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Research Progress on the Treatment of Proteinuria with Traditional Chinese and Western Medicine

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Abstract: Proteinuria is a sign of various kidney diseases. As the concentration of protein in urine increases, it also indicates continuous damage to the kidneys. Therefore, treating proteinuria is particularly important for protecting renal function. The methods of treating proteinuria in traditional Chinese medicine include taking traditional Chinese medicine decoctions orally and various external treatment methods in traditional Chinese medicine. Western medicine mainly focuses on protecting renal function to slow down the decline of renal function when treating proteinuria. Using only traditional Chinese medicine or Western medicine treatment cannot achieve the most ideal effect. Currently, in clinical practice, the combined treatment of traditional Chinese and Western medicine is often adopted to achieve the best therapeutic effect.

1. Introduction

When a large number of fine and dense bubbles are observed in the urine and these bubbles do not dissipate for a long time, it is necessary to detect the protein content in the urine. If the amount of protein excreted in the urine exceeds 150 mg per day, it is considered proteinuria. Proteinuria may be a physiological phenomenon (such as after strenuous exercise or a high-protein diet), or it may be a signal of pathological conditions such as kidney diseases and diabetes. Foamy urine is also considered as a specific manifestation of proteinuria[1]. If it persists for more than one week, or is accompanied by symptoms such as edema, hypertension, hematuria, and increased nocturia, kidney diseases should be considered[2]. In the treatment, Western medicine tends to carry out targeted treatment from a microscopic perspective according to the cause of the disease, while traditional Chinese medicine (TCM) regulates the immune system, improves the microcirculation of the kidneys, and delays the progression of kidney damage from a macroscopic perspective through syndrome differentiation and treatment.

2. The Etiology and Diagnosis of Proteinuria

2.1 Analysis of the Etiology of Proteinuria

When the body is undergoing strenuous exercise, experiencing fever, being exposed to cold, or in a state of mental stress, transient proteinuria may occur, which will resolve spontaneously after the inducing factors are eliminated. When adolescents stand for a long time, orthostatic proteinuria may occur [3]. The proteinuria disappears after lying flat and resting, which is related to the compression of the renal veins, leading to an increase in the permeability of the glomerular filtration membrane. When the body has persistent proteinuria that does not subside, it may be pathological proteinuria, and kidney or systemic diseases should be considered. Pathological proteinuria is related to abnormalities in glomerular filtration and tubular reabsorption [4], and it can usually be classified into prerenal, renal, and postrenal types. Renal proteinuria is commonly seen in clinical practice. Modern research shows that renal proteinuria is related to glomerular hyperfiltration, decreased tubular reabsorption function, and the entry of plasma proteins or other tissue proteins into the urine [5]. The state of glomerular hyperfiltration can cause chronic damage to podocytes and the glomerular microvascular system. This pathological change will further induce proteinuria symptoms, promote the process of renal interstitial fibrosis, and ultimately lead to a progressive decline in renal function [6]. The tubular reabsorption function is related to two major receptors, megalin and cubilin. If there are genetic or acquired dysfunctions of megalin and cubilin, it will lead to abnormal kidney development, reducing the reabsorption ability of the proximal tubules for filtered proteins, thus resulting in proteinuria [7]. When there are various infections, injuries, and a decrease in immunity in the body, for example, in patients with multiple myeloma, a large amount of immunoglobulin light chains will be excreted, forming overflow proteinuria. Its formation mechanism has no direct relation to the patient's own renal function [8].

2.2 The examination and diagnostic criteria of proteinuria

When examining proteinuria, it is necessary to comprehensively consider qualitative analysis, quantitative analysis, and etiological analysis. Early and timely detection as well as differential diagnosis are of great significance for the treatment of kidney diseases. The examination of proteinuria mainly relies on urine specimens. Common examination methods include routine urine examination, 24-hour urinary protein quantification, urinary microalbumin detection, urine sediment microscopy, and urinary protein electrophoresis. Each examination method has its own clinical application scope and diagnostic value. Routine urine examination is the preferred method for patients with kidney diseases to initially detect abnormal urine protein. It is convenient, inexpensive, and rapid, and can reflect the health status of the human urinary system and even the whole body [9]. When the urine protein is positive (+) in the qualitative test, it indicates an increase in protein in the urine. 24-hour urinary protein quantification can accurately determine the total amount of protein in the urine within 24 hours. Its normal reference value is less than 150mg/24h. It is the "gold standard" for diagnosing proteinuria and can evaluate the severity of the disease. In the actual clinical operation process, the collection of 24-hour urine is too cumbersome, and the difficulty of collecting samples is relatively high, resulting in the final value not being able to accurately reflect the actual amount of urine protein in patients[10].In recent years, some studies have shown that the albumin-creatinine ratio in the first morning urine (UACR) has a good consistency with 24-hour urinary protein quantification, and there is a good linear relationship between the two. Relevant international guidelines have gradually begun to promote the use of UACR to evaluate the severity of proteinuria in patients[11].Urine sediment microscopy is used to observe red blood cells, white blood cells, casts, etc. in the urine, which can assist in determining

the cause of the disease. Urinary protein electrophoresis is mainly used to distinguish the types of urine protein. When diagnosing monoclonal gammopathy, urinary protein electrophoresis can evaluate the heavy chain and light chain isotypes of monoclonal immunoglobulin (MIg) and the presence of monoclonal free light chains through visual inspection[12].

3. Research Progress on the Treatment of Proteinuria with TCM

3.1 TCM 's Understanding of Proteinuria, and Its Etiology and Pathogenesis

TCM does not have the concept of proteinuria. Proteinuria is a concept formed by drawing on the research of modern medical biochemistry. According to the nature of proteins, it can be understood as "essence and refinement". Therefore, proteinuria should fall into the categories of "turbid urine" and "the leakage of essence and refinement downward". Since proteinuria often leads to edema in patients, it is also related to the disease of "edema" [13].TCM believes that the occurrence of proteinuria is related to the three viscera of the "lung, spleen, and kidney". Its nature can be divided into deficiency and excess, with the main causes including kidney deficiency, spleen deficiency, lung deficiency, damp-heat, blood stasis, etc. The physiological function of the kidney is reflected in "governing the storage of essence". However, if there is deficiency of kidney qi, it cannot retain the essence and refinement, allowing the essence and refinement substances to be excreted with urine, forming proteinuria. As the essence and refinement substances in the urine are excreted, it will exacerbate the deficiency of kidney essence, further leading to the imbalance of yin and yang in the kidney, and aggravating the occurrence and development of proteinuria. The physiological function of the spleen is reflected in "governing transportation and transformation". The spleen has the ability to transport and transform the essence of water and grains. If there is spleen deficiency, there will be insufficient production of qi and blood, and it cannot nourish the kidney essence, leading to kidney deficiency, which in turn affects the sealing and storing function of the kidney, causing the essence and refinement to leak out. In addition, spleen deficiency can also lead to the sinking of the middle qi, unable to raise the clear and lower the turbid, causing the essence and refinement substances to flow downward into the bladder and be excreted with urine, forming proteinuria[14].The lung has the physiological function of "governing dispersion and descent". The lung is located in a high position and is the source of water above. Together with the kidney, it promotes the normal distribution and excretion of body fluids. If there is deficiency of lung qi, it will lead to the retention of water-dampness inside the body, affecting the smoothness of the water passages, hindering the circulation of qi and blood, and further aggravating the abnormal qi transformation function of the kidney, causing the essence and refinement substances to leak out and forming proteinuria. The pathogenic factors of damp-heat flow downward into the bladder, scorching and injuring the kidney collaterals. This not only leads to the leakage of essence and refinement substances, forming proteinuria, but also causes the blood to go astray due to heat, forming hematuria, and aggravating the damage to the kidney[15].Blood stasis blocks the kidney collaterals, leading to the unsmooth circulation of qi and blood in the kidney, and then leading to kidney deficiency. The sealing and storing function of the kidney fails, unable to retain the essence and refinement substances, forming proteinuria[16].

3.2 The Theories, Prescriptions and Medicinal Herbs of TCM in the Treatment of Proteinuria

TCM considers proteinuria as a "turbid urine" disorder, which is related to various kidney diseases in Western medicine. Different syndromes are determined based on different clinical manifestations, and different prescriptions are selected for treatment. Regarding the classification of proteinuria syndromes, different TCM practitioners have different views, but there is a consensus in

identifying syndromes such as deficiency of both the spleen and kidney, downward flow of damp - heat, kidney yin deficiency, or kidney yang deficiency.

Professor Li Jianying proposed that the core pathogenesis of refractory nephrotic syndrome is "deficiency of spleen-kidney qi, blockage of damp-heat and blood stasis, and endogenous generation of yin fire". He advocated using the Shengyang Yiwei Decoction as the basis, adopting a comprehensive treatment method of protecting the spleen and kidney, promoting yang and removing dampness, and dissipating yin fire. By combining TCM and Western medicine, significant curative effects have been achieved in reducing proteinuria and delaying kidney damage. Professor Li Jianying believes that proteinuria is one of the manifestations of refractory nephrotic syndrome. Its pathogenesis is the deficiency of spleen-kidney qi, which leads to insufficient generation of vital qi, leakage of essence, and the formation of a vicious cycle. In clinical medication, he uses sweet-warm herbs such as Astragalus membranaceus and Codonopsis pilosula to nourish the vital qi of the spleen and stomach, and combines them with wind-like herbs such as Cimicifuga foetida and Bupleurum chinense to promote the rise of clear yang and restore the function of the spleen-stomach pivot. He also uses wind-like herbs such as Notopterygium incisum, Angelica pubescens, and Saposhnikovia divaricata to dispel damp-turbidity, coordinates with Poria cocos and Alisma orientale for promoting diuresis and removing dampness, and uses a small amount of Coptis chinensis for purging fire with its bitter-cold property[17].

Professor Ba Yuanming proposed that the core pathogenesis of proteinuria in chronic nephritis is "latent pathogen invading the collaterals and deficiency of both qi and yin". He advocated stage - based treatment and targeted treatment with precise herb pairs, emphasizing the coordination of TCM and Western medicine to delay kidney damage. He believes that the pathogenesis is that exogenous pathogens such as wind, dampness, heat-toxin, or endogenous phlegm and blood stasis lurk in the body. Due to the deficiency of healthy qi, these pathogens cannot be cleared in time. Over time, they penetrate deep into the kidney collaterals. After the kidney collaterals are damaged, the qi and blood circulation is not smooth, forming micro-masses (renal fibrosis), and eventually developing into chronic renal failure. He combines the theory of latent pathogens with the theory of collateral diseases, advocates early promoting blood circulation and removing blood stasis to block the progression of the disease, and reveals the essence of the recurrent proteinuria in chronic nephritis[18]. Professor Lei Genping proposed that the core pathogenesis of proteinuria in chronic kidney disease is "deficiency of the spleen and kidney and blockage of damp-heat and blood stasis". He advocated taking nourishing, supplementing, astringing, and promoting blood circulation to remove blood stasis as the basis, and combining with methods such as warming yang, clearing heat, and dispelling wind for stage-based treatment. Professor Lei Genping believes that the kidney is the root of storage, and the spleen is the source of transformation. When the qi of the spleen and kidney is deficient, the essence cannot be firmly retained, resulting in proteinuria. He emphasizes that "a long-term illness will definitely lead to deficiency, and blood stasis will form when the pathogen enters the collaterals". Blood stasis is both a pathological product and a factor that aggravates kidney damage. People who have received hormone treatment or have a damp-heat constitution are prone to have damp-heat. The invasion of wind pathogen into the lungs can induce or aggravate proteinuria, which is related to the kidney meridian passing through the throat. He often uses the self-formulated "Qidi Gushen Decoction" to nourish the spleen and kidney and astringe protein, and uses the Guizhi Fuling Pill as the basic prescription to improve the hypercoagulable state and delay renal fibrosis[19].

3.3 The application of external treatment methods of TCM in the treatment of proteinuria

Li Yuting et al.[20]randomly divided 90 patients with proteinuria in stages 2-3 of chronic kidney

disease (CKD) of the spleen-kidney qi deficiency type into a treatment group and a control group. The treatment group was given the Yiqi Qufeng Decoction combined with acupuncture treatment on the basis of the control group. The acupoints Shenshu (BL23), Pishu (BL20), Mingmen (GV4), Guanyuan (CV4), and Qihai (CV6) were selected for treatment. After 90 days of treatment, the levels of 24-hour urine protein quantification, urinary microalbumin, urinary α1-microglobulin, and urinary β2-microglobulin in the treatment group were significantly lower than those before treatment, and the differences were statistically significant ($P<0.05$). Moreover, the levels of the above-mentioned indicators in the treatment group were significantly lower than those in the control group, and the differences were statistically significant ($P<0.05$). The combination of acupuncture and traditional Chinese medicine treatment can significantly improve proteinuria, delay the progression of kidney disease, and help patients relieve clinical discomfort symptoms. Professor Yu Renhuan often uses traditional Chinese medicine combined with tuina (Chinese massage) to treat proteinuria in children. He manipulates the Neibagua (an area on the palm) and pushes along the spleen-stomach meridians of the lower legs to strengthen the spleen and regulate the stomach. It can also be combined with kneading Zhongwan (CV12), Shenque (CV8), and pinching the spine to strengthen the spleen and kidney[21]. External treatment methods in traditional Chinese medicine also include acupoint application. Commonly used acupoints include Shenshu (BL23), Pishu (BL20), Sanjiaoshu (BL22), Mingmen (GV4), Sanyinjiao (SP6), and Guanyuan (CV4), etc. According to clinical needs, external treatment methods such as traditional Chinese medicine enema, traditional Chinese medicine bath, and auricular point pressing with seeds can also be selected.

4. Research Progress on the Treatment of Foamy Urine with Western Medicine

4.1 Conventional Therapeutic Drugs for Proteinuria in Western Medicine

The treatment of proteinuria in Western medicine focuses on controlling the causes and protecting the kidneys. The selection of drugs needs to be combined with the pathological type, renal function, and overall physical condition. Commonly used drugs include antihypertensive drugs, antidiabetic drugs, hormones, diuretics, anticoagulants, etc. ACEI/ARB antihypertensive drugs are frequently used. They can inhibit the RAAS, reduce intraglomerular pressure, and decrease proteinuria. If blood pressure is difficult to control, calcium channel blockers may be used in combination. Sodium-glucose cotransporter 2 inhibitors are chosen as antidiabetic drugs. They can reduce glomerular hyperfiltration and improve renal blood flow while lowering blood sugar, thus reducing proteinuria. Glucocorticoids are selected as hormone drugs. They work together through multiple mechanisms such as inhibiting the inflammatory response, regulating the immune system, stabilizing the glomerular basement membrane, and promoting protein reabsorption to reduce proteinuria. Clinically, thiazide diuretics, loop diuretics, and spironolactone are commonly used. They reduce kidney damage by improving electrolyte disorders and alleviating edema. Anticoagulants are mainly used to prevent thrombosis in the hypercoagulable state of nephrotic syndrome. Since statins can reduce low-density lipoprotein to alleviate vascular calcification and improve the permeability of the glomerular filtration membrane, they are also often used clinically.

4.2 Targeted Drugs for Treating Foamy Urine in Western Medicine

According to the specific type of kidney disease, targeted therapeutic drugs need to be selected, and various immunosuppressants are commonly used. When the effect of hormone drug treatment is not obvious, there may be steroid-resistant nephrotic syndrome, and cyclophosphamide can be selected[22]. It reduces the activity of immune cells by inhibiting cell proliferation, thereby alleviating the immune damage of the kidneys. Azathioprine reduces the proliferation of immune

cells by inhibiting DNA synthesis and is often used in the treatment of diseases such as chronic nephritis. Methotrexate reduces DNA synthesis by inhibiting dihydrofolate reductase and inhibits the proliferation of immune cells. It is often used for refractory nephrotic syndrome. For membranous nephropathy, tacrolimus can be used. It can selectively inhibit T-cell activation, protect podocytes, and have an anti-fibrotic effect to reduce proteinuria. Cyclosporine reduces the activation of T-cells by inhibiting the activity of calcineurin, thereby suppressing the immune response. It is often used for anti-rejection treatment after kidney transplantation and can also be used for refractory nephrotic syndrome. Rituximab[23]is an anti-CD20 monoclonal antibody. By specifically binding to the CD20 antigen on the surface of B cells, it eliminates B cells and reduces antibody-mediated immune damage. It is suitable for refractory nephrotic syndrome and lupus nephritis. Tafasitamab is a dual-target receptor-antibody fusion protein. By binding to the dual targets of BLyS/APRIL, it inhibits the maturation and differentiation of B cells and reduces kidney damage caused by humoral immune responses. It is suitable for lupus nephritis and IgA nephropathy. Eculizumab reduces glomerular inflammation and damage and improves renal function by inhibiting the activation of the complement system, thus effectively reducing proteinuria. Tofacitinib reduces the production of inflammatory factors and the activation of immune cells by inhibiting the JAK-STAT signaling pathway, thereby alleviating the inflammatory response and damage of the kidneys and reducing proteinuria.

4.3 Research on Surgical Intervention for Proteinuria

Surgical interventions for the treatment of proteinuria are applicable to specific types of kidney diseases, such as obesity-related glomerulopathy (ORG), renal tumors, or severe kidney injuries. ORG[24] is a kidney disease closely associated with obesity, mainly manifested by proteinuria and declining renal function. Bariatric surgery can significantly improve insulin resistance and reduce the metabolic burden on the kidneys by reducing body weight, which has a remarkable effect on improving proteinuria and renal function in patients with ORG. Renal surgeries include nephrectomy and kidney transplantation. Nephrectomy is suitable for patients with renal tumors or severe kidney injuries. It can remove the damaged kidney tissue and reduce the source of proteinuria. Kidney transplantation[25] is applicable to patients with end-stage renal disease. By providing a healthy kidney, it can restore normal renal function and thus reduce proteinuria.

5. Conclusions

The pathogenesis of foamy urine can generally be summarized as deficiency of both the spleen and kidney, and blockage of dampness-heat and blood stasis. The treatment mainly focuses on invigorating the spleen and kidney, clearing heat and removing dampness, resolving turbidity and detoxifying, and astringing the essence. A large number of clinical trials have confirmed that traditional Chinese medicine has a good clinical effect in the treatment of proteinuria, with low side effects and good safety, and is valuable for long-term use. Western medicine treats proteinuria by starting with protecting renal function and reducing kidney damage caused by various complications. With the development of medical science and technology, emerging therapeutic drugs continue to appear. Although they have the advantage of targeted therapy, it is necessary to properly select the indications; otherwise, they may be toxic to the human body. In the future, a treatment plan combining traditional Chinese and Western medicine for proteinuria can be adopted, which will also be a research hotspot.

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