HDL abnormalities in nephrotic syndrome and chronic kidney disease

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Abstract | Normal HDL activity confers cardiovascular and overall protection by mediating reverse cholesterol transport and through its potent anti-inflammatory, antioxidant, and antithrombotic functions. Serum lipid profile, as well as various aspects of HDL metabolism, structure, and function can be profoundly altered in patients with nephrotic range proteinuria or chronic kidney disease (CKD). These abnormalities can, in turn, contribute to the progression of cardiovascular complications and various other comorbidities, such as foam cell formation, atherosclerosis, and/or glomerulosclerosis, in affected patients. The presence and severity of proteinuria and renal insufficiency, as well as dietary and drug regimens, pre-existing genetic disorders of lipid metabolism, and renal replacement therapies (including haemodialysis, peritoneal dialysis, and renal transplantation) determine the natural history of lipid disorders in patients with kidney disease. Despite the adverse effects associated with dysregulated reverse cholesterol transport and advances in our understanding of the underlying mechanisms, safe and effective therapeutic interventions are currently lacking. This Review provides an overview of HDL metabolism under normal conditions, and discusses the features, mechanisms, and consequences of HDL abnormalities in patients with nephrotic syndrome or advanced CKD.

Normal HDL confers protection against cardiovascular disease (CVD), oxidative stress, and systemic inflammation through its potent anti-inflammatory, antioxidant, and antithrombotic activities and through mediation of the reverse cholesterol transport pathway[1]. Kidney disease can induce marked alterations in lipid metabolism and the serum lipid profile, which can in turn accelerate disease progression and development of associated comorbidities, such as CVD. Numerous factors influence the nature of lipid disorders in patients with kidney disease, including the presence and severity of proteinuria and renal failure, dietary and drug regimens, pre-existing genetic disorders of lipid metabolism, and renal replacement therapies (haemodialysis, peritoneal dialysis, and renal transplantation).

Heavy glomerular proteinuria (nephrotic syndrome) results in marked hypercholesterolaemia; hypertriglyceridaemia; increased levels of ApoB-containing lipoproteins (including very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and LDL), lipoprotein(a), ApoB, ApoC, and ApoE, and an increased ApoC-III:ApoC-II ratio; and profound changes in the serum cholesterol:triglyceride, free cholesterol:esterified cholesterol and lipoprotein phospholipid:protein ratios[2]. Patients with nephrotic syndrome typically exhibit HDL cholesterol levels within or below the normal limits (although levels might occasionally be elevated), but the HDL cholesterol:total cholesterol ratio is frequently decreased compared to the ratio in those with normal renal function.

Patients with CKD and minimal proteinuria and patientd with end-stage renal disease (ESRD) who are maintained on haemodialysis commonly exhibit total serum cholesterol and LDL cholesterol concentrations within or below the normal limits, but the serum triglycerides, VLDL, IDL, chylomicron remnants, and oxidized LDL levels are often increased compared to levels in individuals with normal renal function[3–6]. Renal replacement modalities and kidney transplantation can markedly modify lipid profiles of patients with ESRD. Compared to patients on haemodialysis, patients on peritoneal dialysis frequently exhibit elevated total cholesterol and LDL cholesterol levels. This variation with dialysis modality is caused by notable losses of proteins in the peritoneal dialysis fluid effluent that mimics nephrotic syndrome in functionally anephric individuals[3,4]. Heavy uptake of glucose from the peritoneal dialysis fluid can also lead to a rise in plasma triglyceride levels[3]. Other factors that modify the serum lipid profile in this population include systemic inflammation, malnutrition, use of lipid-altering drugs (such as statins and fibrates), and exposure to

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Key points

- Heavy glomerular proteinuria (nephrotic syndrome) and advanced chronic kidney disease (CKD) can elicit profound changes in the structure and function of HDL
- HDL abnormalities in nephrotic syndrome impair reverse cholesterol transport and consequently promote foam cell formation, atherosclerosis, and glomerulosclerosis
- HDL abnormalities in nephrotic syndrome are largely due to lecithin–cholesteryl acyltransferase (LCAT) deficiency caused by urinary losses, elevated plasma cholesterol ester transfer protein levels, hypoalbuminaemia, and/or reduced expression levels of hepatic HDL docking receptor (SRB1)
- HDL abnormalities in CKD are caused by deficiencies in ApoA-1, ApoA-2, LCAT, paraoxonase-1, glutathione peroxidase, elevated levels of ACAT-1, and increased oxidative and myeloperoxidase modifications to HDL cargo
- Oxidative and myeloperoxidase modifications to ApoA-1, ApoA-2 and SRB1 impair HDL-mediated reverse cholesterol transport and HDL antioxidant and anti-inflammatory activity
- HDL abnormalities contribute to endothelial dysfunction, accelerated atherosclerosis, oxidative stress, and systemic inflammation in patients with CKD

sevelamer — a phosphate binding resin that markedly lowers serum cholesterol levels by binding and sequestering bile acids in the intestinal tract[7,8]. Furthermore, use of steroids and certain immunosuppressive medications, such as rapamycin and calcineurin inhibitors, that are frequently administered to renal transplant recipients can also affect lipid metabolism and serum lipid profile[3].

This Review discusses the functions of HDL and the mechanisms underlying its production and metabolism under normal conditions. The characteristics, mechanisms, and consequences of HDL abnormalities that can occur in patients with nephrotic syndrome, CKD, and ESRD are analysed, and the current treatment options available for these patient populations are discussed.

HDL

HDL production and reverse cholesterol transport

Reverse cholesterol transport is the process by which cholesterol is extracted from peripheral tissues by HDL, carried in the plasma, and disposed of in the liver. Nascent HDL is formed in the circulation through the partial protein lipidation of ApoA-1 and ApoA-2 with phospholipids and cholesterol, which is facilitated via binding to the membrane-associated transporter, ABCA-1 (REF. 9). In vascular tissue, nascent HDL binds to ABCA-1 that is expressed on the plasma membrane of the lipid-laden macrophages. The binding of HDL to ABCA-1 triggers the activation of cholesterol ester hydrolase (CEH), which hydrolyses intracellular cholesterol esters and causes the release of free cholesterol and its subsequent transfer to the surface of the nascent HDL particle. This process is opposed by ACAT, which esterifies cholesterol within the macrophage. Once on the HDL particle surface, free cholesterol is re-esterified by lecithin–cholesteryl acyltransferase (LCAT), which facilitates storage of cholesterol in the core of the HDL particle and transforms lipid-poor HDL_3 into cholesterol ester-rich HDL_2, which is then released in the circulation[9] (FIG. 1). In addition to receiving cholesterol from lipid-laden macrophages, HDL receives a considerable amount of cholesterol from other cell types, including adipocytes, skin fibroblasts, and skeletal muscle cells[1,9]. Other important sources of lipids and apoproteins that are acquired by HDL are ApoB-containing lipoproteins and circulating albumin[10]. Hydrolysis of triglycerides in VLDLs and chylomicrons (lipoprotein particles) by lipoprotein lipase (LPL) in the capillaries that perfuse adipose tissue and skeletal muscle leads to the release of phospholipids, which are then transferred to HDL by phospholipid transfer protein (PLTP). In addition, cholesterol ester transfer protein (CETP) modifies the HDL lipid content by transferring part of the HDL cholesterol ester cargo to IDL and LDL in exchange for triglycerides (FIG. 1). Finally, albumin transfers its free cholesterol cargo to HDL in the circulation[10–12].

In the liver, cholesterol ester-rich HDL_2 binds to the HDL docking receptor SRB1, where the HDL cholesterol ester cargo is removed, the triglyceride and phospholipid contents are hydrolysed by hepatic lipase, and the contents are internalized by the liver and the lipid-poor HDL particle is released into the circulation to repeat the cycle[13]. Changes in any of these steps can have a considerable effect on the structure and function of HDL.

Biologic functions of normal HDL

HDL is the principal vehicle for reverse cholesterol transport and has a critical function protecting against foam cell (fat-laden macrophage) formation and atherosclerosis. The numerous protective functions served by normal HDL are outlined in more detail below (FIG. 2).

Enhancement of endothelial function. HDL enhances endothelial function through the activation of endothelial nitric oxide synthase (eNOS), which increases the production of nitric oxide. This process is achieved by Akt-mediated phosphorylation of eNOS upon HDL binding to its receptors, SRB1 and S1P3[14–16]. The antioxidant activity of HDL can also limit the uncoupling of eNOS and inactivation of nitric oxide by inhibiting the production of reactive oxygen species (ROS) by binding ABCG1 (FIG. 2).

Antioxidant and anti-inflammatory activity. Normal HDL serves as a key driver against oxidative stress and the formation of proinflammatory oxidized lipids and lipoproteins via its constituent antioxidant enzymes, paraoxonase-1 and glutathione peroxidase, which can inhibit and/or reverse LDL oxidation. Moreover, HDL serves a protective role against systemic inflammation by removing oxidized phospholipids and fatty acids from LDL, VLDL, and IDL, removing endotoxin and serum amyloid-A from the circulation[17,18], and promoting their disposal in the liver. Finally, normal HDL inhibits the attachment of monocytes to endothelial cells by inhibiting expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) on endothelial cells[19,20] and CD11b on monocytes[21] (FIG. 2).

Prevention of endothelial cell apoptosis. Oxidative stress and inflammation are common features of CKD and

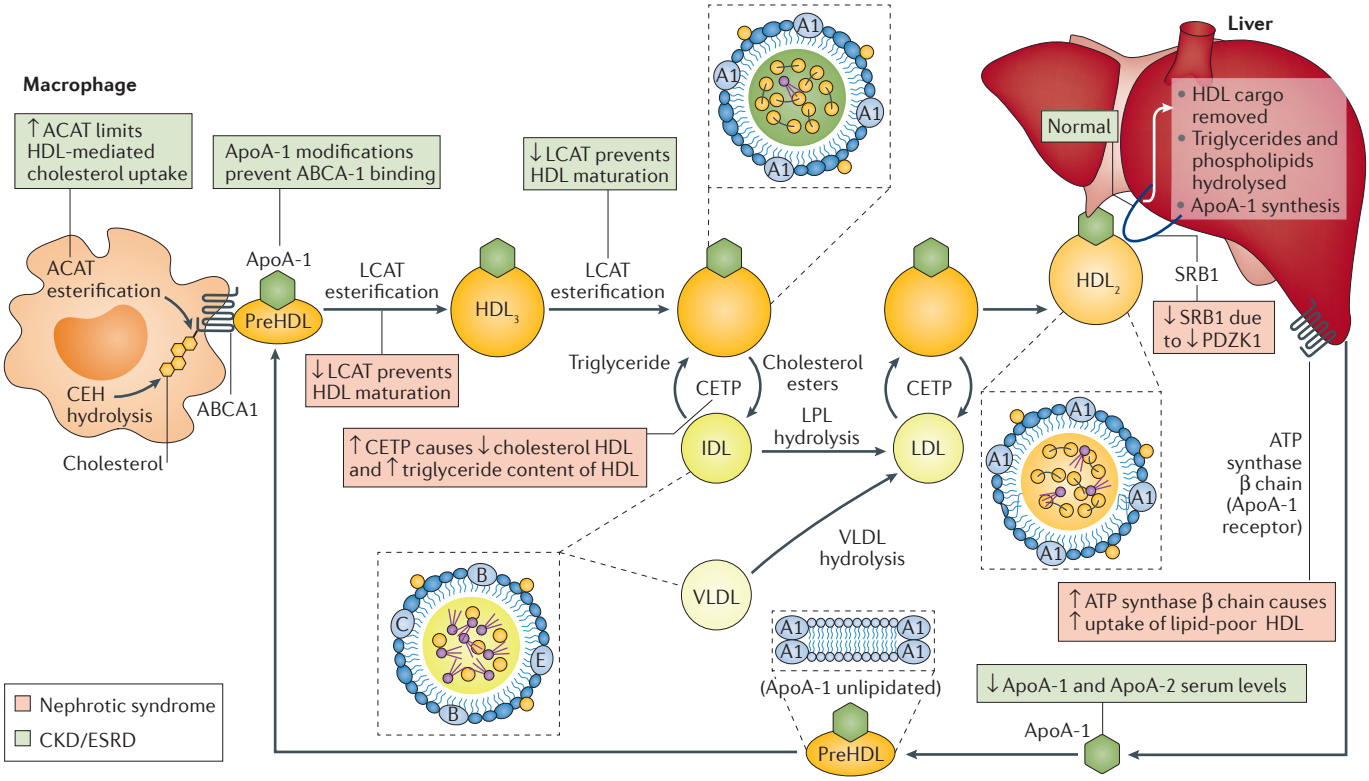

Figure 1 | **Production and metabolism of HDL via reverse cholesterol transport.** ApoA-1 and ApoA-2 are synthesized and released in the circulation by the liver. Nascent HDL is formed in the circulation from the partial lipidation of ApoA-1 and ApoA-2 by phospholipids and cholesterol. In the vascular tissue nascent HDL binds to the ABCA-1 on lipid-laden macrophages to trigger the activation of cholesterol ester hydrolase (CEH), release of free cholesterol, and its transfer to the surface of HDL. Free cholesterol is then re-esterified by lecithin–cholesteryl acyltransferase (LCAT) and stored in the core of the HDL particle. This process leads to the transformation of lipid-poor discoid HDL3 to spherical cholesterol ester-rich HDL2 particles, which then detach and are released into the circulation. Uptake of cholesterol by HDL is opposed by ACAT-1, which favours intra-cellular retention of cholesterol by promoting its esterification. In the circulation, cholesterol ester transfer protein (CETP) transfers part of the HDL cholesterol-ester cargo to intermediate density lipoprotein (IDL) and LDL in exchange for triglycerides. In the liver, cholesterol ester-rich HDL2 binds to the HDL docking receptor, SRB1, which accommodates the removal of HDL cholesterol-ester cargo and hydrolysis of its triglyceride and phospholipid contents by hepatic lipase for uptake by the liver. After unloading the lipid cargo, the lipid-poor HDL detaches from SRB1 and returns to the circulation to repeat the cycle. HDL structure and function are impaired in both nephrotic syndrome and chronic kidney disease (CKD). HDL abnormalities in nephrotic syndrome are caused by a combination of LCAT deficiency (caused by its loss in the urine), increased CETP, hepatic HDL docking receptor (SRB1) deficiency, and upregulation of the hepatic HDL endocytic receptor (β chain of ATP synthase). HDL abnormalities in CKD are caused by a combination of ApoA-1, ApoA-2, and LCAT deficiencies, upregulation of ACAT-1 in renal and vascular tissue, and carbamylation, oxidation, and myeloperoxidase modification of ApoA-1 and SRB1, which limit the binding capacity of HDL to its receptors. ESRD, end-stage renal disease.

promote endothelial cell injury and apoptosis. Acting via its constituent ApoA-1 and sphingosine-1 phosphate (S1P) proteins, HDL lowers caspase-3 activity, inhibits the formation of ROS, and prevents apoptosis of endothelial cells[22–24]. In addition, normal HDL facilitates the repair, migration, and proliferation of endothelial cells and increases the number of circulating endothelial progenitor cells — events that are essential for vascular repair and prevention of plaque formation[25–27] (FIG. 2). In this context HDL was shown to stimulate the repair of a wounded bovine aortic endothelial cell monolayer cultured in serum-free medium in a concentration-dependent manner[25]. Likewise, HDL can promote endothelial cell growth and proliferation in a FGF-dependent manner[26,27].

Antithrombotic effects. Pathologic endothelial cell activation stimulates the expression of prothrombotic factors, such as tissue factor, P-selectin, and E-selectin, which initiate a coagulation cascade and promote platelet activation and adhesion[28]. Normal HDL exerts antithrombotic effects by inhibiting the expression of tissue factor, P-selectin, E-selectin, platelet activating factor, and thromboxane A-2 and promotes the expression of anti-thrombin-3, protein C, and protein S[29]. Furthermore, increased production of nitric oxide by HDL inhibits platelet activation and adhesion. Finally, activation of phospholipase A2 by oxidized LDL promotes platelet aggregation and adhesion[30]; therefore, reversal and/or prevention of LDL oxidation by normal HDL prevents oxidized-LDL-mediated platelet activation[31] (FIG. 2).

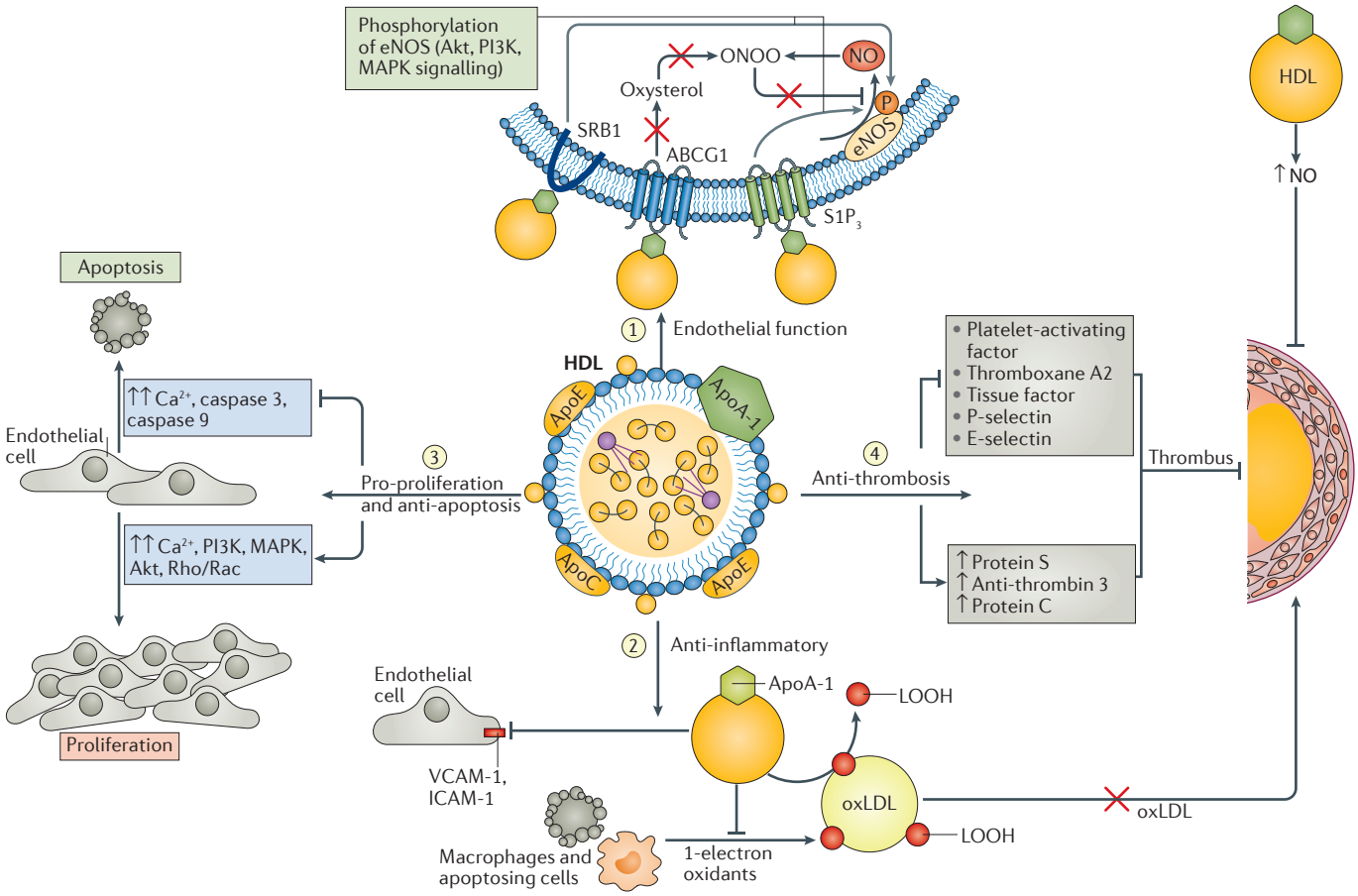

Figure 2 | **Protective functions of HDL.** HDL serves several important protective functions in addition to its role in mediating reverse cholesterol transport. HDL enhances endothelial function (1) through the activation of endothelial nitric oxide synthase (eNOS) and production of nitric oxide (NO) by Akt-mediated phosphorylation of eNOS in response to HDL binding to SRB1 and S1P3. In addition, the antioxidant activity of HDL can also limit the uncoupling of eNOS and inactivation of nitric oxide by reactive oxygen species (ROS) by binding the ABCG1 receptor. Normal HDL serves a protective role against oxidative stress via the actions of its constituent antioxidant enzymes, paraoxonase and glutathione peroxidase. HDL mitigates systemic inflammation (2) by removing oxidized phospholipids and fatty acids from oxidized LDL, very low density lipoprotein (VLDL), and intermediate density lipoprotein (IDL), limiting the formation of oxidized phospholipids, and by removing circulating endotoxins and serum amyloid A and their disposal in the liver. Moreover, normal HDL prevents inflammation by inhibiting the expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) on endothelial cells and the expression of CD11b on monocytes, thereby limiting the attachment of monocytes to endothelial cells. HDL promotes growth and prevents injury and apoptosis of endothelial cells (3) by lowering caspase-3 activity and reducing ROS generation. In addition, normal HDL facilitates repair, migration, and proliferation of endothelial cells and increases the number of circulating endothelial progenitor cells—events that are essential for vascular repair and prevention of plaque formation. Normal HDL exerts antithrombotic effects (4) through the inhibition of tissue factor, P-selectin, E-selectin, platelet activating factor, and thromboxane A-2 expression and promotion of anti-thrombin-3, protein C, protein S, and nitric oxide production. oxLDL, oxidized LDL; P, phosphorylated .

Nephrotic syndrome

Abnormalities of HDL metabolism

As discussed above, patients with nephrotic syndrome typically present with serum HDL cholesterol levels that are within or below the normal limits but an HDL cholesterol:total cholesterol ratio that is consistently reduced compared to healthy controls[32]. Furthermore, the maturation of cholesterol ester-poor HDL_3 to cholesterol ester-rich HDL_2 is often impaired in these patients, which leads to an increase in HDL_3 and a decrease in HDL_2 in the circulation[33]. This phenomenon is indicative of impaired HDL-mediated reverse cholesterol transport and can, in part, account for the pro-atherogenic effects of proteinuria. The disorders detailed below have been shown to contribute to the abnormalities in HDL structure and function in nephrotic syndrome (FIGS 3 and 4).

Acquired LCAT deficiency. Free cholesterol on the surface of HDL is rapidly re-esterified by LCAT in the presence of its cofactor ApoA-1. Cholesterol ester then sinks to the core of the HDL particle due to its hydrophobic properties. LCAT-mediated esterification of free cholesterol on the surface of HDL is critical for maximal extraction of cholesterol from target cells and

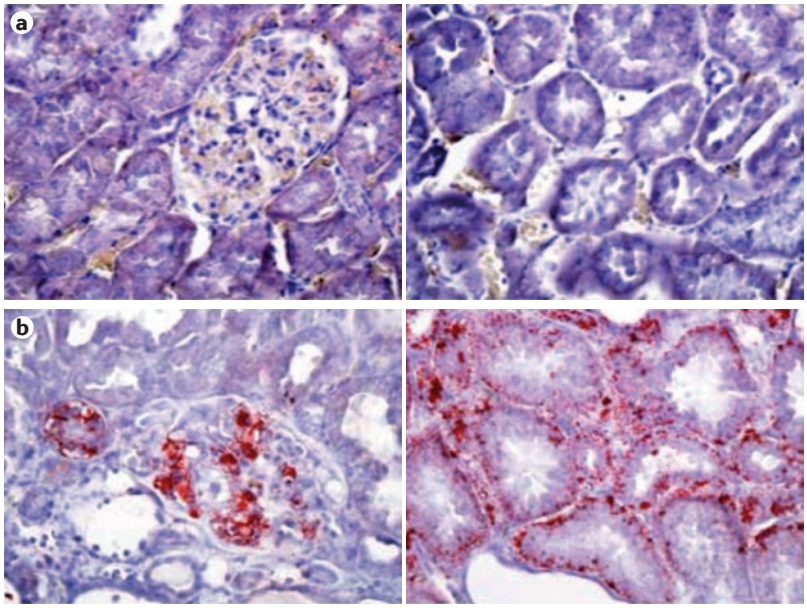

Figure 3 | **Lipid accumulation in renal cortical tissue of rats with nephrotic syndrome. a** | Oil red O stained photomicrographs of renal cortical tissues from a normal control rat. **b** | Oil red O stained photomicrographs of renal cortical tissues from a rat with puromycin aminonucleoside-induced nephrotic syndrome. The kidney tissue in nephrotic rats shows heavy accumulation of lipids (red deposits) in the glomerular mesangium and in proximal tubular epithelial cells.

maturation of nascent HDL3 to cholesterol ester-rich HDL2[34]. Given the pivotal role of LCAT in the maturation of HDL, the hypothesis that impaired maturation of HDL in nephrotic syndrome may be due to acquired LCAT deficiency was proposed and tested in a rat model of puromycin aminonucleoside-induced nephrotic syndrome[35]. A marked reduction in the plasma concentration and enzymatic activity of LCAT was identified, despite normal hepatic mRNA expression. This effect was associated with (and primarily caused by) heavy urinary losses of LCAT in the nephrotic animals, which is not surprising as the molecular weight of LCAT (63 kD) is similar to that of albumin, the heavy urinary loss of which is the defining feature of nephrotic syndrome. Nephrotic syndrome, therefore, causes an LCAT deficiency, which contributes to impaired cholesterol enrichment of HDL (FIG. 1).

Hypoalbuminaemia. HDL acquires the majority of its cholesterol cargo directly via ABCA-1-mediated and ABCG1-mediated pathways, but also receives a notable amount from albumin, which serves as a carrier of free cholesterol from the peripheral tissues to the circulating HDL3[36]. Consequently, hypoalbuminaemia — a cardinal feature of nephrotic syndrome — can contribute to the presence of cholesterol ester-poor HDL in nephrotic syndrome (FIG. 1).

Increased CETP levels. CETP mediates the transfer of cholesterol esters from HDL2 to IDL in exchange for triglycerides, and has an important role in the transformation of IDL to LDL. A substantial elevation of serum CETP has been shown in patients with nephrotic syndrome[37–39]. Elevated levels of CETP contributes to an over-abundance of cholesterol-poor HDL3 and a scarcity of cholesterol-rich HDL2 in nephrotic syndrome, by depleting the cholesterol esters and raising the triglyceride cargo of HDL. This effect compounds the effect of LCAT deficiency.

Under normal conditions, cholesterol ester-rich HDL donates ApoE and ApoC to the nascent VLDL and chylomicrons — a process that is essential for the binding of VLDL and chylomicrons to the endothelium and their lipolysis by LPL[4]. After undergoing lipolysis, the VLDL and chylomicron remnants return ApoE and ApoC to HDL, which is important for the clearance of LDL and chylomicron remnants. LCAT deficiency in nephrotic syndrome limits the formation of cholesterol ester-rich HDL that serves as the ApoE and ApoC donor to nascent VLDL and chylomicrons. Impaired maturation of HDL, therefore, contributes to the dysregulation of triglyceride-rich lipoproteins in patients with nephrotic syndrome[40]. ApoE enrichment of HDL might simultaneously interfere with HDL binding to SRB1 and might render ApoE a target for endocytosis via hepatic LDL receptor-related protein (LRP).

Hepatic SRB1 deficiency. The final step in HDL-mediated reverse cholesterol transport involves the reversible binding of cholesterol ester-rich HDL to SRB1 on the hepatocyte plasma membrane. One study that aimed to explore the effect of nephrotic syndrome on the hepatic HDL docking receptor found a marked reduction in SRB1 protein abundance despite its normal mRNA expression. These data implicate that a post-transcriptional or post-translational mechanism underlies the observed deficiency of SRB1[41]. The stability of SRB1 in the hepatocyte plasma membrane is dependent on its adaptor protein, PDZK1[42]. PDZK1 is associated with the basolateral plasma membrane in hepatocytes, where it interacts with the C-terminal cytoplasmic domain of SRB1 via its N-terminal PDZ domain[42]. PDZK1 is the predominant adaptor protein for SRB1 and has a critical role in HDL-mediated reverse cholesterol transport[42]. Downregulation of PDZK mRNA and protein expression was identified in nephrotic animals[43], thus confirming the mechanism of acquired SRB1 deficiency in nephrotic syndrome. SRB1 deficiency contributes to the atherogenic diathesis by compromising reverse cholesterol transport.

Hepatic HDL endocytic receptor upregulation. The β chain of ATP synthase is a principal component of the mitochondrial inner membrane protein complex but is also present in the hepatocyte plasma membrane. Unlike SRB1, which has a high affinity for reversible binding of cholesterol-rich HDL, the cell surface-associated ATP synthase β chain serves as an ApoA-1 receptor and mediates endocytosis of the lipid-poor HDL (FIG. 1). This process depends on the generation of ADP, which is produced by the activated ATPase function of the receptor in response to its binding with ApoA-1[44]. Marked upregulation of this receptor has been detected in the liver of nephrotic animals[43].

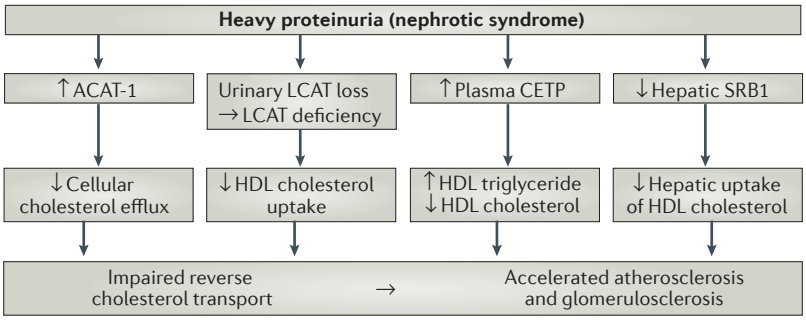

Figure 4 | **Consequences of nephrotic syndrome on lipid metabolism.** Nephrotic syndrome results in an upregulation of kidney and vascular tissue ACAT-1 expression, urinary losses and reduced plasma lecithin–cholesteryl acyltransferase (LCAT) concentration, an elevation of plasma cholesterol ester transfer protein (CETP), and a reduction in hepatic HDL docking receptor, SRB1. These events work in concert to promote the formation and accumulation of cholesterol ester-poor and triglyceride-rich HDL particles, impairment of reverse cholesterol transport, and increase the risk of atherosclerotic cardiovascular disease and glomerulosclerosis.

Hepatic lipase deficiency. The triglyceride contents of HDL are markedly elevated in nephrotic syndrome. HDL acquires the majority of its triglyceride content from IDL and LDL, in a process mediated by CETP[11]. Under normal conditions, HDL binding to the SRB1 docking receptor in the liver accommodates hydrolysis and removal of its triglyceride and phospholipid contents by hepatic lipase[9]. *In vitro* analyses have demonstrated a marked reduction in heparin-releasable lipase activity in the livers of nephrotic rats compared to control rats[45]. Moreover, marked downregulation of hepatic lipase expression and activity in hypercholesterolaemic Imai rats with spontaneous focal segmental glomerulosclerosis, and rats with puromycin aminoglycoside-induced nephrotic syndrome has also been reported[46,47]. Acquired hepatic lipase deficiency, therefore, contributes to triglyceride enrichment of HDL in nephrotic syndrome.

Consequences HDL abnormalities

Impairments of triglyceride and energy metabolism. The scarcity of cholesterol ester-rich HDL in nephrotic syndrome contributes to an impairment of VLDL and chylomicron metabolism, and limits the delivery of lipids to myocytes for energy production and to adipose tissue for storage[48]. The contribution of HDL abnormalities to the pathogenesis of impaired VLDL metabolism in nephrotic syndrome has been clearly demonstrated *in vivo*, where impaired endothelial binding and LPL-mediated lipolysis of VLDL in nephrotic rats could be corrected by infusion of HDL from healthy animals[49,50]. These findings have been further supported by *in vitro* experiments that showed defective maturation of nascent VLDL in the presence of nephrotic HDL and its subsequent correction with the addition of normal HDL[40]. The negative effect of HDL abnormalities on triglyceride and energy metabolism is compounded by acquired deficiencies in lipoprotein lipase and VLDL receptor in skeletal muscle, adipose tissue, and the myocardium in rats with nephrotic syndrome[51,52]. Together, the associated HDL abnormalities and lipoprotein lipase and VLDL receptor deficiencies make a considerable contribution to the pathogenesis of hypertriglyceridaemia, triglyceride enrichment of VLDL, impaired chylomicron and VLDL clearance, prolonged postprandial lipaemia, and impaired energy metabolism in nephrotic syndrome.

Progression of CVD and kidney disease. Proteinuria is a well-recognized risk factor for accelerated progression of CVD and CKD. One of the several underlying mechanisms by which proteinuria promotes CVD and progression of CKD is HDL dysfunction. HDL dysfunction contributes to the accumulation of atherogenic and proinflammatory chylomicron remnants, IDL, and abnormal LDL particles[3,4]. Uptake of these abnormal lipoproteins by macrophages and glomerular mesangial cells, coupled with impaired HDL-mediated reverse cholesterol transport, contributes to accelerated atherosclerosis and glomerulosclerosis[6].

Nephrotic syndrome promotes the filtration of different proteins, including lipid binding proteins such as albumin, ApoA, and ApoE. Uptake of the filtered lipid-containing proteins leads to the accumulation of lipids in proximal tubular epithelial and glomerular mesangial cells (FIG. 4). These events can promote glomerulosclerosis and tubular damage and dysfunction[6].

CKD and ESRD

Abnormalities of HDL metabolism

HDL cholesterol levels are substantially reduced in the majority of patients with advanced CKD and ESRD. This effect is associated with elevated HDL triglyceride and reduced HDL phospholipid contents, a diminished cholesterol ester-rich: cholesterol ester-poor HDL ratio[4,6,53,54], and impaired HDL antioxidant, anti-inflammatory, and reverse cholesterol transport capacity[55,56]. Although HDL cholesterol is reduced in the majority of patients with ESRD, a proportion of patients show a marked elevation in HDL cholesterol that is paradoxically associated with increased cardiovascular and overall morbidity and mortality[57–59]. In contrast to healthy individuals, HDL in patients with ESRD is severely oxidized, exerts proinflammatory effects, and contains large amounts of albumin, lipoprotein-associated phospholipase A2, and serum amyloid A1. The underlying mechanisms responsible for the abnormalities of HDL structure, function and metabolism in patients with CKD and ESRD are outlined below (FIG. 5).

Reduced serum ApoA-1 and ApoA-2 concentrations. Patients with ESRD exhibit marked reductions in serum ApoA-1 and ApoA-2 levels[53] due to a combination of reduced biosynthesis and increased catabolism of these proteins. Initial studies showed high catabolism of ApoA-1 in patients with ESRD maintained on haemodialysis[60], marked impairment of ApoA-1 biosynthesis in uraemic animals, and a marked reduction of ApoA-1 production by hepatocytes cultured in media containing plasma from uraemic individuals[61,62]. Subsequent studies have identified mRNA instability as a primary mechanism for uraemia-induced suppression of ApoA-1 biosynthesis by human hepatocytes[63]. In addition, ApoA-1

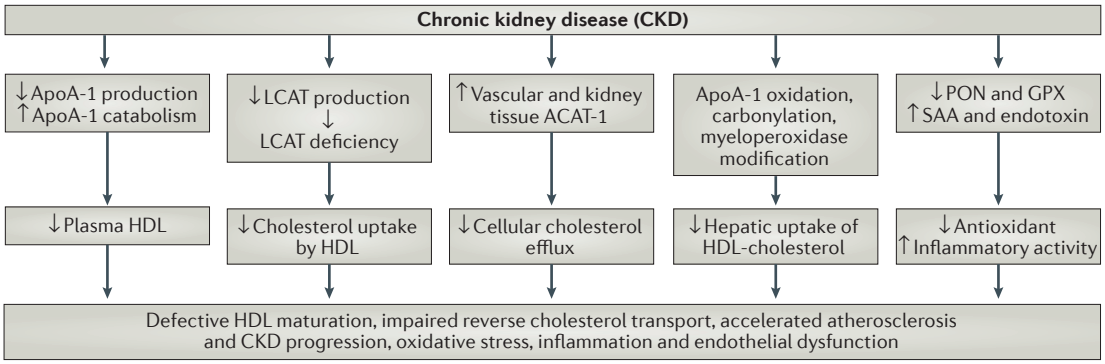

Figure 5 | **Consequences of CKD on lipid metabolism.** Chronic kidney disease (CKD) results in a reduction in plasma concentrations of ApoA-1, ApoA-2, lecithin–cholesteryl acyltransferase (LCAT), paraoxonase, and glutathione peroxidase (GPX), oxidation, myeloperoxidase-mediated modification and carbamylation of ApoA-1, and elevated concentrations of ACAT-1 in kidney and vascular tissue. These events work in concert to prevent the formation of cholesterol ester-rich HDL particles, impair reverse cholesterol transport, intensify the prevailing systemic oxidative stress and inflammation and increase the risk of atherosclerotic cardiovascular disease and CKD progression. PON, paraoxonase; SAA, serum amyloid A.

autoantibodies are frequently detected in patients with ESRD and can contribute to an ApoA-1 deficiency in those maintained on haemodialysis for an extended period[64]. A reduction in ApoA-1 in part contributes to a diminished HDL concentration in this population.

LCAT deficiency. Serum LCAT activity and concentration levels are markedly diminished in patients with ESRD[65–67]. Moreover, hepatic LCAT production is downregulated in rat models of CKD and is the primary cause of LCAT deficiency[68–70]. Given the critical role of LCAT in the formation of cholesterol ester-rich HDL and reverse cholesterol transport, an associated LCAT deficiency makes a notable contribution to CKD-associated impaired HDL maturation and HDL dysfunction.

Upregulation of ACAT. The reduction in serum LCAT in CKD is compounded by a marked upregulation of ACAT-1 in vascular and renal tissue[71–73]. ACAT-1 facilitates intracellular retention of cholesterol and promotes foam cell formation by catalysing the esterification of free cholesterol in macrophages and mesangial cells. By competing with intracellular cholesterol ester hydrolase, domination of cellular ACAT-1 in the vascular and kidney tissues serves as a major impediment to HDL-mediated uptake (FIG. 1).

Altered HDL protein constituents. Systemic oxidative stress, inflammation, and uraemia lead to oxidation, carbamylation, and myeloperoxidase-mediated modification of ApoA-1 and other protein constituents of HDL. Such modifications to ApoA-1 have been shown to impair HDL-mediated reverse cholesterol transport and promote atherosclerosis by limiting the binding of HDL to its receptors, including ABCA-1[74–77]. These processes can in part account for atherogenic diathesis in this population, and oxidative modification of HDL has been demonstrated in patients with ESRD[78,79].

Triglyceride enrichment of HDL. As observed in nephrotic syndrome, a reduction in HDL cholesterol in advanced CKD and ESRD is coupled with an elevated HDL triglyceride content. This effect is primarily caused by a deficiency of hepatic triglyceride lipase, which is a well-documented consequence of CKD and ESRD[80–82].

Defective reverse cholesterol transport. The ability of HDL to remove cholesterol from lipid-laden macrophages via ABCA-1 is markedly reduced in patients undergoing haemodialysis compared to that of healthy controls[83]. A series of studies have demonstrated an accumulation of neutral lipids in the artery wall and kidneys of rat models of CKD, despite upregulation of ABCA-1 and ABCG1[84,85]. These findings excluded ABCA-1 or ABCG1 deficiency as a potential cause of impaired HDL maturation and reverse cholesterol transport in advanced CKD. However, as noted above, the oxidative and myeloperoxidase-mediated modifications of ApoA-1 that occur in CKD[78,79] lower the binding affinity of HDL to the ABCA-1 transporter, and as such, impairs the ability of HDL to promote cholesterol efflux. This phenomenon can contribute to defective HDL maturation, impaired reverse cholesterol transport, and accelerated atherosclerosis in CKD. In addition, hypoalbuminaemia, which is commonly present in highly inflamed and malnourished patients with ESRD can, in part, contribute to a reduced HDL cholesterol level by limiting the receptor-independent transfer of albumin-bound cholesterol to HDL[36].

CETP. Unlike patients with nephrotic syndrome who have increased serum CETP levels, serum CETP concentration and activity are normal in patients undergoing haemodialysis. A role for CETP in the pathogenesis of reduced HDL cholesterol concentration and elevated triglyceride content found in the majority of this patient population has been excluded[86,87].

SRB1. No marked difference in liver SRB1 mRNA or protein expression levels has been found in rats with CKD induced by 5/6 nephrectomy compared to control animals[88]. These findings exclude SRB1 deficiency

as a cause of impaired reverse cholesterol transport in CKD, which differs from that observed in nephrotic syndrome[41]. The proportion of cholesterol ester-poor HDL is markedly increased in patients with CKD and is preferentially targeted for degradation via the SRB1 endocytic receptor.

Impaired HDL anti-inflammatory activity. In addition to causing HDL deficiency and disrupting reverse cholesterol transport, advanced CKD and ESRD severely impair the antioxidant activities of HDL. Marked reductions in HDL antioxidant capacity have been shown in patients with ESRD who are maintained on haemodialysis[78]. This reduction is accompanied by, and in part caused by, a notable reduction in paraoxonase-1 and glutathione peroxidase[78,89]. In addition, the anti-inflammatory activity of HDL is markedly reduced in patients with ESRD[53,79]. In contrast to HDL in healthy individuals, HDL in patients undergoing haemodialysis can stimulate the production of inflammatory cytokines (such as TNF, IL-6, and IL-1β), as shown in isolated macrophages *in vitro*[83]. This effect was associated with a marked reduction in HDL anti-chemotactic activity. Other studies have confirmed that HDL lacks anti-inflammatory properties in the majority of patients with ESRD, and in many cases can promote the production of inflammatory cytokines by macrophages *in vitro*[18]. The proinflammatory activity of HDL has been attributed to the presence of serum amyloid A in patients with ESRD. Shotgun proteomics identified 49 HDL-associated proteins in a uraemia-specific pattern[18]. In particular, HDL from patients with ESRD was enriched in SP-B, ApoC–2, serum amyloid A, and α-1-microglobulin/bikunin precursor. Serum amyloid A mimicked the proinflammatory properties of uraemic HDL by promoting the production and release of inflammatory cytokines. Furthermore, an inverse association between the serum amyloid A content of HDL and anti-inflammatory potency was found in the study population.

HDL oxidation and subsequent reduction of its antioxidant and anti-inflammatory activity in patients with advanced CKD are largely caused by prevailing systemic oxidative stress and inflammation, as is common in other chronic inflammatory disorders[90,91]. Systemic oxidative stress and inflammation are major contributors to the pathogenesis of CKD-associated abnormalities in HDL structure and function[92–94].

Consequences of HDL abnormalities

Cardiovascular disease. The HDL abnormalities described in CKD and ESRD can have several adverse consequences. The ability of HDL to prevent or reverse oxidation of LDL and phospholipids is markedly reduced by CKD-induced deficiencies in ApoA-1, paraoxonase-1, and glutathione peroxidase. The combination of reduced HDL antioxidant capacity and prevailing oxidative stress in CKD results in the formation and accumulation of oxidized LDL and phospholipids, and their subsequent uptake by macrophages and resident cells. In addition, oxidative modification of HDL (which limits its binding affinity for ABCA-1 transporter), increased ACAT-1 activity (which favours intra-cellular retention of cholesterol), and LCAT deficiency (which limits uptake of cholesterol by HDL), work in concert to compromise the ability of HDL to extract excess cellular cholesterol. Together, heightened cholesterol influx and impaired cholesterol efflux promote foam-cell formation, and accelerates atherosclerosis and CVD in the CKD population. In support of this hypothesis, one study has shown an association between HDL oxidation and increased risk of cardiovascular and overall morality in patients with ESRD[57].

Progression of CKD. In addition to contributing to the development of CVD, HDL deficiency and dysfunction might also contribute to the progression of renal disease in patients with CKD. This proposal is based on the following premises. Firstly, local and systemic inflammation is centrally involved in the pathogenesis and progression of CKD. Given the well-known antioxidant and anti-inflammatory properties of HDL, deficiency and dysfunction of HDL might contribute to the severity of oxidative stress and inflammation and promote the progression of kidney disease. Secondly, endothelial dysfunction and nitric oxide deficiency are common features of CKD[95,96]. As discussed, normal HDL is involved in maintaining endothelial function and nitric oxide production, which is critical in preserving tissue perfusion and preventing leucocyte adhesion and infiltration. Deficiency and/or dysfunction of HDL, therefore, can contribute to the severity of inflammatory cell infiltration in renal tissues. Finally, similar to macrophages, glomerular mesangial cells can take up oxidized lipids and lipoproteins[6]. In addition, uptake of filtered lipid-carrying proteins by the proximal tubules in patients and animal models with proteinuria can lead to the accumulation of lipids in proximal tubular epithelial cells[6]. These events can contribute to CKD progression by promoting glomerulosclerosis and tubular damage and dysfunction[97,98]. By preventing and reversing oxidation of lipoproteins, as well as mediating the removal of the intracellular lipid stores, normal HDL can limit the accumulation of cellular lipids in the renal tissue as it does in the vascular wall. Consequently, HDL deficiency and dysfunction can potentially contribute to lipid-mediated kidney injury and dysfunction.

Inflammation. Patients with advanced CKD commonly exhibit endotoxaemia, which can contribute to the pathogenesis of systemic inflammation[99,100] via uraemia-induced disruption of the intestinal epithelial barrier structure and function and alteration of the gut microbiome[101]. HDL avidly binds and disposes endotoxins in the liver in order to minimize the inflammatory response. HDL deficiency, therefore, might contribute to the severe endotoxaemia and associated systemic inflammation observed in patients with ESRD, and might also contribute to poor outcomes following microbial infection.

Thrombosis. Normal HDL limits platelet adhesion and activation and serves as an anti-thrombotic factor. HDL

deficiency and/or dysfunction can contribute to vascular access thrombosis, which is a major complication in the dialysis population[102].

Endothelial dysfunction and hypertension. Endothelial dysfunction and hypertension are common features of advanced CKD and major contributing factors to the pathogenesis of CVD in this population. These abnormalities in part result from a deficiency of nitric oxide, which is caused by downregulation of eNOS, an accumulation of the eNOS inhibitor, asymmetrical dimethylarginine, and ROS-mediated degradation of nitric oxide[103]. A number of studies have revealed the presence of large amounts of symmetrical dimethyl arginine (SDMA) — which blocks the uptake of L-arginine by endothelial cells — in HDL from patients with advanced CKD[104]. By limiting the availability of L-arginine, SDMA can contribute to nitric oxide deficiency, endothelial dysfunction, hypertension, and CVD in CKD.

Impaired VLDL metabolism. HDL abnormalities contribute to CKD-induced impairment of VLDL and chylomicron metabolism, which primarily result from reduced LPL and hepatic lipase expression and activity[83,105]. Reductions in the ApoC–2 (the LPL cofactor) and ApoE (the ligand for endothelial binding) contents of VLDL and chylomicrons contribute to diminished LPL activity in CKD[55]. These abnormalities are primarily caused by a CKD-induced defect in the maturation of HDL3 to HDL2, which serves as an ApoC and ApoE donor to nascent VLDL and chylomicrons.

Treatment strategies

Statins

With the exception of rosuvastatin, which intensifies proteinuria and accelerates progression of kidney disease, statins are generally effective in retarding CKD progression and reducing cardiovascular complications in patients with mild-to-moderate CKD[106]. In contrast, statins are ineffective and potentially harmful in the majority of patients undergoing haemodialysis, except in the minority who have hypercholesterolaemia[107–109]. In my opinion, the effectiveness of statins (or lack thereof) is not dependent on the stage of CKD, but rather the presence or absence of hypercholesterolaemia. Statins should, therefore, only be used in hypercholesterolaemic patients regardless of the severity of their CKD and be avoided in those with normal or subnormal cholesterol levels. In addition to limiting cholesterol biosynthesis, statins suppress the production of numerous important intermediaries and alternative by-products of the mevalonate pathway, which are essential for cellular and mitochondrial function[110]. One such by-product is coenzyme Q_{10}, which is essential for mitochondrial electron transfer function; its depletion by statins contributes to well-known complications, including myopathy and liver injury[110]. Clinical trials have demonstrated that plasma levels of coenzyme Q_{10} markedly drop below the normal range upon initiation of statin therapy[111]. Use of statins in patients with normal or low levels of cholesterol can, in my opinion, only cause harm and no benefit.

Fibrates

Fibrates (PPAR-α agonists) and niacin are the predominant available pharmaceutical agents that exert a specific effect on HDL. The PPAR-α agonist gemfibrozil, can reduce triglyceride levels, raise HDL levels, and reduce the likelihood of fatal and nonfatal myocardial infarction in patients with mild-to-moderate CKD with coronary disease and low HDL cholesterol[112,113]. However, treatment with gemfibrozil has been shown to cause sustained elevation of serum creatinine in individuals with and without CKD [112,113]. This phenomenon, together with the common interaction of PPAR-α agonists with several commonly used drugs, such as statins, warfarin, repaglinide, and β-adrenergic blockers has raised concern about the safety of fibrates in this population.

Niacin

Niacin can substantially increase HDL cholesterol levels and lower triglyceride levels at high doses[114]. The poor tolerability and adverse effects of niacin, however, has limited its use in the CKD population. The most common adverse effect of niacin is skin flushing, which occurs in the majority of patients[115]. In addition, niacin can cause hepatotoxicity, hyperuricaemia, and hyperglycaemia[116,117]. The induction of hyperglycaemia and new onset diabetes mellitus by high doses of niacin can be harmful in patients with CKD, both with or without diabetes mellitus[118].

Conclusions

HDL is essential for maintaining good health due to its mediation of reverse cholesterol transport and its potent anti-inflammatory, antioxidant, and antithrombotic functions. Nephrotic syndrome and CKD can induce profound alterations in the structure and function of HDL. The HDL cholesterol:total cholesterol ratio is consistently reduced and maturation of cholesterol ester-poor HDL to cholesterol ester-rich HDL is impaired in patients with nephrotic syndrome, which reflects an impairment in reverse cholesterol transport. HDL abnormalities and impairment of reverse cholesterol transport in nephrotic syndrome are caused by a constellation of LCAT deficiency resulting from losses in the urine, elevation of serum CETP, downregulation of SRB1, and upregulation of the β chain of ATP synthase. These HDL abnormalities contribute to the development of atherosclerotic cardiovascular disease, thromboembolic complications, and lipid accumulation in glomeruli and proximal tubular epithelial cells, which can lead to progression of kidney disease.

HDL cholesterol levels are substantially reduced in the majority of patients with ESRD who are maintained on haemodialysis, and patients with advanced CKD and minimal proteinuria. In addition, HDL triglyceride is elevated, cholesterol ester-rich:cholesterol ester-poor HDL ratio is markedly reduced, HDL antioxidative and anti-inflammatory capacity are reduced, and reverse cholesterol transport is impaired. These abnormalities are caused by a combination of ApoA-1, ApoA-2, LCAT, paraoxonase-1, and glutathione peroxidase deficiencies,

as well as upregulation of vascular tissue ACAT-1, and oxidative modifications to HDL cargo. These effects contribute to accelerated CVD, systemic inflammation, oxidative stress, and CKD progression. Although therapeutic interventions that aim to reverse or markedly ameliorate proteinuria are effective in improving HDL abnormalities in nephrotic syndrome, safe and effective drugs that are capable of correcting HDL abnormalities in patients with advanced CKD or ESRD are presently lacking and is an area in need of further research.

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Competing interests statement

The author declares no competing interests.