Medicine Insights

*Review*

# Mechanisms of Diabetic Kidney Disease from the Perspective of Sphingolipid Metabolism

**Xiaohong Li[1], Lengtan Zhao[1] and Puyuan Hu[2,*]**

[1] College of Integrated Chinese and Western Medicine, Shaanxi University of Chinese Medicine, Xianyang, China
[2] School of Basic Medical Sciences, Shaanxi University of Chinese Medicine, Xianyang, China
* Correspondence: Puyuan Hu, School of Basic Medical Sciences, Shaanxi University of Chinese Medicine, Xianyang, China

**Abstract:** Diabetic kidney disease (DKD) is a chronic complication driven by disorders of glucose metabolism, with a protracted course that current treatments can hardly reverse. Related mechanisms, including glucolipotoxicity, insulin resistance, neuroinflammation, and renal fibrosis, jointly participate in the pathological process. Sphingolipid metabolism can maintain the balance of cell membrane structure and signal transduction and participates in cell proliferation, differentiation, apoptosis, immune inflammation, and myelin sheath formation. This review systematically compiles the pathological changes of sphingolipid metabolism in DKD, with emphasis on analyzing the roles of ceramide (Cer) and sphingosine-1-phosphate (S1P) in the injury of podocytes, mesangial cells, and the tubulointerstitium, and discusses potential therapeutic strategies targeting sphingolipid metabolism in light of the latest research advances, aiming to provide a new theoretical basis for the mechanistic study and clinical intervention of DKD.

**Keywords:** sphingolipid metabolism; diabetic kidney disease; ceramide; sphingosine-1-phosphate

## 1. Introduction

The pathogenesis of diabetic kidney disease (DKD) is complex, covering multiple pathological links such as metabolic disorders and inflammatory responses, and it has now become the leading cause of end-stage renal disease [1]. According to statistics, approximately 40% of patients with diabetes will develop DKD, and its pathological features include glomerular mesangial matrix expansion, podocyte injury, and tubulointerstitial inflammation and fibrosis [2]. Previous studies have mostly focused on classical mechanisms such as hyperglycemia, hemodynamic abnormalities, and activation of the renin–angiotensin system (RAS). Currently, the mechanisms of lipid metabolism disorders in DKD have received considerable attention [3]. In various kidney diseases, the expression profiles of sphingolipids and their metabolites are altered, suggesting that they may participate in the occurrence and development of these diseases [4]. Sphingolipids are important components of cell membrane lipid rafts and are also bioactive signaling molecules that regulate cell proliferation, apoptosis, inflammation, and fibrosis [5]. Changes in the composition of cholesterol and sphingolipids in lipid rafts can affect insulin signal transduction and participate in the occurrence of diabetes and its complications [6].

Ceramide (Cer), as the core molecule of sphingolipid metabolism, can participate in the occurrence and progression of diabetes through multiple mechanisms, including inducing β-cell apoptosis, aggravating insulin resistance, and inhibiting insulin gene expression, and specific Cer species or ratios may serve as biomarkers of diabetes risk [7]. At the same time, sphingosine-1-phosphate (S1P) is another class of key bioactive metabolite, and studies have shown that S1P is associated with the mechanisms of various kidney diseases such as DKD and lupus nephritis [8]. A metabolomics study showed that patients with DKD exhibit significant sphingolipid metabolism abnormalities, with

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abnormally elevated levels of metabolites such as sphingomyelin and phosphatidylcholine [9].

In summary, this review sorts out the research on sphingolipid metabolism and DKD, focuses on analyzing the mechanistic roles of Cer, S1P, and others, and discusses therapeutic strategies for intervening in DKD by targeting sphingolipid metabolism.

## 2. Overview of Sphingolipid Metabolism and Its Physiological Functions in the Kidney

Sphingolipid metabolism comprises synthesis, hydrolysis, and clearance; under physiological conditions, Cer and S1P jointly maintain the normal functions of glomerular and renal tubular epithelial cells. Under high-glucose conditions, Cer increases, leading to podocyte injury, glomerulosclerosis, and tubulointerstitial fibrosis. Changes in the sphingolipid profile precede the appearance of microalbuminuria; therefore, sphingolipid metabolites can serve as one of the early biomarkers [10].

### *2.1. Basic Pathways of Sphingolipid Metabolism*

The initial step of sphingolipid metabolism is completed in the endoplasmic reticulum: serine and palmitoyl-CoA are condensed under the catalysis of serine palmitoyltransferase (SPT) to generate 3-ketodihydrosphingosine, which is reduced to dihydrosphingosine; the latter is converted, under the catalysis of ceramide synthase (CerS), into dihydroceramide and is finally dehydrogenated to produce Cer. This is one of the main sources of intracellular Cer, and its flux is strictly regulated by SPT activity. As an intermediate product of sphingolipid metabolism, Cer can also be generated through the hydrolysis of sphingomyelin by sphingomyelinase or through the salvage pathway, and its level is precisely regulated by the multiple key enzymes mentioned above. Studies have shown that the accumulation of specific Cer species is closely related to the progression of diabetes and its complications [7].

Cer is further metabolized into sphingosine, which is phosphorylated by sphingosine kinase (SphK) to generate S1P; S1P is degraded by S1P lyase into hexadecenal and phosphoethanolamine, or dephosphorylated by S1P phosphatase back to sphingosine, thereby maintaining the dynamic balance of sphingolipid metabolism. The synthesis, hydrolysis, and clearance links are closely connected, and a shift in enzyme activity in any link can cause the accumulation or depletion of specific molecules. For example, the expression and localization of SphK1 in intrinsic renal cells have been confirmed to be distributed in glomerular mesangial cells, proximal tubules, and principal cells of the collecting duct [10]. S1P exerts protective effects in kidney diseases, and regulating this pathway is of great significance for preventing the onset of kidney diseases and reducing mortality [8].

### *2.2. Physiological Roles of Sphingolipid Molecules in Renal Cells*

Cer and sphingomyelin are structural components of the plasma membrane and important constituents of lipid rafts. Once cholesterol and sphingolipids change, the structure and function of lipid rafts are affected accordingly, which may in turn interfere with insulin signal transduction [6]. Cer participates in maintaining the structural integrity of glomerular podocytes and the barrier function of renal tubular epithelial cells. Sphingomyelinase-mediated hydrolysis of sphingomyelin maintains the dynamic balance of sphingolipids inside and outside renal cells. Studies have shown that changes in the activity of acid sphingomyelinase (ASMase) and neutral sphingomyelinase in the urine of diabetic rats can serve as biomarkers of early renal injury [10]. After binding to its G protein-coupled receptor (GPCR), S1P regulates the proliferation and survival of glomerular endothelial cells, the cytoskeletal rearrangement of podocytes, and the maintenance of polarity of renal tubular epithelial cells. In addition, sphingosine and SphK1 play important roles in endocytic membrane trafficking, and the conversion of sphingosine into its phosphorylated product S1P participates in regulating vesicle formation and membrane transport processes [11].

## 3. Association between Sphingolipid Metabolism and Renal Pathology

The differential distribution of Cer, sphingosine, and S1P in different renal cell types is associated with the lesion site and severity of DKD. A metabolomics study found that the mechanism by which Alpinia oxyphylla exerts its protective effect on DKD model mice is related to the regulation of disorders in sphingolipid metabolism, glycerophospholipid metabolism, and their metabolites, and the differential metabolites mainly include sphingomyelin and phosphatidylcholine [9]. Chaihuang Yishen granules can improve the abnormal metabolism of various sphingomyelins and phosphatidylcholines in the renal cortex of DKD rats and delay the progression of DKD [12]. Metabolomics studies have shown that changes in the renal sphingolipid metabolism profile precede the appearance of microalbuminuria. When plasma creatinine has not yet changed, changes in the activity of exosomal sphingomyelinase and ceramidase in urine can be detected, suggesting their potential as predictive markers of early renal injury [10].

### *3.1. Sphingolipid Metabolism Disorders Leading to Podocyte Injury in DKD*

Excessive accumulation of Cer triggers mitochondrial dysfunction, inactivation of survival signals, and cell apoptosis. The sphingomyelinase pathway remodels membrane microdomains and weakens the integrity of the slit diaphragm, whereas S1P counteracts this by maintaining the podocyte cytoskeleton through receptor signaling, although this protection weakens in the diabetic state as the receptor profile changes.

#### 3.1.1. Ceramide Accumulation and Podocyte Apoptosis

Cer metabolism disorder is the core link of podocyte injury in DKD. C16:0 Cer selectively accumulates under conditions of high glucose and insulin resistance [13]. Disordered podocyte lipid metabolism leads to podocyte injury, and abnormal sphingolipid metabolism can damage the structure and function of podocytes through multiple pathways [14]. Accumulated Cer can form permeability channels in the outer mitochondrial membrane, promoting the release of cytochrome c and the activation of the caspase cascade, and podocytes enter apoptosis. As the number of podocytes decreases, the integrity of the slit diaphragm is destroyed accordingly. Studies have shown that inhibiting Cer accumulation can reverse podocyte reactive oxygen species (ROS) generation and cell death caused by combined stimulation with high glucose, free fatty acids, and angiotensin II [15]. Cer can also activate protein phosphatase 2A (PP2A), causing the anti-apoptotic protein Bcl-2 to be dephosphorylated and inactivated, aggravating the apoptotic sensitivity of podocytes. Studies have found that mitochondrial ceramidase metabolizes mitochondrial Cer into sphingosine and then into S1P, upregulating Bcl-2 protein expression, indicating that podocyte apoptosis may be determined by the metabolic flux between Cer and sphingosine rather than by the absolute level of a single molecule [16]. Podocyte-specific Cers6 knockout can alleviate podocyte apoptosis and proteinuria in diabetic mice. Further studies have shown that podocyte-specific Cers6 knockout can ameliorate glomerular injury and inflammatory responses in diabetic mice, whereas podocyte-specific Cers6 overexpression is sufficient to induce proteinuria; mechanistically, CerS6-derived Cer(d18:1/16:0) can bind to mitochondrial voltage-dependent anion channel 1 (VDAC1), after which mitochondrial DNA (mtDNA) leaks and activates the cyclic GMP-AMP synthase–stimulator of interferon genes (cGAS–STING) signaling pathway [17].

#### 3.1.2. S1P Signaling and Podocyte Protection

Podocytes express S1P receptors (S1PR) 1–5, among which the signaling pathway mediated by S1PR1 exerts protective effects on maintaining the integrity of the podocyte cytoskeleton and the function of the slit diaphragm. Thus, S1P is a key regulator of multiple renal cell functions, including matrix remodeling [18]. High glucose downregulates SphK1 expression in podocytes, leading to reduced S1P production, impaired S1PR1-mediated Rac1 activation and actin rearrangement, and aggravated podocyte foot process fusion. Hypoxia-inducible factor 2$\alpha$ (HIF-2$\alpha$) can inhibit the

transcription of SPHK1 by binding to its promoter region and reduce S1P synthesis, thereby ameliorating lipid metabolism disorders and injury in DKD podocytes [19].

In contrast, S1PR2 has the opposite effect to S1PR1 in podocytes: its activation can induce enhanced RhoA signaling and cytoskeletal disorganization, promoting podocyte injury, and under diabetic conditions, the imbalanced S1PR1/S1PR2 expression ratio aggravates podocyte lesions. Sphk2 gene knockout can prevent streptozotocin (STZ)-induced nephropathy and proteinuria, and its protective effect is associated with increased expression of Wilms tumor suppressor gene 1 (WT1) and nephrin and reduced macrophage infiltration [18]. Pharmacological activation of SphK1 or exogenous supplementation with S1PR1 agonists can reduce podocyte injury and proteinuria in diabetic animal models. In addition, S1PR1 has been identified as a protective anti-ferroptosis target gene in DKD, and Smad2 affects its expression and promotes podocyte ferroptosis by recruiting methyltransferase-like 3 (METTL3) to perform N6-methyladenosine (m6A) modification of the S1PR1 gene [20]. The traditional Chinese medicine compound Yi-Shen-Hua-Shi granules can regulate sphingolipid metabolism and other pathways through the gut–kidney axis by modulating the gut microbiota and serum metabolites, thereby ameliorating DKD [21].

#### 3.1.3. Sphingomyelinase Pathway and Podocyte Membrane Structural Injury

The expression and activity of ASMase are significantly increased, and it can catalyze the hydrolysis of sphingomyelin in the podocyte membrane to generate Cer, further altering the composition of membrane lipid microdomains and the localization of slit diaphragm proteins. Sphingomyelin phosphodiesterase acid-like 3b (SMPDL3b) is a lipid raft enzyme that can convert sphingomyelin into Cer. Increased SMPDL3b expression impairs insulin receptor isoform B (IR-B)-dependent pro-survival signaling by interfering with the binding of the insulin receptor to caveolin-1 (Cav-1) at the plasma membrane, and podocyte-specific Smpdl3b deficiency is sufficient to restore ceramide-1-phosphate (C1P) content in the renal cortex and prevent the progression of DKD [22]. Cer can form lipid platforms on the podocyte membrane, recruiting NADPH oxidase components and promoting ROS generation and oxidative stress injury. SMPDL3b also participates in the regulation of innate immunity in podocytes, and its knockdown can attenuate the expression of interferon-β (IFN-β) and C-X-C motif chemokine ligand 10 (CXCL10) in the Toll-like receptor 3 (TLR3) signaling pathway induced by poly(I:C)[23]. Neutral sphingomyelinase 2 (nSMase2) translocates from the cytoplasm to the podocyte membrane under diabetic conditions and participates in tumor necrosis factor-$\alpha$ (TNF-$\alpha$)-mediated podocyte injury and the upregulation of intercellular adhesion molecule expression. ASMase gene knockout or pharmacological inhibition can preserve podocyte slit diaphragm structure and glomerular filtration barrier function and reduce diabetic proteinuria. In summary, the sphingomyelinase pathway plays an important pathogenic role in DKD podocyte injury by altering the lipid composition and membrane microdomain structure of the podocyte membrane, and targeting this pathway may provide new strategies for DKD treatment [24].

### *3.2. Sphingolipid Metabolism Disorders Promote Glomerulosclerosis and Tubulointerstitial Fibrosis*

Sphingolipid metabolism disorders affect every cellular compartment of the kidney; in addition to podocytes, they also involve mesangial cells, renal tubular epithelial cells, and others. Cer accumulation drives mesangial cell proliferation and matrix deposition and can also amplify pro-inflammatory signals. S1P receptor-dependent signaling may either maintain tubular polarity to counteract the above injuries or, via S1PR2, drive myofibroblast transformation and matrix accumulation. The Cer–S1P axis may become the converging point of research linking the pathological mechanisms of glomerulosclerosis and tubulointerstitial fibrosis.

#### 3.2.1. Sphingolipid Metabolism, Mesangial Cell Proliferation, and Extracellular Matrix Deposition

When glomerular mesangial cells are exposed to an environment of high glucose and abnormal lipid metabolism, an imbalance in the sphingolipid metabolism pathway is triggered. Cer can activate multiple downstream signaling cascades. Studies have shown that elevated Cer can activate protein kinase Cζ (PKCζ) and NADPH oxidase 4 (NOX4), thereby promoting the expression of transforming growth factor-β1 (TGF-β1) and the secretion of fibronectin, and the mesangial matrix thus progressively expands [25]. TGF-β1 is a well-recognized core pro-fibrotic factor, and its upregulation aggravates the pathological phenotypic transformation of mesangial cells, whereas NOX4-mediated oxidative stress is closely related to mesangial cell injury and inflammatory responses [24]. In addition, Cer can also directly promote mesangial cell proliferation and the synthesis of type IV collagen by activating the p38 mitogen-activated protein kinase (p38 MAPK) and c-Jun N-terminal kinase (JNK) signaling pathways, further accelerating mesangial matrix expansion [26].

S1P in mesangial cells constitutes another parallel branch: S1P activates the expression of connective tissue growth factor (CTGF) and platelet-derived growth factor-B (PDGF-B) via S1PR2/3 and promotes mesangial cell proliferation and extracellular matrix accumulation in autocrine and paracrine manners [27]. CerS2 expression is upregulated in diabetic mesangial cells. Its product, long-chain Cer (C16:0), can specifically promote the release of the cytokines interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1), further amplifying the local inflammatory microenvironment [28].

#### 3.2.2. Role of Sphingolipid Metabolism in Renal Tubular Epithelial Cell Injury and Interstitial Fibrosis

Renal tubular epithelial cells also undergo sphingolipid metabolism reprogramming in the diabetic state, and Cer accumulation is one of its core events. Cer can activate protein phosphatase 1 (PP1) to dephosphorylate eukaryotic translation initiation factor 2α (eIF2α), thereby inhibiting protein translation and inducing apoptosis, ultimately leading to tubular atrophy [25]. This mechanism coupling translational inhibition with apoptosis suggests that Cer has a toxic effect that cannot be ignored in tubular injury.

S1P maintains the polarity of renal tubular epithelial cells through S1PR1, whereas in diabetes, SphK1 activity decreases and the S1P/Cer ratio decreases, thereby promoting epithelial–mesenchymal transition (EMT)[26]. EMT is an important cytological basis of tubulointerstitial fibrosis, and the imbalance of sphingolipid homeostasis plays a key driving role in it. In addition, Cer can also activate the NLR family pyrin domain containing 3 (NLRP3) inflammasome, promoting renal tubular epithelial cells to secrete interleukin-1β (IL-1β) and interleukin-18 (IL-18), initiating interstitial inflammatory responses and activating fibroblasts [24]. In in vivo experiments, tubular epithelial cell-specific S1PR1 deficiency can aggravate interstitial fibrosis in the unilateral ureteral obstruction (UUO) model, which suggests that S1P signaling has a protective role in tubulointerstitial fibrosis [27]. Cer accumulation and weakened S1P signaling together constitute an important metabolic basis for renal tubular epithelial cell injury and interstitial fibrosis.

### *3.3. Inflammatory and Fibrotic Signaling Network Mediated by Sphingolipid Metabolism*

In addition to directly affecting intrinsic renal cells, sphingolipid metabolism disorders also build a complex inflammatory and fibrotic signaling network that drives the progression of DKD. Cer can recruit tumor necrosis factor receptor-associated factor 2 (TRAF2) and receptor-interacting protein 1 (RIP1) to form a ceramide signalosome; this signal activates the nuclear factor-κB (NF-κB) pathway and drives the transcriptional expression of pro-inflammatory and pro-fibrotic factors [25]. This signalosome closely links sphingolipid metabolism with classical inflammatory pathways, amplifying the local renal inflammatory cascade. As for the fibrotic effect, S1P activates the RhoA/Rho kinase pathway through S1PR2, promoting the transformation of fibroblasts into myofibroblasts and the expression of α-smooth muscle actin (α-SMA), thereby accelerating matrix deposition [27]. Imbalanced metabolism of Cer and S1P can also affect

the polarization direction of macrophages—Cer promotes M1-type pro-inflammatory polarization, whereas S1P promotes M2-type anti-inflammatory polarization through S1PR1, and the imbalanced M1/M2 ratio in diabetes aggravates renal interstitial inflammation [24]. Sphingolipid metabolism intermediates such as C1P and S1P can regulate pericyte–myofibroblast transformation and pericyte detachment, participating in renal interstitial microvascular rarefaction and the fibrotic process [26]. The above multi-level signaling network indicates that sphingolipid metabolism intermediates are key nodes linking inflammation and fibrosis in DKD renal interstitial fibrosis.

## 4. Conclusion

The pathogenesis of DKD involves multiple levels, and treatment strategies are complex. Based on the research literature on sphingolipid metabolism and DKD, this review proposes that the dynamic imbalance between Cer accumulation and S1P signaling may be the key link running through its pathological process. Cer participates in podocyte injury and renal tissue fibrosis. S1PR1 signaling maintains endothelial barrier integrity and inhibits inflammatory cascades, with definite renoprotective effects. At the level of therapeutic translation, small-molecule inhibitors targeting SPT, CerS6, and ASMase have shown renoprotective effects in animal models. However, the leap from animal models to clinical application still faces many challenges: sphingolipid metabolism has significant tissue and cell type specificity, and systemic intervention may bring off-target effects; moreover, the metabolic background of patients with DKD is far more complex than that of animal models, and concomitant medications and glycemic control status may modify the efficacy and safety of sphingolipid-targeted drugs. Therefore, future research should focus on cell type-specific sphingolipid metabolism profiles in the kidney, perform validation work for early diagnosis and prognostic markers, and make corresponding preparations for the development of kidney-selective sphingolipid pathway modulators.

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