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Lipid alterations in renal patients and cardiovascular repercussions

Abstract

Interventions aimed at cardiovascular prevention in patients with chronic kidney disease differ among non-dialysis dependents, by the degree of dysfunction and proteinuria, from those in advanced and final stages of chronic renal failure or in that undergoing kidney transplantation. Thus, early diagnosis of renal dysfunction and control of risk factors are fundamental to reduce the main clinical outcomes. However, according to recent clinical studies, the effects of treatment to reduce the risk of death and cardiovascular morbidity in patients with chronic kidney disease are not as promising as in the general population. Further research and investigations with new therapeutic options, which can benefit these patients, who are at high cardiovascular risk, are clearly necessary. Statins should be used for all patients with chronic kidney disease when indicated. Remembering that the benefits were observed in patients with chronic kidney disease in early stages; in the more advanced stages, the use is questionable. Statins in dialysis patients should be indicated with caution, since the value of reducing LDL-c in patients with chronic dialysis kidney disease is less established and may be associated with a higher risk of stroke. From clinical studies with PCSK9 inhibitors, especially ODYSSEY, there is benefit for both LDL and lipoprotein reduction (a), non-HDL cholesterol, apoliprotein B and triglycerides. It should be emphasized that mortality in more advanced stages of chronic kidney disease involves multiple factors, in addition to the reduction of LDL-c. The complex relationship between inflammation, cholesterol and mortality in the final stages of chronic kidney disease requires a better understanding.

Keywords: chronic kidney disease, lipid profile, nephrotic syndrome, glomerular filtration rate, hypertension, albuminuria, lipid-lowering, PCSK9

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Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HDL-c, high density lipoprotein cholesterol; IDL, intermediate density lipoprotein; LDL, low density lipoprotein; LDL-c, low density lipoprotein cholesterol; LPL, lipoprotein lipase; NS, nephrotic syndrome; PCSK9, proprotein convertase subtilisin/kexin Type 9; LDL, very low-density lipoproteins

Introduction

Nephrotic syndrome (NS) is one of the most prevalent kidney diseases in children and adults, characterized by massive proteinuria, edema, hypoalbuminemia and hyperlipidemia. Patients usually present with edema and fatigue, with no evidence of heart failure or severe liver disease. Diagnosis of NS requires confirmation of important proteinuria (3gr/d or protein/creatinine ratio > 2 to 3mg/mg creatinine) and serum hypoalbuminemia. The causes may be secondary to metabolic diseases such as diabetes and amyloidosis, autoimmune, infections, neoplasms, medications or primary. Hyperlipidemia is a classic feature of NS, related to hypoproteinemia and low plasma oncotic pressure, which results from the loss of proteins in the urine.

Metabolism of triglyceride-rich lipoproteins: NS proteinuria results in increased triglyceride content of lipoproteins rich in apolipoprotein B, with elevations of very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoprotein (LDL) and lipoprotein (a), in addition to the prolongation of postprandial lipemia. These changes result from the reduction of intravascular lipolysis due to lipoprotein lipase dysfunction (LPL) in addition to urinary LPL loss in the nephrotic process.

The main factor for reducing LPL activity is the lower synthesis of the GPIHBP1 protein (endothelium-derived glycosylphosphatidylinositol anchored binding protein 1), responsible for anchoring LPL to the endothelium, besides serving as a ligand for chylomicrons and VLDLs. The loss of function of this protein reduces the intravascular lipolysis capacity of LPL.

HDL-2 rich in cholesterol esther, usually "lends" the aposE and aposCII and CIII to VLDLs and chylomicrons, essential process for lipolysis and removal of the circulation of lipoproteins rich in triglycerides and their remnants. In NS, due to the scarcity of HDL-2 rich in cholesterol esther, there is a reduction in apoE content and apoCII (LPL activator) and apoCIII (LPL inhibitor) in lipoproteins rich in triglycerides, contributing to lower intravascular lipolysis and elevation of plasma triglycerides.

NS leads in hepatic lipase deficiency, which contributes to hypertriglyceridemia in addition to the accumulation of atherogenic particles of IDL. Patients with NS have a marked increase in serum proprotein convertase subtilisin cexin type 9 (PCSK9) that degrades the LDL receptor (LDLR), reducing the removal of LDL particles and increasing plasma low density lipoprotein (LDL-c) cholesterol.

NS presents increased expression of the enzyme acyl-CoA cholesterol acyltransferase-1 (ACAT-1) in vascular and renal tissue and urinary loss with reduction of the serum level of lecithin cholesterol acyltransferase ester (LCAT), reducing reverse cholesterol transport.

The sharp increase in cholesterol ester transfer protein (CETP) leads to an additional depletion of HDL cholesterol and enrichment with triglycerides, further reducing plasma concentrations of high

density lipoprotein cholesterol (HDL-c). Lipoprotein (a) increases in nephrotics increase the risk of thromboembolic and cardiovascular complications. Consequences of lipid alterations in NS: accumulation of LDL, IDL, chylomicrons and atherogenic remnants associated with the reduction of reverse cholesterol transport, contribute to the development and progression of atherosclerosis and cardiovascular diseases.

The prevalence of coronary atherosclerosis is higher in patients with NS. Lipid alterations are associated with the severity of proteinuria and contribute to the progression of both renal and cardiovascular disease, frequent in this population. High plasma lipid levels increase cardiovascular risk of outcomes especially in adults (no data available in children). The chronic use of corticosteroids and other potentially toxic therapies, resistance to clinical remission exposing the patient to the nephrotic environment for long periods, urinary loss of antithrombotic factors and increased synthesis of prothrombotic factors contribute to the atherosclerotic and thromboembolic risk typical of this disease.[1]

The uptake of abnormal lipoproteins by glomerular mesangial cells results in glomerulosclerose; resorption of filtered albumin and other lipoproteins leads to lipid accumulation with increased cytotoxicity of proximal tubular epithelial cells, which may result in loss of nephrons, development and progression of chronic kidney disease. Despite the potential benefit of dyslipidemia treatment, it is important to note that there are no criteria for a dyslipidemia threshold at which treatment should be initiated for patients with NS.

Renal disease guidelines: improving overall outcomes for the management of glomerular disease state that "the treatment of hyperlipidemia in patients with glomerular disease should generally follow the guidelines that apply to those at high risk of developing cardiovascular disease". No definitive data are available on when an intervention should occur. Instead, the possible benefits and risks of the intervention or treatment of dyslipidemia need to be considered on a case-by-case basis. Most nephrologists would consider the establishment of lipid-lowering interventions in patients who remain openly nephrotic for several months. Interestingly, a small study of 40 adult patients who had recurrent NS as children, showed that the occurrence of cardiovascular disease in this cohort was similar to that of the general population, suggesting that recurrent NS during childhood is not an increased risk factor for cardiovascular disease in adulthood.

Serum lipid reference values in diabetic patients: all diabetic patients should have their lipid profile determined at least once a year.[2,3] The recommended reference values for serum lipids of patients with diabetes mellitus are similar to those aimed at secondary prevention of coronary atherosclerotic disease. Therefore, the ideal values of LDL-c and triglycerides are respectively those lower than 100mg/dL and 150mg/dL, while HDL-c levels should always be higher than 35mg/dL (Table 1).[4,5]

Patients with chronic kidney disease (CKD) not dependent on dialysis have a risk of cardiovascular (CV) death ten times higher than that of the general population, and in dialysis patients, the risk is even higher. With 50% of those in the final stage, they die of cardiovascular disease.

This relationship between CKD and cardiovascular disease is well established, with multiple interactions and common risk factors. CKD is an independent risk factor for coronary artery disease. The risk of CV events in CKD patients is inversely proportional to the rate of glomerular filtration (GFR), growing from 45-59ml/min. Proteinuria, regardless of age, gender, GFR and diabetes mellitus, increases the risk of coronary artery disease and perpetuates chronic renal failure. Although traditional CV risk factors are highly prevalent in CKD, these patients are excluded from CV prevention studies.[6]

Patients with CKD should be considered at very high risk for addressing CV risk factors, and it is necessary to evaluate factors such as the degree of GFR reduction and the presence of comorbidities (Class One, Evidence level C).[7] Lowering blood pressure is the most effective measure to mitigate the progression of CKD and reduce CV risk, regardless of the drug used.

Stage 3 CKD (GFR 30-60), albuminuria between 30-300mg/24h or urinary albumin-creatinine ratio 30-300 mg/g configure target organ injury and establish additional risk. Blood pressure targets for patients undergoing conservative treatment, according to the etiology of CKD and urinary albumin excretion, are (Table 2)[8]

In CKD, the risk relationship between dyslipidemia and cardiovascular disease is not linear. However, during the progression of CKD, abnormal removal of lipoproteins, due to the decline of glomerular filtration, is the mechanism that aggravates lipid alterations, resulting in qualitative and quantitative alterations of lipid profile (Table 3).[9]

Statin data in patients with non-dialysis CKD are derived from subgroup, post hoc and meta-analysis analyses.

The SHARP study, which included 6.247 patients with mean GFR of 26.6mL/min treated with S20 (Sinvastatin 20) + EZE10 (Ezetimibe 10) versus placebo, showed a significant reduction in CV events during a 4.9-year follow-up. These benefits did not extend to patients with CKD-dialysis. In the ALLIANCE study, the use of atorvastatin was associated with a 28% reduction in CV events in CKD patients.

The Pravastatin Pooling Project, evaluating data from 3 clinical trials with pravastatin versus placebo, demonstrated a significant reduction in CV events in coronary patients with moderate CKD[11]. PCSK9i inhibitors (PCSK9i): in individuals with hypercholesterolemia with impaired renal function, defined as eGFR 30–59, to those without impaired renal function eGFR ≥60. A total of 4.629 hypercholesterolemic individuals without or with IRF, pooled from eight phase-3 ODYSSEY trials, were on alirocumab 150mg or 75/150mg every 2weeks versus placebo or ezetimibe. Overall, 10.1% had impaired renal function and over 99% were receiving statin treatment.[12]

Fibrates are understudied drugs in CKD due to a concept that may worsen CKD. In the FIELD study, compared to placebo, fenofibrate reduced CV events in diabetic patients with moderate CKD (eTFG between 30-59), but in end-stage patients the frequency of events was similar. A recent post-hoc analysis of the ACCORD study, bringing together 2,636 patients from the fenofibrate arm, when compared to placebo, the frequency of albuminuria was lower and the decline of GFR and GFR slower, but with no significant difference in the incidence of CKD. More randomized studies are needed to elucidate the risk/benefit ratio of fibrate use in CKD patients in all stages of evolution.[11] Baseline LDL-C in alirocumab and control groups was comparable in subgroups analyzed. LDL- C reduct ions at week 24 ranged from 46.1 to 62.2% or 48.3 to 60.1% with alirocumab among individuals with or without impaired renal function, respectively. Similar reductions were observed for lipoprotein (a), non-high-density lipoprotein cholesterol, apolipoprotein B, and triglycerides.[12]

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The Position paper of Italian Society of Nephrology; Lipid Management in CKD patients states a position paper discussing the management of dyslipidemia in patients with chronic kidney disease. The consequences of impaired renal function on CVD risk as well as effects on plasma lipids and lipoproteins are discussed. The different therapeutic options, including the trials that evaluated these therapies, are discussed systematically, including indications, mechanisms of action, indications, etc. The six medication classes reviewed are statins, ezetimibe, fibrates, bile acid sequestrants, omega-3 fatty acids, and PCSK9ab. Therapeutic goals for LDL-c and triglycerides, as endorsed by the major guidelines: KDIGO, ACC/AHA, and ESC/EAS. Lipid management is advocated for all CKD patients with stage 3 CKD or worse and includes renal transplant patients.[13]

Table 1 Reference values of LDL-c, triglycerides and HDL-c in diabetic patients

Lipids	Values (mg/dL)	
	Desirable	Not desirable
LDL-c	<100	≥100
Triglycerides	>150	≥150
HDL-c	≥35	<35

Table 2 Blood pressure targets according to albuminuria

	Albuminuria <30mg/24hours	Albuminuria > 30mg/24hours
Chronic non-diabetic kidney disease	<140/90mmHg	<130/80mmHg
Preferred drug	Any	ACE inhibitor or ARB
Diabetic chronic kidney disease	<130/80mmHg	<130/80mmHg
Preferred drug	Any	ACE inhibitor or ARB

Table 3 Lipid parameters and nephrological conditions

Parameter	CKD 1–5	Nephrotic syndrome	Hemodialysis	Peritoneal dialysis
Total cholesterol	↗	↑↑	↔↓	↑
LDL cholesterol	↗	↑↑	↔↓	↑
HDL cholesterol	↓	↓	↓	↓
Non-HDL cholesterol	↗	↑↑	↔↓	↑
Triglycerides	↗	↑↑	↑	↑
Lipoprotein (a)	↗	↑↑	↑	↑↑
ApoA-I	↘	↗	↓	↓
ApoA-IV	↗	↑↘	↑	↑
Apolipoprotein B	↗	↑↑	↔↓	↑

The guidelines for treatment in CKD groups are (Table 4)[10]

Table 4 Guidelines for treatment in chronic kidney disease groups

Groups of chronic kidney disease	Recommendations
Non-dialysis	- In adults ≥ 50years with TFGe ≥ 60mL/minute per 1.73m^2, statin treatment is recommended (Degree of Recommendation: I; Level of Evidence: B) - In adults ≥50years with TFGe ≤60mL/minute per 1.73m^2, treatment with statins or statins/combination of ezetimib is recommended (Degree of Recommendation: IIa; Level of Evidence: A) - In adults 18 to 49years, statin treatment is recommended if you have one or more of the following risk factors (Degree of Recommendation: IIa; Level of Evidence: B): known coronary disease; diabetes mellitus; previous ischemic stroke Estimated incidence of coronary death or non-fatal myocardial infarction >10% in 10 years
Dialysis	- In patients with adult chronic kidney disease on dialysis, the onset of statin or the combination of statin/ezetimib is not recommended (Degree of Recommendation: IIa; Level of Evidence: A)
Kidney transplantrecipients	- In adult patients with kidney transplantation, statin treatment is recommended (Degree of Recommendation: IIa; Evidence Level: B) TFGe: estimated glomerular filtration rate.

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Conclusion

In summary: interventions aimed at CV prevention in CKD patients differ among non-dialysis-dependent patients by the degree of dysfunction and proteinuria, those in advanced and final stages of chronic renal failure or those undergoing kidney transplantation. Thus, early diagnosis of renal dysfunction and control of risk factors are fundamental to reduce the main clinical outcomes. However, according to recent clinical studies, the effects of treatment to reduce the risk of death and CV morbidity in CKD patients are not as promising as in the general population.

Further research and investigations with new therapeutic options, which can benefit these patients, who are at high risk CV, are clearly necessary.[9]

We should use statins for all CKD patients when indicated. Remembering that the benefits were observed in CKD patients in early stages; in the more advanced stages, the use is questionable. Statins in dialysis patients should be indicated with caution, since the value of reducing LDL-c in CKD-dialysis patients is less established and may be associated with a higher risk of stroke. From clinical studies with PCSK9 inhibitors, there is benefit for both LDL and lipoprotein reduction (a), non-HDL cholesterol, apoliprotein B and triglycerides.[12] It should be emphasized that mortality in more advanced stages of CKD involves multiple factors, in addition to the reduction of LDL-c. The complex relationship between inflammation, cholesterol and mortality in the final stages of CKD requires a better understanding.[12]

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Conflicts of interest

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