduction in LDL that can be achieved with TLCs is generally modest. Therefore, TLCs alone are usually insufficient to reduce the LDL to the goal of <100 mg/dl. In patients who cannot reduce LDL to <100 mg/dl by diet, a statin should be added, provided that there is no evidence of acute or chronic liver disease. Diet should be continued as an adjunct to the statin [14].

Nephrotic Syndrome

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 [17].

This pattern of abnormalities is due to several pathogenetic mechanisms. First, urinary protein loss stimulates an increased LDL synthesis. It is likely that proteinuria with the resultant hypoalbuminemia leads to an upregulation of 3-hydroxy-3-methylglutaryl CoA reductase [18].

This is due to a reduction in intra-hepatic free cholesterol because of a lower expression of the LDL-r. In fact recently published studies indicate that patients with NS exhibit an acquired LDL-r deficiency [19].

Moreover, these alterations lead to an increased intrahepatic activity of acyl-CoA cholesterol acyltransferase (ACAT), of the above-mentioned 3-hydroxy-3-methylglutaryl CoA reductase and to a downregulation of cholesterol 7α-hydroxylase (an enzyme that catalyzes the limiting reaction of cholesterol catabolism which starts bile acid biosynthesis). Finally, this intrahepatic compensative mechanism determines the increased circulating LDL level typical of NS (fig. 3).

Conversely, low HDL with a poor maturation of HDL-3 to cholesterol-rich HDL-2 is due to acquired lecithin-cholesterol acyltransferase deficiency secondary to abnormal urinary losses of this enzyme [20].

Impaired clearance of chylomicrons and VLDL has emerged as the dominant factor for the increased serum triglyceride concentration. Furthermore, the status of hypertriglyceridemia arises from increased hepatic VLDL synthesis driven by upregulation of hepatic acyl-CoA diaglycerol acyltransferase [21].

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 as well as to the progression of renal failure [22].

Among the renal populations, proteinuric patients are at particularly high risk, as apparent from the observation of an almost 6-fold increased incidence of myocardial infarction in such patients [23].

Proteinuria-associated lipid abnormalities play a main role in the high cardiovascular risk in proteinuric patients, and thus provide an important treatment target based on statins administration.

In opposition, despite the above lipoprotein changes, Lechner et al. [24] have not shown a consistent relationship between NS, in the absence of uremia, and an increased risk of CVD.

Therapeutic Measures

In patients with proteinuria, a mild protective effect by statin treatment is suggested by the meta-analysis of Fried et al. [25] who reported on 13 randomized trials with small numbers of patients who were treated for short periods of time.

A study conducted on 43 patients with idiopathic NS has shown that the addition of fluvastatin (20 mg/day) to the basic therapy significantly reduced cholesterolemia (about 40%), proteinuria (60%) and increased serum levels of albumin (60%) [26].

Results similar to those of Gheith et al. [26] were obtained by Valdivesio et al. [27] after administration of atorvastatin (10 mg/day) in 10 dyslipidemic patients with hypoalbuminemia and proteinuria >3.5 g/24 h.

Rayner et al. [28] showed that, in patients with NS, alone the use of a diet low in lipids led to a minimal reduction in plasma cholesterol levels associated with little change in the urinary excretion of protein and normalization of serum albumin levels in the absence of treatment pharmacology.

Experience to date suggests that statins offer the most effective therapy and are relatively safe, at least in short-term studies. The benefits of treatment remain unproven but may include a reduction in cardiovascular risk and preservation of residual renal function.

Lipids and Progression of CKD

Numerous animal studies have demonstrated that lipoprotein abnormalities appear to cause primary renal injury and can contribute to the progression of established renal disease regardless of etiology [29].

Hyperlipidemia can potentially accelerate progression of renal disease by several mechanisms. Reabsorption of fatty acids, phospholipids, and cholesterol contained in the filtered proteins (albumin and lipoproteins) by tubular epithelial cells can stimulate tubulointerstitial inflammation, foam cell formation, and tissue injury [30].

The accumulation of lipoproteins in glomerular mesangium can promote matrix production and glomerulosclerosis with the native and oxidized lipoproteins, particularly LDL, which stimulate production of matrix proteins by cultured mesangial cells and promote generation of proinflammatory cytokines, which can lead to recruitment and activation of circulating and resident macrophages [31].

A secondary analysis of the Modification of Diet in Renal Disease (MDRD) study demonstrated that low HDL cholesterol and triglyceride-rich lipoproteins were correlated with an unfavorable effect on the progression of renal disease [32]. Although experimental studies tend to support the hypothesis of detrimental impact of dyslipidemia on the progression of CKD, results of clinical studies, however, have been inconsistent as they have shown detrimental effects of high concentrations of triglycerides or low levels of HDL cholesterol [32], triglyceride-rich lipoproteins [33], apoB [34], and total cholesterol [35].

The existence of a link between dyslipidemia and oxidative stress in the pathogenesis of renal damage was shown in uninephrectomized rats, in which hyperlipidemia increased glomerular and tubulointerstitial infiltration and aggravated glomerulosclerosis [36].

Statins are highly effective in inhibiting progression of renal damage in numerous experimental models, mainly through their pleiotropic effects. Possible pathways for the protective action of statins, other than any hypocholesterolemic effect, are cellular apoptosis/proliferation balance, inflammatory cytokine production, and signal transduction regulation [37, 38].

Apoptosis also plays an important role in the kidney, preventing glomerular hypercellularity and scarring following experimental mesangial proliferating nephritis, and it has been suggested that it is a critical mechanism governing glomerular remodeling and the return to normal cellularity after inflammatory injury [39].

In an experimental model, Buemi et al. [40] observed a significant increase in apoptosis in cultures of human myocytes containing sera from fluvastatin-treated patients. Thus, a statin-dependent increase in apoptosis may explain the beneficial effect of these drugs in some forms of human glomerulonephritis [41]. In vivo studies suggested a variety of mechanisms whereby statins may have an impact on renal endothelial function [42, 43].

The proposed renal-protective mechanism is based on in vitro observations that statins impede the normal reabsorption of albumin in the proximal tubule. Mevalonate, a metabolite in the cholesterol synthetic pathway, is reduced in patients on statins and it is necessary for the normal reabsorption of albumin in the proximal renal tubule [44].

In summary, although statins may increase tubular proteinuria initially, they may reduce inflammation, slow fibrosis, and result in less proteinuria in the long-term [45]. In contrast, meta-analyses of participants with CVD in randomized controlled studies with statins, who had impaired renal function and/or proteinuria, show a modest though statistically significant reduction in the loss of eGFR with statins (except in patients with diabetic nephropathy or glomerulonephritis) as well as a modest significant reduction in proteinuria or albuminuria. However, the data on a reduction in proteinuria are currently not sufficient or compelling enough to justify recommendations to use statins with the rationale of attenuating the rate of loss of renal function [46].

Hemodialysis

Several observational studies have documented a 'strange' association between lower total cholesterol and mortality which was higher in patients with end-stage renal disease. This phenomenon represents a seemingly paradoxical reversal of the well-established association of higher lipid levels with mortality in the general population [47].

The well-known association of high cholesterol levels with increased mortality in the general population was not observed in dialysis patients without malnutrition or inflammation. If patients suffered from these conditions, a high cholesterol concentration was associated with a better outcome which might be explained by the cholesterol-lowering effect of systemic inflammation and malnutrition [48].

A similar interaction was described by Iseki et al. [49], who showed higher mortality with higher total cholesterol only in dialysis patients with serum albumin levels of >4.5 g/dl. Besides this interaction with malnutrition/inflammation, many other factors might contribute to the reverse epidemiologic findings in dialysis patients [50].

In patients who are on hemodialysis (HD), LDL cholesterol levels are generally normal, but triglyceride levels are high and HDL cholesterol levels are low. However, the Kidney Disease Outcomes Quality Initiative (K/DOQI) guideline review on dyslipidemias in patients with CKD found that 55.7% of patients who are on HD had LDL cholesterol levels of >100 mg/dl [51].

The lipid and apolipoprotein profile that characterizes predialytic renal failure remains essentially unchanged during long-term HD, with qualitative and quantitative alterations [52]. Several mechanisms might contribute to the impaired metabolism of LDL and IDL in uremic patients. However, the dialysis technique may result in additional defects in lipid homeostasis (such as increased catabolic rate of Apo A-I) that reinforce the clinical expression of these mechanisms [53].

It has been shown, for example, 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 Apo A-I and HDL cholesterol levels [54].

Another factor that can potentially affect lipoprotein metabolism in HD patients is the repeated use of heparin as an anticoagulant. Heparin releases LPL from the endothelial surface and thus its chronic use may result in LPL depletion and defective catabolism of triglyceride-rich lipoproteins. Näsström et al. [55] have demonstrated that the LPL activity rose rapidly when dalteparin was administered during dialysis treatment interfering with the LPL system and involving a depletion in LPL stores.

Therapeutic Measures
The work group for K/DOQI published the Clinical Practice Guidelines for Managing Dyslipidemias in CKD and proposed the adoption of Adult Treatment Panel III LDL-cholesterol targets for individuals with stage 5 CKD [15, 56].

A Cochrane review, published in 2004, concluded that statins decreased serum cholesterol in dialysis patients as effectively as in the general population, but no conclusions were made about the effects of statins on cardiovascular mortality [57].

For patients on HD with elevated LDL, choosing statins with limited renal excretion, such as atorvastatin or fluvastatin, may be more important. Atorvastatin and

its metabolites are excreted mostly in bile, and urinary excretion is low, so dosages do not have to be modified as GFR levels fall. Fluvastatin is almost completely metabolized by the liver with <5% excreted in the urine. Simvastatin is almost completely metabolized by the liver [58]. 90% of rosuvastatin is excreted unchanged in the feces and only 10% in urine [59]. Ezetimibe is being used with increasing frequency in many patients to augment the LDL cholesterol-lowering effects of statins and no dosage adjustment of ezetimibe is needed in patients with renal insufficiency [60]. In mixed dyslipidemia, ω–3 fatty acids may play a more prominent role because the National Lipid Association recommends avoiding fibrate use in patients with a GFR of <15 ml/min/1.73 m^2 [61].

Several trials have been conducted, and some are in progress, to define the role of statins in the therapy of patients undergoing HD. The 4D Study (Die Deutsche Diabetes Dialyse Studie) demonstrated that there were no differences between the treated and untreated groups in the primary composite endpoint of cardiac death, stroke, or nonfatal myocardial infarction, and not at all in the atorvastatin group; there was a twofold increase in fatal strokes [62].

There are different explanations for the negative results of the 4D study: many cardiovascular events in dialysis patients were due to arrhythmia or non-ischemic cardiomyopathy, which might not be related to atherosclerosis, and also the atherosclerosis was so advanced that these patients were beyond obtaining benefit from drug therapy.

It is likely that in patients on dialysis the progression mechanisms of coronary heart disease differ from those operating in the general population. Fathi et al. [63] studied the effect of aggressive lowering of LDL cholesterol with atorvastatin comparing patients with primary coronary artery disease without renal dysfunction against patients with advanced renal failure. In non-renal patients the maximum intima/media thickness of the carotid artery decreased significantly by this intervention while it remained unchanged in patients with CKD [63].

Anatomical studies point in the same direction. Schwarz et al. [64] compared the coronary arteries of patients with coronary heart disease who either had no kidney disease or advanced CKD, and stressed that the coronary arteries of CKD patients had a dramatically 5-fold higher prevalence of coronary calcification.

Similar conclusions to those obtained by the 4D trial emerged from the AURORA trial which was a randomized placebo-controlled trial with 2,700 HD patients using rosuvastatin 10 mg/day [65].

The Study of Heart and Renal Protection (SHARP) is a large trial using statins in HD patients [66]. The 3,000 HD patients are randomized to simvastatin 20 mg/day or simvastatin 20 mg/day plus ezetimibe [66].

Peritoneal Dialysis

Patients who are on peritoneal dialysis (PD) tend to have higher LDL cholesterol levels and the K/DOQI guideline review found that 73.2% of patients had LDL cholesterol levels of >100 mg/dl.

Hypertriglyceridemia is the primary lipid abnormality in PD patients [67]. Coexistent insulin resistance and glucose loading from the peritoneal dialysate increase free fatty acid availability and de novo lipogenesis, key triggers to VLDL secretion, and the increased clearance of apolipoproteins across the peritoneal membrane during PD can also trigger profound dyslipidemia [68].

Babazono et al. [69] have underlined how a 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.

There are also mildly elevated LDL cholesterol levels with a marked predominance of highly atherogenic small dense LDL particles in these patients. Furthermore, HDL cholesterol levels are low [57].

PD patients have a more atherogenic lipid profile than HD subjects; they have lower HDL cholesterol, increased LDL/HDL ratio, and higher Lp(a) levels due to the large amounts of protein losses in the dialysate fluid.

Despite this, the cardiovascular mortality rates do not differ between HD and PD patients; the reason for this is the fact that PD individuals have fewer hypotensive episodes and much fewer arrhythmias compared with HD individuals [70].

Therapeutic Measures
Statins also exert several other non-lipid properties that may contribute to cardiac risk reduction in PD patients. These include the improvement in endothelial function, the inhibition of smooth muscle cell proliferation, and the reduction in neointima formation, as well as the reduction in platelet reactivity and aggregation [71].

Another beneficial action of statins on PD patients includes the stimulation of peritoneal fibrinolytic activity to prevent peritoneal fibrin deposition and adhesion development in these patients [72].

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Table 1. Alterations of both lipids and lipoprotein metabolism and respective therapies

Nephropathies	Lipids	Lipoproteins		Therapeutic measures	
Chronic kidney disease	Hypertriglyceridemia Total cholesterol levels are normal or slightly reduced	LDL HDL VLDL	↔ or ↓ ↓ ↑	1 2 3	Therapeutic lifestyle changes Statin to reduce LDL to the goal of <100 mg/dl Fibrates, nicotinic acid and ezetimibe in addition to statin
Nephrotic syndrome	Hypercholesterolemia Hypertriglyceridemia	LDL HDL VLDL	↑ ↓ ↔ or ↑	1 2	Statin to reduce LDL to the goal of <100 mg/dl Fibrates, nicotinic acid and ezetimibe in addition to statin
Hemodialysis	Hypertriglyceridemia Total cholesterol levels are normal, slightly reduced or slightly increased	LDL HDL VLDL	↔ or ↓ ↓ ↑	1 2 3 4	Statins with limited renal excretion Ezetimibe in addition to statin ω–3 fatty acids in mixed dyslipidemia Avoiding fibrate use in uremic patients
Peritoneal dialysis	Hypercholesterolemia Hypertriglyceridemia	LDL HDL VLDL	↑ ↓ ↑	1	Statin to reduce LDL to the goal of <100 mg/dl
Kidney transplantation	Hypercholesterolemia Hypertriglyceridemia	LDL HDL VLDL	↑ ↔ or ↑ ↑	1 2	Statin to reduce LDL to the goal of <100 mg/dl Ezetimibe in addition to statin

LDL = Low-density lipoprotein; HDL = high-density lipoprotein; VLDL = very-low-density lipoprotein; ↓ = decrease; ↑ = increase; ↔ = no change.

Kidney Transplantation

The prevalence of dyslipidemias in kidney transplant recipients is very high. Particularly common are increases in total cholesterol and LDL. Triglycerides are often increased, but HDL is usually normal.

Immunosuppressive agents, e.g., prednisone, cyclosporine (Cya), and sirolimus play a major role in posttransplant dyslipoproteinemia, and they are potential remediable causes of dyslipidemias in patients with CKD and after kidney transplantation.

Glucocorticosteroids cause increases in insulin resistance and hepatic glucose output, causing hyperglycemia to worsen, and an increase in triglycerides and variable changes in HDL cholesterol levels [73].

While azathioprine does not influence glucidic and lipid metabolism, Cya has an effect on lipids, causing an increase in triglycerides and Lp(a) levels.

Artz et al. [74] have shown that the conversion of Cya to tacrolimus, azathioprine or mycophenolate mofetil is followed by a significant decrease in the levels of total and LDL cholesterol and concentrations of triglycerides.

Tacrolimus is similar to Cya concerning its toxicity, while it exerts less effects on lipid metabolism. The main collateral effects of rapamycin assumption are hypertriglyceridemia and hypercholesterolemia associated with thrombocytopenia. It is not clear how soon these agents exert their effects on lipoprotein metabolism.

Therapeutic Measures
In 2004, the National Kidney Foundation introduced guidelines on the assessment and management of dyslipidemias in kidney transplant patients, recommending that kidney transplantation be treated as a 'coronary heart disease risk equivalent' and that LDL should be lowered to <100 mg/dl in these patients [75].

The present guidelines are consistent with those of the American Society of Transplantation, which recommend that lipid profile should be measured during the first 6 months after transplantation, 1 year after transplantation, and annually thereafter. The American Society of Transplantation guidelines also suggest that changes in immunosuppressive therapy, graft function, or CVD risk warrant additional testing [76].

However, the evidence supporting these guidelines came from only one randomized trial in the field, the Assessment of LEscol in Renal Transplantation trial (ALERT trial), and its extension study [77, 78]. ALERT is the first

and only large-scale cardiovascular outcome trial to be conducted in transplant recipients and compared fluvastatin with placebo in 2,102 renal transplant recipients followed for 5–6 years [77].

Cosio et al. [79] reported that lipid-lowering therapy with a statin was associated with a 24% reduction in all-cause mortality in 1,574 patients after renal transplantation.

Wiesbauer et al. [80] studied the association of statin use in a cohort of 2,041 first-time recipients of renal allografts between 1990 and 2003, demonstrating that statin use was independently associated with reduced all-cause mortality in renal transplant recipients and with prolonged patient survival, while no difference in graft survival was detected.

Ezetimibe has also shown efficacy in the therapy of hypercholesterolemia in kidney transplant patients in several studies [81, 82]. López et al. [83] undertook a prospective study of 24 kidney transplant recipients with dyslipidemia who started treatment with 10 mg ezetimibe; statins were being taken by 96% of these patients. None of the 24 patients who were receiving statins managed to lower their levels of total cholesterol or LDL cholesterol to the recommended levels, but the addition of ezetimibe enabled these objectives to be attained [83].

Conclusions

The pathogenesis of abnormal lipid metabolism complicating CKD is complex and the consequences of the resultant dyslipidemia are not properly understood and optimal management remains to be established (table 1).

The primary beneficial effect of statins is the reduction in LDL cholesterol levels. There is a growing literature to suggest that statins may also have beneficial cholesterol-independent effects on endothelial function, inflammation, and perhaps other aspects of vascular function.

Potential indications for statins in patients with renal disease might be to assist in the reduction of proteinuria or to reduce the rate of loss of glomerular filtration (progression) apart from the goal of reducing cardiovascular events.

Currently there is no evidence to support treating HD patients, indeed the lack of cardiovascular benefit with statins in both the AURORA and the 4D suggests that CVD in HD patients is different compared with that in the non-renal population.

There is a need for further research and analysis of data and to explore new approaches and treatment strategies for reducing the high risk of CVD in HD patients.

However, in the future, the results of the ongoing trials, like the SHARP trial, will hopefully put an end to current uncertainties and place recommendations on statin use on more solid footing, for renal patients with CKD in general and HD patients more specifically.

Because statins are relatively safe and the evidence for lowering cholesterol to reduce CVDs is so overwhelmingly positive in non-HD patients, it is reasonable to continue treating these patients until future trials are completed.

Whatever the cause, we believe that the decision for the administration of statins in HD patients should be individualized.

A number of other hypolipidemic drugs that are increasingly being 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.

Recent evidence suggests that statin therapy may also have a renoprotective effect. However, large studies are needed and, in part are already ongoing, to confirm these additional beneficial effects.

As concerns transplant patients, there is a need for individually adjusted immunosuppressive therapy which possibly necessitates the use of hypolipidemic drugs in dyslipidemic kidney graft recipients.

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