DOI: 10.53469/jcmp.2025.07(09).23

Advances in Traditional Chinese Medicine for the Treatment of Diabetic Nephropathy from the Perspective of Glycolipid Metabolism

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Abstract: ***Diabetic kidney disease (DKD) is a major and severe chronic complication of diabetes, with a multifactorial pathogenesis involving glycolipid metabolism disorders, inflammation, oxidative stress, and glomerular injury. Emerging evidence highlights glycolipid metabolism disorders as a central driver in the development and progression of DKD. In traditional Chinese medicine (TCM), DKD is classified under "Xiaoke-related kidney disease," "edema," and "deficiency-fatigue syndromes," with its pathogenesis characterized by deficiency in the spleen and kidney and excess due to phlegm-turbidity, blood stasis, and damp-heat. The concept of "internal obstruction by phlegm-turbidity" aligns with the pathological role of glycolipid disorders. Modern pharmacological and clinical studies further demonstrate that TCM interventions can regulate glycolipid metabolism, improve insulin resistance, and suppress inflammatory and oxidative stress pathways, thereby delaying renal damage. This review discusses the pathogenesis and progression of DKD from the perspective of glycolipid metabolism, providing a theoretical basis for the application of TCM in its treatment.***

Keywords: Diabetic nephropathy, Glycolipid metabolism, Western medicine pathogenesis, Traditional Chinese medicine theory, Traditional Chinese medicine therapy.

1. Introduction

Diabetic kidney disease (DKD), as one of the most serious microvascular complications of diabetes mellitus, has become the leading cause of end-stage renal disease (ESRD) worldwide [1]. According to the International Diabetes Federation, the number of people with diabetes is expected to reach 700 million globally by 2045, accounting for approximately 10.9% of the adult population [2]. Among them, about 40% will eventually progress to DKD [3].

The pathological alterations of DKD involve both metabolic and hemodynamic factors, including activation of the polyol pathway, hexosamine pathway, protein kinase C (PKC) pathway, and the formation of advanced glycation end products (AGEs). These processes induce intracellular signaling activation, oxidative stress, hypoxia, dysregulated autophagy, and epigenetic modifications, ultimately leading to renal inflammation and fibrosis [4]. Glycolipid metabolic abnormalities encompass both disordered glucose metabolism and lipid metabolism. Research has shown that the interplay between glucotoxicity and lipotoxicity exacerbates renal fibrosis and injury by activating these pathogenic pathways [5].

From the perspective of traditional Chinese medicine (TCM), DKD often arises from congenital deficiencies, improper diet, emotional disturbances, or invasion of exogenous pathogenic factors. Prolonged illness depletes qi and yin, damaging the internal organs and leading to the generation of pathological products such as phlegm, dampness, heat, and blood stasis. Literature indicates that the overarching pathogenesis of DKD is characterized by "deficiency in origin and excess in manifestation." The primary deficiency lies in yin deficiency, frequently accompanied by qi deficiency and yang deficiency, while the excess mainly manifests as damp-heat, phlegm-turbidity, and blood stasis. Professor Pi Chiheng [6] pointed out that throughout the course of DKD, prolonged spleen-kidney deficiency and internal dampness accumulation result in the formation of "turbidity," which constitutes a key pathological product throughout disease progression.

Clinically, glycolipid metabolic disorder, often manifested as hyperglycemia and hyperlipidemia, intensifies the onset and progression of DKD, easily generating phlegm-dampness and blood stasis within the body. Therefore, exploring DKD pathogenesis from the perspective of glycolipid metabolism provides important theoretical insights for TCM-based interventions.

2. Glucose Metabolism and Kidney Disease

The kidney participates in the regulation of systemic glucose homeostasis through three distinct mechanisms: (1) releasing glucose into circulation via gluconeogenesis; (2) utilizing glucose from the bloodstream to meet its own energy demands; and (3) reabsorbing glucose from glomerular filtrate [7]. In healthy individuals, urine is essentially glucose-free because nearly all filtered glucose is reabsorbed into circulation. As plasma glucose levels rise, glucose concentration in the glomerular filtrate increases linearly, and renal glucose reabsorption rises accordingly until reaching the maximum reabsorptive capacity (renal threshold). When plasma glucose exceeds this threshold, excessive glucose is excreted in urine, leading to glucosuria [8].

At this stage, the increased glomerular filtration of glucose stimulates enhanced proximal tubular reabsorption of both glucose and sodium, reducing sodium delivery to the macula densa in the distal tubules. This triggers dysregulation of the renin–angiotensin system, elevating intraglomerular pressure. Sustained intraglomerular hypertension exerts mechanical

stress on capillary walls, eventually causing glomerulosclerosis and peritubular capillary rarefaction. Simultaneously, excessive protein filtration into the tubule lumen and subsequent reabsorption by tubular cells induce the synthesis of pro-inflammatory and pro-fibrotic mediators, exacerbating renal injury [4].

Chronic hyperglycemia activates multiple metabolic pathways, including the polyol pathway, hexosamine pathway, PKC pathway, and AGEs-related pathways. These pathways promote the accumulation of reactive oxygen species (ROS), aggravating oxidative stress and mitochondrial damage [9].

2.1 Polyol Pathway

In the polyol pathway, excess glucose is reduced to sorbitol by aldose reductase (AR), accompanied by the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) to $NADP^+$ [10]. Sorbitol, being highly hydrophilic, is poorly metabolized and accumulates intracellularly, leading to increased osmotic stress. Studies have shown that intracellular sorbitol accumulation impairs proximal tubular cell function in diabetic rats [11]. AR, the rate-limiting enzyme of the polyol pathway, plays a critical role in the pathogenesis of diabetic complications and is markedly upregulated in glomeruli of diabetic patients [12].

Animal studies demonstrated that deletion of the AR gene significantly attenuates early DKD progression, reduces urinary albumin excretion, and prevents renal cortical activation of PKC and TGF-β1 as well as glomerular hypertrophy [13]. Subsequently, sorbitol is converted to fructose by sorbitol dehydrogenase, generating NADH and altering the NADH/NAD^+ ratio, thereby causing redox imbalance. Excess fructose can undergo nonenzymatic glycation of proteins, leading to protein dysfunction [14]. Moreover, fructose metabolism bypasses glycolytic regulation via fructokinase, producing excessive acetyl-CoA and consuming large amounts of ATP, thereby promoting protein hyperacetylation and further functional impairment. Consequently, elevated fructose levels exacerbate diabetes and its complications [15].

2.2 Hexosamine Pathway

Under normal physiological conditions, only 2–5% of intracellular glucose enters the hexosamine pathway, generating a small amount of fructose-6-phosphate (Fruc-6-P) [16]. This pathway plays a pivotal role in the biosynthesis of proteoglycans, glycolipids, and glycoproteins. Under hyperglycemia, excess Fruc-6-P is converted to glucosamine-6-phosphate (GlcN-6-P) via the rate-limiting enzyme glutamine: fructose-6-phosphate amidotransferase (GFAT), which is subsequently transformed into UDP-N-acetylglucosamine (UDP-GlcNAc) [17].

UDP-GlcNAc, the donor substrate for O-linked glycosylation, is catalyzed by O-GlcNAc transferase to modify proteins and lipids. Its accumulation leads to excessive O-GlcNAcylation of transcription factors, signaling proteins, and structural proteins, disrupting gene expression and protein function [18]. Furthermore, UDP-GlcNAc enhances ROS generation and activates pro-apoptotic caspase-3, contributing to mesangial cell injury [19].

2.3 PKC Pathway

Protein kinase C (PKC) is a family of serine/threonine kinases primarily activated by diacylglycerol (DAG) [20]. Hyperglycemia elevates intracellular DAG levels, thereby activating PKC. The DAG–PKC axis is a core signaling pathway in DKD pathogenesis. PKC activation induces multiple pathogenic processes: It alters glomerular hemodynamics by upregulating endothelin-1 (ET-1) and inhibiting nitric oxide synthase, leading to intraglomerular hypertension and hyperfiltration, thereby accelerating vascular injury [21]. It enhances pro-fibrotic factor expression (e.g., TGF-β1, CTGF, PAI-1), driving mesangial proliferation, extracellular matrix (ECM) accumulation, and basement membrane thickening, which promote glomerulosclerosis [22]. It stimulates NADPH oxidase, exacerbating oxidative stress, which activates NF-κB signaling and upregulates inflammatory cytokines (MCP-1, TNF-α, IL-6), aggravating renal inflammation [23]. It interacts with MAPK pathways (ERK, JNK, p38), further amplifying fibrotic and proliferative responses [24].

In the glomerular filtration barrier, aberrant PKC activation disrupts podocyte function. Activation of PKC isoforms (PKC-α, PKC-β, PKC-δ) reduces nephrin expression, damages podocyte cytoskeleton, and causes foot process effacement, ultimately leading to barrier dysfunction and proteinuria [25].

2.4 AGEs–RAGE Pathway

The liver and kidneys are primary sites for clearance of advanced glycation end products (AGEs) [26]. Under normal conditions, AGEs filtered by glomeruli are reabsorbed by proximal tubules and subsequently metabolized. In persistent hyperglycemia, accelerated nonenzymatic glycation leads to AGE accumulation in plasma and renal tissues. Concurrently, receptor for AGEs (RAGE) expression is upregulated in glomerular, tubular, and vascular endothelial cells, triggering pathogenic signaling cascades [27].

The AGEs–RAGE interaction activates NADPH oxidase and other oxidative systems, markedly increasing ROS generation and oxidative stress, thereby damaging the glomerular basement membrane and tubular epithelium [28]. Furthermore, AGEs–RAGE signaling activates NF-κB, MAPK (ERK/JNK/p38), and JAK/STAT pathways, upregulating inflammatory cytokines and adhesion molecules, resulting in immune cell infiltration, endothelial and podocyte injury, increased capillary permeability, and proteinuria [29].

Additionally, AGEs–RAGE induces TGF-β1/Smad signaling, stimulating collagen and fibronectin synthesis while suppressing matrix metalloproteinase activity. This promotes excessive ECM accumulation, basement membrane thickening, and glomerulosclerosis, ultimately leading to irreversible renal functional impairment [30].

3. Lipid Metabolism and Kidney Disease

Although DKD has traditionally been regarded as a disorder

driven by hyperglycemia-induced metabolic and hemodynamic alterations, growing evidence indicates that lipid metabolism disorders also play a crucial role in its onset and progression [31]. A global case–control study demonstrated that decreased high-density lipoprotein cholesterol (HDL-C) and elevated triglyceride (TG) levels are independent risk factors for DKD development [32]. Clinically, DKD patients frequently present with dyslipidemia characterized by increased TG, total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), accompanied by decreased HDL-C [33].

3.1 Tubular Lipotoxicity

Abnormal lipid deposition in non-adipose tissues such as the liver, pancreas, skeletal muscle, and kidneys is referred to as ectopic fat accumulation [34]. In the kidney, these deposits not only damage endothelial cells but also spread to adjacent mesangial cells, podocytes, and tubular epithelial cells, contributing to local injury [35].

Renal tubules are among the most metabolically active structures in the kidney, relying heavily on fatty acid oxidation for energy [36]. Lipid accumulation in tubular cells is considered a major driver of lipotoxicity. Tubular lipotoxicity triggers diverse forms of renal injury, including oxidative stress, endoplasmic reticulum (ER) stress, tubular epithelial apoptosis, tubulointerstitial fibrosis, mitochondrial dysfunction, and inflammation [37].

Mitochondrial dysfunction is a critical mechanism underlying ectopic lipid accumulation. In DKD, tubular mitochondria exhibit disrupted cristae and vacuolization, with impaired oxidative phosphorylation and reduced fatty acid β-oxidation, leading to lipid metabolic imbalance [38]. Furthermore, hyperglycemia, dyslipidemia, and albumin overload disrupt protein homeostasis in renal cells, persistently activating ER stress signaling networks. This cascade drives oxidative stress, apoptosis, inflammation, and fibrosis, thereby accelerating DKD progression [39].

3.2 Inflammation and Oxidative Stress

Inflammation and oxidative stress act synergistically to promote oxidative modification of LDL, generating oxidized LDL (ox-LDL). As a potent pro-inflammatory and cytotoxic mediator, ox-LDL directly damages glomerular and proximal tubular epithelial cells, while further stimulating oxidative stress and cytokine release [40]. This process exacerbates proteinuria and accelerates renal functional decline. Lipotoxicity induces inflammatory responses through multiple mechanisms: Accumulated saturated fatty acids, ox-LDL, and lipid intermediates are taken up by cells via scavenger receptors such as CD36, which activate the TLR4/NF-κB pathway, promoting the expression of MCP-1, TNF-α, IL-6 and driving macrophage infiltration and interstitial inflammation [41]. Lipotoxic cell injury releases ROS and activates the NLRP3 inflammasome, leading to IL-1β and IL-18 secretion, further amplifying inflammation and fibrosis [42]. Lipotoxic ER stress disrupts fatty acid oxidation, causing excessive fatty acid accumulation and enhanced ROS production. This not only induces tubular apoptosis but also stimulates pro-fibrotic factor expression, aggravating renal dysfunction [43].

Moreover, lipid metabolism disorders induce oxidative stress mainly via NADPH oxidases (e.g., NOX4) and mitochondrial electron transport chain leakage [44]. Mitochondrial ROS (mtROS) dissociate the TXNIP–Trx complex, activating the NLRP3 inflammasome and propagating inflammatory cascades [45].

Lipid metabolic imbalance also results in intracellular lipid droplet accumulation and reduced fatty acid oxidation (FAO), associated with downregulation of PPARα/PGC-1α signaling and dysregulated inhibition of SREBP-1c. These processes sustain chronic inflammation and oxidative stress, driving glomerulosclerosis, tubulointerstitial fibrosis, and progressive renal decline [46].

4. TCM Theory on Glycolipid Metabolism Disorders and Diabetic Kidney Disease

In traditional Chinese medicine (TCM), DKD is categorized under “Xiaoke-related kidney disease,” “edema,” “deficiency-fatigue syndromes,” and “Guange” (obstructive syndromes). Its pathogenesis is complex, and most TCM scholars believe that prolonged diabetes leads to depletion of yin and qi, impairing yin–yang balance and resulting in a dual deficiency of qi and yin or yin and yang. At the same time, pathogenic excesses such as phlegm, dampness, blood stasis, and toxins combine with the underlying deficiency, forming a complicated mechanism characterized by “deficiency in origin and excess in manifestation.”

Professor Zou Yanqin [47] emphasizes that the core pathogenesis of DKD lies in “spleen–kidney deficiency as the root, with dampness and stasis obstructing the collaterals as the manifestation.” This indicates that the disease is closely related to dysfunction of the spleen and kidney, with dampness and stasis persisting throughout the disease course.

Although TCM has no direct disease concept corresponding to “glycolipid metabolism disorder,” its clinical manifestations align with the categories of “phlegm-turbidity,” “blood stasis,” and “gaozhi (fat accumulation).” As described in Huangdi Neijing, “Food enters the stomach, the essence of grain diffuses upward to the spleen; the spleen transports essence upward to the lung, which regulates water pathways; downward, it is transmitted to the bladder, and water essence is distributed across the channels.” This describes normal metabolic circulation. However, overindulgence in rich, greasy foods, emotional disturbances, or overexertion impair spleen and stomach function, leading to improper distribution of nutrients. This results in accumulation of dampness, phlegm, and turbidity, which circulate internally and obstruct qi and blood flow.

4.1 Pathological Changes of “Gaozhi” (Fat Essence)

In Lingshu · Wulóng Jin Ye Bie, “gaozhi” is described as: “The essence of grains combines to form fat-essence, which permeates the bones, nourishes the brain marrow, and flows downward to the thighs.” It is believed that “gaozhi” originates from the refined essence of food and drink, which not only nourishes the brain and marrow but also moistens and

supports the entire body. Distributed throughout viscera and skin, “gaozhi” condenses into fat or accumulates as oily deposits. While not inherently pathological, it is regarded as a reserve form of vital essence that provides nourishment, warmth, and pr However, excessive intake of rich, greasy foods burdens the middle jiao, impairing spleen function and blocking the normal distribution of nutrients. This results in dampness stagnation, which over time transforms into phlegm-turbidity. As noted in Suwen · Qibing Lun: “It arises from indulgence in rich foods. Such individuals habitually consume sweets and fatty foods. Fat causes internal heat, and sweetness causes fullness; this excess leads to upward overflow of qi, transforming into Xiaoke (diabetes).” This illustrates that excessive accumulation of “gaozhi” not only hinders spleen transportation but also generates damp-heat, disturbing qi dynamics. The retained “gaozhi” transforms into heat, consuming body fluids, first injuring stomach yin (manifested as polyphagia and emaciation), and eventually depleting lung and kidney yin, producing the classical “three excesses” of Xiaoke (polydipsia, polyphagia, polyuria) [48].

4.2 Visceral Dysfunction and Glycolipid Metabolism

As Suwen states: “The five zang organs derive qi from the stomach,” and “the stomach is the sea of the five zang and six fu organs.” When spleen–stomach function is intact, nutrients are properly distributed, with pure qi ascending to the heart and lung while turbid qi descends to the intestines, ensuring smooth metabolism and fluid balance. However, dietary excesses, particularly rich, greasy foods, overwhelm the spleen, causing stagnation and dysfunction.

Li Dongyuan noted in Treatise on the Spleen and Stomach: “When the spleen and stomach are injured internally, a hundred diseases arise.” Spleen deficiency prevents the ascent of clear yang and descent of turbid yin, leading to fluid retention. Prolonged dampness transforms into phlegm, which congeals into turbidity and corresponds to glycolipid metabolic disorders in modern terms. Thus, impaired spleen transportation and internal generation of phlegm-dampness are not only the initial pathogenic factors of DKD but also trigger deeper involvement of other viscera.

Stagnant spleen function also affects the liver’s ability to regulate qi. The liver governs free coursing and dislikes constraint. Impaired liver function leads to qi stagnation, allowing phlegm and dampness to combine with stagnant qi. Constrained liver qi attacks the spleen, worsening dysfunction. Liver constraint may transform into fire, further consuming yin and fluids, exacerbating the essence of Xiaoke. As noted in Suwen · Yin Yang Ying Xiang Dalun: “When the liver suffers from urgency, eat sweet foods to relax it.” Modern preference for sweets as emotional comfort worsens phlegm-damp retention, leading to qi stagnation, phlegm-qi binding, lipid-turbidity accumulation, vascular obstruction, and blood stasis formation.

The kidney, regarded as the root of congenital essence, governs water and urination, and is the direct target organ damaged in DKD. The kidney depends on the spleen and stomach for nourishment; when spleen transport fails, kidney supply is impaired. Damp-phlegm accumulation blocks kidney channels, while kidney qi deficiency leads to impaired fluid regulation, manifesting as turbid urine or proteinuria—hallmarks of renal collateral injury. Suwen states: “The kidney stores essence and governs closure.” When kidney essence is depleted, closure fails, leading to kidney qi deficiency, impaired water metabolism, and clinical manifestations such as lumbar soreness, emaciation, edema, or generalized swelling, indicative of kidney yang deficiency.

Throughout DKD pathogenesis, phlegm-dampness and blood stasis formation are key pathological markers. Dampness arises from spleen deficiency and improper diet, later transforming into heat; blood stasis develops from qi stagnation, phlegm obstruction, and impaired circulation. As noted in Lingshu: “When blood does not move freely, it turns into water.” Dampness obstructs blood flow, causing further stagnation; blood stasis in turn prevents the resolution of damp-phlegm, forming a vicious cycle. Their combination produces “turbid stasis,” which infiltrates kidney collaterals, ultimately resulting in severe obstructive syndromes (“Guange”).

In summary, visceral dysfunction leads to the internal generation and accumulation of phlegm-dampness, blood stasis, and turbidity, progressively damaging renal collaterals. This forms a mixed syndrome of deficiency and excess, with spleen–kidney deficiency as the root and phlegm-dampness and turbid stasis as the manifestations—deficiency within excess, and excess further consuming deficiency.

5. TCM Interventions Targeting Glycolipid Metabolism in DKD

In exploring TCM-based strategies for DKD, interventions guided by the concept of glycolipid metabolism disorder have become an important direction in both research and clinical practice.

For instance, Wu Jie et al. induced glycolipid metabolic disorders in rats through a high-fat, high-sugar diet and intervened with astragalus polysaccharides. The results showed that astragalus polysaccharides inhibited the Wnt1 signaling pathway, reduced oxidative stress, improved mitochondrial function, regulated glycolipid metabolism–related protein expression, thereby lowering blood glucose and lipid levels and reducing apoptosis [49]. Li Xueqian et al. demonstrated in animal studies that ginsenoside Rg1 inhibited the Wnt3a/β-catenin signaling pathway, reduced glucose and lipid levels, alleviated renal inflammation, and improved renal function, exerting protective effects against diabetic renal injury [50].

Flavonoids in rhubarb, such as quercetin, exhibit antioxidant activity and effectively lower TC, LDL-C, TG, and blood glucose levels in patients with hyperlipidemia and diabetes [51]. Danshen (Salvia miltiorrhiza) has also been shown to significantly reduce serum lipid peroxidation products and enhance superoxide dismutase activity in patients with coronary heart disease, demonstrating potent free radical scavenging and anti-lipid peroxidation effects [52]. On this basis, Chen Ying et al. used Shuangdan Oral Liquid (containing tanshinol and paeonol) in DKD rats, showing improvements in lipid metabolism disorders, antioxidant capacity, hemorheology, and renal pathology [53].

Clinical studies also support these findings. For example, Zhenwu Decoction, when applied to DKD patients with phlegm–stasis obstruction, not only improved renal function indicators but also modulated lipid metabolism by lowering TC, TG, and LDL-C levels, while enhancing vascular endothelial growth factor to protect endothelial function [54]. Wuling Powder, rich in polysaccharides and other active compounds, significantly reduced blood glucose and lipids, correcting glycolipid metabolic imbalance [55]. Animal studies further demonstrated that Danggui Buxue Decoction alleviated ER stress in DKD rats, mainly by inhibiting PERK pathway proteins, thereby protecting renal tissue and improving lipid profiles [56].

In a clinical trial involving 186 DKD patients, modified Shenqi Dihuang Decoction significantly reduced blood glucose, renal function indicators, TG, TC, and LDL-C, suggesting protective effects via glycolipid metabolism regulation [57]. Huangkui Capsule significantly improved renal function and lipid metabolism disorders in DKD patients, possibly by reducing serum malondialdehyde (MDA) levels and increasing glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) activity, thereby suppressing oxidative stress [58]. Bailing Capsule, made from fermented Cordyceps sinensis mycelia, contains mannitol, adenosine, and amino acids as its core components. Clinical studies have shown that it significantly reduces proteinuria, protects renal function, and improves lipid metabolism in DKD patients. Its mechanisms may involve antioxidative and anti-inflammatory effects, microcirculation improvement, and inhibition of mesangial cell proliferation [59].

Overall, TCM therapies targeting glycolipid metabolism in DKD emphasize strengthening the spleen for transportation, clearing heat and dampness, and promoting blood circulation to resolve stasis. This holistic approach not only aligns with classical TCM theory but also integrates modern research on metabolic pathways. With its multi-target and multi-pathway regulatory advantages, TCM offers significant translational potential in both clinical and scientific settings for DKD management.

6. Conclusion and Prospects

DKD is one of the most common and severe chronic complications of diabetes, with a multifactorial pathogenesis in which glycolipid metabolism plays a central role throughout disease progression. Glycolipid metabolic disorders are closely linked to the onset and progression of DKD, and effective control of lipid levels can significantly delay disease advancement. Thus, regulating lipid metabolism has become one of the key strategies for DKD prevention and treatment.

The pathological concept of glycolipid metabolism disorder closely corresponds to the TCM theory of “internal obstruction by phlegm-turbidity.” Recent studies have demonstrated that various Chinese herbal medicines, formulas, and active components can delay disease progression through multiple mechanisms, including improving glycolipid metabolism, suppressing inflammation and oxidative stress, and protecting podocytes.

With its advantages of multi-target, multi-pathway, and integrative regulation, TCM provides novel insights for the prevention and management of DKD. In the future, further research should focus on modern elucidation of TCM mechanisms, integrating advanced techniques such as metabolomics and network pharmacology to expand investigations in this field. Such efforts will contribute to providing more effective therapeutic options for patients with DKD.

Fund Project

The Key Industrial Innovation Chain Project of Shaanxi Provincial Department of Science and Technology (Grant No. 2024SF-ZDCYL-03-04); and the “Dual-Chain Integration” Innovation Team Project of Shaanxi Administration of Traditional Chinese Medicine (Grant No. 2022-SLRH-LJ-003).

References

[1] GUEDES M, PECOITS-FILHO R. Can we cure diabetic kidney disease? Present and future perspectives from a nephrologist’s point of view [J/OL]. Journal of Internal Medicine, 2022, 291(2): 165-180.

[2] SAEEDI P, PETERSOHN I, SALPEA P. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition [J/OL]. Diabetes Research and Clinical Practice, 2019, 157: 107843.

[3] ALICIC R Z, ROONEY M T, TUTTLE K R. Diabetic kidney disease: Challenges, progress, and possibilities [J/OL]. Clinical Journal of the American Society of Nephrology, 2017, 12(12): 2032-2045.

[4] SUGAHARA M, PAK W L W, TANAKA T. Update on diagnosis, pathophysiology, and management of diabetic kidney disease [J/OL]. Nephrology, 2021, 26(6): 491-500. DOI:10.1111/nep.13860.

[5] JUNG C Y, YOO T H. Pathophysiologic Mechanisms and Potential Biomarkers in Diabetic Kidney Disease [J/OL]. Diabetes & Metabolism Journal, 2022, 46(2): 181-197.

[6] Liu Chengsheng, Tao Lu, Wan Jian. Experience of Master Physician Pi Chiheng in Treating Diabetic Nephropathy Based on the Theory of “Renal Turbidity. [J]. Journal of Li-shizhen Traditional Chinese Medicine,2025: 1-4.

[7] GERICH J E. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications [J/OL]. Diabetic Medicine, 2010, 27(2): 136-142.

[8] CHAO E C, HENRY R R. SGLT2 inhibition — a novel strategy for diabetes treatment [J/OL]. Nature Reviews Drug Discovery, 2010, 9(7): 551-559.

[9] MATOBA K, TAKEDA Y, NAGAI Y. Targeting Redox Imbalance as an Approach for Diabetic Kidney Disease [J/OL]. Biomedicines, 2020, 8(2): 40.

[10] NAGASU H, SATOH M, KIYOKAGE E. Activation of endothelial NAD(P)H oxidase accelerates early glomerular injury in diabetic mice [J/OL]. Laboratory Investigation, 2016, 96(1): 25-36.

[11] Effects of renal sorbitol accumulation on urinary excretion of enzymes in hyperglycaemic rats [J/OL]. Annals of Clinical Biochemistry, 2001, 38(4): 391-398.
[12] KASAJIMA H, YAMAGISHI S I, SUGAI S. Enhanced in situ expression of aldose reductase in peripheral nerve and renal glomeruli in diabetic patients [J/OL]. Virchows Archiv, 2001, 439(1): 46-54.
[13] LIU H, LUO Y, ZHANG T. Genetic deficiency of aldose reductase counteracts the development of diabetic nephropathy in C57BL/6 mice [J/OL]. Diabetologia, 2011, 54(5): 1242-1251.
[14] Formation of Fructose-Mediated Advanced Glycation End Products and Their Roles in Metabolic and Inflammatory Diseases [J/OL]. Advances in Nutrition, 2017, 8(1): 54-62.
[15] BAEZA J, SMALLEGAN M J, DENU J M. Site-Specific Reactivity of Nonenzymatic Lysine Acetylation [J/OL]. ACS Chemical Biology, 2015, 10(1): 122-128.
[16] SCHLEICHER E D, WEIGERT C. Role of the hexosamine biosynthetic pathway in diabetic nephropathy [J/OL]. Kidney International, 2000, 58: S13-S18.
[17] MARSHALL S, BACOTE V, TRAXINGER R R. Discovery of a metabolic pathway mediating glucose-induced desensitization of the glucose transport system. Role of hexosamine biosynthesis in the induction of insulin resistance. [J/OL]. Journal of Biological Chemistry, 1991, 266(8): 4706-4712.
[18] JOKELA T A, MAKKONEN K M, OIKARI S. Cellular Content of UDP-N-acetylhexosamines Controls Hyaluronan Synthase 2 Expression and Correlates with O-Linked N-Acetylglucosamine Modification of Transcription Factors YY1 and SP1 [J/OL]. Journal of Biological Chemistry, 2011, 286(38): 33632-33640.
[19] SINGH L P, CHENG D W, KOWLURU R. Hexosamine induction of oxidative stress, hypertrophy and laminin expression in renal mesangial cells: effect of the anti-oxidant α-lipoic acid [J/OL]. [2025] [2025-08-26].
[20] NOH H, KING G L. The role of protein kinase C activation in diabetic nephropathy [J/OL]. Kidney International, 2007, 72: S49-S53.
[21] PAN D, XU L, GUO M. The role of protein kinase C in diabetic microvascular complications [J/OL]. Frontiers in Endocrinology, 2022, 13: 973058.
[22] ZHU Y, KATAOKA USUI H, SHARMA K. Regulation of Transforming Growth Factor–Beta in Diabetic Nephropathy: Implications for Treatment [J/OL]. Seminars in nephrology, 2007, 27(2): 153-160.
[23] HU T, RAMACHANDRARAO S P, SIVA S. Reactive oxygen species production via NADPH oxidase mediates TGF-β-induced cytoskeletal alterations in endothelial cells [J/OL]. American Journal of Physiology-Renal Physiology, 2005 [2025-08-07].
[24] TOYODA M, SUZUKI D, HONMA M. High expression of PKC-MAPK pathway mRNAs correlates with glomerular lesions in human diabetic nephropathy. [J/OL]. Kidney International, 2004, 66(3): 1107-1114.
[25] TOSSIDOU I, TENG B, MENNE J. Podocytic PKC-Alpha Is Regulated in Murine and Human Diabetes and Mediates Nephrin Endocytosis [J/OL]. PLOS ONE, 2010, 5(4): e10185.
[26] GUGLIUCCI A, BENDAYAN M. Renal fate of circulating advanced glycated end products (AGE): evidence for reabsorption and catabolism of AGE-peptides by renal proximal tubular cells [J/OL]. Diabetologia, 1996, 39(2): 149-160.
[27] FOTHERINGHAM A K, GALLO L A, BORG D J. Advanced Glycation End Products (AGEs) and Chronic Kidney Disease: Does the Modern Diet AGE the Kidney? [J/OL]. Nutrients, 2022, 14(13): 2675.
[28] CURRAN C S, KOPP J B. RAGE pathway activation and function in chronic kidney disease and COVID-19 [J/OL]. Frontiers in Medicine, 2022, 9 [2025-08-10].
[29] Cellular signalling of the receptor for advanced glycation end products (RAGE) [J/OL]. Cellular Signalling, 2013, 25(11): 2185-2197.
[30] KRUSE J J C M, FLOOT B G J, TE POELE J A M. Radiation-Induced Activation of TGF-β Signaling Pathways in Relation to Vascular Damage in Mouse Kidneys [J/OL]. [2025] [2025-08-10].
[31] KIM Y, LIM J H, KIM M Y. The Adiponectin Receptor Agonist AdipoRon Ameliorates Diabetic Nephropathy in a Model of Type 2 Diabetes [J/OL]. Journal of the American Society of Nephrology : JASN, 2018, 29(4): 1108-1127.
[32] SACKS F M, HERMANS M P, FIORETTO P. Association Between Plasma Triglycerides and High-Density Lipoprotein Cholesterol and Microvascular Kidney Disease and Retinopathy in Type 2 Diabetes Mellitus [J/OL]. Circulation, 2014 [2025-08-15].
[33] HIRANO T. Pathophysiology of Diabetic Dyslipidemia [J/OL]. Journal of Atherosclerosis and Thrombosis, 2018, 25(9): 771-782.
[34] WANG H, ZHANG S, GUO J. Lipotoxic Proximal Tubular Injury: A Primary Event in Diabetic Kidney Disease [J/OL]. Frontiers in Medicine, 2021, 8 [2025-08-15].
[35] BUSUIOC R M, COVIC A, KANBAY M. Protein convertase subtilisin/kexin type 9 biology in nephrotic syndrome: implications for use as therapy [J/OL]. [2025] [2025-08-15].
[36] PAN X. The Roles of Fatty Acids and Apolipoproteins in the Kidneys [J/OL]. Metabolites, 2022, 12(5): 462.
[37] GE M, FONTANESI F, MERSCHER S. The Vicious Cycle of Renal Lipotoxicity and Mitochondrial Dysfunction [J/OL]. Frontiers in Physiology, 2020, 11 [2025-08-15].
[38] ZHOU Y, LIU L, JIN B. Metrnl Alleviates Lipid Accumulation by Modulating Mitochondrial Homeostasis in Diabetic Nephropathy [J/OL]. Diabetes, 2023, 72(5): 611-626.
[39] NI L, YUAN C, WU X. Endoplasmic Reticulum Stress in Diabetic Nephrology: Regulation, Pathological Role, and Therapeutic Potential [J/OL]. Oxidative Medicine and Cellular Longevity, 2021, 2021: 7277966.
[40] ROUMELIOTIS S, GEORGIANOS P I, ROUMELIOTIS A. Oxidized LDL Modifies the Association between Proteinuria and Deterioration of Kidney Function in Proteinuric Diabetic Kidney Disease [J/OL]. Life, 2021, 11(6): 504.
[41] WANG C H, SURBHI, GORAYA S. Fatty acids and inflammatory stimuli induce expression of long-chain acyl-CoA synthetase 1 to promote lipid remodeling in

diabetic kidney disease [J/OL]. Journal of Biological Chemistry, 2024, 300(1) [2025-08-21].
[42] THONGNAK L, PONGCHAIDECHA A, LUNGKAPHIN A. Renal Lipid Metabolism and Lipotoxicity in Diabetes [J/OL]. The American Journal of the Medical Sciences, 2020, 359(2): 84-99.
[43] SAKASHITA M, TANAKA T, INAGI R. Metabolic Changes and Oxidative Stress in Diabetic Kidney Disease [J/OL]. Antioxidants, 2021, 10(7): 1143.
[44] FAN X, YANG M, LANG Y. Mitochondrial metabolic reprogramming in diabetic kidney disease [J/OL]. Cell Death & Disease, 2024, 15(6): 442.
[45] SAHAKYAN G, VEJUX A, SAHAKYAN N. The Role of Oxidative Stress-Mediated Inflammation in the Development of T2DM-Induced Diabetic Nephropathy: Possible Preventive Action of Tannins and Other Oligomeric Polyphenols [J/OL]. Molecules, 2022, 27(24): 9035.
[46] HAN Y Z, DU B X, ZHU X Y. Lipid metabolism disorder in diabetic kidney disease [J/OL]. Frontiers in Endocrinology, 2024, 15 [2025-08-22].
[47] Yan Qianhua, Zou Yanqin. The Treatment of Diabetic Nephropathy by National Chinese Medicine Master Zou Yanqin from Spleen and Kidney [J/OL]. Journal of Nanjing University of Traditional Chinese Medicine 2018, 34(2): 109-111.
[48] Li Mingzhu, Chen Qianfeng, Tao Wenjuan. Prevention and Treatment of Chronic Metabolic Diseases based on the Physiological Characteristics and Pathological Changes of “Lipids” [J/OL]. Journal of Traditional Chinese Medicine,2022, 63(4): 307-311.
[49] WuJie, Liu Xuguang, Feng Xiaoci. Effects Mechanism of Astragalus Polysaccharide on the Disorder of Glucose and Lipid Metabolism in Diabetes Rats via Wnt1 Signaling [J/OL]. Journal of Liaoning University of Traditional Chinese Medicine, 2024, 26(11): 43-51.
[50] Li Xueqian, Zhuo Yingchen, Gao Lei. Ginsenoside Rg1 Passes through Wnt3a β-the Mechanism of the Effect of Catenin Signaling Pathway on Renal Injury in Diabetes Rats [J/OL]. Progress in Modern Biomedicine, 2023, 23(17): 3216-3220.
[51] HUANG H, LIAO D, DONG Y. Effect of quercetin supplementation on plasma lipid profiles, blood pressure, and glucose levels: a systematic review and meta-analysis [J/OL]. Nutrition Reviews, 2020, 78(8): 615-626.
[52] Xing Zhiqiang, Zeng Xuchu, Yi Chuntao, Yuan Feng. Influence of Danshen on Serum Lipid Peroxides and Superoxide Dismutase in Patients with Coronary Heart Disease [J/OL]. Chinese Journal of Integrated Traditional and Western Medicine, 1996(5) [2025-08-23].
[53] Chen Ying, Liu Zhuying, Zhou Fuxing. Effects of Shuangdan Oral Liquid on diabetic nephropathy rat models [J]. Northwest Pharmaceutical Journal, 2016, 31(1): 56-61.
[54] Zhao Feng, Xiang Min. Effect of Zhenwu Decoction in Sydnrome Differentiation and Treatment of Phlegm and Blood Stasis Syndrome of Type 2 Diabetic Nephropathy and Its Influence on Vascular Endothelial Growth Factor [J/OL]. Liaoning Journal of Traditional Chinese Medicine, 2019, 46(11): 2361-2364.
[55] Zhang Xianjie, Luo Zhimin, Luo Yongbiao. Effect and its mechanism of polyporus polysaccharide regulating blood glucose in type 2 diabetic mellitus rats [J]. Journal of Clinical and Experimental Medicine, 2020, 19(24): 2586-2589.
[56] Danggui Buxue decoction regulates autophagy to Improve renal fibrosis in diabetes through miR-27a /PI3K/AKT pathway [J/OL]. Journal of Ethnopharmacology, 2025, 341: 119357.
[57] Zhang Jinjin, Ji Hongyu, Zheng Zhonghua. Effects of Shenqi Dihuang Decoction on Glucose, Lipid Metabolism, and Renal Function in Diabetic Nephropathy with Qi-Yin Deficiency and Blood Stasis [J/OL]. Shenzhen Journal of Integrated Traditional Chinese and Western Medicine, 2024, 34(5): 30-33.
[58] Huangkui capsule, an extract from Abelmoschus manihot (L.) medic, improves diabetic nephropathy via activating peroxisome proliferator–activated receptor (PPAR)-α/γ and attenuating endoplasmic reticulum stress in rats [J/OL]. Journal of Ethnopharmacology, 2016, 189: 238-249.
[59] SHENG X, DONG Y, CHENG D. Efficacy and safety of Bailing capsules in the treatment of type 2 diabetic nephropathy: a meta-analysis [J/OL]. Annals of Palliative Medicine, 2020, 9(6): 3885898-3883898.