

Research Progress on the Formation Mechanism of Renal Fibrosis and the Treatment of Chinese and Western Medicine

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Abstract: Renal fibrosis (RF) is a major pathological cause of late progression of chronic kidney disease and has seriously jeopardized the quality of life of people worldwide. In recent years, with the research on the mechanism of action of renal fibrosis, it has been found that there are many causative factors of renal fibrosis, and modern clinical research has achieved insufficient efficacy for the treatment of renal fibrosis, but the therapeutic effect varies from person to person. The combination of pharmacology indicates that Chinese medicine has shown unique efficacy and application prospects in the prevention and treatment of renal fibrosis. This article is a review of the formation mechanism of renal fibrosis and the progress of research on the role of Chinese and Western medicine in the treatment of RF.

1. Introduction

Chronic kidney disease (CKD) is a hazardous disease. According to studies, from 1990 until 2017, the number of patients with a chronic kidney disease in China could reach 132.3 million [1]. The disease is currently in epidemic proportions. Current treatments for CKD are limited in their effectiveness and can only slow the progression of CKD. Renal fibrosis is the final stage of chronic kidney disease. Based on a large number of previous studies, it has been found that by improving renal fibrosis and slowing the progression of chronic kidney disease [2-3]. With the growing understanding of renal fibrosis, current trials have still not discovered specific targeted drugs to slow down renal fibrosis. Nevertheless, a number of therapies have been proposed that may slow the progression of renal fibrosis, and a brief review of research on Chinese and Western medicine in the prevention and treatment of renal fibrosis is presented.

2. Recognition of renal fibrosis in Western medicine

2.1. The mechanisms of renal fibrosis formation

Renal fibrosis is a major pathological feature of CKD. The pathogenesis of renal fibrosis is not

yet clear, but numerous studies have found a close relationship between the degree of renal impairment and the degree of tubular damage. It includes myofibroblast cells, cytokines and growth factors, as well as metalloproteases and their endogenous inhibitors. The features include: inflammatory cell infiltration, myofibroblast activation and massive extracellular matrix deposition, resulting in structural destruction of the kidney [4].

2.2. Myofibroblasts

Lama et al. proposed that the pathogenesis of renal fibrosis is not only associated with fibroblast overgrowth but also with reduced apoptosis [5]. In the current study, it is generally accepted that fibroblasts and myofibroblasts are the main cells responsible for the accumulation of mesenchymal matrix and for the structural changes that lead to fibrosis [6]. Myofibroblasts are the main source of extracellular matrix during renal fibrosis. Research has demonstrated the lack of myofibroblasts in normal kidney tissue, and in renal fibrosis, large numbers of myofibroblasts can be detectable. The process of fibroblast transformation into myofibroblasts is complex, with various stimulus factors such as inflammation, chemical factors, cytokines and mechanical external environment activating fibroblasts to differentiate and proliferate into myofibroblasts [7]. Fibroblasts in the interstitial matrix of the kidney, by converting to myofibrillar protein (BMyoFB), produce large amounts of extracellular matrix (ECM) including collagen, glycoproteins and proteoglycans and secrete matrix metalloproteinase (MMP) inhibitors such as plasminogen activator inhibitor-1 (PAI-1) and the tissue inhibitors of metalloproteinase TIMP reduce the activity of MMP and the accumulation of ECM, leading to tubulointerstitial fibrosis [8].

2.3. Cytokines

Many studies have found that renal fibrosis is formed by a variety of mediators, including cytokines, growth factors, metabolic toxins, immune complexes and inflammatory mediators. These predisposing factors mediate the development of renal fibrosis by a variety of mechanisms and pathways.

It has been found that the main growth factors that promote fibrosis are TGF- β , EGF, CTGF and bFGF. Many studies have confirmed that transforming growth factor- β (TGF- β) is a key factor in the development of renal fibrosis and that it activates the proliferation of pre-existing fibroblasts. TGF- β has three subtypes, and TGF- β 1 is the most powerful factor that causes renal fibrosis. TGF- β 1 mediates the development of renal fibrosis by mediating smad induction [9]. TGF- β 1 mediates renal fibrosis by inducing ECM production and inhibiting ECM degradation. In addition, it can also mediate the development of renal fibrosis by inducing tubular epithelial-mesenchymal cell transdifferentiation, thereby inducing the transformation of tubular epithelial cells into myofibroblasts [10]. In several in vitro and in vivo experiments, it has been demonstrated that connective tissue growth factor (CTGF) may be involved in the development of renal fibrosis [11]. Liu Hua feng [12] showed that IL-18 may have a role in promoting interstitial fibrosis in the renal disease state. Zhou Lili's team [13] has found that the renal tubular cell-derived exosome OPN activates β -catenin signalling through CD44 signalling, thereby promoting renal fibrosis.

3. The role of Western medicine in the treatment of renal fibrosis

Most researchers agree that by preventing the formation and progression of renal fibrosis, the progression of chronic kidney disease and the development of renal failure can be effectively prevented. However, the current treatment of renal fibrosis is limited to the use of non-specific anti-inflammatory drugs, immunosuppressants and glucocorticoids, but these have little effect and most

have side effects, and there is a lack of effective drugs to treat renal fibrosis clinically.

3.1. Clinical Treatment

Renal fibrosis can be clinically classified into three different stages. The first phase is the inflammatory phase and the main treatment modalities are anti-inflammatory, anticoagulant and antithrombotic; The second stage is fibrogenic and is treated by vasodilatation, anticoagulation and degradation of fibrous scars that have been created; If the kidney progresses to stage last stage, it is difficult to change the nature of the fibrosis once the kidney has developed permanent scarring. Hypertension and diabetes are among the main diseases that contribute to the development of kidney disease. Therefore, controlling blood pressure and blood sugar is particularly important for patients with renal fibrosis. ACEI and ARB combat renal fibrosis by reducing blood pressure, decreasing glomerular perfusion pressure, increasing effective renal blood flow, reducing intraglomerular hypertension, production of cytokines and other inflammatory factors, reducing extracellular matrix proliferation and inhibiting the accumulation of various types of collagen, thus anti-renal fibrosis. The control of hyperglycaemia with oral hypoglycaemic medication and insulin reduces glomerular hyperfiltration and glomerular hypertrophy, delays the appearance of urinary microalbumin, and may even reduce urinary microalbumin.

3.2. Laboratory studies

Pirfenidone (PFD) as a new anti-fibrotic drug, is one of the few drugs that have been shown to slow down or even reverse fibrosis. Xu and his team demonstrated that RFD can inhibit the expression of TGF- β and CTGF in a rat model of renal fibrosis, thereby reducing the conversion of fibroblasts into myofibroblasts and further reducing the deposition of ECM, thus exerting an anti-fibrotic effect on renal fibrosis [14]. Nevertheless, the mechanism of the anti-fibrotic effect of PFD has not been clearly elucidated. Most scholars agree that PFD achieves its antifibrotic effect by inhibiting TGF- β expression.

Bone morphogenetic protein-7 (BMP-7) belongs to the TGF- β superfamily. Expression mainly in kidney and bone tissues, especially high in renal tubules of adult animals. Research demonstrates that BMP-7 is a protective factor for the kidney and has a role in maintaining the structure and function of kidney tissue [15]. As a factor of TGF- β 1, it also contains an anti-fibrotic function. BMP-7 plays an anti-retrofibrotic role by maintaining epithelial cell phenotype, inhibiting apoptosis of renal epithelial cells, activating the degradation of ECM, reducing the expression of various pro-inflammatory factors, affecting the TGF- β 1/Smads transduction pathway and interacting with TGF- β 1 [16].

In recent years, with the development of cell therapy techniques, researchers have discovered that MSCs can be mediated through a variety of mechanisms to improve, delay or even reverse the progression of renal fibrosis. Mesenchymal stem cells (MSCs) are multifunctional stem cells. With the in-depth study of MSCs, MSCs transplantation therapy is discovered to be a novel biologic therapy for chronic kidney disease, improving and delaying the development of renal failure. MSCs were discovered to play an important regulatory role in the EMT process through their immunomodulatory and paracrine mechanisms, thereby delaying tubular EMT and thereby improving renal fibrosis [17]. NAGAISHI et al. [18] established a mouse model of type 1 diabetic nephropathy by streptozotocin and a mouse model of type 2 diabetic nephropathy induced by a high-fat diet and treated with MSCs or MSC exosomes and discovered that the level of TGF- β 1 expression in the kidney tissue was significantly downregulated in both models of diabetic nephropathy, resulting in improved renal function reduction in the mouse model of diabetic nephropathy and thus improved renal fibrosis. In inclusion, statins can reduce renal fibrosis by

lowering proteinuria. Cytokines and targeted drugs can also slow down ECM deposition and delay the onset of fibrosis. Although Western medicine is still the main treatment for renal fibrosis, the side effects, high cost and low efficacy of Western medicine are not satisfactory.

4. The role of Chinese medicine in the prevention and treatment of renal fibrosis

In recent years, the treatment of renal fibrosis in Chinese medicine has been increasingly researched, with the identification of renal fibrosis in Chinese medicine, combined with pharmacological research, the formation of numerous methods of treatment of renal fibrosis. More and more evidence shows the unique advantages of TCM in delaying RF, and is widely recognised and sought after. There is no alternative name for "renal fibrosis" in Chinese medicine, but according to its clinical symptoms and manifestations, it is classified as "oedema, retention of urine, lumbago and guangs" [19]. Combined with the basic theories of Chinese medicine, most modern practitioners believe that RF is mostly a deficiency of the root cause and a deficiency of the symptoms, with the root deficiency being mainly a deficiency of the spleen and kidneys, and the symptoms being mainly turbidity and toxicity, dampness and heat, and blood stasis. For this reason, the current treatment of renal fibrosis in Chinese medicine is mostly based on a combination of treatment to support the positive and dispel the evil. It has been found that Chinese medicine can have a multi-targeted and multi-faceted effect on the prevention and treatment of interstitial fibrosis, thereby slowing down the progression of kidney disease.

4.1. Effect of single herbs on renal fibrosis

An analysis of data mining of Chinese herbal medicines for the treatment of renal fibrosis revealed that Astragalus is widely used as a Qi tonic in the TCM treatment of renal fibrosis [20]. Chen Qing jiang et al. [21] confirmed the ability of Astragalus to slow down the progression of renal fibrosis through the in vitro culture of human renal fibroblasts and the determination of cell proliferation and TGF- β 1 levels by MTT and ELISA chromatography, which implies that Astragalus can slow down the progression of renal fibrosis by inhibiting fibroblast proliferation and TGF- β 1 secretion. Lu Xun [22] et al. used a UUO rat model with the aid of immunohistochemical assays and discovered that astragalus polysaccharide, an extract of Astragalus, could downregulate TGF- β 1, angiotensin II (Ang-II) and tissue inhibitor of metalloproteinase (TIMPs) expression, thereby inhibiting EMT transformation and reducing the secretion of matrix metalloproteinase (MMP-2). TIMPs expression and matrix metalloproteinase 2 (MMP-2) expression, thereby inhibiting EMT transformation, reducing extracellular matrix secretion and inhibiting the progression of renal fibrosis, thus protecting kidney function. The Chinese medicine Panax notoginseng and its active ingredient Panax notoginseng total saponin have anti-fibrotic effects, which can reduce the formation of renal fibrosis by reducing the accumulation of inflammatory factors, decreasing the expression of factors related to renal fibrosis, inhibiting the expression of TGF- β 1, inhibiting EMT, inhibiting the proliferation of myofibroblasts and reducing the aggregation of ECM [23]. Modern pharmacological studies have proven that rhododendron has anti-fibrotic effects [24]. Wang [25] examined the proliferation and IL-6 secretion of human renal fibroblasts induced by different concentrations of rhodopsin by using 3H-TdR infiltration method and FLISA method. The results indicated that the proliferation of human renal fibroblasts and the secretion of IL-6 could be reduced when the concentration of rhodopsin was higher than 30 μ g/ μ L. Cordyceps has immunomodulatory and antitumour effects, acting by tonifying the lungs and kidneys, secreting the essence and benefiting the qi. It has been demonstrated that Cordyceps has an anti-fibrotic effect, inhibiting the proliferation and growth of fibroblasts and the synthesis of extracellular matrix. Cordyceps can decrease serum urea nitrogen and creatinine levels in a 5/6

partial nephrectomy rat model of chronic renal failure, inhibit glomerular hypertrophy, and significantly reduce tubulointerstitial atrophy and ECM accumulation in the rat model [26]. Modern pharmacology has demonstrated that *Salvia miltiorrhiza* has inhibitory effects on human fibroblast cells. Tanshinone IIA can reduce the expression levels of TGF- β 1 and α -SMA on the diseased side of the rat model of renal fibrosis, reduce inflammatory cell infiltration and type I collagen accumulation, and reduce the aggregation of ECM, thus protecting the normal structure of the renal tubules and delaying the development of renal fibrosis [27]. In addition, *Radix Rehmanniae*, *Safflower* and *Rhizoma Chuanxiong* are also useful in the prevention and treatment of renal fibrosis. In conclusion, a number of studies are increasingly showing that single herbs and their active ingredients contain anti-nephrogenic effects.

4.2. The effect of Chinese medicine compounding on renal fibrosis

The use of Chinese herbal compounding in the treatment of renal fibrosis is a commonly used clinical method and its efficacy is well recognized. Liu Jinsong's research [28] found that the *Shenfukang* (composed of *Astragalus membranaceus*, *Radix et Rhizoma przewalskii*, *Radix et Rhizoma Dioscoreae* and *Radix et Rhizoma Rhei*) on the efficacy of UUO rats when, It was found that the levels of 24UP, SCr and BUN, as well as the levels of Smad2 and TGF- β 1 decreased in the rats in the renal rehabilitation group. ($P < 0.05$), and it was more obvious when the dose of *Renfukang* increased. The results suggest that *Renfukang* can reduce renal fibrosis by inhibiting the transduction of TGF β /Smad signaling pathway. Wu Feng et al. [29] used antifibrinogenic preparations (*Salvia miltiorrhiza*, *Radix et Rhizoma Dioscoreae*, Peach kernel, *Radix Angelicae Sinensis*, *Radix et Rhizoma Niubizi*) made by the method of activating blood circulation and resolving blood stasis to study its effects on oxidative stress in UUO rats. Superoxide dismutase (SOD) and glutathione (r-glutamyl cysteinyl +glycine, GSH) were observed to be significantly higher in the antifibrin group compared to the model group ($P < 0.01$), while malondialdehyde (MDA) was significantly lower ($P < 0.01$). MDA decreased significantly ($P < 0.01$). It is suggested that the anti-fibrin group formula ameliorates renal fibrosis by inhibiting oxidative stress in UUO rats and causing down-regulation of TGF- β 1 factor. Fu Xu et al. [30] demonstrated that administration of the same dose to the UUO rat model improved renal function and renal pathological damage in UUO rats. It may be related to the fact that *Astragalus tansy granules* affect EMT and reduce ECM aggregation by down-regulating the expression of Wnt4 and β -catenin in renal tissues. Xiang Caichun et al. [31] used a formula combining the methods of strengthening the spleen, tonifying the kidney and eliminating blood stasis and detoxification, and selected the formula of benefiting the kidney and invigorating blood (composed of *Astragalus*, *Radix Rehmanniae*, *Fructus Lycii*, *Fructus Ligustrum*, *Radix Panax notoginseng*, *Panax notoginseng*, *Danpi*, etc.) The effects on the expression levels of PCIII, IV-C and LN in the rat model of adriamycin-induced renal fibrosis were observed. The results showed that the levels of PCIII, IV-C and LN decreased in the rats of *Yi Ren Ren Ren Wu Xuan Blood Formula*, indicating that *Yi Ren Wu Xuan Blood Formula* reduced the progression of renal fibrosis by antagonizing the proliferation of PCIII, IV-C and LN and reducing the synthesis of ECM. *Huangkui Capsule* are mainly composed of flavonoid compounds, which have antioxidant, anti-inflammatory, anti-platelet aggregation and detoxification effects. Zeng Xuejiao [32] produced a rat model of chronic renal failure using adenine and found that the *Huangkui Capsule* significantly reduced the levels of SCr and BUN, and reduced the extent of tubulointerstitial fibrosis. At present, it has been found that Chinese herbal compounds can reduce the progression of renal fibrosis through various mechanisms and multiple targets. Therefore, herbal compounding plays a role in delaying and reducing the process of renal fibrosis. However, in the current study, the research on single herbal medicine or

herbal compound is still superficial and there is a lack of in-depth research, and there is a lack of uniformity in the study of the target mechanism of single herbal medicine and herbal compound.

5. Summary and prospects

Renal fibrosis is not an independent disease, the kidney tissue is stimulated by long-term adverse factors, mechanical damage, hypertension, bacterial infections, autoimmune diseases and other factors, resulting in damage to kidney cells and glomerular function, causing collagen scarring and aggregation, eventually forming renal fibrosis. To this day, the use of Western or Chinese medicine in the treatment of renal fibrosis is backed by a large body of experimental evidence. At the same time, we also know that it is extremely difficult to completely cure or even change the pathology of renal fibrosis due to the complexity of the mechanism of action of renal fibrosis. In contrast, clinical research on Chinese medicine in renal fibrosis is now mostly generalized to the effect that it is the result of one or more pathways, and the clinical use of Chinese medicine in the treatment of renal fibrosis is relatively homogeneous. There is a lack of systematic research on Chinese medicine compounding, such as drug compounding, drug dosage, therapeutic time window, etc. With the advancement of modern science and technology, research scholars should further strengthen the study of the mechanism of action of Chinese medicine from the perspective of molecular biology and cell biology, or further develop the study of the synergistic mechanism between Chinese and Western medicine, in view of the different mechanisms and links in the pathogenesis of renal fibrosis. In conclusion, as the degree of renal fibrosis is closely related to the degree of impaired renal function, and early intervention in advance can effectively delay the development and progression of renal fibrosis. As research scholars continue to study renal fibrosis, the integration of Chinese and Western medicine should be pursued in order to find an anti-renal fibrosis treatment path. In addition, we should adhere to the "holistic concept and the development of new drugs in combination with modern scientific and technological achievements, in order to meet therapeutic needs.

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