Podocyte Lipotoxicity in CKD

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Abstract

CKD represents the ninth most common cause of death in the United States but, despite this large health burden, treatment options for affected patients remain limited. To remedy this, several relevant pathways have been identified that may lead to novel therapeutic options. Among them, altered renal lipid metabolism, first described in 1982, has been recognized as a common pathway in clinical and experimental CKD of both metabolic and nonmetabolic origin. This observation has led many researchers to investigate the cause of this renal parenchymal lipid accumulation and its downstream effect on renal structure and function. Among key cellular components of the kidney parenchyma, podocytes are terminally differentiated cells that cannot be easily replaced when lost. Clinical and experimental evidence supports a role of reduced podocyte number in the progression of CKD. Given the importance of the podocytes in the maintenance of the glomerular filtration barrier and the accumulation of TG and cholesteryl-rich lipid droplets in the podocyte and glomerulus in kidney diseases that cause CKD, understanding the upstream cause and downstream consequences of lipid accumulation in podocytes may lead to novel therapeutic opportunities. In this review, we hope to consolidate our understanding of the causes and consequences of dysregulated renal lipid metabolism in CKD development and progression, with a major focus on podocytes.

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Introduction

CKD has been estimated to affect 15% of US adults and has a global burden of about 10% (1–3). The rate of CKD in the population has continued to rise due to continuous increases in its major risk factors: diabetes, hypertension, cardiovascular disease, obesity, and aging (2). Despite this large global burden, few options remain available to treat CKD. Furthermore, these options are unable to halt or reverse CKD progression to ESKD, and millions of people need RRTs, such as dialysis or transplant, every year (3). Given the many complications experienced by patients with ESKD on dialysis and the shortage of kidney donations, there is opportunity for new therapies that work alone or in combination with current treatments to target novel pathways. This review will focus on lipid metabolic pathways that we and others have found to be altered in CKD. Although sphingolipids have been shown to be important modulators of kidney cell function, this topic has recently been studied and reviewed (4–6). We will, therefore, focus our attention on renal cholesterol and triglyceride (TG) metabolic pathways in metabolic and nonmetabolic renal disorders.

Dysregulated lipid metabolism was first hypothesized as a mechanism of renal injury in 1982 by Moorhead et al. (7). As evidence of this phenomenon, authors cited observations of cholesteryl ester crystals and lipid droplets (LDs) in renal epithelial cells from patients with nephrotic syndrome, foamy glomerular cells in biopsy specimens from patients with chronic GN, and inverse correlations between circulating lipids and renal function. The authors hypothesized that injury of the glomerular basement membrane caused increased lipoprotein permeability and subsequent lipid accumulation and damage in the glomeruli and tubules (7). Now, nearly 40 years later, renal lipotoxicity is largely recognized as a consequence of kidney disease as we reviewed elsewhere (8), and the possibility that lipid accumulation per se may cause proteinuria is supported by several clinical and experimental studies that will be the focus of this review. Lipotoxicity is defined as the accumulation of excess lipids in nonadipose tissue and is associated with cellular dysfunction and apoptosis (9–11). Inside the cell, excess lipids are stored in LDs—highly dynamic organelles characterized by a TG and cholesteryl ester core protected by a monolayer of phospholipids and proteins. Intracellular lipid accumulation has been shown to cause dysregulated insulin signaling, mitochondrial dysfunction, endoplasmic-reticulum (ER) stress, and apoptosis in renal (4,12–16) and nonrenal cell types (10,17,18). In addition, lysosomes, which are responsible for cholesterol (19) and sphingolipid metabolism (20,21), have been found to be dysfunctional and to lead to podocyte injury in diabetic kidney disease (DKD) (22) and in Fabry disease (16,23,24). Moreover, evidence from human and experimental animals suggests a direct role of lipids—including free fatty acids (FFAs), TGs, and cholesterol—in the initiation and progression of fatty kidney disease (25).

In support of the role of altered glomerular lipid metabolism, glomerular and tubular lipid accumulation correlates with kidney injury in kidney diseases of metabolic and nonmetabolic origin, including DKD.
(6,13) and Alport syndrome (AS) (26–29). In the progression of CKD, analysis of a cohort of patients with diabetes revealed that alterations in glomerular and tubular expression of lipid metabolic genes correlated with a higher abundance of saturated 16- to 20-carbon FFAs; coupled with a lower long-to-intermediate acylcarnitine ratio (a marker of impaired β-oxidation); and an increase in polyunsaturated, long, complex lipids in the sera of patients with CKD (30). Because of these phenomena, many have begun to research the directionality and cause of the observed correlation between lipotoxicity and CKD. This review aims to consolidate and reconcile current knowledge relating to the causes and consequences of lipid accumulation in the kidney, with a specific focus on the podocyte.

Cholesterol as a Driver of CKD

Two of the most common risk factors for the development of CKD are hypertension and diabetes. Interestingly, podocyte cholesterol accumulation has been described in experimental models of both of these conditions, and multiple laboratories have described renal cholesterol accumulation in experimental CKDs (13,14,26). Similar to these experimental data, patient biopsy specimens also show renal cholesterol accumulation in all-cause CKDs (7,31,32), and we have reported altered glomerular expression of lipid-related genes in patients with FSGS enrolled in the NEPTUNE cohort (27). In support of the pathogenic role of altered cholesterol accumulation in CKD, renal complications represent a major cause of morbidity and mortality in patients with lecithin-cholesterol acyltransferase (LCAT) deficiency, a protein involved in cholesterol esterification and reverse transport from peripheral tissues. Due to a mutation in LCAT, these patients have glomerular lipid accumulation, early-onset proteinuria, and progressive renal disease (33). The common finding of cholesterol accumulation across causes of CKD, and the burden of kidney disease in the LCAT-deficient population, makes the understanding of aberrant cholesterol metabolism an urgent objective in the search for modern CKD therapies.

As the crosstalk between metabolic and hemodynamic pathways has been largely studied, it is interesting to note that angiotensin II is able to increase podocyte cholesterol accumulation (34). The increased cholesterol content of angiotensin II-treated podocytes was associated with decreased expression of the cholesterol efflux protein ATP-binding cassette A1 (ABCA1) and increased expression of sterol regulatory element-binding protein 1/2 (SREBP1/2), cholesterol synthesis gene 3-Hydroxy-3-methylglutaryl-3CoA reductase, and the LDL receptor. In this study, treatment with cyclodextrin, a cholesterol-chelating sugar, was able to rescue podocytes from angiotensin II-induced cholesterol accumulation and apoptosis; however, similar to what we have described for DKD (35), hepatic hydroxymethyl glutaryl-CoA inhibition with simvastatin did not have an effect on podocyte cholesterol accumulation and was unable to reduce podocyte apoptosis (34). In fact, reduction of glomerular ABCA1 expression in a cohort of patients with DKD correlates with loss of eGFR (31). In prior experimental studies, we demonstrated that suppression of ABCA1-mediated cholesterol efflux occurs in glomerular diseases of both metabolic and nonmetabolic origin (13,14,27,35). In particular, we demonstrated a causative directional link between TNF expression in glomerular cells and impaired cholesterol efflux via ABCA1, leading to cholesterol accumulation and susceptibility to proteinuria (13,14). In these studies, genetic or pharmacologic induction of ABCA1 is sufficient to rescue from proteinuria in FSGS and DKD. We also reported that cyclodextrin, used as a cholesterol sequestrant, is sufficient to slow CKD progression and podocyte loss in DKD, FSGS, and AS in association with a reduction in renal parenchymal cholesterol accumulation (27,35).

Role of TG and FFAs in CKD

Hypertriglyceridemia has a prevalence of about 10% in the healthy adult population (36); however, about 50% of patients with CKD experience hypertriglyceridemia (36,37). TGs are the major lipid species in LDs and are composed of FFAs and glycerol. Storing imported FFAs in LDs as TGs protects cells from the damaging effects of FFAs (38). These effects have been best documented in the setting of DKD. The transmembrane protein CD36 (also known as scavenger receptor B2) is a multifunctional receptor that mediates the binding and cellular uptake of long-chain fatty acids (FFAs) (39), oxidized LDLs (40,41), and phospholipids (42). Patients with DKD and experimental models have been shown to have increased tubular and glomerular expression of CD36 and a concurrent increase in renal FFA uptake and TG accumulation (31). In podocytes, CD36 has been shown to induce oxidative stress and apoptosis through increased FFA uptake (43), implicating a role of CD36-mediated FFA dysregulation in podocyte injury. More recently, we also demonstrated that the mechanism for nicotine-induced glomerular injury may be linked to increased lipid uptake via CD36 (44). Interestingly, CD36 inhibitor 5A has been shown to ameliorate CKD progression in vivo (45). CD36 is localized at the plasma membrane and is directly involved in FFA uptake, whereas the FA transport protein 4 (FATP4) localizes in ER and drives FFA uptake indirectly by esterification of FAs with CoA through its enzymatic activity (46). These studies suggest CD36 may be a main contributor to FFA uptake in podocyte injury, but FATP4 also contributes to it indirectly. Similar to these findings in a DKD model, we have recently shown increased renal FFA uptake has been described in a model of nonmetabolic CKD, the AS mouse model, where the lack of an α3 chain of collagen IV alters the composition of the glomerular basement membrane and is associated with a compensatory production of collagen I (Col I). This, in turn, causes lipotoxicity via collagen I-induced CD36 activity mediated by the discoidin domain receptor 1 (DDR1) (28). Increased CD36-mediated FFA uptake and intracellular TG accumulation in the AS podocytes suggest a link between matrix composition and lipid metabolism (Figure 1). This finding is supported by others’ observations that conditions that cause altered tissue stiffness can activate SREBP1/2, transcription factors involved in FFA and cholesterol synthesis, and cause lipid accumulation in human mammary epithelial cells (47). More interestingly, ezetimibe, a drug approved by the Food and Drug Administration to treat hypercholesterolemia (48), reduced TG accumulation via interfering with the discoidin domain receptor 1 and CD36 interaction in the AS mouse.
model (Figure 2) (28). Ezetimibe has previously been shown to decrease FFA absorption and intestinal expression of CD36 and FATP4 in mice (49). Similarly, murine hepatic TG accumulation was decreased after ezetimibe administration, in association with decreased expression of CD36, stearoyl-CoA desaturase, acetyl-CoA carboxylase, and SREBP-1c (50). Although the canonic function of CD36 is lipid uptake, CD36 has also been shown to interact with advanced oxidation protein products, thrombospondin 1, advanced glycation end products, and amyloid fibrils.

Figure 1. | Increased Lipid accumulation in Alport Podocytes. Representative images of BODIPY staining demonstrate increased lipid accumulation in cultured, immortalized Alport podocytes from the Col4A3KO mice (a mouse model for Alport syndrome), compared with wild-type podocytes cultured from the wild-type mice.

Figure 2. | Increased CD36 mediated FFA uptake and decreased ABCA1 expression mediated reduced cholesterol efflux lead to increased lipid accumulation and cause podocyte injury. Discoidin domain receptor 1 (DDR1) interacts with CD36 and induces CD36 activity. Increased CD36 activity in CKD mediates increased free fatty acid (FFA) uptake and triglyceride (TG) accumulation. Increased FFA uptake and TG lipolysis cause intracellular FFA overload to mitochondria, resulting in mitochondrial dysfunction. Cholesterol uptake from circulating LDL occurs via the LDL receptor. Esterified cholesterol accumulates in lipid droplets together with TGs. Decreased expression of ATP-binding cassette A1 (ABCA1) in podocytes in the setting of CKD leads to cholesterol accumulation, causing inefficient formation of the oxidative phosphorylation (OXPHOS) complex and increased oxidized cardiolipin accumulation in mitochondria, which leads to production of reactive oxygen species (ROS) and podocyte injury. CE, cholesteryl ester.
(51,52). These binding partners may synergistically, along with lipid remodeling, or independently contribute to renal injury by contributing to fibrosis, inflammation, and apoptosis (43,53).

Increased podocyte uptake of the FFA palmitate has been shown to cause activation of the mammalian target of rapamycin complex 1 (mTORC1) pathway and subsequent apoptosis, mediated by the ER stress proteins CCAAT-enhancer-binding protein homologous protein (CHOP) and protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK) (54). Treatment with the mTORC1 inhibitor rapamycin and raptor knockdown were able to inhibit activation of this pathway and significantly reduce apoptosis (54). Others have observed activation of the mTORC1 pathway in patients and experimental models of DKD (55,56) and FSGS (57,58), indicating the possibility of a conserved pathogenic pathway in metabolic and nonmetabolic CKDs. More recently, mTORC1 hyperactivation was found to lead to impaired renal lipolysis in DKD. Sodium-glucose cotransporter 2 inhibitor (SGLT2i) drugs inhibit the mTORC1 activation in proximal tubules by increasing ketolysis. These data, together with the recent clinical trials suggesting a beneficial effect of SGLT2i in kidney diseases of metabolic (59) and nonmetabolic origin (60), strongly suggest that the renoprotective effect of the SGLT2i on podocytes and tubules may be independent of their systemic glucose-lowering effects (61,62). These findings also suggest FFA uptake and TG lipolysis and may play an important role in podocyte injury in renal disease through their role in mTORC1 activation, and more research is necessary to validate this hypothesis.

**FFA Metabolism and Podocyte Mitochondrial Dysfunction in CKD**

Mitochondria and FFAs are tightly connected via multiple cellular processes. FFAs are building blocks of cellular membranes, signaling mediators, and energy storage molecules (63). The metabolism of FFAs is tightly balanced to avoid intracellular lipid accumulation, cell toxicity, and apoptosis (64,65). Excess cytoplasmic FFAs can damage bioactive lipids and disrupt mitochondrial membrane integrity (66). Clinical and experimental studies suggest that disturbed FFA metabolism in podocytes plays a critical, pathogenic role in obesity-related glomerulopathy and DKD (38). Podocytes are highly susceptible to FFAs (15). Knockdown of any one of the FFAR isoforms (FFAR1, the long- and medium-chain FA receptor, and short-chain of the FA receptors, such as FFAR2 and FFAR3) is sufficient to decrease the lipid-induced macrophycysis that causes podocyte injury (67), implicating that both excessive short-chain and long-chain FFAs may be harmful to the podocytes, even if other studies showed that short-chain FFAs may protect from mitochondrial dysfunction in other tissues and cell types (68). CD36-dependent uptake of palmitic acid has been shown to cause a dose-dependent increase in mitochondrial reactive oxygen species, mitochondrial depolarization, ATP depletion, and apoptosis (43). Accumulated FFAs can also become trapped in the mitochondrial matrix, leading to production of reactive oxygen species, lipid peroxidation, and mitochondrial damage and dysfunction (69–71). In proximal tubule epithelial cells, increased FFA overload leads to defects in mitochondrial respiration with reduced FA oxidation (FAO), increased intracellular lipid deposition, and renal fibrosis (65,72). In the setting of murine and human CKD, FAO genes are downregulated in the kidney (65). It was shown that pharmacologic prevention of cardioliopins oxidation using SS-31 prevents renal lipid accumulation and podocyte loss in DKD mice models (73), implicating the oxidative phenotype associated with mitochondrial dysfunction. We believe these data suggest that further studies linking podocyte lipid accumulation to mitochondrial dysfunction in CKD are needed.

**Interplay of Renal and Systemic TGs**

In addition to previously described renal TG accumulation, it is important to acknowledge that systemic hypertriglyceridemia is also a common finding in patients with CKD and experimental models. In support of a role for altered renal lipid metabolism in these systemic changes, it has been shown that adipocytes treated with the sera of nondiabetic, predialysis patients with CKD show a perilipin 1-dependent increase in TG lipolysis and FFA release into the media (74). These findings corroborate the authors’ conclusion that the diseased kidney is the origin of some unknown circulating factor that is able to stimulate TG catabolism and release. In support of this in vitro finding, patients with DKD, as they progressed throughout the stages of CKD, were observed to have increased circulating, long-chain FFAs and an impaired ability to complete FAO, leading to oxidative stress that is dependent on accumulation of toxic lipid intermediates, such as diacylglycerols and ceramides (30). Changes in sera lipid species were associated with altered glomerular and tubular expression of lipid metabolic genes, implying renal involvement in these systemic changes. Although this study was performed in patients with diabetes, other studies have shown altered systemic TG metabolism in CKD models (26,34,75).

**Renal and Systemic Lipid Management in Patients with CKD**

Patients with CKD have been shown to have renal lipid abnormalities and aberrant, systemic lipid metabolism that contribute to CKD-associated cardiovascular morbidity and mortality. However, our recent findings that renal lipid accumulation occurs in forms of nonmetabolic CKD challenge the hypothesis that systemic and renal lipid metabolism are always linked (26–28). Despite the paradigm shift suggested by these studies, the use of statins is recommended in patients with CKD, irrespective of the presence of hyperlipidemia, because reduced eGFR is an independent cardiovascular risk factor in the CKD populations (76). Although several clinical trials have shown a beneficial effect of statins on cardiovascular end points, they have not been shown to slow the progression of renal disease in these patients (77). The finding that simvastatin has no effect on renal cholesterol accumulation sheds light on these intriguing results from clinical trials using statins (77). Because statins inhibit cholesterol synthesis with no effect on efflux, they may target a pathway in lipid metabolism that is not contributing to CKD pathophysiology and renal...
lipotoxicity. Although cholesterylester transfer protein inhibitors may have been a promising therapeutic option to promote cholesterol efflux from peripheral organs, they were developed to increase the concentration of HDL rather than HDL function (78).

As another major lipid species deregulated in CKD, TGs have been pharmacologically targeted in trials to treat patients with CKD. Fenofibrate are peroxisome proliferator-activated receptor α agonists that are able to decrease systemic and ectopic TG accumulation. In the ACCORD trial, a subset of patients were administered simvastatin with or without fenofibrate. Patients who received the cotreatment had decreased eGFR decline and reduced risk of micro- and macroalbuminuria (79). The FIELD trial yielded similar results, showing that fenofibrate treatment was able to decrease eGFR loss and albuminuria (80). Despite these beneficial effects, both of these studies show that fenofibrate has a negative, but reversible, effect on serum creatinine and have no effect on ESKD progression (79,80). Similar to what has been seen in clinical trials, high fat–induced nephropathy in mice models can be reversed by treatment with fenofibrate. The beneficial effects of fenofibrate in this model were mediated by increased lipolysis, reductions in glomerular lipid accumulation, and oxidative stress (81). The inability of fibrates to slow progression to ESKD in these trials calls into question their clinical utility in the management of CKD; however, their beneficial effect on eGFR and proteinuria provide evidence that altered TG metabolism may be pathogenic in CKD, and this axis should be further studied for more targeted therapies.

In addition to statin and fibrates to systemically eradicate lipid, the inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) serine protease represents a novel mechanism controlling the formation, dynamics, and degradation of chylomicrons and very low density lipoprotein (VLDL) particles. This serine protease is a key regulator of LDL production and composition, and as a measurement of LDL flux in peripheral organs, it has been used to evaluate the effects of different lipoprotein-lowering therapies on LDL metabolism (82). In the context of chronic kidney disease, recent studies have shown that PCSK9 inhibition can improve eGFR and proteinuria (83). However, patients with severely impaired kidney function, the population at the highest cardiovascular risk, have been excluded from those trials (83,87). The relevance of the LDL-independent effects of PCSK9 inhibitors, such as lowering lipoprotein or ameliorating dyslipidemia in patients with nephrotic syndrome, has to be determined (88). Furthermore, nephrotic serum-treated podocyte injury induces plasma PCSK9 because TNF-α could enhance PCSK9-dependent LDL-receptor depletion via e-inhibitor of apoptosis, and knockout of the PCSK9 ameliorates cholesterol and TG level in a mouse model of nephrotic syndrome (89). Because some studies suggest an important contribution to cholesterol influx in kidney disease progression in AS, it would be important to determine their contribution to CKD progression.

Summary and Future Perspectives
Dysregulated lipid metabolism and renal lipid accumulation are not only associated with obesity-related renal disease and DKD, and an increasing amount of data suggests a role in CKDs of nonmetabolic origin, such as FSGS and AS. Due to these findings, renal lipotoxicity has gained considerable attention in recent years, and there has been progress toward understanding the causes and consequences of changes in renal lipids and the cellular pathways involved in the progression of CKD. Despite this, mechanistic details elucidating how the different lipid species interplay to cause podocyte injury and progression of CKD remain elusive. Detailed understanding of the mechanisms controlling the formation, dynamics, and degradation of LDLs may ultimately help us understand the pathogenesis of CKD and allow for the development of new, targeted therapies for the treatment of renal diseases. In addition, noninvasive imaging methods for the detection of different lipid species in the kidney parenchyma should be developed for patient stratification and as a measurement of target engagement.

Disclosures
A. Fornoni is inventor on pending or issued patents (PCT/US11/56272, PCT/US12/62594, PCT/US2019/041730, PCT/US2019/032215, PCT/US13/36484, and PCT 62/674897) aimed at diagnosing or treating proteinuric kidney diseases. She stands to gain royalties from her future commercialization of these patents. A. Fornoni is vice president of L&F Health LLC and is a consultant for ZyVersa Therapeutics, Inc. ZyVersa Therapeutics, Inc. has licensed worldwide rights to develop and commercialize hydroxypropyl-β-cyclodextrin from L&F Research for the treatment of kidney disease. All remaining authors have nothing to disclose.

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Author Contributions
A. Fornoni conceptualized the study; A. Fornoni, J.-J. Kim, and S.S. Wilbon reviewed and edited the manuscript; and J.-J. Kim and S.S. Wilbon wrote the original draft.

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