

Research Progress of Traditional Chinese Medicine and Combination of Traditional Chinese Medicine in the Treatment of Diabetes Nephropathy

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Abstract: *Diabetes nephropathy (DKD) refers to the microvascular disease caused by diabetes, which can affect the whole kidney (including glomerulus, renal tubules, renal interstitium, etc.). Its clinical manifestations are usually from less to more proteinuria, hypertension, progressive decline in renal function, and eventually progress to end-stage renal disease. The Western medicine guidelines advocate comprehensive intervention for multiple risk factors, mainly based on improving unhealthy lifestyle habits, controlling blood sugar, blood pressure, and blood lipids, while using drugs with dual effects of lowering blood sugar and protecting target organs such as the heart and kidneys. A very small number of patients can choose surgical treatment. According to clinical syndrome differentiation, combined with historical literature, Chinese medicine will name it "Xi Xiao", "Shen Xiao", "Turbid Urine", "Edema", "Long Bi", etc. according to its original disease. Based on the etiology and pathogenesis of the above diseases, we have treated diabetes nephropathy through syndrome differentiation, and achieved good clinical results. This article reads the literature, starts from the thinking of traditional Chinese medicine, diverges the clinical diagnosis and treatment ideas, and provides further TCM treatment plans for diabetes nephropathy.*

Keywords: Diabetes nephropathy, Traditional Chinese Medicine treatment, Traditional Chinese Medicine Combination Treatment.

1. Introduction

Diabetes nephropathy (DKD) [1] refers to the microvascular disease caused by diabetes, which can affect the whole kidney (including glomerulus, renal tubules, renal interstitium, etc.) [2] below. The risk factors of diabetes nephropathy include bad living habits, age, course of disease, blood sugar, blood pressure, obesity (especially abdominal obesity), blood lipids, uric acid, environmental pollutants, etc. The pathogenesis of this disease [3] below is relatively complex, mainly related to factors such as podocyte damage, glucose metabolism disorders, insulin resistance, genetic factors, hemodynamic disorders, oxidative stress, endoplasmic reticulum stress, increased expression of inflammatory factors [4], mitochondrial autophagy disorders, and mitochondrial dysfunction caused by hyperglycemia [5]. The diagnosis of diabetes nephropathy mainly depends on the determination of urinary albumin and estimated glomerular filtration rate. The Western medicine guidelines advocate comprehensive intervention for multiple risk factors, mainly based on improving unhealthy lifestyle habits, controlling blood sugar, blood pressure, and blood lipids, while using drugs with dual effects of lowering blood sugar and protecting target organs such as the heart and kidneys. A very small number of patients can choose surgical treatment. Medications mainly include angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, sodium glucose cotransporter 2 receptor inhibitors, mineralocorticoid receptor antagonists, dipeptidyl peptidase 4 inhibitors, prostaglandins, etc. [6,7] which can reduce urinary protein and delay the progression of kidney disease. However, the clinical efficacy is not satisfactory, which can only delay the progress of some diabetes nephropathy, and diabetes nephropathy is more difficult than other types of kidney disease. How to effectively delay the progress of diabetes nephropathy is the difficulty and bottleneck of the disease. In recent years, Chinese medicine has gradually become a research hotspot in the field of

diabetes nephropathy with its advantages of multiple forms, multiple targets, multiple pathways and good clinical efficacy [8].

Through reading the literature, starting from the theory of traditional Chinese medicine, this article sorts out the ideas of diabetes nephropathy in traditional Chinese medicine, provides better clinical diagnosis and treatment ideas from the thinking of traditional Chinese medicine, and provides further TCM treatment plans for diabetes nephropathy.

2. Etiology and Pathogenesis

There is no clear record of it in ancient Chinese medicine books, and it is named "Xi Xiao", "Shen Xiao", "Yun Zhuo", "Edema", etc. based on its primary disease. DKD is characterized by kidney deficiency, diabetes has been prolonged for a long time, which consumes qi and injures yin, damages the five internal organs, and causes diseases such as phlegm, heat, depression, and blood stasis [9,10]. At the beginning of the disease, there is a deficiency of qi and yin, gradually leading to a deficiency of liver and kidney yin; Prolonged illness, Yin damage and Yang damage, and damage to the spleen and kidneys; Late stage of the disease, renal yang decline, and internal cessation of turbidity and toxicity; Or there may be a deficiency of Qi and blood, with all five organs being deficient. Modern doctors believe that the pathogenesis of diabetes nephropathy is characterized by deficiency of the origin and excess of the symptoms, deficiency of kidney yin, and subtle betting as an important pathogenesis. Liu Hongfang et al. [11,12] believe that the core pathogenesis of DKD is the deficiency of true yin and the obstruction of the meridians due to the loss of essence. Therefore, it is necessary to strengthen the astringent and astringent essence to increase true yin; Sun Wei [13] proposed that spleen and kidney deficiency, damp heat and blood stasis are the basic pathological mechanisms of DKD. Wang

Yaoguang et al. [14] emphasized that the pathogenesis of DKD is based on deficiency and excess, which can be specifically classified into four categories: deficiency, dampness, blood stasis, and turbidity. Ben deficiency is the basis of this disease, which can be divided into lung and kidney yin deficiency, qi and yin deficiency, spleen and stomach qi deficiency, and spleen and kidney yang deficiency. Biao Shi can be divided into water dampness, blood stasis, and turbid toxin; Ye Chuanhui [15] mentioned that the location of DKD is in the kidneys, which can be divided into three types: deficiency of sealing and storage, deficiency of qi and yin, deficiency of spleen and kidney, and deficiency of yin and dryness and heat; According to years of clinical experience, the Chinese medical master Zheng Xinwen [16] summarized that the etiology and pathogenesis of DKD are deficiency of elemental endowment elements, and believed that deficiency of lung, spleen, and kidney is the fundamental cause of the disease, while deficiency of phlegm and dampness leading to blood stasis is the standard; Professor Tan Jinchuan [17] proposed that the pathogenesis of diabetes nephropathy should be characterized by “deficiency of vital energy, excessive dryness and heat, and stagnation of triple energizer”; Ding Baozhu et al. [18] believed that internal heat damages yin and consumes qi, causing prolonged illness to enter the meridians, leading to heat stagnation and blood stasis. Internal heat always exists in the development process of the disease; Guo Xiaoyuan et al. [19] believe that inflammation is consistent with the manifestations of “hyperactivity of yang heat and heat induced blood circulation”; Chen Wenying et al. [20] explored based on tongue and pulse images, suggesting that as the disease progresses, DKD gradually transforms from yin deficiency to yang deficiency, the heat image gradually decreases, the cold image appears, and blood stasis worsens. Dampness, phlegm, blood stasis, and heat are important factors in the onset of the disease.

3. Treatment Methods

3.1 Treatment with Monotherapy

The cornus officinalis [21] compound can improve the clinical symptoms of patients with diabetes nephropathy, reduce urinary protein excretion, improve renal function, etc. Its mechanism of action includes inhibiting the secretion of various inflammatory factors such as interleukin-6 (IL-6) in renal tissue, inhibiting the production of advanced glycation end products, reducing the accumulation of cholesterol in renal tubular epithelial cells, and promoting the synthesis of nitric oxide in renal tissue; Tan Ying et al. [22] found that *Tripterygium wilfordii* extract, as the main active ingredient of traditional Chinese medicine *Tripterygium wilfordii*, has pharmacological activities such as anti-inflammatory and immunosuppressive effects, and has the ability to reduce proteinuria and delay renal function deterioration; Research by Shen Jinfeng et al. [23] suggests that allicin may inhibit renal tissue inflammation by suppressing NF- κ B p65 activation, thereby delaying DN progression, and is positively correlated with dosage; Huang Yan et al. [24] found that the aqueous extract of mulberry leaf can improve the structure and function of renal tissue in db/db diabetes mice, and its mechanism may be related to the inhibition of TLR4/MyD88/NF- κ B signaling pathway; The study by Yang Fan et al. [25] suggests that the mechanism of action of Citrus

grandiflorum extract may be to regulate the abnormal expression of glucose transporters, reduce glycosylation, and decrease the expression level of TGF- β 1, thereby playing a role in preventing and treating DKD and protecting kidney damage; Geng Yuxuan et al. [26] used ginkgo biloba extract to inhibit renal inflammation in diabetes nephropathy model mice. The experiment found that ginkgo biloba extract can improve renal injury and alleviate inflammatory reaction in DN model mice, and its mechanism may be related to inhibiting AGES-AGE/RhoA/ROCK signaling pathway and regulating megaphagocyte polarization; Chen Li et al. [27] explored the effective ingredients, potential targets and mechanisms of *Atractylodes Rhizoma* and *Phellodendron Phellodendron* in the treatment of diabetes nephropathy based on network pharmacology. It reflects the characteristics of multi-component, multi-target, and multi pathway treatment of DKD with *Atractylodes macrocephala* and *Phellodendron amurense* herbs. Modern pharmacology believes that *Astragalus membranaceus* has the effects of controlling blood sugar, improving microcirculation, and protecting the kidneys [28]. The emodin in rhubarb can reduce the excretion of urinary protein by the kidneys [29]. Salvianolic acid and tanshinone in Danshen can inhibit the progression of renal fibrosis in diabetic kidney disease through different pathways [30]. Safflower yellow injection can improve the glucose metabolism disorder of early DKD patients and delay the progress of renal fibrosis in DKD [31]. Gujianyu can improve blood stasis caused by glomerular injury, thereby improving diabetes nephropathy [32].

3.2 Treatment Formula

Zhang Zuhong et al. [33] found that the application of Shenqi Dihuang Decoction in the treatment of early diabetes nephropathy is conducive to alleviating the clinical symptoms of patients, and can also effectively control the renal function and blood sugar level of patients. Li Tianhao et al. [34] studied the therapeutic effect of Yiqi Yangyin Xizhuo Tongluo Recipe on diabetes nephropathy. The results show that Yiqi Yangyin Xizhuo Tongluo Recipe can improve renal function, reduce blood sugar, regulate blood lipid levels, and improve patients' quality of life; Huang Saijiao et al. [35] discussed the treatment of diabetes nephropathy with Yuemaijiazhu decoction based on endoplasmic reticulum stress. Yuemaijiazhu decoction is effective in treating DKD patients with spleen kidney yang deficiency, which helps to alleviate the clinical symptoms of patients, improve the renal function and blood sugar level of patients. Its therapeutic mechanism may be related to the inhibition of endoplasmic reticulum stress; Yao Jieqiong et al. [36] explored the idea of delaying the process of renal fibrosis with the addition and subtraction of Hejiezi powder (astragalus, angelica, seaweed, raw oyster, turtle shell), proposed that damp heat plays an important role in the occurrence and development of diabetes nephropathy, and the method of clearing away damp heat is of great significance in the treatment of diabetes nephropathy; Zhao Huiye et al. [37] observed the clinical efficacy of Jianpi Yishen Jiangzhuo Recipe in the treatment of diabetes nephropathy (DKD) and its impact on patients' micro inflammatory state. Taking 80 patients with DKD as the research object, the total effective rate of the treatment group was higher than that of the control group ($P < 0.05$). They concluded that Jianpi Yishen Jiangzhuo Recipe has a definite

clinical efficacy in the treatment of DKD, which can effectively improve patients' micro inflammatory state, improve renal function, improve TCM symptoms, thus slowing down disease progress, and is safe and reliable; Ma Xiuqin et al. [38] observed the therapeutic effect of Buyang Huanwu Decoction combined with Shengjiang Powder on stage III and IV diabetes nephropathy. By comparing the treatment of Buyang Huanwu Decoction combined with Shengjiang Powder and Benazepril Hydrochloride Tablets, they observed the relevant clinical symptoms and relevant test indicators. They found that Buyang Huanwu Decoction combined with Shengjiang Powder had satisfactory therapeutic effect on DKD, which could better reduce urinary protein, delay the process of DKD, and improve the quality of life; Wang Yiqiang et al. [39] found that compared with conventional treatment alone, the clinical symptoms of diabetes nephropathy patients with yin yang deficiency can be better improved by adding Jinkui Shenqi Pill; Li Mei et al. [40] used Zhengqingfengtongning sustained-release tablet to treat patients with diabetes nephropathy and explore its clinical efficacy. The difference between the control group and the treatment group was statistically significant ($P<0.05$), indicating that Zhengqingfengtongning [41] sustained-release tablet could significantly reduce the level of urinary protein in patients with diabetes nephropathy, effectively alleviate the occurrence and development of diabetes nephropathy, and delay its progression to end-stage renal disease; Wang Fei et al. [42] found that the serum containing Suoquan Yishen Formula may improve podocyte EMT and podocyte injury by inhibiting histone demethylase, regulating EMT related markers and podocyte injury factors; Wu Siyu et al. [43] concluded based on the GEO database that Yuye Decoction may protect the kidney and inhibit renal inflammation by affecting the lncRNA miRNA mRNA transcription network of diabetes nephropathy rats, involving multi component, multi target, and multi pathway synergistic effects; Su Fanglin et al. [44] used network pharmacology methods and molecular biology experiments to explore the mechanism of Tangshenbao compound in treating diabetes nephropathy. The results showed that Tangshenbao compound could regulate PI3K-Akt, AGE-RAGE and other signal pathways and play a therapeutic role in diabetes nephropathy by inhibiting the mRNA expression of target genes such as PIK3R1, PIK3CD, MAPK8, STAT3, and ETS-1.

3.3 Combination Therapy

Liu Qing [45] used Shenqi Yishen Recipe combined with western medicine to treat 25 patients with diabetes nephropathy, and achieved good curative effect, which has better improvement effect on the syndrome of spleen and kidney qi deficiency and blood stasis; Zhang Qin et al. [46] observed the effect of self prepared Tongfu Jiangzhuo Jiedu Decoction enema combined with ginkgo biloba and damo injection in the treatment of diabetes nephropathy. The effect is positive, which is beneficial to the improvement of renal function, renal hemodynamics and quality of life; Kong Linglong et al. [47] self-made recipe for invigorating the spleen, tonifying the kidney and activating blood circulation combined with warm acupuncture and moxibustion can reduce the kidney damage of diabetes nephropathy, reduce urinary protein, delay the progress of renal fibrosis, so as to improve the quality of life of patients. By observing and

analyzing the clinical efficacy of self-made recipe and medicine combined with warm acupuncture and moxibustion in treating diabetes patients with yin deficiency and blood stasis and its impact on renal fibrosis indicators, the total effective rate of TCM syndrome efficacy evaluation in the treatment group was significantly higher than that in the control group ($P<0.05$); Wu Weili et al. [48] used Qishen Tongluo Huayu Recipe combined with acupuncture to treat early diabetes nephropathy. After treatment, the blood sugar of patients was effectively adjusted. The TCM syndrome score of patients in the two groups was significantly improved. The serum levels of CHI3L1 and SOCS3 of patients in the two groups were significantly improved ($P<0.05$), and the study group was significantly better than the control group in improving the serum levels of CHI3L1 and SOCS3, with statistically significant differences ($P<0.05$); Liu Ruoshi et al. [49] under the guidance of treating from the kidney, provided a new idea for clinical prevention and treatment of diabetes nephropathy with the combination of Shenqi Dihuang Decoction and eye acupuncture. Shenqi Dihuang Decoction is in harmony with the liver, spleen and kidney, and is a representative prescription for supplementing qi, yin and essence. Eye acupuncture, as a unique acupuncture method created by Peng Jingshan, a professor of traditional Chinese medicine in Liaoning Province, is based on "treating from the kidney", which has a certain role in the prevention and treatment of diabetes nephropathy. Combining acupuncture and medicine can prevent and treat diabetes nephropathy by inhibiting inflammation and other ways; Zhao Huiye et al. [50] observed the clinical efficacy of moxibustion combined with modified Baozhen decoction in the treatment of qi yin deficiency syndrome of diabetes nephropathy and its influence on CT perfusion parameters and Rho/ROCK signal pathway protein. The results showed that the total effective rate of the observation group was 97.3%, significantly higher than that of the control group (81.9%, $P<0.05$). On the basis of symptomatic treatment, moxibustion combined with Baozhen decoction can significantly improve the therapeutic effect of patients with qi yin deficiency syndrome of diabetes nephropathy, and its mechanism may be related to improving CT perfusion parameters and regulating serum Rho/ROCK signal pathway protein; Sun Xiaohong et al. [51] found that Yiqi Yangyin Huoxue Recipe combined with traditional Chinese medicine fumigation has a more obvious therapeutic effect on diabetes nephropathy, which can control blood sugar, reduce blood sugar fluctuation, reduce 24-hour urine protein quantity, and improve renal function.

3.4 Other Treatments

Chinese herbal hot compress is a type of external treatment method in traditional Chinese medicine, which can penetrate the efficacy of drugs into the body through thermal effects, and work synergistically through acupoint stimulation and drug stimulation. Jing Tingting et al. [52] under the guidance of the midnight noon ebb flow theory, using acupoint massage combined with hot compress of traditional Chinese medicine can regulate the spleen and stomach, promote the flow of qi and relieve constipation, effectively reduce constipation symptoms of constipation patients with diabetes nephropathy, improve anorectal function, and regulate intestinal neurotransmitter disorder; Emotional therapy is also a characteristic therapy of traditional Chinese medicine. Wang

Hongxin et al. [53] showed that emotional intervention combined with video health education can reduce the negative emotions of patients with diabetes nephropathy, improve their self-care ability, improve their compliance behavior, and thus enhance the control effect of blood sugar level; Different nursing methods also have a certain impact on the blood sugar level of diabetes nephropathy. Chen Yuzhu [54] randomly enrolled 89 patients with diabetes nephropathy as the research object. According to the random number table method, the included DKD patients were divided into the control group and the research group. Routine nursing and cognitive behavioral nursing combined with diet nursing were performed respectively, to explore the impact of the two nursing methods on the blood sugar level, renal function indicators, and medical compliance behavior of DKD patients. After six months of intervention, the fasting blood sugar and postprandial blood sugar levels, urea nitrogen, and blood creatinine levels in the research group were lower than those in the control group (all $P < 0.05$); The scores of compliance behaviors in the study group, including medication use, self-monitoring, reasonable diet, exercise, and emotional control, were all higher than those in the control group (all $P < 0.05$); During the treatment of diabetes nephropathy, the application of traditional Chinese medicine nursing mode can effectively reduce the level of blood glucose and lipid, improve the renal function of patients, and reduce the blood pressure of patients, which is conducive to their rapid recovery. Therefore, this method is worthy of clinical promotion [55].

4. Conclusion

To sum up, there are many ways to treat diabetes nephropathy with traditional Chinese medicine. Whether it is single medicine, prescription treatment, or combined treatment, it reflects the unique advantages of traditional Chinese medicine in preventing and treating diabetes nephropathy. On the basis of inheritance and development, Chinese medicine experts of all generations constantly pushed through the old to bring forth new ideas, and put forward their understanding and thinking on diabetes nephropathy. The combination of traditional Chinese medicine and modern medicine can significantly enhance the therapeutic effect, intervene in substantive renal pathological changes, and delay the progress of diabetes nephropathy [56]. Therefore, TCM treatment of diabetes nephropathy is worthy of attention, promotion and in-depth research.

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