

Impact of Hyperglycemia and Hyperuricemia on Diabetic Kidney Disease and Research Progress

Liyue Tong¹, Huiling Wang^{2,*}

¹Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China

²Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China

*Correspondence Author

Abstract: *Diabetic Kidney Disease (DKD), as one of the common microvascular complications of diabetes, has become a significant focus of current research regarding its pathogenesis, progression mechanisms, and therapeutic approaches. Among the numerous risk factors for DKD, hyperglycemia and hyperuricemia can synergistically promote the onset and progression of DKD through multiple mechanisms. This article systematically elucidates the impact of hyperglycemia on DKD via mechanisms including the polyol pathway, protein kinase C activation, and advanced glycation end-product formation, as well as the impact of hyperuricemia through inflammatory responses, oxidative stress, and endothelial dysfunction. Furthermore, it explores the synergistic effects of hyperglycemia and hyperuricemia and clinical management strategies for DKD complicated with hyperuricemia, providing a theoretical basis for the treatment of DKD.*

Keywords: Diabetic Kidney Disease, Hyperglycemia, Hyperuricemia, Pathogenesis, Synergistic Effect, Therapeutic Strategies.

1. Introduction

Diabetic Kidney Disease (DKD) is the most common complication of diabetes. Microvascular damage in the kidneys leads to glomerulosclerosis, thickening of the glomerular basement membrane (GBM), and other pathological changes. Over time, 20%-40% of diabetic patients develop DKD, and without intervention, many eventually progress to End-Stage Renal Disease (ESRD). With the continuous global increase in diabetic patients, the prevention and treatment of DKD have become critical topics in international public health research. Hyperglycemia is the hallmark of diabetes and is considered the initiating factor and core mechanism in the development of DKD. Recently, with deepening research into DKD mechanisms, hyperuricemia has been identified as a potential independent risk factor playing a significant role in the disease course. Numerous studies indicate that hyperglycemia and hyperuricemia interact through various molecular mechanisms to jointly injure the kidneys and accelerate DKD progression. This review aims to summarize recent advances in understanding the impacts and mechanisms of hyperglycemia and hyperuricemia on DKD, as well as modern therapeutic approaches, providing theoretical insights for clinical prevention and treatment.

2. Mechanisms of Hyperglycemia-Induced Diabetic Kidney Disease

As the fundamental characteristic of diabetes, hyperglycemia causes renal injury through multiple mechanisms. Increased intracellular oxidative stress in renal cells induced by hyperglycemia is a key mechanism of kidney damage. It also leads to overactivation of the Protein Kinase C (PKC) signaling pathway and the Polyol Pathway (PP) [1]. Under hyperglycemic conditions, reactive oxygen species (ROS) generated during the tricarboxylic acid cycle and oxidative

respiration in renal cell mitochondria increase dramatically, overwhelming cellular antioxidant capacity and impairing renal cell structure and function [2]. This includes podocyte and endothelial cell damage and apoptosis, compromising the glomerular filtration barrier against macromolecular proteins and resulting in massive proteinuria. Renal cell injury further leads to glomerulosclerosis and tubulointerstitial fibrosis, ultimately culminating in ESRD [3].

Overactivation of the PP due to hyperglycemia is another critical mechanism of renal injury. In hyperglycemic states, cellular glycogen synthesis and glucose oxidation are relatively insufficient, leading to increased aldose reductase activity. This accelerates the conversion of glucose to sorbitol, which is then converted to fructose by sorbitol dehydrogenase and subsequently phosphorylated to triose upon crossing the cell membrane [4]. During this process, nicotinamide adenine dinucleotide phosphate (NADPH) is consumed to produce reduced NADPH, increasing intracellular osmolarity. Extracellular fluid enters cells along the osmotic gradient, causing osmotic edema of renal cells and subsequent damage. Concurrently, sorbitol metabolism activates NADPH oxidase, consuming large amounts of NADPH and increasing ROS production, thereby weakening antioxidant defenses, inducing oxidative stress, and further enhancing PP activation. Accumulation of aldose reductase and sorbitol contributes to glomerulosclerosis, damages glomerular endothelial cells and podocytes, and increases glomerular permeability [5]. The polyol pathway can also activate PKC and generate large quantities of Advanced Glycation End-products (AGEs) [1].

Activation of the PKC signaling pathway by hyperglycemia is a major mechanism of renal damage. Hyperglycemia leads to intracellular sorbitol accumulation and myo-inositol depletion, accelerating diacylglycerol synthesis and activating PKC isoforms, particularly PKC- β and PKC- δ [6]. This damages glomerular vasculature, induces massive proteinuria, and causes renal cellular dysfunction [7].

Hyperglycemia impairs podocyte autophagy by affecting nutrient-sensing pathways (e.g., mTOR signaling) and intracellular stress pathways (e.g., oxidative stress), representing another important mechanism of renal injury [8]. Podocyte autophagy effectively eliminates intracellular toxins, collagen fibers, and inflammatory cells. Under hyperglycemic conditions, suppressed autophagy prevents timely toxin removal, accelerates renal damage, promotes collagen fiber accumulation driving fibrosis, and exacerbates inflammation via spreading inflammatory cells, all accelerating DKD progression [9].

The formation and accumulation of AGEs constitute a vital pathway of hyperglycemia-induced renal damage. In persistent hyperglycemic environments, macromolecules such as proteins, lipids, and nucleic acids undergo non-enzymatic glycation to form AGEs. AGEs directly injure renal tissue, alter the functional structure of renal vascular endothelial cells and GBM, and ultimately lead to proteinuria via macromolecular protein leakage [10]. AGEs also bind to their receptor (RAGE), activating transcription factors like Nuclear Factor- κ B (NF- κ B) to promote expression of inflammatory and pro-fibrotic cytokines [11]. Hyperglycemia generates excessive AGEs that impair renal structure and function, while simultaneously slowing AGE clearance by renal cells, creating a vicious cycle of injury. Additionally, AGEs mediate inflammatory responses via the JAK/STAT signaling pathway, increase ROS generation, induce renal tissue fibrosis, and accelerate DKD progression [12].

Endoplasmic Reticulum Stress (ERS) activation under hyperglycemia is a significant mechanism of renal injury. ERS activation disrupts intracellular protein synthesis and cellular metabolism. Studies show ERS causes podocyte injury and apoptosis in mice, leading to impaired glomerular filtration, hyperfiltration, and proteinuria [13].

Overactivation of the Renin-Angiotensin System (RAS) under hyperglycemia is a key mechanism of renal injury. Hyperglycemia stimulates RAS activity, generating excessive Angiotensin II (Ang II). Ang II not only causes intraglomerular hypertension and hyperfiltration but also induces vasoconstrictive dysfunction and alters renal hemodynamics, ultimately forming proteinuria [14]. Moreover, Ang II activates the TGF- β /Smad pathway, promoting extracellular matrix (ECM) deposition, leading to glomerulosclerosis and interstitial fibrosis [15].

Upregulation of inflammatory mediators under hyperglycemia is another critical mechanism of renal injury. Hyperglycemia induces renal cells to produce Monocyte Chemoattractant Protein-1 (MCP-1), recruiting inflammatory cells to renal vessel walls. These cells release Tumor Necrosis Factor- α (TNF- α) and Interleukin-6 (IL-6), causing chronic renal inflammation. Hyperglycemia also mediates inflammation via the JAK/STAT pathway, increases ROS, induces fibrosis, and aggravates inflammation [12]. Chronic renal inflammation damages renal tissues, impairs glomeruli, reduces filtration rate, and causes proteinuria. Over time, this leads to renal fibrosis and further structural/functional deterioration, becoming a major factor in ESRD [16].

3. Mechanisms of Hyperuricemia-Induced Diabetic Kidney Disease

Hyperuricemia produces urate crystals that deposit in renal tissue causing severe damage; thus, increasing research focuses on its impact on DKD. Elevated serum uric acid independently influences DKD progression, causing distinct pathological changes in early and mid-stage DKD. Hyperuricemia participates in DKD pathogenesis through multiple mechanisms, with inflammatory response activation being central. Urate crystals activate the NOD-like receptor protein 3 (NLRP3) inflammasome, enhancing NLRP3/Caspase-1/GSDMD expression, promoting release of pro-inflammatory cytokines like IL-1 β and IL-18, leading to renal structural damage and pyroptosis of tubular epithelial cells [17]. Urate crystals recruit monocytes to the renal intima, where they produce IL-6 and TNF- α , exacerbating chronic renal inflammation and injury [18].

Oxidative stress induced by hyperuricemia is another key mechanism. While normal uric acid levels exert antioxidant effects scavenging ROS, hyperuricemia generates ROS concurrently with xanthine oxidase-catalyzed uric acid production, triggering oxidative stress [19]. Normally, ROS maintains dynamic balance with antioxidant systems for cellular homeostasis and anti-infection defense. However, under hyperuricemia, intracellular uric acid metabolism generates excessive ROS, activating ERK1/2, producing ECM, causing mesangial cell proliferation, glomerulosclerosis, endothelial/podocyte damage, increased glomerular permeability, proteinuria, and red blood cell casts [20]. Massive ECM deposition promotes interstitial fibrosis, accelerating DKD fibrotic progression. Excessive ROS accelerates mitochondrial double-stranded RNA generation/release, causing aberrant protein translation via the PKR/eIF2 α pathway and damaging tubular cells [21].

Renal vascular endothelial dysfunction caused by hyperuricemia is another critical pathway. Hyperuricemia promotes Endothelin-1 (ET-1) secretion, worsening renal vasoconstriction [22]. It activates the aldose reductase pathway, generating ROS, consuming nitric oxide (NO), impairing vasodilation, and exacerbating endothelial injury via ROS oxidation. Hyperuricemia damages endothelial glycocalyx sites, causing glycocalyx shedding, reduced NO synthesis, abnormal blood pressure regulation, increased vascular permeability, and plasma protein leakage. These mechanisms disrupt vascular tone regulation, causing intraglomerular hypertension, ischemic injury, aggravated proteinuria, and renal fibrosis [23, 24].

4. Synergistic Effects of Hyperglycemia and Hyperuricemia

Hyperglycemia and hyperuricemia exhibit significant synergy in DKD pathogenesis. Hyperglycemia increases uric acid production while reducing excretion, leading to hyperuricemia [25]. Firstly, hyperglycemia-induced sorbitol accumulation consumes NADPH during metabolism, weakening antioxidant defenses, inducing oxidative stress,

and increasing uric acid production. Secondly, hyperglycemia-induced osmotic diuresis and tubular damage reduce uric acid excretion. Hyperuricemia exacerbates hyperglycemia-induced renal injury. Urate crystal deposition impairs glucose excretion, while hyperuricemia enhances hyperglycemia-induced oxidative stress and inflammation, synergistically worsening renal damage [17]. Hyperuricemia damages β -cells via the NF- κ B-iNOS-NO pathway, inhibiting pancreatic β -cell function and aggravating insulin resistance, sustaining high blood glucose and renal injury. In type 2 diabetes, hyperuricemia correlates positively with insulin resistance and blood glucose levels [26, 27]. Coexistence of hyperglycemia and hyperuricemia significantly accelerates nephropathy progression.

Both factors synergistically activate pro-fibrotic pathways. Both induce oxidative stress increasing ROS, synergistically exacerbating renal tissue injury. Both promote chronic inflammation via IL-6/TNF- α release, fostering fibrosis and ESRD progression. Shared signaling pathways likely underpin this molecular synergy.

Clinical studies confirm this synergy. A prospective study of 5,479 type 2 diabetic patients found 1,150 (20.99%) had concurrent hyperuricemia [28].

5. Clinical Management and Therapeutic Strategies

Given the close relationship between hyperglycemia and hyperuricemia, DKD prevention requires coordinated management. Glycemic control should follow individualized principles, targeting HbA1c <7% while avoiding hypoglycemia. Novel antidiabetics like Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors and Glucagon-Like Peptide-1 (GLP-1) receptor agonists offer superior glycemic control plus direct renoprotection, making them preferred for DKD [29].

For DKD patients with hyperuricemia, target serum uric acid <360 μ mol/L. Lifestyle interventions include low-purine diet, weight control, and adequate hydration. Xanthine oxidase inhibitors (allopurinol, febuxostat) are first-line pharmacotherapy suppressing uric acid production. Dose adjustment based on GFR is necessary for severe renal impairment [30].

SGLT2 inhibitors are ideal for DKD with hyperuricemia due to triple benefits: glycemic control, uric acid lowering, and renoprotection. RAS blockers (ACEI/ARB) serve as foundational DKD therapy, synergizing with urate-lowering drugs for enhanced renoprotection.

Aldose Reductase Inhibitors (ARIs) suppress PP overactivation, reducing sorbitol accumulation, preventing mesangial proliferation under hyperosmolar conditions, and improving renal cell structure/function. Epalrestat, an ARI, inhibits sorbitol/fructose accumulation and improves renal arterial flow/glomerular microcirculation [31]. Fresh *Cordyceps sinensis* aqueous extract (95% ethanol eluate) shows similar ARI-like effects, inhibiting aldose reductase and scavenging free radicals [1]. Irbesartan combined with *Astragalus* injection significantly reduces IL-6, hs-CRP, and

TNF- α in DKD patients, protecting GBM; increases adiponectin (APN) enhancing antioxidant capacity and ROS clearance [32].

Targeted therapy against DKD mechanisms driven by hyperglycemia/hyperuricemia is a key research direction. Development of targeted therapies/preventives for NLRP3 inflammasome-mediated pyroptosis and drugs targeting shared mechanisms like oxidative stress is ongoing. Tangshenping (Gliquidone) regulates NLRP3 inflammasome expression in DKD rat kidneys, treating inflammation/reducing pyroptosis, and alleviates oxidative stress/microinflammation [33]. Drugs targeting JAK/STAT signaling (*Cordyceps* polysaccharides, *Tripterygium* glycosides/triptolide, *Coptis* polysaccharides, berberine) show efficacy [12]. Traditional Chinese medicines (*Astragalus*, *Salvia miltiorrhiza*, *Yam*) demonstrate renoprotective effects in animal models via multiple mechanisms, warranting further clinical investigation [34].

6. Conclusion

Hyperglycemia and hyperuricemia are two major risk factors for DKD, interacting through multiple mechanisms to accelerate disease progression. Hyperglycemia damages renal tissue primarily via the polyol pathway, inflammation, oxidative stress, podocyte autophagy impairment, PKC pathway, nutrient-sensing pathways, AGE accumulation, ERS, and RAS activation. Hyperuricemia injures kidneys via inflammation, oxidative stress, and endothelial dysfunction. These factors are closely interrelated and act synergistically to accelerate DKD. Clinical management must emphasize combined control using individualized strategies and rational drug selection, especially agents with pleiotropic protective effects like SGLT2 inhibitors. Future research should elucidate precise synergistic mechanisms and develop more effective preventive/therapeutic strategies, offering new avenues for managing DKD with hyperuricemia and improving patient quality of life.

References

- [1] Liu LX, Zhang CH. Research progress on diabetic nephropathy based on polyol pathway[J]. *Guangming Journal of Traditional Chinese Medicine*, 2024, 39(24): 4942-4945.
- [2] Sureshbabu A, Ryter SW, Choi ME. Oxidative stress and autophagy: crucial modulators of kidney injury[J]. *Redox Biol*, 2015, 4: 208-214.
- [3] Luo YL, Zhou SX. Research progress on oxidative stress-induced diabetic nephropathy[J]. *Chronic Diseases Journal*, 2022, 23(10): 1528-1530+1534. DOI: 10.16440/J.CNKI.1674-8166.2022.10.22.
- [4] Xu JW, He JS. Application of novel hypoglycemic agents in diabetic nephropathy treatment[J]. *China Modern Doctor*, 2021, 59(23): 189-192.
- [5] Lan BY. Clinical study on effect of Xiaoke Bitong capsule on polyol metabolic pathway in patients with diabetic peripheral neuropathy[D]. Changchun: Changchun University of Chinese Medicine, 2016.
- [6] Wo GQ, Yao YZ. Relationship between PKC α , PKC β I and early diabetic nephropathy[J]. *Modern Journal of*

- Integrated Traditional Chinese and Western Medicine, 2013, 22(01): 106-108.
- [7] Jiang W, Li Z, Zhao W, et al. Breviscapine attenuated contrast medium-induced nephropathy via PKC/Akt/MAPK signalling in diabetic mice[J]. *Am J Transl Res*, 2016, 8(2): 329-341.
 - [8] Zhou YY, Yin NP. Research progress on pathogenesis and pharmacotherapy of podocyte autophagy in diabetic nephropathy[J]. *Chinese Journal of Microcirculation*, 2025, 35(01): 83-88+96.
 - [9] Li XF. Intervention effect of rapid strength training combined with aerobic exercise on serum uric acid and inflammatory factors in hyperuricemia patients[D]. *Tianjin University of Sport*, 2020. DOI: 10.27364/d.cnki.gttyy.2020.000173.
 - [10] Li YF, Liu J, Huang YH. Research progress on mTOR signaling pathway regulating podocyte autophagy in diabetic nephropathy and intervention of traditional Chinese medicine[J]. *Tianjin Journal of Traditional Chinese Medicine*, 2024, 41(08): 1075-1082.
 - [11] Zhao PM, Wang JQ, Liang YJ. Role of endothelial cell injury in pathogenesis of diabetic nephropathy[J]. *Chinese Journal of Diabetes*, 2016, 24(2): 169-172.
 - [12] Bhattacharjee N, Barma S, Konwar N, et al. Mechanistic insight of diabetic nephropathy and its pharmacotherapeutic targets: an update[J]. *European Journal of Pharmacology*, 2016, 791(11): 8-24.
 - [13] Zhao K, Zhang M, Gai FF, et al. Research progress on active components and compound prescriptions of traditional Chinese medicine treating inflammatory response in diabetic nephropathy based on JAK/STAT pathway[J]. *Journal of Shanxi University of Chinese Medicine*, 2024, 25(07): 819-826. DOI: 10.19763/j.cnki.2096-7403.2024.07.19.
 - [14] Cao Y, Hao Y, Li H, et al. Role of endoplasmic reticulum stress in apoptosis of differentiated mouse podocytes induced by high glucose[J]. *International Journal of Molecular Medicine*, 2014, 33(4): 809-811.
 - [15] Bernardi S, Michelli A, Zuolo G, et al. Update on RAAS modulation for the treatment of diabetic cardiovascular disease[J]. *J Diabetes Res*, 2016, 2016: 8917578.
 - [16] Xie YM, Ren J, Huang QL, et al. Effect of TGF- β RII siRNA on AngII-induced GMC proliferation[J]. *The Journal of Practical Medicine*, 2017, 33(14): 2271-2274.
 - [17] Liu ZZ, Han YR, Zhao FC, et al. Nobiletin suppresses high-glucose-induced inflammation and ECM accumulation in human mesangial cells through STAT3/NF- κ B pathway[J]. *J Cell Biochem*, 2019, 120(3): 3467-3473.
 - [18] Hui DN. Analysis of risk factors for diabetic nephropathy based on clinical big data and mechanism study of uric acid in its occurrence and development[D]. *Shanxi University*, 2024. DOI: 10.27284/d.cnki.gsxiu.2024.000085.
 - [19] Kimura Y, Tsukui D, Kono H. Uric acid in inflammation and the pathogenesis of atherosclerosis[J]. *Int J Mol Sci*, 2021, 22(22): 12394. DOI: 10.3390/ijms222212394.
 - [20] Bao FQ, Tu HY, Fang MS, et al. Research progress on pathology and molecular mechanism of hyperuricemic nephropathy based on animal models[J]. *Laboratory Animal and Comparative Medicine*, 2024, 44(02): 180-191.
 - [21] Duan TY. Role and mechanism of mitochondrial double-stranded RNA in tubular injury of diabetic nephropathy[D]. *Central South University*, 2023. DOI: 10.27661/d.cnki.gzhnu.2023.000372.
 - [22] Zha DQ, Wu SQ, Gao P, et al. Telmisartan attenuates uric acid-induced epithelial-mesenchymal transition in renal tubular cells[J]. *Biomed Res Int*, 2019, 2019: 3851718. DOI: 10.1155/2019/3851718.
 - [23] Liu B, Hong Q, Feng Z. High glucose and high uric acid synergistically aggravate endothelial cell injury via aldose reductase pathway[J]. *Chinese Journal of Kidney Disease Investigation (Electronic Edition)*, 2018, 7(01): 34-38.
 - [24] Zeng Y. Endothelial glycocalyx as a critical signaling platform integrating the extracellular hemodynamic forces and chemical signaling[J]. *Cell Mol Med*, 2017, 21: 1457-1462.
 - [25] Song H, Zhao L, Song YL. Study on risk factors of hyperuricemia in middle-aged and elderly people with hyperglycemia and hyperlipidemia[J]. *Systems Medicine*, 2022, 7(19): 99-102. DOI: 10.19368/j.cnki.2096-1782.2022.19.099.
 - [26] Liu XR, Li Y, Yang B, et al. Correlation between serum uric acid and homocysteine in type 2 diabetic patients and its relationship with insulin resistance[J]. *China Practical Medical*, 2018, 13(17): 32-34.
 - [27] Jia L, Xing J, Ding Y, et al. Hyperuricemia causes pancreatic β -cell death and dysfunction through NF- κ B signaling pathway[J]. *PLoS One*, 2013, 8(10): e78284.
 - [28] Zhang X, Li HX, Shen YY, et al. Survey on status quo and influencing factors of hyperuricemia comorbidity in diabetic patients[J]. *South China Journal of Preventive Medicine*, 2024, 50(05): 455-458.
 - [29] Chinese Diabetes Society. Guidelines for the Prevention and Treatment of Diabetes in China (2024 Edition) [J]. *Chinese Journal of Diabetes Mellitus*, 2025, 17(1): 16-139. DOI: 10.3760/cma.j.cn115791-20241203-00705.
 - [30] Chen J, Zhang XH, Shen J, et al. Study on antioxidant and aldose reductase inhibitory activities of fresh *Cordyceps sinensis*[J]. *Journal of Yangzhou University (Agricultural and Life Science Edition)*, 2020, 41(04): 87-90. DOI: 10.16872/j.cnki.1671-4652.2020.04.015.
 - [31] Chu LC, Song LQ, Yun J, et al. Brief analysis of current treatment status of diabetic nephropathy[J]. *Chinese Journal of Clinical Healthcare*, 2021, 24(01): 140-144.
 - [32] Zhang B, Chen WW, Yu HJ. Effect of irbesartan combined with astragalus injection on oxidative stress and microcirculation disorder indicators in elderly patients with diabetic nephropathy[J]. *Chronic Diseases Journal*, 2018, 19(11): 1602-1603+1606. DOI: 10.16440/j.cnki.1674-8166.2018.11.048.
 - [33] Hu XY, Zhang N, Dong XX, et al. Research progress on prevention and treatment strategies of hyperuricemia[J]. *Journal of Kunming Medical University*, 2019, 40(03): 131-135.
 - [34] Gao K. Study on renal protection of Tangshenping in type 2 diabetic nephropathy rats and its effect on NLRP3/Caspase-1/GSDMD signaling pathway[D]. *Beijing University of Chinese Medicine*, 2020. DOI: 10.26973/d.cnki.gbjzu.2020.001036.
 - [35] Hu MF, Zhu Y. Research progress on traditional Chinese medicine treatment of diabetic nephropathy[J]. *Clinical*

Journal of Traditional Chinese Medicine, 2024, 16(11):
32-37.