

# Research progress in traditional Chinese and Western medicine for renal edema

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**Abstract:** Edema is one of the common symptoms of clinical renal diseases, caused by various primary or secondary renal diseases, belonging to the category of "edema, renal water" in traditional Chinese medicine. The pathogenesis is complex, the clinical manifestations are diverse, and the lesions involve multiple viscera of the whole body. Reasonable effect of integrated Chinese and western medicine therapy in the treatment of renal edema can improve clinical efficacy. The recent years of Chinese and western medicine treatment of renal edema are summarized in this paper.

**Keywords:** Renal Edema; Reserch Progress; Mechanism; Therapy

## 1. Introduction

Renal edema is commonly seen in acute and chronic glomerulonephritis or nephrotic syndrome, and is the most common clinical manifestation of kidney disease, with an incidence rate of 48.7 %<sup>[1]</sup>. It belongs to the category of "edema disease" and "water qi disease" in traditional Chinese medicine. Although the degree of renal edema is not directly proportional to the severity of renal disease, and the severity of edema in clinical practice cannot be used as the main indicator to judge the prognosis of kidney disease, severe water and sodium retention can cause acute and critical complications such as heart failure and acute pulmonary edema. The reasonable treatment of traditional Chinese and Western medicine has a good therapeutic effect on renal edema. This review summarizes the research on the treatment of renal edema with traditional Chinese and Western medicine in recent years.

## 2. Etiology and pathogenesis

### 2.1. Traditional Chinese medicine pathogenesis

Professor Fu Xiaojun<sup>[2]</sup> discusses the treatment of edema from the perspective of "water in the three yin junctions". Professor Fu believes that the relationships between "three yin junctions", "water", and "root", "axis", and "branch" correspond to each other. The "Three Yin" refers to the three Yin meridians of "hand Taiyin lung, foot Taiyin spleen, and foot Shaoyin kidney." The "Three Yin" is the fundamental pathogenesis of the entire water qi disease. Wang Bing once noted, "The Three Yin node refers to the cold accumulation of all the spleen and lung meridians, and the cold accumulation of the spleen and lung transforms into water. The root cause of its pathogenesis is often attributed to dysfunction of the lungs, spleen, and kidneys, as well as the loss of qi; The term "jie" refers to obstruction and astringency. Fu Laolao believed that the loss of qi in the lungs, spleen, and kidneys can be referred to as "jie", the external attack of wind, cold, dampness, and heat can be referred to as "jie", and the stagnation of qi, blood, stasis, and water can be referred to as "jie". The "knot" is a combination of many factors, and many "knots" are interconnected and influenced each other, forming a complex pathogenesis that is both primary and secondary, and inclusive; Regarding "water", Fu Laolao believes that it is both a pathological product and a pathogenic factor. In addition to "water dampness", there are also various forms such as "phlegm", "blood stasis", "turbidity", and "toxin".

The "Suwen · Water Heat Point Theory" also states: "The kidney is the key to the stomach, and the door is not closed properly. Therefore, it gathers water and follows its type. It overflows from the skin, so it is called swelling." Professor Xie Junxia et al.<sup>[3]</sup> treated renal edema from the spleen and stomach, believing that it is the responsibility of the spleen, originating from the kidney, and related to the

stomach. The stomach is responsible for receiving water, which enters the stomach, generates qi, and is transported to the spleen. The spleen is responsible for transportation and transformation, and is the organ that produces water. If stomach deficiency cannot transmit water qi, it can benefit the meridians and organs externally. If the spleen receives water dampness, it becomes diseased, while if the spleen is diseased, it cannot produce water. Causing the water to stop in focus and overflow everywhere, affecting the five internal organs, resulting in edema.

Professor Chen Cuilan<sup>[4]</sup> argues from the perspective of "lung" that the lungs and kidneys interact with each other. "The lungs are the source above water, and the kidneys are the source below water," both of which jointly regulate water metabolism. The lungs regulate qi and breath, regulate water flow, and regulate waterways by promoting the lowering of the qi. If lung function is lost, water distribution and excretion are impaired, and the accumulation stops, it becomes edema, as stated in the "Suwen · Water Heat Point Theory": "Its origin is in the kidney, and its end is in the lungs, all of which have water accumulation."

Mr. Guan Huanjing<sup>[5]</sup> believes that renal edema is a syndrome of deficiency and excess. The original deficiency lies in the deficiency of the lungs, spleen, and kidneys. Qi deficiency cannot promote the movement of body fluids, causing them to stagnate and become edema. Edema can also affect the movement of qi. The actual symptoms are mostly damp heat (toxin), blood stasis, edema, and qi stagnation. Qi circulation leads to blood circulation, qi stagnation leads to blood clotting, and unfavorable blood circulation leads to water. Qi stagnation, blood stasis, and edema often interact with each other. And wind evil is often the initiating factor of the onset<sup>[6]</sup>.

## **2.2. Western medicine mechanism**

The pathogenesis of nephrotic edema is relatively complex and may be mediated by multiple mechanisms. Recent research results have shown that it mainly includes the following aspects:

### **2.2.1. Underfill theory**

A large amount of proteinuria leads to the decrease of plasma albumin level, which leads to the decrease of intravascular colloid osmotic pressure, and the leakage of plasma fluid into the tissue gap to form edema. On this basis, due to the relatively insufficient decrease of blood volume, the sympathetic nerve excitability is increased reflexively, the secretion of angiotensin, aldosterone and antidiuretic hormone in the blood vessel is increased, and the secretion of atrial natriuretic peptide (ANP) is reduced, which promotes the reabsorption of sodium and water in the kidney, further aggravating the edema. However, there is also some controversy about this theory, such as: patients with congenital albumin deficiency do not experience edema<sup>[7]</sup>; DeschênesG et al.<sup>[8]</sup> found that only when the plasma colloid osmotic pressure drops below 8 mmHg, the above balance will be destroyed, causing edema. However, in many years of clinical observation, most patients with nephrotic syndrome have obvious edema when their plasma colloid osmotic pressure is less than 16.5mmHg. Moreover, GeersAB et al.<sup>[9]</sup> studied 88 patients with nephrotic syndrome and found that 14% had increased plasma and blood volume, 84% were normal, and only 2% had low blood volume. Based on the above questions, many scholars have proposed opposite theories.

### **2.2.2. Overfill theory**

It is pointed out that in nephrotic syndrome, the occurrence of water and sodium retention is primary, that is, sodium retention in the kidney leads to increased blood volume, and then exudates to form edema. The formation of this edema is not related to albumin levels. But this mechanism is not fully understood, and about a quarter of patients with nephrotic syndrome can be classified into this category.

### **2.2.3. Renal interstitial inflammation**

Renal interstitial inflammation is involved in the formation of sodium retention and nephrotic edema<sup>[10]</sup>, which is mainly related to the increase of renal tubular sodium reabsorption caused by inflammatory infiltration of renal tubulointerstitium and excessive vasoconstriction medium, and the decrease of sodium filtration caused by changes in glomerular hemodynamics.

### 3. Therapy

#### 3.1. Traditional Chinese Medicine Treatment of Renal Edema

##### 3.1.1. Treatment based on syndrome differentiation

Master Zhang Xuewen<sup>[11]</sup>classified stubborn renal edema into five types based on different causes, pathogenesis, and concurrent symptoms of blood stasis: qi stagnation and blood stasis, qi deficiency and blood stasis, yang deficiency and blood stasis, phlegm stasis obstruction, and dampness heat stasis obstruction.①Qi stagnation and blood stasis syndrome is mainly characterized by promoting qi circulation, removing blood stasis, and promoting diuresis. The prescription is Xuefu Zhuyu Tang;②Qi deficiency and blood stasis syndrome is mainly characterized by tonifying qi, promoting blood circulation, and promoting diuresis. In clinical practice, modified Buyang Huanwu Tang is commonly used;③The treatment of yang deficiency and blood stasis syndrome mainly focuses on warming yang, resolving blood stasis, and promoting diuresis. Shaofu Zhuyu Tang is given, and it is often combined with insect drugs such as leeches and centipedes to promote blood circulation and collaterals;④Phlegm and blood stasis obstruction syndrome is mainly treated by Zhang Laoduo, who focuses on resolving phlegm and turbidity, promoting blood circulation and resolving blood stasis, and is good at treating it with Banxia Baizhu Tianma Tang;⑤In clinical practice, the treatment of dampness heat stasis syndrome is mainly focused on dividing dampness heat, promoting blood circulation, resolving blood stasis, and promoting diuresis, and commonly used with the addition or subtraction of Simiao San.

Professor Ba Yuanming<sup>[12]</sup>proposed on the basis of his understanding of edema that its pathogenesis lies in the stagnation of the Wei surface, the loss of Qi function, the cessation of water dampness, and the formation of positive deficiency and evil. Based on clinical experience and the characteristics of the pathogenesis of this disease, four methods of "promoting", "benefiting", "dissipating", and "supplementing" water treatment were proposed. The "Xuanfa" method often combines Yue Mai Tang with Sheng Yang De Shi Tang to restore the normal physiological function of Qi circulation, fluid circulation, and turbidity reduction in the human body. The "Li Fa" method is used to reduce dampness and turbidity, with the addition or subtraction of Wuling Powder, Fangji Fuling Tang, or Jijiao Lihuang Tang. The translation of 'elimination method' means to eliminate or dissipate. Professor Ba believes that during the onset of edema disease, pathological products such as qi stagnation, phlegm dampness, blood stasis, dampness heat, turbid toxin, etc. can be produced, and these pathological products can become new pathological factors that exacerbate edema. Therefore, for qi stagnation, Chaihu Shugan Powder is used, Erchen Tang is used for phlegm dampness, Danggui Shaoyao Powder is used for blood stasis, Si Tu Tang is used for damp heat, and Niaohuang Wendan Tang is used for turbid toxin. Professor Ba believes that in the treatment of edema, differentiation of symptoms and signs should be used to strengthen the foundation, supplement deficiency and attack pathogenic factors. However, it is also emphasized that the method of tonifying should pay attention to timing. Supplementing too early or obstructing the stomach due to stagnation of qi is not conducive to the elimination of edema. Therefore, in clinical treatment, the combination of Dihuang Tang and Shuilu Erxian Dan is often used to nourish the body and remove water.

Ruan Dongdong et al.<sup>[13]</sup>classified and treated renal edema according to the laws of the six meridians. Divided into 7 types:①The external pathogenic factors of the sun attack the surface, and the syndrome of lung qi imbalance and water obstruction: This syndrome is the early stage of the disease where the six exogenous pathogenic factors invade the human body. It can be divided into the solar stroke syndrome and the solar typhoid cold syndrome. For solar stroke, "Yue Mai Tang" or "Gui Zhi Tang" is given to harmonize the yin and wei, promote lung function and promote water circulation. For solar typhoid fever, a combination of Mahuang Tang is used on a dialectical basis to provide a way out for water evil;②Sun bladder water storage syndrome: The sun surface syndrome enters the body along the meridians, causing the bladder to lose its qi and water channels to be imbalanced. Water dampness accumulates in the lower energizer, and it should be imitated as Wuling Powder to transform qi and promote water circulation;③The transformation of the Sun meridian is the main manifestation of Zhenwu Tang;④Syndrome of Yang Ming mistakenly causing injury to the fluid and mutual accumulation of water and heat: use Zhuling Tang;⑤The Shaoyang Cardinal is unfavorable, and the syndrome of internal cessation of water consumption: the main formula is Xiaochaihu Tang, which is modified and modified;⑥Taiyin water dampness syndrome with internal stasis: To treat this type of disease, one can warm and promote spleen yang, such as Shenzhuo Tang, Shenling Baizhu San;⑦Syndrome of Shaoyin Yang Qi Damage and Water Dampness Overflow: Shaoyin Cold Transformation: Mainly caused by Zhenwu Tang, Shaoyin Heat Transformation: Mainly caused by Zhuling Powder.

Professor Marcuri<sup>[14]</sup>divided edema into three parts and five types based on the location of the disease. In the treatment of lung disease, the method of lifting the pot and uncovering the lid is used to promote lung and diuresis, and Yue Mai Jia Shu Tang is the main ingredient. At the same time, traditional Chinese medicine fumigation can be used appropriately; From the perspective of spleen, the treatment mainly focuses on strengthening the spleen and promoting diuresis, and prefers to use Astragalus membranaceus and Radix Pseudostellariae to replenish qi and strengthen the spleen. Among them, for spleen yang deficiency, the addition or subtraction of solid spleen drink, and spleen qi deficiency, the main prescription is the combination of Sijunzi Tang and Weiling Tang; According to the treatment of kidney deficiency, it can be divided into kidney yang deficiency and kidney yin deficiency. Among them, patients with yang deficiency often experience blood stasis over time, and on the basis of the modified formula Zhenwu Tang and Wuling San, the method of promoting blood circulation and resolving stasis is often used. Patients with kidney yin deficiency have more heat, so the method of nourishing yin, promoting water circulation, and clearing heat is adopted. The formula is Zhuling Tang and Shenqi Dihuang Tang, and appropriate additions are made to fill the kidney essence, nourish yin and yang.

### **3.1.2. Special prescription for treating edema**

Director Ma Hongbin<sup>[15]</sup>believes that in the treatment of renal edema, it is particularly important to protect the spleen and kidney. Therefore, the basic treatment methods include tonifying the spleen and tonifying qi, strengthening the kidney and warming yang, and promoting water and dampness. He established the "Qi Ling Jian Pi Tang". This prescription consists of Wuling San combined with Simiao Wan, Huangqi, Hongshen. In the formula, Huangqi and Red Ginseng are used as the main ingredients, which are sweet, warm, beneficial to Qi, and beneficial to the spleen and stomach; Zexie can promote diuresis and dispel dampness, while also clearing heat. Poria cocos and pork cocos can penetrate lightly and promote diuresis, helping to enhance the power of Zexie in promoting diuresis; Atractylodes macrocephala can invigorate the spleen, dry dampness, promote circulation, convert water into fluid, and transport fluid to the four branches; Atractylodes can dry the spleen dampness internally and disperse dampness pathogenic factors externally; Add Ox Knee to nourish the liver and kidney, strengthen muscles and bones, guide the medicine downward, enter the lower energizer and dispel dampness; Coix seed enters Yangming, dispels dampness, heat, and benefits muscles and collaterals; Gui Zhi Wen Tong Yang Qi, internally assists in bladder gasification, synergistically penetrates and benefits the medication with Bujin Li Shui, and externally disperses the impure evil of the Sun meridian as adjuvants. Together, it plays a role in transforming Qi, promoting water circulation, and removing dampness and heat; Clean the source and clear the flow, and treat both the root cause and the root cause. Zhang Farong<sup>[16]</sup> often uses modified Banxia Xiexin Tang to treat renal edema. He believes that the onset of edema cannot be separated from the imbalance of qi mechanism. When treating it, the focus should be on "qi mechanism" to achieve the goal of expelling water and reducing swelling. Banxia Xiexin Tang should be used in combination with cold and heat, with both hard work and tonifying and reducing. It has a regulating and controlling effect on the whole body's qi function, can restore the body's fluid metabolism, eliminate edema, and treat renal edema, with significant therapeutic effects. And Liu Tongtong et al.<sup>[17]</sup> found in clinical practice that Banxia Xiexin Tang has a significant effect on IgAN patients with gastrointestinal discord symptoms, and can effectively alleviate the symptoms of IgA nephropathy edema. This mechanism may be due to the fact that abnormal intestinal mucosal immune response plays a very important role in the occurrence and progression of IgA nephropathy<sup>[18]</sup>, while Huangqin and Huanglian in Banxia Xiexin Tang can improve intestinal mucosal immune function by promoting the growth of probiotics, inhibiting the proliferation of harmful bacteria, reducing the levels of inflammatory factors in the blood, and thereby improving intestinal mucosal immune function<sup>[19][20]</sup>.

Fangji Huangqi Tang is composed of Fangji, Huangqi, Atractylodes macrocephala, Poria cocos, jujube, ginger, and licorice. Among them, it has anti-inflammatory effects such as preventing selfishness, promoting diuresis, and reducing swelling. Astragalus membranaceus is a necessary medicine for treating superficial deficiency and edema due to deficiency<sup>[21]</sup>. It has the functions of strengthening the spleen, tonifying the middle, nourishing the body, promoting diuresis, and reducing swelling, and both are the rulers. Atractylodes macrocephala and Poria cocos are official medicines, while ginger, jujube, and licorice are auxiliary medicines. Lu et al.<sup>[22]</sup>found that modified Fangji Huangqi Tang can improve renal function, improve inflammatory response neurotransmitters, and alleviate clinical symptoms in patients with refractory edema in nephrotic syndrome.

### **3.1.3. External treatment of Traditional Chinese Medicine**

Peng Lu et al.<sup>[23]</sup>randomly divided 51 patients with renal edema into a control group and an

experimental group using external application of mirabilite. After receiving diuretics, diuretics, and mirabilite for 3 days (one course), the experimental group showed a significant decrease in weight and leg circumference, but there was no significant difference in 24-hour urine output between the two groups. This result indicates that applying mirabilite externally to patients with renal edema not only accelerates swelling reduction but also does not affect the conventional treatment effect. Zhang Chunyan et al.<sup>[24]</sup> also achieved good therapeutic effects in treating renal edema caused by spleen and kidney yang deficiency and dampness stasis syndrome by applying mirabilite to the external application and using Thunder Fire Moxibustion at four acupoints: Guanyuan, Shuishui, Pishu, and Shenshu.

The application of Gansui powder on the navel can also treat renal edema. Wang Na et al.<sup>[25]</sup> randomly divided 67 patients with renal edema into an observation group of 34 and a control group of 33. While receiving Western medicine treatment at the same time, the observation group was treated with Gansui powder vinegar and applied to the navel. After two courses of treatment, the effective rate of the control group was 69.7, and the effective rate of the observation group could reach 87.8%. Among the observation indicators, an increase in urine output and a decrease in leg circumference are obvious, indicating that this method is effective. However, it lacks evaluation of toxic and side effects, and its impact on renal function is still unclear.

Zhao Ping et al.<sup>[26]</sup> used Wenyang Powder (consisting of 30g of Wu Zhuyu, 30g of Aconite, 20g of Dry Ginger, Clove, Astragalus, Cinnamomum Cinnamomum, Corydalis yanhusuo, 10g of Asarum, and 10g of White Mustard Seed) for acupoint application to treat renal edema of spleen and kidney deficiency syndrome. Eighty patients with renal edema due to spleen and kidney deficiency syndrome were randomly divided into a treatment group and a control group of 40 cases each. The control group received routine treatment, while the treatment group received acupoint application of Wenyang Powder for two consecutive courses of treatment. The net body mass, lower limb circumference, and abdominal circumference of the post-treatment group were lower than those of the control group after treatment; There was a statistically significant difference in the grading of edema between the two groups before and after treatment. The efficacy of edema between the two groups after treatment was compared, and the difference was statistically significant.

### **3.2. Western Medicine Treatment**

#### **3.2.1. Evaluation of vascular volume**

It is very necessary to judge the blood volume of renal edema. In patients with low blood volume, the use of diuretics without volume expansion will aggravate hypovolemia, lead to electrolyte disorder, and may also cause kidney damage or even hypovolemic shock. On the contrary, blind dilation in patients with high blood volume can trigger risks such as acute pulmonary edema and heart failure. Sodium excretion fraction and potassium gradient across renal tubules can serve as effective biochemical indicators for determining blood volume. If  $FENa < 1$  and  $TTKG > 60\%$  without the interference of diuretics, it means hypovolemia. In addition, Professor Chen Yipu<sup>[27]</sup> and others also used the increased heart rate in the upright position ( $> 10$  beats/minute), the increased urinary specific gravity ( $> 1.020$ ) and the increased urea nitrogen/blood creatinine ratio (when the unit of serum creatinine and urea nitrogen is mg/dl, the ratio is  $> 20$ ) as indicators to judge hypovolemia. And four highly reliable indicator combinations were selected to determine low blood volume: (1) increased heart rate in upright position, decreased  $FENa$ , and increased  $BUN/Scr$ ; (2)  $FENa$  decrease +  $BUN/Scr$  increase + urine specific gravity increase; (3) Increased heart rate in upright position + increased  $TTKG$  + increased  $BUN/Scr$ ; (4) Increased heart rate in upright position + decreased  $FENa$  + increased  $TTKG$ .

#### **3.2.2. Diuretics**

The choice of diuretics for nephrotic patients should be determined based on their blood volume. ① Increased blood volume: Mild patients with hormone sensitive nephrotic edema usually do not require the use of diuretics. After hormone treatment, the edema quickly subsides, and if necessary, oral thiazide diuretics should be given. To avoid hypokalemia, potassium sparing diuretics can be used. For moderate to severe patients, intravenous administration of loop diuretics should be chosen. (When using loop diuretics, it is recommended to administer a load of intravenous infusion, and then continuously pump to maintain the dose. "Bullet" administration should be avoided to prevent "sodium retention after diuresis". When the diuretic effect is still not ideal, the dosage should be increased, but attention should also be paid to the ceiling effect of diuretics. At present, because the reabsorption of

sodium in distal renal tubules and collecting ducts will be significantly enhanced after the application of loop diuretics, which will reduce the effect of loop diuretics, it is recommended that loop diuretics should be used in combination with oral diuretics acting on distal nephrons and collecting ducts.②Reduced blood volume: Volume expansion therapy should be used in conjunction with loop diuretics.

### 3.2.3. Dilatant

For patients with effective hypovolemia, diuresis should be conducted on the basis of effective volume expansion. The currently used volume extenders in clinical practice include plasma, albumin, low molecular weight dextran, and hydroxyethyl starch.

In clinical application, Zhao Chengguang et al.<sup>[28]</sup> found that plasma infusion has a significantly better therapeutic effect on severe edema than albumin and low molecular weight dextran. Wu Yunrong et al.<sup>[29]</sup> pointed out that the combination of hydroxyethyl starch and furosemide has a better therapeutic effect than low molecular weight dextran glycosides. The combined use of low molecular weight dextran and albumin by Xu Yijun et al.<sup>[30]</sup> significantly improved the efficacy in treating renal edema. However, due to the possibility of allergic reactions in human blood and the difficulty in completely avoiding virus transmission, and more importantly, plasma products are not easily obtained. Therefore, except for the contraindications of plasma substitutes (such as urine volume < 400ml/d), it is recommended to choose plasma substitutes as much as possible.

When the above treatments are ineffective and diuretic resistance occurs, it is necessary to consider using hemodialysis ultrafiltration. Research has shown that<sup>[31]</sup> hemodialysis ultrafiltration can effectively alleviate severe and stubborn edema in patients with nephrotic syndrome, increase urine output, promote renal function recovery, and improve the prognosis of kidney disease.

## 4. Conclusion

Renal edema has various clinical manifestations, with a mixture of deficiency and excess, a combination of dampness, heat, and stasis, and is difficult to heal. It is a refractory disease. Traditional Chinese medicine has accumulated rich experience in this area, with the treatment mainly focusing on strengthening the body and nourishing the foundation, with a focus on tonifying qi, spleen, and kidney. At the same time, it is combined with the principles of promoting lung function, promoting diuresis, clearing heat, resolving blood stasis, resolving dampness, and lowering turbidity to eliminate pathogenic factors. If the treatment effect of traditional Chinese medicine alone is not satisfactory, it should be combined with necessary Western medicine for treatment. The author believes that the use of comprehensive therapies such as integrated traditional Chinese and Western medicine for this disease can greatly improve clinical efficacy and should be promoted and applied in clinical work.

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