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Renal lipid metabolism and lipotoxicity

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Abstract

Purpose of review—Lipid accumulation in nonadipose tissues is increasingly recognized to contribute to organ injury through a process termed lipotoxicity, but whether this process occurs in the kidney is still uncertain. This article briefly summarizes the normal role of lipids in renal physiology and the current evidence linking excess lipids and lipotoxicity to renal dysfunction.

Recent findings—Evidence suggesting that renal lipid accumulation and lipotoxicity may lead to kidney dysfunction has mounted significantly over recent years. Abnormal renal lipid content has been described in a number of animal models and has been successfully manipulated using pharmacologic or genetic strategies. There is some heterogeneity among studies with regard to the mechanisms, consequences, and localization of lipid accumulation in the kidney, explainable at least in part by inherent differences between animal models. The relevance of these findings for human pathophysiology remains to be established.

Summary—Current knowledge on renal lipid physiology and pathophysiology is insufficient, but provides a strong foundation and incentive for further exploration. The future holds significant challenges in this area, especially with regard to applicability of research findings to the human kidney *in vivo*, but also the opportunity to transform our understanding of an array of kidney disorders.

Keywords

free nonesterified fatty acids; kidney disease; lipotoxicity; triglycerides

Introduction

Lipids are fundamental constituents of all living cells. They are the main structural components of biological membranes, are a source and reservoir of energy, interact with proteins to modulate their localization and function, and have key roles in intracellular and intercellular signaling. It is, therefore, not surprising that most cells are endowed with complex machineries to regulate the import, synthesis, storage, utilization, and export of lipids. Some eukaryotic cells have evolved specialized lipid handling functions, one notable example being the capacity of adipocytes to store and manage massive intracellular lipid droplets containing primarily triglycerides. Smaller lipid droplets exist in most other cell types and are increasingly recognized as highly dynamic cellular components with important

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functions that may extend beyond lipid storage [1*,2*]. However, lipid accumulation in cells that are not equipped with the molecular tools to handle large lipid loads has been associated with cellular injury and dysfunction [3*,4-7,8*]. Whether excess lipids are a consequence or a cause of cell injury has not been universally established, but a growing body of evidence suggests that, at least in some tissues and cell types, lipid overload *per se* can be deleterious [5-7,8*,9*,10]. This process has been termed lipotoxicity and has been linked to dysfunction in multiple organs, including the liver, heart, skeletal muscle, and endocrine pancreas [5-7,8*,9*,10,11*,12*]. Lipid accumulation has also been described in the kidney in a variety of pathological and physiological conditions, but whether renal lipids and lipotoxicity contribute to human kidney dysfunction has not been established.

Lipids in renal physiology

The total lipid content of the normal human kidney has been estimated at approximately 3% of wet weight [13,14]. Of this (by mass), more than half are phospholipids, the major constituent of cell membranes, approximately one-fifth are triglycerides, and about one-tenth are free nonesterified fatty acids (FFAs) [13]. For comparison, the total lipid content of normal nonsteatotic human liver is 4-5% of wet weight [15]. In both kidney and liver, triglyceride content exhibits the largest inter-individual variability [13-15].

The kidney can use a relatively wide variety of substrates as fuels, depending on their availability, but substrate utilization may vary by region [16-18]. The mitochondrial β -oxidation of FFA is a major source for renal ATP production, particularly in the proximal tubule, which has a high energy demand and relatively little glycolytic capacity [19-21]. *In vivo* studies using radiolabeled FFA in dogs and measurement of substrate differences between arterial and renal venous blood in humans have shown that the kidney extracts FFAs from the circulation and that FFA oxidation could account for more than half of renal oxygen consumption [22,23]. Importantly, FFA extraction by the human kidney *in vivo* was linearly dependent, over a wide range, on plasma FFA concentration (the higher the arterial FFA concentration, the higher the arteriovenous difference) [23].

The vast majority of plasma FFA is carried on albumin, with unbound FFA representing only a minor fraction (less than 0.01%) [24,25]. Tissue uptake of circulating FFA involves dissociation from albumin, mediated by specific membrane proteins such as FA translocase (CD36) and FA-binding protein (FABP) [26]. In addition, the renal proximal tubule retrieves albumin-bound FFA from the filtrate by receptor-mediated albumin endocytosis [27-30]. There is a significant and ongoing controversy with regard to the actual amount of albumin normally filtered (with values ranging from 0.5-3.5 g/day to upwards of 200 g/day) and with regard to its breakdown in the proximal tubule cell versus intact return to the circulation by transcytosis [31-37]. There is agreement, however, that the glomerular sieving coefficient for albumin is greater than zero, with some albumin normally escaping the filtration barrier and being retrieved by the proximal tubule [27-29,36]. The FFAs carried by this reclaimed albumin likely contribute to the overall energy balance of the proximal tubule.

FFAs delivered to the kidney in excess of its energy needs can be esterified with glycerol and deposited as triglycerides in intracellular lipid droplets. These energy stores can be rapidly mobilized in periods of scarcity, as first suggested by *ex-vivo* experiments in canine kidney slices conducted by Weidemann and Krebs [38] more than 40 years ago. The physical size of individual lipid droplets can vary from submicrometer range (thus, undetectable by light microscopy) [1*] to larger lipid droplets detectable by Oil Red O staining in human kidney samples (Fig. 1).

Whether significant lipid synthesis from nonlipid substrates occurs in the normal kidney is not clear. Similarly, very little is known about lipid export from the kidney. Human kidney specimens *ex vivo* produce apolipoprotein E (Apo-E) [39], and Apo-B has been recently proposed to be critical for renal lipid export in mice [40*]. Arteriovenous FFA concentration difference experiments have shown that the kidney takes up FFA in fasted rats, but adds FFA to the circulation in fed rats [41], suggesting that the transport of FFA between blood and renal cells may be bidirectional. It is conceivable that lipid export could protect the kidney from excessive lipid accumulation in conditions of FFA oversupply. It is also theoretically possible that the proximal tubule retrieves important lipophilic compounds (e.g. vitamins) from the primary urine and returns them to the circulation through lipoprotein export [30].

Lipids in renal pathophysiology

Both plasma and intrarenal lipid disturbances may play a role in renal pathophysiology, as concisely reviewed below.

Role of dyslipidemia

Moorhead *et al.* [42] first outlined the lipid nephrotoxicity hypothesis in 1982, proposing that dyslipidemia may contribute to the progression of renal disease. Dyslipidemia in this context could be triggered by urinary albumin loss leading to a compensatory increase in hepatic lipoprotein synthesis and could in effect be part of a positive feedback loop causing further renal injury [42]. This hypothesis has since garnered significant experimental support and has been recently revised and expanded in a comprehensive review by the same group [43*]. Dyslipidemia may affect the kidney directly by causing deleterious renal lipid disturbances (renal lipotoxicity), as well as indirectly through systemic inflammation and oxidative stress, vascular injury, and changes in hormones and other signaling molecules with renal action [7,43*,44].

Dyslipidemia *per se* is not sufficient to lead to renal injury, but likely contributes to renal injury as part of a multihit mechanism, in combination with other systemic and/or local factors [43*]. Theoretically, the heterogeneity and variable involvement of these factors may explain why the preventive value of statins in human chronic kidney disease is still uncertain, in spite of promising data from small renal outcome trials [45,46] and from meta-analyses [47–50] and subgroup analyses [51–53] of nonrenal trials. Larger ongoing renal outcome trials, including LORD (Lipid lowering and Onset of Renal Disease) [54] and SHARP (Study of Heart and Renal Protection) [55], are expected to dissipate some of this uncertainty. It is, however, important to stress that such trials evaluate renal outcomes with a drug class that affects multiple tissues and organs, in addition to having potential pleiotropic effects independent of lipid lowering [56]. Although the results of these trials will certainly be very important from a clinical practice standpoint, they cannot and should not be interpreted as a yes-or-no verdict confirming or dismissing the direct role of renal lipid disturbances in kidney pathophysiology.

Renal lipid accumulation

The link between lipid accumulation and kidney disease was first suggested more than 150 years ago by Rudolf Virchow [57] in his lectures at the Pathological Institute of Berlin, when referring to ‘fatty degeneration of the renal epithelium as a stage of Bright's disease’ (a historical designation for glomerulonephritis, described earlier in the 19th century by Richard Bright, one of the ‘founding fathers’ of nephrology) [58].

We now have an abundance of animal data showing an association between kidney dysfunction and renal lipid accumulation, including in models of metabolic disease (obesity,

metabolic syndrome, and diabetes mellitus), chronic kidney disease, acute renal injury of several etiologies, as well as aging (Table 1) [40*,59,60,61*,62–67,68*,69–73,74*,75,76*,77–83]. Glomeruli and renal tubules (proximal tubules in particular) seem to be most susceptible to lipid accumulation, but the localization of excess lipids varies between animal models. There may also be species or strain-specific differences in the propensity to accumulate lipids in the kidney, as exemplified by the relative resistance to renal lipid accumulation in Sprague–Dawley rats fed a high-fat diet [67] compared with similarly fed mice [59,60,61*]. Whether these models adequately reflect lipid involvement in human kidney disease is up for debate, including in the case of diabetic nephropathy, for which an accurate animal model is not available as of the date of this review [84*].

The available evidence in humans is much scarcer and less amenable to systematic study. Renal lipid accumulation has been described in several contexts, including hypertensive nephrosclerosis [85], focal segmental glomerulosclerosis [86], minimal change disease [87], hepatorenal syndrome [88], diabetic coma [89], severe whole-body hypothermia [90], as well as in rare genetic disorders, including Fabry's disease [91], familial dysbetalipoproteinemia [92], lecithin–cholesterol acyltransferase deficiency [93], arteriohepatic dysplasia (Alagille's syndrome) [94], and lipoprotein glomerulopathy [95].

The range of conditions that have excess renal lipids and kidney dysfunction as common elements implies that the two may be causally related, but whether renal lipid accumulation is a result or a mediator of renal injury in humans is not known. Animal experiments suggest that causality may be bidirectional and may be highly dependent on pathophysiological context.

Lipid accumulation as a consequence of injury

Renal ischemia–reperfusion in uninephrectomized mice causes triglyceride accumulation in the cortex, particularly in proximal tubules [80]. As mitochondrial aerobic respiration is necessary for ATP production from FFA, it is conceivable that ischemia leads to decreased FFA oxidation and redirects FFA to triglyceride pools. However, this view may be overly simplistic, as triglyceride synthesis does not depend only on FFA availability, but also on the activity of a series of enzymes and on the degree of ATP depletion (severe depletion may in fact inhibit triglyceride synthesis and raise FFA concentration, as the conversion of FFA to fatty acyl-CoA requires ATP). The mechanism of renal triglyceride accumulation may be highly dependent on the type of injury and may involve multiple injury-specific changes in lipid metabolic pathways [96].

Of course, the fact that lipid accumulation may in some cases result from renal injury does not preclude the possibility that accumulated lipids, in turn, lead to further damage. For example, lipid accumulation in the renal proximal tubule during ischemia–reperfusion may cause sustained energy deficit by FFA-mediated mitochondrial injury [97,98].

Lipid accumulation as a cause of injury

There is substantial evidence in animals that excess renal lipids can cause injury. The general approach for such experiments has been to show correlation between renal lipid content and markers of kidney dysfunction in one set of animals, while at the same time using genetic, pharmacologic, or dietary maneuvers to prevent or reduce renal lipid accumulation in another set of animals (Table 1). The concomitant reduction of renal lipids and improvement of histological or functional markers was interpreted to support the causal relationship. Although confounding factors could potentially plague individual experiments using this approach (if, for example, a drug reduces lipid accumulation because it improves kidney function rather than vice versa), this body of data taken as a whole strongly supports

the hypothesis that excess lipids may be toxic for the kidney (renal lipotoxicity). This hypothesis is also supported by experiments in which lipid accumulation was triggered in renal epithelial cells by incubation with FFA and then reduced by starvation, in the absence of whole-animal confounding factors [67,68*].

The general mechanisms of lipotoxicity have been reviewed in detail elsewhere [5–7,8*,9*,10,11*,12*]. The principal determinant of lipotoxicity seems to be excessive intracellular FFA content, leading to accumulation of potentially toxic metabolites such as fatty acyl-CoA, diacylglycerol, and ceramides. Lipotoxic cellular dysfunction and injury occurs through several mechanisms, including the generation of reactive oxygen species, multiple organellar damage, disruption of intra-cellular signaling pathways, release of proinflammatory and profibrotic factors, and lipid-induced apoptosis (lipoapoptosis). Triglycerides are not considered toxic *per se* (and may in fact be protective), but are an active reservoir of FFA and an easily measurable indicator of tissue lipid overload [5,7,99,100]. It is important to note that not all FFAs have the same lipotoxic potential and that the cellular mechanisms of lipotoxicity are highly dependent on cell type [101*]. Consequently, not all studies of lipotoxicity in nonrenal cells or organs may be applicable to the kidney.

Finally, renal lipid accumulation has been linked to changes in gene expression, including the SREBPs (sterol regulatory element-binding proteins), ‘master’ regulators of lipid metabolism [59,61*,71,72,82,83], suggesting that the lipid-loaded kidney is not simply a passive victim of lipid oversupply. Intrarenal lipid metabolic disturbances may be important contributors to renal dysfunction, but the role of these disturbances in human kidney disease remains to be established.

Role of albumin reabsorption

As discussed earlier, FFAs enter the proximal tubule from both the basolateral and the apical (luminal) sides. It has been proposed that increased filtration of FFA-bearing albumin and/or an increased FFA/albumin ratio may contribute to proximal tubule FFA overload and lipotoxicity [102–104] (Fig. 2). Filtered albumin would act in this setting as a ‘Trojan horse’ [105], by delivering a passive but deleterious load of FFA to the proximal tubule performing its physiologic task of albumin reclamation.

Knowing what proportion of the total influx of FFA in the proximal tubule normally occurs via reabsorptive endocytosis of filtered albumin would be helpful to ascertain the relative importance of this pathway for renal lipotoxicity. As no direct experimental data are available to answer this question, a brief quantitative exercise is in order. Assuming that albumin filtration in humans is between 0.5 and 3.5 g/day, of which normally less than 0.15 g/day is excreted, the daily reabsorption of albumin by the proximal tubule (after conversion and rounding) is about 5–50 μmol . As the FFA to albumin molar ratio is normally around 1, it can be inferred that 5–50 μmol of FFA enter the proximal tubule daily with albumin from the lumen. At the upper extreme of the albumin filtration controversy, the same calculation would yield 2–4 mmol of FFA delivered to the proximal tubule from the apical side.

Nieth and Schollmeyer [23] measured a difference of FFA concentration between the brachial artery and the renal vein of approximately 35 $\mu\text{mol/l}$ in humans. Assuming a renal blood flow of 2160 l/day (1.5 l/min), the calculated renal extraction of FFA in 24 h amounts to approximately 75 mmol (but may be less or more if FFA extraction varies circadianly or with feeding). Based on these estimates, the amount of FFA taken up from the proximal tubule lumen is most likely three orders of magnitude less than the amount taken up from the circulation. Even if the normal kidney filters and then reabsorbs massive amounts of albumin, as proposed by Comper and coworkers [36,37,106], and even if all FFAs carried

by albumin are retained in proximal tubule cells (although most of the albumin would in this scenario undergo transcytosis), apical uptake would still account for less than 5% of the total proximal tubule FFA uptake.

Does this mean that apical uptake of FFA-bound albumin could not be an important source of proximal tubule FFA overload and lipotoxicity *in vivo*? Not necessarily. A sustained increase in apical FFA uptake due to increased albumin filtration or increased FFA/albumin molar ratio (Fig. 2b) may still throw the system off balance by cumulative effect. In addition, FFA taken up from the apical and basolateral sides may have distinct intracellular fates, such as targeting of albumin-bound FFA to lysosomes, possibly leading to FFA-induced lysosomal injury [107,108]. These possibilities require further investigation.

Nonlipotoxic effects

Lipid overload may also affect renal function through mechanisms that cannot be classified as lipotoxic. For example, excess FFA in the proximal tubule may compete with glutamine as oxidizable substrates in mitochondria, thus decreasing the production of ammonium [109,110] (Fig. 3). This is compatible with findings in Zucker diabetic fatty (ZDF) rats and in Sprague–Dawley rats fed a high-fat diet, in which plasma FFA levels (and renal lipid accumulation in the case of ZDF rats) were inversely correlated with the urinary excretion of ammonium [67,68*].

Moving beyond glomerulocentricity

Compared with other organs in which lipid accumulation and lipotoxicity may occur (such as the liver, heart, and skeletal muscle), the kidney has a high degree of histological complexity, with individual structures having distinct contributions to the fundamental functional triad of filtration, reabsorption, and secretion, as well as to renal metabolic and endocrine functions. As discussed above, renal lipid accumulation has been described in both glomeruli and tubules, particularly in the proximal segment, and is likely to have different mechanisms and consequences within these different structures. However, most studies of lipids and the kidney to date, from clinical correlations to basic science experiments, have taken a predominantly glomerulocentric stance.

The general term ‘kidney dysfunction’ has been used deliberately in this article instead of ‘kidney disease’, because there is more to normal kidney function than a normal glomerular filtration rate (GFR) and absence of proteinuria. For example, humans with features of the metabolic syndrome have an increased risk of uric acid nephrolithiasis, caused at least in part by reduced renal ammonium excretion resulting in an overly acidic urinary pH, which in turn favors uric acid crystallization [111–115]. This ammonium excretion defect has been attributed to proximal tubular lipid accumulation in a rodent model of metabolic syndrome and in a cell culture model of proximal tubule lipotoxicity [67,68*].

Although the potential links between renal lipid accumulation and kidney disease, as manifested by declining GFR and proteinuria, are undoubtedly of paramount importance, more subtle manifestations of lipid-induced renal tubular dysfunction (such as the one exemplified above) are no less worthy of further investigation.

Conclusion

The study of lipids, lipid accumulation, and lipotoxicity in other organs has gained considerable momentum over the past decade, but the role of lipids in kidney physiology and pathophysiology remains a relatively under-investigated area. Laboratory experiments have provided substantial evidence that intrarenal lipid metabolism disturbances may contribute to renal injury and dysfunction, but the applicability of these findings to human

kidney disease remains to be established. Deciphering the role of lipids in the kidney requires further detailed studies in animal and cell culture models, but would also immensely benefit from potential noninvasive urinary ‘-omic’ assays reflective of intrarenal lipid metabolism in humans.

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References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 411–412).

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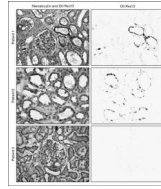


Figure 1. Lipid accumulation in human kidney samples visualized by Oil Red O staining

Kidney surgical specimens were obtained from patients undergoing radical nephrectomy for renal cell carcinoma. Normal kidney cortex samples were dissected by an experienced pathologist, away from the tumor. The samples were frozen, sectioned, and stained with hematoxylin and Oil Red O to visualize the distribution of lipids within renal structures. Left panels are representative images from three different patients (original color images are shown here in gray scale). For each image, a computer-based color deconvolution algorithm was used to separately visualize Oil Red O staining in the red channel (right panels). In these examples, lipid deposits are localized mostly within tubular epithelial cells in patients 1 and 2, but are not detectable in patient 3.

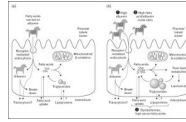


Figure 2. Entry of free nonesterified fatty acids into proximal tubule cells and the role of albumin as ‘Trojan horse’

(a) Under normal conditions, fatty acids enter the proximal tubule cell from the basolateral side as well as from the apical (luminal) side, carried on albumin. Albumin is degraded in lysosomes, but transcytosis has also been proposed. Depending on cellular energy needs, intracellular fatty acids are directed to mitochondrial β -oxidation or to triglyceride stores. (b) Several conditions can theoretically lead to increased fatty acid intake into the proximal tubule cell, including high albumin filtration, high fatty acid to albumin molar ratio, and circulating lipid disturbances. These conditions, alone or in combination, may cause increased intracellular concentration of fatty acids, exceeding the β -oxidative capacity of mitochondria. This leads to intracellular accumulation of triglycerides and to the generation of lipid metabolites with potential toxic effect.

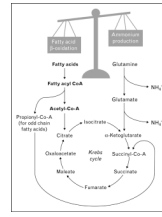


Figure 3. Fatty acids may affect proximal tubule ammonium production by mitochondrial substrate competition

Ammonium (NH_4^+) is produced in the proximal tubule by the metabolism of glutamine to α -ketoglutarate, which then continues in the Krebs cycle. The products of fatty acid β -oxidation also enter the Krebs cycle. Increased intracellular concentration of fatty acids may compete with glutamine as mitochondrial substrate, decreasing its utilization and reducing ammonium production.

Table 1

Renal triglyceride accumulation in animal models^a

| Condition | Animal model | Renal triglyceride accumulation | Ref(s) |
|--|---|--|----------|
| Obesity and metabolic syndrome resulting from high-fat diet | C57BL/6J wild-type and SREBP1c ^{-/-} mice on HFD (60% kcal from fat) | Glomerular and tubulointerstitial Correlated with upregulation of renal SREBPs Prevented in the kidneys of SREBP1c ^{-/-} mice | [59] |
| | C57BL/6J wild-type and PPAR γ ^{+/-} mice on HFD (45% kcal from fat) | Associated with upregulation of renal lipogenic genes Attenuated in PPAR γ ^{+/-} mice (these mice also have less severe metabolic syndrome features) | [60] |
| | DBA/2J mice on HFD (42% kcal from fat) | Prevented by treatment with a FXR agonist acting to downregulate lipogenic genes and upregulate genes involved in lipid oxidation | [61*] |
| Obesity and metabolic syndrome resulting from leptin or leptin receptor deficiency | db/db mice in several genetic backgrounds | In glomeruli and proximal tubule cells Accompanied by differential expression of multiple lipid metabolism and transport genes Decreased by antidiabetic treatment with a GLP-1 agonist | [62–65] |
| | ob/ob mice | In glomeruli and proximal tubule cells | [66] |
| | Zucker diabetic fatty (ZDF) rats | Primarily in proximal tubule cells Reduced by treatment with PPAR γ agonists | [67,68*] |
| | F1 hybrid ZDF/spontaneous hypertensive heart failure (ZS) rats | Primarily in renal tubular cells Not affected by systemic immunosuppressive therapy Reduced by treatment with an antibody against LOX-1 | [69,70] |
| Type 1 diabetes | Streptozotocin-treated SD rats | Glomerular and tubular Accompanied by upregulation of SREBPs in the absence of plasma lipid abnormalities | [71,72] |
| | C57BL/6- <i>Ins2^{Akita}</i> (Akita) mice | Mitigated by treatment with insulin Primarily in glomeruli Accompanied by upregulation of lipogenic genes and downregulation of genes involved in fatty acid oxidation | [73] |
| Other transgenic/knockout models | SREBP-1a overexpression | Within glomerular and tubular cells in C57BL/6J \times SJL mice overexpressing human SREBP-1a controlled by the PEPCK promoter | [72] |
| | Xanthine oxidoreductase (XOR) deficiency | In the lumen of renal tubules of C57BL/6J XOR ^{-/-} mice Associated with upregulation of genes involved in lipogenesis | [74*] |
| Angiotensin II (Ang II)-induced hypertension | Infusion of Ang II by minipump for 7 days in SD rats | Primarily in renal tubular cells in hypertensive rats induced by Ang II but not by norepinephrine Partly suppressed by iron chelation with deferoxamine | [75] |
| Models of chronic renal disease by renal mass reduction | Uninephrectomy in SD rats followed for 3–10 months | Redistribution of fat to nonadipose tissues, including liver, pancreas, adrenals, and kidney Prevented by ACE inhibition Accompanied by upregulation of lipogenic genes, downregulation of genes involved in fatty acid oxidation, and increased expression of the endocytic receptors megalin and cubilin | [76,77] |
| | 5/6 nephrectomy in SD rats and Nagase analbuminemic rats | Marked glomerular lipid deposition after 2 months in Nagase rats, much less in SD rats Prevented by ACE inhibition | [78] |
| Models of acute renal injury | Unilateral ureteral ligation in SD rats | In the cortex and medulla of the obstructed kidney, and to a lesser extent in the contralateral kidney | [79] |
| | Endotoxin nephrotoxicity (LPS injection in CD-1 mice) | In the cortex, including in proximal tubules LPS dose-dependent | [80] |

| Condition | Animal model | Renal triglyceride accumulation | Ref(s) |
|----------------|---|---|---------|
| | Glycerol-induced rhabdomyolysis in CD-1 mice | In the cortex, including in proximal tubules Correlated with the severity of azotemia Inversely correlated with plasma triglyceride levels | [80] |
| | Cisplatin injection in Sv129 mice | Primarily in proximal tubules Prevented by pretreatment with a PPAR α agonist | [81] |
| | Ischemia–reperfusion in uninephrectomized CD-1 mice | In the cortex, including in proximal tubules In mice subjected to 15 min ischemia followed by 18 h of reperfusion, but not in mice subjected to uninephrectomy alone | [80] |
| Normal animals | Aging in C57BL/6J mice | Age-related, in glomeruli and proximal tubule cells Correlated with age-related increase in renal expression of SREBPs Mitigated in part by caloric restriction | [82,83] |
| | Fasting in C57BL/6 mice | Likely due to mobilization of extrarenal lipid stores Exacerbated by in-vivo antisense LNA-mediated knockdown of ApoB | [40*] |

ACE, angiotensin-converting enzyme; ApoB, apolipoprotein B; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; HFD, high-fat diet; LOX-1, oxidized low-density lipoprotein receptor 1; LPS, *Escherichia coli* lipopolysaccharide; PEPCK, phosphoenolpyruvate carboxylkinase; PPAR, peroxisome proliferator-activated receptor; SD, Sprague–Dawley; SREBP(s), sterol regulatory element-binding protein(s).

^a Most articles cited in this table used quantitative biochemical methods to measure tissue triglyceride content and/or staining of kidney sections with Oil Red O or other Sudan dyes. These dyes stain neutral lipids, primarily triglycerides, but also some lipoproteins.