



# Gastrointestinal disorders in chronic kidney disease

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**Abstract:** Chronic kidney disease (CKD) has been a significant health problem globally, affecting about 10.8% of people in China. Gastrointestinal disorders are common and carry significant complications of CKD. Though studies have found multiple mechanisms that may account for the dysfunction, few effective therapies are currently available. Traditional Chinese medicine (TCM) has a significant advantage of attenuating gastrointestinal symptoms by a variety of therapies, but more research needs to be done to explore the effectiveness and mechanism of TCM.

**Keywords:** Chronic kidney disease (CKD); gastrointestinal disorders; traditional Chinese medicine (TCM)

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## Introduction

Chronic kidney disease (CKD) patients commonly experience gastrointestinal disorders, including dysgeusia, anorexia, dyspepsia, hiccups, nausea, and vomiting. It is reported that gastrointestinal symptoms can be apparent in CKD patients at relatively high eGFR levels, long before ESRD, and will become increasingly obvious as the disease progress (1). Gastrointestinal disorders can not only affect the quality of CKD patients' life, but also result in dehydration, electrolyte imbalance, malnutrition, which will further lead to kidney injury (2). The pathogenesis of gastrointestinal disorders in CKD is relatively complex, more than the role of the uremic toxin. However, research on gastrointestinal disorders in CKD is still limited. In this article, we try to review the possible pathogenesis and some traditional Chinese medicine (TCM) therapies on gastrointestinal disorders in CKD.

## Pathogenesis of gastrointestinal disorders in CKD

Various factors are involved in the development of

gastrointestinal disorders, including the accumulation of uremic toxins and the increase of gastrointestinal hormones as kidney function declines, and changes in the intestinal flora. All of these factors can lead to the damage or destruction of the gastric mucosal barrier, or gastrointestinal motility, which will ultimately result in gastrointestinal disorders or lesions.

### *Uremic toxins*

Uremic toxins, such as indoxyl sulfate and hippuric acid that resulted from the decline of kidney function, are important factors that cause gastrointestinal injury. On the one hand, patients with kidney failure have more urea excretion by the gastrointestinal tract, resulting in a significant increase in ammonia and carbonate that broke down by bacteria, which will result in extensive inflammation and erosion of the mucosa. On the other hand, studies have shown that uremic toxin accumulation maybe accounts for gastrointestinal motor dysfunction, exhibiting an increased transit time and a blunted motility, and it can further impair gut smooth muscle contractility. What is more, the increased residence

time of the stools in the colon might further increase the production/absorption of colon-derived uremic toxins and alter the reabsorption of water and electrolytes. Thus a vicious cycle of uremia in the colon is developed (3,4).

### *Gastrointestinal hormones*

Most gastrointestinal hormones need to be excreted by the kidney, so as kidney function declines, many gastrointestinal hormones display increased circulating levels in CKD, such as gastrin, motilin, cholecystokinin, and vaso-intestinal. Altered circulating levels of gastrointestinal hormones could have a strong impact on gut motility. Motilin is an important gastrointestinal hormone that mainly stimulates mechanical motility in the gastrointestinal tract and regulates the contraction rhythm of gastrointestinal smooth muscle as well as the gallbladder. Motilin accumulation in CKD patients will cause gastrointestinal motility disorders and abnormal gastric acid secretion, leading to lesions such as ulcers (5). Gastrin has a similar function with motilin, and it can trigger a contractile response of gastric antral smooth muscle by combining to specific receptors of smooth muscle cells (6). GLP-1 is also reported to play a role in gastric dysfunction. Studies showed that CKD patients exhibited a significantly higher GLP-1 level than controls, and it is strongly correlated with a reduced percentage of normal gastric slow waves and increased gastric dysrhythmia (7).

### *Autonomic nervous system dysfunction*

Gut motility is regulated by the sympathetic system and parasympathetic systems, which inhibit and stimulates gut motility, respectively. Autonomic dysfunction in CKD means increased sympathetic nervous system activity and depressed parasympathetic activity. So it will contribute to the gastrointestinal dysmotility and the delayed transit time. Autonomic nervous system dysfunction can be caused by uremic toxins which can directly damage small nerve fibers, and there are also some other factors, such as the renin-angiotensin-aldosterone system activation, salt retention, decreased nitric oxide bioavailability and cardiovascular remodeling (8).

### *Gastrointestinal motor dysfunctions*

Data showed that about 40% of hemodialysis patients have gastrointestinal symptoms without detectable anatomical/histological lesions, and 60% of patients with

evidenced gastric or duodenal lesions did not exhibit any gastrointestinal symptoms. So the relationship between the pathological lesion and gut dysfunction is not absolutely. It has been reported that the gastrointestinal symptoms in CKD patients are strongly related to gastrointestinal motor dysfunctions (9). Some dysfunctions of the esophagus and stomach motility have already been reported in patients with CKD, as well as colon motor dysfunction (10). The manifestation of gastrointestinal motor dysfunctions can be various. Studies showed that the gastric transit time would be prolonged and gastric myoelectrical activity will be altered in CKD patients, and a significant decrease in duodenum and colon motility can also be observed.

### *Other injury factors*

Recent studies showed that intestinal flora alteration could also be observed in CKD patients mainly manifest as the number and types of probiotics decreased, such as Bifidobacterium, Lactobacillus, while conditioned pathogens increased significantly. Drug damage is another reason related to gastrointestinal disorders in CKD. Cardiovascular disease (CVD) is one of the most common complications in patients with CKD and has been blamed as the most important cause of mortality. CKD patients, so the use of aspirin or other NSAIDs is prevalent in patients with ESRD. Therefore, aspirin usage in these patients may cause peptic ulcers, which may cause gastrointestinal symptoms.

### **TCM therapies**

Though gastrointestinal disorders and symptoms greatly affect the quality of life of CKD patients and could strengthen the kidney injury, there still few we can do to cope with it. Hemodialysis and peritoneal dialysis are effective ways of eliminating uremic toxins and some gastrointestinal hormones. However, to patients in a relatively early stage of CKD, both of them lack scope for their abilities. Proton pump inhibitors (PPI) is the medication that we usually use to attenuated gastric discomfort. However, this kind of medicine may lead to interstitial nephritis.

Gastrointestinal symptoms in CKD patients has long been recognized by TCM. Renal failure was called *Guan ge* in TCM. *Guan* means nausea and vomiting, and *ge* means anuria. TCM not only has a significant advantage in alleviating gastrointestinal symptoms but also can delay the progression of CKD. Chinese herbal medicine is the most common way used in clinical practice. Uremic toxin

is usually considered to be a damp toxin or turbid in TCM, so herbs that have the function of expelling toxin and damp are often used to treat CKD patients with gastrointestinal symptoms, such as Fortune Eupatorium Herb, Glabrous Greenbrier Rhizome or Rhubarb. Besides herbal medicine, many external treatments such as transcolonic therapy and medicine enema are also used in treating gastrointestinal symptoms in CKD. They are used as an alternative to patients, especially those who cannot be tolerant oral herbal medicines. Studies showed that enema with the Rhubarb decoction plus western medicine could improve micro-inflammation, significantly reduce serum creatinine (Scr), blood urea nitrogen (BUN), C-reactive protein (CRP), 24-hour urine protein and interleukin 6 (IL-6) in patients with CKD (11).

## Conclusions

The gastrointestinal complaints are widespread even in the very early stage of CKD. The pathogenesis of gastrointestinal disorders is relatively complex; not all patients with gastrointestinal symptoms have histological lesions. The pathological factors may include uremic toxins and gastrointestinal hormones that will accumulate as kidney function declines, which may lead to autonomic nervous system dysfunction or gastrointestinal motor dysfunctions in patients with CKD. Other factors, such as intestinal flora alteration and drugs, are also critical reasons. TCM showed good clinical efficacy not only in relieving gastrointestinal discomfort but also in improving renal function. However, high-level evidence such as RCT is still lacked to ensure the effect of TCM in treating gastrointestinal disorders in CKD, and more studies need to be focused on this field.

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