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Mechanisms of Inflammation-Fibrosis in Diabetic Nephropathy and Intervention Strategies of Traditional Chinese and Western Medicine

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Abstract: ***Diabetic nephropathy (DKD) is one of the most serious microvascular complications of diabetes. Its pathological process has expanded from a simple metabolic disorder to an "inflammation-fibrosis continuum." Under conditions of high glucose, oxidative stress, and lipotoxicity, immune cell infiltration and abnormal activation of signaling pathways such as NF-κB, NLRP3 inflammasome, and JAK/STAT drive persistent inflammatory responses. Subsequently, fibrosis-related pathways such as TGFβ/Smad and Wnt/β-catenin are significantly upregulated, leading to excessive extracellular matrix deposition, epithelial-mesenchymal transition, and fibroblast activation, ultimately resulting in irreversible renal fibrosis. In terms of treatment, Western medicine drugs such as ACEIs/ARBs, SGLT2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists, and GLP-1 receptor agonists have shown new advantages in delaying disease progression and inhibiting inflammatory fibrosis. Traditional Chinese medicine, through multi-component and multi-target effects, inhibits key pathways such as NF-κB and TGFβ/Smad, improving the progression of inflammation and fibrosis. Clinical and experimental studies suggest that the integration of traditional Chinese medicine (TCM) and Western medicine can create a synergistic effect in controlling metabolism, reducing inflammation, and combating fibrosis, significantly improving proteinuria and renal function. In the future, with the application of biomarkers, in-depth research into molecular mechanisms, and the promotion of the integrated TCM and Western medicine model, the prevention and treatment of diabetic kidney disease (DKD) is expected to enter a new, more precise and comprehensive stage.***

Keywords: Diabetic nephropathy, Inflammation, Fibrosis, Integrated TCM and Western medicine.

1. Introduction

Diabetic kidney disease (DKD) is one of the leading causes of end-stage renal disease worldwide. Its incidence rate continues to rise with the increasing number of diabetic patients, placing a heavy burden on public health systems [1]. Typical pathological changes in DKD include proteinuria, decreased glomerular filtration rate, thickening of the glomerular basement membrane, and tubulointerstitial damage. Traditional views hold that the occurrence of DKD is mainly driven by metabolic disorders such as hyperglycemia, lipotoxicity, and oxidative stress, but this model is no longer sufficient to explain its complex pathological progression. In recent years, a large number of studies have confirmed that chronic inflammatory response plays a central role in the occurrence and development of DKD. Inflammatory cell infiltration, elevated levels of inflammatory factors such as IL-1β, TNF-α, and IL-6, as well as activation of the NLRP3 inflammasome, can all lead to podocyte damage, renal tubular epithelial cell apoptosis, and endothelial dysfunction, thereby promoting the continuous deterioration of DKD [2]. These findings have prompted people to gradually re-understand DKD from a "metabolic disease" to an "inflammatory disease." As research deepens, the pathological progression of DKD is considered to exhibit the characteristics of an "inflammation-fibrosis continuum," meaning that inflammation and fibrosis are not independent events, but rather a dynamic process that promotes each other and gradually worsens [3]. Inflammatory signals can activate fibrotic pathways such as TGFβ/Smad and CTGF, inducing epithelial-mesenchymal transition, endothelial-mesenchymal transition, and fibroblast activation, ultimately leading to excessive extracellular matrix deposition and irreversible damage to the kidney structure. Fibrosis is a key node in the progression of DKD to ESRD, therefore blocking the inflammation-fibrosis axis has become an important direction for treatment [4]. In terms of treatment strategies, although Western medicine has made significant progress in controlling blood sugar, blood pressure, blocking RAAS, and using SGLT2 inhibitors, it is still difficult to completely block the continuous activation of inflammation and fibrosis. Traditional Chinese medicine has multi-target advantages in anti-inflammation, anti-oxidation, improving microcirculation, and inhibiting fibrosis, and more and more studies show that it has potential in delaying the progression of DKD [5]. Therefore, exploring the intervention strategy of combining traditional Chinese and Western medicine from the perspective of the "inflammation-fibrosis continuum" is of great significance for promoting the comprehensive treatment of DKD.

2. Inflammatory Mechanism of DKD

Inflammatory response plays a central role in the occurrence and progression of diabetic nephropathy. Its characteristics include immune cell infiltration, activation of inflammatory signaling pathways and sustained elevation of various inflammatory mediators. These factors jointly promote the structural and functional damage of the kidney [6]. Under the stimulation of high glucose, lipotoxicity and oxidative stress, the local inflammatory microenvironment of the kidney is continuously activated, forming an irreversible pathological process. Immune cell participation is an important starting point for the inflammatory response in DKD. Macrophages are the most important infiltrating cell type, and they show obvious M1/M2 polarization imbalance in the kidney. M1

macrophages secrete pro-inflammatory factors such as TNFα, IL1β and IL6, which promote glomerular sclerosis and renal tubular damage, while the repair function of M2 macrophages is inhibited in DKD, making it difficult to terminate the inflammation [7]. In addition, $CD4^+$T cells and Th1/Th17 cells have also been shown to participate in the inflammatory amplification process of DKD, further aggravating kidney damage by secreting cytokines such as IFNγ and IL17 [8]. Multiple key inflammatory signaling pathways are continuously activated in DKD. NF-κB is one of the core inflammatory regulators, which is rapidly activated under high glucose stimulation, promoting the expression of inflammatory factors such as TNF-α, IL-6, and MCP-1, forming an inflammatory amplification loop [9]. The NLRP3 inflammasome also plays a key role in DKD. Its activation can promote the maturation and release of IL-1β and IL-18, and induce apoptosis of renal tubular epithelial cells and glomerular damage [10]. In addition, the JAK/STAT pathway plays an important role in inflammatory signal transduction, and the continuous activation of STAT3 is closely related to renal tubulointerstitial fibrosis [11]. The MAPK pathway is involved in oxidative stress, apoptosis and expression of inflammatory factors, and is an important regulatory axis of inflammatory response in DKD [12]. Driven by inflammatory pathways, multiple inflammatory mediators are significantly elevated in DKD. Pro-inflammatory factors such as IL-1β, IL-6, and TNF-α not only directly damage renal cells but also promote ECM deposition and fibrosis progression; while MCP-1 recruits more macrophages into the kidney, forming a positive feedback loop of inflammation [7] [9]. Furthermore, activation of the AGEs–RAGE axis also promotes the expression of inflammatory factors, which is an important source of inflammatory response in DKD [12]. Persistent inflammatory response leads to damage to multiple types of renal cells. Podocytes are highly sensitive to inflammatory stimuli, and damage to them can lead to slit membrane destruction and increased proteinuria; renal tubular epithelial cells undergo apoptosis or EMT under the influence of inflammatory factors, promoting interstitial fibrosis; endothelial cell dysfunction disrupts renal microcirculation, accelerating DKD progression [6] [8]. These damages collectively constitute the pathological basis of DKD, making inflammation an indispensable core mechanism.

3. Mechanism of Fibrosis in DKD

Renal fibrosis is a key pathological process in the progression of diabetic nephropathy from early reversible damage to irreversible renal failure. Its core features include excessive deposition of extracellular matrix, activation of fibroblasts, and remodeling of tubulointerstitial structure [13]. The occurrence of fibrosis is closely related to inflammation and is the second half of the "inflammation-fibrosis continuum". The TGFβ/Smad pathway is the core driver of fibrosis in DKD. High glucose, oxidative stress and stimulation by inflammatory factors can significantly upregulate the expression of TGFβ1, activate Smad2/3 phosphorylation, and promote the synthesis of collagen I, III and fibronectin [14]. TGFβ can also inhibit Smad7, thereby forming a continuously activated positive feedback loop, making fibrosis difficult to reverse. In addition, TGFβ can also induce epithelial-interstitial transition (EMT) in renal tubular epithelial cells, enabling them to acquire a fibroblast-like phenotype, further aggravating ECM deposition [15]. Activation of renal fibroblasts is the core event of fibrosis. In DKD, fibroblasts not only originate from the renal interstitium itself, but also from the EMT, endothelial-mesenchymal transition (EndMT), and bone marrow-derived fibroblast-like cells [16]. EndMT is significantly activated under high glucose and inflammatory stimulation, characterized by the loss of markers such as VE cadherin by endothelial cells, and the expression of mesenchymal markers such as α SMA and FSP1, which is one of the important sources of DKD fibrosis [17]. In addition, a variety of pro-fibrotic factors are significantly elevated in DKD. These include CTGF (connective tissue growth factor), PDGF, and AngII, which accelerate fibrosis progression by promoting fibroblast proliferation, migration, and ECM synthesis [18]. Among them, CTGF is considered a key downstream effector molecule of TGFβ, and the two work together to promote ECM deposition, making it an important target for DKD fibrosis.

In terms of signaling pathways, the MAPK pathway plays an important role in fibrosis. High glucose can activate the MAPK pathway, promote ECM synthesis, apoptosis and expression of inflammatory factors, thereby exacerbating fibrosis [19]. In addition, the Wnt/β-catenin pathway is widely activated in DKD, and its continuous activation can induce EMT, promote fibroblast activation and inhibit ECM degradation, which has become a hot topic in recent years [20]. Excessive deposition and degradation imbalance of ECM leads to irreversible damage to kidney structure. In DKD, the imbalance of MMP/TIMP ratio reduces the ability of ECM to degrade, further promoting the accumulation of fibrosis [14] [18]. As ECM continues to accumulate, renal tubular atrophy, capillary dilatation and glomerular sclerosis gradually worsen, eventually leading to a continuous decline in renal function.

4. Chinese and Western Medicine Intervention Strategies for Diabetic Nephropathy

4.1 Western Medicine Intervention Strategies: from Metabolic Control to Inflammation-fibrosis Targeted Therapy

In terms of Western medicine treatment, traditional strategies mainly focus on metabolic control and hemodynamic regulation. Strict blood sugar control, blood pressure control, lipid regulation and blocking of the renin-angiotensin system are the basic measures. Among them, ACEI and ARB have been proven to reduce proteinuria and delay the progression of DKD, and are one of the most widely used treatment methods in clinical practice [21]. However, these measures mainly target metabolic and hemodynamic abnormalities and are difficult to completely block the continuous activation of inflammation and fibrosis. In recent years, new drugs have shown significant advantages in anti-inflammatory and anti-fibrotic effects. SGLT2 inhibitors not only improve blood sugar but also reduce glomerular hyperfiltration, inhibit the expression of inflammatory factors and reduce renal interstitial fibrosis, and are considered a major breakthrough in the treatment of DKD [22]. Finerenone, a nonsteroidal mineralocorticoid receptor antagonist, has shown significant reduction in renal inflammation and fibrosis markers in the FIDELIO-DKD and FIGARO-DKD studies, and is one of the

most promising anti-inflammatory and anti-fibrotic drugs [23]. In addition, GLP-1 receptor agonists such as liraglutide have also been shown to have anti-inflammatory and antioxidant effects, and can improve renal structural damage [24]. In terms of targeted therapy, NLRP3 inflammasome inhibitors, JAK/STAT inhibitors, and TGFβ pathway inhibitors have all shown the potential to inhibit inflammation and fibrosis in preclinical studies [25]. Some novel drugs, such as the antioxidant bardoxolone methyl, have shown improvement in renal function in early clinical trials, but their use has been limited due to safety concerns, suggesting that future drug development needs to strike a balance between efficacy and safety.

4.2 Traditional Chinese Medicine Intervention Strategy: Multi-Target Regulation of Inflammation and Fibrosis

In terms of traditional Chinese medicine treatment, traditional theory holds that the pathogenesis of DKD is mainly "deficiency of the root and excess of the branch," that is, deficiency of the spleen and kidney as the root, and damp-heat, blood stasis, and phlegm as the branches. Modern research shows that these pathogenesis mechanisms are highly consistent with inflammatory response, oxidative stress and fibrosis [26]. Astragaloside A can inhibit NF κB and TGF β/Smad pathways and reduce ECM deposition [27]; Tanshinone IIA can inhibit renal tubular EMT and improve renal interstitial fibrosis [28]; Berberine has multiple effects such as anti-inflammatory, lipid regulation and improvement of intestinal flora, and can significantly reduce DKD inflammation level [29]. In addition, traditional Chinese medicine compound prescriptions such as Liuwei Dihuang Wan, Huangqi Jianzhong Tang and Danshen Yin are widely used in clinical practice. Their multi-component and multi-target characteristics enable them to simultaneously regulate inflammation, oxidative stress, immune response and ECM remodeling, showing unique advantages [30]. In recent years, more and more experimental studies and systematic reviews have shown that traditional Chinese medicine compound prescriptions have certain clinical evidence in improving proteinuria and delaying the decline of renal function. For example, compound preparations based on Astragalus and Danshen significantly reduced the level of inflammatory factors and improved renal tubular interstitial fibrosis in animal models. These results suggest that traditional Chinese medicine (TCM) may provide a supplementary and alternative treatment for DKD through its comprehensive regulatory effects on multiple targets and pathways.

4.3 Synergistic Advantages of Combining TCM and Western Medicine

The advantage of combining TCM and Western medicine in treating DKD lies in the fact that Western medicine can precisely control metabolism and hemodynamics, while TCM can regulate the inflammation-fibrosis axis at multiple targets. The combination of the two can achieve a comprehensive intervention model of "controlling metabolism, anti-inflammation, and anti-fibrosis," thereby significantly reducing proteinuria, improving renal function, and delaying the progression of DKD. Studies have shown that the mechanism of action of combined TCM and Western medicine is closely related to the inhibition of key pathways such as NF-κB, TGF-β/Smad, and NLRP3 [26] [30]. In some clinical trials, patients receiving ACEI/ARB treatment combined with TCM compound treatment experienced a greater reduction in proteinuria and a longer duration of renal function maintenance. This synergistic effect is not only reflected at the molecular mechanism level but also in clinical outcomes. Future research directions should include multicenter randomized controlled trials to further verify the efficacy and safety of integrated traditional Chinese and Western medicine, and explore individualized treatment plans, thereby promoting the establishment of a comprehensive prevention and treatment model for DKD.

5. Summary and Outlook

Diabetic nephropathy (DKD), as one of the most serious microvascular complications of diabetes, has gradually evolved from a simple understanding of metabolic disorders to a new perspective of an "inflammation-fibrosis continuum." Numerous studies have shown that chronic inflammatory responses are not only the result of metabolic abnormalities but also key factors driving renal structural damage and functional decline, while fibrosis is an irreversible stage after persistent inflammation, ultimately leading to renal failure [31]. This shift in understanding provides a new direction for clinical treatment, namely, that on the basis of traditional metabolic control, interventions for inflammation and fibrosis must be addressed simultaneously.

In terms of treatment, Western medicines such as ACEI/ARB, SGLT2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists (finerenone), and GLP-1 receptor agonists have shown significant efficacy in delaying the progression of DKD in clinical trials [32] [33]. These drugs not only improve blood sugar and blood pressure, but also inhibit inflammatory response and fibrosis to some extent. However, existing treatments still have limitations, such as insufficient response to drugs in some patients or limited use due to side effects. Therefore, future research needs to further explore more precise targets, such as the NLRP3 inflammasome, JAK/STAT pathway and TGF β/Smad pathway, in order to achieve more effective dual blockade of inflammation and fibrosis [34]. Traditional Chinese medicine has shown unique advantages in the prevention and treatment of DKD. A large number of experimental and clinical studies have shown that Chinese medicine monomers such as astragaloside A, tanshinone IIA, berberine, etc., as well as compound prescriptions such as Liuwei Dihuang Pills and Danshen Decoction, can significantly improve inflammatory response and fibrosis through the comprehensive regulation of multiple targets and pathways [35] [36]. Its mechanism of action involves the inhibition of key pathways such as NF κB, TGF β/Smad, MAPK, as well as antioxidant, immune regulation and microcirculation improvement effects. In the future, research directions for traditional Chinese medicine should include the analysis of the molecular mechanisms of active ingredients, the development of standardized preparations, and the validation of multi-center clinical trials to promote its application internationally. The prevention and treatment of DKD needs to be based on precision medicine and multidisciplinary collaboration. First, the discovery and application of biomarkers will help in early diagnosis and

efficacy monitoring, such as inflammatory factors, fibrosis-related proteins, and metabolites in urine [37]. Second, integrated research in genomics, transcriptomics, and metabolomics will provide a basis for personalized treatment, helping to identify high-risk populations and develop differentiated intervention plans. Third, the comprehensive treatment model combining traditional Chinese and Western medicine deserves further promotion. By combining the precise metabolic control of Western medicine with the multi-target regulation of traditional Chinese medicine, a more comprehensive therapeutic effect is expected. Finally, future research should also focus on interventions in patients' lifestyles, including diet, exercise, and psychological support, which also play an important role in the regulation of inflammation and fibrosis [38]. In summary, the pathological mechanism of DKD has gradually become clear as an "inflammation-fibrosis continuum," which provides new ideas for treatment. Western medicine has made continuous breakthroughs in precise metabolic control and targeted inflammation-fibrosis, while traditional Chinese medicine has shown unique potential due to its multi-target advantages. In the future, with the application of biomarkers, in-depth research on molecular mechanisms, and the promotion of the integration of traditional Chinese and Western medicine, the prevention and treatment of DKD is expected to enter a new era of greater precision and comprehensiveness.

References

[1] Navarro-González JF, Mora-Fernández C. The role of inflammatory cytokines in diabetic nephropathy [J]. J Am Soc Nephrol, 2008, 19(3):433-442.

[2] Lim AKH, Tesch GH. Inflammation in diabetic nephropathy [J]. Mediators Inflamm, 2012, 2012: 146154.

[3] Klessens CQF, et al. Macrophages in diabetic nephropathy [J]. Kidney Int, 2017, 91(3):574-590.

[4] Mezzano S, et al. NF-κB activation and overexpression of regulated genes in human diabetic nephropathy [J]. Nephrol Dial Transplant, 2004, 19(10):2505-2512.

[5] Shahzad K, et al. NLRP3 inflammasome activation in diabetic kidney disease [J]. Nat Rev Nephrol, 2015, 11(7):398-414.

[6] Brosius FC, et al. JAK/STAT signaling in diabetic kidney disease [J]. Kidney Int Suppl, 2014, 4(1):64-70.

[7] Forbes JM, Cooper ME. Mechanisms of diabetic complications involving AGEs and MAPK pathways [J]. Physiol Rev, 2013, 93(1):137-188.

[8] Liu Y. Renal fibrosis: new insights into the pathogenesis and therapeutics [J]. Kidney Int, 2011, 79(2):144-156.

[9] Ziyadeh FN. Mediators of diabetic renal disease: the case for TGF-β as the major mediator [J]. J Am Soc Nephrol, 2004, 15 Suppl 1:S55-S57.

[10] Hills CE, Squires PE. The role of TGF-β in diabetic nephropathy [J]. Cytokine Growth Factor Rev, 2011, 22(3):131-139.

[11] LeBleu VS, et al. Origin and function of myofibroblasts in kidney fibrosis [J]. Nat Med, 2013, 19(8):1047-1053.

[12] Zeisberg EM, et al. Endothelial-to-mesenchymal transition contributes to renal fibrosis [J]. J Clin Invest, 2008, 118(8):2898-2910.

[13] Gilbert RE, Cooper ME. The tubulointerstitium in progressive diabetic kidney disease [J]. Kidney Int, 1999, 56(5):1627-1637.

[14] Fang L, et al. MAPK signaling in diabetic kidney disease [J]. J Mol Endocrinol, 2020, 65(1):R1-R15.

[15] Zhou L, Liu Y. Wnt/β-catenin signaling and kidney fibrosis [J]. Kidney Int Suppl, 2016, 6(1):84-90.

[16] Brenner BM, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes [J]. N Engl J Med, 2001, 345:861-869.

[17] Heerspink HJL, et al. Canagliflozin and renal outcomes in type 2 diabetes [J]. N Engl J Med, 2019, 380:2295-2306.

[18] Bakris GL, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes [J]. N Engl J Med, 2020, 383:2219-2229.

[19] Mann JFE, et al. Liraglutide and renal outcomes in type 2 diabetes [J]. N Engl J Med, 2017, 377:839-848.

[20] Brosius FC, et al. JAK inhibition in diabetic kidney disease [J]. Kidney Int, 2016, 89:22-24.

[21] de Zeeuw D, et al. Bardoxolone Methyl in type 2 diabetes and stage 4 CKD [J]. N Engl J Med, 2013, 369:2492-2503.

[22] Li P, et al. Traditional Chinese medicine in diabetic nephropathy: mechanisms and clinical evidence [J]. Front Pharmacol, 2020, 11:535.

[23] Zhang Y, et al. Astragaloside IV ameliorates renal fibrosis via TGF-β/Smad inhibition [J]. Phytomedicine, 2019, 62:152949.

[24] Wang X, et al. Tanshinone IIA attenuates renal fibrosis in diabetic rats [J]. J Ethnopharmacol, 2018, 214: 179-189.

[25] Derosa G, et al. Berberine and metabolic inflammation [J]. Clin Lipidol, 2012, 7:567-579.

[26] Zhang Xianjing, Chen Suzhen. Mechanism of action and treatment progress of traditional Chinese medicine in preventing and treating diabetic nephropathy and renal fibrosis [J/OL]. Journal of Shanghai Jiaotong University (Medical Edition), 1-10 [2026-01-25].

[27] Ma Zhanze, Li Han, Li Chongchai, et al. Research progress on the mechanism of action of Astragalus membranaceus and its main active ingredients in preventing and treating diabetic complications [J/OL]. Shizhen Guoyi Guoyao, 1-8 [2026-01-26].

[28] Yao Suyun, Cheng Xiaoping, Tian Yun. Effect of active ingredients of Salvia miltiorrhiza on the treatment of diabetic nephropathy

[29] Wu Wei, Feng Ruting, Han Lin. Systematic review of berberine in the treatment of diabetic nephropathy in mice and humans [J]. Henan Journal of Traditional Chinese Medicine, 2021, 41(11):1756-1764.

[30] Zhang Fengfeng, Yang Qianwen, Chen Yexin, et al. Analysis of TCM etiology, pathogenesis, syndrome differentiation and treatment and medication rules of diabetic nephropathy [J/OL]. Chinese Journal of Experimental Traditional Medical Formulae, 1-14 [2026-01-26].

[31] Thomas MC, et al. Diabetic kidney disease: pathophysiology and implications for management [J]. Lancet Diabetes Endocrinol, 2016, 4(4):303-314.

[32] Fioretto P, et al. SGLT2 inhibitors and the diabetic kidney [J]. Diabetes Care, 2016, 39 Suppl 2:S165-S171.

[33] Perkovic V, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy [J]. N Engl J Med, 2020, 382:2295-2306.
[34] Wanner C, et al. Empagliflozin and progression of kidney disease in type 2 diabetes [J]. N Engl J Med, 2016, 375:323-334.
[35] de Boer IH, et al. Diabetes and CKD: clinical and public health considerations [J]. Kidney Int, 2017, 91(1):21-33.
[36] Tuttle KR, et al. Diabetic kidney disease: a report from KDIGO [J]. Kidney Int, 2014, 86(4):753-764.
[37] Kato M, Natarajan R. Epigenetics and epigenomics in diabetic kidney disease and metabolic memory [J]. Nat Rev Nephrol, 2019, 15(6):327-345.
[38] Tang SCW, Yiu WH. Innate immunity in diabetic kidney disease [J]. Nat Rev Nephrol, 2020, 16(4): 206-222.