Lipid Disorders and Their Relevance to Outcomes in Chronic Kidney Disease

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Abstract
Cardiovascular disease is the major cause of death in patients with chronic kidney disease (CKD). Cardiovascular disease and many other complications of CKD are mediated by oxidative stress, inflammation, and dyslipidemia. This review provides a concise overview of the nature and mechanisms of CKD-induced lipid disorders and their adverse consequences. Lipid abnormalities in end-stage renal disease are characterized by: (a) reduced serum apoA-1 and high-density lipoprotein (HDL) concentrations, impaired HDL maturation and defective HDL antioxidant, anti-inflammatory and reverse cholesterol transport properties; (b) impaired clearance of very low-density lipoprotein and chylomicrons by the muscle and adipose tissue and of their remnants by the liver leading to hypertriglyceridemia, accumulation of intermediate-density lipoprotein and chylomicron remnants, and (c) oxidative modification of LDL and lipoprotein remnants favored by their structural abnormalities, oxidative stress, and impaired HDL antioxidant activity. Together these abnormalities result in: (a) uptake of oxidized LDL and remnant particles by macrophages and resident cells in the artery wall which along with impaired HDL-mediated reverse cholesterol transport causes foam cell formation and atherosclerosis, (b) production of inflammatory mediators and reactive oxygen species by leukocytes and macrophages in response to stimulation by oxidized LDL and phospholipids leading to intensification of oxidative stress and inflammation, (c) dissemination of oxidative stress by circulating oxidized lipids and lipoproteins via lipid peroxidation chain reaction, (d) heightened injurious effects of oxidative stress and inflammation due to diminished antioxidant, anti-inflammatory and antithrombotic activities of HDL, and finally (e) impaired ability of very low-density lipoprotein and chylomicron to deliver lipid fuel to muscle and adipose tissue contributing to muscle weakness and cachexia which commonly occur in end-stage renal disease patients.

Introduction
Accelerated atherosclerosis and cardiovascular disease are the main cause of death in patients with chronic kidney disease (CKD) [1]. Atherosclerosis and cardiovascular disease as well as many other complication of CKD are primarily driven by oxidative stress, inflammation, and lipid disorders [2–8]. This review is intended to provide a concise overview of the CKD-associated disorders...
Effects of CKD on Lipid Profile

The plasma lipid profile frequently evolves during the course of progression of CKD. For instance, patients with mild to moderate CKD, especially those with significant proteinuria, commonly exhibit hypercholesterolemia and elevated low-density lipoprotein (LDL) levels [7]. However, serum total cholesterol and LDL cholesterol concentrations are usually normal or reduced in patients with end-stage renal disease (ESRD) maintained on hemodialysis. Serum triglycerides and very low-density lipoprotein (VLDL) levels are elevated, and clearance of VLDL and chylomicrons and their atherogenic remnants is impaired in patients with advanced CKD or ESRD. This is accompanied by presence of small dense LDL and accumulation of oxidized LDL, intermediate-density lipoprotein (IDL) and chylomicron remnants [7–10]. The other major CKD-induced lipid disorder is significant reduction in serum apoA-1 and high-density lipoprotein (HDL) cholesterol concentration, impaired HDL maturation and defective HDL antioxidant, anti-inflammatory and reverse cholesterol transport (RCT) capacities [7, 8, 11–13].

In ESRD patients, the dialysis modality can significantly affect lipid profile. For instance, unlike hemodialysis patients, peritoneal dialysis patients frequently have elevated serum total cholesterol and LDL cholesterol levels simulating the lipid profile seen in nephrotic syndrome [7, 9, 10]. This phenomenon appears to be due to the losses of proteins in the peritoneal fluid effluent mimicking heavy proteinuria in functionally anephric person [14, 15].

In addition to dialysis modality, plasma lipid profile can be influenced by concomitant genetic disorders of lipid metabolism, severity of inflammation, malnutrition and lipid-altering drugs such as statins, fibrates, steroids, rapamycin, calcineurin inhibitors and sevelamer among others. In this context, binding and sequestration of bile acids by the phosphate-binding resin sevelamer can significantly reduce serum cholesterol level.

The prevailing oxidative stress and inflammation which are constant feature of CKD [2, 3] result in activation of endothelial cells, upregulation of adhesion molecules, expression of chemotactic factors leading to adhesion and infiltration of monocytes and their transformation to macrophages in the artery wall [16]. Simultaneously oxidative stress promotes oxidation of LDL, remnant particles and phospholipids and their uptake by macrophages in the artery wall. This, in turn, results in formation of foam cells, which is a critical step in development and progression of atherosclerosis. The underlying mechanisms responsible for the CKD-induced lipid disorders are briefly described below.

HDL Metabolism and Function in CKD

Physiologic Functions of HDL

As illustrated in figure 1, normal HDL protects against atherosclerosis by several mechanisms [17–19]: (a) inhibition and reversal of lipid and lipoprotein oxidation via HDL’s constituent antioxidant enzymes paraoxonase and glutathione peroxidase; (b) removal and disposal of oxidized fatty acids via apoA1 and lecithin:cholesterol acyltransferase (LCAT); (c) suppression of inflammation via uptake and disposal of endotoxin and oxidized phospholipids by apoA1 and conversion of ox-LDL by paraoxonase; (d) retrieval of surplus cholesterol and phospholipids from vascular and other tissues for disposal in the liver, a phenomenon which is commonly known as RCT; (e) antithrombotic action via platelet-activating factor acetylhydrolase, which is a potent platelet inhibitor; (f) contribution to metabolism of VLDL and chylomicrons and limiting formation of their atherogenic remnants by donating ApoC and ApoE to the nascent chylomicrons and VLDL, a process which is essential for metabolism and clearance of these lipoproteins [20], and (g) contribution to cholesterol enrichment and triglyceride depletion of IDL and its maturation to LDL via cholesteryl ester transfer protein (CETP)-mediated exchange of cholesterol ester for triglycerides. This process is referred to as indirect RCT as it employs LDL to dispose a portion of HDL’s cholesterol cargo in the liver via LDL receptor. This phenomenon is important in conversion of oxidation-prone atherogenic IDL to cholesterol-rich LDL which can be readily removed by the liver. Iatrogenic disruption of this process may have been responsible for paradoxical increase in adverse cardiovascular outcomes despite dramatic rise in HDL cholesterol which resulted in early termination of clinical trials of a CETP inhibitor [21].

RCT is mediated by binding of HDL to ATP-binding cassette transporter type A1 (ABCA1) and ABCG1 (the gate keepers of cholesterol efflux) on the cell membrane [19, 22]. Binding to the ABCA1 transporter initiates active transfer of free cholesterol and phospholipids to the surface of the lipid-poor discoid HDL [19], wherein free
cholesterol is rapidly esterified by LCAT and transferred to the core of HDL. LCAT-mediated esterification of cholesterol is essential for maximal uptake of cholesterol by HDL. Binding of the mature HDL to ABCA1 transporter causes further cholesterol enrichment of HDL and its conversion to cholesterol ester-rich HDL-2. Thereafter, HDL-2 detaches from the cell and begins a journey to the liver, where it binds to the docking receptor SRB-1. SRB-1 accommodates unloading of the HDL’s lipid cargo and its subsequent detachment to repeat the cycle. As noted in the text, CKD results in the reduction (marked by an asterisk) in apoA-1, PON, GPX and LCAT and elevation (marked by a +) of ROS, and scavenger receptors. These disturbances contribute to the CKD-associated HDL deficiency and dysfunction. β-Chain of ATP synthase, which is the HDL endocytic receptor, binds apoA and lipid-poor HDL. Since due to LCAT deficiency and poor binding affinity to ABCA1, uremic HDL is lipid-poor, we speculate that its degradation via this pathway is increased in ESRD patients, thereby replacing the role of the kidney, which is normally the main route of apoA-1 degradation.

HDL Abnormalities in CKD
Serum apoA-1 and HDL cholesterol concentrations are reduced, HDL triglyceride content is elevated, HDL maturation is impaired, proportion of lipid-poor pre-β-HDL is increased and antioxidant, anti-inflammatory and RCT capacity of HDL are greatly reduced in patients with advanced CKD [7, 8, 13, 26]. Advanced CKD is associated with marked reduction in serum concentrations of apoA-I (the main protein constituent of HDL) and apoA-II [7, 11, 26]. The CKD-induced apoA-1 deficiency contributes from the liver to repeat the cycle [24]. Unlike SRB1, the endocytic HDL receptor (β-chain of ATP synthase) mediates uptake and degradation apoA-1 and lipid-poor HDL particles in the liver [25].
to the overall reduction in plasma HDL in the ESRD population which appears to be due to its diminished production [27]. The primary reason for impaired maturation of cholesterol ester-poor pre-β-HDL to mature cholesterol ester-rich HDL in advanced CKD is LCAT deficiency. Serum CETP activity and concentration are markedly reduced in ESRD patients [11, 28], which is due to its diminished production by the liver in CKD [15, 29, 30]. In addition, hypoalbuminemia commonly seen in advanced CKD may, in part, contribute to reduced HDL cholesterol level. Studies conducted in experimental animals with CKD have revealed upregulation of ABCA-1 and ABCG-1 transporters in response to cellular cholesterol overload in the artery wall and remnant kidneys [31, 32], thus excluding their deficiencies as a potential cause of impaired HDL maturation and RCT in CKD. It is of note that oxidative modification of HDL has been shown to limit the affinity of apoA-1 for binding to ABCA-1 transporters [33]. In fact, studies conducted in our laboratories have revealed evidence for marked oxidation of HDL in ESRD patients [11]. Therefore, CKD-induced oxidative modification of HDL can contribute to impaired RCT, defective HDL maturation and accumulation of lipids in the remnant kidney and artery wall in this population.

Clinical studies have found no significant difference in serum CETP concentration or activity between hemodialysis patients and normal control individuals [34, 35]. However, data on the effect of peritoneal dialysis on serum CETP are lacking. Hepatic expression and serum concentration of CETP are elevated in patients with heavy proteinuria [36, 37]. Given the significant losses of proteins with peritoneal dialysis procedure, we speculate that serum CETP may be elevated in patients undergoing peritoneal dialysis.

Reduction in HDL cholesterol in advanced CKD is coupled with elevated HDL triglyceride contents. This is primarily due to deficiency in hepatic triglyceride lipase, which is a well documented consequence chronic renal failure [38–40].

Hepatic SRB-1 is the final destination in HDL-mediated RCT. The effect of ESRD on hepatic expression of HDL docking receptor (SRB-1) and endocytic receptor (β-chain subunit of mitochondrial ATP synthase) in humans is not known. However, studies conducted in our laboratory demonstrated no significant difference in the liver tissue SRB-1 abundance in rats with CKD induced by subtotal nephrectomy [27, 41]. In contrast SRB-1 abundance was significantly reduced in animals with experimental nephrotic syndrome [40]. Based on these observations, we speculate that hepatic SRB-1 may be unchanged in hemodialysis patients and reduced in peritoneal dialysis patients who generally experience significant protein losses in peritoneal dialysate effluent. If true, downregulation of SRB-1 can further compromise HDL-mediated RCT in such patients.

As noted above, HDL possesses potent antioxidant and anti-inflammatory properties which are critical in protection against foam cell formation by preventing oxidation of LDL and activation of leukocyte and endothelial cells. In a recent study, we found marked reductions in HDL antioxidant capacity in ESRD patients maintained on hemodialysis [11]. This was associated with significant reduction in paraoxonase, and glutathione peroxidase, the HDL-associated antioxidant enzymes [11]. In a subsequent study, we found marked reduction in HDL anti-inflammatory activity in ESRD patients [12]. The reduction in HDL antioxidant and anti-inflammatory properties in ESRD is most likely due to the prevailing oxidative stress and inflammation as shown in other conditions [18]. Conversely, reduction in antioxidant and anti-inflammatory properties of HDL in ESRD can intensify the inciting oxidative stress and inflammation.

**Adverse Impact of CKD-Associated HDL Abnormalities**

The CKD-associated HDL deficiency and dysfunction have numerous adverse consequences: (a) CKD-induced reduction in apoA-1, paraoxonase and glutathione peroxidase limits the ability of HDL to prevent or reverse oxidation of LDL and phospholipids. This, in turn, promotes influx of oxidized LDL in macrophages and resident cells in the artery wall and facilitates foam cell formation and atherosclerosis. (b) The CKD-associated oxidative modification of HDL [11] diminishes HDL binding affinity for ABCA-1 transporter which limits RCT. (c) LCAT and apoA-1 deficiencies and hypoalbuminemia accelerate atherosclerosis by limiting RCT. (d) The CKD-induced deficiency of HDL, which is the most potent plasma antioxidant factor, contributes to the severity of the prevailing oxidative stress and its adverse outcomes in this population. (e) As a potent anti-inflammatory component of the plasma, the CKD-induced HDL deficiency and dysfunction contribute to the prevailing inflammatory state and its adverse outcomes in CKD. (f) Since HDL avidly binds and removes endotoxin, its deficiency may contribute to the presence of endotoxia and inflammation in ESRD patients and their poor outcome with microbial infections. (g) Given the antithrombotic effect of normal HDL, its deficiency and dysfunction may contribute to blood access thrombosis.
Disorders of Triglyceride-Rich Lipoprotein Metabolism in CKD

Triglyceride-Rich Lipoprotein Metabolism

Pathways of VLDL and chylomicron metabolism are depicted in figures 2 and 3. VLDL and chylomicrons serve as vehicles for delivery of lipid fuel to the muscle for production of energy and to adipose tissue for storage of energy. This process is mediated by endothelium-bound lipoprotein lipase in the capillaries that perfuse skeletal muscle, adipose tissue and myocardium, wherein this enzyme catalyzes hydrolysis of triglycerides in VLDL and chylomicrons. This results in the release of over 70% of the fatty acid contents of these particles for uptake by the adjacent adipocytes and myocytes and formation of partially lipid-depleted VLDL (IDL) and chylomicron remnants. Chylomicron remnants and a small fraction of IDL are normally cleared by the liver via LDL receptor-related protein (LRP) [44]. Normally, the great majority of IDL particles are converted to LDL. Conversion of IDL to LDL requires cholesterol enrichment of IDL and removal of essentially all of its remaining triglyceride contents. This process involves CETP-mediated exchange of cholesterol esters for triglycerides between HDL and IDL and subsequent clearance of the residual triglyceride content of IDL by hepatic lipase. The cholesterol ester-rich and triglyceride-depleted LDL produced in this manner is then readily cleared by LDL receptor. In addition to lipolytic pathway, VLDL is directly cleared by adipocytes and myocytes via VLDL receptor which is abundantly expressed in the muscle and adipose tissues [45].

Disorders of Triglyceride-Rich Lipoprotein Metabolism in CKD

ESRD results in elevation of serum triglycerides and VLDL concentrations, which is solely due to impaired clearance of VLDL and chylomicrons and accumulation of their oxidation-prone atherogenic remnants [7, 9, 20]. These abnormalities are due to the CKD-induced down-regulation of lipoprotein lipase and VLDL receptor in the adipose tissue, skeletal muscle and cardiac muscle and hepatic lipase and LRP in the liver as well as increased plasma apoC-III (a potent inhibitor of lipoprotein lipase)/apoC-II (activator of lipoprotein lipase) ratio [7, 9].

Nearly all critical steps in metabolism/clearance of VLDL and chylomicrons and their remnants are severely impaired in CKD. For instance, CKD results in marked reduction in lipoprotein lipase activity in humans (as evidenced by diminished post-heparin lipolytic activity) and of lipoprotein lipase expression and activity in experimental animals [7, 20, 46]. Lipoprotein lipase deficiency in CKD is compounded by increased apoCII and reduced apoCII contents of VLDL and chylomicrons, which significantly lowers their ability to activate this enzyme. Moreover, reduced apoE contents of VLDL and chylomicrons limit their ability to bind to the capillary endothelium which is critical for their interaction with lipoprotein lipase and with binding of VLDL to VLDL receptor. Animal studies have demonstrated the contribution of CKD-induced hyperparathyroidism to the pathogenesis of lipoprotein lipase deficiency [47] confirming the observations made in ESRD patients [48]. In addition, impaired HDL maturation, insulin resistance, reduced physical activity and diminished thyroxin to triiodothyronin conversion, which are common features of ESRD, contribute to diminished production and impaired activity of lipoprotein lipase. Finally, recurrent heparinization in the course of hemodialysis procedure is thought to further contribute to lipoprotein lipase depletion in ESRD patients by promoting release and degradation of the tissue-bound stores of this molecule [7].

In addition to causing lipoprotein lipase deficiency, CKD results in significant downregulation of LRP in the liver [49]. This phenomenon can contribute to accumulation of the atherogenic chylomicron remnants and IDL in patients with CKD.

As noted earlier, hepatic lipase plays a crucial part in conversion of IDL to LDL. CKD has been shown to significantly reduce expression and activity of this important enzyme as well [38–40]. The CKD-induced hepatic lipase deficiency can, therefore, contribute to accumulation of IDL, triglyceride-enrichment of LDL and HDL and hyper-triglyceridemia in this population. Likewise, hepatic lipase deficiency can account for triglyceride enrichment of HDL in CKD. Finally, CKD results in marked downregulation of VLDL receptor in the skeletal muscle, heart and adipose tissue [50, 51] which contributes to impaired clearance of VLDL, elevation of serum VLDL and hypertriglyceridemia in CKD patients.

Acyl-CoA:diacylglycerol acyl-transferase (DGAT) catalyzes conversion of diglyceride to triglyceride and as such represents the final step in triglyceride synthesis. Advanced CKD has been shown to significantly reduce hepatic DGAT expression and activity in experimental animals [52]. Based on these observations, increased production may be excluded as a cause of hypertriglyceridemia in advanced CKD or ESRD. However, this may not be true in CKD patients with heavy proteinuria or ESRD patients maintained on peritoneal dialysis. This supposition is based on the observation that heavy proteinuria
Fig. 2. Pathways of VLDL metabolism. Nascent VLDL is produced and released in the circulation by the liver by packaging lipid droplets containing triglycerides (TG), cholesterol ester (CE) and phospholipids in the core of ApoB100. In the circulation, nascent VLDL acquires ApoE and ApoC from HDL-2 to become mature VLDL. In the capillaries perfusing muscles and adipose tissues, VLDL undergoes lipolysis of its TG contents by lipoprotein lipase (LPL), leading to release of 70% of its fatty acid (FA) contents, most of which are taken up by the adjacent adipocytes for energy storage and myocytes for energy production. This leads to formation and release of the VLDL remnant, commonly known as IDL, which undergoes further lipolysis by hepatic lipase and CE enrichment by cholesterol ester transfer protein (CETP) to become LDL. In addition, a small fraction of IDL is removed by the liver via a multifunctional receptor known as LRP. The bulk of IDL is converted to LDL, a process that involves cholesterol enrichment and TG depletion. This process is mediated by the actions of CETP and hepatic lipase. The CE-rich, TG-depleted LDL formed in this manner is then cleared by LDL receptor. In addition to the lipolytic pathway, VLDL is removed in its entirety via VLDL receptor (VLDLr) which is abundantly expressed by adipocytes and myocytes. CKD results in downregulation (marked with an asterisk) of LPL, hepatic lipase, LRP and VLDLr, which collectively account for elevation of serum triglycerides, VLDL, accumulation of IDL and TG enrichment of LDL on the one hand, and diminished availability of lipid fuel for skeletal muscle and storage for adipose tissue in patients with CKD on the other.

Fig. 3. Pathway of chylomicron metabolism. Chylomicrons are the vehicle for delivery of dietary lipid fuel to muscle for energy production and to adipose tissue for energy storage. Nascent chylomicron is produced by packaging lipid droplets containing triglycerides, cholesterol esters and phospholipids in ApoB48. After receiving apoE and apoC from HDL-2, chylomicrons undergo lipolysis by lipoprotein lipase (LPL) in the muscle and adipose tissues leading to formation of chylomicron remnants which are normally cleared by the liver via LRP. CKD results in downregulation (marked with an asterisk) of LPL and LRP, which collectively contribute to impaired clearance of chylomicrons and accumulation of their atherogenic remnants in CKD.
significantly increases hepatic DGAT abundance and activity [53]. If true, more severe hypertriglyceridemia seen in such patients may be due to a combination of increased production and reduced clearance of triglyceride.

Impact of CKD-Associated Defects on VLDL and Chylomicron Metabolism

Impaired clearance of triglyceride-rich lipoproteins and accumulation of their oxidation-prone, atherogenic remnants in patients with advanced CKD has major adverse consequences. (a) By limiting uptake of lipid fuel in the adipocytes and myocytes, downregulation of lipoprotein lipase and VLDL receptor contributes to development of cachexia and diminished exercise capacity in ESRD patients. (b) Accumulation of oxidation-prone IDL, chylomicron remnants, and triglyceride-containing small dense LDL promotes accelerated atherosclerosis. (c) Binding of oxidized LDL and phospholipids to their receptors on immune cells triggers the release of proinflammatory cytokines and chemokines which, in turn, contribute to development and intensification of CKD-associated inflammation. (d) The circulating oxidized lipoprotein remnants disseminate and sustain the flames of oxidative stress throughout the body by initiating lipid peroxidation chain reaction.

In this context, oxidized lipids and lipoproteins are both the cause and consequence of oxidative stress.

In conclusion, CKD results in profound dysregulation of lipid metabolism which in turn contributes to the pathogenesis of cardiovascular disease and numerous other adverse consequences in this population.

References


