



Constipation in Patients With Chronic Kidney Disease

Ra Ri Cha,¹ Seon-Young Park,^{2*} and Michael Camilleri³; the Constipation Research Group of Korean Society of Neurogastroenterology and Motility

¹Department of Internal Medicine, Gyeongsang National University Changwon Hospital, Gyeongsang National University College of Medicine, Changwon, Gyeongsangnam-do, Korea; ²Division of Gastroenterology, Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Korea; and ³Clinical Enteric Neuroscience Translational and Epidemiological Research, Mayo Clinic, Rochester, MN, USA

Constipation is a frequent symptom in patients with chronic kidney disease (CKD). This review outlines the mechanisms and management of constipation in patients with CKD from a physician's perspective. Common causes of constipation in patients with CKD include concomitant medications, low dietary fiber intake, water-restricted diet, lack of physical activity, altered gut microbiota, and reduced gastrointestinal motility. Constipation has a negative impact on overall health, and, in particular, the presence of constipation has been associated with worsening kidney function and increased risk of developing advanced stages of CKD. Although lifestyle and dietary modifications may not always be practical for patients with CKD, they are recommended because they are beneficial as they lower mortality in patients with CKD. The use of laxatives containing magnesium salts, bulking agents, and osmotic laxatives may have insufficient efficacy and may be associated with adverse effects. In contrast, lactulose and lubiprostone have been shown to exhibit reno-protective effects. Linaclotide and plecanatide have very limited systemic absorption and appear safe in patients with CKD. Tenapanor reduces paracellular intestinal phosphate absorption in addition to blocking sodium uptake by enterocytes, and provides additional benefit in patients with CKD who have hyperphosphatemia and constipation. Prucalopride leads to improvements in bowel function and constipation-related symptoms in cases in which response to conventional laxatives are inadequate. However, the dose of prucalopride should be reduced to 1 mg once daily for patients with CKD. In conclusion, there are important advances on the impact and treatment of constipation in patients with CKD.

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Key Words

Chronic kidney disease; Constipation; End-stage renal disease; Laxatives

Introduction

Patients with chronic kidney disease (CKD) have a higher prevalence of constipation, reported to be present in as many as 29.0% of patients on peritoneal dialysis (PD) and 63.0% of patients on hemodialysis (HD).¹ A recent systematic review suggested that the most prevalent gastrointestinal symptom in patients receiving dialysis for end stage renal disease (ESRD) was constipation, with

prevalence ranging from 1.6% to 70.7% in patients on HD, and from 14.2% to 90.3% in patients on PD.² However, the impact, mechanisms, and management of constipation in CKD remains unclear. Common causes of constipation in patients with CKD include low dietary fiber intake, water-restriction, lack of physical activity, concomitant medications, reduced gastrointestinal motility, and altered gut microbiota.

Constipation has a negative impact on overall health. In patients with ESRD, patients with constipation had lower quality of life

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*Correspondence: Seon-Young Park, MD, PhD

Division of Gastroenterology, Department of Internal Medicine, Chonnam National University Hospital, 42 Jaebong-ro, Dong-gu, Gwangju 61572, Korea
Tel: +82-62-220-6296, Fax: +82-62-220-8578, E-mail: drpsy@naver.com

scores.³ In addition, constipation has been associated with adverse clinical outcomes such as the development of advanced stage CKD, cardiovascular events, and mortality in patients with CKD.⁴ Patients receiving PD and experiencing constipation had a higher risk of peritonitis.⁵ Constipation was associated with increased prevalence of bone fractures in pre-dialysis patients with CKD.⁶ For these reasons, constipation increases medical and socioeconomic costs among patients with CKD. Therefore, appropriate attention and management of constipation are needed for the care of patients with CKD. Diet and lifestyle modification, pharmacological and non-pharmacological interventions are applicable for the management of constipation. However, in patients with CKD, the appropriate management of constipation may differ according to renal function and underlying comorbid conditions. Here, we discuss the mechanisms and management of constipation in patients with CKD from a physician's perspective.

Medical Conditions Associated With Constipation in Patients With Chronic Kidney Disease

Patients with ESRD had slower colon transit than healthy controls.⁷ The mechanisms of constipation in patients with CKD include multifactorial and complex etiological factors. Patients with CKD often have predisposing factors such as constipation-inducing medications (iron supplements, antihypertensives, potassium-lowering agents, phosphate binders, diuretics, etc), comorbid diseases and metabolic disorders (diabetes, hypercalcemia, etc). Furthermore, patients with CKD are advised to restrict fiber diets to avoid hyperkalemia or hyperphosphatemia and to restrict water intake to avoid volume overload. Patients with CKD usually perform less physical activity due to underlying comorbid diseases and are unable to perform physical activity while undergoing HD, which typically requires about 4 hours of physical inactivity. In fact, the prevalence of constipation was higher in patients with HD than in patients with PD (63.0% vs 29.0%).¹

Impact of Constipation on Kidney Function

As patients with CKD progressed to ESRD requiring dialysis, the use of laxatives increased and this increased use persisted after renal replacement therapy. A recent retrospective cohort study including about 100 000 United States of (US) veterans showed that the prevalence of constipation identified by prescription rate of laxatives increased up to 37.1% in the 6 months following transition

from CKD to ESRD and remained stable.⁸ Sumida et al⁹ evaluated whether the presence of constipation was related with worsening of renal function and increased the risk of developing CKD in a retrospective cohort study of about 3 500 000 US veterans without CKD during a median follow-up of 7 years. In that study, patients with constipation had a higher occurrence of incident CKD (defined as 2 estimated glomerular filtration rate [eGFR] levels measured 90 days apart of < 60 mL/min/1.73 m² or by a 25.0% decrease from baseline eGFR) and ESRD (defined as initiation of maintenance dialysis or preemptive renal transplantation) than patients without constipation. Moreover, patients with constipation had a greater risk of decline in the eGFR during follow-up.⁹ There are several reports regarding a relationship of constipation with CKD progression even though it has been not fully elucidated.⁸⁻¹¹

In patients with CKD, there are several factors contributing to the gut dysbiosis including intestinal wall edema, low fiber diets, medication use (iron supplements and phosphate binders), and metabolic acidosis, leading to increased permeability and translocation of bacterial metabolites across the intestinal barrier.^{12,13} In addition, microbial urease in the gut hydrolyzes urea and produces large amounts of ammonia (NH₃) and ammonium hydroxide (NH₄OH), which increase intraluminal pH and also contribute to the gut dysbiosis.^{14,15} Furthermore, delayed colon transit itself was associated with high microbial richness and also accompanied by a shift in colonic metabolism from carbohydrate fermentation to protein catabolism.¹³ Protein fermentation in the colon produces several metabolites including precursors of uremic toxins such as p-cresol and indole, which are metabolized to uremic toxin such as p-cresyl sulfate (PCS) and indoxyl sulfate in the colonocytes and/or in the liver. Trimethylamine-N-oxide (TMAO) is oxidized from trimethylamine, which is a metabolite of quaternary amines. These gut-derived uremic toxins are increased in patients with constipation. These toxins are normally excreted by glomerular filtration or renal tubular secretion. However, they accumulate in patients with CKD as renal function declines. Ramos et al¹⁶ demonstrated that, in 43 patients with non-diabetic CKD, patients with constipation showed higher levels of urinary PCS, independent of renal function, suggesting that constipation may lead to production of PCS in patients with CKD. In a separate study, PD patients with constipation tended to have higher PCS.¹⁷ The increased production of gut-derived uremic toxins associated with constipation may also contribute to the increased risk of renal events. These gut-derived uremic toxins have been associated with inflammation and renal fibrosis, suggesting association with progression of CKD.¹⁸ Furthermore, gut-derived uremic toxins are associated with the risk of cardiovascular disease

(especially PCS and TMAO) and related mortality in patients with CKD.^{6,19-22}

Management of Constipation in Patients With Chronic Kidney Disease

Dietary and Lifestyle Modification

There is consensus that lifestyle modifications, including the administration of a fiber-rich diet and increased physical activity, are the first-line therapies for constipation. Dietary fibers with increased fluid intake can effectively improve the symptoms of chronic constipation by increasing the number of bowel movements and reducing colon transit time.²³ However, in patients with CKD, it is difficult to adopt these recommendations. For patients with CKD, clinicians usually recommend restricting fiber-rich foods to prevent hyperkalemia. Many patients with CKD have limited physical activity owing to multiple comorbidities. In addition, non-pharmacological strategies for treating constipation in patients with CKD, such as increasing fiber and fluid intake and the level of physical activity, have not undergone rigorous evaluation.

A typical dietary intervention for constipation is to increase fiber intake, and this has been shown to be beneficial in patients with CKD. In a recent meta-analysis, healthy dietary patterns including fiber-rich vegetables, fruits and grains were associated with lower mortality in patients with CKD (adjusted relative risk, 0.73; 95% confidence interval, 0.63 to 0.83).²⁴ A previous study also reported some beneficial effects of a high-fiber diet such as improvement of bowel function with no change in phosphate level and mild increase in potassium level (4.3 mmol/L to 4.7 mmol/L) in patients underlying PD.²⁵ However, in patients with advanced CKD, fiber-rich vegetables and fruits can cause hyperkalemia and therefore, their intake should be limited.

Patients with CKD, particularly those undergoing dialysis, usually exhibit low physical activity and body function. The notion that exercise improves constipation in the general population is reinforced in a recent systematic review and meta-analysis of randomized controlled trials.²⁶ However, it is unclear whether exercise results in similar efficacy as dietary interventions in patients with CKD or whether exercise relieves constipation in patients with CKD. However, in other studies reports that exercise therapy improves physical function and some clinical symptoms, including restless legs syndrome, in patients undergoing dialysis.^{27,28} In general, regular exercise can have several positive effects on various comorbidities of CKD, and may include beneficial effects on constipation.

Pharmacological Treatment of Constipation in Patients With Chronic Kidney Disease

There are no clear management strategies for constipation in patients with CKD and which over-the-counter drugs are recommended. Potential safety concerns associated with the use of these medications (eg, volume depletion and electrolyte disturbances; hypermagnesemia due to magnesium-containing laxative and drug-induced nephrotoxicity; and renal ischemia from severe hypokalemia) may lead to undertreatment of constipation in patients with CKD.²⁹ However, in patients with CKD, pharmacological treatments are often necessary for treating constipation.³⁰ Currently, bulk-forming laxatives, osmotic laxatives, and stimulant laxatives are available, and relatively new prescription drugs may also be considered (Table). Pharmacological treatments may need to be individualized based on severity of symptoms, co-morbidity and clinical or metabolic complications of CKD such as hyper-phosphatemia.

Bulk-forming laxatives

Bulk-forming laxatives include soluble (eg, psyllium) and insoluble fibers (eg, wheat bran, methylcellulose, and polycarbophil). Bulk-forming laxatives can be used relatively safely as a first-line treatment in patients with constipation; however, they should be used with caution in patients with reduced renal function because increased fluid intake is required along with the bulking agents.³¹ Insoluble dietary fibers may cause side effects such as abdominal pain, bloating, flatulence and nausea, especially in patients with firmer stools. As with dietary fiber, caution is required when prescribing bulking agents for constipation in patients with reduced renal function who are recommended limited fluid intake.

Osmotic laxatives

Magnesium salts are excellent osmotic laxatives with low costs, easy ingestion, and dosage adjustment.³² However, impaired renal function may lead to hypermagnesemia.³³ Thus, it is important to monitor the levels of serum magnesium in patients taking magnesium salts, especially in patients with CKD taking high doses of magnesium oxide. Advanced CKD, older age, and long-term use of magnesium salt are risk factors for hypermagnesemia.³⁴⁻³⁶

Non-absorbable carbohydrates used to treat constipation include hyperosmolar laxatives such as sorbitol, lactulose, and lactitol. Several studies have also reported the reno-protective effects and tolerability of lactulose in patients with CKD.³⁷⁻³⁹ Lactulose is not metabolized by intestinal enzymes and the osmotic effect of the undigested sugar, as well as retention of water and electrolytes in the

Table. Available Pharmacological Treatment Options in Patients With Chronic Kidney Disease

Types	Pharmacologic options	Mechanisms of action and effects	Side effects
Bulk-forming laxatives	Psyllium, wheat bran, polycarbophil, and methylcellulose	Absorbing water in the intestine, thereby increasing the bulk of stools and easier to pass	Abdominal pain, bloating, flatulence, and nausea
Osmotic laxatives	Magnesium salts	Osmotically increase intraluminal fluids by non-absorbable ions and molecules and mainly soften hard stools	Hypermagnesemia Mild: nausea, headache, and lethargy Severe: respiratory failure, complete heart block, and cardiac arrest
	Non-absorbable carbohydrates (lactulose, lactitol, and sorbitol)	Promotes bowel movement by increasing the intestinal osmotic pressure and acidity	Diarrhea, abdominal pain, abdominal distension, and abnormal gastrointestinal sounds
	Polyethylene glycol (PEG3350)	Produces intraluminal osmotic gradients, which lead to fluid retention in the colon cavity and facilitate stool passage	Bloating, flatulence, electrolyte disturbance, diarrhea, abdominal pain, and nausea
Stimulant laxatives	Surfactant laxatives (castor oil and docusate), anthraquinones (aloe, senna, and cascara), and polyphenols (bisacodyl, sodium picosulfate, and phenolphthalein)	Directly irritating the smooth muscle of the colon, and increase water and electrolyte secretion into the intestinal lumen	Abdominal discomfort, pain, cramps, nausea, and incontinence
Chloride channel activators	Lubiprostone	Enhance intraluminal chloride ion secretion and induce spontaneous bowel movement	Diarrhea and nausea
Guanylate cyclase C agonist, chloride secretion	Linacotide and plecanatide	Enhance gastrointestinal fluid secretion and transit and induce spontaneous bowel movement	Diarrhea
Na-H exchange inhibitor	Tenapanor	Enhance colonic fluid secretion and induce spontaneous bowel movements; reduce hyper-phosphatemia	Diarrhea
Selective 5-HT ₄ receptor agonists	Prucalopride	Stimulate peristalsis and accelerates gastrointestinal transit through activation of 5-HT ₄ receptors of myenteric neurons	Diarrhea, nausea, and headache

5-HT₄, 5-hydroxytryptamine receptor 4.

intestinal lumen, result in reduction in nitrogenous waste that would require renal clearance in patients with CKD. In animal models of adenine-induced CKD, lactulose led to the modification of gut microbiota that showed suppression of uremic toxin production and improved renal function.⁴⁰ Therefore, in constipated patients with CKD, lactulose treatment may be expected to have renoprotective effects.

Polyethylene glycol (PEG 3350) is a non-absorbable and non-metabolizable substance that leads to soften the stool and increase the frequency of bowel movements by fluid retention in the colon,⁴¹ relieving chronic constipation^{42,43} without significant adverse events. It does not increase the amount of colonic gas, as it is not metabolized by colonic bacteria. This is associated with less bloating and

flatulence compared to other osmotic agents such as lactulose, and with minor gastrointestinal adverse events (including nausea, diarrhea, and abdominal pain), and no serious adverse events.

Stimulant laxatives

Stimulant laxatives induce propagative contractions of the smooth muscle of the colon and increase water and electrolyte secretion into the intestinal lumen.⁴⁴ These agents include anthraquinones (aloe, senna, and cascara), surfactant laxatives (docusate and castor oil), and polyphenols (sodium picosulfate, bisacodyl, and phenolphthalein). A previous study demonstrated the short-term safety and efficacy of senna with dietary fiber, which was comparable to lactulose in constipated patients with pre-dialysis CKD.⁴⁵ In

a small sample size study, 2 weeks bisacodyl treatment significantly decreased the plasma potassium concentration by enhancing colonic potassium secretion in between dialysis treatments in patients undergoing HD.⁴⁶ However, concerns have been raised regarding the long-term safety and abuse of stimulant laxatives. Therefore, stimulant laxatives are helpful in relieving the symptoms of constipation and can be considered a rescue therapy in cases resistant to conventional laxatives.³¹

Lubiprostone

Lubiprostone is an activator of the type 2 chloride channel that facilitates spontaneous bowel movement.⁴⁷ It enhances intraluminal chloride ion secretion, which results in a passive influx of water and sodium, leading to increased intestinal peristalsis with decreased colon transit time.⁴⁸ Lubiprostone also exerts a reno-protective effect against the progression of CKD, as well as leading to a decrease in the plasma concentration of uremic toxins and improvement of the intestinal microbial community. Based on these observations, its potential therapeutic potential in patients with CKD has been suggested. Lubiprostone also improved renal fibrosis and inflammation in an animal model (adenine-induced) CKD.⁴⁹ Additionally, in a previous study, short- and long-term analyses of electrolyte changes associated with the use of lubiprostone were not associated with clinically meaningful electrolyte imbalance or effect on renal function indices.⁵⁰ Therefore, lubiprostone may be prescribed as a relatively safe and effective drug for patients with CKD.

Linaclotide and plecanatide

Linaclotide and plecanatide are agonists of the guanylate cyclase C receptor and result in chloride secretion in the intestine and the colon; several trials and systematic reviews document their efficacy in treatment of constipation.⁵¹ Regulatory agencies such as the United States Food and Drug Administration provide general recommendations as follows: "In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy."⁵² However, although it is stated that the medication has not been specifically studied in patients who have renal impairment, the prescribing information for linaclotide specifically states that no dose adjustment is necessary based on renal function due to the low systemic availability of the parent drug or its metabolite.⁵³ The same should apply for plecanatide although this is not specifically stated in regulatory documents.

Given that cardiorenal syndrome is a major cause of mortality in patients with CKD, it is interesting to note that linaclotide

ameliorated the gut-cardio-renal axis in an adenine-induced mouse model of CKD and in choline-fed pro-atherosclerotic model.⁵⁴ The study showed that linaclotide decreased the plasma levels of TMAO, a hepatic metabolic product of trimethylamine generated from dietary phosphatidylcholine or carnitine derived by the gut microbiota, which has been linked directly with progression of cardiovascular disease and renal dysfunction. Linaclotide also reduced other uremic toxins, and ameliorated renal inflammation and fibrosis and cardiac fibrosis.

Tenapanor

Tenapanor is a small molecular inhibitor of the sodium/hydrogen ion exchanger-3 (NHE3) used to treat constipation-predominant irritable bowel syndrome.⁵⁵ Tenapanor has minimal systemic absorption and it reduces paracellular intestinal phosphate absorption⁵⁶ and this could be an additional benefit in patients with CKD and hyperphosphatemia. In fact, in a 52-week phase 3 randomized withdrawal study compared to placebo in participants receiving maintenance dialysis, tenapanor reduced serum phosphate concentrations and maintained control of serum phosphate, with an acceptable safety and tolerability⁵⁷ confirming prior trials in USA and Japan.^{58,59} Tenapanor is being proposed as a new treatment option for renal hyperphosphatemia,⁶⁰ in addition to relieving constipation.

Prucalopride

Prucalopride is a highly selective 5-hydroxytryptamine receptor 4 agonist that stimulate peristalsis and accelerates gastrointestinal transit.⁶¹ Several studies have demonstrated that the use of prucalopride leads to improvements in bowel function and constipation-related symptoms in cases in which response to conventional laxatives is inadequate.⁶² However, the use of prucalopride in patients with CKD requires caution. As prucalopride is primarily excreted via urine, its clearance is significantly reduced with area under the prucalopride concentration curve 1.5 to 2.3 fold higher in association with moderate or severe renal impairment.⁶³ A dose-escalation study in 89 elderly constipated nursing home residents treated with placebo, 0.5, 1, or 2 mg prucalopride once daily for 28 days showed plasma prucalopride increased proportionally with administered dose. Prucalopride up to 2 mg once daily for 4 weeks was safe and well-tolerated with no differences in electrocardiogram or a range of Holter-monitoring parameters.⁶⁴ However, although 75.0% patients in that study were being treated for cardiovascular diseases, their renal function was not reported to be impaired at entry or throughout the study.

Acute tubular necrosis has been reported in a single case treated

with prucalopride,⁶⁵ although the causal relationship has not been established. Given these findings, the dose of prucalopride should be reduced to 1 mg once daily for patients with CKD (glomerular filtration rate less than 30 mL/min/1.73 m²), as recommended in the FDA prescriber information.⁶⁶

Conclusion

Constipation is highly prevalent among patients with CKD. Constipation is associated with gut dysbiosis, leading to a shift to protein catabolism in colon and increase of gut-derived uremic toxins, which accumulate as renal function declines. These increased gut-derived uremic toxins worsen kidney function and increase the risks of de novo kidney diseases. Although lifestyle and dietary modifications may not always be clinically feasible for patients with CKD, they are recommended as they are beneficial for lowering mortality in patients with CKD. The use of magnesium salts-containing laxatives, bulking agents, and osmotic laxatives may have insufficient efficacy and safety concerns related to fluid imbalance of hypermagnesemia. Guanylate cyclase-C agonists have very limited systemic absorption and appear safe in patients with CKD. Lactulose, linaclotide and lubiprostone exhibit additional reno-protective effects. The NHE3 inhibitor tenapanor provides additional benefit in patients with CKD, by reducing hyperphosphatemia and constipation. If patients are unresponsive to the primary treatment for constipation, prucalopride may be considered at a reduced dose of 1 mg daily in patients with creatinine clearance < 30 mL/min. Further research on the mechanisms and optimal treatment of constipation and CKD should focus on understanding mechanisms of constipation, the role of microbiota and larger trials of approved drugs in patients with different stages of CKD.

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