Lipid abnormalities in renal disease

Arghya Majumdar MD MRCP David C Wheeler MD FRCP

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An association between lipids and kidney disease was first noted by Virchow, who described 'fatty degeneration' of the renal epithelium in Bright's disease in 1860[1]. Since then the possible adverse effects of dyslipidaemia complicating renal disease have attracted the interest of many investigators. Both qualitative and quantitative abnormalities in lipid profiles have been noted in patients with nephrotic syndrome[2] and chronic renal failure (CRF)[3]. Dialysis does not correct the dyslipidaemia of uraemia but may modify it[4]; and plasma lipid levels can even rise after successful renal transplantation—an effect probably due partly to the adverse impact of some immunosuppressive agents[5]. The cardiovascular consequences of prolonged hypercholesterolaemia in the general population are well known, but whether abnormalities of lipid metabolism contribute to the excess risk of atherosclerosis in patients with CRF is uncertain. Since about half the deaths in patients undergoing dialysis are due to cardiovascular disease, potential risk factors such as dyslipidaemia are receiving close attention. An additional consideration, based on experimental observations in animals, is that lipoproteins may have a direct nephrotoxic effect in the clinical setting of renal failure[6]. On the assumption that correction of abnormal lipid metabolism is desirable, it is important to understand the intricacies of dyslipidaemia in patients with kidney disease and evolve therapeutic strategies. This review briefly outlines the current thinking.

NORMAL LIPOPROTEIN COMPOSITION

Cholesterol and triglycerides are virtually insoluble in plasma and are transported in association with phospholipids and proteins in lipoprotein particles. These comprise an inner core of non-polar lipids (triglyceride and esterified cholesterol) surrounded by an outer envelope of polar molecules (phospholipids, free cholesterol and apoproteins)[7]. Lipoproteins may be separated by ultracentrifugation or electrophoresis, and are classified by density criteria. The exogenous pathway is responsible for the transport and distribution of dietary lipids from the intestine to the liver and the endogenous pathway shuttles cholesterol and triglycerides between the liver and extrahepatic tissues.

Apoproteins (apos) serve to maintain the structural integrity of the particles, modulate the activity of enzymes involved in their metabolism and act as ligands for cell surface lipoprotein receptors[8]. Lipoprotein(a) or Lp(a), is a modified form of low-density lipoprotein (LDL) that is assembled extracellularly from apoprotein(a) and LDL[9]. The apo(a) gene locus is situated on chromosome 6 with the two alleles inherited co-dominantly[10].

DYSLIPIDAEMIA IN NEPHROTIC SYNDROME

Patterns

A high total plasma cholesterol concentration is the most common abnormality found in patients with nephrotic syndrome. Plasma triglycerides may also be raised, especially in patients with heavy proteinuria[2]. The magnitude of lipid abnormality correlates with disease severity, and hyperlipidaemia promptly resolves after remission of nephrotic syndrome[2]. Neither the pattern nor the degree of lipid abnormality is influenced by the nature of the underlying glomerular lesion[11].

In almost all nephrotic patients the number of circulating LDL particles is high; very-low-density lipoprotein (VLDL) concentrations are less likely to be raised. Though high-density lipoprotein (HDL) levels may be normal, there is a reduction in the HDL_2 and an increase in the HDL_3 subfractions due to reduced lecithin:cholesterol acyltransferase (LCAT) activity[2]. This pattern of HDL disturbance, along with increased LDL:HDL ratios and elevated Lp(a) levels, might enhance the risk of atherosclerosis in this group of patients[2]. Apoprotein abnormalities in nephrotic patients usually reflect changes in lipoprotein concentrations. Thus, apoB, the major LDL protein, is increased proportionately more than other apoproteins[12] (Figure 1).

Mechanisms

The mechanisms responsible for raised lipid concentrations in the nephrotic syndrome are not fully understood. Enhanced hepatic synthesis of apoB-containing lipoproteins may account for the rise in cholesterol levels[12,13]. The fact that infusions of albumin or dextran tend to normalize lipoprotein concentrations suggests that a decrease in

Department of Nephrology, University Hospital (Birmingham) NHS Trust, Queen Elizabeth Medical Centre, Edgbaston, Birmingham B15 2TH, UK
E-mail: David.wheeler@university-b.wmids.nhs.uk
Correspondence to: Dr D C Wheeler

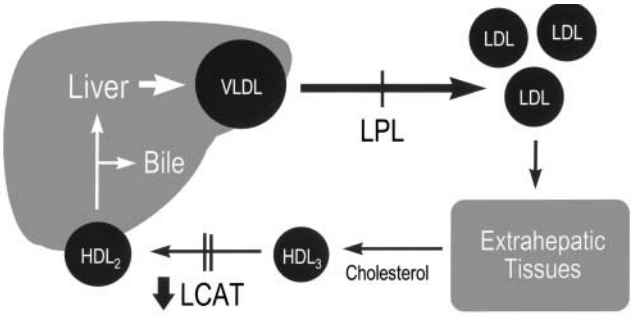

Figure 1 **Lipid abnormalities in nephrotic syndrome.** VLDL=very-low-density lipoprotein; LDL=low-density lipoprotein; IDL=intermediate-density lipoprotein; HDL=high-density lipoprotein; LPL=lipoprotein lipase; LCAT=lecithin:cholesterol acyltransferase. Normally, VLDL is assembled and secreted by the liver and is metabolized by LPL to IDL and LDL. LDL particles deliver lipid to extrahepatic tissues via the apoprotein B/E receptor. Nascent HDL is synthesized by the intestine and liver and matures in the peripheral circulation to HDL_3 and HDL_2. During maturation, HDL particles accumulate and esterify cholesterol derived from cells, a process that requires LCAT. In nephrotic syndrome, hepatic VLDL production is increased, leading to elevated circulating levels of VLDL, IDL and LDL. This is compounded by defective catabolism of these particles in the peripheral circulation as a result of low LPL activity. In addition, receptor-mediated uptake of LDL particles may be impaired. HDL maturation is inhibited as a result of diminished LCAT activity. These defects in the HDL pathway also contribute to impaired catabolism of triglyceride-rich lipoproteins.

oncotic pressure, rather than hypoalbuminaemia *per se*, is the trigger for increased lipoprotein synthesis by the liver[2]. *In-vitro* studies suggest that low oncotic pressure directly stimulates hepatic apoB gene transcription, thereby supporting this hypothesis[14].

Impaired metabolism, rather than increased synthesis, may be responsible for nephrotic hypertriglyceridaemia. The delipidation cascade, in which VLDL is converted to intermediate-density lipoprotein (IDL) and then to LDL by lipoprotein lipase (LPL), is slowed[15]. LDL receptor mediated clearance of LDL and IDL is also reduced[15,16]. This abnormality in triglyceride catabolism is related to renal albumin clearance rather than plasma oncotic pressure—an observation suggesting urinary loss of an unidentified regulator of lipid metabolism[17].

DYSLIPIDAEMIA IN CHRONIC RENAL FAILURE

CRF leads to a complex disturbance of lipoprotein metabolism, the precise manifestations of which may be influenced by other factors such as nutritional state, diabetes and the presence of proteinuria[3] (Figure 2).

Patterns

The characteristic pattern is an accumulation of partially catabolized apoB-containing, triglyceride-rich, particles of the VLDL and IDL classes, leading to hypertriglyceridaemia[3]. The concentration of HDL is decreased, with reduced relative concentrations of free and esterified cholesterol and increased triglyceride content. The concentration of the HDL_2 subfraction is low whilst HDL_3 is normal[3]. Although the concentrations of LDL are not generally increased, there is a predominance of small, dense particles which are particularly susceptible to oxidation, bind weakly to LDL receptors and are cleared slowly from plasma. These small particles are thought to be more atherogenic than larger LDL subfractions[18].

The apoprotein composition of particles is altered with an early and marked increase in apoCIII in VLDL and LDL and a decrease in the apoAI content of HDL. These abnormalities, coupled with changes in the concentrations of the particles, lead to a characteristic decrease in apoAI:CIII ratio, considered to be a hallmark of uraemic dyslipidaemia. This decrease is detectable when the glomerular filtration rate is only moderately reduced and the plasma triglyceride level is still normal. There is also a decrease in the ratio of apoAI to apoB. The ratio of apoCIII:CII is increased although levels of both may be raised. Plasma levels of Lp(a) in patients with CRF are two to three times those in normal controls[19].

Mechanisms

Impaired clearance of apoB-containing triglyceride-rich lipoproteins of hepatic and intestinal origin is the principal abnormality in CRF. This is due to reduced activity of lipolytic enzymes, notably LPL and hepatic triglyceride lipase[3]. Since apoCII activates and apoCIII competitively inhibits LPL, changes in the ratio of these proteins may contribute to impaired activity of this enzyme[20]. Pre-β HDL, a form of apoA1 that is found in the non-lipoprotein fraction of normal plasma and acts as a lipase inhibitor, has also been identified in uraemic plasma[21]. Other factors that may contribute to the uraemic

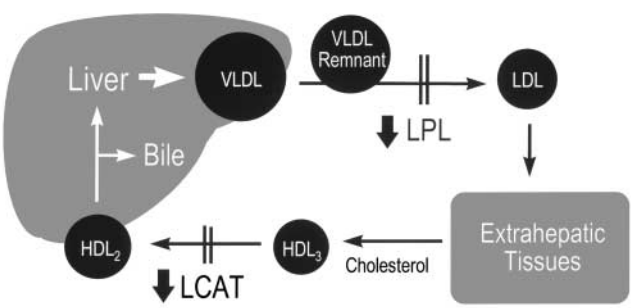

Figure 2 **Lipid abnormalities in chronic renal failure.** There is accumulation of partially catabolized VLDL and chylomicron remnants (not shown) during the earliest stages of uraemia as LPL activity is reduced. There is also reduced activity of LCAT, so that HDL maturation, and thus formation of HDL_2, is impaired, thereby inhibiting the transfer of esterified cholesterol from tissues to the liver (reverse cholesterol transport).

dyslipidaemia include insulin resistance and hyperparathyroidism[3].

EFFECT OF RENAL REPLACEMENT THERAPY

Dialysis

The dyslipidaemia of CRF is not corrected by dialysis, although the lipoprotein patterns may be modified. Raised triglycerides are found in between 30% and 70% of patients undergoing dialysis; hypercholesterolaemia, less commonly observed, is more likely to be present in patients receiving continuous ambulatory peritoneal dialysis (CAPD) than those receiving haemodialysis, probably because of glucose absorption from the dialysate and peritoneal protein loss (5–15 g/day)[22].

In a prospective study involving a large dialysis population, in which correction was made for independent factors, patients on CAPD had higher total cholesterol and apoB concentrations, a higher total:HDL cholesterol ratio and lower apoAI:apoB ratios than individuals receiving haemodialysis[23]. Almost all studies have found higher levels of Lp(a) in patients treated with CAPD than in those receiving haemodialysis[22]. The lipid profile is often improved by high-flux dialysis with biocompatible polysulfone membranes, possibly because of enhanced removal of lipase inhibitors[24].

Renal transplantation

Dyslipidaemia may worsen after a renal transplant and the pattern of abnormality usually changes. Current immunosuppressive regimens combining cyclosporin and corticosteroids have an important contributory role[13]. Two years after transplantation, increased total LDL and HDL cholesterol, decreased VLDL cholesterol, but normal total and VLDL triglycerides have been reported in stable patients receiving cyclosporin, azathioprine and prednisolone[25].

CONSEQUENCES OF DYSLIPIDAEMIA

Cardiovascular

Hypercholesterolaemia and the metabolic cluster of hypertriglyceridaemia associated with low HDL levels and small dense LDL are proven risk factors for ischaemic heart disease in the general population. Whether the more subtle lipoprotein abnormalities observed in the early stages of uraemia promote atherosclerosis is not known. The only available data are derived from small observational studies and are not therefore reliable. For example, Attman *et al.* noted that the apo abnormalities they reported as characteristic of CRF (low apoAI:CIII and apoAI:B ratios) tended to be more marked in dialysis patients with clinical evidence of coronary artery disease[26]. In 129 haemodialysis patients prospectively followed for 4 years, Cressman *et al.* demonstrated that Lp(a) levels were an independent risk factor for cardiovascular events[27]. In contrast Avram *et al.* noted lower cholesterol and apoB levels in dialysis patients who died; because of the direct correlation between serum albumin, total cholesterol and apoB in these patients, this was interpreted as reflecting the severe co-morbid illness and malnourishment of those with the highest chance of dying[23]. To establish whether correction of lipid abnormalities will reduce the risk of ischaemic heart disease, or other cardiovascular complications, in patients with CRF and nephrotic syndrome requires controlled interventional studies of lipid-lowering agents.

Progression of renal disease

Experimental evidence supports the hypothesis that lipids contribute directly to glomerulosclerosis and tubulointerstitial injury and that correction of lipid abnormalities associated with renal disease will slow the progression of chronic renal failure[28,29]. Histological and histochemical studies in animals have shown deposits containing cholesterol, triglycerides, phospholipids, apoproteins and oxidized LDL particles in the kidney[2]. Accumulation of lipids is probably the result of defective clearance via lymphatic channels in the presence of high plasma concentrations. Lipid deposition may promote monocyte infiltration, resulting in release of inflammatory mediators (a process akin to atherosclerosis), disturbed mesangial cell secretory function, mesangial cell death and excess accumulation of matrix components, eventually leading to irreversible scarring[29,30]. Animal work also indicates that an excess of circulating abnormal lipoprotein particles, as found in early renal insufficiency, rather than a raised concentration of normal particles, may contribute to nephrotoxicity[6]. At present there is little information from clinical studies to suggest that lipid-lowering therapy will slow progression of chronic renal disease in man.

Chronic vascular rejection

Evidence from experimental and clinical studies indicates a possible role for dyslipidaemia in progression of chronic vascular rejection (CVR). In observational studies, hypercholesterolaemia both before[25] and after[31] renal transplantation was found to predict graft loss due to CVR. The histopathological hallmark of CVR, intimal hyperplasia, resembles vascular changes observed in early atherosclerotic lesions and the mechanisms leading to these forms of vascular disease may be similar[32].

MANAGEMENT OF RENAL DYSLIPIDAEMIA

The need to treat lipid abnormalities complicating renal disease is unproven. We still do not know whether normalization of lipoprotein profiles will reduce the risk of cardiovascular complications or progression of renal disease. Many clinicians opt for a conservative policy, prioritizing management of other complications of renal disease such as hypertension and anaemia. One might reasonably assume, however, that the well-accepted cardiovascular risk factors present the same hazards to a patient with CRF or nephrotic syndrome as they do to a patient without renal disease. Whilst the results of clinical trials are awaited, the decision to treat must be based on extrapolations from clinical studies in populations without renal disease, taking into account the assessment of an individual patient's risk profile and prognosis[3]—age, sex, cardiovascular history, family history and concomitant risk factors such as hypertension and diabetes.

Many lipid-lowering regimens are effective in patients with chronic renal disease. These include low-saturated-fat diets[2,33], fish-oil supplements[34] and changes in lifestyle including regular exercise. Bile acid sequestrants are limited by their gastrointestinal side-effects. Fibric acid derivatives accumulate in renal failure and, although the newer members of this class seem relatively safe in low dose, there is an increased risk of myositis. Adequate management of underlying renal disease should not be overlooked. For example, lipid abnormalities associated with the nephrotic syndrome usually improve if the disease remits, or may be partially corrected by minimizing proteinuria with an angiotensin converting enzyme inhibitor.

Statins have become the most widely used class of drug in the treatment of hyperlipidaemia complicating chronic renal disease[35], effectively lowering plasma cholesterol in patients with CRF and nephrotic syndrome. They seem relatively safe even at high doses. Rhabdomyolysis can occur, and the risk may be increased if cyclosporin is concurrently prescribed. In addition to lowering plasma lipid levels, statins may have other actions relevant to nephrology. For example, they correct endothelial dysfunction, stabilize established plaques, and modify the coagulation pathway, thereby reducing the likelihood of sudden vascular events[36]. They inhibit mesangial proliferation and may be of use in proliferative glomerular diseases[37]; they also inhibit T-cell cytotoxicity and may reduce the incidence of acute rejection when used in conjunction with current immunosuppressive regimens after organ transplantation[38].

CONCLUSION

The pathogenesis of abnormal lipid metabolism complicating CRF and nephrotic syndrome is complex, the consequences of the resultant dyslipidaemia are not properly understood and optimal management remains to be established. Many nephrologists are already happy to offer their patients lipid-lowering drugs, assuming that correction of dyslipidaemia is desirable; however, the benefits of treatment in terms of both cardiovascular disease prevention and slowing of progressive renal failure are unproven, whilst the safety of long-term therapy needs to be confirmed. Furthermore, the appropriate timing and duration of treatment in patients with renal impairment and nephrotic syndrome remains uncertain. Clearly, large prospective randomized controlled studies with long-term follow-up are required to answer these important questions.

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