Clinical Overview of Prescription of Promoting Blood Circulation and removing blood stasis in Treating Diabetic Nephropathy

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Abstract. Promoting blood circulation and removing blood stasis is an important method of clinical treatment of diabetic nephropathy (DN). Such prescriptions or compound prescriptions have a definite effect after long-term clinical practice. The Prescription of Promoting Blood Circulation and removing blood stasis (PBCRBS) reviewed in this article can improve glucose and lipid metabolism disorders, inhibit the changes in inflammation and promote blood flow of DN, reduce the burden on the kidneys, and delay the pathological changes of DN. This article summarizes the PBCRBS Clinical Overview of prescription in Treating Diabetic Nephropathy.

1. Introduction
World Health Organization estimates that diabetes is the seventh leading cause of death in humans. Uncontrolled diabetes can have serious consequences, such as cardiovascular(CV) events(myocardial infarction, stroke or CV mortality), lower limb amputation and end-stage renal disease[1].

While Diabetic Nephropathy(DN) is one of the most important microvascular complications of diabetes. It accounts for 40%-50% of all cases of end-stage renal disease. Studies have shown that the earlier a treatment plan has a positive effect on vascular changes and prevents the deterioration of the vascular system of diabetic patients, the better which will improve the kidney functions[2].

Chinese traditional medicine also believes that “chronic diseases can transform to collaterals”. As a long-term chronic microvascular disease, DN have some blood stasis block. So promoting blood circulation and removing blood stasis is more in line with the pathophysiological characteristics of DN. The prescriptions of Promoting Blood Circulation and removing blood stasis (PBCRBS) have accurate clinical effects in the treatment of DN and also supported by a large amount of basic experimental data. The author sorted out the relevant researches on the effective prescription treatments of DN in recent years in order to provide ideas for the clinical treatment of DN and further theoretical research.

2. Etiology and pathogenesis
DN has become the main cause of end-stage renal disease (ESRD) in developed countries. Its pathogenesis is very complicated and has not yet been fully elucidated. It involves genetic predisposition factors, abnormal glucose metabolism, blood Flow dynamics changes, inflammatory mechanisms, cytokines and other factors work together as a result [3].
Traditional Chinese medicine believes that DN is "Xiaoke" for long-term illness, secondary to become "Gaozhuo" and "consumptive disease". Tong Xiaolin et al. [4] believe that Pidan (obesity type 2 diabetes) nephropathy is caused by collateral damage on the basis of the syndromes of excess heat and phlegm heat. Over time, deficiency of both qi and yin and blood stagnant in collateral are seen. Xiaodan recognizes (type 2 diabetes and majority of type 1 diabetes) nephropathy is the occurrence of collateral stasis on the basis of insufficient Qi and Yin. Li Yanxi [5] and others believe that due to congenital deficiencies, improper diet, overstrain, and emotional maladjustment, the course of the disease has not been improved for a long time, qi and yin were injured, caused phlegm, blood, dampness, turbidity and other tangible evils. The use of PBCRBS can reduce blood viscosity, reduce the production of inflammatory factors, and protect kidney tissue. Cao Shili [6] believes that chronically ill can bring about a situation that Qi and blood flow unfavorably, which will lead to blood stasis. Qi deficiency is unable to promote blood circulation, resulting in blood stagnation or stagnation of qi, causes blood flow to be blocked, which also makes blood stasis.

3. References Analysis
This paper will focus on analyzing clinical research.

In the clinical study of diabetic nephropathy, there are 16 studies related to promoting blood circulation and removing blood stasis prescription. All the treatment effects are ideal (Tab 1). The research-related Taohong Siwu Decoction (TSD), Buyang Huanwu Decoction (BHD), Danggui Buxue Decoction(DBD), Xufu Zhuyu Decoction (XZD), Danggui Shaoyao San(DSS) is 3 articles, 4 articles, 2 articles, 4 articles, 3 articles respectively (Figure 1.).

![Figure 1. Relative frequency of Clinical Research on Diabetic Nephropathy treated by PBCRBS.](image-url)
Table 1. Analysis of the Effects of PBCRBS on DN in the clinic.

| References | The treatment group | The Control group | The result of treatment group (Effective Or ineffective) |
|------------|---------------------|-------------------|------------------------------------------------------|
| Wang Xian.2019 | TSD and Jingui Shenqi Pill | basic treatment of western medicine | Effective |
| Lei Laogen.2017 | TSD | N/A | Effective |
| Zhou Li.2010 | TSD | N/A | Effective |
| Ye Chengcheng, Zhang Aiming et.al.2016 | BHD | N/A | Effective |
| Leng Wei, Liu Chunyin g et.al.2019 | BHD | N/A | Effective |
| Zhu AnLong.2017 | BHD | N/A | Effective |
| Lin Guobin, Ye renqun et.al.2011 | BHD | N/A | Effective |
| Li yufang, GuoYang et, al.2020 | DBD | N/A | Effective |
| Wang aiuyuan, Han Xiao dong et, al.2020 | DBD | N/A | Effective |
| Li Jinfeng.2020 | XZD | N/A | Effective |
| Chai Yanjun, Zhang Yojie, et al.2016 | XZD | N/A | Effective |
| Bai lin, Sun Zhou.2016 | XZD and Wuling San | Basic treatment of western medicine | Effective |
| Lu yongcheng.2011 | XZD | N/A | Effective |
| Wang Liulin, Li Gang, et al.2019 | DSS | N/A | Effective |
| Chen Huaping, Song Enfeng, et al.2015 | DSS | N/A | Effective |
| Mei Shasha, Song Enfeng, et al.2016 | DSS | N/A | Effective |

4. Clinical Observation on Curative Effect of PBCRBS on DN

4.1. Taohong Siwu Decoction
Wang Xian [7] used this prescription in combination with Jingui Shenqi Pill for tonifying kidney qi in a clinical controlled trial and found that Taohong Siwu Decoction is safer, which can reduce blood sugar
and urine protein content and improve TCM syndromes. Lei laogen [8] found that the prescription has significantly improved blood rheology indicators (plasma viscosity, fibrinogen concentration, hematocrit) and significantly improved the efficacy. Zhou Li [9] combined Taohong Siwu Decoction with irbesartan, founding the experimental group can reduce urine microalbumin excretion rate more significantly. And the combination of the two Decoction has a synergistic effect, which can further reduce urine albumin, and delay diabetic nephropathy progress. Modern pharmacological studies have shown that [10], peach kernels can expand blood vessels, increase organ blood flow, improve blood rheology, and improve microcirculation. Safflower can be anticoagulant, reduce vascular resistance, improve microcirculation, and inhibits platelet aggregation.

4.2. Buyang Huanwu Decoction
Ye Chengcheng [11] studied this prescription compared with the western medicine group, and the cholesterol, urine protein content and blood rheology of the Chinese medicine group were significantly improved. Clinical studies [12] confirmed that the addition of Chinese medicine Buyang Huanwu Decoction as the adjuvant treatment to patients on the basis of western medicine treatment can further enhance the short-term curative effect and exactly inhibit the body's renal fibrosis and oxidative stress. Zhu Anlong [13] using this prescription combined with irbesartan can effectively reduce the serum TNF-α and IL-6 levels in the observation group of the study, reduce urine protein, and improve clinical efficacy. Lin Guobin [14] and other studies found that the prescription can significantly reduce the serumC reactive protein(CRP) and plasminogen activator inhibitor-1(PAI-1) and 24-hour urine protein levels in patients with early DN, which can improve the clinical symptoms of patients.

4.3. Danggui Buxue Decoction
Li Yufang et al. [15] found in their clinical study: after the treatment of Modified Danggui Buxue Decoction combined with Gingui Shenqi Pill for reinforcing Kidney Qi, the SCR,CCR, ET-1 and 24-UP levels of patients were significantly reduced, and the levels of (Serum total cholesterol)TC.(thyroglobuli) TG.LDL-C and(Serum Homocysteine) Hcy were significantly decreased. The levels of HDL-C were significantly increased. Wang Aiyuan [16] et al. treated T2DM nephropathy with Modified Danggui Buxue Decoction can regulate the state of microinflammation, protect kidney functions, and do not increase adverse reactions. Xu Tianfu [17] et al. believed that Astragalus can improve metabolic disorders and relieve swelling by lowering cholesterol. Angelica sinensis cannot onlypromote circulation flow of qi and blood through anti-oxidation and scavenging free radicals but also improve blood perfusion of kidney tissue and other mechanisms. Yang Feixia [18] and others’ pharmacological and clinical studies have found that Danggui Buxue Decoction for Replenishing Blood can inhibit the proliferation of glomerular mesangial cells caused by diabetes, reduce Type IVcollagen, laminoprotein and fibrin, especially high-concentration Danggui Buxue Decoction, has obvious therapeutic value for early diabetic nephropathy.

4.4. Xuefu Zhuyu Decoction
Li Jinfeng’s clinical research found that Xuefu Zhuyu Decoction can significantly regulate the level of peripheral blood’s TNF-α, MCP-1 of patients, which is the related factors to improve kidney function and reduce the level of proteinuria [19]. Chai Yanjun [20] clinically used Xuefu Zhuyu Decoction to treat DN based on the total clinical effective rate and the level of patients’ Urine protein excretion rate(UAER),Serum creatinine (CR), 24-hour urine protein quantification (UP), serotonin nitrogen (BUN) .Compared with the control group, the clinical efficacy of Xuefu Zhuyu Decoction in the treatment of DN is definite. The Research by Bai lin [21] et al. found that Wuling San and Xuefu Zhuyu Decoction have significant clinical effects in the treatment of DN, which can effectively reduce urine protein and blood sugar and improve renal function. Lv Yongcheng [22] et al. found that Xuefu Zhuyu Decoction can reduce urine protein excretion and improve renal microcirculation, which improves the state of micro-inflammation syndrome and decrease the expression of the connective tissue growth
factor(CTGF). Compared with western medicine treatment, Xuefu Zhuyu Decoction has certain advantages about preventing or delaying the occurrence and development of DN.

4.5. Danggui Shaoyao San
Wang Liulin [23] and others clinically applied Danggui Shaoyao San on the basis of conventional treatment and observed that blood total cholesterol, LDL-C, and HDL-C levels were better than before treatment, which better regulated blood lipid metabolism, maintained the kidneys function of patients with stage IV DN and improved the clinical symptoms. After clinical therapy by Chen Huaping and others [24], urinary albumin excretion rates (UAER), TC, TG, fasting blood glucose (FBG) and blood urea nitrogen (BUN) were significantly improved, and the curative effect of the mianjian Chinese medicine treatment group and the traditional Chinese medicine treatment group all better than the western medicine group. After therapy, SCR and hemorheology were significantly improved. Mei Shasha [25] et al. used Danggui Shaoyao San combined with losartan in the therapy of patients with DN, and found that it can significantly reduce proteinuria and blood creatinine, while effectively reducing blood viscosity and inflammatory factors, reducing inflammation, and the effect is more significant than that of losartan group.

5. Evaluation and Prospect
DN has become one of the important outcomes of diabetic complications, which is common and frequent in clinic. However, its pathogenesis has not been elucidated, and there are many influencing factors, such as glucose and lipid metabolism disorders, hemodynamic abnormalities, oxidative stress, inflammatory mediators, cytokines, activation of signaling pathways and so on.

In modern medicine, DN is considered as microvascular disease, which mainly affects the physiological morphology and functions of glomerulus and renal tubules. Therefore, it is of great significance to actively search drugs to prevent the pathophysiological changes and delay the progression of DN. Traditional Chinese medicine has more advantages in the treatment of DN. At present, the main research of traditional Chinese medicine is the pharmacological analysis of single drug, and there is not much research on prescriptions with complex ingredients. The prescriptions or compound prescriptions of PBCRBS mainly focus on the improvement of clinical symptoms, glucose and lipid metabolism and hemodynamics. Further study on the mechanism of PBCRBS in the treatment of DN from clinical observation and cellular aspects will open up a new path for clinical prevention and treatment of DN and development of proprietary Chinese medicine.

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