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Contents

Monthly Volume 12 Number 5 May 15, 2021

OPINION REVIEW

REVIEW

MINIREVIEWS

World Journal of Diabetes

Monthly Volume 12 Number 5 May 15, 2021

Contents

World Journal of Diabetes

Monthly Volume 12 Number 5 May 15, 2021

Contents

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REVIEW

New insights into renal lipid dysmetabolism in diabetic kidney disease

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Abstract

Lipid dysmetabolism is one of the main features of diabetes mellitus and manifests by dyslipidemia as well as the ectopic accumulation of lipids in various tissues and organs, including the kidney. Research suggests that impaired cholesterol metabolism, increased lipid uptake or synthesis, increased fatty acid oxidation, lipid droplet accumulation and an imbalance in biologically active sphingolipids (such as ceramide, ceramide-1-phosphate and sphingosine-1-phosphate) contribute to the development of diabetic kidney disease (DKD). Currently, the literature suggests that both quality and quantity of lipids are associated with DKD and contribute to increased reactive oxygen species production, oxidative stress, inflammation, or cell death. Therefore, control of renal lipid dysmetabolism is a very important therapeutic goal, which needs to be archived. This article will review some of the recent advances leading to a better understanding of the mechanisms of dyslipidemia and the role of particular lipids and sphingolipids in DKD.

Key Words: Diabetes; Lipids; Free fatty acids; ATP-binding cassette transporters sub-class A; Sterol-O-acyltransferase 1; CD36; Sphingolipids; Sphingomyelin phosphodiesterase acid-like 3b; Diabetic kidney disease

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Core Tip: The present review summarizes the recent knowledge about the role of lipids and sphingolipids in the development and progression of diabetic kidney disease (DKD). The main focus is given to the cholesterol and triglyceride metabolism abnormalities, lipid droplet accumulation and role of sphingolipids in DKD.

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INTRODUCTION

Lipids are essential components of a cell plasma membrane with multiple cellular functions, highlighting their importance in cell homeostasis and survival. Diabetic kidney disease (DKD) is often considered to be a consequence of hyperglycemia in a setting of diabetes mellitus. However, lipid accumulation in podocytes, which are specialized epithelial cells lining the urinary surface of the glomerular capillary tuft, has been recently reported to drive the development of DKD[1]. Lipids are also key modulators of insulin signaling in several cell types including the podocyte[2,3].

The toxicity of lipid accumulation (lipotoxicity) in the kidney was first proposed by Moorhead *et al*[4] in 1982 and later updated by Ruan *et al*[5] in 2009, suggesting that lipid dysmetabolism promotes the progression of kidney diseases, including DKD. However, the specific contribution of podocyte lipid dysmetabolism to the pathogenesis and progression of DKD has been largely unexplored. Growing evidence suggests that lipotoxicity-associated renal damage depends not only on the quantity of lipids that accumulate in the kidney but also on the lipid species[6]. In recent years, a clear role of sphingolipids and glycolipids in the pathogenesis of DKD has been also established[7-11]. Given the fact that podocytes, the terminally differentiated epithelial cells in the glomerulus, are main contributors to the proper filtration function in the kidney, changes in their number[12] and function lead to the development and progression of glomerular disease, including DKD. However, what is the cause of podocyte detachment and death in DKD remains largely unknown. We have previously published several reviews related to the role of lipids and sphingolipids in glomerular diseases with focus on insulin signaling[2], inflammation[13], and mitochondria dysfunction[14]. This review is an update on the latest knowledge with regard to the mechanisms contributing to renal lipid dysmetabolism focusing on cholesterol metabolism, fatty acid oxidation, lipid droplet accumulation and sphingolipids and how they contribute to the development and progression of DKD.

CHOLESTEROL METABOLISM ABNORMALITIES IN DKD

In any cell, lipid metabolism encompasses the synthesis and degradation of lipids to meet the body's energy needs. Some lipids are being constantly oxidized, while others are being synthesized and stored. Thus, triacylglycerols are broken into free fatty acids (FFA), which undergo β-oxidation in mitochondria to produce acetyl coenzyme A (CoA), utilized in the tricarboxylic acid cycle or ketogenesis to generate energy. FFA are also involved into other biosynthetic pathways to produce membrane lipids (such as phospholipids, glycolipids, sphingolipids, or cholesterol) or signaling molecules (such as prostaglandins, leukotrienes, and thromboxanes). These metabolic pathways are tightly regulated by enzyme-catalyzed reactions and defects in any of these enzymes is associated with a wide range of health problems.

Podocytes are visceral epithelial cells of the glomerulus, which are involved in filtration and formation of primary urine. Foot processes are the most recognizable characteristic structures of podocytes and the formation of specialized junctions between foot process of neighboring podocytes, known as the slit diaphragm, and of foot processes and the glomerular basement membrane, known as the adhesion

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complex, are important for maintaining glomerular function[15]. The podocyte slit diaphragm is assembled in lipid rafts, which are small specialized plasma membrane domains enriched with cholesterol, sphingolipids and protein complexes with important functions in cellular signaling transduction. Cholesterol of the lipid rafts plays an important role in regulating the organization, localization and function of proteins within the slit diaphragm. Excess of cholesterol negatively affects the binding of slit diaphragm proteins to each other[16], or interferes with the ability of podocyte slit-diaphragm proteins to bind caveolin-1, an important transductor of the insulin receptor signaling in podocytes[17].

Cholesterol is synthesized starting from acetyl CoA in the *de novo* pathway and/or it can be imported from circulating lipoproteins by receptor-mediated endocytosis (influx). Excess cholesterol is released through several distinct pathways (efflux). Tight regulation of these three mechanisms is very important to maintain proper cholesterol metabolism within the cell, as unesterified (free) cholesterol is toxic to cells.

Cholesterol synthesis

Intracellular cholesterol sensing is mainly regulated *via* sterol regulatory element-binding protein (SREBP, and its known isoforms SREBP-1a, SREBP-1c, SREBP-2), an endoplasmic reticulum resident. Increased expression of SREBP1 and SREBP2 has also been reported in glomeruli of DKD patients based on microarray data available from the Nephroseq database[18,19]. Increased expression of SREBP has been described to contribute to kidney damage in obesity-related diabetes and in mice fed on a high fat diet[20-24]. Additional studies demonstrated a role of SREBP1 in the accumulation of lipid droplet in murine models of type 1 diabetes[25]. In support, the inhibition of SREBP isoforms was found to attenuate the renal phenotype such as albuminuria or mesangial expansion in age-related renal disease and in DKD[16-20]. In contrast, a recent study reports that fatostatin treatment of 12-wk-old male mice with streptozotocin-induced diabetes, an inhibitor of SREBP-1 and SREBP-2, prevents glomerular basement membrane thickening, but does not improve albuminuria or hyperfiltration[26]. Thus, further studies are needed to determine if SREBP inhibition may be more beneficial in combination with other therapies to prevent DKD progression.

Cholesterol influx

Cholesterol is transported in the circulation by two major lipoproteins, low-density lipoprotein (LDL) and high-density lipoprotein (HDL). The influx of cholesterol is primarily mediated *via* LDL receptors (LDLR), followed by endocytosis and the formation of LDL-containing vesicles connected to lysosomes. Free cholesterol is then transported to the endoplasmic reticulum (ER) or plasma membrane *via* Niemann Pick C1 or C2 transporters. In the ER, increased free cholesterol levels activate sterol-O-acyltransferase 1 (SOAT1; or acyl-CoA:cholesterol acyltransferase (ACAT1)) to form cholesterol esters for storage in lipid droplet. We recently demonstrated that genetic loss of SOAT1 in diabetic *db/db* mice ameliorates kidney injury by reducing cholesterol esters and lipid droplet accumulation[27]. More recently, proprotein convertase subtilisin/Kexin Type 9 (PCSK9) inhibitors, which have been developed to controlled hyperlipidemia by affecting LDL uptake and clearance in hepatocytes, have been shown to control the hyperlipidemia associated with nephrotic syndrome[28]. As PCSK9 is also expressed in the kidney[29], the contribution of PCSK9 to renal lipotoxicity remains to be explored.

Cholesterol efflux

Excessive cholesterol accumulation in podocytes is also associated with suppressed efflux in both experimental[22,30] and human DKD[6]. Cholesterol efflux from cells, including podocytes, occurs primarily *via* ATP-binding cassette transporters sub-class A (ABCA1), G (ABCG1) and scavenger receptor class B type I (SR-BI). We previously reported that normal human podocytes exposed to serum from patients with type 1 and type 2 diabetes and early stage of DKD are characterized by increased lipid droplet accumulation and reduced expression of ABCA1[3,31,32]. We also found that the expression of ABCA1 correlates with markers of DKD progression clinically and in experimental mouse models (diabetic BTBR *ob/ob* and *db/db* mice)[32]. Studies in diabetic NOD mice also demonstrated significant reduction (48%) of ABCA1 expression in kidneys[30]. While deficiency of ABCA1 is a susceptibility factor in DKD and contributes to the accumulation of lipid droplet in podocytes, it is not sufficient to cause glomerular injury itself[31,32]. Further studies demonstrated that ABCA1 overexpression reduces albuminuria in mice with podocyte-specific activation of

nuclear factor of activated T cells (NFAT)[31], another susceptibility factor for cholesterol-dependent podocyte injury. Interestingly, in human glomerular cells, interleukin 1β has also been shown to inhibit cholesterol efflux possibly *via* suppression of ABCA1 expression[33]. By contrast, pharmacological induction of cholesterol efflux using cyclodextrin or ezetimibe, a small molecule ABCA1 inducer, resulted in amelioration of DKD progression and DKD-like glomerulosclerosis[3,32]. Exendin-4, an agonist of glucagon-like peptide 1, has also been shown to upregulate ABCA1 in glomerular endothelial cells and improve glomerular hypertrophy, basement membrane thickening and mesangial expansion[34]. Interestingly, in diabetic patients (n = 1746, all Caucasians), the ABCA1 rs9282541 (R230) polymorphism has been shown to be associated with increased risk of diabetes, while the ABCA1 rs1800977 (C69T) polymorphism was found to be associated with a significantly reduced risk of hypertriglyceridemia[35]. The rs9282541 polymorphism has also been reported to be associated with susceptibility to type 2 diabetes in patients from Mexico[36]. In contrast, studies in patients with type 2 diabetes (n = 107) from Turkey[37] and in Chinese Han population (n = 508)[38] failed to link ABCA1 rs1800977 polymorphism to lipid dysmetabolism. More recently, an association between LXR-alpha and ABCA1 gene polymorphisms was found to be associated with the risk for DKD in a Chinese population[39]. While ABCA1 mediates cholesterol transport to apolipoprotein A-I (Apo A-I) and pre-β HDL, two other transporters, ABCG1 and SR-BI, mediate cholesterol transport to mature HDL. In mouse models of DKD, significant suppression of ABCG1 and SR-BI was found in mesangial and tubular cells[40].

Taken together, these studies demonstrate that cholesterol accumulation and lipid droplet accumulation may represent a hallmark of DKD[41-43]. Based on our own studies and reports from others, we conclude that cholesterol accumulation in glomerular cells occurs independent of systemic cholesterol levels and that local lipid dysmetabolism contributes to DKD progression in patients with diabetes (Figure 1).

TRIGLYCERIDE METABOLISM ABNORMALITIES IN DKD

Fatty acid uptake

In the blood most of the circulating lipids are present as triglycerides within very low-density lipoprotein (VLDL). Triglycerides are composed of free fatty acid (FFA) and glycerol. Several fatty acid transport proteins (FATPs) control uptake of FFA into a cell. In the kidney, FATP1, FATP2, and FATP4 were shown to be mostly responsible for lipid uptake abnormalities in patients with DKD. Thus, a recent study on a population of type 2 diabetic patients (n = 268) demonstrated that expression levels of FATP1 and FATP2 in plasma are associated with progression of DKD[44]. In support, deletion of FATP2 in different mouse models of DKD (*db/db* and *eNOS-/-* diabetic mice and low dose streptozotocin-induced diabetic mice on a high fat diet) was sufficient to improve the renal outcome[45]. It has been also demonstrated that expression of FATP4 is higher in tubules of mice on a high fat diet[46], suggesting a role of FATP4 in insulin resistance and obesity. Interestingly, levels of FATP4 in *db/db* mice were shown to be elevated in parallel with increased renal lipid accumulation and progression of DKD, which is also associated with vascular endothelial growth factor B (VEGF-B) signaling[1]. In obese Wistar rats on high fat diet increased levels of FFA in glomerular endothelial cells were shown to be associated with microalbuminuria *via* VEGF-NO axis[47]. In patients with type 2 diabetes FATP4 is associated with glomerular filtration rate[48].

Other contributors to the lipid uptake abnormalities in DKD are the fatty-acid binding proteins (FABPs), which belong to a super-family of lipid-binding proteins and recognize long-chain fatty acids as substrates. Thus, urinary liver-type FABP (L-FABP) was shown to be a reliable marker of DKD development and progression in patients with diabetes[49-52]. Interestingly, in spontaneously diabetic Torii fatty rats higher levels of urinary L-FABP were shown, which was ameliorated with Liraglutide treatment[53].

Fatty acid uptake: role of CD36

Cluster of differentiation 36 (CD36), a class B scavenger receptor, is the most important transmembrane glycoprotein that mediates uptake of oxidized LDLs. CD36 is also the main uptake system of FFA in the kidney, where it is highly expressed in proximal and distal epithelial cells, podocytes and mesangial cells. Increased expression of CD36 seems to be associated with kidney damage in DKD. Earlier studies demonstrated that

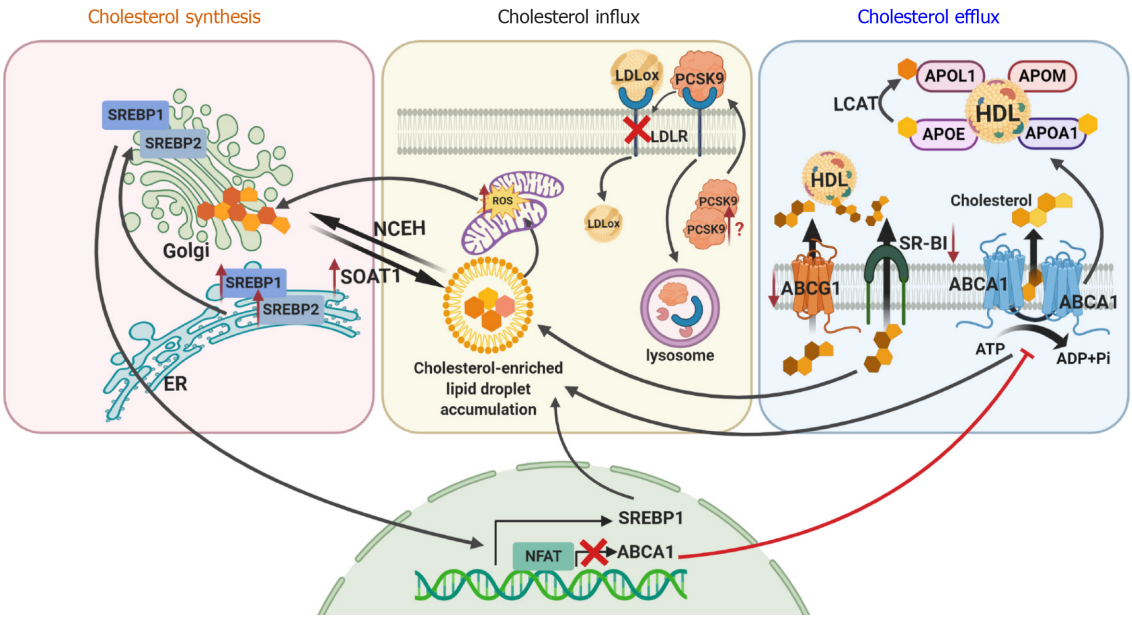

Figure 1 Cellular dyslipidemia in diabetic kidney disease affects cholesterol synthesis, influx and efflux. Sterol regulatory element-binding protein 1 or 2 (SREBP1 and SREBP2) is transported from the endoplasmic reticulum to the Golgi apparatus, where it is cleaved followed by translocation to the nucleus to initiate cholesterol synthesis. Newly synthesized free cholesterol is then converted into esterified cholesterol by sterol O-acyltransferase 1 (SOAT1) or is transported to the plasma membrane for efflux by ATP-binding cassette subfamily A member 1 (ABCA1), subfamily G member 1 (ABCG1) or scavenger receptor class B type I (SR-BI). Cholesterol uptake from circulating low density lipoproteins (LDLs) is mediated by LDL receptor (LDLR). In diabetic kidney disease (DKD), overexpression of SREBP1 and SREBP2 and decreased expression of ABCA1, ABCG1 and SR-BI results in accumulation of cholesterol inside a cell and increased reactive oxygen species production. Accumulation of free cholesterol activates SOAT1, leading to over-production of esterified cholesterol, which is toxic to cells. Overexpression of proprotein convertase subtilisin kexin 9 may also contribute to DKD *via* enhanced degradation of the LDLR, resulting in increased levels of circulating LDL cholesterol. This image was created using BioRender software (www.BioRender.com). SREBP1: Sterol regulatory element-binding protein 1; SREBP2: Sterol regulatory element-binding protein 2; ER: Endoplasmic reticulum; SOAT1: Sterol O-acyltransferase 1; NCEH: Neutral cholesterol ester hydrolase; LDLox: Oxidized low density lipoprotein; PCSK9: Proprotein convertase subtilisin kexin 9; LDLR: Low density lipoprotein receptor; ROS: Reactive oxygen species; LCAT: Lecithin:cholesterol acyltransferase; APOL1: Apolipoprotein L1; APOE: Apolipoprotein E; APOM: Apolipoprotein M; APOA1: Apolipoprotein A1; HDL: High density lipoprotein; ABCA1: ATP-binding cassette subfamily A member 1; ABCG1: Subfamily G member 1; SR-BI: Scavenger receptor class B type I; ATP: Adenosine triphosphate; ADP: Adenosine diphosphate; Pi: Inorganic phosphorus.

high glucose-mediated overexpression of CD36 induces apoptosis in renal tubular epithelial cells[54,55] and podocytes[56]. Interestingly, CD36 has also been shown to facilitate chronic inflammation, oxidation stress and fibrosis in proximal tubular cells under hyperglycemic conditions[57]. Using human podocytes, our studies suggest a novel mechanism where discoidin domain receptor 1 (DDR1), a tyrosine kinase activated by collagen I, interacts with CD36 and leads to increased CD36-dependent FFA uptake[58]. Another study demonstrated that astragaloside IV inhibits overexpression of CD36 in human glomerular mesangial cells and diabetic rats (Sprague Dawley) in response to palmitate-induced FFA accumulation and attenuates FFA uptake, oxidative stress and fibrosis[59].

In mouse podocytes treated with palmitic acid increased expression of CD36 has been shown in association with increased reactive oxygen species (ROS) production and apoptosis[60]. In mice with transgenic overexpression of CD36 in the kidney, accumulation of lipids and triglycerides in kidneys was demonstrated[61]. Additionally, CD36 is involved in the generation of other cell-specific responses *via* toll-like receptors (TLRs) 2, 4 and 6[62-64], CD9[65], or integrin[66] leading to the activation of pyrin domain-containing 3 (NLRP3) and nuclear factor kappa B (NF-kB) signaling pathways[67,68]. Indeed, CD36 can also recognize advanced oxidation protein products and advanced glycation end products, which are also involved in inflammatory pathway activation[69], including the kidney[57].

In patients with DKD increased expression of CD36 was reported[55,60]. Interestingly, a circulating soluble form of CD36 (sCD36), whose derivation is not entirely clear, may play a role as a cellular source of CD36 in diabetic patients and correlates with insulin resistance[70,71]. A recent study demonstrated elevated levels of sCD36 in both plasma and urine of patients with DKD[72]. However, while one study suggests that sCD36 Levels are elevated in patients with type 2 diabetes and proposes to use it as a biomarker[73], another study reports no differences in the sCD36 Levels between patients with type 1 and type 2 diabetes[74].

Thus, CD36 has an important role in the lipid homeostasis in the kidney with an important role in the crosstalk between CD36 Ligands and inflammation or apoptosis signaling pathways. Therefore, CD36 may represent a promising target for therapeutic intervention. However, further studies of the role of CD36 in DKD progression are needed to answer the questions: (1) How is sCD36 formed in patients with diabetes and what is the tissue-specific role of sCD36? (2) What are the particular mechanisms of increased FFA uptake in tubular cells *vs* podocytes? And (3) What are the mechanisms involved in the kidney cell-specific regulation of CD36 levels or function (tubular cells *vs* podocytes)? A better understanding of the mechanisms regulating the FFA uptake in rodents and its translation to humans will be a determinative factor in the development of novel peptides aimed at regulating CD36 Levels with minimum off-target effects.

Fatty acid oxidation

Fatty acid oxidation (FAO), also called beta oxidation, is the aerobic process of fatty acid (short-, medium- or long-chain saturated fatty acyl coenzyme A, acyl-CoA) breakdown that occurs in mitochondria to provide energy from fats. During FAO, acetyl coenzyme A (acetyl-CoA), five molecules of ATP, and water are generated. Interestingly, FAO covers more than half of renal oxygen consumption. In the setting of kidney disease, genes that are associated with FAO are significantly downregulated in kidneys of mice and humans[61], which is also associated with increased fatty acid synthesis and higher intracellular lipid deposition. We have recently reported that human podocytes cultured in the presence of serum from DKD patients have significantly decreased expression of FAO genes (PPARα, ACADM, ACOX1/2), which was also observed in mouse models of DKD and in our mouse model of ABCA1 deficiency[32]. In a longitudinal study on American Indians with type 2 diabetes (n = 92), a significant reduction of FAO has been shown, which was also associated with lower abundance of C16-C20 acylcarnitines[75]. Pharmacological or genetic increase in FAO has been shown to be beneficial to improve kidney disease progression[61].

Peroxisome proliferator-activated receptors (PPARs) play a key role in the regulation of FAO in the kidney. PPARg, one of the PPARs isoforms, is highly expressed in different compartments of a nephron while decreased expression contributes to diabetes-associated kidney damage. Activation of PPARg (using thiazolidinediones) is associated with attenuation of kidney function in diabetic patients and mouse models of DKD[76-78]. Recently, a role of micro-RNA-27a (miR-27a) in the regulation of PPARg activity was demonstrated[79], suggesting miR-27a as a potential therapeutic target in DKD. In a streptozotocin-induced diabetic mouse model of DKD, activation of PPARδ ameliorates diabetes-associated renal damage [80]. Lack of PPARα, another PPAR isoform, has also been shown to accelerate DKD in a streptozotocin-induced diabetic mouse model[81]. Tesaglitazar, the PPARα/g dual agonist, markedly attenuated albuminuria and lowered collagen deposition in kidneys of db/db mice[82]. In contrast, use of a PPARα agonist, CP-900691, showed no effect on albuminuria and amelioration of DKD in the *BTBR ob/ob* diabetic mouse model[83]. Therefore, while activation of PPARg seems to have constitutive renoprotective effects in DKD, the role of PPARα activation in improving renal function remains questionable. A summary of the suggested mechanism of triglyceride abnormalities in DKD is shown in Figure 2.

SPHINGOLIPIDS IN DKD

Sphingolipids are important components of cell homeostasis. Sphingolipids are a class of lipids composed of hydrophobic and hydrophilic regions with variable fatty acid composition. In recent years, sphingolipids and sphingolipid metabolites have been recognized as important regulators of cell signaling contributing to the development and progression of numerous diseases. The most studied sphingolipid metabolites are ceramide, sphingosine-1-phosphate (S1P) and ceramide-1-phosphate (C1P), which have been shown to regulate cell differentiation, membrane fluidity, protein anchoring, immune activation, insulin sensitivity, autophagy, and cell death. The role of S1P signaling in renal cells and in kidney diseases has been extensively reviewed[84].

Ceramide

In kidney cortices of diabetic *db/db* mice, elevated levels of long-chain ceramides (C14:0, C16:0, C18:0, C20:0) and decreased levels of very-long-chain ceramides (C24:0,

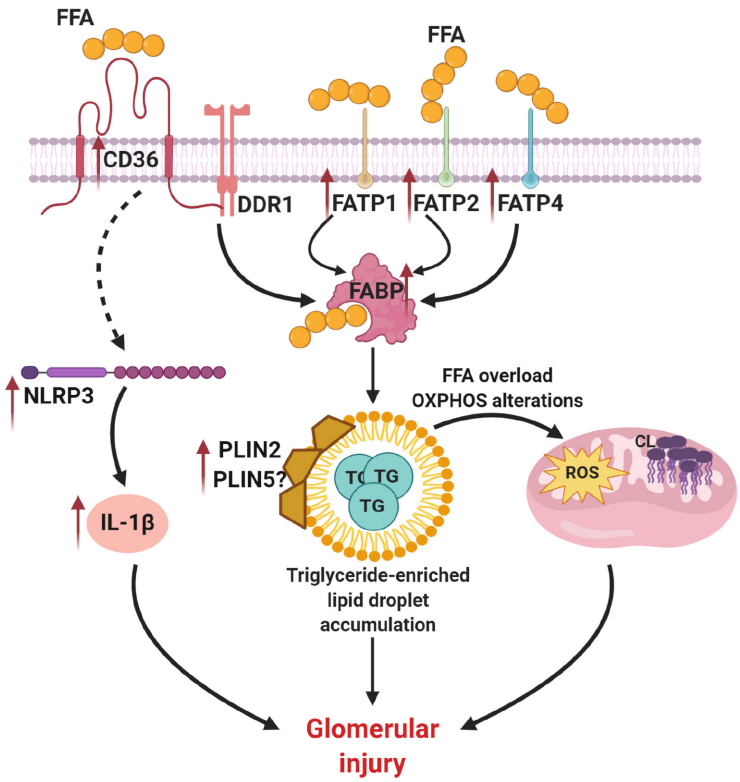

Figure 2 Abnormalities in triglyceride homeostasis contribute to lipid droplet accumulation in diabetic kidney disease. Increased expression of scavenger receptor class B (CD36), fatty acid transporter protein 1 (FATP1), FATP2, FATP4 and fatty acid-binding protein leads to accumulation of fatty acids inside a cell, abnormalities in triglyceride (TG) metabolism and formation of TG-enriched lipid droplets. Altered activity of perilipin protein family members (PLIN2 and possibly PLIN5) also contributes to lipid droplet formation. In turn, accumulation of TG-enriched lipid droplet causes alteration in oxidative phosphorylation, cardiolipin accumulation and reactive oxygen species overproduction. Together with increased expression of NLR family pyrin domain containing 3 and interleukin 1β CD36 overexpression causes podocyte injury in diabetic kidney disease. This image was created using BioRender software (www.BioRender.com). FFA: Free fatty acid; DDR1: Discoidin domain receptor 1; FATP1: Fatty acid transporter protein 1; FATP2: Fatty acid transporter protein 2; FATP4: Fatty acid transporter protein 4; FABP: Fatty acid transporter protein; NLRP3: NLR family pyrin domain containing 3; PLIN2: Perilipin protein family member 2; PLIN5: Perilipin protein family member 5; TG: Triglyceride; OXPHOS: Oxidative phosphorylation; ROS: Reactive oxygen species; IL-1β: Interleukin 1 beta.

C24:1) have been described[85], which is in accordance with our own studies[7]. In support of previous studies, ceramide accumulation was associated with increased reactive oxygen species production in OLEFT rats and in mice fed on a high-fat diet with DKD[86]. Elevated levels of long-chain ceramides (C16:0, C18:0 and C20:0)[87,88] and very-long-chain ceramides (C22:0, C24:0)[88] were also found in patients with early or overt DKD. Podocyte-specific deletion of the acid ceramidase main catalytic subunit (*Asah1* gene) results in elevated ceramide levels in glomeruli and development of nephrotic syndrome in mice[89]. In patients with DKD enrolled into ONTARGET and TRANSCEND-randomized controlled trials rs267734 gene variant of ceramide synthase 2 (CerS2), a CerS2 isoform with high expression in the kidney, has been shown to be associated with increased albuminuria[90].

Sphingosine-1-phosphate

In the setting of diabetes, increased levels of S1P in plasma of rodents with type 1[91] or type 2 diabetes[92] have been reported. In mice with streptozotocin-induced diabetes increased renal levels of S1P were also reported[93,94]. Recent studies in mice and humans demonstrated that mutations in *SGPL1* gene, which encodes S1P lyase 1, are associated with the development of nephrotic syndrome[9,10,95]. In rats with streptozotocin-induced DKD the use of an unselective S1P receptor agonist (FTY720) was found to have a renoprotective effect[96]. Interestingly, plasma levels of S1P in patients with type 2 diabetes negatively correlate with levels of albuminuria, while less S1P is observed in patients with macroalbuminuria[97]. A role of S1P lyase activity reduction has been demonstrated to contribute to the development of podocyte-based kidney toxicity in wildtype rodents[11]. Furthermore, S1P receptor signaling plays a significant role in glomerular injury. Five S1P receptors (S1PR1-S1PR5) exist, of which S1PR1 to S1PR4, but not S1PR5, are expressed in the kidney[98]. In mouse models of DKD, activation of S1PR1 or inhibition of S1PR2 prevented the renal injury

phenotype[96]. Using a single cell RNA sequencing approach to profile glomerular cells in mouse models of DKD (streptozotocin-induced diabetic endothelial nitric oxide synthase-deficient mice), significantly lowered expression of S1P receptor 3 (S1PR3) in mesangial cells was demonstrated[99]. Previous studies also revealed a significant role of sphingosine kinase (SPHK), an enzyme that generates S1P from sphingosine, in the kidney fibrosis in STZ-induced diabetic mice and in humans with DKD[100]. In a mouse model of alloxan-induced diabetes, increased glomerular SPHK1 expression and activity were demonstrated leading to S1P accumulation[101]. In addition, SPHK1 upregulation was demonstrated in STZ-induced mouse model of DKD, where it protects from the fibrotic process[100]. A more detailed review on the role of S1P signaling in the kidney was previously published by us[84].

Ceramide-1-phosphate

Even less is known about the role of C1P in the kidney. In contrast to S1P, C1P is most likely released from damaged cells[102]. Our studies demonstrated that increased sphingomyelin phosphodiesterase acid-like 3b (SMPDL3b) in the *db/db* mouse model of DKD is associated with a state of C1P deficiency in podocytes[7]. SMPDL3b is a lipid-raft associated protein[103] that regulates plasma membrane fluidity[104] by blocking access of ceramide kinase, an enzyme that generates C1P from ceramide, to ceramide[8]. We also reported that elevated expression of SMPDL3b occurs in glomeruli of patients with DKD[105] and that SMPDL3b overexpression in podocytes results in the accumulation of S1P[106]. In support, podocyte-specific deficiency of *Smpdl3b* resulted in restoration of the renal C1P content in association with delayed DKD progression in diabetic mice[7]. To the contrary, others demonstrated that the knockout of ceramide kinase in mice is sufficient to prevent glomerular disease[107]. However, it remains to be established how bioactive sphingolipids contribute to the development of DKD and what are the best options for their use as possible biomarkers or therapeutic targets.

Glycosphingolipids

Dysmetabolism of other sphingolipids, such as gangliosides (mainly GM3, which is the most abundant ganglioside in the kidney), has also been reported to contribute to development of DKD[108]. Increased levels of sialic acid, a component of gangliosides, were found in patients with DKD and positively correlated with blood glucose, HbA1c, creatinine and microalbuminuria[109]. Increased GM3 species (C16:0, C18:0, C20:0, C22:0, C24:0) in kidney cortex from diabetic rats at an early stage of DKD have also been described[110]. Interestingly, GM3 was found to contribute to diabetic nephropathy *via* the alteration of pro-survival receptor-associated Akt signaling[111]. Another study reported that levels of glycosylated sphingolipids, such as lactosyl-ceramide, are associated with microalbuminuria in patients with type 1 diabetes[112]. A proposed mechanism indicating how dysregulation of sphingolipid metabolism contributes to DKD is shown in Figure 3.

LIPID DROPLET ACCUMULATION IN DKD

Lipid droplet (or lipid bodies) are lipid-rich cellular organelles that regulate storage and hydrolysis of lipids or serve as a reservoir for cholesterol and acyl-glycerol in different eukaryotic cells. Structurally, lipid droplets are composed of a neutral lipid core (triacylglycerol and cholesteryl esters) and a phospholipid monolayer. In an eukaryotic cell, lipid droplet formation may be induced by different stimuli, such as growth factors, long-chain unsaturated fatty acids, oxidative stress and inflammatory stimuli (reviewed in Ref.[113]). Once intracellular, the fatty acids can form part of the triglyceride and phospholipid components of the lipid droplet[114,115]. Increased lipid droplet accumulation is observed in patients with DKD[6] and mouse models of DKD[116,117]. We previously showed that treatment of human podocytes with serum from patients with DKD results in lipid droplet accumulation[3]. Kidneys of hyperglycemic mice (STZ-induced diabetes) are characterized by the concomitant presence of oxidative stress markers-positive (xanthine oxidoreductase and nitrotyrosine with tail-interacting protein of 47 kDa) lipid droplets in glomerular and/or tubular cells[117]. In Sprague-Dawley rats with STZ-induced diabetes, increased advanced glycation end products have been shown to cause lipid droplet accumulation[118].

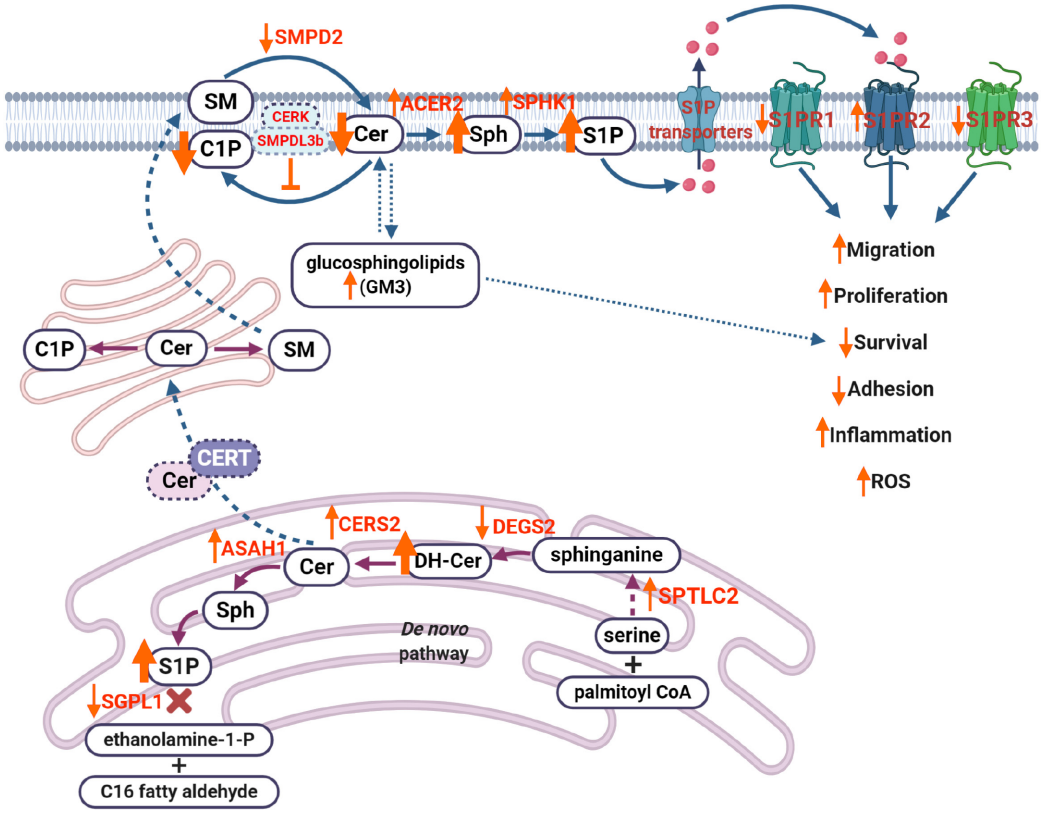

Figure 3 Dysregulation of sphingolipid metabolism contributes to the progression of diabetic kidney disease. Decreased activity of desaturase (DEGS2) results in the accumulation of dihydroceramides. Increased activity of ceramide synthase 2 (CERS2) leads to increased production of ceramide (Cer), which leads to increased production of sphingosine (Sph) and sphingosine-1-phosphate (S1P) *via* decreased activity of sphingosine-1-phosphate lyase 1. Cer can also be translocated to the Golgi apparatus *via* ceramide transport protein, where it results in production of sphingomyelin. At the plasma membrane, decreased activity of sphingomyelin phosphodiesterase 2 affects Cer production, while elevated activity of alkaline ceramidase 2 increases levels of Sph, which, in turn, leads to accumulation of S1P *via* increased activity of sphingosine kinase 1. Overproduction of S1P results in increased S1P efflux *via* S1P transporters (such as ATP-binding cassette transporters ABCA1, ABCG1, ABCC1 and S1P transporter SPNS2), where S1P can act as a paracrine factor to activate S1P receptor signaling (primarily, S1P receptors 1-3, S1PR1, S1PR2, S1PR3), leading to dysregulation of many cellular processes, including migration, proliferation, survival or inflammation. Accumulation of gangliosides (GM3) can also affect cell survival in diabetic kidney disease. This image was created using BioRender software (www.BioRender.com). SMPD2: Sphingomyelin phosphodiesterase 2; SM: Sphingomyelin; C1P: Ceramide-1-phosphate; CERK: Ceramide kinase; SMPDL3b: Sphingomyelin phosphodiesterase acid-like 3b; Cer: Ceramide; Sph: Sphingosine; S1P: Sphingosine-1-phosphate; S1PR1: Sphingosine-1-phosphate receptor 1; S1PR2: Sphingosine-1-phosphate receptor 2; S1PR3: Sphingosine-1-phosphate receptor 3; GM3: Ganglioside M3; CERT: Ceramide transport protein; SGPL1: Sphingosine-1-phosphate lyase 1; DH-Cer: Dihydroceramide; ASAH1: N-acylsphingosine amidohydrolase 1; CERS2: Ceramide synthase 2; DEGS2: Delta(4)-desaturase, sphingolipid 2; SPTLC2: Serine palmitoyltransferase 2; CoA: Acyl-coenzyme A; ROS: Reactive oxygen species.

While the composition of lipid droplets is not very well investigated, perilipins are the best characterized proteins of the lipid droplet coat. This family of perilipin proteins includes perilipin 1 (PLIN1), perilipin 2 (PLIN 2), perilipin 3 (PLIN 3), perilipin 4 (PLIN 4) perilipin 5 (PLIN 5). Not much data about the role of these proteins in DKD development and progression, and a recent case report suggests that mutation in *PLIN1* may be associated with DKD-like kidney damage in a patient with type 4 familial partial lipodystrophy[119]. Another randomized case-control study of an Iranian population (n = 200) showed an association of the polymorphism rs4578621 in the *PLIN* gene with type 2 diabetes[120]. Interestingly, decreased *Plin1* expression was reported in adipocytes of *db/db* mice, while deficiency of *Plin1* in adipose tissue in wildtype mice resulted in insulin resistance and secretion of pro-inflammatory lipid metabolites, such as prostaglandins[121]. Expression of *PLIN2* is significantly upregulated in kidneys from diabetic *db/db* mice[122] and in podocytes of patients with DKD[1], which may indicate that increased PLIN2 expression may contribute to increased lipid droplet accumulation in the diabetic kidney. Similarly, increased levels of urinary *PLIN2* were reported in patients with DKD[123]. To date, no studies examining the role of other perilipin proteins in DKD have been performed. A role for *PLIN5* in diabetes has recently been suggested as upregulation of *PLIN5* in β-cells was shown to improve glucose tolerance in isolated islets from mice or human[124]. Because *PLIN5* is also expressed in kidneys[125] under PPAR control, it would be important to investigate its role in lipid-associated kidney diseases in future investigations.

Among other factors contributing to lipid droplet accumulation in the kidney, autophagy has been shown to regulate lipid metabolism and lipid droplet formation[126-128] and to significantly contribute to renal fibrosis progression in kidney diseases. Serine/threonine protein kinase 25 (STK25), which plays an important role in skeletal muscle metabolism, is also highly expressed in human and rodent kidney[129] and was shown to aggravate renal lipid accumulation and exacerbate kidney injury in a high-fat diet mouse model of DKD[130].

CONCLUSION

The kidney is a target organ of the harmful effects of lipotoxicity in diabetes, suggesting that, similar to the liver, chronic kidney disease is a form of fatty kidney disease. In this review, we summarize new research trends and new scientific knowledge acquired within the past few years that have shed light on the role of particular lipids in diabetes-associated kidney injury. However, our knowledge with regard to the cross-talk between glucose homeostasis and lipid metabolism in health and disease remains incompletely understood and further research is needed. Similarly, more insight into the role of specific lipids in podocyte physiology is required to answer remaining questions. Which lipids are toxic to the podocytes? What factors are driving the pathophysiology of lipid accumulation in podocytes? Which lipids might be the best targets for possible therapeutic intervention in DKD? Answering these questions will help to pave the way to new diagnostic and therapeutic approaches in DKD.

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