Lipids and Renal Disease

Roberto Trevisan, Alessandro R. Dodesini, and Giuseppe Lepore

Unit of Diabetology, Ospedali Riuniti di Bergamo, Bergamo, Italy

Chronic renal disease is accompanied by characteristic abnormalities of lipid metabolism, which appear as a consequence of nephrotic syndrome or renal insufficiency and are reflected in an altered apolipoprotein profile as well as elevated plasma lipid levels. Experimental and clinical studies have suggested a correlation between the progression of renal disease and dyslipidemia. High cholesterol and triglyceride plasma levels have been demonstrated to be independent risk factors for progression of renal disease in humans. The underlying pathophysiologic mechanisms for the relationship between lipid levels and progression of renal disease are not yet fully understood, although there are data that oxidative stress and insulin resistance may mediate the lipid-induced renal damage. In the animal model, lipid-lowering agents seem to ameliorate glomerular damage, preventing glomerulosclerosis and interstitial fibrosis. Although evidence from clinical studies indicates that statin therapy is associated with significant benefit in individuals with established chronic renal failure, whether lipid reduction can slow the renal functional decline awaits a primary renal outcome lipid-lowering therapy study.


Diabetes and hypertension are the leading cause of ESRD in the United States. In both individuals with and without diabetes, microalbuminuria is predictive of future proteinuria, progressive decline in renal function, accelerated atherosclerosis, and increased cardiovascular mortality (1,2). One study showed that the combination of microalbuminuria and mild renal insufficiency confers a risk for cardiovascular events even higher than that observed in patients with a coronary heart disease and a normal renal function (3). Although several factors may explain this association between renal and cardiovascular disease, there is growing evidence that hyperlipidemia contributes not only to cardiovascular disease but also to renal disease progression.

Epidemiologic Evidence

All patients with chronic disease experience a secondary form of dyslipidemia that mimics the atherogenic dyslipidemia of insulin-resistant patients. This is characterized by an increase in serum triglycerides with elevated VLDL, small dense LDL particles, and low HDL cholesterol. All of these particles are characterized by triglyceride-rich apolipoprotein B (apoB)-containing complex lipoproteins, which have a significant atherogenic potential (4).

That dyslipidemia is not just secondary to renal disease was shown clearly in diabetes: In both type 1 and type 2 diabetes, an unfavorable lipid profile is present at a very early stage of albuminuria, when GFR is normal or elevated (5–7). The concentration of total cholesterol, VLDL, LDL cholesterol, and triglycerides rises with increasing albumin excretion rate in patients with type 1 diabetes. In addition, there is an increase in LDL mass and atherogenic small dense LDL particles, which correlates with the plasma triglycerides concentrations (8). HDL levels also tend to be reduced with a disadvantageous alteration in their composition. Similarly, in the nondiabetic population, those with microalbuminuria have similar lipid abnormalities (9).

Lipids as Progression Promoters

Studies in a variety of animal models have shown that hypercholesterolemia accelerates the rate of progression of kidney disease (10). A high-fat diet causes macrophage infiltration and foam cell formation in rats, leading to glomerulosclerosis (11).

In humans more than a decade ago, a relationship between serum cholesterol levels and GFR decline was shown in 31 patients with type 1 diabetes and established overt nephropathy (12). In those with a total cholesterol level >7 mmol/L, the rate of decline in GFR was at least three times higher than in those with a level <7 mmol/L. The power of serum cholesterol levels in predicting the progression of diabetic nephropathy in type 1 diabetes was confirmed by a Danish group in a study of 301 patients who had diabetes and overt nephropathy and were followed up for 7 yr (13).

A similar finding also was found in patients with type 2 diabetes and overt nephropathy. A post hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study showed in a large group of patients with type 2 diabetes that both total cholesterol and LDL cholesterol measured at baseline were independent risk factors for ESRD (14).

The predictive power for renal disease progression also has been observed before the appearance of microalbuminuria, at least in diabetes. Ravid et al. (15) demonstrated in a prospective study of 574 patients with type 2 diabetes and normal renal function at baseline that a high cholesterol level was associated with a significantly higher incidence of microalbuminuria as well as of cardiovascular events.

Samuelsson et al. (16) demonstrated a strong correlation between triglyceride-rich apoB-containing lipoproteins and the rate of progression in nondiabetic patients with chronic kidney dis-
ease. Muntner et al. (17) then showed that people with low HDL cholesterol and hypertriglyceridemia at baseline have a higher risk for having a loss of renal function. That all of the participants in this study (12,728 participants in the Atherosclerosis Risk in Communities) had a baseline creatinine <2 mg/dl in men and <1.8 mg/dl in women suggests hypertriglyceridemia in the initiation of mild renal insufficiency. That high triglycerides levels are an independent predictor of renal disease also was confirmed in a prospective study of 297 patients with type 1 diabetes (18).

Mechanisms

Progressive renal failure, especially that associated with proteinuria, is accompanied by abnormalities of lipoprotein transport. Typically, the dyslipidemia is reflected predominantly in increased serum levels of triglycerides with high levels of VLDL, apoB and pre-β HDL, and low levels of HDL and of apoA. Cholesterol levels may be very high in proteinuric patients (4).

This pattern of abnormalities is due to several pathogenetic mechanisms. First, urinary protein loss stimulates an increased LDL synthesis by the liver. It is likely that proteinuria with the resultant hypoalbuminemia leads to an upregulation of 3-hydroxy-3-methylglutaryl CoA reductase with a consequent hypercholesterolemia (19). 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. Lipoprotein lipase (LPL) is the rate-limiting step in lipolysis of chylomicrons and VLDL. LPL binds to heparan sulfate proteoglycans on the cell surface of endothelium. In proteinuric renal diseases, a downregulation of LPL protein abundance and enzymatic activity was found (4). These events are largely responsible for profound abnormalities in lipoprotein metabolism in nephrotic syndrome and chronic renal failure’s rendering these lipoproteins more atherogenic.

Regarding the mechanisms by which abnormal serum lipid levels may contribute to renal disease progression, there is evidence that circulating lipids bind to and become trapped by extracellular matrix molecules (10), where they undergo oxidation increasing the formation of reactive oxygen species such as superoxide anion and hydrogen peroxide (21). The resultant reduction in the actions of endothelium-derived vasodilators/growth inhibitors, such as prostacyclin and nitric oxide, with maintenance or increased formation of endothelium-derived vasoconstrictors/growth promoters, such as angiotensin II, endothelin-1, and plasminogen activator inhibitor-1, has significant vascular and renal pathophysiologic consequences. Macrophages phagocytize oxidized lipids and undergo a transition to foam cells. Macrophage-derived foam cells release cytokines that recruit more macrophages to the lesion and influence lipid deposition, endothelial cell function, and vascular smooth muscle cell proliferation. Glomerular cells mimic some of these characteristics of cells in the atherosclerotic vessel wall (22); therefore, similar pathogenetic mechanisms may contribute to the progression of atherosclerosis and chronic kidney disease.

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 (23). Oxidative stress, with the resultant increased reactive oxygen species generation, contributed significantly to these chronic degenerative processes.

It also is possible that some of the deleterious effects of lipids on kidney are mediated by other mechanisms that are responsible for the adverse lipid profile that is present in patients who are susceptible to renal damage. As stated earlier, all patients with chronic disease experience a secondary form of dyslipidemia that mimics the atherogenic dyslipidemia of insulin-resistant patients (24). This observation raises the possibility that the insulin resistance syndrome may underlie or mediate the association between lipids and a loss of renal function.

Recently a strong, positive, and significant relationship between the metabolic syndrome and risk for chronic renal disease and microalbuminuria was found in a large nondiabetic general population (25). Insulin resistance characterizes type 1 diabetes in patients with albuminuria and their first-degree relatives without diabetes (26,27) and underlies many of the alterations of diabetic nephropathy, including high BP, lipid abnormalities, increased left ventricular mass, and a family history of hypertension and cardiovascular disease (24). These observations and a recent study by Orchard et al. (28) suggest that insulin resistance is likely to precede and play a role in the vascular damage of diabetic nephropathy.

Evidence of Lipid Involvement in Renal Damage: Effect of Statins

In recent years, the inhibition of 3-hydroxy-3-methylglutaryl CoA reductase by statins has demonstrated beneficial effects in different models of progressive renal failure (29). It is interesting that some of the beneficial effects of statins can be seen independent of the cholesterol reduction. In an elegant study by Zoja et al. (30), it was shown that a combined angiotensin-converting enzyme inhibitor and statin therapy had a remarkable antiproteinuric effect with a significant improvement in renal function. Drug combination limited glomerulosclerosis, tubular damage, and interstitial inflammation, compared with placebo or drugs alone.

In vitro studies have established clearly that statins influence important intracellular pathways that are involved in the inflammatory and fibrogenic responses, which are common components of many forms of progressive renal injury (29). Statins also inhibit proliferation of cultured mesangial cells and renal epithelial tubular cells through their capability to suppress the formation of intermediate metabolites of the mevalonate pathway, particularly the nonsterol isoprenoids, which seem to be essential in cell replication (31).

Although there is not yet a large intervention study on the effect of statin therapy in the progression of renal damage, there is evidence from post hoc analyses to suggest that statins are likely to be effective in the treatment of renal disease. This topic is developed elsewhere in this issue. However, a multifactorial strategy that combined glycemic therapy, lipid lowering, BP control, and
aspirin reduced both cardiovascular and renal end points by 50% in patients with type 2 diabetes and microalbuminuria (32).

References


