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Review article

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Kidney lipid dysmetabolism and lipid droplet accumulation in chronic kidney disease

Alla Mitrofanova[1,2], Sandra Merscher[1,2] & Alessia Fornoni[1,2]

Abstract

Chronic kidney disease (CKD) is a global health problem with rising incidence and prevalence. Among several pathogenetic mechanisms responsible for disease progression, lipid accumulation in the kidney parenchyma might drive inflammation and fibrosis, as has been described in fatty liver diseases. Lipids and their metabolites have several important structural and functional roles, as they are constituents of cell and organelle membranes, serve as signalling molecules and are used for energy production. However, although lipids can be stored in lipid droplets to maintain lipid homeostasis, lipid accumulation can become pathogenic. Understanding the mechanisms linking kidney parenchymal lipid accumulation to CKD of metabolic or non-metabolic origin is challenging, owing to the tremendous variety of lipid species and their functional diversity across different parenchymal cells. Nonetheless, multiple research reports have begun to emphasize the effect of dysregulated kidney lipid metabolism in CKD progression. For example, altered cholesterol and fatty acid metabolism contribute to glomerular and tubular cell injury. Newly developed lipid-targeting agents are being tested in clinical trials in CKD, raising expectations for further therapeutic development in this field.

Sections

[1]Katz Family Division of Nephrology and Hypertension, Department of Medicine, University of Miami, Miller School of Medicine, Miami, FL, USA. [2]Peggy and Harold Katz Family Drug Discovery Center, University of Miami, Miller School of Medicine, Miami, FL, USA. e-mail: afornoni@miami.edu

Key points

- Lipids and lipid-related enzymes have a major role in modulating the function of glomerular and tubular cells, and can drive chronic kidney disease (CKD) irrespective of circulating lipid levels.
- The mechanisms that initiate the accumulation of kidney lipids might differ between CKD of different aetiologies. Thus, the accumulation of kidney lipids in diabetic kidney disease is driven by increased glucose and fatty acids levels owing to insulin resistance, whereas in glomerulonephritis, inflammation can disrupt normal kidney lipid metabolism.
- Several lipid species, such as cholesterol, triglycerides, fatty acids and phospholipids, are dysregulated in podocytes, endothelial and tubular cells, and contribute to CKD progression.
- Accumulation of kidney parenchymal cholesterol occurs in association with impaired reverse cholesterol transport in diseases of both metabolic and non-metabolic origin, and contributes to CKD progression.
- Accumulation of fatty acids triggers mitochondrial and kidney cell damage by promoting inflammation, including cellular sterile inflammation, via innate immune system activation and fibrosis; lipophagy has a protective effect.

Introduction

Diabetes and hypertension are the most common causes of chronic kidney disease (CKD)[1], and tubulointerstitial fibrosis is recognized as the main histopathological finding associated with CKD progression and kidney failure. However, the contribution of podocytes to CKD cannot be underestimated, as podocyte density in the kidney glomerulus is the main predictor of CKD progression, especially in the early stages of disease[2]. This association is of particular relevance because podocytes are terminally differentiated cells, although podocyte regeneration can occur in experimental models of glomerular disease[3–5]. Inflammation, myofibroblast activation, oxidative stress and cellular lipid accumulation contribute to the initiation and progression of kidney fibrosis[6]. However, despite a better understanding of the mechanisms responsible for CKD progression and the rapid rise in the clinical development of new drugs over the past decade, a large proportion of patients with CKD continue to progress to kidney failure. Therefore, alternative therapeutic options that target novel pathways are needed.

Lipids are important components of the cell membrane that also have a pivotal role in energy production, cellular signalling transduction, cell homeostasis and survival. Patients with familial hyperlipidaemia are at a higher risk of developing CKD, which suggests that systemic lipids might also contribute to CKD[7]. Elevated triglycerides (TGs) and reduced high-density lipoprotein cholesterol (HDL-C) levels seem to be independent risk factors associated with the onset of advanced CKD[8]. The protein and lipid composition of circulating lipoproteins has also gained a lot of attention. For example, TG distribution among lipoprotein subclasses (quantified by targeted nuclear magnetic resonance spectroscopy) was strongly associated with glomerular filtration rate and albuminuria in a cohort of adult patients with type 1 diabetes[9]. Similarly, the protein composition of HDL differed between patients with CKD and healthy individuals[10]. However, although CKD-associated dyslipidaemia has been extensively studied, less is known about the contribution of kidney parenchymal lipid metabolism to CKD progression.

The healthy kidney has a relatively low lipid content, but lipid accumulation occurs in early CKD and promotes disease progression[11]. Among different cell types, lipid accumulation in the early stages of CKD has been mostly studied in podocytes and tubular cells. Further studies are needed to elucidate the role of lipid metabolism in endothelial cells, mesangial cells and infiltrating monocytes. In podocytes, the slit diaphragm, which is a crucial structure to the glomerular filtration barrier, is assembled in lipid rafts, which are specialized membrane domains enriched in cholesterol and sphingolipids. These lipid species have pivotal roles in the assembly of slit diaphragm proteins and in signal transduction. Lipid accumulation in the kidney parenchyma contributes to CKD development and progression, irrespective of the presence of systemic hyperlipidaemia and occurs in diseases of both metabolic and non-metabolic origin. For example, many clinical and experimental studies have demonstrated that kidney lipid accumulation occurs independently of hyperlipidaemia in the context of diabetic kidney disease[11–14], hypertensive nephrosclerosis[15,16], focal segmental glomerulosclerosis[17–19], minimal change disease[20] and Alport Syndrome[21–23]. These observations challenge the concept that excess ectopic lipid accumulation in kidney cells is a consequence of hyperlipidaemia, and that systemic and kidney lipid metabolism are directly linked (Box 1). In addition, although statins are effective LDL cholesterol-lowering agents, their use has not been consistently associated with reduced CKD progression[24]. Of note, patients with familial lecithin:cholesterol acyltransferase (LCAT) deficiency have extremely low or undetectable high-density lipoprotein cholesterol (HDL-C) levels and develop nephrotic syndrome leading to CKD and kidney failure. This finding suggests a role for impaired cholesterol efflux in the pathogenesis of CKD[25].

Fat accumulation in the kidney parenchyma was first described in 1883 and defined as 'fatty kidney'[26]. However, whether this fat is a cause or a consequence of kidney disease remained a matter of debate until experimental studies established a cause–effect relationship between fat content, kidney fibrosis and CKD progression (discussed below). In addition to kidney parenchymal fat, accumulation of fat in the kidney sinus (that is, the peri-renal area bounded from the hilum of the kidney to the edge of the kidney parenchyma) compresses the kidney lymphatics and veins. This effect increases kidney hydrostatic pressure and activates the renin–angiotensin–aldosterone system, which might have an important role in obesity-induced kidney injury.

In this Review, we discuss the clinical and experimental evidence of pathogenic lipid droplet (LD) accumulation in the kidney parenchyma, as well as the molecular mechanisms by which cholesterol, fatty acids, TGs and LD accumulation contribute to the progression of CKD. We also consider current and emerging therapeutic strategies for the treatment and prevention of lipid-induced nephrotoxicity.

Kidney energy metabolism

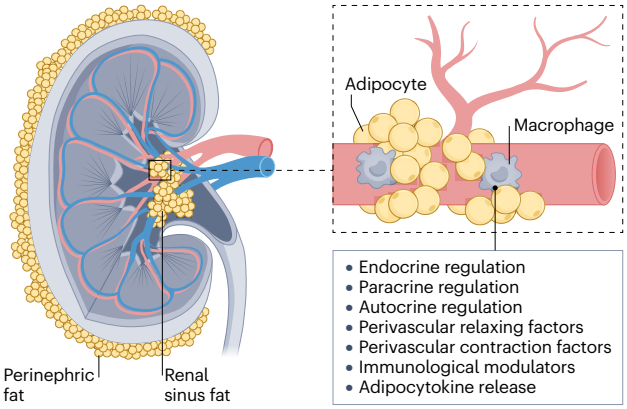
Although glucose is the preferred energy substrate in the kidney, lipids can serve as an alternative energy source, particularly when glucose levels are low[27]. Lipolysis occurs in the cytoplasm and is the process whereby TGs are broken into free fatty acids (FFAs) and glycerol. The resulting fatty acids (FAs) then undergo a process called β-oxidation (also termed FA oxidation (FAO)) to form acetyl-CoA, whereas glycerol enters the glycolysis pathway directly. Excessive acetyl-CoA generation

Box 1

Interplay of kidney and systemic lipids

Several molecules are involved in the interplay of kidney and systemic lipids in chronic kidney disease (CKD), including low-density lipoproteins (LDL), high-density lipoproteins (HDL), the renin–angiotensin–aldosterone system, pro-inflammatory cytokines, insulin signalling and adipokines. The formation of foam cells (that is, macrophages that ingest LDL) characterizes various glomerular diseases, including diabetic kidney disease (DKD), focal segmental glomerulosclerosis (FSGS), nephrotic syndrome or Alport Syndrome[240], which suggests systemic lipid-mediated toxicity. Elevated plasma LDL levels and foam cell formation stimulate the release of pro-inflammatory cytokines and accelerate inflammation, thereby contributing to kidney dysfunction by affecting lipid metabolism and causing oxidative stress[241]. Low HDL is an independent risk factor for kidney disease development[242,243] and might be associated with reduced plasma concentrations of lecithin-cholesterol acyltransferase (LCAT), which is an enzyme involved in the removal of cholesterol from the blood. In patients with CKD, low LCAT concentrations and activity lead to defective cholesterol esterification, impaired pre-HDL maturation and accelerated metabolism of lipoprotein particles[244]. Importantly, a higher triglyceride-to-HDL-cholesterol ratio is another independent risk factor for the incidence and progression of CKD[245–247].

Notably, growing evidence suggests that lipid accumulation inside kidney cells contributes to CKD development, irrespective of the presence of hyperlipidaemia[12,61]. Glomerular tumour necrosis factor (TNF) rather than systemic TNF is a major driver of lipid dysmetabolism in FSGS[116], whereas ATP-binding cassette subfamily A member 1 (ABCA1) deficiency is associated with lipid accumulation in podocytes treated with sera from patients with type 1 and type 2 diabetes[13,116] and deletion of *Abca1* renders mice susceptible to DKD. In mouse models of DKD, increased expression of sterol regulatory element-binding proteins (SREBPs) and CD36 leads to triglyceride and cholesterol accumulation in the kidney via regulation of LDL receptors and fatty acid uptake. Importantly, the intracellular accumulation of lipids induces the generation of reactive oxygen species, endoplasmic reticulum stress and mitochondrial dysfunction, which further increases the lipid surplus in the cell.



can overload the Krebs cycle and lead to the conversion of acetyl-CoA into ketone bodies, which serve as a fuel source if glucose levels are low. However, if glucose levels are high, excess acetyl-CoA can be converted into FAs, triglycerides, cholesterol, steroids and bile salts in a process called lipogenesis. Storage of imported FFAs as TGs can protect cells from the damaging effects of excessive FFA accumulation. Importantly, podocytes and tubular cells are vulnerable to lipid accumulation, which can result in mitochondrial stress, inflammation, actin cytoskeleton remodelling, insulin resistance, ER stress and, eventually, cell death.

Of note, lipid abnormalities can be present in the early stages of CKD, which is characterized by increased levels of TGs, and of small dense and oxidized low-density lipoprotein, and decreased levels of high-density lipoprotein (HDL)-cholesterol (HDL-C). A 2022 report showed that in diabetic kidney disease (DKD) models, tubule-specific deletion of *Pacs2*, which encodes a protein associated with lipid metabolism, resulted in severe tubular injury, accompanied by increased lipid synthesis and uptake, and decreased cholesterol efflux[28]. Of note, lipin-1-deficient mice have lower kidney lipid content than wild type controls, which suggests that lipins might be key contributors to the development of fatty kidneys[29]. Interestingly, the contribution of systemic and kidney lipids to CKD development and progression might differ (Box 1).

Fatty acid metabolism in CKD

The kidney is a mitochondria-rich organ with high energy demand. Under physiological conditions, the substrate preferences in different kidney regions reflect the demand for ATP in these areas — glomeruli tend to use glucose, whereas kidney tubules tend to use FAs[30]. Generally, FAO is the preferred energy source in hypermetabolic cells such as tubular cells, which leads to the breakdown of FFAs to produce ATP, whereas podocytes, endothelial cells and mesangial cells in glomeruli rely mainly on glycolysis and use FAO as an alternative source of energy in altered metabolic conditions, such as low glucose[31,32]. FAs enter a cell primarily via FA protein transporter 1 (FATP1), FATP2 or FATP4, which are associated with most lipid uptake abnormalities in patients with DKD[33,34], and CD36, which is a class B scavenger receptor and a long-chain FA transporter that is highly expressed in proximal and distal epithelial cells, podocytes and mesangial cells[35] (Fig. 1). CD36 can be present as a circulating soluble molecule (sCD36), which is mainly derived from endothelial cells in healthy individuals but originates from erythrocytes in patients with type 2 diabetes[36]. In patients with DKD, sCD36 was found to be a source of cellular CD36, and sCD36 levels correlate with insulin resistance[37–39]. However, data on sCD36 levels in plasma and urine of patients with DKD are inconsistent[40] and the mechanism by which sCD36 modulates lipid uptake and metabolism remains unknown and requires further investigation.

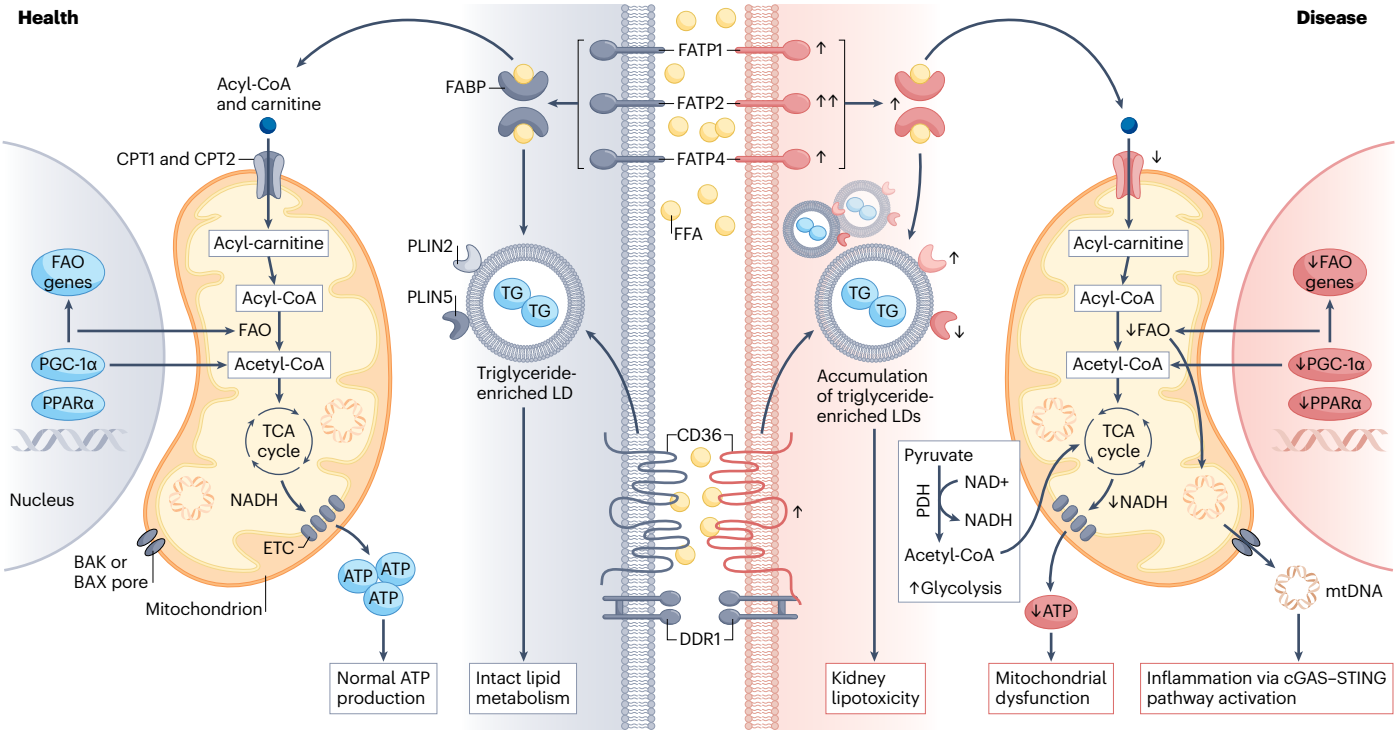


Fig. 1 | Main mechanisms of fatty acid dysregulation in health and CKD. Under physiological conditions, diet-derived triglycerides and cholesterol are broken down into free fatty acids (FFAs) and glycerol. Fatty acid transporters such as fatty acid transporter proteins (FATP1, FATP2, FATP4), which are mostly responsible for FFA transport in tubules, and scavenger receptor class B (CD36), which is mostly responsible for FFA transport in podocytes, import FFAs into the cell, where they undergo fatty acid oxidation (FAO; also known as β-oxidation) or are stored as lipid droplets (LDs). In disease conditions, based on data from animal models of chronic kidney disease (CKD), increased activity of FATP1, FATP4 and, predominantly FATP2, lead to FFA overload in kidney cells. Additionally, the interaction of discoidin domain receptor 1 (DDR1) and CD36 contributes to increased FFA uptake into kidney cells, as demonstrated in a mouse model of experimental Alport Syndrome, and accumulation of triglyceride-enriched lipid droplets (LDs). Moreover, the altered activity of perilipin protein family members PLIN2 (upregulated in mice with CKD) and PLIN 5 (downregulated in mice with CKD) contributes to triglyceride-enriched lipid droplet accumulation and kidney lipotoxicity. Data from patients with CKD suggest that increased activity of fatty acid-binding proteins (FABPs), leads to the excessive delivery of fatty acids to mitochondria for further oxidation. However, decreased expression of carnitine palmitoyltransferases — CPT1 and CPT2 — which transport Acyl-CoA into mitochondria, leads to decreased FAO, ineffective NADH production, reduced electron transport chain (ETC) activity and inadequate ATP levels, leading to mitochondrial dysfunction. Data from animal models also suggest that suppression of mitochondrial biogenesis genes (especially peroxisome proliferator activated receptor γ (PPARγ) coactivator 1α (PGC-1α) and PPARα) leads to mitochondrial DNA (mtDNA) instability, which leaks into the cytosol and promotes inflammation via cyclic GMP–AMP synthase (cGAS) and stimulator of interferon response (STING) signalling. Additionally, in CKD, tubular cells switch from FAO to glycolysis for energy production; consequently, glucose is used to produce pyruvate, which is further utilized to produce acetyl-CoA via pyruvate dehydrogenase (PDH) to increase ATP production.

FA-binding proteins (FABPs), which are lipid-binding proteins that recognize long-chain FAs as a substrate, also contribute to abnormal lipid uptake in CKD. Accordingly, high urinary levels of liver-type FABP (L-FABP; also known as FABP1) in DKD[41,42] and of adipocyte FABP (A-FABP; also known as FABP4) in minimal change disease[43] are markers of disease development and progression. Another study suggested that serum levels of FABP4 could predict cardiovascular disease development in patients with CKD who are not receiving dialysis[44].

FAO is a process of FFA breakdown in mitochondria and peroxisomes. Although most long-, medium- and short-chain fatty acids are oxidized in mitochondria, the oxidation of very long-chain fatty acids, fatty dicarboxylic acids and bile intermediates occurs in peroxisomes[45]. Interestingly, in the case of mitochondrial FAO deficiency, peroxisomal FAO metabolizes long- and medium-chain fatty acids[46]. Acetyl-CoA carboxylase (ACC), which is a central enzyme involved in FAO and FA biosynthesis, exists in two isoforms. ACC1 is highly expressed in the liver and adipose tissue, and ACC2 is present in highly metabolic organs such as skeletal muscle, heart and kidney. Activity of both ACC isoforms is tightly regulated by AMP-activated protein kinase (AMPK), sterol regulatory element-binding protein 1a (SREBP1a), 1c (SREBP1c) and carbohydrate response element-binding protein (ChREBP). In turn, mitochondrial transcription factor peroxisome proliferator activated receptor γ (PPARγ) coactivator 1 (PGC-1) α and β can stimulate expression of SREBP1a and SREBP1c. In the kidney, increasing TG levels are associated with elevated expression levels of SREBP-1c and chREBP[14]. Moreover, expression of SREBP was increased in the kidneys of patients with CKD[47], in the glomeruli of patients with DKD[48] and in the kidneys of patients with obesity-related diabetes compared with healthy individuals, and in mice fed a high-fat diet compared with normal diet controls[49]. In these mice, high SREBP was associated with kidney lipid accumulation and progression of kidney injury. Therefore, FAO, lipogenesis and cholesterol metabolism (Fig. 2) are tightly connected, and changes in one system can also affect the others.

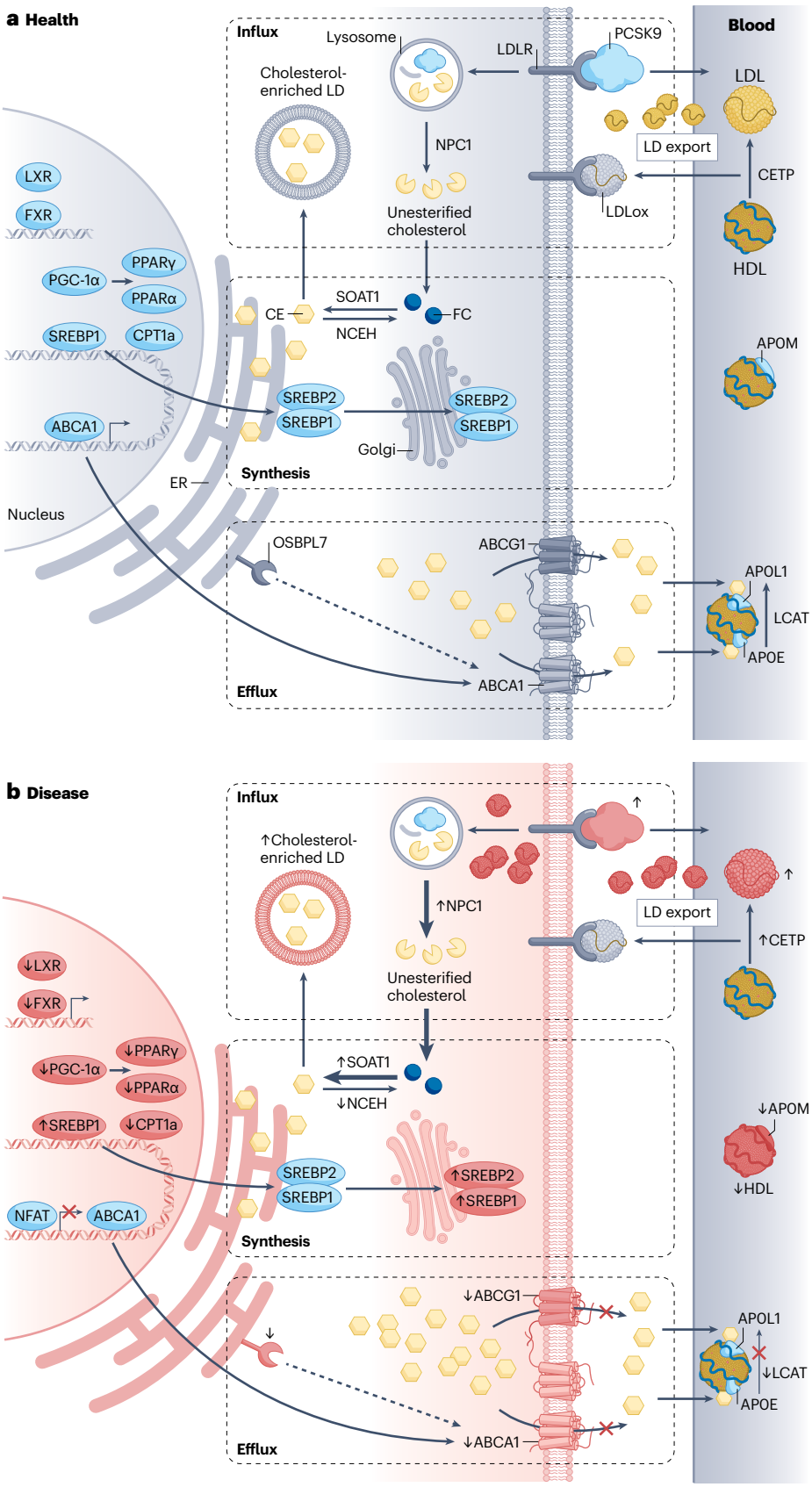


Fig. 2 | Main mechanism of cholesterol dysregulation in health and CKD. **a**, Physiologically, sterol regulatory binding proteins 1 (SREBP1) and 2 (SREBP2) are transported from the endoplasmic reticulum to the Golgi apparatus, where they are cleaved, followed by translocation to the nucleus to initiate cholesterol synthesis. Newly synthesized cholesterol is then converted into esterified cholesterol (CE) by sterol O-acyltransferase 1 (SOAT1) or is transported to the plasma membrane for efflux via ATP-binding cassette subfamily A member 1 (ABCA1) and subfamily G member 1 (ABCG1). Cholesterol influx from circulating low-density lipoproteins (LDL) is mediated by the LDL receptor (LDLR); the proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes LDLR degradation by binding to the LDLR on the cell surface and facilitating its internalization into the endosomes. Niemann–Pick C1 (NPC1) in the late lysosomes regulates levels of unesterified cholesterol. **b**, In chronic kidney disease (CKD), based on data from human and animal models, the downregulation of peroxisome proliferator-activated receptor (PPAR)-gamma coactivator (PGC-1α), which is a key regulator of the PPAR family, decreases the expression of fatty acid oxidation (FAO)-related genes. Decreased expression of liver X receptor (*LXR*) and farnesoid X receptor (*FXR*) and increased expression of *SREBP1* initiate cholesterol synthesis. Compared with physiological conditions, in CKD, elevated SOAT1 activity and decreased activity of neutral cholesterol ester hydrolase (NCEH) increase CE formation from free cholesterol (FC) and lead to its accumulation as CE lipid droplets (LDs). Moreover, excess cholesterol cannot be exported effectively owing to decreased expression of ABCA1 and ABCG1 (as a result of inhibited nuclear translocation of nuclear factor of activated T cells (NFAT)), which also contributes to CE LD formation. Animal models of CKD also indicate that decreased activity of oxysterol-binding protein like 7 (OSBPL7) contributes to decreased ABCA1 activity. Reduced uptake of high-density lipoprotein (HDL) and increased cholesterol uptake from circulating LDLs mediated by LDLRs also contribute to high levels of unesterified cholesterol. Accumulation of free cholesterol activates SOAT1, leading to over-production of esterified cholesterol, which is toxic to cells. Overexpression of PCKS9 might also contribute to CKD via enhanced degradation of the LDLR, resulting in increased levels of circulating LDL cholesterol. Additionally, decreased levels of high-density lipoproteins (HDL) lower circulating levels of apolipoproteins M (APOM), E (APOE) and L1 (APOL1).

Changes in lipid uptake by podocytes in CKD

CD36 is a very important receptor for FA uptake in podocytes[50]. High glomerular and tubular CD36 expression was associated with kidney injury in CKD, through a process that involved the induction of podocyte apoptosis via activation of NLR family pyrin domain-containing 3 (NLRP3)[51]. High levels of CD36 in the plasma membrane also cause lipotoxicity and LD accumulation in podocytes, and have been implicated in kidney lipotoxicity in mice with experimental Alport Syndrome via the collagen I–discoidin domain receptor 1 (DDR1) pathway[52]. High-fat diet in mice increased kidney CD36 expression, and palmitic acid treatment of podocytes elevated CD36 levels in vitro. By contrast, the CD36 inhibitor sulfo-N-succinimidyl oleate decreased lipid accumulation, reactive oxygen species (ROS) production and actin cytoskeleton rearrangement in treated podocytes compared with controls[53]. Additionally, in vitro overexpression of heart-type FABP (H-FABP; also known as FABP3) in podocytes increased fatty acid-induced podocyte injury[54]. In patients with obesity-related glomerulopathy, elevated H-FABP expression correlated with proteinuria, HDL cholesterol (HDL-C) and homeostatic model assessment-insulin resistance (HOMA-IR); H-FABP expression correlated weakly with albuminuria in the *db/db* mouse model of DKD[55]. Interestingly, vascular endothelial growth factor B (VEGFB) promotes FA accumulation via FATP4 upregulation in the glomeruli of *db/db* mice, and of mice with a high-fat diet or STZ-induced DKD[56].

Changes in lipid uptake by proximal tubules in CKD

Under certain pathological conditions, such as nephrotic syndrome, proximal tubules can absorb lipids from urine (apical side) or from the blood vessels (basal side)[57]. However, whether such bidirectional uptake of lipids affects kidney function directly remains unclear. Although studies in animal models suggest that high-fat diets can lead to severe progression of kidney disease, elevated serum TG levels were not conclusively associated with kidney disease in patients with CKD[58]. Similar to podocytes, CD36 overexpression was associated with tubular injury in CKD as it induces apoptosis in tubular epithelial cells[59] and facilitates chronic inflammation, fibrosis and oxidation stress in proximal tubular cells[60]. Interestingly, in a mouse model of CD36 overexpression, elevated FA accumulation was observed as early as 8 weeks of age, whereas markers of fibrosis were increased by 20 weeks of age compared with wild type controls[61], suggesting that CD36 might contribute to early disease progression but is likely not a major initiator of tubular injury as there was no evidence of profibrotic marker expression in 8-week-old mice.

Kidney FATP2 (also known as SLC27A2) primarily localizes to proximal tubular epithelial cells along the apical but not the basolateral membrane, and seems to be the dominant FA transporter in these cells[62]. In the unilateral ureteral obstruction (UUO) mouse model of fibrosis, *Fatp2* deletion or pharmacological inhibition using small molecule inhibitors protected from tubular lipotoxicity[63]. In a pharmacologically induced nephrotoxicity mouse model (specifically, zoledronate administration at 3 mg/kg/week), transforming growth factor-β (TGFβ) mediated increases in FATP2 (ref. 64), which indicates a link between inflammation, fibrosis and alterations in lipid metabolism in the kidney.

In summary, FFA uptake in podocytes or tubular cells has similar downstream effects, and CD36 and FATP2 have an important role (Fig. 1). However, further investigations are necessary and might reveal cell-specific mechanisms of lipid uptake in different kidney cells, which, in turn, could provide novel insights into their specific contribution to CKD progression.

Changes in FAO in podocytes in CKD

Podocytes have a high energy demand owing to their complex structure and function. FAO in podocytes is regulated by several key enzymes and signalling pathways, including PPARα and AMPK. Decreased expression of PPARγ, where variant 1 (γ1) is one of the highly expressed isoforms in glomeruli and podocytes[65], and of PPARα contributes to DKD[66–68], whereas activation of PPARδ ameliorates diabetes-associated kidney damage[69]. Reduced AMPK expression and FA overload lead to decreased FAO and enhanced lipogenesis in models of podocyte injury induced by a high-fat diet[70]. Importantly, sirtuin 1 (SIRT1), which is a regulator of AMPK activity, is also significantly reduced in rodent models of DKD, whereas podocyte-specific SIRT1 overexpression or pharmacological activation of SIRT1 in OVE26 mice (a mouse model with a mutation in the insulin gene that mimics severe early-onset type 1 diabetes) with established proteinuria, is sufficient to slow DKD progression and reduce glomerular oxidative stress[71].

Obesity-associated abnormalities in FAO also result in the development of kidney injury. In podocytes, high glucose reduced β-oxidation of FAs via several mechanisms including decreased expression of PPARα, acyl-CoA dehydrogenase medium chain (ACADM) or acyl-CoA oxidase 1/2 (ACOX1/2)[13], increased acetyl-CoA carboxylase 2 (ACC2) activity in mitochondria[72], increased expression of CD36 and accumulation of ceramides[73,74]. In obesity-related nephropathy models, reduced nuclear respiratory factor 2 (NRF2), which is a key modulator of mitochondrial biogenesis, along with suppressed expression of the key FAO enzyme long-chain acyl-CoA synthetase-1 (ACSL1), is associated with high lipid deposition in the kidney compared with non-obese controls[75]. Genetic studies indicate that ACC2 is also associated with proteinuria in type 2 diabetes[76,77] and ACC2 inhibition in podocytes mitigated hyperglycaemia-induced de novo lipogenesis[78], primarily via a SIRT1–PGC1α axis[72].

Changes in FAO in tubular cells in CKD

In the human kidney, the expression of FAO genes correlates with fibrosis and transcriptional factors that control mitochondrial biogenesis also regulate FAO[79]. Accordingly, expression of PPARα and oestrogen-related receptor-γ (ESRRA), which is a nuclear receptor that regulates numerous genes involved in mitochondrial and metabolic functions, was lower in the kidneys of patients with CKD than in non-CKD patients and lower in proximal tubular cells of CKD animal models than in healthy controls[61,80]. Interestingly, although PPARα and ESRRA deletion in mice does not cause kidney injury, it increases susceptibility to acute kidney injury (AKI) and fibrosis[80–83]. Using an UUO mouse model, one study showed that genetic or pharmacological inhibition of STAT6, which is a transcription factor that inhibits the expression of PPARα, reduces kidney lipid accumulation and fibrosis, and enhances FAO[84]. In addition, using the same mouse model, another group demonstrated a novel mechanism that contributes to tubulointerstitial fibrosis via alteration of the activating transcription factor 6α (ATF6α)–PPARα axis[85]. Specifically, activation of ATF6α, which is a transcriptional factor involved in the unfolded protein response and is an upstream regulator of FA metabolism, suppressed PPARα expression significantly, which reduced FAO and resulted in lipotoxicity in proximal tubular cells and subsequent fibrosis in the tubulointerstitial compartment.

Intriguingly, a 2023 report showed the presence of a robust Crabtree effect (that is, a rapid glucose-induced inhibition of oxygen consumption that results in a shift from energy-efficient aerobic respiration to insufficient glycolysis) in several types of proximal tubule epithelial

cells (PTECs), including HK-2 cells, human primary kidney PTECs, isolated murine PTECs and the kidney cortex from *db/db* mice[86]. Although no obvious explanation for why PTECs shift to energy-insufficient glycolysis exists, an adaptive mechanism to decrease ROS production or pseudohypoxia (that is, a state of NADH/NAD redox imbalance due to uncontrolled hyperglycaemia[87]) could contribute to the Crabtree effect.

Altered lipid metabolism can also contribute to autosomal-dominant polycystic kidney disease (ADPKD); murine kidney epithelial cells lacking *Pkd1* have defective FAO but intact glycolysis[88]. Another study also revealed decreased PPARα expression in ADPKD in association with decreased expression of other important genes involved in FAO and oxidative phosphorylation (OXPHOS), such as *Cd36*, *Slc27a2*, *Cpt1a*, *Cpt1b*, *Acox1*, *Etfb*, *Etfdh* and *Ppargc1a*[89].

The role of PPARα in CKD has been additionally recognized to be associated with ageing. Expression of PPARα and FAO-related proteins (CPT1α, ACOX1) is significantly lower in ageing rats (24 months old) than in younger rats (6 months old); this decrease is accompanied by lipid accumulation in tubular epithelial cells and increased expression of PPARα-targeting microRNA-21 (ref. 83). The same study demonstrated an age-related increase in the kidney expression of lipid-related proteins (SREBP1, farnesoid X receptor (FXR), liver X receptor (LXR), retinoic acid receptor (RXR) or ChREBP in Sprague Dawley rats, similar to what had been previously observed in C56BL/6 mice[90]. Treatment of Sprague Dawley rats with the PPARα/β activator MHY2013 normalized lipid metabolism in tubular epithelial cells and reduced kidney fibrosis in ageing rats[91], further underlining the importance of PPAR–FAO axis in the regulation of lipid homeostasis in the kidney.

Further, expression of CPT1, which resides in the mitochondrial outer membrane and regulates mitochondrial uptake of FAs, is reduced in human CKD samples and in the UUO mouse model of kidney fibrosis compared with healthy controls[61]. CPT1 is important for the transfer of FA esters into mitochondria. CPT1 deficiency leads to kidney malfunction owing to a decrease in ATP production, whereas mice with tubular *Cpt1* overexpression are protected from the development of kidney fibrosis[92]. Another study demonstrated that loss of Krüppel-like factor 15 (KLF15), which is a zinc-finger transcriptional mediator of FAO that is highly enriched in the proximal tubule and occupied the promoter region of CPT1 and ACAA2, is associated with kidney fibrosis in mice and correlated independently with estimated glomerular filtration rate (eGFR), and with expression of *PPARα* and *CPT1A* in human kidney samples[93]. Mitochondrial transcriptional factor A (TFAM) also seems to have an important role in kidney fibrosis as its deficiency leads to leakage of mitochondrial DNA into the cytosol and activation of a novel and vital innate immune signalling pathway — the cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway[94]. This pathway might represent another mechanism underlying the development of kidney fibrosis.

Peroxisomal FAO in CKD

Most studies performed to date have focused on the role of mitochondrial FAO in kidney injury but little attention has been given to peroxisomes. The pioneering data on peroxisomes in the pathogenesis of kidney injury originate from ischaemia–reperfusion models of AKI. In peroxisomal β-oxidation, very long-chain (>22 carbons) FAs are broken down into acetyl-CoA molecules, which can be further processed by the cell to generate energy. However, as peroxisomes do not have respiratory chain enzymes, peroxisomal β-oxidation is not directly coupled to ATP generation and most energy is released as heat[95]. Notably, peroxisomes and LDs are in physical contact within the cell[96], and peroxisomal β-oxidation might be involved in the regulation of cellular lipolysis via an intricate pathway that controls adipose TG lipase protein levels[97]. In AKI, peroxisomes become damaged, and peroxisomal β-oxidation decreases with the duration of kidney ischaemia[98,99]. In cisplatin-induced AKI, treatment with fibrate, which is a PPARα agonist, increases the number of peroxisomes and L-FABP levels in proximal tubules, and ameliorates kidney damage[100]. Interestingly, in STZ-induced DKD in mice, enhanced oxidation of dicarboxylic acids by peroxisomes resulted in lipid accumulation via the metabolite succinate[101]. Similarly, another study demonstrated that a mismatch between FAO and catalase activity accelerated DKD progression in the STZ model[102]. In addition, diabetic mice with a *Cat* deletion had increased proteinuria, serum creatinine and FFA levels, in association with significantly increased mitochondrial ROS levels in mesangial cells, compared with controls. These findings support the idea of a close interaction between mitochondrial and peroxisomal pathways[103]. Moreover, increased SIRT5 expression and decreased malonylation, which was previously shown to lead to increased glucose flux in DKD[104], is associated with increased peroxisomal β-oxidation in the kidney cortex of *db/db* mice, similar to what was observed in the tubulointerstitium of Southwestern Native Americans with type 2 diabetes and DKD[105].

Overall, current research underlines the importance of FAO and peroxisome β-oxidation in the pathogenesis of kidney diseases, and in podocyte and proximal tubular cell injury. However, although the role of dysfunctional peroxisomes and a dysregulated mitochondria–peroxisome axis in the development of kidney injury has become clearer, further research is necessary to elucidate how these factors might contribute to kidney disease progression.

Cholesterol metabolism in CKD

Cellular cholesterol homeostasis (Fig. 2) is another important component of kidney lipid metabolism. Cholesterol accumulation due to impaired reverse cholesterol transport is commonly observed in patients with CKD, including patients with DKD[11], nephrotic syndrome[106], kidney disease associated with Alport Syndrome and uraemia[107]. Although kidney disease is associated with elevated levels of 3-hydroxy-3-methylglutaryl-coenzyme A[108] (HMG-CoA), which is the rate-limiting enzyme of cholesterol synthesis, statins, which are HMG-CoA reductase inhibitors, do not affect CKD progression significantly, despite having a major role in cardiovascular protection[109].

In earlier studies, the use of agonists of FXR, which is a key regulator of kidney cholesterol homeostasis, had a kidney-protective effect via the downregulation of SREBP-1c, stearoyl-CoA desaturase-1 and acetyl-CoA carboxylase synthesis, and the upregulation of PPARα, CPT1a, PGC-1α, uncoupling protein-2 (UCP-2) and lipoprotein lipase (LPL)[110,111]. Additionally, FXR and G protein coupled bile acid receptor TGR5 (also known as GPBAR1) had a renoprotective role in mouse models of diabetes and DKD. Induction of FXR or TGR5 reduced fibrosis, inflammation and lipid accumulation effectively via stimulation of AMPK–SIRT1–PGC1a–SIRT3–ERRα signalling and inhibition of ER stress, hypoxia-inducible factor (HIF) signalling and glucose transporter 1 (GLUT1; also known as SLC2A1)[112]. LXR, together with RXR, controls the expression of ATP-binding cassette transporters (ABCA1 and ABCG1)[113], which are responsible for cholesterol efflux, reduce the expression of the inflammation mediators and control the activity of kidney Na-Pi transporters[114]. Reduced expression of ABCA1 correlated with DKD progression in clinical and experimental models of DKD,

which was associated with increased podocyte LD accumulation in the absence of glomerular injury[13]. In Chinese patients with DKD and type 2 diabetes, LXRα rs7120118 was associated with a high risk of DKD development, whereas ABCA1 rs2230806 was associated with a high risk of DKD without hypercholesterolaemia[115]. Genetic or pharmacological ABCA1 overexpression reduced albuminuria in mouse models of DKD and slowed DKD progression[12,13,116]. In mouse models of adriamycin-induced nephropathy and experimental Alport Syndrome, a small molecule ABCA1 inducer that is currently being tested in phase II trials protected from the development of CKD and targeted the intracellular cholesterol receptors oxysterol binding protein like 7 (OSBPL7) directly[117].

Subtilisin/kexin type 9 serine protease (PCSK9), which regulates cholesterol homeostasis through its ability to reduce LDL receptor (LDLR) levels on the plasma membrane, has gained attention owing to the high efficiency of PCSK9 inhibitors in the treatment of dyslipidaemia (see below). Of note, in a high-fat diet mouse model of kidney injury, decreased levels of circulating PCSK9 promoted CD36-dependent kidney lipid accumulation[118], suggesting that circulating PCSK9 protects against diet-induced kidney injury. However, an earlier study suggested that high plasma PCSK9 levels in nephrotic syndrome, both in humans and in a mouse model, are associated with podocyte damage and that *Pcsk9* loss ameliorated dyslipidaemia[119]. Importantly, in patients with mutations in genes encoding LDLRs or PCSK9, hyperlipidaemia is not frequently associated with the development of CKD[120,121], suggesting that altered kidney lipid metabolism, rather than the deposition of circulating lipids in the kidney, contributes to disease progression.

Changes in podocyte cholesterol metabolism in CKD

Dysregulation of cholesterol metabolism is one of the hallmarks of podocyte injury in CKD (Fig. 2) — cholesterol accumulation has been demonstrated in the glomeruli of mice with DKD, focal segmental glomerulosclerosis (FSGS) and Alport Syndrome[21]. Podocytes treated with serum from patients with DKD have increased cholesterol and LD accumulation in association with reduced ABCA1 expression compared with podocytes exposed to healthy human serum[12]; we observed similar features in kidney biopsy samples collected at early CKD stages in the same patient population. Another study reported the accumulation of LDs in the cell body of podocytes from patients with DKD, in whom the glomerular expression of ABCA1 was also downregulated and correlated positively with eGFR[11].

Unlike in healthy controls, suppression of ABCA1 might also drive cardiolipin-dependent mitochondrial dysfunction and increase podocyte susceptibility to injury in DKD[13], whereas in patients with FSGS, glomerular ABCG1 expression is significantly upregulated compared with healthy controls and ABCA1 expression is unchanged[21]. Among several potential stimuli, local glomerular tumor necrosis factor (TNF) expression caused cholesterol-dependent podocyte apoptosis in FSGS and DKD via reduction of ABCA1-mediated cholesterol efflux and decreased cholesterol esterification by sterol-O-acyltransferase 1 (SOAT1)[116]. Interestingly, genetic *SOAT1* deletion in ABCA1-deficient human podocytes resulted in free cholesterol accumulation in the absence of glomerular injury, whereas loss of SOAT1 in a mouse model of DKD reduced cholesterol esters and LD accumulation in podocytes[22]. These findings suggest that pharmacological inhibition of SOAT1 might represent an additional therapeutic strategy for CKD.

In experimental FSGS and Alport syndrome, a small-molecule ABCA1 inducer targeting OSBPL7 (ref. 117) had a very strong protective effect, which suggests that intraorganellar lipid trafficking might contribute to CKD progression and should be investigated further. Cholesterol accumulation in podocytes via a SIRT6–ABCG1 axis was also reported in angiotensin II-infused mice[122]. Subsequent studies demonstrated a role for junctional adhesion molecule-like protein (JAML) in mediating podocyte lipid metabolism through regulation of the SIRT1–SREBP1 axis in DKD. JAML deficiency caused reduced neutral lipid deposition in glomeruli from mice and in podocytes treated with high glucose[123].

Increased TG uptake leads to podocyte apoptosis and glomerulosclerosis, which might be related to elevated hepatic diacylglycerol O-acyltransferase (DGAT) expression and activity[124]. In patients with primary nephrotic syndrome, angiopoietin-like protein 3 (ANGPTL3), which is an endogenous inhibitor of lipoprotein lipase, correlates positively with cholesterol, TGs and LDL[125]. Deletion of *Angptl3* in mice resulted in lower proteinuria levels after lipopolysaccharide (LPS) stimulation, which might be due to ANGPTL3-dependent regulation of podocyte integrin β3 and α-actinin-4 (ref. 126); these proteins are the main regulators of cytoskeletal rearrangement in podocytes. By contrast, global deletion of the gene coding for the key lipolysis enzyme adipose triglyceride lipase (ATGL) in mice resulted in albuminuria accompanied by ectopic deposition of fat in the kidney. Podocyte-specific ATGL deficiency resulted in apoptosis, increased ROS production and redistribution of F-actin fibres[127]. Finally, the discovery that high-risk genetic variants of apolipoprotein 1 (APOL1) are associated with CKD in individuals of West African ancestry[128] have raised the possibility of a new APOL1-related mechanism of podocyte injury linked to lipid metabolism[129,130].

Changes in tubular cell cholesterol metabolism in CKD

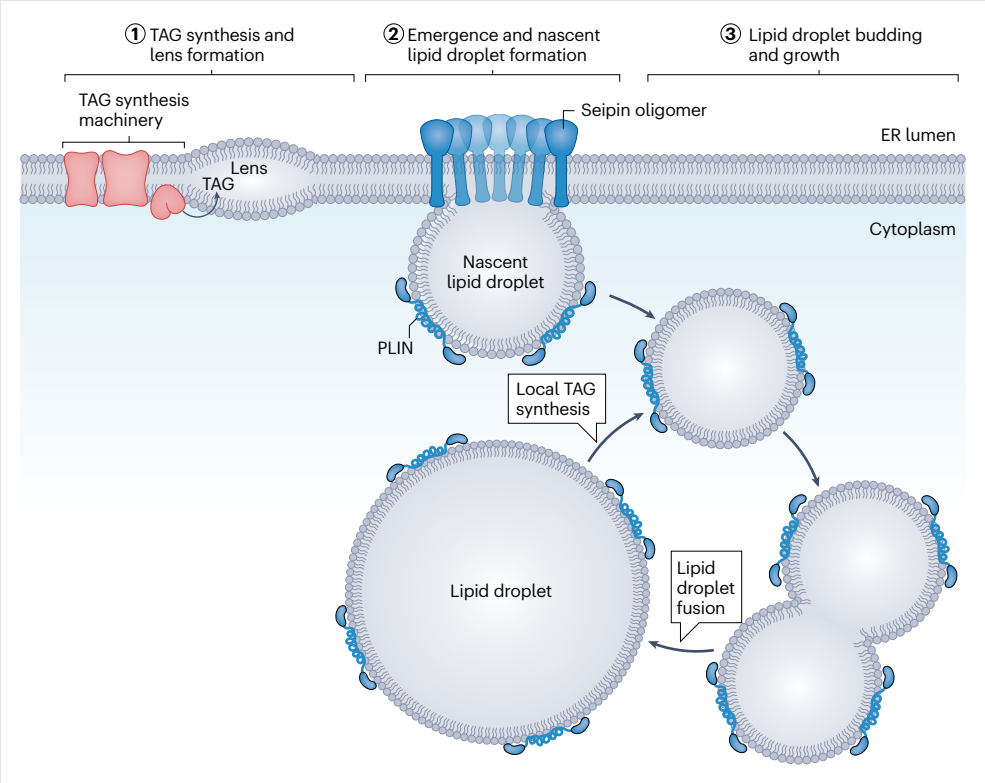
Kidney fibrosis is accompanied by alterations in the cholesterol metabolism of tubular cells, similar to the changes observed in podocytes. Accordingly, FXR attenuates kidney fibrosis[131,132], regulates glucose metabolism[133], lipogenesis and mitochondrial biogenesis-related pathways[134] in DKD, and reduces TGFβ–SMAD signalling and inflammatory responses in kidney mesangial cells[135]. In *Ldlr* heterozygous mice fed a high-cholesterol diet followed by induction of kidney fibrosis, an anti-PCSK9 vaccine (PCSK9Qβ-003) reduced total cholesterol and associated LDL-C effectively, with upregulation of LDLR, VLDLR and SREBP2 (ref. 136). Interestingly, LDLR deletion in tubular epithelial cells from mice with experimental Alport Syndrome was sufficient to extend lifespan[23].

Compared with wild type animals, selective deletion of *Abca1* in the principal cells of murine kidney cortical collecting ducts increased cholesterol levels, which was associated with elevated ROS, reduced ATP levels and increased blood pressure via stimulation of the epithelial sodium channels[137]. ABCG1 expression was also reduced significantly in mesangial and tubular cells from mouse models of DKD compared with healthy controls[138]. Additionally, dysregulated cholesterol metabolism in kidney tubules has been suggested to lead to the formation of cholesterol crystals, which can cause kidney inflammation and injury[21,139]. Cholesterol crystal deposition in tubules in patients with nephrotic syndrome correlated strongly with serum cholesterol levels, but not with proteinuria or the type of glomerulonephritis[140].

These data indicate that lipid accumulation seems to affect glomeruli and kidney proximal tubules to a greater extent than other kidney compartments. However, the localization of excess lipids varies among animal models, and the extent to which these models accurately reflect lipid-related kidney disease in humans remains controversial.

Box 2

Lipid droplet structure, biogenesis and degradation



Lipid droplets (LDs) are composed of a neutral lipid core consisting of triacylglycerols (TAG) and cholesteryl esters surrounded by a phospholipid monolayer that is studded with integral and peripheral proteins. Two main classes of proteins have been identified: class I proteins, where insertion of typical hydrophobic membrane hairpins occurs in the endoplasmic reticulum (ER), and class II proteins, which are recruited to the LD surface directly from the cytosol. The best-characterized family of LD coat proteins is the perilipins class II protein family, which includes perilipins (PLIN) 1–5 (ref. 248). The membrane proteins have many different functions that control different aspects of LD dynamics (growth and degradation), positioning inside the cell and association with other organelles. A diverse set of phospholipid species is also present in LDs, where phosphatidylcholine and phosphatidylethanolamine are the most abundant, followed by phosphatidylinositol[141]. The life cycle of LDs involves multiple steps and begins in the ER, where TAG and cholesterol ester synthesis enzymes deposit neutral lipids between the ER leaflets to form a lens[141] (see figure). Within the next step, seipin, which is one of the key LD biogenesis factors, is recruited to the lens to initiate the growth of the LD followed by emergence of LDs in the cytosol due to differences in the surface tension of the ER leaflets, which is determined by asymmetrical protein binding and phospholipid composition. Further growth of LDs might occur through fusion or local lipid synthesis. Lipolysis and autophagy are two main catabolic pathways of LDs into free fatty acids. Lipolysis relies on the direct activation of LD-associated lipases, such as adipose triglyceride lipase, hormone-sensitive lipase and monoglyceride lipase. Lipophagy controls LD degradation (Box 3) via its association with GTPase Rab7 (ref. 249). Interestingly, chaperone-mediated autophagy has a role in the selective degradation of the PLIN family[250,251]. Figure adapted from ref. 141, Springer Nature Limited.

Lipid droplet accumulation is a hallmark of CKD

LDs are universal ancient, conserved lipid storage organelles that modulate lipid and energy homeostasis in most cells, from yeast to humans (Box 2). In adipocytes, which specialize in lipid storage, LD formation is a physiological process, whereas in other cell types, including podocytes and kidney tubular cells, LD formation is indicative of impaired cellular homeostasis and might represent a mechanism of cellular protection against lipotoxicity. After their initial formation, LDs undergo various fusion processes, ripening, coalescence or lipophagy (that is, autophagic LD degradation) (Box 3). LDs are highly dynamic organelles and their number, size, subcellular localization and composition vary widely between different cells or even within the same cell type, which reflects the cellular metabolism and cycles of nutrient availability and energy demand (Box 2). Moreover, LDs establish contacts with several other cellular organelles, such as the ER, peroxisomes, mitochondria and lysosomes (or vacuoles in yeast), which are crucial to the normal life cycle of LDs and their functions[141].

LD functions include lipid storage, transport, synthesis and hydrolysis. However, according to the latest proteomic and lipidomic analyses, LDs also participate in membrane trafficking, protein storage and degradation, signal transduction, detoxification and nucleic acid handling[142]. Multiple studies have identified kidney lipid deposition as a phenomenon observed in (and a hallmark of) clinical and experimental CKD of both metabolic and non-metabolic origin. Accordingly, LDs accumulate in fibrotic human kidneys[61], mostly in tubular and interstitial cells owing to high levels of circulating lipids, altered

Box 3

Lipophagy as a contributor to chronic kidney disease

Lipophagy is a type of selective autophagy that targets lipid droplets (LDs) and is an essential mechanism for maintaining LD homeostasis. Lipophagy begins with the recognition of cargo by the autophagosomal membrane through interaction with the microtubule-associated protein 1 light chain 3 (MAP1-LC3), which then promotes the movement of cytoplasmic adipose triglyceride lipase (ATGL) to LDs and initiates LD catabolism through the deacetylase SIRT1 and interaction with the LIR domain[252]. Lipases (such as patanin-like phospholipase domain-containing enzymes) induce the recruitment of triglycerides and sterol esters, thereby contributing directly to the formation of the autophagosome[252]. Lipophagy is regulated by the nutritional status of the cells through the regulatory farnesoid X receptor (FXR), peroxisome proliferator-activated receptor-α (PPARα), cAMP-responsive element-binding protein 1 (CREB), mechanistic target of rapamycin (mTOR) or AMP-activated protein kinase (AMPK)[253–255]. In diabetes mellitus, lipophagy is reduced[256] compared with controls. Autophagy-impaired *Atg7*-knockout mice have structural and functional defects in pancreatic β-cells and glucose intolerance[257]. In mice with a *Atg5* deletion in proximal tubular cells, LDs increased in animals starved for 48 h compared with fed controls, an effect that was associated with high plasma levels of fibroblast growth factor 21 (ref. 27). Another study showed decreased lipophagy in the *db/db* mouse model of diabetic kidney disease and in human proximal tubular cells exposed to high glucose; this reduction was reversed with AdipoRon, which is an adiponectin receptor activator that promotes autophagy[256]. An earlier study also confirmed that lysosomal dysfunction leads to autophagic stress in diabetic kidney disease[258], which might be due to activation of the advanced glycation end-product (AGE)–AGE receptor (RAGE) axis[259]. Therefore, targeting lipophagy might represent another therapeutic approach in the management of kidney injury associated with metabolic dysfunction.

lipid metabolism and impaired cellular function. LDs also accumulate in patients with DKD[11,143], in whom high glucose levels cause insulin intolerance and impair the ability of cells to uptake glucose for energy production, resulting in increased reliance on lipids as an alternative source of energy. Moreover, in vivo studies have reported LD accumulation in different models, including mice fed a high-fat diet[144], angiotensin II-treated rats[145], DKD models[22,28,146,147], experimental Alport Syndrome[21,22,52] and the UUO-induced mouse model of fibrosis[148,149]. In support, in vitro data from HK-2 cells treated with FFAs[150], mouse podocytes isolated from mice with experimental Alport Syndrome[52], human podocytes treated with serum from DKD patients[12] and a high-fat diet *Drosophila* model of CKD[151] also showed LD accumulation, which occurs in association with the modulation of genes involved in FAO, or cholesterol uptake and efflux (see below).

Perilipins (PLIN), which are the best-characterized proteins of the LD coat, have gained attention owing to their involvement in CKD pathogenesis, as demonstrated in several clinical and experimental studies. For example, a case report unveiled an association between DKD-like kidney damage in a patient with type 4 familial partial lipodystrophy and a *PLIN1* gene mutation[152]. Importantly, degradation of PLIN1 was reported in patients with obesity[153] and TNF was shown to cause PLIN1 degradation[154], thereby closing the loop between obesity-associated inflammation, which might result in elevated levels of lipolysis, and impaired TG storage in adipose tissue. By contrast, PLIN2 expression was upregulated significantly in kidney tubular cells from diabetic *db/db* mice[155], and in podocytes[56] and urine[143] from patients with DKD.

To date, no studies have examined the role of other PLIN family proteins in DKD. Data from our laboratory suggest that PLIN5 deficiency contributes to podocyte injury in CKD associated with Alport Syndrome via excessive TG lipolysis and insufficient transfer of FAs from LDs to mitochondria[156]. Of note, PLIN5 deficiency in human podocytes might be associated with increased expression of sphingomyelin phosphodiesterase acid-like 3b (SMPDL3b)[157], an enzyme of the sphingolipid signalling pathway that we found to regulate ceramide-1-phosphate levels in podocytes[158,159] and which also localizes to LDs. Compared with wild type controls, human podocytes with *SMPDL3B* knockdown had higher PLIN5 expression, which was associated with LD accumulation, possibly owing to increased expression of FATP3, FATP5, FABP5 and FABP7 in podocytes[157]. *SMPDL3B* knockdown also led to an increase in chaperone-mediated autophagy, which is an essential mechanism of LD-associated protein removal, and higher levels of proteins such as heat shock cognate protein (HSC70) and lysosome-associated membrane protein 2A (LAMP2A); these effects were abrogated with the PLIN5 inhibitor selonsertib[157]. Accordingly, *Plin5* expression was markedly reduced in murine podocytes with hyperglycaemia-induced damage[160], whereas *Plin5* overexpression was sufficient to overcome high glucose-induced podocyte damage, via enhanced activity of the AKT–GSK-3β–NRF2 axis. Interestingly, the early phase of injury in an ischaemia–reperfusion injury mouse model was characterized by accumulation of PLIN2-positive LDs in proximal tubular cells; these LDs were also associated with a rapid decline in kidney function in DKD[161]. By contrast, PLIN2-positive LD accumulation was not detected in a UUO mouse model of CKD[162].

Among other factors that contribute to LD homeostasis in CKD, APOL1 contributes to the formation of cholesterol esters and to cholesterol efflux in cells and associated with FSGS and glomerulonephritis. In primary human podocytes, wild type (G0) APOL1 were localized predominantly to LDs, whereas the CKD risk variant APOL1 proteins (G1 and G2) were localized to the ER; shifting APOL1 localization from the ER to LDs reduced the autophagic flux and cellular death[130]. In a mouse model of FSGS, APOL1 G1 risk allele expression correlated positively with an increased number of LD in the kidney cortex[129]. Therefore, the presence of APOL1 risk variants seems to increase the susceptibility of kidney cells to lipid-associated injury and CKD progression. Apolipoprotein M (APOM) is also altered in patients with CKD[163], but its potential role in LD accumulation, and CKD development or progression, remains to be established. A Nephrotic Syndrome Study Network (NEPTUNE) cohort showed that glomerular APOM expression and plasma levels were lower in patients affected by glomerular diseases than in healthy controls. In these studies, reduced APOM correlated directly with eGFR, suggesting that plasma APOM might be a novel biomarker of glomerular disease progression[164]. Of note, even cytoskeletal proteins that were not thought to have a role in lipid metabolism, such as JAML, were found to regulate lipid metabolism and increase LD accumulation

in DKD sera-treated podocytes and mouse models of DKD[123]. Our studies demonstrated that impaired cholesterol efflux through ABCA1 is a major contributor to lipid dysmetabolism and CKD progression. However, LD accumulation linked to ABCA1 deficiency alone does not cause kidney failure in experimental models[13] and in patients with Tangier disease, who have low levels of HDL-C[165].

Role of kidney sinus fat and kidney parenchymal fat in CKD

In CKD, lipid dysmetabolism also manifests as ectopic deposition of excess lipids in non-adipose organs such as the liver, heart, pancreas and kidney[166]. In the kidney, ectopic fat often deposits in the perirenal space, kidney sinus and kidney parenchyma, and seems to act as perivascular adipose tissue (PVAT; that is, fat tissue that surrounds the blood vessels) in the kidneys (Box 4). Kidney parenchymal fat deposition, whereby ectopic fat is deposited in the kidney cortex and medulla, is associated with kidney cell injury, glomerulosclerosis, interstitial fibrosis and proteinuria[167]. Moreover, kidney sinus fat volume correlated negatively with the number of prescribed anti-hypertensive medications and stage II hypertension[168], and with eGFR[169], in a non-diabetic cohort of individuals at risk of developing diabetes[170]; an association with microalbuminuria was also reported. Moreover, high amounts of kidney sinus and kidney parenchymal fat are a risk factor for CKD development in patients with diabetes[152,171,172]. In a cross-sectional study of asymptomatic participants, accumulation of adipose tissue in the kidney sinus was associated with the expression of KIM-1 and fibroblast growth factor 21 (FGF-21)[173], which are markers of kidney injury. However, an 18-month clinical trial (NCT01530724) from the Dietary Intervention Randomized Controlled Trial (DIRECT) Group suggests that decreased kidney sinus fat and kidney parenchymal fat are associated with improved hepatic parameters rather than improved kidney function[174]. It would be interesting to know how current standard-of-care treatments affect kidney parenchymal fat accumulation, as sodium–glucose co-transporter 2 (SGLT2) inhibitors have an important mTORC1-mediated metabolic effect in patients with type 2 diabetes[175], and the non-steroidal mineralocorticoid receptor antagonist finerenone activates AMPK[176]. Of note, SGLT2 inhibitors might also affect kidney lipid metabolism in glomerular cells in non-metabolic CKD, as demonstrated by the use of empagliflozin in experimental Alport Syndrome[177].

Kidney sinus fat and parenchymal fat adipocytes secrete pro-inflammatory adipokines leading to kidney inflammation, fibrosis and dysfunction. Adipokines such as resistin had a negative effect on the kidney in patients with DKD[178] and correlated with peripheral arterial disease in patients with non-dialysis CKD stages 3–5 (ref. 179). Notably, the anti-contractile effect of PVAT, which is one of its essential functions for the maintenance of vascular resistance, is completely abolished in mice fed a high-fat diet and in New Zealand obese mice, and is substantially reduced in the *ob/ob* mouse model of DKD[180,181]. This defect might lead to endothelial dysfunction and contribute to hypertension development.

PVAT and LD accumulation are strongly associated. However, whether the extent of LD accumulation within PVAT adipocytes can be used as a marker of the metabolic state of a tissue remains controversial. In obesity, for example, adipocytes within PVAT tend to have larger LD than PVAT adipocytes found in lean individuals. This difference seems to be associated with a deficiency in activating transcription factor 3 (ATF3) in mice fed a high-fat diet[180]. Interestingly, seipin, which is a key protein in LD biogenesis, has a role in PVAT morphology and vascular homeostasis, as its deletion results in impaired vessel relaxation and significantly reduces PVAT volume[182]. Deletion of *Plin1* in mice leads to spontaneous hypertension and reduced PVAT mass, as well as increased basal lipolysis, angiotensin II secretion, macrophage infiltration and oxidative stress[183]. A high-fat diet also induces an increase in areas containing $CD68^+$ CC-chemokine ligand 2 (CCL2; also known as $MCP1)^+$ myeloid cells in PVAT. Several immune receptors, including Toll-like receptors (TLRs)[184], receptors for advanced glycation end-products[185], NLRP3[186] and TNF receptors[187], are expressed in PVAT. This observation suggests that PVAT-associated activation of the innate immune response in the kidney might also contribute to CKD pathogenesis. Accordingly, a high-fat diet increased PVAT-specific expression of TLR2 and TLR4, with downstream activation of nuclear factor-kappa B (NF-κB)[188,189]. These early findings were confirmed in a subsequent study in which female rats were fed a Western diet (that is, a diet high in fat and sugar) — upregulation of high motility group box 1 (HMGB1) and TLR4 signalling in PVAT increased ROS levels and activation of the local inflammatory response[190]. Other studies suggested that STING, which has a key role in the innate immune response to cytosolic DNA[191], is also expressed in PVAT and contributes to the pathogenesis of kidney fibrosis[94], APOL1-induced kidney injury[192], minimal change disease[193], DKD and experimental Alport Syndrome[194]. Many aspects of the role of PVAT and, in particular, of kidney sinus fat and parenchymal fat, in health and disease, remain to be explored.

Therapeutic prospects

Lipid-lowering therapies in kidney diseases have been studied for many years, in particular classic serum lipid-modifying therapies, but new studies have led to the development of novel approaches and drugs that target cellular lipid synthesis, uptake, trafficking and metabolic

Box 4

Structure and function of kidney perivascular adipose tissue

Perivascular adipose tissue (PVAT) refers to fat that closely surrounds most blood vessels (except in the brain) and acts as an endocrine organ that secretes soluble mediators. Most intriguingly, PVAT is different from classical adipose tissue and varies from location to location, developmentally and functionally[260–262]; the origin of PVAT remains largely unknown. Kidney sinus fat is associated with kidney blood vessels, nerve fibres and lymphatic channels, and is considered to act as PVAT. PVAT in kidney vessels is thicker than in other organs and appears to be more functionally active[263]. Structurally, kidney PVAT comprises adipocytes, preadipocytes, fibroblasts, macrophages, T cells and other immune cells that are in close contact with the vessel wall. Functionally, PVAT produces a variety of molecules, such as adipokines (including adiponectin, leptin and resistin), inflammatory mediators such as tumour necrosis factor, IL-6 or CC-chemokine ligand 2 (CCL2), nitric oxide, reactive oxygen species and angiotensin II[184]. Therefore, PVAT can produce molecules that promote inflammation, hypertension and atherosclerosis, which are all factors that contribute to the development and progression of chronic kidney disease.

pathways (Table 1), as well as molecules that target mitochondrial lipid metabolism.

Statins are the most commonly used lipid-lowering medications, given their extensive benefits in patients with cardiovascular disease. This beneficial effect was noted with both hydrophilic (fluvastatin and pravastatin) and lipophilic (atorvastatin, lovastatin, simvastatin) statins[195]. However, although the use of statins is recommended owing to its proven contribution to reducing the cardiovascular risk in patients with CKD[196], no data suggest that statins can slow CKD progression.

Niacin is a vitamin with a pivotal role in cellular metabolism, including cholesterol and TG metabolism. In patients with CKD stages 2–4, diabetes and dyslipidaemia, niacin reduced total cholesterol, TGs, LDL-C and phosphorus levels, and increased HDL-C[197]. Interestingly, an increase in niacin intake was inversely associated with CKD in a Japanese population with the rs883484 polymorphism in *PTGS1*, which is involved in the inflammatory response, conversion of arachidonic acid to prostaglandin, regulation of the angiogenesis activity of endothelial cells, and the enzymatic activity of COX1 and peroxidase proteins[198]. However, further research is needed to determine if niacin alone or in combination with other lipid-lowering drugs is more beneficial to patients with CKD.

Fibrates are a type of amphipathic carboxylic acid and represent a class of drugs utilized in the management and treatment of dyslipidaemia, as they are generally effective in lowering elevated plasma TG and cholesterol levels. Fibrate monotherapy lowers TG levels and decreases cardiovascular risk in the general population[199]. However, whether fenofibrates can slow CKD progression remains controversial. Interestingly, pemafibrate, which is a novel selective PPARα agonist, decreased serum TGs without affecting serum creatinine and eGFR levels in patients with CKD[200]. Moreover, changing the treatment from fenofibrate or bezafibrate to pemafibrate decreased serum creatinine and increased eGFR significantly in 16 patients enrolled in the study[200]. By contrast, a meta-analysis of data from 20,176 patients treated with fibrates showed that albuminuria improved, but not serum creatinine levels or eGFR, irrespective of the presence or absence of diabetes[201]. Experimentally, the use of gemfibrozil in a mouse model of ageing improved kidney oxidative stress and histological parameters[202], and the use of pemafibrate in mice with fatty acid overload nephropathy attenuated tubular injury significantly, decreased FFA content and oxidative stress, and increased kidney expression of FA metabolism genes[203].

Thiazolidinediones (TZD) are synthetic ligands of PPARγ. Troglitazone inhibited albuminuria development in STZ-induced mouse[204] and rat[205] models of DKD. Another TZD, pioglitazone, also improved kidney function in Otsuka Long-Evans Tokushima Fatty (OLETF) rats based on mesangial expansion levels[206]. Additionally, agents such as Wy14643 and prostaglandin J2 induced PPARα and PPARγ in mice by increasing the expression of *Lxra* and *Abca1*, and APOA1-mediated cholesterol efflux[207]. However, the efficacy of TZDs in patients with CKD remains controversial.

Cyclodextrins are sugar molecules bound together in rings of various sizes. β-cyclodextrin reduced cholesterol accumulation and apoptosis in podocytes in vitro and protected from kidney disease progression in mouse models of DKD in vivo[12]. A similar effect was demonstrated in the NFATc1nuc FSGS mouse model[116] and in a mouse model of experimental Alport Syndrome[21]. Of note, cyclodextrin does not increase ABCA1-mediated cholesterol efflux[208] but reduces the cellular cholesterol content through its ability to form inclusion complexes with hydrophobic molecules[209]. Thus, cyclodextrin remains an interesting drug development opportunity for diseases characterized by ABCA1 deficiency and is currently in clinical development for patients affected by several forms of CKD.

ABCA1 inducers are used to promote cholesterol efflux in different kidney diseases. Thus, treatment of DKD mice (*db/db*) with the ABCA1 inducer A30 reduced oxidative stress, decreased albuminuria and restored podocyte foot processes[13]. ABCA1 inducers were also beneficial in the prevention and the treatment of established CKD in experimental models of Alport Syndrome and FSGS[117]. The newly synthesized non-lipogenic ABCA1 inducer CL2-57 increased ABCA1 expression with no effect on HDL-C, improved insulin sensitivity in liver and muscles, and reduced inflammation in mice fed a high-fat diet[210]. Moreover, the glucagon-like peptide-1 receptor agonist (GLP1-RA) exendin-4, not only increased ABCA1 expression in adipocytes, hepatocytes and pancreatic cells, but also lowered

Table 1 | Potential therapeutic targets of lipid-modifying agents

Lipid-modifying agent	Target	Effect
Statins (fluvastatin, pravastatin, atorvastatin, lovastatin, simvastatin)	HMG-CoA	↓LDL, ↑HDL
Fibrates (pemafibrate, bezafibrate, fenofibrate)	PPARs	↓TGs ↓FFA ↓Oxidative stress ↑FAO
ABC inducers (A30, CL2-57, Exendin-4)	ABCA1	↓Oxidative stress ↓Inflammation ↑Cholesterol efflux
ABC inducers (GW3965, DMHCA, T0901317)	ABCG1	↑Cholesterol efflux
PCSK9 inhibitors (alirocumab, evolocumab, inclisiran)	PCSK9	↓LDL
Ezetimibe	CD36	↓LDL, ↓FFA
β-cyclodextrin	Cholesterol	↑Cholesterol efflux
SSO	CD36	↓Kidney lipids
5A	ApoA-I	↓Kidney lipids
SS-31	Cardiolipin	↓Kidney lipids
Niacin	GPR109A	↓LDL ↓TGs ↓Cholesterol ↓Phosphorus ↑HDL
LDL apheresis	LDL?	↓LDL ↓VLDL ↓ApoA ↓TGs ↓TNF ↓IL-8

ABCA1, ATP-binding cassette subfamily A member 1; ABCG1, ATP-binding cassette subfamily G member 1; APOA-I, apolipoprotein I; CD36, scavenger receptor class B; FAO, fatty acid oxidation; FFA, free fatty acids; GPR109A, G protein coupled receptor 109A (or niacin receptor 1); HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IL-8, interleukin 8; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin kexin 9; PPARs, peroxisome proliferator-activated receptors; TGs, triglycerides; TNF, tumour necrosis factor; VLDL, very low-density lipoprotein.

kidney cholesterol and increased cholesterol efflux from glomerular endothelial cells[211].

Ezetimibe is an inhibitor of cholesterol absorption inhibitor that was initially developed to target Niemann-Pick C1 Like-1 (NPC1L1). This drug, when used in combination with statin, can reduce cardiovascular events in patients with CKD[212] but its effects on CKD progression remain to be investigated. In a study in patients with type 2 diabetes and albuminuria, ezetimibe reduced kidney parenchymal fat content when administered to patients with high levels of kidney fat[213]. Interestingly, we found that ezetimibe inhibited the interaction between CD36 and DDR1, thereby suppressing CD36-mediated FA uptake in a mouse model of Alport Syndrome, as well as decreasing TG content in the kidney parenchyma[52]. These observations support the idea of ezetimibe repurposing for patients with CKD. Of note, other inhibitors of CD36 had a renoprotective effect and reduced kidney lipotoxicity, including sulfo-N-succinimidyl oleate (SSO)[214], which is a specific inhibitor of the 5 A FA-binding site[215] on CD36, an ApoA-I-mimetic peptide that promotes cholesterol efflux, or SS-31 (ref. 216), which targets cardiolipin.

PCSK9 inhibitors are monoclonal antibodies that sequester PCSK9 and prevent LDLR catabolism, thereby increasing LDLR density. Accordingly, alirocumab[217] and evolocumab[218] reduced LDL-C levels effectively in patients with CKD stage 3. In the ORION-3 trial, inclisiran, which is a fully chemically modified small interfering RNA (siRNA) conjugated to triantennary-N-acetylgalactosamine that inhibits PCSK9 synthesis, also reduced LDL-C levels in patients at risk of cardiovascular disease[219]. Interestingly, PCSK9 inhibitors reduced diet-induced kidney lipotoxicity in experimental models by lowering surface CD36 expression[118].

LDL apheresis is a non-surgical therapy that rapidly removes LDL-C, very low-density lipoproteins (VLDLs), lipoprotein A and TGs from blood. Early studies showed that LDL apheresis also reduced inflammatory cytokines (TNF and IL-8) present in the blood of patients with nephrotic syndrome[220]. The use of LDL apheresis in patients with familial hypercholesterolaemia was also beneficial when other drugs had failed to reduce LDL-C to target levels[221,222]. An ongoing clinical trial (NCT04088799) will test LDL apheresis therapy in patients with FSGS. This study was designed based on case series of paediatric patients with steroid-resistant nephrotic syndrome[223] and preliminary results on changes in proteinuria observed in adults with eGFR as low as 30 ml/min/1.73 m^2 (POLARIS study)[224]. Although this therapy seems to ameliorate lipid-mediated disease progression, and reduce systemic inflammation and lipid-induced vascular changes, further studies are needed to clarify the efficacy of LDL apheresis in controlling lipotoxic kidney injury and CKD progression.

Importantly, anti-diabetic agents such SGLT2 inhibitors, which prevent glucose reabsorption in the kidney and slow DKD progression[225], might have a strong effect on the regulation of lipid metabolism. For example, empagliflozin decreased cholesterol levels and tubular LD accumulation in *db/db* mice and, in combination with metformin, lowered advanced glycation end-products and the kidney fat fraction in patients with diabetes compared with those treated with metformin alone[226]. Empagliflozin also reduces TG content in the kidney cortex of mice with non-metabolic kidney diseases, as we have recently demonstrated in experimental Alport Syndrome[177]. The EMPA-REG OUTCOME trial also showed that empagliflozin reduced the risk of the composite secondary kidney outcome[227] and improved kidney function based on eGFR and urinary albumin-to-creatinine ratio, regardless of baseline albuminuria or eGFR[228]. In the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, canagliflozin also had kidney benefits independently of baseline glycated haemoglobin (HbA_{1c}) levels or the stage of CKD[229]. Finally, the DAPA-CKD trial and the EMPA-KIDNEY trial[230] demonstrated a similar beneficial effect on CKD progression in patients without diabetes[231], really demonstrating that SGLT2i may have renoprotective effects that are independent of glycaemic control.

Metformin is another useful drug in the treatment of type 2 diabetes as it increases insulin sensitivity, reduces intestinal glucose absorption, increases peripheral glucose uptake and reduces hepatic gluconeogenesis. Despite the risk of lactic acidosis, a retrospective study on a cohort of 10,426 patients with type 2 diabetes showed that metformin decreases the risk of all-cause mortality and kidney failure incidence in patients with CKD[232]. Notably, cumulative evidence from in vivo models of cyclosporin A-induced kidney fibrosis[233], 5/6 nephrectomy[234] and adenine diet-induced CKD[235] suggests that the renoprotective impact of metformin extends beyond its anti-hyperglycaemic effect. Sulfonylureas, which lower glycaemia by stimulating the pancreas to produce more insulin, are also used in patients with CKD[236], but monotherapy with metformin in patients with kidney disease was associated with a lower risk of major adverse cardiovascular events than sulfonylurea[237].

GLP-1 RAs, such as liraglutide, semaglutide and dulaglutide, have demonstrated improved secondary microvascular outcomes in cardiovascular safety trials (LEADER (NCT01179048) and SUSTAIN-6 (NCT01720446)) and anti-albuminuric effects[238]. Additionally, dipeptidyl peptidase-4 (DPP4) inhibitors are known to increase incretin hormone levels, which stimulate insulin secretion and reduce glucose production by the liver and have been shown to be effective in glycaemic control in CKD patients[239].

Conclusions

In conclusion, disease-specific abnormalities in cholesterol and fatty acid metabolism might impact kidney health negatively and contribute to CKD development and progression. However, despite the considerable progress made in our understanding of lipid metabolism in the kidney, many questions remain unanswered. Thus, more research is needed to investigate how excessive lipid accumulation promotes fibrotic processes in the kidney and what the major disease-specific triggers driving lipid dysmetabolism are. In particular, whether inflammation triggers lipid accumulation or lipid-induced inflammation leads to CKD progression and oxidative stress, which in turn results in mitochondrial dysfunction, ER stress and cell injury, is still unclear. Moreover, the mechanisms by which lipids affect the function and viability of different cell types are not fully understood. The relationship between parenchymal lipids and systemic lipids also deserves further investigation. Finally, the development of non-invasive reliable imaging methods to measure kidney fat and large-scale studies to determine if kidney fat content can be used to stratify patients at risk of CKD progression and to monitor response to treatment are needed.

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A.M. researched data for the article, made substantial contributions to discussions of the content and wrote the manuscript. S.M. and A.F. reviewed or edited the manuscript before submission.

Competing interests
A.F. and S.M. are inventors on pending or issued patents (US10.183.038, US10.052.345) aimed at diagnosing or treating proteinuric kidney diseases and therefore stand to gain royalties from their future commercialization. A.F. is Chief Scientific Officer of L&F Health LLC, holds equity interests in L&F Research and is the inventor of assets developed by ZyVersa Therapeutics. ZyVersa has licensed worldwide rights to develop and commercialize hydroxypropyl-β-cyclodextrin for the treatment of kidney disease from L&F Research. A.F. also holds equity in River 3 Renal Corporation. S.M. holds equity interest in L&F Research. A.M. declares no competing interests.

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