MEDS Clinical Medicine (2022)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2022.030113
ISSN 2616-1907 Vol. 3 Num. 1

Research Progress of Yiqi Huoxue Method on Diabetic Kidney Disease

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Keywords: yiqi huoxue diabetic kidney disease

Abstract: diabetic kidney disease is a relatively serious and common complication of diabetes, and it is one of the common microvascular complications. Incidence rate is increasing year by year. Traditional Chinese medicine believes that traditional Chinese medicine with the function of Supplementing Qi and activating blood circulation can promote angiogenesis. Angiogenesis is closely related to the mechanism of traditional Chinese medicine of Supplementing Qi and generating blood, removing blood stasis and generating new, such as “generating pulse” and “generating muscle”, so as to provide new ideas for clinical practice.

1. Introduction

With the continuous change of people's lifestyles, the incidence of diabetes mellitus (DM) is increasing year by year worldwide, and it is expected that by 2045, the number of diabetics will reach 700.2 million, and the prevalence will increase by 10.9%. Type 2 diabetes mellitus is the most common type of diabetes in the clinic, and the awareness and control rate of DM is extremely low, resulting in a large number of PATIENTS with DM gradually progressing and developing serious microvascular complications[1-2]. Among them, diabetic kidney disease (DKD) is one of the common microvascular complications when diabetes progresses, is a more serious and common diabetic complication, among many complications, has a relatively high incidence, seriously threatens the safety of patients' lives, and has become the first cause of end-stage renal disease (ESRD) in China[3]. Relevant data statistics show that the incidence of diabetic nephropathy in patients with type 2 diabetes is about 30.00%, and the incidence rate in patients with type 1 diabetes is about 22.00%[4]. Diabetic nephropathy has no obvious symptoms in the early stage of the disease, is highly insidious, and is easily overlooked. Clinical manifestations are a large number of proteinuria, hypertension, edema symptoms, some patients can appear anemia and other microvascular lesions, if the disease control is not ideal, secondary renal failure and other endangering patients' lives, so explore and find new treatment options, for high treatment effect and improve the prognosis is crucial.

2. Renal Fibrosis is the Key Pathological Process in the Development of Diabetic Kidney Disease

Renal fibrosis is a common pathological pathway of diabetic nephropathy and the development of various chronic kidney diseases to end-stage renal failure. Its main manifestations are: excessive aging deposition of extracellular matrix, excessive mesenchymal transformation of renal tubular epithelial cells, excessive activation of fibroblasts and proliferation of vascular wall [5]. Renal fibrosis is a series of complex pathological changes such as inflammatory infiltration of renal interstitial cells caused by the damage of normal renal cells caused by chronic renal disease or urinary obstructive disease, so as to form renal tubulointerstitial fibrosis. This process is an irreversible and progressive pathological change and the final way, It will eventually lead to abnormal renal function. Modern studies have found that the main characteristics of renal fibrosis are inflammatory cell infiltration, myofibroblast activation and a large amount of extracellular matrix deposition, and finally destroy the normal renal structure. This process involves the activation and intensification of a variety of signal pathways and cytokines to promote inflammatory factors The release of fibrogenic cytokines such as growth factors forms the local microenvironment of renal fibrosis.

3. Inhibition of Epithelial Mesenchymal Transitiation (EMT)

Epithelial mesenchymal transition (EMT) is one of the main factors of renal fibrosis. EMT refers to the biological process that epithelial cells are transformed into cells with interstitial phenotype through specific procedures. Its occurrence is that they lose their inherent phenotype and gradually change into mesenchymal under the stimulation of inflammatory factors and fibrogenic factors. This process is of great significance for the occurrence and development of fibrosis [6-7]. ECM over deposition is caused by EMT activation of renal interstitial fibroblasts / myofibroblasts, which plays a crucial role in the formation of renal fibrosis [8-9]. Studies have shown that more than 30% of interstitial fibroblasts differentiate from renal epithelial cells through EMT. Therefore, EMT is an important mechanism leading to renal fibrosis. Generally, when EMT occurs in renal tubular epithelial cells, it will produce extracellular matrix (ECM) components such as fibronectin, smooth muscle actin and a large amount of collagen, which will lead to ECM deposition and finally form renal fibrosis [10].

4. Wnt/B-Catenin Signaling Pathway

Wnt/β-catenin signal transduction pathway is an important signal pathway in biological evolution, which is closely related to embryonic growth, morphological development, tissue stability, balance of energy metabolism and maintenance of stem cells [11]. In normal somatic cells,β-catenin As a cytoskeletal protein, catenin forms a complex with E-cadherin at the cell membrane, which plays a role in maintaining the adhesion of homotypic cells and preventing cell movement. Only when the extracellular Wnt signal molecule binds to the specific receptor frizzled protein on the cell membrane, the intracellular dishevelled protein is activated, resulting in the inactivation of gsk3b β- Catenin avoids the fate of being phosphorylated and degraded, β- Catenin can accumulate in the cytoplasm. When the concentration of β-catenin in cytoplasm reaches a certain level, it can transfer to the nucleus and enter the nucleus β- Catenin regulates the target gene TCF/ LEF and starts the transcription of CyclinD1, andl, c-myc and other target genes, resulting in cell proliferation, differentiation and maturation, leading to the occurrence of tumors and other diseases [12]. Studies have found that Wnt/ β- Catenin signaling pathway is not only involved in the occurrence and development of tumors, but also closely related to the occurrence and development of renal diseases such as polycystic kidney and IgA nephropathy [13].

4.1 Relationship between Wnt/B-Catenin Signaling Pathway and Renal Fibrosis

The formation and development of renal fibrosis is a dynamic pathological process, involving the abnormal expression and regulation of a variety of cytokines and signal pathways [14], such as TGF- β 1. IGF and JAK / STAT pathway [15], PI3K pathway, Wnt/ β-Catenin pathway, etc. at present, Wnt/ β-catenin signal pathway is deeply studied. In renal fibrosis, A large amount of β-catenin accumulates and activates the expression of fibrosis related genes [16]. Epithelial mesenchymal transformation is an important process of renal fibrosis. When EMT occurs, it leads to the increase of extracellular matrix and the excessive deposition of extracellular matrix, resulting in the formation of renal fibrosis. In recent years, The research of Wnt/β-catenin signaling pathway in the pathological process of DKD has become a hot spot [17]. Wnt protein is a highly conserved secretory glycoprotein, which is the starting protein of this signal pathway. The expression level of this protein shows an upward trend in the model of renal fibrosis [18]. In the presence of Wnt, it can be prevented by a series of processes β- Catenin is phosphorylated and degraded. After reaching a certain level, it transfers into the nucleus and combines with t cytokine / lymphoid enhancer (TCF/LEF) transcription factor to enhance or weaken the expression level of some specific genes [19]. Studies have shown that blocking Wnt gene expression can reverse renal interstitial fibrosis. Since the occurrence and development of renal fibrosis is affected by β-catenin, The influence of catenin signaling pathway and mediated target genes through the intervention of Wnt/ β- Catenin signaling pathway may become a new target to delay the progression of renal fibrosis.

4.2 Wnt/B-Cateninsignal Pathway, Podocyte EMT

In the process of diabetic nephropathy, various pathogenic factors induce changes in morphology and function of podocyte, including foot fusion, podocyte number or density reduction, podocyte apoptosis, podocyte hypertrophy, and epithelial-mesenchymaltransition (EMT), etc. [20]. Among them, as the main manifestation of podocyte injury, podocyte EMT is not only the initiating factor of inducing renal fibrosis, but also the target of various Chinese and Western drugs to delay the progress of DKD [21-22]. The study shows that Wnt signaling involves multiple pathways, including EMT signaling/ β-Catenin pathway has attracted more and more attention and has become a research hotspot in the field of tissue fibrosis [23-24].

5. TCM Treatment of Diabetic Renal Fibrosis

5.1 Discussion on TCM Pathogenesis of Renal Interstitial Fibrosis

There are many causes of kidney disease, including many pathological factors and various clinical manifestations, but the essence can be summarized by “deficiency, toxin and blood stasis”. “Deficiency” refers to the deficiency of healthy qi and Qi and blood; “Poison” refers to substances that damage the body, both exogenous and endogenous; “Blood stasis” refers to vein stasis, mainly refers to “kidney collateral stasis”. It refers to that the disease lasts for a long time and phlegm and blood stasis block the kidney collateral. Its pathogenesis is “deficiency is the foundation, poison is the evil, and blood stasis is the fruit”, which is the pathological change of deficiency and excess.

“Deficiency” is the pathological basis of disease occurrence. Traditional Chinese medicine believes that Qi is the most basic material constituting the human body and maintaining human life activities. It

has the functions of promoting, warming, gasification, defense, nutrition, fixation and regulation. Qi is the beauty of blood. Qi can move blood, and Qi deficiency leads to blood stasis. “Women's good recipe · tiaojingmen”: “blood is the essence and Qi of water and valley... Therefore, although the heart governs the blood, spleen and stomach, the blood is born by itself”, “the kidney stores essence, and the essence is formed by blood” (on the sources of various diseases · the symptoms of asthenia and fatigue)”“ those who Nourish Qi secrete their body fluid, inject it into the pulse and turn it into blood ”(Lingshu evil guest). According to the above, we can see the essence, nourishment Qi, body fluid The essence is the material basis for generating blood, and the physiological functions of kidney storing essence, governing body fluid, kidney governing bone and marrow are all derelict due to disease, resulting in blood deficiency and no new blood.

“Poison” is the key to the progress of the disease. External poison is also the foreign poison, including the six pathogenic poisons of external infection and the poison of epidemic disease. Internal toxin is an endogenous toxin, which is closely related to the abnormal function of Zang Fu organs and the operation of Qi and blood. Due to the lack of drainage of metabolites in the body and the continuous deposition of pathological products, the pathogenic factors become more and more hyperactive. In modern medical research, the fibrogenic factors such as the activation of interstitial cells, the infiltration of local renal tissue of inflammatory cells and the high expression of aldosterone in the course of renal interstitial fibrosis are similar to those of Turbid Toxin, and play a key role in the whole process of renal disease.

“Blood stasis” is the inevitable result of kidney disease for a long time. The formation of blood stasis in traditional Chinese medicine is mostly attributed to Qi deficiency, qi stagnation, cold coagulation, heat burning and falling and flapping injury. According to the theory of “long illness entering the collaterals”, kidney diseases that do not heal over the years must see varying degrees of blood stasis. In the understanding of TCM pathogenesis of renal interstitial fibrosis, renal collateral stasis can reflect its pathological characteristics. Most kidney diseases have a long course of disease and are difficult to heal. Although some of them do not have the appearance of blood stasis, for “those who have been ill for a long time and do not go away, try their blood collaterals and give out their blood” (Yellow Emperor's Internal Classic), it shows that there must be blood stasis and stagnation in the collaterals of the kidney for a long time. In clinical practice, ye Tianshi summarized the view that the disease “lies in the meridians and Qi at the beginning, and enters the collaterals and blood for a long time”.

5.2 Treatment of Diabetic Nephropathy by Invigorating Qi and Activating Blood Circulation

The concept of blood vessel in traditional Chinese medicine includes “blood vessel and blood collateral”, in which the collateral theory and angiogenesis theory are highly unified. Traditional Chinese medicine believes that traditional Chinese medicine has the function of invigorating blood vessels. Angiogenesis is closely related to the mechanism of traditional Chinese medicine, such as supplementing qi and generating blood, removing blood stasis and generating new, such as “generating pulse”, “generating muscle” and so on. According to the theory of “generating pulse” in traditional Chinese medicine, the generation of pulse starts from the congenital origin, and the kidney plays an important role in the blood. From the perspective of traditional Chinese medicine, “generating pulse” is to use Qi supplementing and blood generating drugs to restore the blood circulation of the originally blocked blood vessels. Deng Wenchao et al. [25] found that Astragalus can down regulate Wnt4 β- The expression of catenin can protect renal podocyte injury, delay the fibrosis process of renal interstitial

cells in diabetic rats, increase the average vessel density and up regulate the level of VEGF protein, and induce angiogenesis. Peach kernel, Ligusticum chuanxiong, Angelica sinensis and safflower can improve human microcirculation and inhibit thrombosis and platelet aggregation. The compatibility of Astragalus and safflower can promote the expression of VEGF and angiogenesis; The plasmin like components in earthworm can increase the blood supply of glomerulus, reduce the viscosity of blood, improve renal function and human microcirculation, and adsorb bun and Sr in blood and digestive tract.

6. Conclusion

To sum up, based on pathogenesis, “deficiency, stasis and poison”, Turbid Toxin causing stasis, toxic as the cause and stasis as the result, under the guidance of the theory of “Qi supplementing and activating blood circulation”, “generating muscle and generating pulse”, the new theory of clinical practice is focused on the core theory of the pathogenesis of diabetic nephropathy. It is conducive to the improvement of patients' condition, which needs to be demonstrated by more animal experiments and clinical studies.

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