中国临床研究 Chin J Clin Res, September 2025, Vol.38, No.9

Cite as: Yang LP, Su XL, Wang LH. Aberrant energy metabolism in diabetic renal tubular injury [J]. Chin J Clin Res, 2025, 38(9): 1355-1359.

DOI: 10.13429/j.cnki.cjcr.2025.09.004

Aberrant energy metabolism in diabetic renal tubular injury

YANG Liping, SU Xiaole, WANG Lihua

Nephrology Department, Second Hospital of Shanxi Medical University, Taiyuan, Shanxi 030001,China

Corresponding author: WANG Lihua,E-mail: lihuawang236@126.com

Abstract: Energy metabolism is closely related to the development of various diseases. With the increasing prevalence of diabetes year by year, diabetic kidney disease (DKD), as a common vascular complication of diabetes, is also on the rise. In the past, glomerular injury was considered as the main pathogenesis of DKD, but more and more evidence shows that renal tubular injury is an important factor that causes DKD. There is aberrant cellular energy metabolism in renal tubular injury in diabetes, suggesting that aberrant energy metabolism may play a potential role in the development and progression of renal tubular injury in diabetes. This article reviews the pathophysiological mechanism of aberrant energy metabolism in diabetic renal tubular injury in recent years.

Keywords: Energy metabolism; Diabetes; Diabetic kidney disease; Renal tubular injury; Lipid metabolism; Phospholipid metabolism

According to data released by the International Diabetes Federation (IDF) in 2021, approximately 537 million adults aged 20-79 years worldwide live with diabetes, and this number is projected to rise to 783 million by 2045 [1]. Diabetic kidney disease (DKD) is one of the common microvascular complications of diabetes and a primary cause of chronic kidney disease and end-stage renal disease.

Current studies have shown that renal tubular injury may precede early glomerular changes in DKD [2]. In the urine of patients with early-stage diabetes, several biomarkers of proximal tubular cell injury can be detected, while there is no obvious glomerular damage at this stage, indicating that proximal tubular injury is an early lesion [3]. Animal experimental studies have found that downregulated expression of silent information regulator 1 (SIRT1) in proximal tubules exacerbates glomerular changes and impairs glomerular function in diabetic mice [4].

The proximal tubule is the primary site of reabsorption and requires a large amount of adenosine triphosphate (ATP) to maintain normal physiological functions, making it more susceptible to various metabolic and hemodynamic factors associated with diabetes. In the context of diabetes, mitochondrial function is impaired, and the aerobic glycolysis pathway is enhanced to provide sufficient energy for maintaining tubular function [5]. Currently, the abnormal energy metabolism processes in diabetic tubular injury have gradually become a research focus. This article reviews the pathophysiological mechanisms of abnormal energy metabolism in diabetic tubular injury in recent years.

1 Energy metabolism of renal tubular cells under normal physiological conditions

Normal physiological activities of cells require a large amount of energy to drive, and mitochondria serve as the structural basis for cellular energy production. Most of the mitochondria in the kidney are concentrated in the renal cortical region where renal tubular epithelial cells are located [6]. Therefore, tubular epithelial cells (TECs) are the core site of energy metabolism in the kidney. Under normal physiological conditions, the energy metabolism of TECs mainly relies on fatty acid oxidation (FAO) in mitochondria to generate adenosine triphosphate (ATP), rather than producing ATP through the glycolytic pathway to meet their energy demands. This may be attributed to the abundant content of enzymes related to FAO in TECs, while the content of key enzymes regulating glycolysis is very low, and this method is also more efficient than glucose oxidation [7-8].

2 Energy metabolism of renal tubular cells in diabetic conditions

In a hyperglycemic state, increased glucose enters the mitochondrial oxidative respiratory chain of tubular epithelial cells (TECs), promoting the production and release of reactive oxygen species (ROS), which further accelerates cell apoptosis. Hyperglycemia can also activate the polyol pathway and induce excessive sorbitol production, further leading to TEC injury, mitochondrial dysfunction, and alterations in cellular energy metabolism [9]. Transcriptomic studies have shown that in a hyperglycemic state, the expression of genes related to fatty acid, glucose, and amino acid metabolism in TECs is reduced, with particularly downregulated expression of enzymes and regulatory factors involved in fatty acid metabolism, thereby leading to impaired FAO in renal tubular cells [10]. The energy source of renal tubular cells shifts from mitochondrial oxidative phosphorylation to aerobic glycolysis of glucose to adapt to energy metabolism disorders in TECs. This process is termed metabolic reprogramming, first proposed by Warburg [11]

and initially discovered in tumor cells. This phenomenon has also been found to play important roles in various non-tumor cells. However, metabolic reprogramming of TECs under hyperglycemic conditions may promote the progression of renal fibrosis. Therefore, early restoration of normal energy metabolism in TECs has emerged as a novel strategy for treating DKD [12].

2.1 Glucose metabolism in renal tubular cells

In a hyperglycemic state, renal tubular cells can metabolize glucose through aerobic glycolysis to produce ATP and maintain normal physiological functions. However, abnormal expression of related enzymes and regulatory factors during this process can also exacerbate TEC damage and mitochondrial dysfunction [13]. Currently, the most extensively studied protein are adenosine monophosphate (AMP)-activated protein kinase (AMPK) and pyruvate kinase isozyme type M2 (PKM2).

2.1.1 AMPK

AMPK is a key cellular energy sensor that can be activated under conditions of energy depletion. In renal models of diabetic mice, decreased AMPK activity has been observed, with its downstream peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) in an inhibited state [14]. This may be due to diabetes-induced accelerated rate of ATP production via aerobic glycolysis in renal tubular cells, thereby reducing AMPK activity and inhibiting PGC-1α expression [15]. This animal study also found reduced renal mitochondrial biogenesis and superoxide production in diabetic mice, consistent with decreased glucose oxidation. In contrast, activation of AMPK enhanced superoxide production and mitochondrial function, while alleviating renal injury. On the other hand, sphingomyelin and its metabolites play important roles in cellular activities. In diabetic mouse models, sphingomyelin accumulated in mesangial cells was found to inhibit the activity of AMPK and PGC-1α, and increase lactate and ATP production [16]. This suggests that in DKD, anabolic metabolism of sphingomyelin promotes the aerobic glycolysis pathway and rapid ATP synthesis, thereby inhibiting the AMPK and PGC-1α pathways, leading to mitochondrial dysfunction and oxidative stress, and ultimately exacerbating renal tissue damage.

2.1.2 PKM2

PKM2 is a rate-limiting enzyme in glycolysis, which can exist in cells in an inactive tetrameric state or active monomeric or dimeric states [17]. In the context of DKD, PKM2 undergoes phosphorylation, and its tetrameric state is isomerized into a dimeric state. This promotes the phosphorylation of signal transducer and activator of transcription 3 (STAT3) and nuclear factor kappa-B (NF-κB), as well as the expression of intercellular adhesion molecule-1, thereby initiating inflammatory cell infiltration and promoting the progression of DKD. PKM2 can also promote the phosphorylation of eukaryotic translation initiation factor 2-alpha kinase 2, which in turn activates the Nod-like receptor protein 3 (NLRP3) and absent in melanoma 2 (AIM2)-mediated inflammasome, thereby promoting macrophage activation and the release of inflammatory factors, playing an important role in the progression of DKD [18]. Researchers have also confirmed that inhibiting PKM2 phosphorylation can suppress renal inflammatory responses, thereby preventing the development of DKD [19]. A study by Qi *et al.* [20] found that PKM2 activation increases glycolytic flux, reduces the levels of toxic glucose metabolites such as sorbitol and methylglyoxal, enhances mitochondrial biogenesis and mitochondrial metabolism to improve or even reverse mitochondrial dysfunction, thereby delaying DKD progression. Therefore, PKM2 may become an important target for interfering with the occurrence and development of DKD.

2.2 Lipid metabolism in renal tubular cells

In the renal pathological tissues of patients with DKD, massive lipid accumulation is observed in cells. Alterations in regulatory factors related to lipid metabolism lead to abnormal lipid accumulation, thereby affecting renal function [21]. A lipidomic analysis of the early renal cortex in DKD rats revealed distinct lipidomic profiles in the kidney. In the renal cortex of DKD rats, levels of neutral lipids (including triacylglycerols, diacylglycerols, free fatty acids, and cholesteryl esters) and lysophospholipids are increased, while most phospholipids—predominantly phosphatidylethanolamine (PE)—show a decreasing trend. Most sphingolipids, including ceramides and their derivatives, exhibit an increasing trend [22]. In a hyperglycemic environment, dysregulation of lipid metabolism in renal tubular cells further impairs tubular epithelial cell (TEC) function, which is primarily associated with imbalances in lipid uptake, metabolism, and synthesis, lipid accumulation, and dysregulation of related phospholipid metabolism.

2.2.1 Increased fatty acid uptake

TECs primarily take up fatty acids via the fatty acid transporter CD36 located on the cell surface. Studies have shown that hyperglycemia induces upregulation of CD36 mRNA and protein expression in the renal proximal tubules of DKD patients, enhancing fatty acid uptake and causing lipid accumulation that impairs renal function [23]. Upregulated CD36 activates the NLR family pyrin domain containing 3 (NLRP3) and NF-κB signaling pathways, promoting inflammatory responses and exacerbating renal injury [24-27]. Therefore, it is reasonable to hypothesize that inhibiting CD36 expression in the early stages of diabetes could reduce fatty acid uptake by TECs, suppress inflammatory activation, decrease lipid accumulation, and ameliorate tubular injury.

2.2.2 Increased fatty acid synthesis

Fatty acid synthesis is regulated by sterol regulatory element-binding proteins (SREBPs), which play a crucial role in lipid homeostasis. SREBPs have three isoforms: SREBP-1a, SREBP-1c, and SREBP-2, associated with the synthesis of fatty acids, triacylglycerols, and cholesterol, respectively [28]. Under hyperglycemic conditions,

SREBP expression is activated, promoting the expression of acetyl-CoA carboxylase (ACC) and fatty acid synthase, ultimately increasing fatty acid synthesis [29]. In transgenic mice with renal overexpression of SREBP-1a, increased SREBP expression upregulates transforming growth factor-β (TGF-β) and vascular endothelial growth factor, leading to enhanced lipid synthesis and accumulation [30]. SREBPs also induce TGF-β transcriptional activity and activate the TGF-β/small mothers against decapentaplegic (SMAD) fibrotic signaling pathway by binding to the promoter region of fibrosis-related genes (e.g., TGF-β), further exacerbating renal injury [31].

Increased cholesterol uptake and synthesis also promote DKD progression. SREBP2 enhances cholesterol uptake via receptors such as low-density lipoprotein receptor, CD36, scavenger receptor A, and lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), and stimulates cholesterol synthesis through hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase [31]. Reverse cholesterol transport—a key cholesterol clearance mechanism that transports excess cholesterol from peripheral tissues to the liver for metabolism and excretion—is dysregulated in DKD patients and diabetic mouse models, as evidenced by downregulated expression of genes related to reverse cholesterol transport, indicating its association with DKD [32].

2.2.3 Abnormal fatty acid oxidation metabolism

Patients with DKD exhibit significantly impaired renal FAO (Fatty Acid Oxidation) capacity. In both DKD patients and DKD mouse models, significantly downregulated expression of enzymes and regulatory factors related to fatty acid metabolism has been observed [32]. Inhibition of fatty acid oxidation in TECs can lead to ATP depletion, cell death, dedifferentiation, and intracellular lipid accumulation, with the observation of a fibrotic phenotype [33]. Lipid accumulation caused by reduced FAO is inseparable from the progression of DKD, and several enzymes and regulatory factors play important roles in this process.

AMPK, a heterotrimeric protein kinase, is involved in regulating lipid metabolism pathways in addition to its role in DKD glucose metabolism mentioned above, with phosphorylation of its subunits playing a key role [34]. Carnitine palmitoyl transferase 1 (CPT-1), a critical rate-limiting enzyme in FAO, has its activity regulated by the AMPK-ACC-malonyl-CoA axis. AMPK activation inactivates ACC by inhibiting its phosphorylation; inactivation of ACC reduces downstream malonyl-CoA production, thereby weakening its inhibitory effect on CPT-1, promoting FAO, and reducing lipotoxicity [35]. In addition, other targets of AMPK in inhibiting lipid metabolism include phosphorylating SREBP1c (a transcription factor encoding ACC) and suppressing SREBP1c expression [36]. Therefore, it is hypothesized that enhancing AMPK activation may serve as a novel target for DKD treatment.

Peroxisome proliferator-activated receptor α (PPAR-α), a member of the nuclear receptor family of ligand-activated transcription factors, is primarily expressed in proximal renal tubules and the ascending limb of the loop of Henle [37]. Most enzymes involved in FAO are regulated by PPAR-α, which is currently recognized as a key transcriptional regulator maintaining the balance of fatty acid oxidation metabolism. Under hyperglycemic conditions, PPAR-α expression may be suppressed, leading to reduced FAO and potentially exacerbating TEC injury and inflammatory responses. Animal studies have demonstrated that STAT6 transcriptionally inhibits PPAR-α and its FAO-related target genes via sis-inducible elements in the protein promoter region, thereby promoting renal fibrosis [38]. The PPAR-α agonist fenofibrate reduces inflammatory factor expression in DKD rats by activating PPAR-α, inhibits the NF-κB pro-inflammatory pathway, ameliorates lipid accumulation, prevents tubulointerstitial fibrosis, and exerts renal protective effects [39]. Another study showed that proximal tubular PPAR-α alleviates renal fibrosis and inflammation in mice with unilateral ureteral obstruction by reducing intraepithelial TGF-β and extracellular matrix protein production [40]. Since DKD and obstructive nephropathy are major causes of renal fibrosis, further research is needed to determine whether proximal tubular PPAR-α can alleviate DKD-related renal fibrosis through these pathways. Thus, activating PPAR-α may represent an effective strategy to reduce renal inflammation and fibrosis in DKD, thereby controlling renal injury.

PGC-1α, a transcription factor that regulates mitochondrial biogenesis and the expression of most rate-limiting enzymes in the FAO pathway, shows significantly reduced mRNA expression in the renal tubules of DKD patients [17]. In addition to PPAR-α, PGC-1α is a key regulator of genes involved in mitochondrial FAO [41]. Increased PGC-1α expression protects TECs and delays renal interstitial fibrosis progression through mechanisms such as reducing ROS and inhibiting NLRP3 inflammasome activation [42-43]. Studies have shown that SIRT1 enhances its transcriptional coactivator function by deacetylating PGC-1α, thereby promoting mitochondrial biogenesis and energy metabolism; SIRT1 is also regulated by AMPK [44]. Furthermore, PGC-1α inhibits apoptosis and alleviates TEC injury by regulating the expression of mitochondrial dynamics-related proteins and apoptosis-related proteins [45]. Current research indicates that PGC-1α acts through multiple mechanisms in diabetic tubular injury, including mitochondrial protection, antioxidant effects, energy metabolism regulation, anti-inflammation, and apoptosis inhibition, making it a potential target for DKD treatment.

2.2.4 Lipid accumulation

In diabetes, renal tubular cells exhibit an imbalance in fatty acid uptake, oxidation, and anabolic metabolism, leading to excessive fatty acid production that exceeds the tubular utilization capacity. Excess fatty acids are accompanied by triacylglycerol formation and deposition in renal tubules. Such abnormal lipid accumulation in non-adipose tissues, which can cause dysregulation of cellular homeostasis and cell damage, is termed

lipotoxicity [46]. Excessive lipid accumulation results in mitochondrial dysfunction in TECs, abnormal cellular energy metabolism, and subsequent renal injury manifestations including oxidative stress, inflammatory responses, TEC apoptosis, and tubulointerstitial fibrosis [47].

Lipid accumulation induces renal injury through multiple mechanisms. First, lipid accumulation disrupts the mitochondrial structure of tubular cells, impairs enzyme activity in the mitochondrial respiratory chain, increases oxygen free radicals, and generates large amounts of ROS. As signaling molecules, ROS can activate extracellular regulated protein kinases (ERK) and p38 mitogen-activated protein kinase (MAPK) pathways, regulate NF-κB activation, and initiate transcription of genes encoding inflammatory factors such as cyclooxygenase 2, tumor necrosis factor-α, interleukin (IL)-1β, and IL-18, thereby promoting inflammatory cell infiltration and inducing inflammatory responses. Second, ROS can also activate the phosphatidylinositol-3-kinase (PI3K) pathway and its downstream protein kinase B (Akt) and ERK1/2, leading to activation of the NLRP3 inflammasome and caspase-1, which results in inflammatory cell death [48-49]. Third, mitochondrial structural damage impairs oxidative phosphorylation, reduces ATP production, activates AMPK-γ, and further triggers downstream P53 protein, inducing cellular expression of Bax and Bak. This regulates mitochondrial release of cytochrome C, ultimately leading to cell apoptosis with the involvement of ROS [50]. In addition, ROS can induce the expression of fibro genic factors such as TGF-β and plasminogen activator inhibitor-1 (PAI-1), thereby promoting tubulointerstitial fibrosis and exacerbating tubular injury [51].

3 Abnormal phospholipid metabolism

In recent years, the role of phospholipids and their metabolites in kidney diseases has attracted attention. Phospholipids are widely present in nature and perform important physiological functions, playing a crucial role in maintaining cell membrane stability and regulating cell signal transduction.

Lipidomic analysis of the renal cortex in early DKD rats revealed significant alterations in phospholipid metabolism, characterized by a decrease in most phospholipids, predominantly PE. PE collectively influences the progression of DKD by regulating lipid metabolism, participating in cell signal transduction, affecting the process of renal fibrosis, and maintaining cell membrane stability and function [22]. Lysophosphatidic acid (LPA), a naturally occurring glycerophospholipid, can regulate various biological responses by binding to lysophosphatidic acid receptors (LPARs). Studies have found that LPAR1 expression is significantly upregulated in diabetic mouse models, while inhibiting LPAR1 expression alleviates diabetic renal injury [52].

The role of sphingomyelin and its metabolites in kidney diseases has also been extensively studied. Sphingosine-1-phosphate (S1P), an important regulatory factor in fibrotic diseases, is generated by phosphorylation of sphingosine by sphingosine kinase (SPHK) and exerts its effects by acting on S1P receptors (S1PRs). The SPHK1-S1P-S1PRs axis plays a vital role in the occurrence and development of renal interstitial fibrosis. S1P activates Rho kinase by acting on S1PR2, induces the differentiation of TECs into a myofibroblast phenotype, and promotes the progression of renal interstitial fibrosis during DKD [53]. However, current research on the mechanisms underlying the role of abnormal phospholipid metabolism in DKD-induced tubular injury still has many issues to be further explored to identify new targets for DKD treatment.

4 Summary

TECs are the center of renal energy metabolism. Under hyperglycemic conditions, TECs are injured, and their energy metabolism mode shifts from FAO to aerobic glycolysis to maintain the normal physiological functions of renal tubules. The expression of the fatty acid transporter CD36 in TECs is significantly upregulated, leading to increased fatty acid uptake. The expression of SREBPs that regulate fatty acid synthesis is increased, while the expression and activity of key regulatory factors (AMPK, PPAR-α, PGC-1α) involved in FAO of TECs are decreased. These changes result in reduced FAO, exacerbate renal lipid accumulation, cause mitochondrial dysfunction and cellular energy metabolism imbalance, and induce a series of injuries such as oxidative stress, inflammatory responses, renal tubular cell apoptosis, and renal interstitial fibrosis, further aggravating tubular injury. Meanwhile, PKM2, an enzyme related to aerobic glycolysis, is activated and improves mitochondrial biogenesis and function by regulating the downstream signal PGC-1α, maintaining the balance of cellular energy metabolism. Currently, the mechanisms by which abnormal phospholipid metabolism induces diabetic tubular injury remain to be further investigated, aiming to provide new therapeutic insights for preventing and treating the occurrence and development of diabetic tubular injury.

Conflict of interest None

Reference

[1] Lovic D, Piperidou A, Zografou I, et al. The growing epidemic of diabetes mellitus[J]. Curr Vasc Pharmacol, 2020, 18(2): 104-109.

[2] Ugarte F, Santapau D, Gallardo V, et al. Urinary extracellular vesicles as a source of NGAL for diabetic kidney disease evaluation in children and adolescents with type 1 diabetes mellitus[J]. Front Endocrinol, 2021, 12: 654269.

[3] Chen JC, Wang XY, He Q, et al. YAP activation in renal proximal tubule cells drives diabetic renal interstitial fibrogenesis[J]. Diabetes, 2020, 69(11): 2446-2457.

[4] Hasegawa K, Wakino S, Simic P, et al. Renal tubular Sirt1 attenuates diabetic albuminuria by epigenetically suppressing Claudin-1 overexpression in podocytes[J]. Nat Med, 2013, 19(11): 1496-1504.

[5] Yao L, Liang XH, Qiao YJ, et al. Mitochondrial dysfunction in diabetic tubulopathy[J]. Metabolism, 2022, 131: 155195.

[6] Bugarski M, Martins JR, Haenni D, et al. Multiphoton imaging reveals axial differences in metabolic autofluorescence signals along the kidney proximal tubule[J]. Am J Physiol Renal Physiol, 2018, 315(6): F1613-F1625.

[7] Console L, Scalise M, Giangregorio N, et al. The link between the mitochondrial fatty acid oxidation derangement and kidney injury[J]. Front Physiol, 2020, 11: 794.
[8] Gewin LS. Sugar or fat? renal tubular metabolism reviewed in health and disease[J]. Nutrients, 2021, 13(5): 1580.
[9] Chen LM. Value of focusing on renal tubular injury in diagnosis and treatment of diabetic nephropathy[J]. Chin J Diabetes Mellit, 2021, 13(10): 921-925. **[In Chinese]**
[10] Lee LE, Doke T, Mukhi D, et al. The key role of altered tubule cell lipid metabolism in kidney disease development[J]. Kidney Int, 2024, 106(1): 24-34.
[11] Warburg O. On the origin of cancer cells[J]. Science, 1956, 123(3191): 309-314.
[12] Zhu ZJ, Chen XH, Ding GH. Research progress on the role of energy metabolism disorder of renal tubular epithelial cells in acute renal injury[J]. Chin J Nephrol, 2020, 36(12): 965-969. **[In Chinese]**
[13] Zhang GS, Darshi M, Sharma K. The Warburg effect in diabetic kidney disease[J]. Semin Nephrol, 2018, 38(2): 111-120.
[14] She YQ, Yu M, Wang L, et al. Emerging protective actions of PGC-1α in diabetic nephropathy[J]. Oxid Med Cell Longev, 2022, 2022: 6580195.
[15] Ye KL, Zhao YL, Huang W, et al. Sodium butyrate improves renal injury in diabetic nephropathy through AMPK/SIRT1/PGC-1α signaling pathway[J]. Sci Rep, 2024, 14(1): 17867.
[16] Miyamoto S, Hsu CC, Hamm G, et al. Mass spectrometry imaging reveals elevated glomerular ATP/AMP in diabetes/obesity and identifies sphingomyelin as a possible mediator[J]. EBioMedicine, 2016, 7: 121-134.
[17] Kuo CW, Chen DH, Tsai MT, et al. Pyruvate kinase M2 modification by a lipid peroxidation byproduct acrolein contributes to kidney fibrosis[J]. Front Med, 2023, 10: 1151359.
[18] Park YS, Han JH, Park JH, et al. Pyruvate kinase M2: a new biomarker for the early detection of diabetes-induced nephropathy[J]. Int J Mol Sci, 2023, 24(3): 2683.
[19] Chen DQ, Han J, Liu H, et al. Targeting pyruvate kinase M2 for the treatment of kidney disease[J]. Front Pharmacol, 2024, 15: 1376252.
[20] Qi WE, Keenan HA, Li Q, et al. Pyruvate kinase M2 activation may protect against the progression of diabetic glomerular pathology and mitochondrial dysfunction[J]. Nat Med, 2017, 23(6): 753-762.
[21] Tu QM, Jin HM, Yang XH. Lipid abnormality in diabetic kidney disease and potential treatment advancements[J]. Front Endocrinol, 2025, 16: 1503711.
[22] Hou BY, He P, Ma P, et al. Comprehensive lipidome profiling of the kidney in early-stage diabetic nephropathy[J]. Front Endocrinol, 2020, 11: 359.
[23] Schelling JR. The contribution of lipotoxicity to diabetic kidney disease[J]. Cells, 2022, 11(20): 3236.
[24] Hou YJ, Wang Q, Han BS, et al. CD36 promotes NLRP3 inflammasome activation via the mtROS pathway in renal tubular epithelial cells of diabetic kidneys[J]. Cell Death Dis, 2021, 12(6): 523.
[25] Chen YL, Zhang J, Cui WG, et al. CD36, a signaling receptor and fatty acid transporter that regulates immune cell metabolism and fate[J]. J Exp Med, 2022, 219(6): e20211314.
[26] Shahzad K, Fatima S, Khawaja H, et al. Podocyte-specific Nlrp3 inflammasome activation promotes diabetic kidney disease[J]. Kidney Int, 2022, 102(4): 766-779.
[27] Li XH, Dong X, Zhang LY, et al. Astragaloside IV attenuates renal tubule injury in DKD rats via suppression of CD36-mediated NLRP3 inflammasome activation[J]. Front Pharmacol, 2024, 15: 1285797.
[28] Xu XF, Jin WM, Chang RY, et al. Research progress of SREBP and its role in the pathogenesis of autoimmune rheumatic diseases[J]. Front Immunol, 2024, 15: 1398921.
[29] Wang Y, Liu TT, Wu Y, et al. Lipid homeostasis in diabetic kidney disease[J]. Int J Biol Sci, 2024, 20(10): 3710-3724.
[30] Wang TN, Chen X, Li RZ, et al. SREBP-1 mediates angiotensin II-induced TGF-β1 upregulation and glomerular fibrosis[J]. J Am Soc Nephrol, 2015, 26(8): 1839-1854.
[31] Dorotea D, Koya D, Ha H. Recent insights into SREBP as a direct mediator of kidney fibrosis via lipid-independent pathways[J]. Front Pharmacol, 2020, 11: 265.
[32] Rong J, Zhang ZX, Peng XY, et al. Mechanisms of hepatic and renal injury in lipid metabolism disorders in metabolic syndrome[J]. Int J Biol Sci, 2024, 20(12): 4783-4798.
[33] Bao YN, Shan QY, Lu KD, et al. Renal tubular epithelial cell quality control mechanisms as therapeutic targets in renal fibrosis[J]. J Pharm Anal, 2024, 14(8): 100933.
[34] Ovens AJ, Scott JW, Langendorf CG, et al. Post-translational modifications of the energy guardian AMP-activated protein kinase[J]. Int J Mol Sci, 2021, 22(3): 1229.
[35] Steinberg GR, Hardie DG. New insights into activation and function of the AMPK[J]. Nat Rev Mol Cell Biol, 2023, 24(4): 255-272.
[36] Barbhuiya PA, Yoshitomi R, Pathak MP. Understanding the link between sterol regulatory element binding protein (SREBPs) and metabolic dysfunction associated steatotic liver disease (MASLD)[J]. Curr Obes Rep, 2025, 14(1): 36.
[37] Libby AE, Jones B, Lopez-Santiago I, et al. Nuclear receptors in the kidney during health and disease[J]. Mol Aspects Med, 2021, 78: 100935.
[38] Li JZ, Yang YJ, Li QM, et al. STAT6 contributes to renal fibrosis by modulating PPARα-mediated tubular fatty acid oxidation[J]. Cell Death Dis, 2022, 13(1): 66.
[39] Jin L, Hua H, Ji Y, et al. Anti-inflammatory role of fenofibrate in treating diseases[J]. Biomol Biomed, 2023, 23(3): 376-391.
[40] Li SY, Mariappan N, Megyesi J, et al. Proximal tubule PPARα attenuates renal fibrosis and inflammation caused by unilateral ureteral obstruction[J]. Am J Physiol Renal Physiol, 2013, 305(5): F618-F627.
[41] Tan HWS, Anjum B, Shen HM, et al. Lysosomal inhibition attenuates peroxisomal gene transcription via suppression of PPARA and PPARGC1A levels[J]. Autophagy, 2019, 15(8): 1455-1459.
[42] Zhang LW, Liu J, Zhou FF, et al. PGC-1α ameliorates kidney fibrosis in mice with diabetic kidney disease through an antioxidative mechanism[J]. Mol Med Rep, 2018, 17(3): 4490-4498.
[43] Nam BY, Jhee JH, Park J, et al. PGC-1α inhibits the NLRP3 inflammasome via preserving mitochondrial viability to protect kidney fibrosis[J]. Cell Death Dis, 2022, 13(1): 31.
[44] Yang XP, Liu QH, Li YP, et al. The diabetes medication canagliflozin promotes mitochondrial remodelling of adipocyte via the AMPK-Sirt1-Pgc-1α signalling pathway[J]. Adipocyte, 2020, 9(1): 484-494.
[45] Huang QW, Chen HB, Yin K, et al. Formononetin attenuates renal tubular injury and mitochondrial damage in diabetic nephropathy partly via regulating Sirt1/PGC-1α pathway[J]. Front Pharmacol, 2022, 13: 901234.
[46] Opazo-Ríos L, Mas S, Marín-Royo G, et al. Lipotoxicity and diabetic nephropathy: novel mechanistic insights and therapeutic opportunities[J]. Int J Mol Sci, 2020, 21(7): 2632.
[47] Giardini E, Moore D, Sadlier D, et al. The dual role of lipids in chronic kidney disease: Pathogenic culprits and therapeutic allies[J]. Atherosclerosis, 2024, 398: 118615.
[48] Lin JW, Cheng A, Cheng K, et al. New insights into the mechanisms of pyroptosis and implications for diabetic kidney disease[J]. Int J Mol Sci, 2020, 21(19): 7057.
[49] Luo C, Urgard E, Vooder T, et al. The role of COX-2 and Nrf2/ARE in anti-inflammation and antioxidative stress: Aging and anti-aging[J]. Med Hypotheses, 2011, 77(2): 174-178.
[50] Patel VA, Massenburg D, Vujicic S, et al. Apoptotic cells activate AMP-activated protein kinase (AMPK) and inhibit epithelial cell growth without change in intracellular energy stores[J]. J Biol Chem, 2015, 290(37): 22352-22369.
[51] Wang N, Zhang C. Oxidative stress: a culprit in the progression of diabetic kidney disease[J]. Antioxidants (Basel), 2024, 13(4): 455.
[52] Li HY, Oh YS, Choi JW, et al. Blocking lysophosphatidic acid receptor 1 signaling inhibits diabetic nephropathy in db/db mice[J]. Kidney Int, 2017, 91(6): 1362-1373.
[53] Zhang XW, Ritter JK, Li NJ. Sphingosine-1-phosphate pathway in renal fibrosis[J]. Am J Physiol Renal Physiol, 2018, 315(4): F752-F756.

Submission Received:2025-02-03/**Revised:**2025-06-28

·研究进展·

能量代谢异常在糖尿病肾小管损伤中的研究进展

杨丽萍，　苏晓乐，　王利华
山西医科大学第二医院肾内科，山西 太原 030001

摘要：能量代谢与多种疾病的发生密切相关。随着糖尿病的患病率的逐年上升，糖尿病肾病作为糖尿病常见的血管并发症，其发病率也呈上升趋势。过去肾小球损伤被认为是糖尿病肾病的主要发病机制，但越来越多的证据表明肾小管损伤是引起糖尿病肾病发生的重要因素。糖尿病肾小管损伤中存在细胞能量代谢异常现象，提示能量代谢异常在糖尿病肾小管损伤发生与发展中的潜在作用。本文就近年来能量代谢异常在糖尿病肾小管损伤中的病理生理机制进行综述。

关键词：能量代谢；糖尿病；糖尿病肾脏病；肾小管损伤；脂质代谢；磷脂代谢
中图分类号：R587.1　R692.6　**文献标识码：**A　**文章编号：**1674-8182(2025)09-1314-05

Aberrant energy metabolism in diabetic renal tubular injury

YANG Liping, SU Xiaole, WANG Lihua
Nephrology Department, Second Hospital of Shanxi Medical University, Taiyuan, Shanxi 030001, China
Corresponding author: WANG Lihua, E-mail: lihuawang236@126.com

Abstract: Energy metabolism is closely related to the development of various diseases. With the increasing prevalence of diabetes year by year, diabetic kidney disease (DKD), as a common vascular complication of diabetes, is also on the rise. In the past, glomerular injury was considered as the main pathogenesis of DKD, but more and more evidence shows that renal tubular injury is an important factor that causes DKD. There is aberrant cellular energy metabolism in renal tubular injury in diabetes, suggesting that aberrant energy metabolism may play a potential role in the development and progression of renal tubular injury in diabetes. This article reviews the pathophysiological mechanism of aberrant energy metabolism in diabetic renal tubular injury in recent years.

Keywords: Energy metabolism; Diabetes; Diabetic kidney disease; Renal tubular injury; Lipid metabolism; Phospholipid metabolism

据国际糖尿病联合会2021年发布的数据，全球范围内20~79岁的成年人中约5.37亿患有糖尿病，预计到2045年将上升至7.83亿[1]。糖尿病肾病(diabetic kidney disease，DKD)是糖尿病常见的微血管并发症之一，也是慢性肾脏疾病和终末期肾脏疾病的主要原因。

目前的研究表明，肾小管损伤可能先于DKD早期肾小球改变[2]。在早期糖尿病患者的尿液中可以检测到一些近端肾小管细胞损伤的标志物，而此时肾小球没有明显损伤，说明近端肾小管损伤是一种早期病变[3]。动物实验研究发现，近端肾小管沉默信息调节因子1(silence information regulator 1，SIRT1)表达下调会加剧糖尿病小鼠肾小球的变化，影响肾小球功能[4]。

近端小管是发生重吸收作用的主要场所，需要大量的三磷酸腺苷(adenosine triphosphate，ATP)来维持正常的生理功能，更容易受到糖尿病相关的各种代谢和血流动力学因素的影响。在糖尿病情况下，线粒体功能受损，有氧糖酵解途径增强以提供足够能量维持肾小管功能[5]。目前糖尿病肾小管损伤的异常能量代谢过程逐渐成为研究热点，本文就近年来能量代谢异常在糖尿病肾小管损伤中的病理生理机制进行综述。

1　正常生理状态下肾小管细胞的能量代谢

细胞正常生理活动需要大量能量来驱动，线粒体则是细胞产生能量的结构基础，肾脏的绝大部分线粒体集中在肾小管上皮细胞所在的肾皮质区[6]，因此，肾小管上皮细胞(tubular epithelial cells，TECs)是肾脏进行能量代谢的核心场所。在正常生理状态下，TECs的能量代谢主要依赖于线粒体中的脂肪酸氧化(fatty acid oxidation，FAO)来产生ATP，而不是通过糖酵解途径产生ATP满足其能量需求。这可能归功于TECs中与FAO相关的酶含量丰富，而调节糖酵解的关键酶含量却很低，而且这种方式也较葡萄糖氧化更加高效[7-8]。

2　糖尿病状态下肾小管细胞的能量代谢

高糖状态下，较多的葡萄糖进入TECs线粒体氧化呼吸

DOI:10.13429/j.cnki.cjcr.2025.09.004
通信作者：王利华，E-mail：lihuawang236@126.com
出版日期：2025-09-20

QR code for English version

链，促进氧自由基的产生与释放，进一步促进细胞凋亡，高糖还可以导致多元醇途径的激活并产生大量山梨醇，进一步导致TECs受损，线粒体功能障碍，细胞能量代谢发生改变[9]。转录组学显示在高糖状态下TECs的脂肪酸、葡萄糖以及氨基酸代谢相关基因表达均减少，但脂肪酸代谢相关酶及调节因子的表达尤其下调，进而导致肾小管细胞FAO减弱[10]。肾小管细胞的能量来源由线粒体氧化磷酸化转变为葡萄糖有氧糖酵解途径，以适应TECs能量代谢障碍，此过程被称为代谢重编程，最早由Warburg[11]提出并发现于肿瘤细胞中，而该现象也被发现于多种非肿瘤细胞中发挥重要作用。然而，高糖状态下TECs的代谢重编程可能会促进肾脏纤维化的发展，因此，早期恢复TECs正常的能量代谢成为了治疗DKD的新策略[12]。

2.1　肾小管细胞的糖代谢　在高糖状态下，肾小管细胞可通过有氧糖酵解代谢葡萄糖产生ATP维持正常生理功能，但该过程中相关的酶和调节因子表达异常也会加重TECs的损害和线粒体功能障碍[13]。目前研究比较多的是单磷酸腺苷（adenosine monophosphate，AMP）活化的蛋白激酶（AMP-activated protein kinase，AMPK）和丙酮酸激酶M2（pyruvate kinase isozyme type M2，PKM2）。

2.1.1　AMPK　AMPK是一种主要的细胞能量传感器，可在能量消耗的状态下被激活。在糖尿病小鼠的肾脏模型中发现AMPK活性降低，其下游的过氧化物酶体增殖物激活受体γ辅激活因子-1α（peroxisome proliferator-activated receptor γ coactivator-1α，PGC-1α）呈抑制状态[14]，可能是由于糖尿病导致肾小管细胞有氧糖酵解产生ATP的速率加快，从而降低了AMPK活性并抑制PGC-1α的表达[15]。该动物研究还发现糖尿病小鼠肾脏线粒体生物合成及超氧化物产生减少，与葡萄糖氧化减少相一致，而AMPK的激活增强了超氧化物的产生和线粒体功能，同时减轻了肾脏损伤。另一方面，鞘磷脂及其代谢产物在细胞活动中发挥重要作用，在糖尿病小鼠模型中发现系膜细胞中积聚的鞘磷脂可抑制AMPK和PGC-1α的活性，并增加乳酸和ATP的产生[16]，这提示在DKD中，鞘磷脂的合成代谢促进了有氧糖酵解途径和ATP的快速合成，进而抑制AMPK和PGC-1α通路，导致线粒体功能障碍和氧化应激，最终加重肾脏组织损伤。

2.1.2　PKM2　PKM2是糖酵解过程中的限速酶，能以无活性的四聚体状态或活性单体或二聚体状态存在于细胞内[17]。在DKD背景下，PKM2发生磷酸化，四聚体状态异构为二聚体状态，促进信号转导因子和转录激活因子（signal transducer and activator of transcription，STAT）3和核因子κB（nuclear factor kappa-B，NF-κB）磷酸化以及细胞间黏附分子-1的表达，从而启动炎症细胞浸润，促进DKD的进展。PKM2还可以促进真核生物翻译起始因子2-α激酶2的磷酸化，进而激活核苷酸结合寡聚化结构域样受体蛋白（nucleotide-binding oligomerization domain-like receptor protein，NLRP）3和黑色素瘤缺乏因子2介导的炎症小体，从而促进巨噬细胞激活，并释放炎症因子，在DKD进展中发挥重要作用[18]。研究人员也证实了可通过抑制PKM2磷酸化抑制肾脏炎症反应，进而预防DKD的发生[19]。Qi等[20]的一项研究发现，PKM2激活增加糖酵解通量，降低山梨醇和甲基乙二醛等毒性葡萄糖代谢物水平，增加线粒体生物发生、增强线粒体代谢来改善甚至逆转线粒体功能障碍，进而延缓DKD进展。因此，PKM2可能成为干扰DKD发生发展的一个重要靶点。

2.2　肾小管细胞的脂代谢　在DKD患者的肾脏病理组织中发现细胞中有大量脂质蓄积，与脂质代谢相关的一些调节因子的改变导致脂质的异常堆积，进而影响肾功能[21]。一项对DKD大鼠早期肾皮质脂质组分析的研究发现肾脏中存在明显的脂质组特征。在DKD大鼠肾皮质中，包括三酰甘油、二酰甘油、游离脂肪酸和胆固醇酯在内的中性脂质和溶血磷脂的水平升高，而以磷脂酰乙醇胺（phosphatidylethanolamine，PE）为主的大多数磷脂水平呈下降趋势，鞘脂类包括神经酰胺及其衍生物大部分呈升高趋势[22]。高糖环境下，肾小管细胞脂质代谢的紊乱将进一步影响TECs功能，其主要与脂质的摄取、代谢和合成不平衡、脂质积累以及相关磷脂代谢的失衡有关。

2.2.1　脂肪酸摄入增加　TECs主要通过位于细胞表面的脂肪酸转运蛋白CD36摄取脂肪酸。研究发现，高糖可诱导DKD患者肾脏近端小管中CD36 mRNA和蛋白表达上调，增强了脂肪酸的摄取，引起脂质堆积影响肾功能[23]。上调的CD36可导致NLRP3和NF-κB信号通路的激活，促进炎症反应，加重肾脏损伤[24-27]。因此，可以合理猜测，在糖尿病早期可以通过抑制CD36的表达减少TECs的脂肪酸摄取及炎症反应激活，减少脂质积累，改善肾小管损伤。

2.2.2　脂肪酸合成增加　脂肪酸合成过程受固醇调节元件结合蛋白（sterol regulatory-element binding proteins，SREBPs）的调节，SREBPs在脂质稳态调节中发挥重要作用，SREBPs有三种不同亚型，即SREBP-1a、SREBP-1c和SREBP-2，分别与脂肪酸、三酰甘油和胆固醇合成相关[28]。在高糖条件下，SREBPs的表达被激活，促进乙酰辅酶A羧化酶（acetyl-CoA carboxylase，ACC）和脂肪酸合成酶的表达，最终导致脂肪酸合成增加[29]。在肾脏过表达SREBP-1a的转基因小鼠中发现，SREBP表达的增加通过增加转化生长因子β（transforming growth factor-β，TGF-β）和血管内皮生长因子的表达，导致脂质合成增加和脂质积累[30]。SREBPs还可以诱导TGF-β转录活性以及通过与纤维化相关基因（即TGF-β）的启动子区域结合，激活TGF-β/果蝇母本抗生存因子（small mother against decapentaplegic，Smad）纤维化信号通路，进一步导致肾损伤[31]。

胆固醇摄入及合成的增加也会促进DKD的进展。SREBP2可以促进低密度脂蛋白受体、CD36、清道夫受体A、血凝素样氧化型低密度脂蛋白受体1（lectin-like oxidized low-density lipoprotein receptor-1，LOX-1）等受体摄入胆固醇并促进羟甲基戊二酰辅酶A（hydroxy methylglutaryl coenzyme A，HMG-CoA）还原酶合成胆固醇[31]。胆固醇逆转运可以将外周组织多余的胆固醇转运至肝脏，最后经过代谢排出体外，是一种重要的胆固醇清除机制，在DKD患者及糖尿病小鼠模型中发现了胆固醇外流率降低和胆固醇逆转运相关的基因表达下调，表明胆固醇的逆转运与DKD相关[32]。

2.2.3　脂肪酸氧化代谢异常　DKD患者肾脏FAO能力明显

减弱，在DKD患者以及DKD小鼠模型中均发现与脂肪酸代谢相关酶和调节因子的表达明显下调[32]。抑制TECs的脂肪酸氧化可引起ATP耗竭、细胞死亡、去分化和细胞内脂质积累，并观察到纤维化表型[33]。因FAO减弱而导致脂质蓄积与DKD发展密不可分，该过程中一些酶及调节因子发挥重要作用。

AMPK是一种异三聚体蛋白激酶，除参与上述DKD的糖代谢过程外，还参与脂质代谢通路的调节，其亚基的磷酸化在其中发挥重要作用[34]。FAO过程中重要的限速酶——肉碱棕榈酰转移酶1（carnitine palmityl transferase 1，CPT-1），其活性受AMPK-ACC-丙二酰辅酶A轴的调节。AMPK激活通过抑制ACC磷酸化致使其失活，ACC失活后导致其下游的丙二酰辅酶A生成减少，其对于CPT-1的抑制作用减弱，从而发挥促进FAO的作用，减少脂毒性[35]。此外，AMPK抑制脂质代谢的其他靶点包括磷酸化SREBP1c（编码ACC的转录因子）和抑制SREBP1c的表达等[36]。因此，推测加强AMPK的激活可能成为DKD治疗中的新靶点。

过氧化物酶体增殖物激活受体α（peroxisome proliferator-activated receptor α，PPAR-α）是配体激活转录因子的核受体家族之一，主要在近端肾小管及髓袢升支中表达[37]。参与FAO过程中的大多数酶均受PPAR-α调节，目前认为，PPAR-α是维持脂肪酸氧化代谢平衡的重要转录调节因子。在高糖条件下，PPAR-α的表达可能会受到抑制，导致FAO减少，进而可能加剧TECs的损伤和炎症反应。动物实验研究发现STAT6可通过位于蛋白质启动子区域的sis诱导元件转录抑制PPAR-α及其FAO相关靶基因的表达，促进肾纤维化的发展[38]。PPAR-α激动剂非诺贝特可以通过激活PPAR-α降低DKD大鼠炎症因子表达，进而抑制NF-κB的促炎途径，改善脂质积累，并防止肾小管间质纤维化，对肾脏起到保护作用[39]。另一项研究发现，近端肾小管PPAR-α通过减少上皮细胞内TGF-β和细胞外基质蛋白的产生，减轻单侧输尿管梗阻模型小鼠的肾纤维化和炎症[40]。由于DKD及梗阻性肾病是诱发肾脏纤维化的主要病因之一，近端肾小管PPAR-α是否可以通过上述途径减缓DKD肾脏纤维化有待进一步研究。因此，激活PPAR-α可能成为减轻DKD肾脏炎症及纤维化进而控制肾损伤的有效方法。

PGC-1α是一种转录因子，可调节线粒体的生物发生以及FAO途径中多数限速酶的表达，在DKD患者的肾小管中发现PGC-1α的mRNA表达水平显著降低[17]。线粒体FAO过程中的基因除受PPAR-α调控外，PGC-1α也是其重要的调节因子[41]。PGC-1α的表达增加可以减少活性氧的产生和抑制NLRP3炎症小体的激活等机制，保护TECs并延缓肾间质纤维化进展[42-43]。研究发现，SIRT1通过去乙酰化PGC-1α，上调其转录共激活功能，进而促进线粒体生物合成和能量代谢，而SIRT1同时受AMPK调节[44]。此外，PGC-1α通过调节线粒体动力学相关蛋白以及凋亡相关蛋白的表达，来抑制细胞凋亡，减轻TECs损伤[45]。目前的研究表明，PGC-1α在糖尿病肾小管损伤中通过多种机制发挥作用，包括线粒体保护、抗氧化、能量代谢调节、抗炎和抑制细胞凋亡等，可能成为DKD治疗的潜在靶点。

2.2.4　脂质蓄积　在糖尿病中，肾小管细胞对脂肪酸摄取、氧化及合成代谢失衡，导致脂肪酸产生过剩，超过肾小管对脂肪酸的利用率，过量的脂肪酸伴随三酰甘油形成并沉积于肾小管中，像这种非脂肪组织中的脂质异常蓄积可导致细胞稳态失调和细胞损伤，该现象称为脂毒性[46]。过量的脂质蓄积导致TECs线粒体功能障碍，细胞能量代谢异常，进而出现氧化应激、炎症反应、TECs凋亡以及肾小管间质纤维化等一系列肾脏损伤表现[47]。

脂质积累可通过多种机制导致肾脏损伤。首先，脂质的累积可使肾小管细胞的线粒体结构破坏，影响线粒体呼吸链中酶的活性，引起氧自由基增多，产生大量活性氧，活性氧作为信号分子可激活细胞外信号调节激酶（extracellular regulated protein kinases，ERK）、丝裂原活化蛋白激酶（p38 mitogen-activated protein kinase，MAPK）通路，调节NF-κB的活化，启动炎症因子包括环氧合酶2、肿瘤坏死因子α、白细胞介素（interleukin，IL）-1β和IL-18等基因的转录，使炎症细胞聚集，诱导炎症反应。其次，活性氧还可以活化磷脂酰肌醇3-激酶（phosphatidylinositol-3-kinase，PI3K）通路及其下游蛋白激酶B和ERK1/2，激活炎症复合体NLRP3，活化caspase1导致炎症性细胞死亡[48-49]。再者，线粒体结构破坏，氧化磷酸化过程受阻，ATP生成减少，激活AMPK-γ，进而激活其下游P53蛋白，诱导细胞表达Bax和Bak。调节线粒体释放细胞色素C，在活性氧的参与下最终导致细胞凋亡[50]。此外，活性氧还可诱导TGF-β、纤溶酶原激活物抑制因子-1（plasminogen activator inhibitor-1，PAI-1）等促纤维形成因子的表达，进而促进肾小管间质纤维化，加剧肾小管损伤[51]。

3　磷脂代谢异常

近年来，磷脂及其代谢产物在肾脏疾病中的作用引起关注。磷脂在自然界中普遍存在，承担着重要的生理功能，在维持细胞膜稳定性以及调节细胞信号转导过程中发挥重要作用。

对早期DKD大鼠的肾皮质脂质组进行分析，发现磷脂代谢显著改变，表现为以PE为主的多数磷脂的降低，而PE可以通过调节脂质代谢、参与细胞信号传导、影响肾脏纤维化进程、维持细胞膜稳定性和功能等共同影响DKD的进展[22]。溶血磷脂酸（lysophosphatidic acids，LPA）作为一种天然存在的甘油磷脂，可以通过与溶血磷脂酸受体（lysophosphatidic acids receptor，LPAR）结合来调节各种生物反应。研究发现，在糖尿病小鼠模型中LPAR1的表达显著升高，而抑制LPAR1的表达减轻了糖尿病肾损伤[52]。鞘磷脂及其代谢产物在肾脏疾病中的作用也被广泛研究，鞘氨醇-1-磷酸（sphingosine-1-phosphate，S1P）是纤维化疾病的重要调节因子，由鞘氨醇激酶（sphingosine kinase，SPHK）磷酸化鞘氨醇产生，作用于S1P受体（S1P receptors，S1PRs）发挥作用。SPHK1-S1P-S1PRs轴在肾间质纤维化的发生、发展中发挥着重要作用，S1P通过作用于S1PR2激活Rho激酶，诱导TECs分化为肌成纤维细胞表型，促进DKD病程中的肾间质纤维化进展[53]。但目前关于磷脂代谢在DKD肾小管损伤中的作用机制的研究仍有大量问

题需进一步探索，以寻找DKD治疗的新靶点。

4 总　结

TECs是肾脏能量代谢中心。在高糖状态下，TECs损伤，其能量代谢方式发生转变，由FAO转向有氧糖酵解途径供能以维持肾小管正常的生理功能。TECs的脂肪酸转运蛋白CD36的表达显著上调，脂肪酸摄取增多，调控脂肪酸合成的SREBPs表达增加，参与TECs的FAO的关键调节因子AMPK、PPAR-α、PGC-1α的表达及活性下降，导致FAO减少，加剧肾脏脂质蓄积，导致线粒体功能障碍，细胞能量代谢失衡，引起氧化应激、炎症反应、肾小管细胞凋亡以及肾间质纤维化等一系列损伤，进一步加重肾小管损伤。同时，与有氧糖酵解相关的酶PKM2被激活并通过调节下游信号PGC-1α来改善线粒体的生物发生及功能，维持细胞能量代谢的平衡。目前，关于磷脂代谢异常引发糖尿病肾小管损伤的相关机制还有待进一步深入研究，以期为防治糖尿病肾小管损伤的发生与发展提供治疗新思路。

利益冲突　无

参考文献

[1] Hossain MJ, Al-Mamun M, Islam MR. Diabetes mellitus, the fastest growing global public health concern: Early detection should be focused[J]. Health Sci Rep, 2024, 7(3):e2004.

[2] Ugarte F, Santapau D, Gallardo V, et al. Urinary extracellular vesicles as a source of NGAL for diabetic kidney disease evaluation in children and adolescents with type 1 diabetes mellitus[J]. Front Endocrinol, 2021, 12: 654269.

[3] Chen JC, Wang XY, He Q, et al. YAP activation in renal proximal tubule cells drives diabetic renal interstitial fibrogenesis[J]. Diabetes, 2020, 69(11): 2446-2457.

[4] Hasegawa K, Wakino S, Simic P, et al. Renal tubular Sirt1 attenuates diabetic albuminuria by epigenetically suppressing Claudin-1 overexpression in podocytes[J]. Nat Med, 2013, 19(11): 1496-1504.

[5] Yao L, Liang XH, Qiao YJ, et al. Mitochondrial dysfunction in diabetic tubulopathy[J]. Metabolism, 2022, 131: 155195.

[6] Bugarski M, Martins JR, Haenni D, et al. Multiphoton imaging reveals axial differences in metabolic autofluorescence signals along the kidney proximal tubule[J]. Am J Physiol Renal Physiol, 2018, 315(6): F1613-F1625.

[7] Console L, Scalise M, Giangregorio N, et al. The link between the mitochondrial fatty acid oxidation derangement and kidney injury [J]. Front Physiol, 2020, 11: 794.

[8] Gewin LS. Sugar or fat? Renal tubular metabolism reviewed in health and disease[J]. Nutrients, 2021, 13(5): 1580.

[9] 陈莉明. 聚焦肾小管损伤在糖尿病肾脏病诊治中的价值[J]. 中华糖尿病杂志, 2021, 13(10): 921-925.

[10] Lee LE, Doke T, Mukhi D, et al. The key role of altered tubule cell lipid metabolism in kidney disease development [J]. Kidney Int, 2024, 106(1): 24-34.

[11] Warburg O. On the origin of cancer cells[J]. Science, 1956, 123 (3191): 309-314.

[12] 朱子敬, 陈星华, 丁国华. 肾小管上皮细胞能量代谢障碍在急性肾损伤中作用的研究进展[J]. 中华肾脏病杂志, 2020, 36 (12): 965-969.

[13] Zhang GS, Darshi M, Sharma K. The Warburg effect in diabetic kidney disease[J]. Semin Nephrol, 2018, 38(2): 111-120.

[14] She YQ, Yu M, Wang L, et al. Emerging protective actions of PGC-1α in diabetic nephropathy [J]. Oxid Med Cell Longev, 2022, 2022: 6580195.

[15] Ye KL, Zhao YL, Huang W, et al. Sodium butyrate improves renal injury in diabetic nephropathy through AMPK/SIRT1/PGC-1α signaling pathway[J]. Sci Rep, 2024, 14(1): 17867.

[16] Miyamoto S, Hsu CC, Hamm G, et al. Mass spectrometry imaging reveals elevated glomerular ATP/AMP in diabetes/obesity and identifies sphingomyelin as a possible mediator [J]. EBioMedicine, 2016, 7: 121-134.

[17] Kuo CW, Chen DH, Tsai MT, et al. Pyruvate kinase M2 modification by a lipid peroxidation byproduct acrolein contributes to kidney fibrosis[J]. Front Med, 2023, 10: 1151359.

[18] Park YS, Han JH, Park JH, et al. Pyruvate kinase M2: a new biomarker for the early detection of diabetes-induced nephropathy[J]. Int J Mol Sci, 2023, 24(3): 2683.

[19] Chen DQ, Han J, Liu H, et al. Targeting pyruvate kinase M2 for the treatment of kidney disease[J]. Front Pharmacol, 2024, 15: 1376252.

[20] Qi WE, Keenan HA, Li Q, et al. Pyruvate kinase M2 activation may protect against the progression of diabetic glomerular pathology and mitochondrial dysfunction[J]. Nat Med, 2017, 23(6): 753-762.

[21] Tu QM, Jin HM, Yang XH. Lipid abnormality in diabetic kidney disease and potential treatment advancements[J]. Front Endocrinol, 2025, 16: 1503711.

[22] Hou BY, He P, Ma P, et al. Comprehensive lipidome profiling of the kidney in early-stage diabetic nephropathy[J]. Front Endocrinol, 2020, 11: 359.

[23] Schelling JR. The contribution of lipotoxicity to diabetic kidney disease[J]. Cells, 2022, 11(20): 3236.

[24] Hou YJ, Wang Q, Han BS, et al. CD36 promotes NLRP3 inflammasome activation via the mtROS pathway in renal tubular epithelial cells of diabetic kidneys[J]. Cell Death Dis, 2021, 12(6): 523.

[25] Chen YL, Zhang J, Cui WG, et al. CD36, a signaling receptor and fatty acid transporter that regulates immune cell metabolism and fate[J]. J Exp Med, 2022, 219(6): e20211314.

[26] Shahzad K, Fatima S, Khawaja H, et al. Podocyte-specific Nlrp3 inflammasome activation promotes diabetic kidney disease[J]. Kidney Int, 2022, 102(4): 766-779.

[27] Li XH, Dong X, Zhang LY, et al. Astragaloside Ⅳ attenuates renal tubule injury in DKD rats via suppression of CD36-mediated NLRP3 inflammasome activation[J]. Front Pharmacol, 2024, 15: 1285797.

[28] Xu XF, Jin WM, Chang RY, et al. Research progress of SREBP and its role in the pathogenesis of autoimmune rheumatic diseases [J]. Front Immunol, 2024, 15: 1398921.

[29] Wang Y, Liu TT, Wu Y, et al. Lipid homeostasis in diabetic kidney disease[J]. Int J Biol Sci, 2024, 20(10): 3710-3724.

[30] Wang TN, Chen X, Li RZ, et al. SREBP-1 mediates angiotensin Ⅱ-induced TGF-β1 upregulation and glomerular fibrosis [J]. J Am Soc Nephrol, 2015, 26(8): 1839-1854.

[31] Dorotea D, Koya D, Ha H. Recent insights into SREBP as a direct mediator of kidney fibrosis vialipid-independent pathways [J]. Front Pharmacol, 2020, 11: 265.

[32] Rong J, Zhang ZX, Peng XY, et al. Mechanisms of hepatic and renal injury in lipid metabolism disorders in metabolic syndrome[J]. Int J Biol Sci, 2024, 20(12): 4783-4798.

[33] Bao YN, Shan QY, Lu KD, et al. Renal tubular epithelial cell quality control mechanisms as therapeutic targets in renal fibrosis[J]. J Pharm Anal, 2024, 14(8): 100933.

[34] Ovens AJ, Scott JW, Langendorf CG, et al. Post-translationalmodifications of the energy guardian AMP-activated protein kinase[J].

Int J Mol Sci, 2021, 22(3): 1229.
[35] Steinberg GR, Hardie DG. New insights into activation and function of the AMPK[J]. Nat Rev Mol Cell Biol, 2023, 24(4): 255-272.
[36] Barbhuiya PA, Yoshitomi R, Pathak MP. Understanding the link between sterol regulatory element binding protein (SREBPs) and metabolic dysfunction associated steatoticliver disease (MASLD)[J]. Curr Obes Rep, 2025, 14(1): 36.
[37] Libby AE, Jones B, Lopez-Santiago I, et al. Nuclear receptors in the kidney during health and disease[J]. Mol Aspects Med, 2021, 78: 100935.
[38] Li JZ, Yang YJ, Li QM, et al. STAT6 contributes to renal fibrosis by modulating PPARα-mediated tubular fatty acid oxidation[J]. Cell Death Dis, 2022, 13(1): 66.
[39] Jin L, Hua H, Ji Y, et al. Anti-inflammatory role of fenofibrate in treating diseases[J]. Biomol Biomed, 2023, 23(3): 376-391.
[40] Li SY, Mariappan N, Megyesi J, et al. Proximal tubule PPARα attenuates renal fibrosis and inflammation caused by unilateral ureteral obstruction[J]. Am J Physiol Renal Physiol, 2013, 305(5): F618-F627.
[41] Tan HWS, Anjum B, Shen HM, et al. Lysosomal inhibition attenuates peroxisomal gene transcription via suppression of PPARA and PPARGC1A levels[J]. Autophagy, 2019, 15(8): 1455-1459.
[42] Zhang LW, Liu J, Zhou FF, et al. PGC-1α ameliorates kidney fibrosis in mice with diabetic kidney disease through an antioxidative mechanism[J]. Mol Med Rep, 2018, 17(3): 4490-4498.
[43] Nam BY, Jhee JH, Park J, et al. PGC-1α inhibits the NLRP3 inflammasome via preserving mitochondrial viability to protect kidney fibrosis[J]. Cell Death Dis, 2022, 13(1): 31.
[44] Yang XP, Liu QH, Li YP, et al. The diabetes medication canagliflozin promotes mitochondrial remodelling of adipocyte via the AMPK-Sirt1-Pgc-1α signalling pathway[J]. Adipocyte, 2020, 9(1): 484-494.
[45] Huang QW, Chen HB, Yin K, et al. Formononetin attenuates renal tubular injury and mitochondrial damage in diabetic nephropathy partly viaregulating Sirt1/PGC-1α pathway[J]. Front Pharmacol, 2022, 13: 901234.
[46] Opazo-Ríos L, Mas S, Marín-Royo G, et al. Lipotoxicity and diabetic nephropathy: novel mechanistic insights and therapeutic opportunities[J]. Int J Mol Sci, 2020, 21(7): 2632.
[47] Giardini E, Moore D, Sadlier D, et al. The dual role of lipids in chronic kidney disease: Pathogenic culprits and therapeutic allies[J]. Atherosclerosis, 2024, 398: 118615.
[48] Lin JW, Cheng A, Cheng K, et al. Newinsights into the mechanisms of pyroptosis and implications for diabetic kidney disease[J]. Int J Mol Sci, 2020, 21(19): 7057.
[49] Luo C, Urgard E, Vooder T, et al. The role of COX-2 and Nrf2/ARE in anti-inflammation and antioxidative stress: Aging and anti-aging[J]. Med Hypotheses, 2011, 77(2): 174-178.
[50] Patel VA, Massenburg D, Vujicic S, et al. Apoptotic cells activate AMP-activated protein kinase (AMPK) and inhibit epithelial cell growth without change in intracellular energy stores[J]. J Biol Chem, 2015, 290(37): 22352-22369.
[51] Wang N, Zhang C. Oxidative stress: aculprit in the progression of diabetic kidney disease[J]. Antioxidants (Basel), 2024, 13(4): 455.
[52] Li HY, Oh YS, Choi JW, et al. Blocking lysophosphatidic acid receptor 1 signaling inhibits diabetic nephropathy in db/db mice[J]. Kidney Int, 2017, 91(6): 1362-1373.
[53] Zhang XW, Ritter JK, Li NJ. Sphingosine-1-phosphate pathway in renal fibrosis[J]. Am J Physiol Renal Physiol, 2018, 315(4): F752-F756.

收稿日期:2025-02-03 **修回日期**:2025-06-28 **编辑**:王国品

(上接第1313页)

[40] Söderberg D, Kurz T, Motamedi A, et al. Increased levels of neutrophil extracellular trap remnants in the circulation of patients with small vessel vasculitis, but an inverse correlation to anti-neutrophil cytoplasmic antibodies during remission[J]. Rheumatology, 2015, 54(11): 2085-2094.
[41] Kessenbrock K, Krumbholz M, Schönermarck U, et al. Netting neutrophils in autoimmune small-vessel vasculitis[J]. Nat Med, 2009, 15(6): 623-625.
[42] Sethi S, Fervenza FC. Membranous nephropathy-diagnosis and identification of target antigens[J]. Nephrol Dial Transplant, 2024, 39(4): 600-606.
[43] Ismail G, Mircescu G, Ditoiu AV, et al. Risk factors for predicting venous thromboembolism in patients with nephrotic syndrome: focus on haemostasis-related parameters[J]. Int Urol Nephrol, 2014, 46(4): 787-792.
[44] Gao CY, Xie R, Yu CY, et al. Procoagulant activity of erythrocytes and platelets through phosphatidylserine exposure and microparticles release in patients with nephrotic syndrome[J]. Thromb Haemost, 2012, 107(4): 681-689.
[45] 刘思远, 李志鹏, 郑心. 乙肝肾的研究进展[J]. 黑龙江中医药, 2016, 45(6): 70-72.
[46] 刘华锋, 郭赟, 洪涛. 乙肝感染与肾脏疾病防治现状及研究进展[J]. 中国中西医结合肾病杂志, 2024, 25(1): 1-3.
[47] 王瑞石, 刘志红, 陈燕, 等. 肾小球膜性病变的病因分析及流行病学特点[J]. 肾脏病与透析肾移植杂志, 2006, 15(5): 416-421, 437
[48] Monova DV, Todorov T, Monov S. Risk factors associated with outcomes in patients with Henoch-Schönlein purpura nephritis[J]. Nephrol Dial Transplant, 2023, 38(Supplement_1): gfad063c_2777.
[49] 宋均亚. 儿童紫癜性肾炎风险预测模型的初步构建及消风散治疗过敏性紫癜的机制研究[D]. 济南: 山东中医药大学, 2020.
[50] 温杰, 杜三军, 王晓美, 等. 血清白三烯B4和白三烯E4联合检测对变应性紫癜肾炎及其预后的诊断价值[J]. 医学临床研究, 2018, 35(2): 314-316.
[51] Li JH, Tong DX, Wang Y, et al. Neutrophil extracellular traps exacerbate coagulation and endothelial damage in patients with essential hypertension and hyperhomocysteinemia[J]. Thromb Res, 2021, 197: 36-43.
[52] Konig MF, Andrade F. A critical reappraisal of neutrophil extracellular traps and NETosis mimics based on differential requirements for protein citrullination[J]. Front Immunol, 2016, 7: 461.
[53] van Dam LS, Rabelink TJ, van Kooten C, et al. Clinical implications of excessive neutrophil extracellular trap formation in renal autoimmune diseases[J]. Kidney Int Rep, 2019, 4(2): 196-211.

收稿日期:2024-07-19 **修回日期**:2024-12-08 **编辑**:石嘉莹