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Research Progress on the Pathogenesis of Diabetic Kidney Disease and Its Treatment with Traditional Chinese Medicine

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Abstract: ***Diabetic kidney disease (DKD) is one of the most common microvascular complications of diabetes mellitus and the leading cause of end stage renal disease (ESRD) worldwide. Of note, its prevalence is escalating rapidly both globally and in China. However, the pathogenesis of DKD is highly complex and remains incompletely elucidated to date. Recent studies have suggested that the pathogenesis of DKD may involve renal injury attributable to oxidative stress, inflammatory responses, autophagy dysregulation, and overactivation of the renin–angiotensin–aldosterone system (RAAS). Traditional Chinese Medicine (TCM) offers unique insights and therapeutic advantages in the management of DKD, with herbal formulas and classical decoctions having demonstrated favorable clinical efficacy. This article provides a comprehensive review of the pathogenesis of DKD and the relevant research on TCM interventions, aiming to offer novel perspectives for both investigative and clinical applications of TCM in the treatment of DKD.***

Keywords: Diabetic kidney disease, Mechanisms, Traditional Chinese medicine, Oxidative stress.

1. Introduction

Diabetic kidney disease (DKD) is one of the most common microvascular complications of diabetes mellitus and a leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide [1]. According to data released by the GBD 2021, the global number of adults with diabetes reached 537 million, accounting for 10.5% of the adult population — approximately one in ten adults—and it is projected that by 2050, the total number of people with diabetes will surge from 529 million to 1.3 billion [2]. Diabetes has thus become one of the major diseases posing a serious threat to human health globally. In China, the incidence of diabetes has also been increasing year by year. Studies have shown that in 2019, the crude incidence rate of diabetes in China was 265.45 per 100,000 population, and the age-standardized incidence rate was 204.31 per 100,000, representing increases of 63.12% and 15.93%, respectively, compared with 1990. The crude mortality rate was 12.16 per 100,000, and the age-standardized mortality rate was 9.44 per 100,000, representing increases of 105.41% and 2.61%, respectively, over the same period [3]. Moreover, with the rising number of diabetic patients, the prevalence of DKD has increased substantially. Approximately one-third of diabetic patients will develop DKD after a latency period of several years [4]. From 1990 to 2019, the age-standardized incidence rate of type 1 DKD in China showed an upward trend (APC = 0.04%, $P < 0.001$), while the age-standardized mortality rate (APC = −0.021%, $P < 0.001$) and DALY rate (APC = −0.013%, $P < 0.001$) exhibited downward trends. For type 2 DKD, the overall disease burden in China demonstrated an increasing trend (age-standardized incidence rate APC = 0.014%, age-standardized mortality rate APC = 0.001%, DALY rate APC = 0.027%; all $P < 0.001$) [5]. Therefore, there is an urgent need to comprehensively elucidate the pathogenesis of DKD and to identify targeted therapeutic agents. Recent studies have shown that Traditional Chinese Medicine (TCM) can lower blood glucose levels and ameliorate renal injury in the treatment of DKD, thereby offering novel perspectives for TCM-based therapeutic approaches [6].

2. Pathogenesis of Diabetic Kidney Disease

2.1 Oxidative Stress

Oxidative stress is a common product of multiple pathways involved in the pathogenesis of DKD and plays a critical role in its development. Diabetes mellitus is a chronic disease characterized by reduced insulin secretion or insulin resistance, and oxidative stress plays a key role in its onset and progression [7]. In diabetic kidney disease, persistent hyperglycemia leads to excessive production of reactive oxygen species (ROS), which in turn triggers oxidative stress damage and results in renal dysfunction. Moreover, overproduction of ROS can activate the NLRP3 inflammasome, leading to the activation of various inflammation-related cytokines, including interleukin-1β and interleukin-18, thereby inducing inflammatory responses and promoting collagen deposition, which contributes to renal fibrosis [8]. In the early stage of DKD, the proximal renal tubule is the primary target of oxidative stress, manifesting as vacuolar acidophilic structures, accumulation of PAS-positive material, and accelerated oxidative stress. In addition, in damaged proximal tubules, RAGE expression is upregulated, suggesting aberrant activation of the AGEs-RAGE signaling pathway, and oxidative-modified mitochondria accumulate through the impaired autophagy/lysosomal system [9]. Furthermore, oxidative stress-mediated mitochondrial damage plays a role in the pathogenesis of DKD [10].

2.2 Inflammatory Response

Inflammatory processes and immune cells are involved in the development and progression of diabetic kidney disease (DKD). In both human and experimental DKD, infiltration of monocytes/macrophages and activated T lymphocytes in the glomeruli and interstitium, as well as enhanced activation of

the Nlrp-3 inflammasome, have been observed [11]. In addition, the inflammatory cytokine CCL20 may participate in the NF-kappaB signaling pathway and regulate TH17 cells to influence the inflammatory progression of DKD [12]. Studies have shown that the expression of cell adhesion molecules, chemokines, and pro-inflammatory cytokines is increased in renal tissues of diabetic patients and animal models, and that diabetic kidney injury is ameliorated in mice deficient in pro-inflammatory molecules, suggesting that microinflammation is one of the pathogenetic mechanisms of DKD [13]. Moreover, cells involved in innate and adaptive immune responses can target the kidney due to increased expression of immune-related localization factors, and immune cells subsequently activate pro-inflammatory responses, including the release of autocrine and paracrine factors, further amplifying inflammatory damage to the kidney [14]. Of note, oxidative stress and the inflammatory response usually interact with each other and synergistically promote the progression of DKD.

2.3 Autophagy

Autophagy is a cellular process that degrades intracellular protein aggregates and damaged organelles through the lysosomal pathway [15]. To date, the role of autophagy in the development and progression of diabetic kidney disease (DKD) remains controversial. However, substantial evidence supports the view that the persistent hyperglycemic environment in DKD impairs autophagic activity in resident renal cells [16]. In rat models of both type 1 and type 2 diabetes, increased levels of the autophagy-related protein p62 have been observed in podocytes and tubular epithelial cells. In addition, clinical studies have found that renal tissues from patients with type 2 diabetes contain abundant p62 protein [17,18]. Furthermore, another clinical study has also revealed abundant p62 protein in the renal tissues of patients with type 2 diabetes [19]. The signaling pathways that regulate autophagy are mainly composed of three nutrient-sensing pathways: the mammalian target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), and silent information regulator 1 (SIRT1), along with intracellular stress-response signaling pathways. Some studies have indicated that an imbalance exists between autophagy-related nutrient-sensing pathways and intracellular stress-response pathways during the initiation and progression of DKD [20]. Moreover, inhibition of autophagy may lead to the accumulation of reactive oxygen species in mitochondria, which may contribute to the initiation of early diabetic kidney disease. Deficiency of autophagy in the kidneys of diabetic animals can render renal tubular cells more susceptible to hypoxia and endoplasmic reticulum stress, and may promote the progression of diabetic kidney disease [21].

2.4 Overactivation of the Renin–Angiotensin–Aldosterone System

Angiotensin II (Ang II) is the major active component of the RAAS, exerting rapid effects such as vasoconstriction and increased aldosterone secretion, which are essential for maintaining effective circulation. In diabetic kidney disease, RAAS activation may lead to abnormal renal hemodynamics, including elevated intraglomerular pressure, rearrangement of the podocyte cytoskeleton, and alterations in slit diaphragm components, ultimately impairing glomerular filtration function [22]. Angiotensinogen (AGT) is converted to angiotensin I (Ang I) by renin, and then to biologically active angiotensin II (Ang II) by angiotensin-converting enzyme (ACE). Ang II mediates renal injury through binding to its receptor AT1. RAAS activation promotes diabetic renal damage, and Ang II, via the AT1 receptor, increases intraglomerular pressure, leading to proteinuria, renal sclerosis, and fibrosis. In addition, other non-hemodynamic effects of Ang II, such as increased expression and release of pro-inflammatory and pro-fibrotic mediators, may also be involved in the pathogenesis of DKD [23]. Studies have demonstrated that inhibition of the RAAS can slow the progression of chronic kidney disease (CKD), characterized by reduced proteinuria and preservation of stable renal function [24]. Therefore, overactivation of the RAAS is inextricably linked to the pathogenesis of DKD.

3. Etiology and Pathogenesis of DKD in Traditional Chinese Medicine

The understanding of diabetes mellitus in Traditional Chinese Medicine (TCM) dates back to antiquity, where it was classified under the category of Xiaoke disease (wasting-thirst disorder). Its primary etiological factors and pathogenesis include improper diet, emotional dysregulation, congenital insufficiency, and deficiency of kidney yin, manifesting as a syndrome of yin deficiency with internal heat—where yin deficiency constitutes the root and dry-heat the manifestation. Early records of Xiaoke can be found in the Yellow Emperor's Inner Classic (Huangdi Neijing): "Spleen-dan (pi dan) … such patients must have consumed excessive sweet and fatty foods; fatness generates internal heat, sweetness causes central fullness, hence the qi overflows upward and transforms into Xiaoke." As for the treatment of Xiaoke, the earliest prescription is recorded in Zhang Zhongjing's Treatise on Cold Damage (Shanghan Lun), which states: "For febrile disease without high fever, with dry mouth and thirst, restlessness, and mild aversion to cold, Baihu Jia Renshen Tang (White Tiger plus Ginseng Decoction) is indicated." This employs the method of supplementing qi and nourishing yin to treat Xiaoke.

In TCM, DKD can be categorized under the disease entities of Xiaoke, edema (Shuizhong), retention of urine (Guange), and consumptive disease (Xulao). The kidney is considered the "foundation of innate constitution" and is responsible for governing water and storing essence. Long-standing diabetes impairs kidney qi, leading to kidney yin deficiency, which fails to generate yang qi, and over time progresses to deficiency of both yin and yang. Because patients with DKD present with microalbuminuria in the early stage and progress to heavy proteinuria—with proteinuria persisting throughout the disease course, often accompanied by hyperglycemia, hyperlipidemia, and hyperuricemia—Zhou Yujun proposed that "turbid toxin" (zhuo du) is a major pathological product of DKD and may also serve as one of the predisposing conditions for its occurrence. Based on different stages of DKD, the syndrome patterns are mainly classified as phlegm-turbidity with damp-toxin, phlegm-stasis with turbid-toxin, blood-stasis with turbid-toxin, and healthy-qi deficiency with turbid-toxin [25]. Currently, most TCM scholars consider that the pathogenesis of DKD is rooted in constitutional kidney

deficiency. The statement in Lingshu • Wubian—"Those with weakness in all five viscera are prone to Xiaodan (consumptive thirst)"—also supports the theory that congenital insufficiency predisposes to DKD. Congenital deficiency leads to spleen and kidney vacuity, and then pathogenic dampness, turbidity, stasis, and toxin become lodged in the vessels, triggering the disease [26].

Professor Yang Yufeng considers Liu Wansu's theory of "dry-heat with depressive stagnation" (zaore fuyu) to be of great significance in explaining the pathogenesis of DKD. He elaborates that endogenous dry-heat, with depression and stagnation internally, leads to deficiency of both spleen and kidney and obstruction of collaterals by blood stasis, resulting in DKD [27]. This theory shares common ground with the widely accepted "yin deficiency with internal heat" framework. The kidney is the foundation of innate constitution, and the spleen is the foundation of acquired constitution. In TCM, these two viscera are vital for human health and mutually support each other. Renal disorder, with decline of the gate of life fire (mingmen), leads to failure to warm the spleen, resulting in splenic disease; conversely, splenic disorder, with spleen yang deficiency, may over time impair kidney yang. Based on this theory, Professor Shi Yan holds that spleen deficiency is the fundamental basis for DKD and proposed the theory of "spleen governing transportation and transformation balance." In his view, splenic dysfunction prevents the normal transport and transformation of water and grain essences, generating turbid stasis, which is the key pathogenic factor in DKD [28].

In TCM, "collaterals" (luo mai) are the fine branches of the meridian system, crisscrossing throughout the body to distribute qi and blood and nourish all tissues. Kidney collaterals, as a subtype, are closely related to renal function. Prolonged disease affecting the kidney and injuring the kidney collaterals can give rise to various kidney-related disorders. Professor Guo Dengzhou, based on the TCM collateral disease theory, proposed that DKD is often associated with wind-pathogen invasion that damages the kidney collaterals [29]. Furthermore, based on the theory that "prolonged illness enters the collaterals," Yang Ruigeng et al. also believe that the pathological basis of DKD is deficiency of kidney collaterals, with the fundamental pathogenesis being "collateral deficiency with mass accumulation" (luo xu jia ju), and that wind-pathogen is an important contributing factor. They describe a pathological evolution of "collateral deficiency → mass accumulation → wind generation," where these three stages may occur sequentially or coexist concurrently [30].

Six-meridian syndrome differentiation (liu jing bian zheng) holds significant importance in TCM. Tang Yiting et al., from the perspective of six-meridian differentiation, pointed out that the kidney pertains to the Shaoyin meridian, which governs the pivot mechanism (shuji). Dysfunction of the Shaoyin pivot impairs the body's water metabolism, giving rise to DKD. The disorder of the Shaoyin pivot leads to blood stasis obstructing collaterals, internal dryness due to meridian depletion, and water accumulation internally, all of which contribute to the pathogenesis of DKD [31]. In summary, most scholars agree that the pathogenesis of DKD can be broadly summarized as constitutional deficiency — predominantly spleen and kidney deficiency—with turbidity, stasis, and wind-pathogen also being important pathogenic factors. TCM, with its holistic approach and integration of syndrome-based differentiation and meridian-based differentiation, plays an indispensable role in the treatment of DKD.

4. Traditional Chinese Medicine Treatment for DKD

4.1 Monomeric Compounds

Chinese herbal medicines possess advantages such as multi-target, multi-component, and multi-pathway actions, thereby offering a broad therapeutic scope and unique benefits in treating complex and chronic diseases. Therefore, for DKD—a complex chronic condition—TCM treatment holds significant importance. The medicinal properties of Chinese herbs are classified into five flavors: pungent, sweet, bitter, sour, and salty, each with distinct characteristics. As the disease location of DKD is in the kidney, with predominant kidney yang deficiency accompanied by turbidity and stasis, the therapeutic principle should emphasize sweet- and pungent-flavored herbs to warm and tonify the spleen and kidney, promote qi circulation, and activate blood, thereby achieving optimal therapeutic efficacy. The active components of Panax quinquefolius (American ginseng) and Carthamus tinctorius (safflower) have been shown to be effective in treating early-stage DKD, with 24 active constituents identified, of which 72 corresponding drug targets are associated with early DKD, effectively inhibiting early DKD nephritis and protecting renal function, which is of great significance for DKD treatment [32]. Total gypenosides from Gynostemma pentaphyllum can increase miR-125 expression, thereby suppressing inflammatory responses and improving cellular immune function in DKD, thus achieving therapeutic effects [33]. Treatment with Ganoderma lucidum polysaccharide peptide significantly reduced the apoptosis rate in renal tissue of mice, while also inhibiting inflammatory responses and oxidative stress, thereby ameliorating renal injury in DKD mice [34]. Anemarrhena saponins from Anemarrhena asphodeloides can reduce serum blood urea nitrogen (BUN), creatinine, and 24-hour urinary protein levels in renal tissue, and also decrease Smad3 protein expression while enhancing Smad7 protein expression, thereby inhibiting renal fibrosis and alleviating renal injury in DKD rats [35]. In addition, astragalosides, active components of Astragalus membranaceus (Huangqi), active components of Hedysarum polybotrys (Hongqi), total paeony glycosides from Paeonia lactiflora, and polysaccharides from Dendrobium and Polygonatum sibiricum have all been reported to delay renal damage and protect the kidneys [36].

4.2 Chinese Patent Medicines

Chinese patent medicines are pharmaceutical products manufactured from Chinese medicinal materials according to specified formulas and processing techniques, under the guidance of TCM theory. They are characterized by stable properties, reliable efficacy, relatively low toxicity and side effects, and convenience in administration, portability, and storage. Common dosage forms include injections, oral liquids, and oral solid formulations. The active ingredients in

Huangkui Capsule (Abelmoschus manihot) can improve renal function by lowering blood glucose, reducing 24-hour proteinuria, and decreasing BUN and creatinine levels, thereby delaying the progression of DKD [37]. Qishi Shenshu Capsule may alleviate renal pathological injury and improve renal fibrosis in DKD mice by inhibiting the TGF-β1/Smad2/3 signaling pathway, thereby reducing urinary microalbumin- to-creatinine ratios [38]. Qidan Tang Granule ameliorates renal injury by regulating the PI3K/Akt signaling pathway and decreasing the protein expression of p-PI3K/PI3K and p-Akt/Akt in renal tissue homogenates [39].

4.3 Herbal Formula Therapy

In ancient TCM, DKD falls within the categories of Xiaoke (wasting-thirst), Guange (retention of urine), and Shuizhong (edema). Its nature is characterized as "deficiency in the root and excess in the manifestation." The treatment of DKD primarily focuses on tonifying the kidney, supplementing qi and nourishing yin, activating blood, and promoting diuresis to reduce edema. The Bushen Jiangzhuo Formula (Kidney-Tonifying and Turbidity-Descending Formula), which is based on Liuwei Dihuang Pill and composed of Astragalus membranaceus, Dioscorea opposita (Shanyao), Codonopsis pilosula (Dangshen), Salvia miltiorrhiza (Danshen), Epimedium brevicornum (Yinyanghuo), and Euryale ferox (Qianshi), has been shown to promote SIRT1 expression to suppress pro-inflammatory cytokine levels and inhibit the MAPK/NF-κB signaling pathway to reduce inflammatory responses, thereby ameliorating renal injury and providing new insights for DKD treatment [40]. Professor Sun Wei, based on the fundamental pathogenesis of DN—yang deficiency and yin injury—proposed a staged differentiation and treatment approach using methods of warming yang and protecting yin. In the early stage, Professor Sun developed the "Qi and Yin Deficiency Formula for Diabetic Nephropathy" to support the healthy qi of the lung, spleen, and kidney while addressing both qi and yin deficiencies. In the middle stage, he formulated the "Spleen-Strengthening, Kidney-Tonifying, and Dampness-Resolving Formula" to resolve dampness and unblock stagnation while preventing injury to yin. In the late stage, he used the "Diabetic Nephropathy Formula for Kidney Deficiency with Damp-Turbidity Pattern" to warm yang and protect yin, while expelling pathogenic factors [41]. In addition, Professor Bi Liming [42] emphasizes the use of classical formulas and six-meridian differentiation, frequently employing classic TCM prescriptions such as Huangqi Guizhi Wuwu Decoction (Astragalus and Cinnamon Twig Five-Herb Decoction), Shenqi Pill (Kidney Qi Pill), Wuling Powder (Five-Ingredient Powder with Poria), Baihe Dihuang Decoction (Lily and Rehmannia Decoction), Baihu Jia Renshen Decoction (White Tiger plus Ginseng Decoction), and Fangji Fuling Decoction (Stephania and Poria Decoction) for treating DKD, with satisfactory outcomes. Since the pathogenesis of DKD is associated with injury to kidney collaterals, Professor Guo Dengzhou emphasizes tonifying deficiency and unblocking collaterals in the treatment of DKD. For the pattern of qi and yin deficiency with DKD, he selects modified Buyang Huanwu Decoction to supplement qi, activate blood, nourish yin, and unblock collaterals. For the pattern of wind lurking in kidney collaterals, he uses modified Shengjiang Powder to dispel wind and clear heat, and to ascend the clear and descend the turbid. For spleen-kidney yang deficiency pattern, he employs Zhenwu Decoction to warm yang, promote diuresis, strengthen the spleen, and dry dampness. For the pattern of mass obstructing collaterals, he uses modified Didang Decoction to transform turbidity, eliminate masses, and unblock and tonify the kidney collaterals [29]. Notably, Chen Guiping used warm needling (warm acupuncture) combined with Zhenwu Decoction to treat DKD of the spleen-kidney yang deficiency pattern, and the study concluded that modified Zhenwu Decoction combined with warm needling has good clinical efficacy in improving renal function in DKD patients [43].

5. Summary and Future Perspectives

The pathogenesis of diabetic kidney disease is complex, and TCM has demonstrated therapeutic advantages in its management. However, several issues currently exist. Although some clinical studies on TCM interventions for DKD have shown potential positive effects, the quality of these studies is uneven, which compromises the overall strength of the evidence in this field. Moreover, the long-term efficacy and underlying mechanisms of TCM for DKD remain insufficiently investigated. At present, research on monomeric compounds for DKD is more extensive than that on herbal formulas, possibly due to the complexity of formulas and the difficulty in controlling research variables. Nevertheless, TCM treatment has always emphasized a holistic approach; a formula, as a combination of multiple herbs, involves each herb playing a distinct role—sovereign, minister, assistant, and courier—with specific proportional ratios, which together achieve the maximum therapeutic effect. Therefore, future studies should place greater emphasis on the holistic concept, starting from the formula itself, focusing on clinical efficacy, so as to provide new ideas for the treatment of DKD and to generate new evidence for TCM-based therapies.

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