

Research Progress on Chinese Medicine Treatment of Diabetic Nephropathy

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Abstract: Diabetic nephropathy is a type of renal microvascular disease caused by diabetes, and it is also an important cause of chronic renal failure. In the treatment of this disease, modern medicine mainly adopts methods such as lowering blood sugar, lowering blood pressure, regulating lipid metabolism, improving microcirculation, and reducing inflammatory stimulation. Western medicine does not show significant efficacy in relieving the symptoms of patients with diabetic nephropathy and alleviating the progression of the disease, and there are many adverse reactions. Therefore, the research on traditional Chinese medicine for diabetic nephropathy has received widespread attention from modern scholars. The differentiation and staging of this disease in traditional Chinese medicine is currently not unified. The traditional Chinese medicine treatment of diabetic nephropathy is divided into internal treatment (treatment based on staging, differentiation, prescription verification, and formulation) and external treatment (acupuncture, ear press pellet, and moxibustion). However, scholars have not yet formed unified opinions on the pathogenesis, differentiation and staging, and treatment of diabetic nephropathy, and there is no consistent diagnosis and treatment standard. The research on traditional Chinese medicine treatment of diabetic nephropathy still has a long way to go.

1. Introduction

Diabetic nephropathy (diabetic nephropathy, DN) is a microvascular disease that occurs in the kidney, secondary to diabetes; at the same time, the formation of chronic renal disease and end-stage renal disease, the primary cause is also DN [1]. By 2030, the number of people with diabetes worldwide is expected to reach 439 million. At the same time, one of the most common complications of type 2 diabetes is DN, so it is urgent to improve the symptoms of diabetic nephropathy and control the development of DN [2]. The main principles of western medicine for the treatment of DN are: reducing blood sugar, controlling blood pressure, regulating lipid metabolism, improving microvessels, reducing inflammatory stimulation, etc [3]. However, the therapeutic effect is limited, and the adverse reactions are more obvious, so modern scholars pay more attention to the role of traditional Chinese medicine in the treatment of diabetic nephropathy. Scholars of traditional Chinese

medicine have found that traditional Chinese medicine has great advantages in improving the clinical manifestations of patients with DN and delaying the occurrence and development of DN. This article will overview the etiological factor and pathogenesis of diabetic nephropathy, clinical classification, TCM stages, TCM treatment methods and other aspects.

2. The etiological factor and pathogenesis

2.1. Ancient doctors' understanding of the etiological factor and pathogenesis of DN

Looking back to the ancient medical books, DN does not have this term. According to the manifestations of the disease: hunger and excessive eating, turbid urine, edema, dark complexion, nausea, vomiting, constipation and etc can belong to the scope of diseases such as turbid urine, edema, Guange, retention of urine and so on. "DN can be divided into three types in accordance with the lung, stomach and kidney. The manifestations of kidney deficiency include drinking more water when thirsty, frequent urination, and the floating of an oily substance in urine, which is as sweet as bran... The lower limbs are more prone to edema, accompanied by symptoms of yin deficiency [4]. The contents discussed in the "Wai Tai Mi Yao" are similar to the clinical manifestations such as proteinuria and edema. This medical book believes that the occurrence of DN is related to a preference for fatty foods, taking Wushi powder in childhood, unrestrained sexual activity, and heat generation in the five organs and six organs, and so on. The famous doctor Ye Tianshi of the Qing Dynasty once said, "The San Xiao is actually due to Yin deficiency and Yang excess, insufficient body fluid, and vigorous qi in the five organs." Some people point out that the pathogenesis of DN is related to Yin deficiency and Yang heat. However, the author of "The Three Xiaos Theory" [6], Liu Wansu believes that insufficient kidney water in the lower jiao cannot restrict the heart fire of the upper jiao, leading to dry throat, thirst, and frequent urination. "The Shengji Zonglu "says, "Shenxiao is caused by excessive sexual activity and taking Wushi San in childhood, resulting in extreme lack of essence and blood". All of the above indicate the etiology of Shenxiao [7].

2.2. Research on etiological factor and pathogenesis of DN by modern TCM scholars

Professor Yan Bing [8] believes that the occurrence of DN is closely related to the spleen and kidney, and the spleen is the acquired foundation. Spleen deficiency will not only affect the function of other viscera, but also affect the metabolism of water; the kidney is the congenital foundation, in which the memory of yuan yin and yuan yang plays an important role in the process of water metabolism. At the same time, the pathogenesis of blood stasis continues throughout the development of diabetic nephropathy, so he emphasizes the use of drugs for promoting blood circulation and removing blood stasis in the treatment of DN patients. Professor Zhang Lan [9] pointed out that the pathogenesis of early DN is deficiency of spleen and kidney, with phlegm-dampness and blood stasis throughout. Its essence is that deficiency in origin and excess in superficiality. Zhang Daning [10] believes that the pathogenesis of diabetic nephropathy is complex, involving multiple internal organs. The basic pathogenesis of diabetes is dryness-heat due to deficiency of yin, and the disease is often recurrent. Deficiency is the starting factor, dampness is the basic pathological condition, and blood stasis is accompanied by the whole process of the disease. Xiao Yao [11] pointed out that many factors lead to deficiency of both qi and yin, resulting in diabetes. Phlegm-dampness and blood stasis formed in the development of diabetes over a long period of time accumulate in the kidney collaterals, forming "micro-zheng jia", which affects the generation and operation of qi and blood. Therefore, the production of DN is: Yin deficiency, "micro-zheng jia", deficiency of qi and blood, yin and yang deficiency.

Nan Zheng [12] focuses on the pathogenesis of DN, emphasizing the importance of the disease

site "San Gao" and "Meng Yuan". Professor Nan believes that "San Gao" mainly refers to the pancreas, which is a subsidiary organ of the spleen, and together with the spleen, it generates qi and blood to nourish the whole body. Membrane source refers to the channel connecting the skin and muscles, as well as the gap between the organs and organs. Professor Nan Zheng believes that the weakness of the five internal organs, insufficient innate endowment, a preference for fat, sweetness, and thick taste, and the feeling of the evil energy of the six evils can lead to the occurrence of thirst quenching disease. Prolonged thirst quenching, damage to ointment, loss of qi in the three jiao, and the development of toxic pathogens such as phlegm turbidity, blood stasis, and damp heat adhesion can invade the kidney meridians and retain the membrane for a long time. The evil energy lingers in the membrane for a long time, which is also the reason why DN is difficult to heal due to its migration.

Nan He [13] discussed that Professor Zhao further put forward the theoretical thought of "kidney collaterals and Fu Feng" in inheriting the academic thought of "micro-zheng jia" of Lv Renhe, a master of traditional Chinese medicine. Professor Zhao believes that the formation of "micro-zheng jia" is not only related to dampness and heat, qi stagnation, turbid phlegm and blood stasis, but also to wind evil. When the disease dissipates thirst for a long time, it leads to deficiency of both qi and yin, long time and kidney, deficiency of the collaterals of the kidney, and wind evil takes advantage of deficiency. "When evil gathers, its qi will inevitably become weak." At the same time, wind evil can be divided into external wind and internal wind. The disease dispels thirst, heat injures yin, and the extreme heat produces wind; diabetes causes yin deficiency of liver and kidney, and yin deficiency leads to wind; "micro-zheng jia" is formed in the process of diabetes, which hinders the movement and production of qi and blood, and blood deficiency leads to wind. Both internal and external wind can damage kidney collaterals and lead to the occurrence of DN. Although modern TCM experts have different views on the pathogenesis of DN, they basically agree that diabetes nephropathy is essentially a mixture of deficiency and excess, and blood stasis runs through the whole process of the disease. The etiology and pathogenesis of DN are very complex, often due to congenital deficiencies, weak organs, improper diet, extreme emotions, excessive sexual exertion, and the feeling of evil energy, which can damage the spleen Qi causes the spleen to be unable to move and transform, resulting in internal dampness and turbidity. If left untreated, heat accumulates and damages yin. If left untreated, yin deficiency and qi deficiency occur, as well as spleen deficiency and kidney deficiency. The spleen is the hub of the middle jiao, and the human body relies on the nourishment of qi and blood generated by the essence of the spleen. Moreover, the movement of water and liquid is closely related to Metabolism is mainly held accountable to the spleen and kidney organs. Damage to the spleen and kidney can lead to imbalanced distribution of qi, blood, and body fluids, resulting in pathological products such as phlegm dampness, blood stasis, and qi stagnation.

3. Traditional Chinese Medicine Treatment

3.1. Traditional Chinese Medicine Staging Treatment

The pathogenesis of diabetes nephropathy is complex, and the disease is difficult to cure. The pathogenesis of each stage is slightly different. Modern scholars have different opinions on the diagnosis and treatment of DN by stages and syndrome differentiation. But generally speaking, TCM scholars believe that DN can be divided into three stages: early stage, middle stage and late stage. Professor Ni Qing [14] advocates dividing DN into early, middle, and late stages based on its symptoms and Western medical physical and chemical testing indicators. In the early stages, patients mainly exhibit symptoms such as dizziness, limb fatigue and weakness, mental fatigue and fatigue, abdominal distension, and excretion of urine containing trace amounts of protein or no urine protein. Ni Shi proposed to treat from the perspective of the spleen and stomach; In the mid-term, the patient showed symptoms of urine turbidity and edema, while physical and chemical tests showed persistent

proteinuria and elevated blood creatinine. He advocated treating it by tonifying the spleen and kidney, strengthening the kidney and astringent essence; Late stage patients may experience symptoms such as increased edema, obvious urine turbidity, and frequent nocturia, mainly characterized by kidney yang deficiency. Therefore, he proposed to tonify the spleen and kidney yang qi. Gao Jining [15] commonly uses the method of even reinforcing-reducing to treat DN. He believes that DN is a chronic disease, and Junbu Junxie method are not conducive to the treatment of DN. In terms of diagnosis and treatment, Gao Lao divides DN into three stages. In the early and middle stages, it is more common to see the syndrome of Qi and Yin deficiency, while in the middle and late stages, it is more common to see the syndrome of spleen and kidney yang deficiency. Professor Wei Junping [16] has found through many years of clinical research that the specific symptoms of early DN patients are not obvious, and the disease is located in the upper jiao. Treatment is aimed at clearing heat and generating fluids, nourishing yin and qi, and striving to reverse DN; In order to delay the progression of DN, the mid stage disease is located in the spleen and stomach of the middle energizer, tonifying the spleen and kidney, promoting diuresis and removing blood stasis; In the late stage of DN, the focus is mainly on the liver and kidney below the lesion site. The treatment is to warm the kidney and assist yang, promote diuresis and reduce swelling, and improve the clinical symptoms of patients.

3.2. Traditional Chinese Medicine Classification and Treatment

Traditional Chinese medicine has not yet formed a unified standard for the syndrome differentiation and classification of DN, but it is generally based on the pathogenesis of mixed reality and virtuality of diabetes nephropathy. Chen Hongyu [17] is skilled in treating DN from the liver and kidney organs. Based on traditional Chinese medicine theories (The theory of mutual generation of the five elements and the theory of essence and blood), Professor Chen advocates that DN can be divided into liver and kidney deficiency syndrome, liver depression and qi stagnation syndrome, qi stagnation and water stagnation syndrome, and blood stasis obstruction syndrome. However, from the overall treatment principle of DN, he emphasizes the care of liver and kidney yin fluid, and does not forget to promote blood circulation and remove stasis throughout the entire process of the disease. Therefore, when selecting drugs, Professor Chen generally chooses products that nourish the liver yin and liver blood, nourish the kidneys and fill the essence. The selection of blood stasis drugs is divided into vine type drugs and insect type drugs. Bu Xianchun [18] old Chinese doctors summarized their experience in treating senile diabetes nephropathy for many years, and concluded that DN should be divided into the type of deficiency of both qi and yin, the type of deficiency of both yin and yang, the type of phlegm stagnation and the type of blood stasis. He advocates the use of Shen Qi Di Huang Tang for the treatment of patients with Qi Yin deficiency syndrome; For the Yin Yang deficiency syndrome, it is suitable to support Yang and benefit Yin, and Guifu Shenqi Pill is selected for treatment; For patients with phlegm obstruction syndrome treated with the method of dispelling phlegm and removing turbidity by Bu Lao, Erchen Tang was selected as a modified formula; Long term illness leads to blood stasis, so Bu Lao also proposed using Taohong Siwu Tang to treat the syndrome of blood stasis obstructing collaterals. Professor Sun Yuzhi [19] is skilled in using the methods of tonifying qi and nourishing yin, promoting blood circulation and removing stasis to treat DN. Sun often uses a self-formulated formula for tonifying the kidney and promoting blood circulation (composed of astragalus, *Atractylodes macrocephala*, *Angelica sinensis*, etc.) to treat DN patients In clinical practice, which has a significant therapeutic effect. Professor Yang [20] believes that the clinical classification of DN can be roughly divided into four types: Yin deficiency heat excess syndrome, Qi Yin deficiency syndrome, spleen kidney deficiency syndrome, and toxin turbidity obstruction syndrome.

4. Traditional Chinese Medicine Internal Treatment Method

4.1. Experience formula treatment

Modern Chinese medicine scholars have increased their exploration of DN, formed their own theoretical understanding, and developed empirical formulas that are convenient for clinical use. Professor An Haiyan [21] adopts a combination of staging and classification to treat DN based on syndrome differentiation, with the Xin Run Tong Luo method as the overall treatment principle. She believes that the main pathogenesis of DN is "kidney meridian stasis obstruction", which belongs to which is the syndrome of deficiency in origin and excess in superficiality, and the disease can be divided into three stages. In the early stage, the pathogenesis was characterized by deficiency of both qi and yin, combined with dryness and heat, and the initial formation of phlegm and blood stasis. At this time, the disease was mainly characterized by deficiency, with excess sandwiched between deficiency and excess. Professor An used spicy and cool herbs such as honeysuckle and forsythia to penetrate the meridians and reach the pathogenic heat of the kidney meridians; And add products such as *Ophiopogon japonicus* and Shengdi to nourish yin and produce fluids; Add Huangqi, yam and other ingredients to nourish yin and nourish qi; Finally, peach kernel and *Angelica sinensis* were added to promote blood circulation and remove blood stasis. She believes that the pathogenesis of mid-term DN is the deficiency of spleen and kidney yang qi, and the manifestation of blood stasis obstructing the kidney meridians is more severe. Therefore, she chooses drugs such as Guizhi, Cinnamon, *Asarum*, *Cistanche deserticola*, and *Morinda officinalis*, which are Xin Wen and Yang boosting, to Huaqi Bujin, and then adds Ezhu, Sanleng, and other herbs to eliminating zheng and dispersing blood stasis. In the later stage of DN, Professor An chose eliminating dampness with aromatics drugs. Due to the formation of blood stasis and turbid toxins for a long time, he used blood activating drugs such as leeches and scorpions, as well as support healthy energy with *angelica sinensis* and white peony. Ma Jian [22] realized that DN is closely related to the spleen and kidney, and the overall pathogenesis of this disease is yin deficiency, dryness and heat, as well as blood stasis. Based on his years of medical experience, he classified DN into Qi and Yin deficiency type, spleen and kidney deficiency type, turbid toxin obstructing collaterals type, etc. Among them, the Qi and Yin deficiency type selected the self-formulated Tang Shen Kang formula (Huangqi, Shengdi, Huangjing, *Poria cocos* and other drugs). Professor Tong Xiaolin [23], based on years of clinical observation and summary, concluded that deficiency, stasis, and turbidity are important pathogenesis of DN. Therefore, in terms of treatment, it is advisable to "nourish the right and tonify deficiency, remove stasis and disperse turbidity", and choose a self-formulated formula containing three ingredients: astragalus, rhubarb, and leech powder.

4.2. Prescription treatment

Yin Bei et al. explored the mechanism of Liu Wei Di Huang Wan in treating DN through network pharmacology and molecular docking methods. The results showed that Liu Wei Di Huang Wan was correlated with mitochondrial dysfunction and vascular endothelial insulin resistance, providing a possible direction for further research on the mechanism of Liu Wei Di Huang Wan's action against DN. In an experiment on diabetes model mice, Li Xin [25] et al. divided 17 mice into treatment group (Shengqing Jiangzhuo suspension by gavage), model group (normal saline by gavage) and blank control group (normal saline by gavage). Two months later, the detection of renal related biochemical indicators proved that Shengqing Jiangzhuo capsule had a renal protective effect in the disease model mice. Wang Huiling [26] administered Shuilu Dihuang capsule to diabetes rats by gavage for 2 months, and found that the drug had advantages in reducing blood sugar and controlling urinary protein. Zhang Xiaoyan [27] selected patients with Qi and Yin deficiency as the observation objects, with a control group (conventional treatment with Irbesartan) and an observation group (control group with Shen Qi Di Huang Tang). After 8 weeks of clinical observation, it was found that Shen Qi Di

Huang Tang has significant therapeutic effects on DN patients.

5. Traditional Chinese Medicine External Treatment

There are many kinds of external treatment of DN with traditional Chinese medicine. This article reviews the treatment of DN with acupuncture and moxibustion, ear point pressing beans, and moxibustion. Huang Hai et al. [28] divided 40 DN model rats into a model group and did not provide intervention; The electroacupuncture group was given electroacupuncture stimulation to bilateral kidney acupoints and Zusanli acupoints; Autophagy inhibitor group, rats were injected with 3-MA; The electroacupuncture+3-MA group was treated with electroacupuncture and injection of 3-MA intervention, with 10 rats in each group. After 6 weeks of intervention, it was found that electroacupuncture has the effect of inhibiting weight loss in DN rats, improving renal function, and reducing fasting blood sugar; In addition, electroacupuncture can also alleviate pathological damage to the kidneys and have the effect of improving insulin resistance. Tang Ming [29] selected 68 patients with DN as the treatment group (conventional western medicine treatment plus warm acupuncture and moxibustion) and the control group (conventional western medicine treatment alone). After three months of intervention, each clinical observation index showed that warm acupuncture and moxibustion had a significant effect on improving the renal function of DN patients. Yao Yuhong [30] divided 180 patients with stage II and III DN into two groups, namely the control group and the observation group. The control group received 12 weeks of intervention with losartan potassium, while the observation group received the same duration of intervention with the Fuyuan San combined with ear acupoint pressing beans. Clinical follow-up observation was conducted for 2 years, and it was ultimately concluded that the combination of modified Fuyuan powder and ear acupoint pressing beans has an effect on improving the treatment effect of patients with this disease. The study by Ye Luna et al. [31] showed that patients who received routine treatment with ear acupoint pressing beans combined with acupoint application had lower levels of systolic and diastolic blood pressure, and overall incidence of complications compared to patients who received routine treatment alone. After early treatment with basic therapy combined with valsartan and moxibustion in Huanghai [32], the average 24-hour urine microalbumin, urine microalbumin, and other water levels in patients were lower than those treated with basic therapy combined with valsartan alone ($P<0.05$).

6. Summary

Diabetes nephropathy is the primary cause of chronic kidney disease and end-stage kidney disease, which has brought serious economic burden to patients and their families. Western medicine does not have a significant effect on reducing patient symptoms and alleviating disease in the treatment of DN, and has many adverse reactions. Through the research of numerous scholars, it has been found that traditional Chinese medicine has advantages in improving the clinical symptoms of DN patients and delaying the progression of the disease. However, traditional Chinese medicine has not yet formed a consistent standard for the differentiation and staging of diseases, and active efforts from scholars are needed to determine the diagnosis and treatment plan for clinical systems.

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