Review Article

Hyperlipidaemia in Chronic Kidney Disease

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Abstract

Cardiovascular disease is a major cause of mortality and morbidity in patients with chronic kidney disease (CKD). The prevalence of hyperlipidaemia or dyslipidaemias is much higher compared to the general population. Total or low-density lipoprotein (LDL) cholesterol is highest in patients with chronic renal impairment. The majority of patients with CKD do not develop renal failure; indeed, most of them die of cardiovascular causes before the development of renal failure. The K/DOQI (Kidney Disease Outcomes Quality Initiative) guidelines on dyslipidaemias in CKD suggest that all patients should therefore be evaluated for dyslipidaemias. They should have a complete fasting lipid profile with total, LDL and high-density lipoprotein cholesterol, and triglycerides measured to identify those at risk and those who require treatment. Generally, the treatment approach parallels that suggested by the National Cholesterol Education Program Adult Treatment Panel III guidelines, in which the main focus of treatment is the level of LDL cholesterol. Patients with CKD should be considered a "very high risk" category and aggressive therapeutic intervention initiated to reduce the risk of cardiovascular events.

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Key words: Cardiovascular disease, Dyslipidaemia, LDL cholesterol, Proteinuria, Statins

Introduction

Patients with chronic kidney disease (CKD) are at an increased risk for cardiovascular disease and have a higher prevalence of hyperlipidaemia (or dyslipidaemias) than the general population.[1,2] The risk of cardiovascular disease (CVD) varies depending on the type of lipid abnormalities, the target population, the cause of renal disease and the degree of reduction in glomerular filtration rate (GFR). In patients with pre-existing CVD, the presence of CKD is associated with an increased risk of recurrent cardiovascular events.[3] Conversely, most patients with CKD do not develop kidney failure. The majority (58%) of patients die from cardiovascular causes, making CVD the leading cause of death in patients with CKD.[4] Indeed, even mild renal insufficiency has been shown to be associated with increased rates of cardiovascular events.[5,6] Furthermore, patients on dialysis have 10 to 20 times higher cardiovascular mortality rates than the general population.[7] Therefore, it is important to screen all patients with CKD for dyslipidaemias and treat them appropriately as they are considered "a very high-risk" group for CVD.[2]

Prevalence of Hyperlipidaemia (Dyslipidaemias)

The National Cholesterol Program (NCEP) Adult Treatment Panel (ATP) III guidelines indicate that the upper limit of normal for total cholesterol is 240 mg/dL (6.21 mmol/L), low-density lipoprotein (LDL) cholesterol is 130 mg/dL (3.36 mmol/L), triglycerides (TG) is 200 mg/dL (2.26 mmol/L) and the lower limit for HDL cholesterol is 35 mg/dL (0.91 mmol/L).[8] Various studies have shown that the prevalence of hyperlipidaemia or dyslipidaemias in patients with CKD is higher than in the general population.[2] The severity of lipid abnormalities also correlates with the degree of proteinuria and is a common complication in patients with CKD and nephrotic syndrome (proteinuria >3 g/day). Though not all nephrotic patients have reduced glomerular filtration rate (GFR), when CKD populations are stratified into those with or without nephrotic syndrome, patients with nephrotic syndrome have a higher prevalence of lipoprotein abnormalities compared to those without nephrotic syndrome[2] (Table 1).

Chronic Kidney Disease with Nephrotic Syndrome

Almost all patients with nephrotic syndrome (proteinuria >3 g/day) have an abnormal lipid profile. The total and LDL cholesterols are invariably elevated, TG is often increased and the HDL cholesterol reduced.[2] The degree of hyperlipidaemia correlates directly with the severity of the

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proteinuria, and inversely with the serum albumin.[9] As reduced GFR is by itself associated with hyperlipidaemia, the strong and independent correlation between proteinuria and reduced GFR also increases the risk of hyperlipidaemia and proteinuria.[10] Conversely, proteinuria has an inverse correlation with the level of HDL cholesterol.[11] These risk factors likely predispose patients with nephrotic syndrome to an increased risk of coronary artery disease.[12]

Among nephrotic patients, lipoprotein abnormalities were similar between diabetics and non-diabetic patients in a small study and both groups have elevated (TG), LDL and VLDL cholesterol and low HDL cholesterol.[13,14] However, patients with diabetic CKD have lipoprotein abnormalities that are a reflection of renal insufficiency, similar to that of patients with renal insufficiency due to other causes. These abnormalities however may be further accentuated by the diabetes and the abnormal metabolic control.[14]

Chronic Kidney Disease without Nephrotic Syndrome

There have been few studies reporting the prevalence of dyslipidaemias in patients with CKD who do not have nephrotic syndrome (Table 1). However, it has been suggested that the prevalence is lower than in those with nephrotic syndrome.[2] Generally, the prevalence of hyperlipidaemia increases with deteriorating renal function, with the degree of hypertriglyceridaemia and elevation of HDL cholesterol being proportional to the severity of renal impairment. However, diabetic CKD patients have higher TG and lower HDL cholesterol than their non-diabetic counterparts,[14] suggesting that diabetes itself exacerbates lipid abnormalities in patients with renal impairment.

Hyperlipidaemia and Progression of Kidney Disease

It has long been suggested that hyperlipidaemia could cause renal injury and contribute to the progression of renal disease.[15] There have been a number of observational studies showing that lipid abnormalities are associated with a reduction in kidney function in the general population. It is uncertain if it is the lipid abnormalities that cause the reduction in kidney function, or if impaired renal function or proteinuria itself cause both the lipid abnormalities and reduction in renal function. Most studies have been small and a meta-analysis of these studies to assess the effect of lipid reduction on the progression of renal disease has shown that lipid reduction may preserve GFR and reduce proteinuria.[16] More recent studies have shown that HMG-CoA reductase inhibitors (statins) can reduce proteinuria and slow the decline in renal function.[17-19] The effect of statins in reducing the decline in GFR was more significant in patients with proteinuria.[17]

Furthermore, it has been well established that proteinuria contributes to the progression of renal disease.[16,20] Despite optimal medical management with interventions to achieve tight blood pressure[21] and blood glucose control,[22] the use of angiotensin converting enzyme (ACE) inhibitor[23] and angiotensin II receptor blocker (ARB)[24] or combined therapy,[25] patients with renal failure are at risk for progressive deterioration of their renal function. Statins have been shown to reduce proteinuria and delay the rate of progression of renal disease in patients with proteinuria and hypercholesterolaemia.[17,18] These benefits are in addition to the effects of ACE inhibitor and ARB. However, recent data have suggested that statins have effects beyond lipid reduction and may have a beneficial anti-inflammatory effect in patients with normal or low cholesterol levels.[26,27] In addition to their lipid-lowering effects, statins can influence important pathways that are involved in the inflammatory and fibrogenic responses, which are commonly associated with many forms of progressive renal injury such as reduction in TGF-β production and inhibition of the proliferative actions of platelet-derived growth factor.[28,29]

Finally, statins can decrease coronary events in patients without cardiovascular disease and also reduce the mortality rates in patients with pre-existing coronary artery disease.[30,31] Even for those with serum cholesterol levels as low as 3.5 mmol/L and in diabetics without coronary artery disease or high cholesterol, statins have been demonstrated to be beneficial.[32,33] In patients with moderate CKD (GFR of 30 to 59.99 mL/min per 1.73 m^2), statins have been demonstrated to reduce the incidence of cardiovacular events.[34]

Evaluation of Dyslipidaemias

The recent Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines for the management of hyper-

Table 1. Lipid Abnormalities by Target Population

	Total cholesterol >240 mg/dL (6.21 mmol/L)	LDL cholesterol >130 mg/dL (3.36 mmol/L)	HDL cholesterol <35 mg/dL (0.91 mmol/L)	Triglycerides >200 mg/dL (2.26 mmol/L)
General population	20%	40%	15%	15%
CKD with nephrotic syndrome	90%	85%	50%	60%
CKD without nephrotic syndrome	30%	10%	35%	40%

To convert mg/dL to mmol/L, multiply triglycerides by 0.01129, cholesterol by 0.02586
(Adapted from Kasiske BL[2]).

lipidaemia in patients with kidney disease suggest that all adults with CKD should be evaluated for lipid abnormalities.[35] Assessment of hyperlipidaemia should include a complete fasting lipid profile with total, LDL and HDL cholesterol, and TG.[35] The NCEP ATP III suggests that anyone with elevated cholesterol or other forms of hyperlipidaemia should undergo clinical or laboratory evaluation for secondary dyslipidaemias before starting on anti-lipid therapy.[8,36] The ATP III guidelines also recommend treatment for dyslipidaemias with normal or low LDL cholesterol, which is often associated with metabolic or insulin resistance syndrome.[8,36] As in the ATP III guidelines, all major treatments are based on the levels of TG, LDL and non-LDL cholesterol.

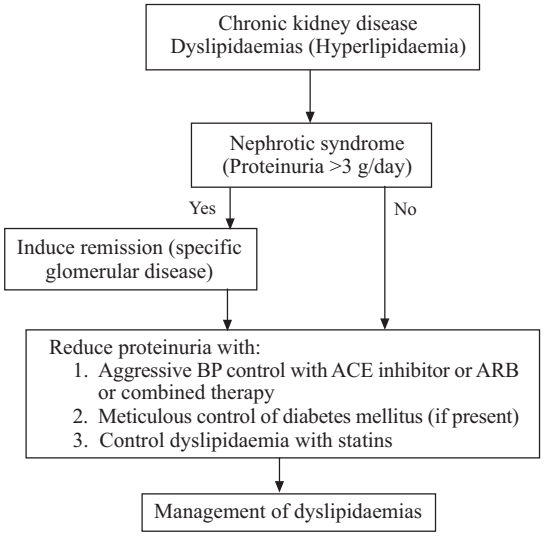
Treatment of Dyslipidaemias

In general, the treatment approach to adult patients with CKD parallels that recommended by the ATP III guidelines.[8] However, in CKD patients with nephrotic syndrome, the best treatment is to induce remission of nephrotic syndrome. If this is not possible, any reduction in urinary protein excretion will be beneficial as the severity of hyperlipidaemia is proportional to the degree of proteinuria.[9] All patients with elevated lipid levels should be treated with a lipid-lowering diet, which is effective in reducing total cholesterol and LDL cholesterol levels in those with nephrotic syndrome.[2] However, diet does not completely correct the lipid abnormalities and very often, hypolipidaemic medications are required in conjunction with diet. The HMG-CoA reductase inhibitors (statins) are effective in lowering the total and LDL cholesterol and also TG in those with nephrotic syndrome.[2]

The treatment of diabetic patients with nephrotic syndrome is similar to that of non-diabetic patients. Those diabetic patients with very high TG may require a fibrate alone or in combination with a statin. However, caution should be exercised in those patients with impaired renal function in treating them with fibrate, statins or combined therapy, as they are at higher risk for drug-induced rhabdomyolysis. Furthermore, meticulous control of diabetes can also help in improving the dyslipidaemias.

The ATP III reports have identified LDL cholesterol as the primary target for lipid-lowering therapy[8,37,38] and have found that lowering LDL cholesterol levels reduces the risk for cardiovascular events. In patients with high fasting TG ≥500 mg/dL (≥5.65 mmol/L), the initial goal of treatment is to prevent acute pancreatitis. The target is to achieve TG level <500 mg/dL and suggested treatment is with therapeutic lifestyle changes (which includes diet, weight reduction, increased physical activity and abstinence from alcohol) followed by a fibrate or niacin.[8]

The recent K/DOQI guidelines on the management of dyslipidaemias suggest the following (Fig. 1):



Dyslipidaemias	Target	Treatment
TG ≥500 mg/dL (5.64 mmol/L)	TG <500 mg/dL (5.64 mmol/L)	TLC + Fibrate or Niacin
LDL ≥100-129 mg/dL (2.57-3.34 mmol/L)	LDL <100 mg/dL (2.57 mmol/L)	TLC + Low-dose statin
LDL ≥130 mg/dL (3.36 mmol/L)	LDL <100 mg/dL (2.57 mmol/L)	TLC + Maximum-dose statin
TG ≥200 mg/dL (2.26 mmol/L) and Non HDL ≥130 mg/dL (3.36 mmol/L)	Non-HDL <130 mg/dL (3.36 mmol/L)	TLC + Maximum-dose statin

ACE inhibitor: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BP: blood pressure; TLC: therapeutic lifestyle changes

Fig. 1. The algorithm for the management of dyslipidaemias in CKD patients.

1. For those patients with LDL cholesterol levels between 100 and 129 mg/dL (2.57 to 3.34 mmol/L), the aim is to achieve LDL <100 mg/dL (2.57 mmol/L) and the treatment is by initial therapeutic lifestyle changes, followed by a low-dose statin.[35]
2. For those with LDL ≥130 mg/dL (3.36 mmol/L), lifestyle changes alone are insufficient as a low-dose statin is often added to the initial therapy. The target is LDL <100 mg/dL (2.57 mmol/L) and the dose of statin increased to maximum doses as required.
3. For those CKD patients with TG ≥200 mg/dL (2.26 mmol/L) and non-HDL cholesterol ≥130 mg/dL (3.36 mmol/L), the aim is to achieve non-HDL cholesterol <130 mg/dL. Initial treatment comprises lifestyle changes plus a low-dose statin which is increased as required.[35]

The therapeutic lifestyle changes for adults with CKD include:

1. Diet (in consultation with a dietitian)
2. Physical activity
3. Moderate intake of alcohol
4. Smoking cessation

It is important that when there is evidence of protein-energy malnutrition, diet should be used judiciously, particularly in patients with nephrotic syndrome on protein restriction. As patients with CKD often have other nutritional problems, it is important that an experienced dietitian is involved in the care of these patients.

Since the publication of the NCEP ATP III, new data from major clinical trials have emerged. The NCEP report on the implications of the recent trials since the earlier ATP III guidelines has recommended that in high-risk patients, the LDL cholesterol target should be <100 mg/dL (2.57 mmol/L), and in very high-risk patients, the target should be <70 mg/dL (1.81 mmol/L).[39] Clinical trials are currently underway to prove the hypothesis that an LDL cholesterol level much lower than 70 mg/dL (1.81 mmol/L) may be beneficial in providing further cardiovascular protection.

Conclusions

Patients with CKD are at high risk of developing cardiovascular disease and they have a higher prevalence of dyslipidaemias compared to the general population. Most CKD patients do not develop kidney failure but die as a result of CVD. It is recognised that CVD begins in the early stages of CKD. Therefore, it is important not only to identify these patients early but also to treat their dyslipidaemias intensively before they develop end-stage renal disease. Most patients will require lifestyle modification and lipid-lowering therapy. CKD patients should be considered as patients at very high risk for CVD and treated accordingly.

REFERENCES

1. Culleton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D. Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. Kidney Int 1999;56:2214-9.
2. Kasiske BL. Hyperlipidemia in patients with chronic renal disease. Am J Kidney Dis 1998;32:S142-S156.
3. Weiner DE, Tighiouart H, Stark PC, Amin MG, MacLeod B, Griffith JL, et al. Kidney disease as a risk factor for recurrent cardiovascular disease and mortality. Am J Kidney Dis 2004;44:198-206.
4. Shulman NB, Ford CE, Hall WD, Blaufox MD, Simon D, Langford HG, et al; The Hypertension Detection and Follow-up Program Cooperative Group. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. Hypertension 1989;13(Suppl):I80-I93.
5. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 2003;108:2154-69.
6. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med 2001;134:629-36.
7. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol 1998;9(12 Suppl): S16-S23.
8. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
9. Appel GB, Blum CB, Chien S, Kunis CL, Appel AS. The hyperlipidemia of the nephrotic syndrome. Relation to plasma albumin concentration, oncotic pressure, and viscosity. N Engl J Med 1985;312:1544-8.
10. Keane WF, Eknoyan G. Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. Am J Kidney Dis 1999;33:1004-10.
11. Bianchi S, Bigazzi R, Campese VM. Microalbuminuria in essential hypertension: significance, pathophysiology, and therapeutic implications. Am J Kidney Dis 1999;34:973-95.
12. Ordonez JD, Hiatt RA, Killebrew EJ, Fireman BH. The increased risk of coronary heart disease associated with nephrotic syndrome. Kidney Int 1993;44:638-42.
13. Joven J, Villabona C, Vilella E. Pattern of hyperlipoproteinemia in human nephrotic syndrome: influence of renal failure and diabetes mellitus. Nephron 1993;64:565-9.
14. Attman PO, Nyberg G, William-Olsson T, Knight-Gibson C, Alaupovic P. Dyslipoproteinemia in diabetic renal failure. Kidney Int 1992;42: 1381-9.
15. Moorhead JF, Chan MK, El-Nahas M, Varghese Z. Lipid nephrotoxicity in chronic progressive glomerular and tubulo-interstitial disease. Lancet 1982;2:1309-11.
16. Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. Kidney Int 2001;59: 260-9.
17. Tonelli M, Moye L, Sacks FM, Cole T, Curhan GC; Cholesterol and Recurrent Events Trial Investigators. Effect of pravastatin on loss of renal function in people with moderate chronic renal insufficiency and cardiovascular disease. J Am Soc Nephrol 2003;14:1605-13.
18. Bianchi S, Bigazzi R, Caiazza A, Campese VM. A controlled, prospective study of the effects of atorvastatin on proteinuria and progression of kidney disease. Am J Kidney Dis 2003;41:565-70. Erratum in: Am J Kidney Dis 2004;43:193.
19. Lee TM, Su SF, Tsai CH. Effect of pravastatin on proteinuria in patients with well-controlled hypertension. Hypertension 2002;40:67-73.

20. Ruggenenti P, Perna A, Remuzzi G; GISEN Group Investigators. Retarding progression of chronic renal disease: the neglected issue of residual proteinuria. Kidney Int 2003;63:2254-61.
21. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med 1994;330:877-84.
22. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977-86.
23. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; The Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 1993;329:1456-62. Erratum in: N Engl J Med 1993;330:152.
24. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-9.
25. Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. Lancet 2003;361:117-24. Erratum in: Lancet 2003;361:1230.
26. Blanco-Colio LM, Tunon J, Martin-Ventura JL, Egido J. Anti-inflammatory and immunomodulatory effects of statins. Kidney Int 2003;63:12-23.
27. Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moye LA, Goldman S, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. Circulation 1998;98:839-44.
28. McFarlane SI, Muniyappa R, Francisco R, Sowers JR. Clinical review 145: Pleiotropic effects of statins: lipid reduction and beyond. J Clin Endocrinol Metab 2002;87:1451-8.
29. Oda H, Keane WF. Recent advances in statins and the kidney. Kidney Int (Suppl) 1999;71:S2-S5.
30. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-9.
31. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349-57.
32. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.
33. Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003;361:2005-16.
34. Tonelli M, Isles C, Curhan GC, Tonkin A, Pfeffer MA, Shepherd J, et al. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. Circulation 2004;110:1557-63.
35. K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. Am J Kidney Dis 2003;41(4 Suppl):I-IV,S1-S91.
36. Fedder DO, Koro CE, L'Italien GJ. New National Cholesterol Education Program III guidelines for primary prevention lipid-lowering drug therapy: projected impact on the size, sex, and age distribution of the treatment-eligible population. Circulation 2002;105:152-6.
37. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). JAMA 1993;269:3015-23.
38. National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Chloesterol in Adults (Adult Treatment Panel II). Circulation 1994;89:1333-445.
39. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al; National Heart, Lung and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227-39.