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Progress of Modern Research on IgA Nephropathy Syndrome of Blood Stasis

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Abstract: IgA nephropathy is the most common glomerulonephritis worldwide. Blood stasis syndrome is one of the most common pathogenic factors of IgA nephropathy, and blood stasis is the main factor to accelerate the progression of the disease in the later stage of the disease. Modern medicine provides a scientific and objective basis for blood stasis syndrome in relation to kidney pathology and biochemical indexes. In the theory of traditional Chinese medicine, the formation of blood stasis is both vacuity and substance, and stasis caused by vacuity is often the initiating factor, while evil substance is the secondary factor that aggravates blood stasis. Deficiency syndrome is caused by deficiency of lung, spleen and kidney function during repeated attacks and chronic process of IgA nephropathy. At the same time, water dampness, dampness-heat, dampness-turbidity and other solid evils further aggravate blood stasis syndrome. In this paper, the etiology and pathogenesis of IgAN syndrome of blood stasis in traditional Chinese medicine and the modern objective study of blood stasis syndrome in nephrology are systematically expounded.

1. Introduction

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. 30% - 40% of patients within 20 to 30 years after the diagnosis eventually lead to end-stage renal disease (endstagerenaldisease, ESRD) [1]. The prevalence of IgA nephropathy is significantly different in different races and regions, with the highest incidence in Asian countries (up to 40-50%) and the lowest incidence in the United States (10%-20%) [2]. The pathogenesis of IgA nephropathy is now widely accepted as the "four blows" theory, with increased synthesis of cyclic abnormal galactose IgA1 (Gd-IgA1) in IgA nephropathy (Hit1). Gd-IgA1 is recognized by IgG and IgA antibodies to form IgA1 immune complexes (Hit2 and Hit3), which deposit in the mesangial region of the glomerulus to activate mesangial cells, induce the proliferation and secretion of extracellular matrix, cytokines and chemokines, and ultimately lead to kidney injury [3]. IgAN diagnosis depends on pathological and histological changes of its characteristic, especially the predominantly IgA immune complex deposition in the glomerular [4]. Clinically, the main manifestations are gross hematuria or microscopic hematuria with or without proteinuria, and renal insufficiency and severe hypertension

may occur in some patients [5]. Blood stasis syndrome is one of the most common syndromes of IgA nephropathy.A study on the distribution of TCM syndrome types in 1016 patients with IgAN found that dampness-heat syndrome and blood stasis syndrome were the most common among the pathogenic factors, of which stasis syndrome accounted for 28.9%[6]. Modern medicine has revealed the modern pathological basis of blood stasis syndrome from the perspective of microscopic differentiation, such as abnormal vascular function, blood circulation disorders, thrombosis and so on. In 2006, the Chinese Association of Traditional Chinese Medicine formulated the diagnosis, syndrome differentiation and efficacy evaluation of primary nephrotic syndrome. Blood stasis syndrome includes the main syndrome: (1) hematuria with microscopic examination of red blood cells; (2) Long course of illness, or lumbago, or dark complexion; (3) The renal pathology showed capillary loop occlusion, intravascular microthrombosis, glomerular balloon adhesion, scar, extracellular matrix accumulation. Secondary symptoms: (1) Abnormal hemodynamics, high blood viscosity; (2) Urinary fibrin degradation products (FDP) increased.It provides a reference index for the microscopic differentiation of blood stasis syndrome of kidney disease through symptoms, laboratory indicators, histopathology and other aspects [7].

2. Understanding of the etiology and pathogenesis of blood stasis syndrome in IgA nephropathy

2.1. Deficiency of spleen and kidney is the root cause of stasis

Deficiency of healthy qi is often the initial cause or initiating factor of blood stasis syndrome. The core is mainly the deficiency of lung, spleen and kidney. As the root of Yuan Yin Yuan Yang, the source of Qi and blood biochemistry of the spleen and stomach, the deficiency of the spleen and kidney is the key. "On Su Wen ·Regulating the Scriptures" said: "Blood and qi are not harmonious, all diseases are born of change". "Medical forest correction" said: "Qi is vacuity, will not be able to reach the blood vessels, blood vessels will stop and leave stasis". IgA nephropathy is a progressive disease, its disease repeated and prolonged difficult to cure, chronic disease damage spleen and kidney, Qi deficiency, blood stasis. Just as "reading medical Essays ·Deficiency and deficiency tonifying diarrhea" said: "Qi deficiency is not enough to push blood, then blood must be blood stasis. "At the same time, the frequent use of cytotoxic drugs in the treatment of IgA nephropathy further aggravates the deficiency of the spleen and kidney. Therefore, Qi deficiency causing stasis is the main cause of blood stasis syndrome in IgA nephropathy.

Kidney Yang is the root of a Yang. "Medical Yuan ·Five elements Shengke Theory" cloud: "The qi of the true Yang in the kidney, fine warming and nurturing, the Yang of each zang-fu organ. "Chronic illness hurts the spleen and kidney Yang, and the movement of qi and blood is lost in the warm xu and push of kidney Yang, resulting in deficiency cold endogenous. As the book Soul-thorse and Ulcer says, "When cold evil creatures are in the veins, they weep blood, but when they weep blood, they cannot heal. "Cold congealing blood, blood astringency and blood stasis.

In some cases, due to the patient's hyperyang body, or overeating spicy and warm dry products, or water and dampness stop accumulation of heat and stagnation, or the use of glucocorticoids and other warm products in the treatment and burn kidney Yin, resulting in true Yin deficit. Before the onset of IgA nephropathy, there are often pharyngitis, tonsillitis and other upper respiratory tract infections. In the theory of traditional Chinese medicine, the loss of kidney Yin is often aggravated by the evil of external wind and heat in the body. Water does not control fire and causes phase fire to be overactive, frying Yin fluid, then blood concentration is not smooth and blood stasis endogenous.

2.2. Deficiency of spleen and kidney is the root cause of stasis

Stasis caused by excess evil is often closely related to dampness evil. "On Blood Syndrome" said:

"Sick blood and sick water form each other's reasons. "As the most common pathological product of kidney disease, dampness is closely related to the formation of blood stasis. In the different stages of IgA nephropathy, it is often manifested in different forms, which are often manifested as three pathologic attributes: wet, wet and hot, wet and turbid.

Water dampness and blood stasis: the three viscera of lung, spleen and kidney are dysfunctional, body fluid generation, transport and excretion disorders, water dampness internal, spilling over the skin will be edema, water dampness and blood stasis are pathological products and pathogenic factors, water dampness and blood stasis often affect each other, blood stasis aggravates the accumulation of water dampness, water dampness obstructs blood flow and further aggravates the formation of blood stasis, as stated in the Synopsis of Golden Chamber: "Blood does not flow smoothly to form water.

Wet blood stasis: water is long accumulated in the body, and the external wind and heat evil or take glucocorticoid, water and heat intercoalesce into damp and heat evil. The dampness pathogen has the characteristics of adhesion and heavy turbidity, which is similar to the disease characteristics of IgA nephropathy with repeated attacks and lingering course. If the dampness and heat interlock, the dampness-heat toxin obstructs the three jiao, blocking the qi machinery, preventing blood flow and blood stasis, at the same time, the heat inflammation will hurt the blood collaterality, forcing blood overflow, and hematuria. As in the theory of traditional Chinese medicine, "the blood that leaves the meridians is blood stasis".

Wet turbidity blood stasis: IgA disease course is long and easy to relapse, water wet long accumulated in the body, excretion is not smooth, stored into poison, wet turbidity is also known as water poison. Water toxicity affects the rise and fall of qi and blood flow, resulting in blood stasis. A large number of modern research developments have found that the evil of dampness seen in clinical practice is often related to the degree of increase of small and medium-sized molecular substances such as creatinine and urea nitrogen in the blood at the stage of chronic renal failure, and is mostly positively related to blood viscosity. This also conforms to the ancient theory of "dirty blood will inevitably coagulate and become blood stasis".

3. Modern study on kidney stasis syndrome

3.1. Correlation between kidney stasis syndrome and laboratory indicators

Modern microquantitative study of blood stasis syndrome found that damp-heat syndrome of kidney disease not only has clinical specificity, but also has a certain correlation with many laboratory examination indicators. Wan Tingxin et al. studied the correlation between the symptoms and laboratory indicators of 4 common TCM pathogens in 266 cases of primary IgA nephropathy and found that chronic kidney disease (CKD) stage 3 was more common in blood stasis syndrome, and its serum creatinine (SCr) was significantly higher than that of the other 3 groups, and eGFR was significantly lower. Blood stasis syndrome is correlated with lower APTT and higher FIB, indicating that blood stasis syndrome is closely related to the formation of hypercoagulability [8]. Yu Jiangyi et al. found that in 251 patients with chronic kidney disease, total cholesterol (TC) and low density lipoprotein (LDL-C) were significantly increased in patients with blood stasis syndrome, while high density lipoprotein (HDL-C) was significantly decreased. Meanwhile, SCr level was significantly increased in patients with blood stasis syndrome, and renal function was more significantly decreased when blood stasis syndrome was accompanied by dampness-heat. It indicates that blood stasis is closely related to renal function decline and hyperlipidemia syndrome [9]. Li Shen et al. conducted syndrome scores on 174 patients with primary glomerular disease, among which 159 patients with blood stasis syndrome (91.38%), and found that the correlation between blood stasis syndrome scores and clinical indicators was studied. Blood stasis syndrome score was significantly correlated with 24-hour urinary protein quantification (UTP), cholesterol (CHO), hemoglobin (HB), plasma albumin (ALB) and other indicators, indicating that blood stasis syndrome is a "high incidence" syndrome of chronic glomerular diseases. Moreover, UTP, CHO, HB, ALB and other indicators can be used as

quantitative reference indicators for the differentiation of blood stasis syndrome [10]. It was found that in 59 patients with IgA nephropathy with blood stasis syndrome, plasma markers of vascular endothelial injury such as vascular hemophilia factor (vWF), soluble vascular cell adhesion factor (sVACM) and heparin-binding epidermal growth factor (HB-EGF) were significantly higher than those in healthy group and other TCM syndrome groups. It can be used as the basis for microscopic differentiation of blood stasis syndrome of IgA nephropathy [11]. Li Xiaoming made TCM differentiation of 52 cases of primary glomerular disease (PGD), including 23 cases in the blood stasis syndrome group, accounting for 44.23%, 29 cases in the non-stasis syndrome group, accounting for 29 cases, and 20 cases in the healthy control group. Plasma endothelin (ET) and platelet a granular membrane protein 140 (GMP-140) levels were measured in each group, and it was found that the levels of ET and GMP-140 in the blood stasis syndrome group were significantly higher than those in the non-stasis syndrome group, and the levels of ET and GMP-140 in the healthy control group were the lowest [12]. GMP-140 is a membrane glycoprotein located in the secreted granules of platelets and endothelial cells. When expressed on activated platelets and endothelial cells, GMP-140 promotes the rapid adhesion of white blood cells to the endothelium at the site of tissue injury and the interaction between platelets and white blood cells at the site of inflammation and bleeding, and is involved in pathological inflammation, thrombosis and tumor metastasis [13]. Endothelin is produced mainly by endothelial cells, but also by kidney cells, such as epithelial cells and mesangial cells. Under pathological conditions, the binding of endothelin to receptors can lead to vasoconstriction, inflammation, and cell damage, which further lead to abnormal kidney function [14,15]. In conclusion, blood hypercoagulability caused by platelet activation caused by GMP-140 elevation and the strong vasoconstriction effect of ET may be one of the important pathological bases for the formation of blood stasis syndrome of kidney disease.

3.2. Correlation between kidney stasis syndrome and histopathology

Focal or diffuse mesangial cells and mesangial matrix proliferation were the basic pathological types in patients with IgA nephropathy. The diffuse deposition of IGA-dominated immune complexes in the mesangial region of the kidney was detected by immunofluorescence. On the basis of these pathological changes, a variety of pathological changes can occur, and active and chronic pathological changes need to be evaluated after diagnosis. The active pathological changes included mesangial hyperplasia, capillary hyperplasia, capillary loop necrosis, crescent body and so on. Chronic pathological changes include capillary loop sclerosis, balloon adhesion, renal tubule atrophy, renal interstitial fibrosis, arteriosclerosis and other changes [16]. Studies have shown that blood stasis syndrome has certain correlation with some pathological features. Accompanied by gross hematuria or asymptomatic microscopic hematuria is the characteristic clinical manifestation, traditional Chinese medicine believes that "blood from menstruation is blood stasis", indicating that blood stasis syndrome almost runs through IgAN. The characteristics of chronic pathological changes such as glomerular sclerosis, glomerular fibrous crescent body, balloon adhesion and interstitial fibrosis are not easy to fix and difficult to cure for a long time, which are similar to the pathogenic characteristics of blood stasis accumulation in traditional Chinese medicine theory. A study on the correlation between TCM syndrome types and pathological tissues of 1010 patients with IgA nephropathy found that blood stasis syndrome accounted for 78.3%, and Katafuchi score, globular sclerosis score and interstitial fibrosis score were significantly increased in blood stasis syndrome, which could be considered as one of the factors contributing to the poor prognosis of IgAN [17]. Some researchers believe that the destruction of blood vessels and the disturbance of blood operation caused by celluline-like necrosis and microthrombus formation are consistent with the pathogenic characteristics of blood stasis [18]. A comparative study on the pathological damage degree of 115 IgA nephropathy patients with stasis syndrome and non-stasis syndrome found that renal tubule atrophy score, segment-sclerosis ratio and vascular score in the stasis syndrome group were significantly higher than those in the non-stasis syndrome group. Meanwhile, it was found that renal

tissue fibrinogen associated antigen (FRA) was deposited more heavily in the stasis syndrome group. In the severe blood stasis syndrome group, the proportion of positive FRA deposition above (++) was higher [19]. These results indicate that blood stasis can significantly aggravate the pathological damage of glomeruli, renal tubules, renal interstitium and intrarenal artery, and affect the pathological process, outcome and prognosis of IgA nephropathy.

4. Study on the application of Chinese medicine for promoting blood circulation and removing blood stasis in renal diseases

Traditional Chinese medicine has achieved satisfactory results in the prevention and treatment of IgA nephropathy. Promoting blood circulation and removing blood stasis plays an important role in the treatment of kidney diseases by traditional Chinese medicine. A large number of modern studies have found that activating blood circulation and removing blood stasis can significantly improve kidney function, intervene in the progression of kidney pathological injury, and delay the progression of IgA nephropathy.

Leech is a powerful drug to promote blood circulation and remove blood stasis, "Shennong Herbal Classic" recorded leech taste salty, bitter, flat, slightly cold, toxic. The main expel evil blood, blood stasis month closed, blood stasis accumulation without children, waterways, and abortion. Modern studies have found that hirudin, its main active component, has strong anti-coagulation and anti-platelet aggregation effects, and is used in patients undergoing coronary angioplasty, in the treatment of deep vein thrombosis, and as a substitute for heparin in patients with heparin-induced thrombocytopenia [20]. Studies have found that hirudin interferes with glomerular sclerosis by down-regulating the expression level of transforming growth factor-β (TGF-β) in the mesangium, suggesting that hirudin can delay interstitial fibrosis and improve blood stasis in IgA nephropathy [21].

Radix paeoniae, ligusticum Chuanxiong, Salvia miltiorrhiza and angelica were the most commonly used drugs for promoting blood circulation and removing blood stasis in the treatment of chronic glomerulonephritis. In order to study the effect of tetramethylpyrazine on the apoptosis of renal cells in rats with ischemia-reperfusion injury, Sun Lijiang ET al. observed the levels of plasma superoxide dismutase (SOD), lipid peroxidase propylene glycol (MDA) and endothelin-1 (ET-1) in tetramethylpyrazine injection treatment group, ischemia-reperfusion group and normal control group, and conducted apoptosis detection on renal pathology in the three groups. It was found that the SOD level in the ligustrazine treatment group was significantly higher than that in the ischemia-reperfusion group, and the levels of MDA, ET-1 and apoptosis index of kidney tissue were significantly lower than those in the ischemia-reperfusion group, indicating that ligustrazine has a good anti-ischemic injury effect and can significantly reduce apoptosis [22]. Yu Xin et al. used total Paeoniae glycosides (TPG) to treat diabetic nephropathy (DKD) model rats, and explored the relationship between the antioxidant matrix of TPG and the Nrf2/HO-1 pathway in the classical anti-oxidative stress nucleus, and found that the expression levels of Nrf2 and HO-1 proteins and SOD activity in the TPG treatment group were significantly higher than those in the model group. The degree of renal tissue fibrosis was lower than that of the model group, indicating that TPG may reduce DKD oxidative stress and improve renal fibrosis through the Nrf2/HO-1 pathway [23]. Studies have found that Astragalus Angelica mixture can reduce the level of angiotensin II (Ang-II) and continuously enhance the levels of nitric oxide synthase (eNOS) and nitric oxide (NO) in the early stage of injury in rats with unilateral ureteral obstruction model, thereby reducing vascular tension and improving the state of renal hypoxia injury [24]. Studies suggest that salvia miltiorrhiza injection can inhibit renal interstitial fibrosis by inhibiting extracellular matrix (ECM) synthesis, TGF-β expression, and fibroblast proliferation and activation [25].

Activating blood circulation and removing stasis drugs have certain advantages in inhibiting inflammatory response. It has been found that "Dachuanchongfang", a classic prescription composed of Chuanxiong and Gastrodia ligusticum with the main function of promoting blood circulation and

removing blood stasis, can inhibit the activation of NF-κB induced by lipopolysaccharide (Lps) by reducing the expression and phosphorylation of IκBα and p65, resulting in a good anti-inflammatory effect [26] Immunoinflammatory response is an important link in promoting the occurrence and progression of kidney diseases. The increased intestinal mucosal permeability of IgAN patients is more likely to lead to the release of intestinal microbial products such as lipopolysaccharide (LPS) and lipid cholic acid into the blood [27]. It has been found that the release of LPS can further stimulate the activation of TLR4 in cultured peripheral B cells, leading to methylation of Cosmc, resulting in IgA1 galactosylation defect [28]. Network pharmacological studies have found that the treatment of achyranthes for membranous nephropathy involves a variety of signaling pathways. The active components of achyranthes, such as Quercetin and Berberine, affect MAPK signaling pathway and IL-17 signaling pathway by acting on JUN, MAPK1, IL-6, TNF-α and other targets. It further inhibited the downstream NF-KB signaling pathway, reduced the release of cellular inflammatory factors, and alleviated proteinuria and edema in patients with membranous nephropathy [29].

More and more Chinese medicine studies have found that Chinese medicine for promoting blood circulation and removing blood stasis has extensive effects on reducing renal ischemia and hypoxia, improving hemodynamics and delaying renal fibrosis, and these kidney injuries are consistent with the pathological characteristics of blood stasis in Chinese medicine theory.

5. Summary

To sum up, from the perspective of TCM differentiation, IgA nephropathy syndrome of blood stasis is based on the deficiency of spleen and kidney, marked by water dampness, wet turbidness, damp-heat accumulation of evil, deficiency and accumulation, and blood stasis. A large number of microscopic quantitative studies on blood stasis syndrome in modern medicine have found that blood stasis syndrome has a certain correlation with laboratory examination indicators and histopathology of kidney disease, which provides a way of thinking for microscopic differentiation of blood stasis syndrome of kidney disease. A large number of modern studies have found that Huoxue Huayu drug has obvious improvement effect on chronic changes such as kidney blood circulation disorder, hypoxia, kidney fibrosis, and so on, and has the significance of traditional Chinese medicine in the treatment of kidney disease. In terms of the formation mechanism of blood stasis syndrome in IgA nephropathy, there is a lack of comprehensive studies covering disease and syndrome combined with pathology, immunity, biochemistry, cytology and other aspects. In terms of treatment, due to the complexity of research on the effective ingredients of traditional Chinese medicine, the pharmacological mechanism and efficacy of a large number of drugs for promoting blood circulation and removing blood stasis are not very clear. The improvement of these problems has profound significance to the optimization of TCM diagnosis and treatment system.

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