

## Molecular mechanisms of disorders of lipid metabolism in chronic kidney disease

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### 1. ABSTRACT

Chronic kidney disease (CKD) is a progressive condition marked by protracted kidney damage which over time can lead to end stage renal disease (ESRD). CKD can be categorized into different stages based on the extent of renal damage and degree of renal dysfunction with ESRD requiring renal replacement therapy considered the final stage. It is important to note that CKD in all of its forms is associated with accelerated atherosclerosis, cardiovascular (CV) disease and poor CV outcomes. While a number of factors contribute to the high risk of CV mortality in this patient population, dyslipidemia is considered to be a key player in the pathogenesis of CV disease in CKD. Molecular mechanisms responsible for CKD-associated lipid disorders are unique and greatly influenced by the stage of renal disease, presence and degree of proteinuria and in patients with ESRD, modality of renal replacement therapy. This article provides a detailed overview of the molecular mechanisms which cause dyslipidemia and the nature of lipid disorders associated with CKD and ESRD.

### 2. INTRODUCTION

The prevalence of chronic kidney disease (CKD) continues to increase worldwide and it is estimated that there are approximately 25 million patients with moderate to severe CKD (stage III-V) in the United States (U.S.) (1). Furthermore, recent projection estimates indicate that China may have a higher prevalence of patients with CKD than the U.S. in the near future (2, 3). Therefore, CKD is a

global epidemic with significant societal, healthcare, and economic consequences the full impact of which remains to be fully realized. It is important to note that while progressive loss of renal function in CKD is an important contributor to morbidity and mortality, the majority of these patients succumb to CV disease and its complications rather than renal failure (4). Therefore, understanding the mechanisms responsible for CKD-associated CV disease and mortality has significant preventive and therapeutic value. In this regard, it is well known that renal disease and injury are associated with substantial alterations in lipid metabolism and plasma lipoprotein profile. While the CVD associated with CKD is complex with many elements contributing to its pathogenesis, it is likely that dyslipidemia is one of the factors which plays a causative role in the CV complications of CKD including the development and progression of atherosclerosis (5) (6, 7). There are several important factors which can alter lipid metabolism and influence the nature of lipid abnormalities observed in patients with CKD. These include stage and severity of kidney disease, presence and degree of proteinuria and features unique to each modality of renal replacement therapy. While we will briefly mention some of the unique features of dyslipidemia associated with proteinuria and specific modalities of renal replacement therapy, a detailed discussion of these topics is beyond the scope of this review. In this manuscript, we provide an overview of the nature of lipid disorders and the molecular mechanisms responsible for these abnormalities in patients with CKD. factor

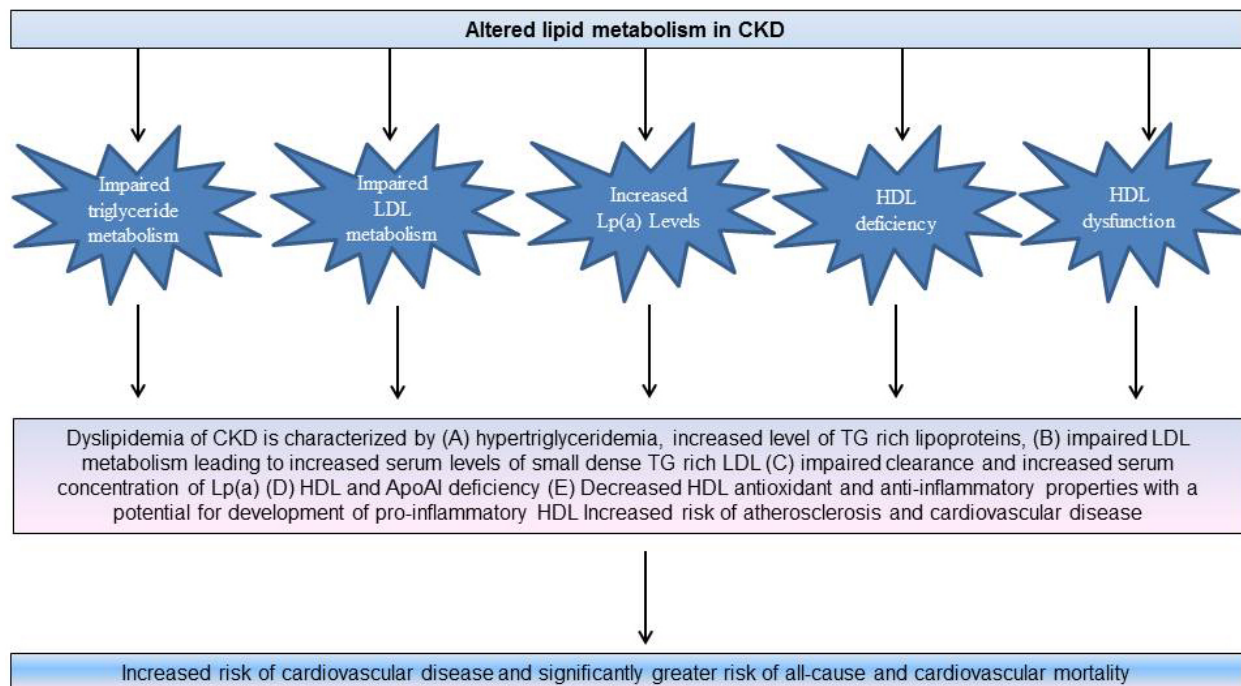


Figure 1. Features of CKD-associated dyslipidemia.

### 3.1. Dyslipidemia of CKD and ESRD

Dyslipidemia in the majority of CKD patients without significant proteinuria and in ESRD patients maintained on hemodialysis is characterized by hyper-triglyceridemia, elevated plasma levels of very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and chylomicron remnants, accumulation of oxidized lipids and lipoproteins, low plasma concentration of apolipoprotein A I (ApoAI) and high density lipoprotein (HDL) cholesterol levels (Figure 1) (8–10). Unlike patients with heavy proteinuria who have hypercholesterolemia, serum cholesterol and low density lipoprotein (LDL) cholesterol values are frequently within or below the normal limits in ESRD patients maintained on hemodialysis and CKD patients without nephrotic range proteinuria. In addition, their LDL is highly atherogenic and consists of small-dense particles containing significant amounts of residual triglycerides (10–12). Furthermore, plasma concentration of lipoprotein(a), (Lp(a)), specially the low molecular Lp(a), is elevated and contributes to the risk of cardiovascular events in CKD/ESRD patients (13, 14). However, CKD patients with significant proteinuria often exhibit hypercholesterolemia and elevated plasma LDL concentrations. Likewise, losses of protein in peritoneal dialysis fluid can result in hypercholesterolemia and elevated LDL level in ESRD patients maintained on peritoneal dialysis (15, 16). Finally, plasma HDL level is elevated in a minority of ESRD patients who exhibit a paradoxically higher risk of overall and cardiovascular mortality (17).

#### 3.1.1. Alterations in triglyceride and triglyceride-rich lipoprotein metabolism

In order to understand the pathogenesis of abnormal triglyceride metabolism in CKD, we provide a brief overview of the physiological processes which are key to triglyceride homeostasis under normal conditions. The main vehicles for transport and delivery of triglycerides in the plasma are very low density lipoprotein (VLDL) and chylomicrons. These triglyceride-rich lipoproteins provide a vital source of fatty acids for cells/tissues in the body which rely on them for generation and storage of energy. Fatty acids absorbed in the intestine by enterocytes are assembled into triglycerides and incorporated into apolipoprotein B-40 (ApoB-40) within the intestinal cells forming nascent chylomicrons which are then released into the lymphatic and eventually systemic circulation. Meanwhile, hepatic triglycerides are packaged together with cholesterol esters and phospholipids in apolipoprotein B-100 (ApoB-100) to form nascent VLDL and released into the circulation. It is in the serum that VLDL and chylomicrons acquire apolipoprotein E (ApoE) and C (ApoC) from cholesterol ester-rich high density lipoprotein-2 (HDL-2). The acquisition of these apolipoproteins is a critical step in the normal metabolism of triglyceride-rich lipoproteins given that their binding to the endothelial surface within the capillaries is dependent on ApoE. Once bound to the endothelium of capillaries in peripheral tissues, the enzyme lipoprotein lipase (LPL), which is responsible for hydrolysis of the triglyceride content

and release of fatty acids from these lipoproteins, is activated via apolipoprotein CII (ApoCII). The release of fatty acids via action of LPL leads to transformation of VLDL to intermediate density lipoprotein (IDL) and chylomicrons to chylomicron remnants. Most of the fatty acids released in this process are taken up by the neighboring cells and either stored or used as a source of energy. Meanwhile, IDL and chylomicron remnants re-enter the circulation where the chylomicron remnants are eventually cleared by the hepatic low density lipoprotein (LDL) receptor-related protein (LRP). In the case of IDL, it undergoes further alteration when its triglyceride and phospholipid contents are exchanged with cholesterol ester from HDL-2 through the action of cholesterol ester transfer protein (CETP). In addition, the triglyceride and phospholipid content of IDL are further removed by the enzyme hepatic lipase for uptake by the liver. The latter steps result in depletion of triglyceride component and enrichment of IDL with cholesterol esters which leads to its transformation into LDL, a lipoprotein that normally does not contain significant amounts of triglycerides. It is important to note that a portion of circulating VLDL content can also be cleared by the VLDL receptor, a member of the LDL receptor family which binds and internalizes VLDL. This receptor is highly expressed in tissues such as myocyte and adipocytes which rely on triglycerides for production and storage of energy (18, 19).

It is well known that CKD is associated with impaired clearance of chylomicrons, VLDLs and their remnants which leads to a significant increase in the serum triglycerides (20). There are several molecular mechanisms which explain these abnormalities. First, there is a significant reduction in VLDL receptor that can lead to diminished VLDL clearance (21–23). This was demonstrated in studies using animals with experimental CKD in whom cardiac and skeletal muscle mRNA expression and protein abundance of VLDL receptor were significantly reduced when compared with controls (21). These findings are further supported by recent evidence which revealed that elevated VLDL and chylomicron levels in diabetic patients with CKD are associated with decreased hepatic production of VLDL-ApoB-100, hence identifying decreased apolipoprotein removal rather than increased synthesis, as a major cause of hypertriglyceridemia in this patient population (24). Another critical mechanism responsible for hypertriglyceridemia in CKD is significantly reduced LPL enzyme level and activity (25, 26). As the rate-limiting step in hydrolysis of fatty acids in chylomicrons and VLDL, LPL plays a crucial role in triglyceride and energy metabolism. Similar to the VLDL receptor, LPL is highly expressed in cells involved in energy metabolism. The enzyme is synthesized within the cells and released into the extracellular space where it binds to the endothelium of capillaries via interaction of its positively charged heparin-binding domains with the negatively charged heparan sulfate

proteoglycans (27). This is mainly achieved via the endothelium-derived glycosylphosphatidylinositol-anchored binding protein 1 (GPIHBP1) which anchors LPL on the endothelium in addition to serving as the ligand for binding of chylomicrons (28, 29). This allows LPL to make contact with and mediate hydrolysis of triglycerides in chylomicrons and VLDL. LPL function is typically assessed by measuring its enzymatic activity in heparin-treated tissue or plasma given that heparin can dislodge and release LPL from the endothelium. As mentioned earlier, ApoCII content of triglyceride-rich lipoproteins plays a key role in this process by activating LPL. This is in contrast to apolipoprotein CIII (ApoCIII) which has been shown to inhibit LPL function. The molecular mechanisms underlying decreased LPL expression and activity in CKD are several folds. First, the ratio of ApoCIII to ApoCII is significantly increased in patients with CKD leading to an overall inhibitory effect on LPL activity (9, 30). Furthermore, secondary hyperparathyroidism, which commonly occurs in CKD and progressively becomes more severe with advancing renal disease, has been shown to down regulate LPL mRNA expression and its protein abundance in animals with experimental CKD (31–35). The deleterious impact of hyperparathyroidism on LPL level was further confirmed in studies which showed that post-heparin plasma lipolytic activity is significantly improved in CKD-animals who underwent parathyroidectomy (36). Another important mechanism responsible for LPL dysfunction in CKD is GPIHBP1 deficiency. As mentioned earlier, GPIHBP1 plays a key role in LPL function and metabolism by anchoring LPL to endothelium and enhancing its interaction with triglyceride rich lipoproteins such as chylomicrons. It has been shown that animals with experimental CKD have a significant reduction in mRNA expression and protein abundance of GPIHBP1 in skeletal muscle, myocardium and adipose tissue when compared with normal controls (37). Studies in patients with ESRD on maintenance hemodialysis have also confirmed marked reduction of plasma post-heparin lipolytic activity (38–40). It is thought that heparin anticoagulation used to prevent clotting in hemodialysis circuit causes the release and degradation of the endothelium-bound LPL which ultimately leads to LPL deficiency (41). In addition, heparinization of patients on hemodialysis leads to release of angiotensin-like proteins (ANGPTL) 3 and 4 which in turn cause hypertriglyceridemia. ANGPTL4 is a glycoprotein which is expressed in the liver, small intestine, skeletal muscle, myocardium and adipose tissue (42, 43). Binding of ANGPTL4 to LPL leads to conversion of LPL from active dimer to inactive monomer hence leading to LPL inhibition. Consequently, upregulation of ANGPTL4 causes impairment of VLDL and chylomicron metabolism and promotes hypertriglyceridemia through inactivation of LPL. It has been shown that plasma ANGPTL4 levels in patients with ESRD on maintenance hemodialysis are several folds higher than control subjects and

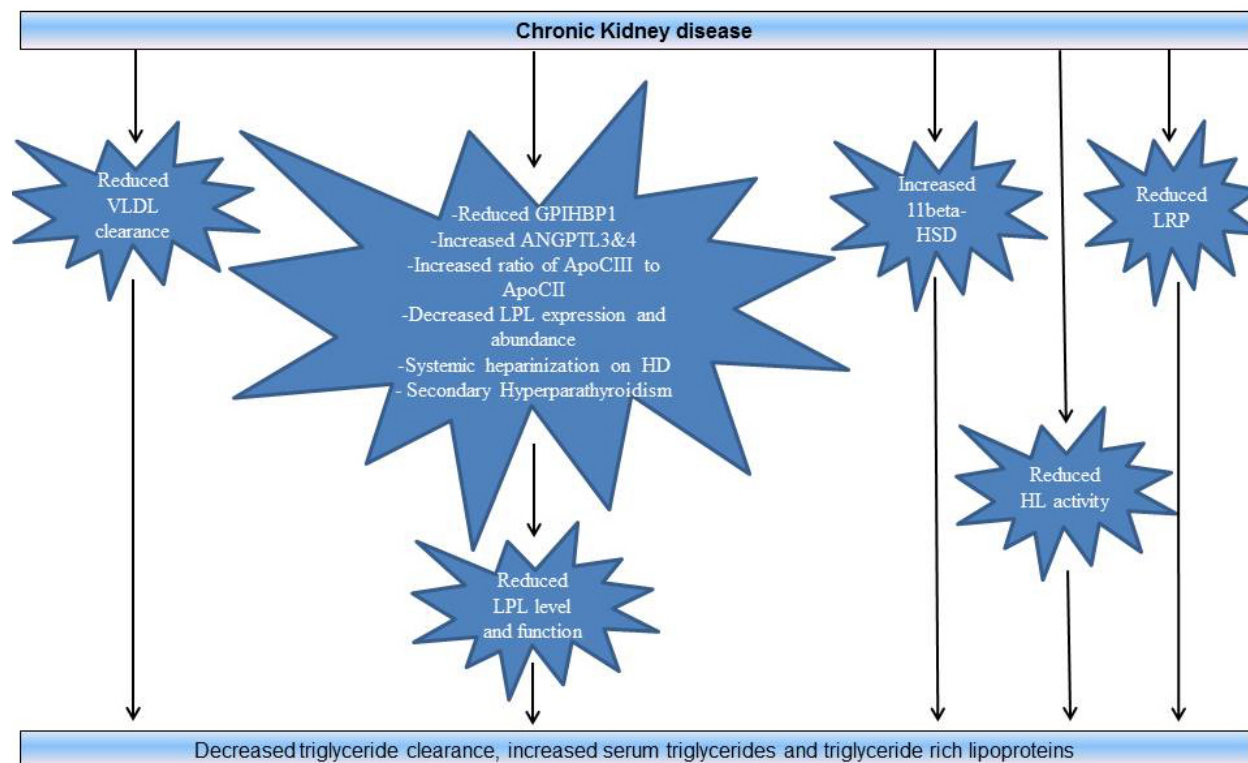


Figure 2. Features of abnormal triglyceride metabolism in CKD.

correlate positively with the serum free fatty acid levels (44). It is also important to note that ANGPTL4 inhibits hepatic lipase, thereby, limiting removal of HDL and IDL triglyceride content by the liver which can further increase plasma concentration of triglycerides (45). The deleterious effects of ANGPTL4 and ANGPTL3 on LPL is mitigated by GPIHBP1, which stabilizes this enzyme and prevents its inhibition (46). Therefore, increased serum concentrations of ANGPTL4 and 3 accompanied with reduced protein abundance of GPIHBP1 work together to cause significant LPL dysfunction in CKD and ESRD (47). It should also be noted that other factors which reduce LPL expression and activity such as insulin resistance, reduced physical activity, and diminished thyroxin (T4) to-triiodothyronin (T3) conversion commonly occur in advanced CKD and therefore can contribute to LPL deficiency (48–51). Another important mechanism responsible for abnormal triglyceride metabolism in CKD is LDL receptor-related protein (LRP) deficiency. Hepatic *LRP* gene expression and protein abundance is significantly reduced in animals with experimental CKD when compared to controls (52).

The intracellular enzyme, 11beta-hydroxysteroid dehydrogenase (11beta-HSD), catalyzes the conversion of inert cortisone to active cortisol and corticosterone. The 11beta-HSD type 1 which is a predominant version of the 11beta-HSD in most cells

catalyzes the regeneration of active glucocorticoids and, thereby amplifies the cellular actions of glucocorticoids. The 11beta-HSD1 is widely expressed in liver, adipose tissue, muscle, pancreatic islets, adult brain, inflammatory cells, and gonads (53). Recent *in vitro* experiments and *in vivo* studies of animal models of CKD demonstrated that CKD results in elevation of hepatic 11beta-HSD1, which by amplifying the intracellular glucocorticoid signaling contributes to upregulation of lipogenic genes, accumulation of intracellular lipids, and elevation of serum glucose, fatty acids and triglycerides (54, 55).

Taken together, hypertriglyceridemia of CKD is caused by a number of mechanisms including LPL and LRP deficiency and dysfunction, VLDL receptor deficiency and upregulation of hepatic 11beta-HSD type 1 (see figure 2).

### 3.1.2. Alterations in cholesterol and low density lipoprotein metabolism

While CKD is associated with abnormal cholesterol and cholesterol ester-rich lipoprotein metabolism, the nature of these abnormalities can be more accurately described as dyslipidemia given that nonproteinuric CKD is not commonly associated with elevated serum concentrations of total or LDL cholesterol. In fact, serum total and LDL cholesterol

concentrations are typically within the normal range in patients with the most advanced stages of CKD requiring maintenance hemodialysis therapy. This is in contrast to patients with nephrotic range proteinuria or ESRD patients on peritoneal dialysis who commonly have elevated levels of LDL and total cholesterol. To understand the mechanisms responsible for these findings we first provide a brief overview of the processes involved in cholesterol homeostasis and metabolism under normal conditions.

The two sources of cholesterol are dietary absorption and endogenous production. Endogenous production of cholesterol is typically offset by its catabolism via conversion to bile acids. The rate limiting enzyme in cholesterol biosynthesis is HMG-CoA reductase and the rate-limiting enzyme in cholesterol catabolism is cholesterol 7 $\alpha$ -hydroxylase. Cholesterol esters produced by the liver or other peripheral tissues are transported in the serum via cholesterol-ester rich lipoproteins, mainly LDL. Under normal conditions, the great majority of IDL particles are converted to LDL through the action of enzymes such as LPL, CETP and hepatic lipase. This process leads to cholesterol enrichment and extraction of residual triglyceride contents of IDL hence transforming it to LDL. LDL particles are removed from the circulation via LDL receptor which is expressed in the liver and peripheral tissues including macrophages and mesangial cells. In the liver, newly synthesized or imported cholesterol is esterified by acyl-CoA cholesterol acyltransferase (ACAT) which allows for its intracellular storage in cytoplasmic vesicles or packaging and secretion in VLDL. By promoting esterification and intracellular retention of cholesterol in the peripheral tissues, increased ACAT activity can promote lipid toxicity and foam cell formation. In addition, by decreasing intracellular free cholesterol, ACAT plays an important role in transcriptional and posttranslational regulation of cellular cholesterol production machinery. Chronic kidney disease in the absence of heavy proteinuria does not significantly change the expression or activities of either HMG-CoA reductase or cholesterol 7 $\alpha$ -hydroxylase (56). This is in contrast to CKD with nephrotic range proteinuria which leads to significant up-regulation of HMG-CoA reductase gene expression, protein abundance, and enzymatic activity (57). Furthermore, patients with ESRD maintained on chronic peritoneal dialysis also demonstrate similar serum lipid profile given that significant protein loss in the peritoneal dialysate effluent can mimic heavy proteinuria (15). It has been shown that hepatic LDL receptor expression is unchanged in experimental models of CKD without significant proteinuria (56). However, in the presence of significant glomerulosclerosis and heavy proteinuria, hepatic LDL receptor deficiency develops leading to hypercholesterolemia (16). Meanwhile, it has been shown that CKD is associated with significant

up-regulation of ACAT gene expression, protein abundance, and enzymatic activity in the liver, kidney and vascular tissues (58–60). Increased ACAT activity leads to accumulation of intracellular lipids which can cause lipotoxicity and atherosclerosis. While the latter abnormalities may play a role in the aberrant cholesterol metabolism in CKD, a more nuanced and yet critical component of CKD-associated dyslipidemia remains the defective transformation of IDL to LDL. As mentioned earlier, hepatic lipase and skeletal muscle and adipose tissue LPL deficiencies in CKD lead to impaired conversion of triglyceride-rich IDL to triglyceride-depleted cholesterol-rich LDL (22, 61). Therefore, LDL composition in patients with advanced CKD is altered such that it mostly consists of small and dense particles (small dense LDL) which contain abnormally high levels of residual triglycerides (26, 62). These LDL particles are considerably more prone to oxidation and more difficult to clear by LDL receptor. In this regard, there is also substantial evidence indicating that advanced CKD is associated with increased serum levels of Lp(a). Lp(a) is an atherogenic and prothrombotic lipoprotein that structurally consists of a modified LDL particle which has a highly glycosylated ApoA linked to ApoB-100 by a disulfide bridge. Lp(a) exerts its atherogenic effects by promoting LDL oxidation, inhibiting fibrinolysis via competition with plasminogen binding sites, and facilitating monocyte adhesion (63–65). Elevated serum levels of small isoforms of Lp(a) are considered a risk factor for CVD and elevated Lp(a) concentrations are resistant to lipid lowering drugs such as HMG-CoA reductase inhibitors (statins). Serum Lp(a) levels were found to be elevated in patients with ESRD on hemodialysis and it has been shown that the plasma residence time of these particles is doubled when compared to subjects without CKD (66). The rate of synthesis for Lp(a) in these patients was found to be similar to that of controls and hence it is less likely that increased synthesis is a factor in elevated serum Lp(a) levels (67, 68). On the other hand, it is likely that increased serum Lp(a) levels in CKD are caused by lack of renal catabolism of this lipoprotein. This assumption is supported by the observation that restoration of kidney function by transplantation is associated with decreased Lp(a) levels (13). Since the routine methods used to measure cholesterol do not distinguish between LDL and Lp(a) derived cholesterol, serum LDL cholesterol measurement reflect the cholesterol contents of both lipoproteins. Therefore, while the serum LDL cholesterol level may be in the normal range in patients with advanced CKD, their elevated serum Lp(a) content may significantly contribute to the total measured or calculated LDL cholesterol levels. Therefore, it is not surprising that patients with advanced CKD and ESRD suffer from a significantly increased risk of CV disease and mortality despite of the fact that a majority of them lack hypercholesterolemia and elevated LDL cholesterol levels which traditionally has been

associated with worse CV outcomes (69). It is also conceivable that accumulation of proatherogenic Lp(a) and oxidized small dense LDL which can contribute to the oxidative stress and inflammation of CKD make a significant impact on the atherogenic diathesis in this patient population regardless of serum total and LDL cholesterol levels.

### 3.1.3. Alterations in high density lipoprotein metabolism

There are numerous studies which demonstrate that in the general population increasing serum concentrations of HDL cholesterol are associated with reduced risk of CV disease and mortality and improved outcomes (70, 71). Indeed, HDL is a multifaceted lipoprotein that not only plays a key role in disposal of surplus cholesterol from the peripheral tissue (reverse cholesterol transport) but also possesses key antioxidant, anti-inflammatory and antithrombotic properties which play a crucial role in its overall protective effect. Hence, more important than serum HDL cholesterol concentrations are its functional properties. The significance of this point is becoming more apparent given emerging evidence that under certain conditions, such as chronic inflammations in patients with advanced CKD, HDL may be transformed into a proinflammatory particle which can play a causative role in CV disease (72). In order to understand the molecular processes by which HDL may become dysfunctional, we first provide a brief overview of the processes involved in HDL metabolism and its associated functions under normal conditions.

The initial step in generation of HDL is synthesis of its protein backbone which is mostly made up of ApoA1 and to a minor extent apolipoprotein AII (ApoAII). After being generated in the liver and intestines, these apolipoproteins are released into the circulation where they bind hepatic and intestinal ATP-binding cassette transporter A1 (ABCA-1) and acquire phospholipids and cholesterol, forming the nascent (lipid-poor) HDL particle (73–75). Furthermore, binding of nascent HDL to ABCA-1 and ATP-binding cassette transporter G1 (ABCG-1) on peripheral tissue (such as macrophages) leads to activation of cholesterol ester hydrolase (CEH) and mobilization of surplus intracellular cholesterol in the form of free cholesterol and its efflux to the surface of the lipid-poor HDL particle (73–77). In addition, HDL acquires considerable amounts of lipids and phospholipids from the circulating ApoB-containing lipoproteins (such as chylomicrons and VLDL and IDL). Free cholesterol is then re-esterified by lecithin-cholesterol acyltransferase (LCAT) and this conversion generates hydrophobic cholesterol esters that become embedded in the core of the lipid-poor discoid HDL particle, an action which can be described as “loading” of the HDL particle. This process results in the transformation of discoid lipid-poor HDL3 into

cholesterol ester-rich spherical HDL2, also known as mature HDL (78). Maturation of HDL is important given that lipid-poor HDL can be removed from the circulation and degraded by hepatic beta chain ATP synthase. HDL also receives triglycerides from IDL and LDL in exchange for cholesterol esters through the action of the CETP. Subsequently, the excess lipids and other cargo are transported back to the liver. HDL at this point can bind to its hepatic receptors including scavenger receptor-B1 (SR-B1). Binding of HDL to SR-B1 does not result in its internalization; rather it docks and unloads its lipid content via the actions of lipoprotein and hepatic lipase. Docking of HDL allows for it to subsequently be released back into the circulation in its lipid and triglyceride-depleted form to repeat this cycle (73–76). This process which involves removing excess lipids and triglycerides from the peripheral tissue (such as lipid-laden macrophages) to be metabolized in the liver is called reverse cholesterol transport and is a critical aspect of HDL function.

In addition to reverse cholesterol transport, HDL possesses a number vital anti-inflammatory, antioxidant, and antithrombotic properties (79). The HDL complex contains a large number of proteins including antioxidant enzymes such as paraoxonase-1 and glutathione peroxidase which can inhibit/reverse oxidative damage caused by reactive oxygen species (ROS) (78). HDL also has antithrombotic activity via its association with the platelet-activating factor (PAF) acetyl hydrolase (80). Furthermore, there is a growing body of evidence indicating that through various mechanisms HDL has important anti-inflammatory activity (81). For example, HDL by itself can prevent LDL or cytokine-induced production of pro-inflammatory cytokines such as monocyte chemoattractant protein-1 (MCP-1) (82, 83). In addition, HDL and ApoA1 are able to prevent adhesion of monocytes to endothelial cells, by reducing LDL-induced expression of adhesion molecules such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 on endothelial cells and CD 11b on monocytes (84, 85). In fact, the significant anti-inflammatory properties of ApoA1 have led to the potential use of ApoA1 mimetic peptides as a therapeutic tool in treatment of a variety of inflammatory conditions (86, 87). The health benefits of HDL anti-inflammatory function go beyond its cardioprotective role as there is evidence that HDL can also play a role in prevention/reversal of chronic systemic inflammation by removing oxidized phospholipids and fatty acids from other lipoproteins and by eliminating proinflammatory molecules such as endotoxins and serum amyloid-A (SAA) (88–90). Consequently, HDL has a number of functional characteristics which go beyond its role in reverse cholesterol transport and make significant contributions to its overall protective effects.

There are three components in abnormal CKD-associated HDL metabolism and function. First,

CKD is associated with significant ApoA1 and HDL deficiency and this can lead to diminished reverse cholesterol transport and reduced HDL function. Second, CKD is associated with defective HDL maturation and impaired reverse cholesterol transport which is mainly driven by impaired ApoA1 mediated cholesterol efflux, LCAT deficiency and ACAT overexpression. Finally, CKD is associated with a significant decrease in HDL antithrombotic, antioxidant and anti-inflammatory activity which can be a cause and consequence of oxidative modification of HDL as displayed in patients with ESRD (91). Consequently, HDL deficiency, impaired maturation and HDL dysfunction can lead to intensification of oxidative stress, inflammation and accumulation of oxidized LDL and phospholipids creating a proatherogenic and inflammatory milieu leading to adverse outcomes (92).

CKD and its progression to ESRD result in significant abnormalities in HDL size, content, and metabolism (79). Advanced CKD is associated with decreased serum HDL cholesterol levels and impaired maturation of HDL from discoid cholesterol ester-poor HDL to spherical cholesterol ester-rich HDL (8, 17, 93, 94). One of the underlying mechanisms for HDL deficiency in CKD is reduced plasma ApoA1 levels which as shown in a series of *in vivo* and *in vitro* studies is caused by instability of ApoA1 RNA and down-regulation of its hepatic biosynthesis (95, 96). In addition, patients with CKD and ESRD on maintenance hemodialysis have been shown to have increased catabolism of ApoA1 which compounds its reduced production (97, 98). Furthermore, patients with ESRD have been found to have a high prevalence of anti-ApoA1 autoantibodies which can cause functional ApoA1 deficiency and dysfunction (99). Another important factor that contributes to HDL dysfunction in CKD is oxidative and myeloperoxidase-induced modifications of ApoA1 which by limiting the ability of HDL to bind to ABCA-1, impair reverse cholesterol transport in CKD (100) (101). A major mechanism responsible for impaired maturation of HDL in CKD is significant downregulation of hepatic LCAT mRNA expression and reduced plasma LCAT level and activity which by limiting conversion of free cholesterol to cholesterol esters limits uptake of cholesterol by HDL (102–106) (107). Furthermore, there is increased HDL triglyceride content in patients with ESRD which is most likely due to reduced LPL and hepatic lipase activity given that serum CETP levels and activity are normal in these patients (35, 108, 109). Additionally, CKD leads to marked upregulation of renal and arterial ACAT1 which favors storage of intracellular lipids in the form of cholesterol esters hence decreasing the availability of free cholesterol for uptake by HDL (58–60).

There is accumulating evidence that CKD is associated with significant impairment of HDL antioxidant and anti-inflammatory properties

(79, 110). The impairment of the HDL antioxidant activity in ESRD patients is associated with significant reduction of the HDL-associated antioxidant enzymes, paraoxonase1 and glutathione peroxidase (107, 111). Furthermore, reduced HDL anti-oxidant and anti-inflammatory properties have been demonstrated in CKD patients regardless of their age, gender, stage of CKD, comorbidities or renal replacement modalities (112–114) (115). There is also emerging evidence that advanced CKD and ESRD are not only associated with significantly reduced HDL anti-inflammatory activity, but in a subset of patients HDL paradoxically becomes proinflammatory in nature (116, 117). This was shown in a series of studies which showed that HDL from hemodialysis patients had reduced anti-chemotactic activity and paradoxically stimulated production of inflammatory cytokine by immune cells (113, 118). The pro-inflammatory characteristics of ESRD patients' HDL were found to be associated with presence of atherogenic protein content including lipoprotein enriched with serum amyloid A whose pro-inflammatory actions were demonstrated by *in vitro* experiments (119). The pro-inflammatory nature of HDL can intensify the pervasive oxidative stress and inflammation in ESRD patients. In fact, there is evidence that increased oxidized ApoA1 levels are associated with a high risk of cardiovascular mortality in hemodialysis patients (120). The clinical significance of the above mentioned abnormalities are highlighted in recent studies that have shown the association of elevated serum HDL cholesterol levels with improved CV mortality is significantly diminished in patients with reduced estimated GFR (121). In addition, we have shown that in patients with ESRD on maintenance hemodialysis, reduced serum triglyceride to HDL ratio and elevated serum HDL cholesterol levels were paradoxically associated with increased CV and all-cause mortality (122). A recent study in a large cohort of U.S. veterans found that the lowest and highest deciles of serum HDL cholesterol levels were associated with significantly increased risks of incidence and progression of CKD (123). Hence, elevated serum HDL cholesterol concentrations are not necessarily associated with improved outcomes in patients with CKD (121). This combined with the fact that HDL from patients with CKD/ESRD on maintenance hemodialysis has been shown to have impaired reverse cholesterol transport capabilities that can lead to HDL dysfunction and account for the paradoxical associations of serum HDL level with outcomes noted in epidemiologic studies (124, 125).

#### 4. SUMMARY AND PERSPECTIVE

CKD results in profound changes in lipid metabolism and plasma lipid profile characterized by hypertriglyceridemia, elevated triglyceride-rich lipoproteins, increased small dense LDL, elevated Lp(a) and decreased plasma level, altered

composition and impaired function of HDL and accumulation of atherogenic and proinflammatory oxidized lipoproteins. The abnormalities of lipid metabolism contribute to the prevailing systemic inflammation, oxidative stress, and the high incidence of cardiovascular and overall morbidity and mortality in this population. In addition, impaired delivery of lipid fuel to the skeletal muscle and adipose tissues which results in hypertriglyceridemia plays a major part in the pathogenesis of wasting syndrome, weakness and diminished physical capacity commonly observed in patients with advanced CKD. The currently available therapeutic agents used to treat dyslipidemia in the general population are not effective in ameliorating CKD-associated lipid disorders. Given the deleterious role that altered lipid metabolism may play in the pathogenesis adverse outcomes in CKD population, novel and effective diagnostic and therapeutic strategies are urgently needed to improve outcomes in this vulnerable and expanding population. In this regard, it is important to note that evaluation of the composition and functional aspects of lipids/lipoproteins in CKD may not only provide valuable information regarding risk of CVD and mortality, but also can be used in identifying potential therapeutic targets. For instance, recent clinical studies in non-CKD patients have shown a strong correlation between in vitro HDL cholesterol efflux capacity and incidence/prevalence of CVD<sup>126</sup>. While HDL cholesterol efflux capacity has not been found to have the same prognostic value in patients with CKD, further detailed evaluations of these aspects of lipoprotein function (such as HDL antioxidant and anti-inflammatory properties) may uncover important information which can be of value in the care of patients with CKD<sup>127–129</sup>. Future studies are needed to further delineate the role of these developing areas of lipid and lipoprotein research in the pathogenesis, progression and mortality of CVD associated with CKD.

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