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Cardiol Clin 23 (2005) 363–372

CARDIOLOGY
CLINICS

Kidney Disease and Cardiovascular Disease: Implications of Dyslipidemia

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Chronic kidney disease causes significant burdens to patients and health care systems worldwide. The incidence and prevalence of chronic kidney disease and end-stage renal disease (ESRD) are high and are increasing at impressive rates. The National Health and Nutrition Examination Survey III (1989–1994) reported that 7.6 million persons (or 4.3% of the population) in the United States had moderately decreased glomerular filtration rate (30–59 mL/min/1.73 m^2) (Table 1). Furthermore, between 1998 and 2010, the incidence of kidney failure in the United States is expected to double, from 320,000 to 650,000 cases [1].

Chronic kidney disease and ESRD are often associated with diabetes, hypertension, and dyslipidemia. The leading cause of ESRD in the United States is diabetes, which was associated with 40% of new cases of ESRD between 1994 and 1999 [2]. Diabetes is associated with increased risks for renal disease and cardiovascular disease and is often associated with dyslipidemia. The worldwide prevalence of type 2 diabetes has been increasing in recent years; the increase is thought to be related to obesity from increasing caloric intake and reduced physical activity. The number of patients requiring dialysis or transplantation is expected to increase as the number of patients with type 2 diabetes continues to grow and as patients with hypertension live longer.

Cardiovascular disease (coronary heart disease, cerebrovascular disease, peripheral vascular disease, and disorders of cardiovascular perfusion [heart failure and left ventricular hypertrophy]) is common in patients with kidney disease, with and without concurrent diabetes, and carries high risks for morbidity and mortality in these patients. The risks of coronary heart disease and death from myocardial infarction are increased in patients with microalbuminuria or proteinuria evidence of kidney disease [3]. Atherosclerosis is common in patients with kidney disease [4], and these patients also have a high prevalence of cardiomyopathy [5]. Mortality resulting from cardiovascular disease is 10 to 30 times more common in patients undergoing dialysis than in the general population [6]. More than half of the deaths of patients with ESRD are from cardiovascular causes [7]. Because of their high mortality from cardiovascular disease, many patients with chronic renal disease may not survive long enough to develop ESRD.

The risk factors for cardiovascular disease in patients with chronic kidney disease parallel those in the general population (eg, age, diabetes, hypertension [especially systolic], left ventricular hypertrophy, and dyslipidemia) but may be different in their level of impact and duration in patients with kidney disease [8]. Given that they occur early in the progression of kidney disease (as was shown, for example, by Culleton [9], the Hypertension Detection and Follow-up Program [10], and the Hypertension Optimal Treatment Study [11]), it is important to treat them as early and effectively as possible to slow the development of irreversible cardiac and renal changes [12].

Urinary protein excretion is an important additional risk factor for cardiovascular disease in kidney disease and is also an important method for measuring the severity and progression of

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doi:10.1016/j.ccl.2005.03.004

Table 1
Stages of chronic kidney disease

Stage	Description	GFR mL/min/1.73 m^2	Prevalence[d]	
			N (1000)	%
1[a,b]	Kidney damage with normal or increased GFR	$\geq$90	5900	3.3
2[a,b]	Kidney damage with mildly decreased GFR	60–89	5300	3.0
3[a]	Moderately decreased GFR	30–59	7600	4.3
4[a]	Severely decreased GFR	15–29	400	0.2
5[c]	Kidney failure	<15 or dialysis	300	0.1

Abbreviation: GFR, glomerular filtration rate.

[a] Data for stages 1–4 from National Health and Nutrition Examination Survey III (1988–1994). Population of 177 million aged 20 years or more.

[b] For stages 1 and 2, kidney damage was assessed by spot albumin/creatinine ratio greater than 17 mg/g (men) or 15 mg/g (women) on two measurements.

[c] Data for stage 5 include approximately 230,000 patients treated by dialysis and assumes 70,000 additional patients not receiving dialysis. Percentages total more than 100% because the National Health and Nutrition Examination Survey III may not have included patients receiving dialysis. GFR estimated from serum creatinine using MDRD study equation based on age, gender, race, and calibration for serum creatinine.

[d] For stages 1–4 (*Data from* US Renal Data System. USRDS 1998 annual data report. Bethesda, National Institutes of Health National Institute of Diabetes; 1998.)

From National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 Suppl 1):S1–266; with permission from the National Kidney Foundation.

kidney disease. Proteinuria is often assessed with untimed spot urine sample collection [2]. Microalbuminuria is diagnosed when urinary albumin excretion is 30 to 300 mg/24 hours or more than 3 mg/dL (dipstick). Microalbuminuria and overt proteinuria are considered to be markers of glomerular and endothelial damage and are risk predictors for cardiovascular morbidity and mortality in patients with essential hypertension, type 1 and type 2 diabetes, diabetic or nondiabetic renal disease, and in the general population [13–30].

Dyslipidemia is present in up to 60% of patients with chronic kidney disease or undergoing dialysis [31] and in 60% of patients who have had kidney transplantation [32]. This article reviews the nature of dyslipidemia in the context of chronic kidney disease; diabetes, lipids, and kidney disease; renal failure and lipids; possible mechanisms for the interaction between kidney disease and dyslipidemia; and treatment interventions for patients with kidney disease and dyslipidemia.

The nature of dyslipidemia in the context of chronic kidney disease

Dyslipidemia has been shown to be associated with cardiovascular disease in patients with and without diabetes and frequently accompanies diabetic nephropathy. Abnormal lipid levels are thought to play a role in acceleration of atherosclerotic micro- and macrovascular disease.

Patients with normal renal function and common types of hyperlipidemia generally do not develop renal insufficiency, indicating that the normal glomerulus has mechanisms to prevent accumulation of lipoproteins. A pre-existing renal disorder with mesangial dysfunction seems to be a prerequisite for lipoprotein accumulation in the glomeruli [33].

The roles that lipids may play in development and progression of renal disease have been studied since 1860 [34] and have been investigated in several animal models [35]. Kamanna et al [34] have summarized the study of the cell biology and histopathology of kidney disease and hyperlipidemia. Hyperlipidemia is common in patients with renal disease. The abnormalities in lipids and lipoproteins in renal disease have varied in experimental reports, however, and have often included hypertriglyceridemia, hypercholesterolemia, and increased low-density lipoprotein cholesterol (LDL) with low, normal, or high levels of high-density lipoprotein (HDL) cholesterol [36]. Increased triglyceride-rich very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) have been reported in chronic kidney disease [34]. Some [37–39], but not all [40], studies in patients with proteinuria have shown an association between total cholesterol and deterioration of renal function after controlling for proteinuria in multivariate models. Observational [37,41–47] and prospective studies [48] have shown that low HDL was one of the determinants of rate of decline of renal function. The community-based Atherosclerosis Risk in Communities study showed a relationship between glomerular filtration rate (GFR) and atherosclerotic cardiovascular disease [49]. The relative risk for an increase of 0.3 mg/dL in serum creatinine over 3 years in patients with serum creatinine levels higher than 1.6 mg/dL (men) or 1.4 mg/dL (women) was 1.40 for triglycerides, 1.18 for total cholesterol, 1.16 for lipoprotein (a), 1.13 for LDL, and 0.78 for HDL [49]. In patients with microalbuminuria and essential hypertension, which commonly accompany chronic renal disease, high levels of LDL, triglycerides, apolipoprotein B (apoB), lipoprotein (a), and low HDL may be present [50].

Lipoproteins are characterized by density properties or apolipoprotein composition. Studies that include measurements of apolipoprotein levels have shown that early- and later-stage kidney disease may not be associated with a classic atherogenic hyperlipidemia profile but may involve characteristic changes in lipoprotein metabolism, plasma apolipoprotein profile, and individual apoB-containing proteins [51–53]. apoB-containing lipoproteins are found in VLDL, IDL, and LDL. There are several types of apoB-containing lipoproteins, which are characterized by specific composition of minor apolipoproteins (apoC, apoE, and others) and lipid constituents (triglycerides and cholesterol), metabolic properties, and relative atherogenicity [54]. Whereas nephrotic syndrome and heavy proteinuria are associated with increased formation of cholesterol-rich apoB-containing lipoprotein in LDL and VLDL, the characteristic feature in renal failure is the accumulation of intact or partially metabolized triglyceride-rich lipoprotein in IDL and VLDL [54]. A significantly decreased plasma apoA-I/apoC-III ratio is the hallmark lipid abnormality in renal disease [52,55]. This ratio reflects the reduced apoA-I and apoA-II levels, moderately elevated apoB and apoE, and significantly increased apoC-III levels [56]. This hyperlipidemic profile seems to be caused by faulty catabolism and removal of cholesterol-rich apoB-containing lipoproteins because of reduced activity of lipolytic enzymes, compositional changes in the lipoproteins that render them poor substrates for lipolysis, and decreased receptor-mediated uptake of lipoproteins [51]. Clinical studies have reported on the possible relationship between apoB-containing lipoproteins and kidney disease: a reduced plasma apoA-1/apoB ratio was associated with a slightly steeper decline of creatinine clearance in patients with moderate renal insufficiency [41]; plasma apoB and LDL significantly correlated with the rate of progression of renal insufficiency [42]; and total cholesterol, LDL, and apoB were significantly associated with rate of decline in renal function [57]. In another study, baseline total cholesterol, LDL, and apoB (but not triglycerides) were associated with decline of renal function in patients with chronic renal insufficiency [57].

Diabetes, lipids, and kidney disease

In diabetic patients, even small amounts of urinary albumin may be associated with substantial changes in lipid profile [58]. Studies in patients with type 1 or type 2 diabetes have shown an association between total cholesterol or LDL level and the rate of progression of renal disease [54]. For example, in a study of patients with type 1 diabetes and nephropathy, higher total cholesterol, triglycerides, and apoB levels were correlated with more rapid renal function decline [37]. Total triglyceride and VLDL triglyceride concentrations were markedly increased in a type 2 diabetes population [59], whereas total cholesterol was not increased in another type 2 diabetes population after correction for gender, age, and duration of diabetes [60]. A review of dyslipidemia in type 2 diabetes was recently published [61].

Renal failure and lipids

The particularly high risk of cardiovascular complications in patients with ESRD is associated with traditional risk factors (including dyslipidemia); factors associated with chronic renal failure; and emerging risk factors, such as inflammation and hyperhomocysteinemia [62]. Total cholesterol levels may be similar or even lower in nondiabetic patients with ESRD versus the general population; this finding is attributed to the pervasive malnutrition in ESRD. In fact, a low cholesterol level has been associated with worse outcome in some patients [63], but in other studies higher total cholesterol and LDL levels predicted cardiac death in diabetic patients receiving dialysis [64]. As in chronic kidney disease, renal failure is accompanied by an abnormal apolipoprotein profile. The current recommendation is that dyslipidemia in patients with renal failure should be treated [62,65].

High triglycerides, decreased HDL, and high lipoprotein (a) levels may be seen in patients receivng hemodialysis and peritoneal dialysis [66]. Hemodialysis can moderately attenuate dyslipidemia, sometimes resulting in normal levels of total cholesterol and LDL with or without increased levels of atherogenic lipoproteins [67]. Peritoneal dialysis may aggravate lipid abnormalities, in particular by increasing LDL levels through increased cholesterol-rich apoB-containing lipoproteins [68]. The associations between lipid abnormalities and ESRD outcome have been inconsistent [66].

Dyslipidemias are common in transplantation patients. Total cholesterol and LDL levels are typically elevated, and triglycerides are often increased. The HDL level is usually normal [36].

Possible mechanisms for the interactions between kidney disease and dyslipidemia

There are several hypotheses regarding the relationship between urinary albumin excretion, kidney disease, and lipid abnormalities [50,69]. Kidney disease may increase lipid levels, and some of the lipid abnormalities associated with kidney disease may cause cardiovascular complications. In patients with kidney disease, increased total cholesterol, LDL, and lipoprotein (a) levels could be secondary to urinary protein loss [70–73]. Even early renal disease may cause changes in lipoprotein profile that can be atherogenic [52]. The IDLs that are elevated in kidney disease are atherogenic because of their size and ability to penetrate the arterial intima [53].

On the other hand, lipid abnormalities could contribute to kidney damage. In the presence of renal disease, lipoproteins may play a role in renal injury in a way that is analogous to their involvement in atherosclerosis [74–76]. This possibility is supported by studies showing that kidney function may be improved by pharmacologic agents that lower lipid levels [77,78]. Experimental data support the hypothesis that dyslipidemia contributes to glomerular and interstitial injury of the renal parenchyma [74]. Glomerular mesangial cells and vascular smooth muscle cells have similarities that suggest that accumulation of lipids in mesangial cells, analogous to an atherosclerotic process in smooth muscle cells, may cause or accelerate glomerulosclerosis [79,80]. LDL causes monocytes to adhere to endothelial cells, and this adhesion may be an important factor in inflammatory glomerular disease [81,82].

Treatment interventions for patients with kidney disease and dyslipidemia

Nonpharmacologic interventions are important for the control of lipids in all patient populations. The Steno-2 study showed a significant benefit of intensive, multifactorial treatment (diet, exercise, smoking cessation, therapy with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, vitamin and mineral supplementation, oral hypoglycemic agent [if needed], and treatment of hypertension or dyslipidemia) on risk factors for cardiovascular disease in patients with type 2 diabetes and microalbuminuria [83].

Clinical trials have shown that statin therapy reduces the risk of adverse cardiovascular outcomes in patients at risk of cardiovascular disease, even in those with normal lipid levels. For example, in the Heart Protection Study [84] simvastatin therapy significantly reduced the incidence of major coronary events and ischemic stroke in patients with normal lipid levels who had cerebrovascular disease, other occlusive arterial disease, or diabetes. Patients with type 2 diabetes and at least one other risk factor for cardiovascular disease (hypertension, retinopathy, high cholesterol level, or smoking) who were treated with atorvastatin experienced significant decreases in serious cardiovascular outcomes and stroke in the Collaborative AtoRvastatin Diabetes Study [85,86].

Treatments that lower proteinuria (eg, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers) may lower lipid levels. Lipid-lowering therapy is often desirable in patients with kidney disease and hyperlipidemia, however. At present, it seems that lipid regulation decreases the incidence of coronary vascular events and other vascular complications in patients with kidney disease, but there are not yet enough data to determine definitively whether lipid regulation slows progression of kidney disease. A meta-analysis of controlled clinical trials showed that lipid-lowering therapy slowed the rate of decline in GFR and showed a tendency toward decreased proteinuria in patients with renal disease. The reduction in GFR was 0.16 (0.03–0.27) mL/min per month, which compares favorably to the effect of angiotensin-converting enzyme inhibitor therapy on rate of change in renal function [87]. Statin therapy has been shown to be effective for improving lipid levels and kidney function [78,88] and for secondary prevention of cardiovascular events in patients with chronic renal insufficiency [89]. In the Heart Protection Study, simvastatin significantly decreased the aging-related rise in serum creatinine levels in diabetic and nondiabetic patients [90]. Similarly, patients in the simvastatin group had a significantly smaller decrease in estimated GFR during the trial.

Currently, there are no prospective, randomized trial results reporting the effects of the management of dyslipidemia on cardiovascular outcomes in patients with chronic kidney disease. The statin (simvastatin)-selective intestinal cholesterol absorption inhibitor (ezetimibe) combination is being tested in the Study of Heart and Renal Protection study, which includes patients with chronic kidney disease or receiving dialysis without dyslipidemia and no history of myocardial infarction or coronary revascularization [91]. The primary outcome being investigated is a composite of serious cardiovascular events.

In more advanced kidney disease, lipid-lowering treatment with statin therapy reduced cholesterol-rich apoB-containing lipoproteins in patients with nephrotic syndrome [92]; reduced total cholesterol, LDL and triglycerides levels and increased HDL levels in patients undergoing continuous peritoneal dialysis [93]; and has been associated with reduced cardiovascular and total mortality in patients in patients with ESRD [94]. The extent of lipid lowering with statin therapy in patients with peritoneal dialysis or hemodialysis is similar to that in patients without renal disease [95–98].

The Assessment of Lescol in Renal Transplantation study was the first prospective, randomized trial of the effects of dyslipidemia management on cardiovascular outcomes in transplantation patients [99]. It assessed the effect of fluvastatin in renal transplant recipients with mild-to-moderate hypercholesterolemia (total cholesterol of 4.0–9.0 mmol/L; 155–348 mg/dL), except for those with a history of myocardial infarction, for whom the upper limit of total cholesterol was 7.0 mmol/L (270 mg/dL). The primary objective was to investigate the effects of fluvastatin on major adverse cardiac events. Fluvastatin lowered LDL levels by 32%. Although there was not a significant effect on the combined cardiovascular end point (cardiac death, nonfatal myocardial infarction, or coronary revascularization), there were significant reductions in cardiovascular deaths and nonfatal myocardial infarction. The observed cardiac event rate was lower than predicted in this trial, and it had insufficient power to detect a significant reduction in the chosen primary end point. The beneficial proportional reduction in cardiovascular events was similar to those of statins in other populations.

Additional lipid-related studies are underway in the ESRD population. One example is the Die Deutsche Diabetes Dialyse Studie [100], which will test the hypothesis that atorvastatin decreases the rate of cardiovascular mortality and of nonfatal myocardial infarction in patients with type 2 diabetes receiving hemodialysis. A secondary end point is mean percentage change in lipid profile from baseline in patients for whom the baseline LDL level is 80 to 190 mg/dL (2.1–4.9 mmol/L) and triglyceride level is less than 1000 mg/dL (11.4 mmol/L). The results of this study should be published in 2005.

Lipid-lowering measures are indicated in patients with all stages of renal disease because of their increased risk of cardiovascular complications. The number of patients who reach lipid goals has been disappointing; reasons given have included failure of physicians to test for and treat dyslipidemia (before and concurrently with cardiovascular disease) and failure of patients to follow treatment recommendations, including taking medication as directed. Although little information is currently available about the impact of lipid treatment in patients with chronic kidney disease (no available data) or transplantation (one study), the National Kidney Foundation cites the benefit of lipid therapy in the general population as additional support for lipid management in patients with kidney disease. Currently, the National Kidney Foundation recommends strict control of lipoprotein levels for patients with kidney disease (Fig. 1) [36,65].

Summary

Cardiovascular complications are common in patients with kidney disease. Regulating the lipid levels in these patients is important so that the risks of kidney and cardiovascular complications can be minimized. Lipid regulation decreases the incidence of coronary vascular events and other vascular complications in patients with kidney disease; however, whether lipid regulation slows

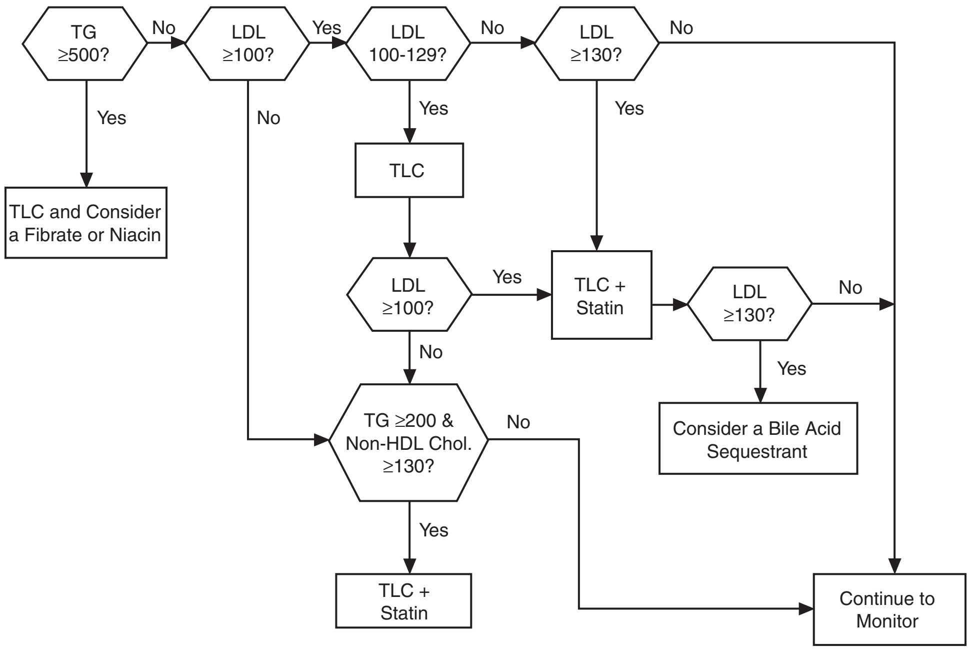

Fig. 1. Treatment of dyslipidemia in adults with kidney disease as recommended by the National Kidney Foundation. Units are mg/dL. HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides, TLC, therapeutic lifestyle changes. (*From* National Kidney Foundation. K/DOQI clinical practice guidelines for managing dyslipidemias in chronic kidney disease. Am J Kidney Disease 2003;41(Suppl 3):S40; with permission and Kasiske B, Cosio FG, Beto J, et al. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Am J Transplant 2004;4(Suppl 7):28; with permission from the National Kidney Foundation.)

progression of kidney disease is not yet known. Additional studies of the implications of dyslipidemia in patients with kidney disease are needed.

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