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Analyzing the Therapeutic Effect of Kidney Tonifying, Blood Activating and Knot Dispersing Formula in the Treatment of IgA Nephropathy based on "State-targeted Diagnosis"

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Abstract: ***IgA nephropathy (IgAN), characterized by its unique deposition of immune complexes in the glomerular mesangial zone, is one of the most common primary glomerulonephritis worldwide. Clinical and pathological studies have found that IgAN is characterized by kidney deficiency and blood stasis, and the in-hospital preparation of tonifying the kidney, activating blood and dispersing knots approach has obvious therapeutic effects on IgAN with tubulointerstitial injury. In this paper, starting from the theory of "state-target identification" of academician Tong Xiaolin, we explored the characteristics of the formula of Kidney Tonifying Formula and analyzed its mechanism of action in treating IgAN by tonifying the state of kidney deficiency, resolving the state of blood stasis and combining with the results of the research on the pharmacology of traditional Chinese medicines for the purpose of precise targeting. It is concluded that the use of targeting and combination of formulas in the treatment of IgAN can better regulate the overall balance of the patient's body and promote the recovery and reconstruction of renal function.***

Keywords: State-targeted diagnosis, IgA nephropathy, Formula for tonifying the kidney, Activating blood and dispersing knots, "Deficiency" state, "Complex stasis" state**.**

1. Introduction

IgA nephropathy (IgAN) is the most common primary glomerular disease worldwide, and up to 40% of IgAN patients develop end-stage renal disease (ESRD) [1], during the onset of hematuria, proteinuria, or generalized edema and other manifestations, which is one of the main causes of chronic renal failure. Tong Xiaolin academician put forward the "state target combination" theory, in which "state" that is, the body's balance of yin and yang is broken, qi, fluid, blood, internal organs imbalance and show different bias. The "target" refers to the specific diseases, clinical symptoms, physical and chemical indicators that appear under the imbalance of yin and yang in the organism. Our nephrology department after observing a large number of renal histopathology found that: under the microscope of glomerulosclerosis, balloon adhesion and interstitial fibrosis, glomerular fibrous crescent, intrarenal arteriolar lesions, etc. have the characteristics of fixed, long-term, and Chinese medicine "blood stasis veins and channels" similar to the same time, while the genetic predisposition of the genetic changes in the IgAN At the same time, the genetic predisposition of IgAN and the change of genes indicate that the patient has the characteristics of insufficient endowment and deficiency of kidney element, and clinically, with the development of the disease, it has the characteristics of deficiency of qi and blood stasis. The formula is a self-produced preparation of Shaanxi Provincial Hospital of Traditional Chinese Medicine, which uses the microscopic identification of kidney as the main evidence and combines with the clinical phenotype to explore and summarize the pathogenesis of IgAN as insufficiency of kidney qi and stagnation of kidney collaterals, and legislates the legislation of benefiting the kidney to dissipate stagnation and eliminate blood stasis, which has a clear clinical efficacy. These findings coincided with the "state-target combination" theory of academician Tong. Therefore, based on the theory of state-target identification, this study analyzed the characteristics of the formula of Kidney Tonifying and Blood Promoting Knot Dispersing Formula, and explored its mechanism of treating IgAN by regulating the state and hitting the target.

2. IgAN Etiology and Pathogenesis

IgAN is a clinicopathological syndrome with varying severity of clinical manifestations, characterized by recurrent proteinuria, gross or microscopic hematuria, and pathological changes characterized by IgA1 deposition in the glomerular plasma membrane, proliferation of plasma cells and stromal dilatation, and tubulointerstitial lesions [2]. Currently, the internationally recognized pathogenesis of IgAN is the "quadruple whammy" theory [3], which suggests that the pathogenesis of IgAN involves the deposition of immune complexes, complement activation, and the release of inflammatory factors.

IgAN does not have a corresponding name in traditional Chinese medicine (TCM). According to the clinical symptoms of IgAN, it can be categorized as "blood in urine", "kidney wind", "deficiency labor", "edema", "lumbago", "edema" and "lumbago" [4,5]. According to Prof. Wang Zimin, the causes of this disease are divided into internal and external causes, the internal causes are deficiency of the body, internal injuries due to seven emotions, overwork, etc., and the external causes are dietary irregularities, invasion by external evils, and prolonged residence in wetlands, etc [6]. Prof. Jim Yongli [7] also believes that internal and external causes work together to lead to the development of IgAN, and

that external causes are due to the sensation of external evils (e.g., wind, dampness, heat, etc.), while internal causes are mostly due to the disorders of the lungs, spleens, and kidneys. From this, it can be seen that the core pathogenesis of IgAN in Chinese medicine is the syndrome of positive deficiency and evil solidity, and the syndrome of mixed deficiency and solidity. In the acute stage, evil and solid are generally dominant, and current studies have shown that the evil and solid symptoms in TCM correlate with some of the pathologic features of IgAN [8]. For example, small artery wall vitreous degeneration, glomerulosclerosis, and renal interstitial fibrosis are similar to the pathogenic features of "gathering dampness into phlegm" and "strange diseases with many phlegm" in TCM [9]. And because it has a fixed, long-term characteristics, and Chinese medicine "blood stasis" similar to the disease. Chronic stage of the disease over a long period of time leads to deficiencies in the liver, spleen and kidneys, which in turn leads to abnormalities in the intake and distribution of essence and micro-substances, resulting in the formation of a syndrome of deficiency or a mixture of deficiencies and realities.

3. State Target Discrimination and IgAN

Academician Tong Xiaolin was the first to propose the concept of "state-target diagnosis", which is a new strategy for clinical diagnosis and treatment of Chinese medicine and an innovative diagnosis and treatment model of Chinese medicine in the context of modern medicine. "State" refers to the division of a certain stage in the complete process of a disease, and it is the basic mechanism that highly summarizes the common developmental law of modern diseases, reflecting the dynamics, status and posture of the disease.

According to the etiology and pathogenesis of IgAN as well as the process of disease development, combined with modern pathological observation, it is summarized that it generally conforms to the pathogenesis of the evil knot state→ renal deficiency state→ network stasis state [10]. The "target" is the various symptoms, signs and abnormal indicators produced on the basis of the "state", of which the symptoms and signs are the "target" and the abnormal indicators are the "target". "Target" [11]. The "target" of IgAN is mainly reflected in sore throat, fatigue, edema, lumbar pain, nocturnal urination, foamy urine, etc., and the "target" is mainly reflected in urinary protein, hematuria and hematocrit. The "target" is mainly reflected in urinary protein, hematuria, high blood creatinine, high uric acid, hypertension and so on. Clinical diagnosis of IgAN should pay attention to its "target" and "target".

4. Kidney Tonifying, Blood Activating and Knot Dispersing Formula to Regulate the State and Target to Benefit the Kidney and Disperse Knots and Resolve Stasis in the Treatment of IgAN

Based on the traditional theories of the classic "Su Wen - Tang Liquid and Mash Liling", "Ping Zhi Yu Quan Heng, remove Ivana Chen Ch Chop straw ..... to open the ghost gate and clean the house", and organically combining the microscopic pathological changes with the traditional Chinese medicine, we proposed that IgAN glomerulosa cells proliferation, proliferation of the mesangial matrix, tubular atrophy, renal interstitial fibrosis is the "renal micrococcus" hypothesis, and the patients with immunodeficiency, mucosal immunity after the onset of the disease is the key to the development of the disease, and the Chinese medicine congenital renal qi insufficiency, the dietary disorders, the spleen and kidney loss of nourishment in line with the causes affect each other, resulting in spleen and kidney deficiencies, the spleen and kidney deficiency and the spleen and kidney loss of nutrients, and the various causes affect each other, resulting in the spleen and kidney deficiency. The causes influence each other, resulting in spleen and kidney deficiency, phlegm and stasis. Based on removing the stagnant straw, promoting phlegm-dampness, resolving blood stasis to disperse the knot, and taking into account the tonicity of the internal organs, the formula is to benefit the kidneys to disperse the knot and resolve the stasis of the kidneys and kidneys and activate the blood to disperse the knot, composed of Cornu Cervanthes Pantotrichum, fried Cortex Eucommiae, Cuscutae, Golden Cherry Seed, Spleen of the Immortal Spirit, vinegared Pelletus Versicolor, Chinese Yogurt, Curcuma longa, Curcuma longa, and so on. In recent years, from the theoretical mechanism, clinical observation and other studies, it was found to have fewer side effects and contraindications to medication, and to have the effect of delaying the deterioration of renal function and reducing urinary protein in patients with IgAN with interstitial tubular injury [12]. This time, the authors further analyzed the mechanism of action of Kidney tonifying, blood activating, and knot dispersing formula in treating IgAN from the aspect of modulation and targeting.

4.1 Tonify the Liver, Spleen and Kidneys at the Same Time to Replenish the Deficiency State

Astragalus is warm in nature, sweet in taste, and enters the lung and spleen meridians, with the effect of replenishing qi and rising yang, fixing the surface and stopping sweating, inducing diuresis and eliminating swelling, generating fluid and nourishing blood, and promoting stagnation and paralysis. The new compilation of materia medica" cloud: "the astragalus is the holy medicine to replenish qi". Yam is sweet and flat, belonging to the spleen, lung, kidney meridian, also has the effect of replenishing qi, the two together for qi weakness, tiredness and fatigue and other symptoms have significant therapeutic effects. The trace elements and nutrients contained in both herbs, such as amino acids and vitamins, can also supplement the body's nutrition and improve the body's resistance and immunity. Cuscuta is sweet, pungent and warm in nature. Cuscuta chinensis is sweet, pungent and warm in nature, which can warm and tonify kidney yang, and its pungent flavor can benefit kidney qi. It is a commonly used medicine in the treatment of chronic kidney disease by contemporary medical practitioners, and together with Jinchuuzi, which has strong astringent power, it can tonify the kidney qi and consolidate the essence of the kidneys, which can be used to target the treatment of proteinuria. For proteinuria caused by edema and other real false evidence can also be used, to play the effect of "plugging the cause of the plug" [13]. Epimedium is pungent, sweet, warm. Attributed to the liver, kidney meridian. It has the function of tonifying kidney yang, strengthening muscles and bones, and dispelling

wind-dampness. The combination of these drugs can replenish yang and benefit qi, resolve dampness and eliminate swelling, and improve the symptoms of edema, lumbago and cold knees in IgAN patients.

“Su Wen - five runs of the Great Theory” cloud: “the north of the birth of cold ..... kidneys born bone marrow, marrow born liver”, revealing the close relationship between the liver and kidney organs interconnected and interacting with each other. Liver blood, kidney essence, IgAN patients commonly persistent microscopic hematuria or intermittent hematuria, long-term liver blood loss, kidney essence depletion, kidney essence deficiency, lack of source, and can be the mother of the disease and the child, liver and kidney deficiency. Cornu Cervi Pantotrichum is sour, astringent, slightly warm, and belongs to the liver and kidney meridians. It is commonly used to supplement yin and yang in traditional Chinese medicine, which can nourish the liver and kidney as well as sealing and fixing. Cortex Eucommiae is sweet and warm in nature. Slightly bitter in flavor. It belongs to liver and kidney meridians. It has the effect of tonifying the liver and kidney, and strengthening the muscles and bones. The two herbs work together to tonify the liver and kidney.

In terms of targeting, modern medicine has shown that Astragalus can promote the recovery of damaged glomerular capillaries and renal tubular function [14]. Astragaloside IV, the main bioactive component in Astragalus, has the pharmacological effects of lowering blood glucose, proteinuria and protecting the renal tubules [15]. Zheng Huanhuan et al. [16] found that Astragalus injection is beneficial in reducing proteinuria and blood uric acid in IgAN patients. Cuscuta chinensis is rich in pharmacological effects, which can effectively regulate the level of reproductive endocrine hormones, inhibit apoptosis and autophagy imbalance of granulocytes, inhibit oxidative stress, improve mitochondrial function as well as regulate the immune system. Su Shanggui et al. [17] found that the hydroalcoholic extract of gold cherry can regulate the expression of related proteins, effectively improve the renal function and reduce proteinuria in IgAN patients. Zhao Jin et al. [18] found that Epimedium glycosides could inhibit the increase of urinary protein, serum creatinine and urea nitrogen levels and improve renal dysfunction in IgAN rats. Yi-Wen Chen et al. [19] used Eucommia granules in the treatment of hypertensive nephropathy and found that it could effectively control the blood pressure of hypertensive nephropathy patients and better reduce the level of urinary protein, thus improving renal function. Modern pharmacological studies have shown that Cortex Eucommiae contains components such as cyclic enol ether terpenoids, phenylpropanoids, lignans, flavonoids, etc., which have obvious vasodilating and antihypertensive effects [20].

In summary, the above drugs are paired with the liver, spleen and kidney to regulate the deficiency state, replenish qi and diuresis together, and at the same time enhance the body’s immunity, reduce urinary protein, and hit the target in order to improve the clinical symptoms.

4.2 Activate Blood Circulation and Eliminate Blood Stasis to Regulate the Stasis State of Collaterals

Prof. Wang Shirong analyzed the connotation of IgAN disease progression and complex pathology and concluded that the pathogenesis of the disease is mainly “kidney complex disorder” [21]. Modern research shows that the kidney is characterized by “microscopic blood stasis” [22]. Ye Tianshi Yun: “Long-term diseases enter the collaterals”, “collaterals are characterized by blood stasis”. Danshen is slightly cold in nature, bitter in flavor, and enters the heart meridian and liver meridian. It has the effects of activating blood circulation to remove blood stasis, promoting menstruation and relieving pain, clearing the heart and removing vexation, cooling the blood and eliminating carbuncles. Modern medical practitioners often use Salvia miltiorrhiza to treat diseases caused by “blood stasis” as a pathogenic factor. Red peony is slightly cold in nature, bitter in taste, belonging to the liver meridian, with the effect of cooling blood and clearing heat, dispersing blood stasis and relieving pain, and facilitating urination. Wu detailed cloud “the liver is the master of blood, also the master of blood ..... liver depression for a long time is blood stasis”, the liver loss of excretion, gas line is not smooth, the inability to transport blood, blood stagnation into stasis. The Compendium of Materia Medica says: “turtle shell is the medicine of blood division of the syncopal liver meridian, and the liver is the master of blood”. It is salty in taste, slightly cold in nature, belongs to liver and kidney meridians, and has the efficacy of nourishing yin and submerging yang, reducing fever and removing steam, softening hardness and dispersing knots, and resolving blood stasis and promoting blood circulation. Prof. Tong Xiaolin proposed that cirrhosis of the liver has a root pathogenesis of stasis and obstruction of blood channels, and proposed the effective basic formula of Salvia divinorum, Paeonia lactiflora, and turtle shell in vinegar for the treatment of cirrhosis of the liver [23]. According to the principle of “treating the same disease with the same treatment”, the combination of these three medicines can also play a role of activating blood and clearing up the blood channels, eliminating stasis and generating new ones, and softening and dispersing hardness and nodularity in the treatment of IgAN.

Modern research has shown that danshen can be widely used in the inhibition of renal fibrosis through the inhibition of oxidative stress, anti-inflammatory and anti-fibrotic effects [24]. In terms of targeting, studies have found that its active ingredient, danshen polyphenolates, is not only effective in lowering blood pressure [25], but also in lowering urinary protein and blood creatinine [26]. A study on the extract of Paeonia lactiflora found that it has the effect of lowering SCr, BUN, and protecting renal function, and the improvement of renal morphology is manifested in the improvement of glomerular fibrosis [27].

Turmeric, Curcuma longa belongs to the same ginger family turmeric plants, both taste bitter, pungent, warm. It belongs to the liver and spleen meridians. Turmeric has the efficacy of promoting blood circulation and qi circulation, and relieving menstruation and pain. Curcuma longa has the efficacy of promoting blood circulation, eliminating accumulation and relieving pain. The two together can enhance the work of blood, and at the same time with astragalus, in order to benefit the qi and blood, complementary but not stagnant, long-term use without harming qi and blood of the disadvantages. In addition, “if blood is unfavorable, it will become water”, “if

accumulated water is not dispersed, it will become drink", "if accumulated drink is not dispersed, it will become phlegm", and phlegm and stagnation will stagnate in the kidney, which will accelerate the progress of the disease. Therefore, the use of stagnant silkworms, which has the effect of resolving phlegm and dispersing stagnation, enhances the therapeutic effect.

Studies have shown that curcumin reduces urinary protein content, blood uric acid and blood creatinine concentrations, and improves renal fibrosis by reducing oxidative stress and apoptosis in mice with diabetic nephropathy [28]. Pharmacological studies have found that curcumol significantly inhibits inflammatory responses, reduces inflammatory mediator levels, and improves renal function in rats with chronic renal failure after 5/6 nephrectomy [29]. Wang Huihui et al. [30] found that stiffworms can effectively reduce 24h urine protein, improve lipid metabolism, down-regulate the expression of nitric oxide synthase and endothelin-1 in renal tissues in rats with thylakoid proliferative glomerulonephritis, and further attenuate inflammatory response and play a renoprotective role.

To sum up, the above drugs are used together in the treatment of IgAN, activating blood circulation, removing blood stasis and clearing collaterals in order to regulate the "collaterals stasis state", slowing down renal fibrosis, slowing down glomerulosclerosis, and hitting the target to protect renal function.

5. Summary and Outlook

Academician Tong Xiaolin's "State Target Identification" model effectively realizes the complementary advantages of Chinese and Western medicines, and not only inherits the essence of Chinese medicine's "identification and treatment" in clinical treatment of diseases, but also integrates the idea of modern medicine's precise medical treatment, aiming at realizing the goals of individualized and precise treatment. The aim is to realize individualized and precise treatment. Combined with the idea of "diagnosis and treatment", we explored the mechanism of IgAN treatment with the formula of tonifying the kidney, activating blood and dispersing knots, and found that the formula could not only regulate the state of emptiness, but also dissolve the state of blood stasis. On the basis of macro-regulation, it emphasizes micro-targeting and provides targeted treatment for common "targets" and "targets", with significant therapeutic effect of simultaneous regulation of state and target. With the deepening of modern Chinese medicine pharmacology research, more Chinese medicines will be tapped in the future for their targeting ability. State-targeted diagnosis and treatment will be applied and promoted in more fields. We have reason to believe that in the near future, this therapeutic concept will lead the treatment of kidney disease to a new era of more accurate and more efficient.

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