

Discussion on the Application of the Thought of "Chronic Disease Entering Collaterals" in Diabetic Nephropathy

Feng Tiantian^{1,a}, Xiao Yang^{2,b,*}, Wang Likun^{1,c}, Yang Hang^{1,d}

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

²Shaanxi Provincial Hospital of Chinese Medicine, Xi'an, Shaanxi, 710003, China

^a2088352668@qq.com, ^b99641710@qq.com, ^ckunyaha@163.com, ^d1076880297@qq.com

*Corresponding author

Keywords: Long-term disease entering collaterals; diabetes mellitus; nephropathy; collateral disease; theoretical treatment

Abstract: Diabetic nephropathy (diabeticnephropathy, DN) is one of the most common microvascular complications of diabetes. The main clinical symptoms are varying degrees of proteinuria, edema, hypertension and progressive decline of renal function, and renal failure in the late stage. Diabetic nephropathy belongs to the category of "Xiaxiao", "edema" and "turbid urine" in traditional Chinese medicine, which is also called "Xiaoke nephropathy" in modern medicine. "Long illness entering collaterals" is a treatment thought created by Ye Tianshi, a famous doctor in Qing Dynasty, which clearly puts forward the content of "qi knot in light at the beginning, blood injury in collaterals for a long time". The evolution law of the disease from superficial to deep, from surface to inside, from qi to blood is discussed from different angles. The theory divides collateral disease into deficiency and excess, which is always characterized by collateral stasis, and its main pathological changes are qi stagnation in collaterals, blood stasis or phlegm blockage. And established various methods of Xinwei Tongluo, thus forming a complete theory of collateral disease, creating a precedent for the etiology and pathogenesis of the disease to treat from collaterals. Traditional Chinese medicine classifies diabetic nephropathy as collateral disease, and collateral deficiency and blood stasis is its basic pathogenesis. Blood stasis runs through diabetic nephropathy and is the key factor in the occurrence and development of diabetic nephropathy. This paper discusses its application in diabetic nephropathy from the combination of the thought of "long-term disease entering collaterals" and modern medical micro-syndrome differentiation.

1. The formation and Development of collateral Disease Theory

The academic thought of "long illness entering collaterals" has a long history, which has been recorded as early as in the Internal Classic, the concept of "meridians" was recorded for the first time, and the basic composition and route of the meridian system were determined, and the physiological functions of the meridians were clarified. For example, "Lingshu Benzang" said: "Meridians, so the blood qi and yin and yang, muscles and bones, also beneficial to the joints." This is a summary of the function of meridians (collaterals) in life activities. "Lingshu Hai Lun" said: "the husband's twelve meridians belong to the mansion inside, and the outer collaterals lie in the limbs." The meridian

system plays a unified and coordinated role, connecting the viscera, limbs, facial features, muscles and bones into an organic whole. In addition, it also expounds the pathogenesis changes of meridians and guides the clinical diagnosis and treatment [1]. In the synopsis of the Golden Chamber in the Eastern Han Dynasty, Zhang Zhongjing discussed the syndromes related to the pathogenesis of "collateral stasis", such as liver disease, jaundice, edema, arthralgia syndrome and fatigue, and initiated the methods of activating blood circulation, removing blood stasis and dredging collaterals, which were not reported by the predecessors, which can be described as the inheritance of the theory of long-term disease into collaterals, creating a precedent for syndrome differentiation and treatment of collateral diseases. During the Ming and Qing dynasties, Wu Jutong as a representative created a perfect method for the treatment of collateral diseases, which laid a solid theoretical foundation for the treatment of collateral diseases in later generations. Wu Yiling's academic viewpoint of "three-dimensional network system" is popularized and applied to clinical and scientific research [2]. The theory of collateral disease has made great progress in the Qing Dynasty, mainly represented by Ye Tianshi. "long illness entering collaterals" and "prolonged pain entering collaterals" were put forward by Ye Tianshi on the basis of inheriting Zhang Zhongjing's "diagnosis and treatment of collateral diseases", which also marks the maturity of the development of collateral diseases. Ye Tianshi put forward the idea that "the qi knot is light at the beginning, but the blood injury enters the collaterals for a long time", and he also applied the thought of collateral diseases to febrile diseases, and the prescription for the treatment of collateral diseases has also been developed. Put forward the famous viewpoint of "collaterals with Xin as catharsis", and create the great method of dredging collaterals. Specifically, diseases can be divided into deficiency and excess, and those who are real are mainly Xinwen Tongluo, Xinrun Tongluo, Xinxiang Tongluo, insect ants Tongluo; those who belong to deficiency, put forward that "the deficiency of collaterals is the most suitable for tonifying", and there are Xingantong tonifying and nourishing Tongtong. The analysis of its drug use can be divided into two aspects: on the one hand, drugs for dredging collaterals (drugs that enter collaterals), such as drugs for entering collaterals, drugs for insects, etc.; on the other hand, attention should be paid to the compatibility of drugs for dredging collaterals on the basis of syndrome differentiation and treatment. That is, the combination of dredging collaterals and other treatments [3].

2. Collaterals and kidney collaterals

The progression of diabetic nephropathy is related to the course of diabetes. Most diabetic nephropathy occurs on the basis of long-term poor blood glucose control, so it accords with the characteristics of "long-term disease entering collaterals". Collaterals are the branches of meridian system [4], which are subdivided into fifteen different collaterals, sun collaterals, floating collaterals and blood collaterals, as well as Yin collaterals, Yang collaterals, visceral collaterals, fu collaterals, collaterals and entanglement collaterals. its unique physiological functions include osmosis of blood gas, mutual infiltration of blood, penetration of Ying Wei, ensuring meridian circulation, etc., which is the bridge and hub of qi and blood nutrition in meridians[5]. The glomerulus is composed of a mass of capillaries, and each capillary intersects with each other, forming a capillary network, with a large distribution of capillaries and slow blood flow, which coincides with the characteristics of collaterals in traditional Chinese medicine. The flow of qi and blood in collaterals is slow, and the more it stays, the deeper it is. At the same time, it also determines the characteristics of collateral disease, which is easy to enter and difficult to get out, and easy to accumulate and form. "Acupuncture and moxibustion Dacheng" reads: "Meridians 12, collaterals 15". "Its internal root is in the kidney, which is the foundation of life." Collaterals are graded layer by layer, extending to the kidney as kidney collaterals. Kidney collaterals have the physiological basis of "branches elsewhere, network distribution, crisscross, thin and narrow", so evil is easy to enter but difficult to get out, evil qi is easy to stagnate,

and stasis is most likely to occur [6].

3. The relationship between DN and congestion

3.1. Phlegm and Blood stasis blocking collaterals is the basis of collateral Disease of DN

According to traditional Chinese medicine, "deficiency of phlegm and blood stasis" is not only the basis of collateral disease, but also the pathological basis of kidney collateral disease. Specifically, phlegm in traditional Chinese medicine is not only the pathogenic factor of the disease, but also the pathological product of abnormal body fluid metabolism. Phlegm fluid blocks the movement of qi and blood, affects water metabolism, causes a wide range of diseases and is varied, as the saying goes, "phlegm is mostly caused by phlegm". In the progress of diabetic nephropathy, phlegm drink runs through the whole process. Unregulated diet, excessive fat and sweet taste, endogenous phlegm drink, impaired spleen and stomach function, spleen does not disperse essence, kidney failure, resulting in proteinuria; on the other hand, phlegm drink endogenous, damp-heat blocking collaterals, stubborn phlegm in the kidney collaterals, easy to enter and difficult to get out, long-term accumulation, damage to kidney qi, a long time can lead to the occurrence of diabetic nephropathy. Blood stasis refers to the pathological products formed by slow stagnation or stagnation of blood in the body. It is characterized by affecting water and fluid metabolism, affecting the formation of new blood, blocking qi and so on. In the state of diabetic nephropathy, abnormal glucose metabolism, heavy glucose load of kidney, increase of glomerular volume and capillary surface area lead to the increase of glomerular blood flow and capillary intravascular pressure. Due to the high perfusion pressure of glomeruli, it leads to the increase of intravascular blood viscosity, blood hypercoagulability, poor blood flow, slow blood flow and blood stasis, which is in line with the characteristics of diabetic nephropathy. Lu Renhe [7] put forward the theory of "microcosmic formation" in the complication of diabetic nephropathy. It is considered that the pathogenesis of blood stasis does exist in diabetic nephropathy and its complications, but the blood stasis of DN complications is caused by diabetes, which cannot be cured or cannot be cured for a long time, entering collaterals, damaging yin and consuming qi, phlegm stagnation and heat and blood stasis cementing each other, forming mini-syndrome. Wu Yiling [8-9] put forward that the accumulation of collaterals is the pathological change of diabetic nephropathy. "Lingshu hundred Diseases at the beginning" said: "stay in the pulse, stay but not go, rest and accumulate. "Or Sun pulse, or collaterals, or meridians", collaterals accumulation is evil qi to retain collaterals, stasis or stasis for a long time, blood stasis and phlegm accumulation block the formation of kidney collaterals. In short, in the progress of diabetic nephropathy, phlegm stasis throughout, is its main pathological changes, in the treatment of diabetic nephropathy, we should also pay attention to its role.

3.2. DN promotes the formation of congestion

DN is a microvascular complication of diabetes, characterized by hyperfiltration and Mesangial matrix dilatation, resulting in renal hypertrophy, glomerular basement membrane thickening, subsequent podocyte and glomerular injury, and renal tubule injury, resulting in glomerulosclerosis and tubulointerstitial fibrosis. The pathogenesis of DKD is multifactorial, and many structural, hemodynamic and inflammatory pathophysiological processes are involved in the occurrence and development of the disease. The main results are as follows: (1) due to long-term hyperglycemia, the renal blood flow is on the high side, resulting in osmotic effect, resulting in high glomerular perfusion, damage to renal capillaries, stenosis or even occlusion of renal vascular lumen, and aggravation of renal injury; hyperglycemia leads to renal hypertrophy through the production of advanced glycation end products (AGEs), oxidative damage and hypoxia. Polyol, protein kinase C (PKC) and

hexosamine pathway are also involved in the pathogenesis of DKD caused by hyperglycemia. All of these pathways can stimulate a variety of growth factors, including insulin-like growth factor-1, epidermal growth factor, platelet-derived growth factor, vascular endothelial growth factor, transforming growth factor- β (TGF- β) and angiotensin II (AngII). (2) DN can damage renal vascular endothelial cells, accumulate a large number of platelets, and cause thrombosis. (3) The occurrence and development of DN is closely related to inflammation, such as tumor necrosis factor, interleukin-1, interleukin-6 and so on. Studies have shown that these inflammatory mediators have an important effect on blood stasis syndrome and may play an important role in promoting thrombosis [10]. Hyperglycemia causes cell damage and triggers the release of pro-inflammatory mediators, including chemokines such as tissue necrosis factor- α (TNF- α) and interleukin-1 (IL-1), adhesion molecules and injury-related molecular patterns. This leads to the recruitment of inflammatory cells, such as macrophages, monocytes, activated T lymphocytes, and nodal receptor protein 3 (Nlrp-3) inflammation-masome to the kidney. The accumulation of macrophages in glomeruli produces cytokines, reactive oxygen species (ROS) and proteases, which lead to renal injury and fibrosis, leading to the progression of DKD. (4) Modern studies have shown that the occurrence of DN is also related to oxidative stress. Chronic hyperglycemia also stimulates the production of polyol pathway AGEs and activates PKC, resulting in the increase of ROS level and oxidative stress level. Increased renal ROS levels can lead to damage to essential cellular components and DNA, as well as endothelial dysfunction, which is a landmark feature of T2DM and DKD. Endothelial dysfunction is characterized by decreased bioavailability of nitric oxide and increased oxidative stress. The decrease of endothelial nitric oxide synthase leads to the increase of ROS production and oxidative stress, which is related to the progress of DKD in the experimental animal model.

4. Treatment of Diabetic Nephropathy from collateral Disease

For diabetic nephropathy under the guidance of the thought of "chronic disease entering collaterals", we think that from the point of view of the word "Tong", we think that the kidney collaterals should be used as a function, as a tonic, and as a tonic. In fact, some traditional Chinese medicines with the effect of promoting blood circulation, removing blood stasis and dredging collaterals have been widely recognized in the treatment of diabetic nephropathy, and it has been shown that its main mechanism [11] is as follows: (1) constricting renal small vessels, reducing capillary permeability and reducing urinary protein. (2) Improve blood circulation, especially microcirculation, increase the supply of blood oxygen in kidney, promote the absorption of necrotic tissue, accelerate the repair and regeneration of injured tissue, inhibit glomerular fibrosis, malacia or absorption of proliferative lesions, and speed up the recovery of renal function. Specific treatment is divided into the following five aspects: first, long-term disease must be stasis, in the treatment of diabetic nephropathy, *Salvia miltiorrhiza*, safflower, peach kernel and other drugs should be used to activate blood circulation and remove blood stasis. Professor Xu Lingdong et al. [12] in the study of treating DKD patients with phlegm, removing blood stasis and dredging collaterals showed that it has a good effect of reducing protein and blood viscosity. Professor Guo Dengzhou [13] showed in the experiment of DKD rats that the therapeutic methods of invigorating qi and blood stasis and dredging collaterals, such as *Radix Astragali*, *Dilong*, *Salvia miltiorrhiza* and *Wusaohe*, can delay the progress of DKD. Second, long-term illness will be deficiency, long-term illness into collaterals is often due to deficiency, so we should pay attention to tonifying deficiency, with tonifying as the pass, treatment often choose yam, cooked *Rehmannia*, Chinese wolfberry, *Ligustrum lucidum*, *Cornus officinalis* and so on, in order to tonify kidney and fill essence, nourish meridians and collaterals [14]. Yu Ying and Ren Yuezhong [15] self-made Buxu Tongluo Jiangtang recipe (*Radix Astragali*, Yam, *Radix Paeoniae Alba*, *Radix Rehmanniae*, *Ligusticum chuanxiong*, *Gynostemma pentaphyllum*, *Salvia*

miltiorrhiza, Safflower, etc.) can not only replenish qi and nourish yin, activate blood circulation and remove blood stasis, but also reduce blood glucose and blood lipid, regulate immunity, antioxidation, improve microcirculation, improve the condition of early DN patients and delay complications. Third, for the syndrome of long-term pain and blood stasis, Ye Tianshi praised Zhang Zhongjing's treatment of dredging collaterals, pointing out that the insect medicine "ascends those who fly, descends those who walk, and moves quickly". The meritocratic "chasing the evil of deep mixed qi and blood" and "searching and eliminating the evil mixed in collaterals" makes the treatment of insects dredging collaterals become a prominent feature of the treatment of collateral diseases. Even for the syndrome of deficiency of collaterals, Ye Tianshi also believes that "the place of extreme deficiency is the place of tolerating evil", advocating that "the deficiency of collaterals is the most appropriate to tonify and tonify" and use "Xin Gan Wen Bu, supplemented by popular venation". Tabanworms, leeches, scorpions, turtle beetles, dung beetles, black snakes, earth dragons and other drugs are often selected to search the wind and dredge collaterals. It is found that *Hirudo* has anticoagulant and antithrombotic effect, and its decoction extract can reduce whole blood specific viscosity and plasma specific viscosity. The experimental results in vitro suggest that *Hirudo* has the effect of activating fibrinolytic system and can directly dissolve thrombus [16]. In the treatment of DN, it can not only reduce urinary protein, but also delay renal deterioration. Thrombolytic peptide extracted from *Trionyx sinensis* is also a better clinical drug for removing blood stasis [17]. *Dilong* can not only clear collaterals, but also has the effect of anticoagulation and antithrombosis. It has been proved that it can inhibit platelet aggregation or directly degrade fibrin and fibrinogen to dissolve thrombus [18]. Fourth, phlegm drink is the pathogenic factor and pathological product in the occurrence and development of diabetic nephropathy. "Spleen is the source of phlegm and lung is the cause of storing phlegm". In the course of treatment, we should consider resolving phlegm, tonifying spleen and dredging collaterals from the point of view of spleen, lung and kidney. *Pinellia ternata*, tangerine peel, gallbladder Nanxing and other drugs are often used. Fifth, long-term disease into the collaterals, phlegm, blood stasis accumulated in the kidney collaterals, over a long period of time, the formation of the disease, so in the process of treatment, we should pay attention to the compatibility of *Trigonella*, zedoary, leeches, peach kernels and other drugs.

5. Examples of experience cases

The patient, Meng, male, 49 years old, complained of mental fatigue and dry mouth for more than 10 years with sore waist and knees for more than 4 months. Self-reported patients with "diabetes" for more than 10 years, oral hypoglycemic drugs, subcutaneous injection of insulin (specific unknown) alternate treatment, blood sugar when high and sometimes low. Since April, the shape of thin limbs is cold, waist and knees are sore and weak, frequent urination, turbid urine, fatigue and drowsiness, hand and foot heart fever, dizziness and tinnitus, night sweats, skin itching. The tongue is red, the coating is less and dry, and the pulse is heavy and thin. Auxiliary examination: urine routine: urine protein 3 +. Traditional Chinese medicine diagnosis: Xiaoke disease nephropathy. Syndrome differentiation: sugar poison injures the kidney and deficiency of both yin and yang. Western medicine diagnosis: diabetic nephropathy, treatment principles: tonifying the kidney and nourishing essence, detoxification and balance. Prescription: *Yishen Tiaozhong* decoction with modified flavor. Composition: *Radix Astragali* 35g, *Rhizoma Polygonatum* 35 g, cooked land 28g, *Cornus officinalis* 14g, *Cortex moutan* 10g, *alisma alisma* 10g, *Poria cocos* 10g, *Salvia miltiorrhiza* 17.5g, *Schisandra chinensis* 7g, *Trichosanthes* 17g, cinnamon 3G, mulberry branch 3G, floating wheat 30g, *Baimao* root 30g. Six doses, one dose a day, fried in water. The second diagnosis: the upper part of the suit was weak and cold, the waist and knees were obviously relieved, the frequency of urination decreased, dry mouth, hot hands and feet, night sweats were obviously improved. The tongue is light red, the

moss is few, the pulse is heavy and thin. Fasting blood glucose (7.1mmol/l) and postprandial blood glucose (8.2mmol/l) were measured. Urine routine: urine protein 2 +. The upper part was followed by 12 doses. Three diagnoses: the symptoms continue to decrease, the tongue is pale, the moss is few, and the pulse is heavy. Since then, with syndrome differentiation and treatment for more than 4 months, the symptoms of the patients have disappeared, the urine protein (-) and blood sugar are basically normal.

Note: sugar poison injures, blood stasis and toxin knot each other, and for a long time it hurts the kidney. Kidney yin and yang, essence qi are deficiency, so the shape of cold limbs, fatigue and tiredness. Kidney deficiency constrains no right, so frequent urination; kidney deficiency, spleen does not disperse essence, Shuigu fine injection, and see turbid urine; dizziness and tinnitus, waist and knees sore and weak, kidney deficiency essence deficiency, brain pulp loss, kidney viscera failure sign; Yin deficiency is internal heat, deficiency fire internal disturbance, so see hand and foot heart heat; yin essence deficiency, skin loss of maintenance, so skin itching; red tongue, few but dry fur, fine pulse are caused by sugar evil injury kidney, yin and yang deficiency. The prescription uses astragalus, Huangjing, salvia miltiorrhiza, mulberry twig to tonify the qi of the five internal organs, remove blood stasis in the body, dispel wind and heat and dredge collaterals; ripe ground filling essence and tonifying kidney; Fructus Corni tonifying essence and strengthening kidney; Chinese yam tonifying spleen yin and taking essence, so that spleen qi is healthy and kidney essence is active. Three drugs are combined to achieve the purpose of three tonifying; Poria cocos, alisma alisma and Cortex moutan are combined to clear away deficiency heat, prevent and nourish greasy; Cistanche deserticola and cinnamon warm and tonify kidney yang; Schisandra chinensis, floating wheat, white thatch root, trichosanthus clear heat and cool blood, collect yin and promote fluid, clear heart and stop perspiration; all medicines are used together to play the function of tonifying kidney and nourishing essence, detoxification and strengthening.

6. Summary

To sum up, we mainly start from Ye Tianshi's thought of "chronic disease entering collaterals", combine collateral disease theory with modern medical microscopic syndrome differentiation, macroscopic and microscopic, and analyze the pathogenesis and pathological characteristics of kidney collaterals in diabetic nephropathy. From the formation and development of collaterals theory, the relationship between collaterals and kidney collaterals, and the collateral disease basis of diabetic nephropathy, we finally discussed the treatment of diabetic nephropathy. That is, "take communication as supplement and use as application", and discuss it from five aspects.

References

- [1] Li Shunmin, *Modern Nephrology [M]*. Beijing: China traditional Chinese Medicine Publishing House, 2019: 270
- [2] Zang Ningzi, Pang Lijian, Zhu Lingyun, et al. *The Origin and Development of collateral Theory [J]*. *Journal of Liaoning University of traditional Chinese Medicine*, 2014 *Journal* 16 (10): 66-69
- [3] Li Jinyong, *Jingui want to give a brief speech [M]*. Beijing: people's Health Publishing House 2008
- [4] Wang Xiaohe. *Editor. History of Chinese Medicine [M]*. Beijing: science Press, 2000.156.
- [5] Xu Cankun, Cao Yiling, Xie Fang. *treatment of chronic complications of diabetes from collaterals [J]*. *Shandong Journal of traditional Chinese Medicine*, 2002 21 (7): 390
- [6] Jia Xiuqin, Zhang Xiaoli, Yang Jihong, et al. *Study on kidney collaterals of chronic kidney disease based on modern literature [J]*. *Chinese Journal of Integrated traditional Chinese and Western Medicine Nephropathy*, 2016, 17 (8): 751-752.
- [7] Lu Renhe, Zhao Jinxi, Wang Shidong. *Clinical study of diabetes and its complications [J]*. *New traditional Chinese Medicine*, 2001: 33 (3): 3-5
- [8] Wu Yiling. *Characteristics and changes of pathogenesis of collateral disease [J]*. *Journal of difficult and difficult Diseases*, 2004 *Tantra* 3 (5): 282

- [9] Wu Yiling, Wei Cong, Jia Zhenhua, etc. Treatment of Diabetic Nephropathy from collateral Diseases and related Research [J]. *Journal of difficult Diseases* 2007 ; (6): 350
- [10] Ma Xiaojuan, Yin Huijun, Chen Keji. research progress on the relationship between blood stasis syndrome and inflammation [J]. *Chinese Journal of Integrated traditional Chinese and Western Medicine*, 2007 27 (7): 669-672.
- [11] Bai Yaling, Cai Jimin, Xu Qingyou, etc. Application of the theory of "chronic disease entering collaterals" in diabetic nephropathy [J]. *Journal of difficult Diseases* 2006;1671- 6450(2006)04- 0278- 02
- [12] Xu Lingdong, Guo Huijiang. Treatment of 82 cases of Diabetic Nephropathy by removing Blood stasis and activating Blood Circulation and dredging collaterals [J]. *Liaoning Journal of traditional Chinese Medicine*, 2000,527 (1): 17-18
- [13] Guo Dengzhou, Wang Yuehua, Bian Dong, et al. Effect of Huoxue Huayu Xiaozhuo Tongluo Herbal Medicine on angiotensin system in Rats with Diabetic Nephropathy [J]. *Journal of traditional Chinese Medicine*, 2010, 51 (1): 75 -78
- [14] Huang Xuekuan. Professor Guo Ziguang's clinical experience in applying the theory of "long illness entering collaterals" [J]. *Teaching and Education of traditional Chinese Medicine*, 2000,519 (1): 59-60.
- [15] Yu Ying, Ren Yuezhong. Clinical observation of self-made Buxu Tongluo Jiangtang recipe in the treatment of early Diabetic Nephropathy [J]. *Chinese Science and Technology of traditional Chinese Medicine*, 2018 25 (5): 747-749.
- [16] Xiu Xia, Nie Haiyan, Han Hongxia, et al. A review of chemical constituents and pharmacological effects of leeches [J]. *Chinese Tropical Medicine*, 2005 minute 5 (8): 1733-1734.
- [17] Zhang Xiaoli, Li Kun. Isolation, purification and thrombolytic activity of polypeptides from *Trionyx sinensis* [J]. *Chinese Journal of Experimental Pharmaceutics*, 2013, 19 (14): 53-55.
- [18] Liu Wenya, Wang Shudong. Research Progress on Pharmacological Action of Dilong [J]. *Chinese Journal of Integrated traditional Chinese and Western Medicine*, 2013jue 33 (2): 282-285.9.