

The Staged Treatment of Diabetic Nephropathy Based on the Principle of “Using Collaterals for General Use”

Lijuan Zhang¹, Xiaohui Li^{2,*}

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

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

*Correspondence Author

Abstract: *The basic pathogenesis of diabetic nephropathy collateral disease is the syndrome of deficiency and excess of deficiency and excess of deficiency and excess of deficiency and excess of deficiency and excess of deficiency and deficiency of spleen and kidney, and the obstruction of kidney collateral by water dampness, phlegm and blood stasis and toxin. Therefore, dredging collaterals is the key treatment method. Based on this, this paper proposes the methods of replenishing qi, nourishing Yin and dredging collaterals, activating blood circulation, removing blood stasis and dredging collaterals, promoting water and removing dampness and dredging collaterals, collecting wind and dredging collaterals, nourishing kidney and detoxifying collaterals, warming Yang and dredging collaterals, which provide new ideas and methods for the treatment of diabetic nephropathy.*

Keywords: Diabetic Nephropathy, Collateral disease, Collateral-dredging method.

1. Introduction

Diabetic Kidney Disease (DKD) is a disease caused by diabetic microangiopathy and glomerular sclerosis, which leads to progressive renal function damage. It is one of the common complications of diabetic patients. It is estimated that by 2030, there will be 643 million diabetic patients in the world, and 30%-40% of them will progress to diabetic nephropathy [1]. Diabetic nephropathy (DN) is clinically characterized by persistent proteinuria and/or progressive decline in renal function. Diabetic nephropathy has no specific symptoms in the early stage, but with the progress of the disease, renal failure occurs, and the course of the disease enters the End stage renal disease (ESKD), which requires renal replacement therapy, seriously affecting the quality of life and survival time of patients. The occurrence of DKD is related to glucose metabolism disorder and renal hemodynamic changes, which in turn lead to renal oxidative stress, angiotensin II activation and inflammatory response, which not only affect the kidney, but also affect multiple organs of the whole body [2]. At present, western medicine treatments for patients with diabetic nephropathy include: reducing cardiovascular risk, controlling blood glucose, controlling blood pressure, inhibiting RAS, and new therapies including sodium-glucose cotransporter 2 inhibitors (SGLT-2i) inhibitors. However, some studies have shown that even with the above treatment methods, the majority of DKD patients still have an irreversible development trend of proteinuria and renal function, and the clinical symptoms have not been significantly improved, and there are adverse drug reactions [3]. Collateral disease is a disease caused by various factors, such as abnormal circulation of qi, blood, body fluid and obstruction of collaterals. In recent years, traditional Chinese medicine (TCM) based on the theory of collateralism has certain advantages in improving proteinuria, reducing renal injury, delaying renal function decline and improving quality of life in patients with DKD, and there are no obvious adverse

reactions. Chinese medicine to diabetic nephropathy due to “edema”, “kidney”, “block and repulsion” disease categories, such as winding said epidemiological analysis on the basic pathogenesis of diabetic nephropathy is the certificate of standard this virtual to real, vital qi is deficient, and qi stagnation and blood stasis, phlegm, drinks, water, wet poison and pathological products produced block renal collateral [4]. Treatment should know to eliminate pathogenic, regulating zang-fu.

2. Collateral Disease and Diabetic Nephropathy

2.1 Origin and Development of Collateral Disease Theory

The main research field of collateral disease is “venous-vascular system disease”, including cardiovascular and cerebrovascular disease, arrhythmia, chronic heart failure, peripheral vascular disease, diabetic vascular complications [5]. The theory of collateral disease was first introduced in Huangdi Neijing, which put forward the concept of “collaterals” for the first time and laid the theoretical foundation for collaterals and collaterals. Zhang Zhongjing, in the Eastern Han Dynasty, was the first to open the collaterals with Xinwen and warm, and to open the collaterals with insect drugs, which laid the foundation for the clinical differentiation and treatment of collaterals. The theory of collaterals made a major breakthrough and progress, represented by Ye Tianshi’s Clinical Guideline Medical Records in the Qing Dynasty. It was proposed that “long illness enters the collaterals” and “long pain enters the collaterals”, which made the theory of collaterals disease become mature [6]. In the modern era, Professor Wu Yiling combined with modern medical concepts, constantly developed and innovated. Through repeated verification of clinical practice and experimental research, the theoretical system of collateral disease was gradually improved.

2.2 Diabetic Nephropathy is Treated from the Perspective of Renal Collateral Disease

The different zangfu tissues of collaterals are also called heart collaterals, lung collaterals, liver collaterals, brain collaterals, kidney collaterals [7]. The collaterals of the kidney are small and dense, which have the function of sealing and storing essential qi and regulating the metabolism of body fluid. They store essence and fluid densely but do not discharge, detoxify and urinary diarrhea but do not hide [8]. The nephron is composed of renal corpuscles and tubules, and the glomerulus is composed of capillary loops. The process of exchange of kidney collaterals, fluid and blood is completed between the capillary loops. Professor Dai Enlai proposed that the perfusion structure of the renal collateral is similar to that of the glomerular capillary network in modern medicine. Academician Wu Yeling also proposed that the network structure of the spatial distribution of renal capillaries divided by layers of renal arteries is similar to the theory of “Sun Luo-microvessels” [9]. Therefore, it can be considered that the renal microvessels are affiliated to the renal collaterals, and the progress of diabetic kidney disease is consistent with the theory of “entering the collaterals after long illness” of traditional Chinese medicine. It is concluded that diabetic nephropathy can be treated from the perspective of collaterals and belongs to the category of “collaterals” and “kidney-collaterals”.

2.3 Choroidal Block is the Key to the Formation of Collateral Disease

The key to the formation of collateral diseases is that the collaterals are susceptible to the invasion of external pathogens, leaving the collaterals behind, or the collaterals are empty after a long illness, and the collaterals are deficient in qi, blood, Yin and Yang, resulting in the imbalance of qi and blood circulation of the collaterals, and the endogenesis of phlegm, turbidity, dampness and stasis, blocking the collaterals. The concept of “meridian” was first put forward in Zhang Zhongjing’s *Jin-Guiyao Lue* (Synopsis of Prescriptions of the Golden Chamber) in the Eastern Han Dynasty. “Congestion and obstruction of blood vessels” was a highly summary of the occurrence and development of the pathological evolution of venous diseases. Ye Tianshi first proposed that “long illness enters the collaterals” and “long pain enters the collaterals” in his *Medical Records of Clinical Guidelines*. It is believed that collaterals are divided into deficiency and excess, and are always characterized by obstruction of collaterals. The main lesions are qi stagnation, blood stasis or phlegm obstruction in the collaterals [10]. In modern times, Professor Wu Yiling summarized and established the modern theory of collaterals and collaterals, pointing out that the pathological changes of clinical patients with collaterals disease are a dynamic process, “the stagnation of collaterals, the blockage of collaterals, the stagnation of collaterals due to heat and poison, the deficiency of collaterals and the damage of collaterals”, and expounded the different stages of collaterals [11].

3. DKD Based on Stage Syndrome Differentiation and Treatment Based on “Collaterals are Used for General Purposes”

3.1 Early Stage of Diabetic Nephropathy

The clinical symptoms of early DKD are not particularly obvious, and the common clinical features include persistent proteinuria and edema [12]. According to the Guidelines for the Prevention and Treatment of Diabetic Nephropathy in Traditional Chinese Medicine, in the early stage of DKD, patients are wasting-and-thirst after a long illness, and glycotoxic fever damages Yin and consumes qi, most of them are deficient in both qi and Yin, and lose their kidney and vessels [13]. They are characterized by tiredness, low voice, dry mouth and throat, limb weakness, night sweat, shortness of breath, irritability, irritability and insomnia, dizziness or dizziness. Premature ejaculate, palpitation and chest tightness, pale or dark complexion, wrong nails, pain or numbness of limbs, dark red tongue and thin body, thin yellow tongue coating, heavy and astringent pulse [14]. In the treatment, attention should be paid to invigorating qi, nourishing Yin and clearing collaterals. Professor Liang Lige treated 60 patients with DKD with Shenqi Dihuang decoction (Radix pseudorhoeae, Radix astragalii, rhubarb, cinnamon twig, peach seed, Angelica sinensis, cherry seed, Radix sapidus, licorice), and the effective rate was 91.7% [15]. The biochemical abnormalities such as blood glucose and blood lipids were effectively improved. Liu Jianxun used Yiqi Yangyin Tongluo decoction (Astragalus membranaceus, Radix rehmanniae, Radix scrophulariae, Radix officinalis, Rhizoma officinalis, Rhizoma officinalis, Eumoides ulmoides, Salvia miltiorrhiza, Tongren, safflower, Dilong, mulberry branch, Jixueteng) and found that it could improve renal function and reduce inflammatory response in patients with DKD [16]. Yiqi-yangyin-tongluo Decoction can inhibit the apoptosis of renal tubular epithelial cells and inflammatory response by regulating the expression of miR-485-5p through lncRNA Urothelial carcinoma associated 1 (UCA1), thus playing a renal-protective role [17].

It is recorded in *Reading Medical Essays* that “Qi deficiency is not enough to push blood, so there must be blood stasis.” For a long time, kidney deficiency will inevitably show blood stasis. Kidney is the congenital origin, kidney Yang promotes the movement of qi, pneumatics promotes the movement of blood, qi deficiency is the movement of blood astringency and blood stasis. Therefore, kidney deficiency and blood stasis syndrome is also one of the main syndrome types of early DKD patients. Most patients have soreness and weakness of waist and knee, fixed pain of waist, numbness of limbs, tinnitus and deafness, sexual dysfunction, tongue ecchymosis, and astringent pulse. The principle of treatment is to strengthen the root and benefit the kidney, tonify qi and nourishing Yin, and promote blood circulation and dredging collaterals [18]. Professor Xu Lingdong used the method of activating blood circulation, removing blood stasis and clearing collaterals in the treatment of DKD patients, which showed that this method had the effect of reducing protein and blood viscosity [19]. In the DKD rat experiment, Professor Guo Dengzhou showed that the treatment methods of nourishing qi, removing blood stasis and clearing collaterals, such as Astragalus membranaceus, earthworm, Salvia miltiorrhiza, and aconitum aconitum, had a good effect on delaying the progress of DKD [20]. Modern studies have found that the commonly used drugs for promoting blood circulation, removing blood stasis and dredging collaterals,

such as Tue, lede, and earthworm, can delay the occurrence and development of diabetic nephropathy by improving hemodynamics, anti-oxidation, regulating cytokines, reducing the extracellular matrix of cytokines, and inhibiting the proliferation of glomerular mesangial cells. Baoshen-tongluo recipe is composed of Astragalus membranaceus, processed Rehmanniae, Cuscutazi, Liu Jienu, Guijuanyu, leeches, salvia miltiorrhiza and other drugs. On the basis of the drugs for tonifying kidney and qi, the whole prescription is supplemented with insect drugs, which plays the role of tonifying kidney, activating blood and dredging collaterals. Clinical trials have confirmed that Baoshen-Tongluo decoction has a good clinical effect in the treatment of DKD [21]. Baoshen-tongluo Decoction can alleviate podocyte injury in DKD, and its mechanism may be related to up-regulating the expression of Nephhrin in podocyte, down-regulating the expression of Desmin, and reducing podocyte apoptosis [22].

3.2 Middle Stage of Diabetic Nephropathy

In the middle stage of DKD, qi deficiency of spleen and kidney cannot transport water dampness, and qi deficiency cannot warm and promote blood circulation, resulting in the internal dampness and turbidity, and the pathological products of water intoxication and blood stasis. The pathogenesis is spleen and kidney deficiency, sealing and convergence failure, qi stagnation and blood stasis, and dampness. Most of the patients had swollen face and limbs, turgor urine, waist pain, heavy head and body fatigue, fatigue, abdominal distention, frequent urination, swarthy or dark face, increased nocturia, dark lips and claws, dim or dark red tongue, thin white or white greasy fur, heavy or thin astringent pulse [23]. Lishi Huayu Tongluo decoction (Fuling, red peony root, loofah, Lonicerae japonica, Astragalus membranaceus, Radix astragali, Radix astragali, Radix maogeni, Radix tujum, Niuxi) can significantly improve the clinical symptoms of patients with DKD, reduce mAlb/Cr, and delay the progression of renal function deterioration. Ma Li have achieved good clinical efficacy in the treatment of proteinuria and serum creatinine level in patients with renal failure in the middle stage of DKD by promoting spleen and nourishing kidney and promoting dampability, removing blood stasis and clearing collaterals [24]. Qiu Ping observed that Yiqi Lishi Huayu decoction could not only improve the level of proteinuria in patients with DKD, but also reduce serum inflammatory factors, improve vascular endothelial function, and correct hemodynamic abnormalities [25]. Yin Zhenxiang on the basis of conventional western medicine treatment, added Yangyin Yiqi, Lishi Huayu decoction to treat patients with DKD in the middle stage, achieved satisfactory results, especially can significantly reduce the serum creatinine level of patients and delay the decline of renal function [26].

3.3 The Middle and Late Stage of Diabetic Nephropathy

In the late stage of DKD, both qi and Yin are deficient, Yin is impaired and Yang is deficient, both Yin and Yang are deficient, and there are toxic and pathogenic reserves such as blood stasis and collateral obstruction, water drinking and dampness. Internal obstruction of Yang deficiency and blood stasis is the root of wasting-and-thirst and the key to systemic complications. Only strengthen kidney WenYangFang when

soup with kidney pills and supports to fly worm, plus astragalus, supporting the whole party, filling and elimination, has explored nourish Yin, promoting blood know lu, kidney drain turbidity effect, suitable for kidney Yin and Yang are two eccentric, Yang deficiency and blood stasis resistance of diabetic nephropathy. Wenyang Tongluo decoction warm Yang and open the collaterals, promote water and reduce swelling, achieve the purpose of treating both symptoms and root causes, and has the effect of regulating immunity, lowering blood sugar and lipids, anti-oxidation, enhancing immunity, so as to protect kidney function. It can effectively improve the blood glucose, blood lipid and clinical symptoms of diabetic nephropathy in the late stage, and the clinical effect is good [27]. Tongluo-yishen-wenyang Decoction is a combination of Shenqi pills and Diedang decoction to remove tabanworm and astragali astragali. The whole prescription is used to strengthen the body and dispel pathogenic factors. It has the effects of warming Yang and nourishing Yin, activating blood circulation and dredging collaterals, and nourishing kidney and reducing turbidity. It can reduce the expression level of Wnt4 and β -catenin, and improve the renal injury caused by the activation of Wnt/ β -catenin signaling pathway [28].

Wind is the long of all diseases, which is easy to attack the body surface, the lung is connected to the skin and hair, and the kidney meridian is connected to the lung. If the lung and kidney are insufficient, the wind pathogen is multiplied by the kidney deficiency and lies in the kidney collaterals. Or liver and kidney deficiency, internal wind germination, and each due to external wind pathogens, disturbance of the kidney collateral, can make the kidney of the seal failure, aggravate urine protein. Patients in the middle and late stages of DKD have symptoms related to wind pathogens such as urine foam, facial edema, dizziness, and pruritus. Diabetic kidney disease may not have obvious clinical manifestations in the early stage, but once it enters the stage of massive proteinuria, the disease progresses rapidly and changes greatly, and rapidly progresses to the stage of renal failure [29]. Professor Zhao Jinxi believes that the above characteristics of diabetic kidney disease are in line with the characteristics of “good actions and changes in number”. For “renal collaterals FuFeng pathogenesis,” a “wind differentiation” DKD is more frequently used functions of nourish medicine, medicine (such as drugs. Professor Zhao Jinxi Yiqi Qufeng Tongluo decoction (Astragalus membranaceus, Jijianyu, Burar Fructum, Pangshanlongus, Silkbud) can inhibit the excessive activation of P38-MAPK signaling pathway in mesangial cells of diabetic kidney disease, and inhibit the excessive secretion of inflammatory related cytokines such as MCP-1, ICAM-1, IL-1 β , IL-6, TNF- α , TGF- β 1 [30]. In the Medical Records of Zhang Yuqing, it is recorded that “once the pathogen enters the meridian, it is easy to enter and difficult to exit, and the potential can not escape without getting tired”. Scorpion, centipede, silkworm, Weiling xian, pangshanlong, etc. Both scorpion and centipede can dispel wind, relieve spasticity, relieve collaterals and pain [31]. It is recorded in Yu Catalpa Yao jie that the frozen silkworm can “activate the collaterals and open the meridians, drive the wind and open the bi”. It tastes salty and spicy and has the effect of drying dampness and dissipating phlegm, collecting the wind and clearing the collaterals. It can eliminate the evil qi of the kidney collaterals and promote the smooth of the body’s

collaterals. The above three are insect drugs, which can be searched and eviscerated, dredged up meridians and collaterals, and have the function of dispelling wind and soothing wind. Panglong is just pure and thick, and has the function of dispelling wind and dampness, activating blood circulation and clearing the lung and eliminating phlegm. Professor Zhu Liangchun and Tong Xiao-lin are good at using large amount of pangshanlong in the treatment of nephropathy. It can excise rheumatism and evil blood, make the kidney unobstructed, and can also get rid of phlegm. It can also get into the lung, clear the lung and dissipate phlegm, so as to promote the metabolism of water and fluid.

3.4 Late-stage Diabetic Nephropathy

In the late stage of DKD, the deficiency of five zang organs and the accumulation of pathological products such as phlegm, turbidity, blood stasis, and poison in the body, enter the collaterals after a long illness, and the damage and stasis of the kidney collaterals lead to renal dysfunction. A series of pathological changes occur, including the internal arrest of turbidity and poison, the damage of the kidney collaterals, and a variety of symptoms. A series of pathological changes occur. When the poison occurs on the muscle surface, the skin is pruritus [32]. Turdy poison on the offense, stomach disorder and healthy nausea and vomiting, loss of appetite; Kidney deficiency, turbid poison congestion three jiao, kidney can not open, there is oliguria or anuria and other "pass" performance. Qi and Yin deficiency and blood stasis syndrome, patients often see fatigue, less qi lazy speech, dry mouth, waist and knee soft, dizziness more dreams, or frequent urination more urine, hands and feet heart heat, palpitations, thin tongue, tongue dark or ecchymosis, less dry moss, pulse heavy thin asthenia. Clinical use of detoxifying the collaterals and protecting the kidney method, commonly used American ginseng, wolfberry, astragalus, raw rehmanniae, motherwort, salvia miltiorrhiza, earthdragon, rhubarb, coptis, hazel flowers and other treatment of wasting-and-wasting-and-wasting-nephropathy. Yishen Jiedu Tongluo capsule has the effect of activating blood circulation, removing blood stasis, nourishing liver and kidney, dredging and detoxifying. It has a significant effect on the treatment of DKD, which can reduce inflammatory factors, blood lipid and blood glucose levels, improve renal function of patients, and effectively delay the progression of DKD.

4. Summary

In the early stage of diabetic nephropathy, Shenqi Dihuang decoction and Yiqi Yangyin Tongluo decoction were used to promote blood circulation and remove blood stasis of kidney deficiency and blood stasis. In the middle stage, the prescription is Tongluo Lishi Huayu Tongluo decoction for promoting water and removing dampness. In the middle and late stage, the feng-clearing formula is selected to benefit qi and Qufeng-clearing; In the late stage, poison-damaged kidney collaterals are beneficial to the kidney, detoxifying and dredging the collaterals, and Yang deficiency is warming Yang and dredging the collaterals.

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