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Feature Article

New Goals and Strategies of Chinese Medicine in Prevention and Treatment of Chronic Kidney Disease*

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ABSTRACT Chronic kidney disease (CKD) is a clinical syndrome with a series of clinical manifestations and metabolic disorders caused by many diseases, which are characterized by progressive deterioration or irreversible damage of renal structures and functions. With the progress of epidemiological research, CKD has brought about huge economic and psychological burdens. There is a considerable risk of cardiovascular events or death than progression to end-stage renal disease for patients. Particular attentions should be paid to the new goals of reducing cardiovascular events and all-cause mortality. It is important to analyze the etiology and pathogenesis according to patients' ages, regions, primary disease as well as different stages of disease, and choose the appropriate therapeutic strategies accordingly. In clinical practice, due to the uncertainty of therapeutic effects of modern medicine based on the risk factors, it is necessary to use Chinese medicine (CM) to delay the disease progression and reduce comorbidities. Turbid toxin and blood stasis are two critical pathological factors worthy of concerns in the theory of CM. In addition, appropriate use of CM may help improve the quality of life of patients with CKD.

KEYWORDS chronic kidney disease, Chinese medicine, strategies, turbid toxin, blood stasis

Chronic kidney disease (CKD) is a chronic non-communicable disease that affects human health seriously. In China, the prevalence of CKD is 10.8%, which is similar to high-income countries such as the United States. Globally, CKD has been the second fastest growing cause of death after human immunodeficiency virus.[1] When the glomerular filter rate (GFR) progressively drops to less than 15 mL/min per 1.73 m^2, a person will reach end-stage renal disease (ESRD), and about 80% of ESRD patients in developed countries receive renal replacement therapy.[2] Besides, CKD patients also face a greater risk of cardiovascular (CV) events or death than progression to ESRD.[3] It is necessary to propose a new goal of reducing CV complications and all-cause mortality in the treatment of CKD. However, CV events did not decrease definitely in the CKD population despite the traditional CV risk factors such as hyperlipidemia and hypertension are controlled.[2] Fortunately, many Chinese patients with CKD can benefit from Chinese medicine (CM). Therefore, understanding the disease characteristic and the basic pathogenesis from the perspective of CM will play an important role in seeking new therapeutic strategies and curing this disease.

Treatment on Different Primary Diseases of CKD

Given the complexity of CKD, it is crucial to assess the primary diseases of CKD patients with different ages, regions and other characteristics. Different from adults, the etiology of CKD in children is mainly related to congenital and hereditary. Low birth weight, premature infants, and congenital anomalies of the kidney and urinary tract are common causes in children with CKD.[4] So far, over 150 genetic mutations have been discovered to be associated with renal development or to specifically affect glomerular and renal tubular functions. Most of these genetic mutations can lead to CKD progression. For instance, polycystic kidney disease, a major subtype of renal dysplasia, is caused by an abnormal primary ciliary

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gene in renal tubular epithelial cells.[5] However, most children's glomerular diseases are caused by abnormal genes or acquired defects in podocytes. Hereditary metabolic abnormalities, such as primary hyperoxalurias and cystinosis, are rare but extremely important causes of CKD in children.[6] From my view, the pathogeny of CKD in children is insufficient innate endowment. Therefore, the treatment in CM can mainly focused on tonifying congenital Shen (Kidney) qi.

CKD is very common in the elderly, but the definition of CKD based on estimated GFR (eGFR) can lead to overdiagnosis among senior persons, which brings some psychological and economic burden. The risk of all-cause mortality associated with decreased eGFR declines with age, so the diagnosis of CKD in the elderly requires a combination of etiology and other risks.[7] CM theory believes that the elderly manifest more syndromes of qi deficiency and blood stasis with the decline of Shen qi, which is closely related to the background of modern medicine that elderly patients with CKD often suffer from cognitive dysfunction and atherosclerosis. Therefore, the therapeutic strategies aiming at asthenia and stasis are commonly used in elderly patients with CKD.

Besides, impacts of CKD vary among different regions. A systematic review revealed that geographic remoteness were associated with higher CV event rates and higher mortality in CKD populations.[8] Also, different primary diseases of CKD should be emphasized owing to different characteristics, for example, the new pathogenesis of IgA nephropathy highlights the unbalance of gut microbiota, and the potential therapeutic targets may be related to uremic toxins from the intestine.[9] While for patients with diabetic nephropathy, urinary albumin is an important factor affecting the progression of the disease to ESRD. Among diabetic patients with impaired renal functions, those without proteinuria had a low risk of progression to ESRD, which was 5%, in the Chronic Renal Insufficiency Cohort Study in the United States.[10] Aimed at these factors, it is necessary for CM to find the key pathogenesis of each disease to carry out effective treatment according to syndrome differentiation.

Treatment on Different Stages of CKD

According to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline, CKD is divided into G1–G5 phases according to glomerular filtration level.[11] It is particularly important for CM to carry out treatment based on syndrome differentiation in different stages. In the stages 1–2, the pathological manifestations are main syndromes of primary diseases such as qi-yin deficiency or qi-blood deficiency, and pathogenic factors such as wind-heat, damp-heat, heat-toxic and blood stasis often aggravate these syndromes. It is important to relieve exterior syndromes, accompanied by eliminating heat and detoxicating. As CKD develops, turbid syndromes gradually appear, and turbidity turns into turbid toxin. Thus supplementing qi, nourishing and activating blood, removing dampness and turbid toxin are the main treatments in the stage 3 of CKD. In the stages 4–5 of CKD, with further decay of qi and blood and the transforming from damp-turbidity to damp-heat, the triple energizer is obstructed and accompanied by improper ascending and descending. Therefore, it is vital to take measures to clear the triple energizer in this situation, such as supplementing qi and strengthening the Xin (Heart) in the upper energizer, harmonizing the Wei (Stomach) and descending turbidity in the middle energizer, and removing damp-turbidity in the lower energizer. Treatment of these key pathogenesis and syndromes affecting disease achieved significant effects. For example, our team applied Fuzheng Quzhuo Oral Liquid (扶正祛浊口服液, FZQZ) with the effects of qi-invigorating, blood-activating, dampness-reducing and turbidity-purging on CKD patients, and found that there was a significant difference between the FZQZ and placebo groups in the post-trail phase in the occurrence of composite endpoint events (13.79% *vs*. 27.59%, log rank χ^2=8.04, *P*=0.005), which were defined as the initiation of long-term dialysis, CKD-related death, or the doubling of serum creatinine (Figure 1).[12]

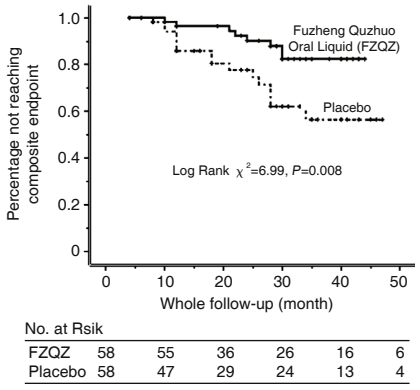

Figure 1. Kaplan-Meier Curve for Composite Endpoint Events throughout Entire Follow-Up Period

Treatment on Different CM Pathogenesis of CKD

With the decrease of GFR, cardiovascular disease (CVD) is more significantly associated with CKD. A majority of patients with CKD die as a result of CVD when their renal disease is still in the early stages. In addition, the risk of CV mortality is 10–30 times higher in the dialysis population than the general population.[13] For patients with high risks of CVD, such as hyperlipidemia and hypertension, the use of statins and antihypertensive drugs may not bring benefits in reducing CV events and all-cause mortality. For hyperlipidaemia, statins may effectively reduce total and low-density cholesterol concentrations and proteinuria, but had no effect on slowing CKD progression.[14] For hypertension, a meta-analysis reported that intensive blood pressure lowering could reduce the risk of renal failure in patients with CKD and proteinuria. However, there was no optimum protection on the risk of CV events or death for the level of controlled blood pressure in CKD patients.[15] In addition, clinical practice guidelines recommend that all dialysis patients presenting with acute coronary syndrome should be treated as in the non-dialysis population, however, the harms of antiplatelet treatment, such as bleeding, might exceed the benefits.[16,17] With the limitations of modern medicine in the treatment of risk factors of CVD associated CKD (CKD-CVD), it is essential to emphasize the unique pathophysiological characteristics of CKD to improve clinical outcomes. Increasing evidence suggest that uremic toxins are potentially non-traditional risk factors of CKD-CVD.[18] Therefore, combined with the pathophysiological mechanisms of CKD, it is important to find the key pathogenesis of CM related to clinical endpoint events of CKD-CVD based on uremic toxins. Turbid toxin and blood stasis are two key pathological factors of uremic toxins in CM theory.

Turbid Toxin

Progressive loss of renal clearance in CKD patients is accompanied by a series of retention of metabolites. Many of them have shown biological activity that can affect the function of cells and organs, thus leading to clinical uremic syndrome. These solutes are called uremic toxins, which are equivalent to the category of turbid toxin in CM. According to European Uremic Toxin Working Group, based on their possible clearance, they are usually classified as small molecule water-soluble compounds, protein-bound compounds, and medium molecular substances.[19] When the uremic toxins are elevated at the early stage of CKD, the patients may not have any clinical manifestations. Laboratory examinations of modern medicine amount to the extension of 4 diagnostic methods of CM, which provide a certain reference for the treatment of CM. When it comes to treatment, first, it is necessary to choose a reasonable diet to regulate gastrointestinal function and reduce the generation of turbid toxin. Second, it is important to promote the excretion or removal of turbid toxin, such as the method of removing damp-turbidity or adsorption. In addition, attentions should be paid to using CM with detoxification and blood-activating effects, in case of the damage caused by turbid toxin to Xin, Shen and blood vessels.

Blood Stasis

In the process of CKD, renal vascular lesions and ischemic changes are obvious, which belong to the category of blood stasis in CM. In China, hypertensive nephrosclerosis, primary glomerulonephritis and diabetic nephropathy are 3 major diseases leading to ESRD. Pathological manifestations of renal arterioles are subcortical arteriosclerosis, intrarenal arterial stiffening, arteriolar sclerosis, and hyalinosis. Ischemia is the earliest signal of fibrosis, so ischemic changes of glomeruli are characterized by ischemic collapse of glomerululi, followed by ischemic sclerosis, and accompanied by tubular interstitial inflammation and fibrosis. Renal angiopathy in primary nephrosis is related to the progression of renal fibrosis and renal failure. Nasri, et al[20] indicated that vasculopathy plays an important role in the aggravation of IgA nephropathy. In clinical work, we found that there were obvious ischemic changes in the renal pathology of patients with primary nephropathy but without hypertension (Figure 2). Diabetic nephropathy is generally considered to be diabetic glomerulopathy characterized by microangiopathy and renal angiopathy. For example, the renal biopsy of a patient with diffuse proliferative diabetic nephropathy (type Ⅱa) in our ward exhibited pretty clear ischemic sclerosis and vascular disorders (Figure 3). Moreover, the Atherosclerosis Risk in Communities Study revealed that central arterial stiffness may be an important pathophysiologic phenotype of vascular disease in CKD. Previous study has shown that blood stasis syndrome is closely related to the clinical manifestations and pathological changes of renal disease.[21] Therefore, the stiffness of blood

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vessels or the pathological findings of renal biopsy, such as glomerular ischemic collapse and sclerosis, and arteriolar hyaline degeneration, can be used as microscopic manifestations of blood stasis syndrome. Aimed at the treatment of blood stasis syndrome, the importance of replenishing qi should be attached to activate blood, so as to remove blood stasis without harming vital qi.

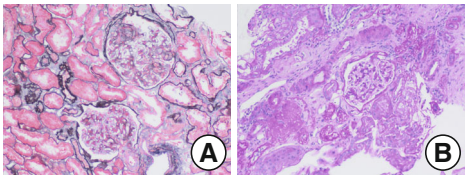

Figure 2. PASM-Masson and PAS Staining in Kidney of A 46-Year-Old Male IgA Nephropathy Patient with Normal Blood Pressure (×100)

Notes: Ischemic kidney injuries and vascular disorders: glomerulosclerosis, glomerular ischemic collapse and sclerosis, mild diffuse hyperplasia of glomerular mesangial cells and matrix, with focal and segmental aggravation, thickening of arteriolar wall with hyaline degeneration. These renal ischemic injuries are objective evidence of blood stasis syndrome in Chinese medicine. A: PASM-Masson staining of kidney; B: PAS staining of kidney

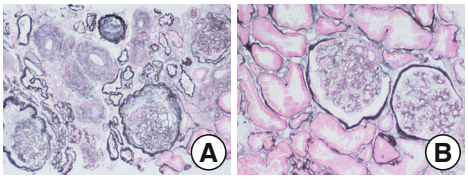

Figure 3. PASM-Masson Staining in Kidney of A 66-Year-Old Male Patient with Diabetic Nephropathy (×100)

Notes: Ischemic renal structure and vascular disorders: centrally distributed ischemic sclerosis, glomerulosclerosis, mild diffuse hyperplasia of glomerular mesangial cells and matrix, with mild diffuse thickening of the basement membrane, thickening of arteriolar wall with hyaline degeneration, stenosis of the lumen. These pathological manifestations are the extensions of blood stasis syndrome in Chinese medicine.

Improving Quality of Life of CKD Patients

From the early stage of CKD, the quality of life (QOL) of CKD patients has been declining with the decrease of GFR. Decreased QOL can be used as an independent predictor of disease progression and CV and all-cause mortality.[22] The prevention and treatment of CKD need to take patients' QOL and the impact of treatment on subjective well-being into consideration. Treatment should benefit survival. If the QOL declines, some patients may refuse the treatment. Until now, little attention has been focused on incapacity such as impaired physical function, asthenia, cognitive dysfunction, emotional health problem (including depression and anxiety) and declined health-related QOL in CKD patients, especially the elderly. People with CKD have an increased risk of cognitive dysfunction compared with people without CKD, closely associated with reduced QOL.[23] According to CM theory, cognitive dysfunction is related to the damage of brain orifice caused by turbid pathogens, such as turbid toxin and blood stasis, on the basis of deficiency of Shen essence. Therefore, there is a great need to explore the crucial evidence about the insufficiency of viscera function and qi-blood and yin-yang related to clinical outcomes.

In conclusion, it is necessary to establish CKD prevention and treatment programs from the basic condition of disease, according to the patients' personal and geographical characteristics and even the exposure of genetic and environmental factors, combined with different primary disease and possible endpoint events. To achieve the aims of reducing CV complications and all-cause mortality and improving QOL in the treatment of CKD, therapeutic strategies should be based on the key pathogenesis of deficiency of vital qi and mutual obstruction of turbid toxin and blood stasis.

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