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Constipation in chronic kidney disease: it is time to reconsider

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Abstract

Constipation is highly prevalent in patients with chronic kidney disease (CKD) and is primarily characterized by decreased intestinal motility. This chronic disorder affects the quality of life of patients. However, nephrologist and dialysis clinicians have long had a disproportionately limited understanding of constipation. Accumulating evidence has revealed a relationship between constipation and cardiovascular disease and CKD. The pathogenesis of constipation in CKD patients is multifactorial: decreased physical activity, comorbidities affecting bowel movement, such as diabetes mellitus, cerebrovascular disease, and hyperparathyroidism, a restricted dietary intake of plant-based fiber-rich foods, and multiple medications, including phosphate binders and potassium-binding resins, have all been implicated. CKD is associated with alterations in the composition and function of the gut microbiota, so-called gut dysbiosis. Recent studies showed that CKD-related gut dysbiosis decreased intestinal motility via intestinal inflammation or the increased generation of gut-derived uremic toxins, such as indoxyl sulfate and p-cresyl sulfate. Furthermore, the gastrointestinal secretion of mucin was found to be decreased in CKD animal models, which may delay colonic transit by diminished lubrication in the alimentary tract. Thus, CKD-related gut dysbiosis may play a role in constipation, but limited information is currently available. Since constipation is often intractable, particularly in CKD patients, every available means needs to be employed in its treatment. The effects of probiotics, prebiotics, and synbiotics on the composition of the gut microbiota and gut-derived uremic toxins have been increasingly reported. However, their effects on stool consistency or frequency in CKD patients remain unclear. Some laxatives may be beneficial for improving not only bowel habits but also gut dysbiosis. Further studies are required to elucidate the CKD-specific pathogenesis of constipation and develop novel effective treatment options.

Keywords: Constipation, Chronic kidney disease, Dialysis, Uremic toxins, Intestinal motility, Gut microbiota, Gut dysbiosis, Chronic inflammation

Background

Constipation is a worldwide health issue and its median prevalence was reported to be 14% in adults overall and 33.5% in those aged over 60 years [1], with a higher susceptibility in females and individuals under a low socioeconomic status [1, 2]. The chronic symptoms of constipation reduce the quality of life of patients as well as social activities [1, 3]. Although substantial healthcare costs are consumed to treat this disorder, many patients are not satisfied with treatment because of the lack of efficacy [3]. Constipation often emerges as a secondary manifestation of a number of diseases, including endocrine/metabolic diseases (diabetes mellitus [DM], hypothyroidism, hypercalcemia, and hyperparathyroidism), myopathic conditions (amyloidosis and scleroderma), neurological diseases (autonomic neuropathy, cerebrovascular disease, Parkinson's disease, and spinal cord injury), psychological conditions (depression and cognitive impairment), structural abnormalities (colonic and anal stricture, inflammatory bowel disease, and obstructive colonic mass), and chronic kidney disease (CKD) [1]. In a review by Murtagh et al., constipation was identified as the third most common symptom after fatigue and pruritus, with a prevalence of 57%, among the various symptoms exhibited by patients with end-stage kidney disease (ESKD) [4]. Despite its high prevalence, nephrologists

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and dialysis clinicians have a limited understanding of constipation. In contrast to ischemic heart disease, stroke, and severe infection, constipation is not a life-threatening complication in CKD, except in rare cases of colonic bleeding due to stercoral ulcers [5]. However, several cohort studies have shown that constipation is associated with increased mortality in the general population [6], which may be explained by the relationship between constipation and colon cancer [7, 8] and cardiovascular disease (CVD) [9–11]. Furthermore, a nationwide cohort study from the United States including 3 million veterans reported that constipation was associated with the higher incidence of CKD (hazard ratio, 1.13) and ESKD (hazard ratio, 1.09) [12]. More severe constipation was associated with the incrementally higher risk for each renal outcome. We have to change our prejudice that "constipation is not important in CKD." Although the pathogenesis of this complication is highly complex and multifactorial, accumulating evidence is prompting us to consider the relationship between constipation and CKD-related gut dysbiosis.

Prevalence of constipation in CKD

Chronic constipation is classified to three categories based on colonic transit and anorectal function [1]: normal transit constipation, slow transit constipation, and defecatory disorders. Normal transit constipation is the most common form encountered by clinicians [13]. Patients report symptoms that they consider to be consistent with constipation, such as hard stools or a perceived difficulty with evacuation. Most of these patients are treated empirically with dietary fiber or osmotic laxatives and responded well. Defecation disorders are a group of functional abnormalities of the pelvic floor or anorectum leading to the symptoms of constipation [13]. Slow transit constipation may be caused by dysfunctions in colonic smooth muscle or neural innervation, resulting in neural colonic motor abnormalities [14]. Wu et al. reported that the colonic transit time of patients treated with hemodialysis (HD) or peritoneal dialysis (PD) was significantly longer than that of age and sex-matched healthy subjects [15]. Delayed intestinal transit was also observed in CKD animal models [16–18]. Thus, constipation in CKD may primarily be classified as the slow transit type.

The reported prevalence of constipation widely ranges depending on the population investigated and how constipation is defined. If constipation is defined by the subjects themselves, its prevalence is higher, whereas it is more likely to be low based on objective definitions [2]. The definition of constipation differs between healthcare professionals and patients; the former generally define constipation based on stool frequency, whereas the latter define it as straining, hard stools, difficulty in passing stools, discomfort with defecation, or the feeling of incomplete evacuation [19, 20]. The Rome diagnostic criteria, which are expert consensus criteria for diagnosing functional gastrointestinal disorders, are a standardized, widely used method. The newest Rome IV criteria, released in May 2016, define functional constipation as shown in Table 1 [2]. According to these criteria, the diagnosis of constipation needs to be made after the exclusion of irritable bowel syndrome with predominant constipation (IBS-C). The basis of functional constipation is considered to involve delayed colonic transit and a failure to relax the pelvic floor muscles during defecation, whereas the pathophysiology of IBS-C involves a disorder in the brain–gut interaction with the predominant symptom of abdominal pain [21]. The differentiation of these disorders depends on the prominence of abdominal pain in IBS-C, which may be challenging in clinical practice. Actually, previous studies showed not only a diagnostic overlap [21–23] but also the migration of patients between these diagnoses over time [21]. Therefore, some authorities posed a question regarding the feasibility of the Rome criteria for the diagnosis of constipation [1, 24]. The Bristol Stool Form Scale (BSFS) [25], shown in Table 2, is another method

Table 1 Rome IV diagnostic criteria for functional constipation and irritable bowel syndrome with constipation

Diagnostic criteria for functional constipation[a]

1. Must include 2 or more of the following[b]:
   a. Straining during more than 25% of defecations
   b. Lumpy or hard stools (the Bristol Stool Form Scale[c] 1-2) more than 25% of defecations
   c. Sensation of incomplete evacuation more than 25% of defecations
   d. Sensations of anorectal obstruction/blockage more than 25% of defecations
   e. Manual maneuvers to facilitate more than 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
   f. Fewer than 3 spontaneous bowel movements per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome

Diagnostic criteria for irritable bowel syndrome with predominant constipation[d]

1. Recurrent abdominal pain, on average, at least 1 day per week in the last 3months, associated with 2 or more of the following criteria:
   a. Related to defecation
   b. Associated with a change in frequency of stool
   c. Associated with a change in form (appearance) of stool
2. More than 25% of bowel movement with Bristol stool form type 1 or 2, and less than 25% of bowel movement with Bristol stool form type 6 or 7

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis
[b]For research studies, patients meeting criteria for opioid-induced constipation should not be given a diagnosis of functional constipation because it is difficult to distinguish between opioid side effects and other causes of constipation. However, clinicians recognize that these 2 conditions might overlap
[c]The Bristol Stool Form Scale is shown in Table 2
[d]Irritable bowel syndrome subtype can only be confidently established when the patient is evaluated off medication used to treat bowel habit abnormalities

Table 2 Bristol Stool Form Scale

Type	Stool form
1	Separate hard lumps, like nuts (hard to pass)
2	Sausage-shaped but lumpy
3	Like a sausage but with cracks on the surface
4	Like a sausage or snake, smooth and soft
5	Soft blobs with clear-cut edges
6	Fluffy pieces with ragged edges, a mushy stool
7	Watery, no solid pieces, entirely liquid

that is often used to estimate constipation. The BSFS reflects the colonic transit time: stool forms 1 and 2 are associated with slower transit, and stool forms 6 and 7 with more rapid transit [26]. The functions of the colon are to absorb water and electrolytes and transport waste to the rectum. Under a physiological state, the colon receives approximately 1.5 L of liquid effluent daily from the small intestine, with 200–400 mL being excreted in stools [13]. The removal of water from fecal slurry is time-dependent and actively regulated. Sodium is reabsorbed from luminal contents through several active transport channels, with water following passively in response to osmotic gradients. On the other hand, colonic secretion is mediated through chloride channels, which are generally quiescent, leading to a net absorption of water and electrolytes [13]. Thus, stools that remain in the colon longer become drier and harder. However, laxatives are regularly administered to a substantial proportion of CKD patients [15, 27, 28] and strongly affect stool frequency and consistency. The cessation of laxatives in order to diagnose constipation is troublesome in clinical practice.

Tables 3 and 4 show the prevalence of constipation reported in nondialysis-CKD patients [29, 30] and dialysis patients [15, 27–29, 31–36], respectively. Cano et al. reported a higher prevalence of constipation in dialysis patients in a comparison with age and sex-matched community subjects (31.1% vs. 10.1%, $P < 0.001$) [32]. In dialysis patients, the definition/criteria of constipation are varied and its prevalence widely ranged between 14.2 and 71.7%. The Rome criteria and BSFS have only been employed in a few studies. Regarding nondialysis-CKD patients, limited data are available on the prevalence of constipation [29, 30]. Further studies are required to clarify whether constipation increasingly occurs in proportion with the progression of CKD. The incidence of constipation after the induction of dialysis therapy is another important issue. Previous studies consistently reported that the prevalence of constipation was lower in PD patients than in HD patients [15, 29, 32, 34, 35], even with matching for age, sex, and dialysis duration [35]. A dialysis modality-based lifestyle, higher dietary fiber intake, and smaller amounts of potassium-binding resins and phosphate binders may explain this lower prevalence of constipation in PD patients. In PD, however, clinicians should pay attention to constipation because of its association with peritonitis [37].

Potential factors inducing constipation in CKD

A vast number of factors are vital for normal intestinal motility, such as the nervous system (central, enteric, and autonomic), immune system, endocrine system, bile acid metabolism, mucus secretion, gut microbiota, and products of intestinal fermentation [14]. Disturbances in any of these systems may contribute to the symptoms of constipation. In the setting of CKD, the pathogenesis of constipation is more complex and multifactorial. Discussions on the potential pathogenic link between CKD-related gut dysbiosis and constipation/intestinal dysmotility are of importance.

Gut dysbiosis

Gut dysbiosis, which refers to alterations in the composition and function of the gut microbiota, has been attracting increasing attention due to its association with various diseases, including obesity, atherosclerosis, DM, cancer, and CKD [38]. Dietary components that escape digestion in the small intestine are fermented through metabolism by the gut microbiota. There are two main pathways of fermentation: saccharolytic and proteolytic fermentations. Saccharolytic fermentation is more favorable because of the beneficial metabolites produced, such as short-chain fatty acids (SCFA, acetates, propionates, and butyrates). In proteolytic fermentation, ammonia, amines, and a number of uremic toxin precursors (thiols, phenols, and indoles) are generated. The relationship between CKD and gut

Table 3 Prevalence of constipation in patients with nondialysis-CKD

Authors (Year), country	No. of subjects	Age (year)	Renal function	Definition of constipation (Prevalence [%])
Yasuda et al. (2002), Japan [29]	105	59.1 ± 11.9	Unknown	Meeting 1 and 2, or 3 (59.9) 1. Stool consistency: moderate or severe 2. Straining: always or almost always 3. Bowel movements < 3 times/week
Ramos et al. (2019), Brazil [30]	43	59.0 ± 13.5	eGFR 21.3 ± 7.9 mL/min/1.73m^2	Rome III criteria (34.9) BSFS type 1 and 2 (32.6)

Abbreviations: *BSFS* Bristol Stool Form Scale, *eGFR* estimated glomerular filtration rate

Table 4 Prevalence of constipation in dialysis patients

Authors (Year), country	No. of subjects	Age (year)	Dialysis duration	Definition of constipation (Prevalence [%])
Hammer et al. (1998), Austria [31]	HD, 105	Unknown	Unknown	Straining, hard stool, or bowel movements < 3 times/week (40.0)
Yasuda et al. (2002), Japan [29]	HD, 268; PD, 204	HD, 56.4 ± 11.7 PD, 50.0 ± 13.7	Unknown	Meeting 1 and 2, or 3 (HD, 63.1; PD, 28.9) 1. Stool consistency: moderate or severe 2. Straining: always or almost always 3. Bowel movements < 3 times/week
Wu et al. (2004), Taiwan [15]	HD, 56; PD, 63	HD, 53.1 ± 10.6 PD, 50.3 ± 11.0	Unknown	Laxative use (HD, 35.7; PD, 15.9)
Cano et al. (2007), United Kingdom [32]	HD, 100; PD, 48	Unknown	Unknown	Meeting at least 2 of the following symptoms (HD, 33.0; PD 27.1) 1. Bowel movements < 3 times/week 2. Hard or lumpy stool 3. Straining 4. Feeling of incomplete emptying 5. Sensation that the stool cannot be passed 6. Need of manual maneuvers
Bossola et al (2011), Italy [33]	HD, 110	64.6 ± 14.8	6.5 ± 6.3 years	Self-defined (27.3)
Hatakeyama et al (2013), Japan [27]	HD, 112	60.2 ± 10.8	11.6 ± 6.5 years	Laxative use (27.7)
Zhang et al. (2013), China [34]	HD, 478; PD, 127	HD, 53.0 ± 14.2 PD, 45.2 ± 13.1	HD, 53.4 ± 14.9 months PD, 49.6 ± 10.4 months	Rome III criteria (HD, 71.7; PD, 14.2)
Dong et al. (2014), China [35]	HD, 182; PD, 112	HD, 58.7 ± 14.4 PD, 59.7 ± 14.2	HD, 55.5 ± 38.5 months PD, 48.9 ± 31.0 months	Gastrointestinal Symptom Rating Scale (HD, 36.3; PD, 17.9)
Ramos et al. (2015), Brazil [36]	HD, 290	Unknown	Unknown	Rome III criteria (32.8)
Ikee et al. (2016), Japan [28]	HD, 136	67 ± 12	103 ± 103 months	Laxative use (66.2)

HD hemodialysis, *PD* peritoneal dialysis

dysbiosis is widely recognized and involved in the concept of the gut–kidney axis. In this setting, the contraction of bacterial families possessing SCFA-forming enzymes and the expansion of families possessing urease, uricase, and indole- and p-cresol-forming enzymes occurs, and microbial metabolism consequently shifts to a predominantly proteolytic fermentation pattern due to uremia-related biochemical changes in the gut environment [39]. Gut-derived uremic toxins, such as indoxyl sulfate (IS), p-cresyl sulfate (PCS), and trimethylamine-N-oxide (TMAO), accumulate in the bodies of CKD patients via their increased generation as well as decreased renal excretion. These toxins induce oxidative stress and proinflammatory responses [39, 40]. On the other hand, since butyrates promote the expression of tight junction proteins in the gut epithelium [41], the contraction of SFCA-producing bacteria impairs the integrity of the gut epithelium and results in the translocation of lipopolysaccharides in the circulation. Thus, gut dysbiosis is one of the main causes of chronic inflammation in CKD, which leads to the progression of CVD [40, 42, 43] and CKD itself [40, 42] and strongly influences patient morbidity and mortality [44]. It is notable that gut dysbiosis was observed even in patients with mild CKD with estimated glomerular filtration rate of 76 ± 15 mL/min/1.73 m^2 [45]. In kidney transplantation, the gut microbiota may be associated with graft survival and its composition was altered by transplantation [46].

A recent experimental study by Hoibian et al. suggested a mechanism that links CKD-related gut dysbiosis to constipation [16]. In this study, adenine-induced CKD mice showed a 1.8-fold longer gastrointestinal transit time than the control mice. Resected colons from control mice were then incubated with the plasma of healthy subjects or HD patients. Colons incubated with uremic plasma exhibited a blunted level of contraction from those incubated with healthy plasma. Colons were subsequently incubated with uremic toxins at the concentration encountered in ESKD patients. The incubation with IS or PCS decreased the maximal force of colonic contractions. These findings demonstrated that some uremic toxins impair intestinal motility. Ramos et al. supported this hypothesis by a clinical study including 43 nondiabetic, nondialysis-CKD patients [30]. In this study, constipation defined by BSFS type 1-2 stools was associated with an increased level of serum PCS independently of renal function and dietary fiber intake. Decreased intestinal motility may impact uremic toxin generation by increasing the availability of amino acids to be fermented in the colon [30]. Accumulated uremic toxins, in turn, affect intestinal motility, thereby forming a vicious cycle.

Another pathogenic factor that potentially links CKD-related gut dysbiosis to constipation may be intestinal inflammation. Yu et al. showed that intestinal motility in CKD rats underwent 5/6 nephrectomy was significantly

decreased compared with that in the control rats [17]. The expression levels of interleukin-6, tumor necrosis factor-α, and inducible nitric oxide synthesis were increased in the gut of uremic rats. Using the same animal models, Nishiyama et al. showed that uremia induced gut dysbiosis, intestinal dysmotility, a decreased amount of feces, as well as intestinal inflammation [18]. Of note, antibiotic therapy improved intestinal dysmotility, fecal amounts, and the expression of cytokines. In addition, they reported that in an ex vivo procedure similar to Hoibian's study, an incubation with spermine had a negative impact on intestinal motility, whereas that with IS did not [18]. This discordance may be attributable to the difference in IS concentration and in the incubation time.

Attempts to identify the pathogenic factors linking CKD-related gut dysbiosis to constipation have only just begun. Limited information is currently available on this issue. However, these attempts deserve more attention because they may contribute to the development of novel treatment options for constipation in CKD and additionally lead to the suppression of CKD and CVD.

Lifestyle

Population-based surveys have reported a relationship between decreased physical activity and constipation [1]. Physical activity is lower in dialysis patients than in healthy subjects [47, 48], and markedly lower in older patients [47]. Lower activity was observed even during interdialytic periods [48]. Moreover, Yasuda et al. reported that 78.5% of HD patients suppressed the urge to defecate during HD sessions [29]. Furthermore, many HD patients use laxatives every other day, not every day, to avoid defecation during HD sessions. These findings may partly explain the high prevalence of constipation in HD patients.

Comorbidities

Various comorbidities that induce secondary constipation, such as DM, autonomic neuropathy, and cerebrovascular disease, are common in CKD patients. Although DM is recognized to cause constipation [1], a substantial body of evidence negates this association [49, 50]. Sommers et al. recently reported that the prevalence of constipation defined by BSFS type 1-2 stools was similar between diabetic and nondiabetic subjects in a nationally representative sample of adults in the USA [50]. Of note, impaired kidney function was more frequent in diabetic subjects with constipatoin than in those without constipation. On the other hand, Yamada et al. showed that peripheral neuropathy of the lower extremities correlated with the symptoms of constipation, irrespective of the presence of diabetic nephropathy or retinopathy [51]. In our previous study including 136 HD patients, DM was independently associated with constipation defined by laxative use [28].

Although primary hyperparathyroidism causes constipation [52], to the best of our knowledge, the influence of secondary hyperparathyroidism on constipation has not yet been investigated.

Medications

A large number of medications, such as serotonin (5-hydroxytriptamine [5-HT]) receptor blockers, opioids, anticholinergic agents, anticonvulsants, antihypertensive agents, antidepressants, and chemotherapy agents, may cause constipation [1]. Regarding drug-induced constipation, difficulties are associated with identifying the causal drug in CKD patients who receive many types of medications. Although reducing drugs potentially inducing constipation is essential in the management of constipation, it may be difficult in some patients with multiple severe complications. However, potassium-binding resins and phosphate binders may more frequently induce constipation than other drugs. A previous study reported that the relative risk of constipation was 1.32 in HD patients taking potassium-binding resins relative to those not taking these agents [29]. Among phosphate binders, sevelamer appears to more frequently induce constipation [53]. Sevelamer is known to improve lipid profiles via the adsorption of bile acids [54, 55]. Since bile acids increase propagated colonic contractions and the secretion of water and electrolytes in the colon [56], sevelamer-induced constipation may be partly attributed to bile acid adsorption by the drug itself. Iron-containing phosphate binders, such as sucroferric oxyhydroxide and ferric citrate, may induce diarrhea instead of constipation [57, 58]. It is important to note that iron supplementation may have a favorable or unfavorable influence on the gut microbiota [59–61].

Dietary restrictions

The intake of fiber-rich vegetables and fruits is restricted in order to inhibit hyperkalemia in patients with advanced CKD, particularly in HD patients. The mean value of dietary fiber intake previously reported in HD patients ranged between 5.9 and 16.6 g/day [29, 62–65]. In the general population, some epidemiological studies supported a relationship between low fiber intake and constipation [1]. Soluble fiber may accelerate intestinal transit via hydrophilic properties and the osmotic effects of fermentation by-products. Insoluble fiber accelerates transit by increasing the stool biomass, leading to the direct stimulation of secretion and motility [2]. However, the effects of dietary fiber therapy on constipation have been shown to depend on the category of constipation. According to a clinical study by Voderholzer et al., 85% of patients with normal transit constipation showed the attenuation of symptoms following a dietary fiber treatment, whereas 63% of those with slow transit

constipation did not respond to this therapy [66]. Considering these findings, the relationship between a reduced fiber intake and constipation may not be so sufficient in CKD patients. On the other hand, fiber intake is associated with reduced cardiovascular and cancer mortality [67]. Moreover, the benefits of a plant-based diet for CKD patients have been increasingly reported [68]. Further studies are required to more clearly demonstrate the benefits of dietary fiber as a main source of prebiotics.

Decreased fluid intake has been implicated as a cause of constipation in dialysis patients. However, we previously reported no significant differences in interdialytic weight gain between patients with and without constipation [28]. Wu et al. showed that interdialytic weight gain correlated with a longer colonic transit time [15]. It may be conceived that greater fluid intake may soften stools or enhance lubrication in the alimentary tract, but mucin is far more effective for lubrication. Decreased mucin secretion and the lower viscosity of gastric secretions have been reported in non-CKD patients with constipation, which may delay colon transit due to diminished lubrication [69]. It is important to note that the decreased secretion of mucin has also been observed in CKD rats, and this was increased by the administration of butyrates [70].

Oxidative stress

Oxidative stress has been suggested to play a role in colonic motor dysfunction in DM [71, 72]. DM represents a state of oxidative stress as a result of the hyperglycemia-induced generation of reactive oxygen species. Using specimens obtained by intestinal biopsy and colectomy from diabetic subjects, Chandrasekharan et al. demonstrated the loss of enteric neurons induced by increased oxidative stress [71]. As described above, gut-derived uremic toxins have the potential to activate oxidative stress [39, 40], which may lead to decreased intestinal motility.

Hyperhomocysteinemia

Homocysteine is an intermediate in methionine metabolism, and its plasma level increases in ESKD patients. Hyperhomocysteinemia has been suggested to contribute to the increased risk of CVD in this population [73]. In an experimental study by Givvimani et al., cystathionine β-synthase heterozygous knockout mice, well-known models of hyperhomocysteinemia, showed decreased intestinal motility [74]. Consistent with this finding, we reported that the increased plasma level of total homocysteine in HD patients was independently associated with constipation after adjustments for age, sex, and DM [28].

Possible interventions for constipation in CKD

Constipation in CKD is challenging to treat successfully due to its multifactorial nature. Therefore, every possible approach to ameliorate constipation needs to be considered. The expected goals of the following interventions may include: regular bowel movement, improvement of stool continence and incomplete evacuation, amelioration of gut microbiota composition, and decreased synthesis of harmful uremic toxins.

Probiotics, prebiotics, and synbiotics

Since gut dysbiosis is suggested to be associated with constipation, agents favorably affecting the growth or activity of beneficial microbiota may be a promising option for the treatment of constipation. Probiotics are live microorganisms that confer health benefits on the host. Prebiotics are indigestible food ingredients that include dietary fiber, oligosaccharides, polysaccharides, and resistant starches. Synbiotics refer to a combination of probiotics and prebiotics. A meta-analysis by Dimidi et al. revealed that probiotics reduced the whole-gut transit time in non-CKD patients by 12 hours and increased stool frequency by 1.3 times/week [75]. Similarly, prebiotics and synbiotics improved stool frequency and consistency [76]. On the other hand, limited information is currently available on their effects on bowel habits in CKD patients. Nakabayashi et al. reported that a synbiotic treatment for 2 weeks significantly increased stool quantities in HD patients [77]. Furthermore, hard stools appeared to soften. In nondialysis-CKD patients, fiber supplementation significantly increased stool frequency from 1.4 ± 0.2 to 1.9 ± 0.3 times/day [78]. In both studies, bowel habits were estimated as a secondary outcome. Further studies are required to examine the effects of these agents on stool frequency, stool consistency, and intestinal motility in CKD patients.

The effects of these agents on the composition of the gut microbiota and gut-derived uremic toxins have been increasingly reported. Based on a meta-analysis by McFarlane et al. [79], Mafra et al. did not recommend probiotics as a sole intervention, but suggested an increased intake of foods with a high content of prebiotics in CKD patients [38]. Further studies are required to establish a more effective, sophisticated prescription of these agents.

Laxatives

Osmotic laxatives are widely used in CKD, but their effect may be insufficient as a sole therapy in a substantial proportion of patients, particularly in ESKD patients. In these patients, Mg-containing laxatives may induce hazardous hypermagnesemia [80, 81]. Bulk-forming laxatives and polyethylene glycol have to be taken with a relatively large amount of water. Therefore, they are

mainly treated with stimulant laxatives. This class of laxative stimulates peristalsis by directly irritating the smooth muscle of the colon and also increases fluid secretion. Progressive increases in the doses of these agents may be attributable to hypo-functioning in the bowel process, the loss of intrinsic innervation action, and laxative tolerance effects [82]. On the other hand, controversy exists regarding the tolerance effects and structural or functional alterations of the colon induced by stimulant laxatives [83, 84]. It currently remains unclear whether the long-term use of stimulant laxatives is safe and reasonable. The American Gastroenterological Association mentioned that stimulant laxatives may be used as "rescue" agents in cases resistant to osmotic laxatives [1].

As a novel class of laxatives, intestinal secretagogues, such as lubiprostone, linaclotide, elobixibat, and tenapanor, recently exhibit efficacy against chronic constipation [85, 86]. Lubiprostone is a chloride channel activator that increases water secretion into the intestinal lumen and enhances colonic transit. In HD patients, lubiprostone was reported to increase stool frequency significantly from 1.8 ± 1.3 to 4.5 ± 1.5 times/week [87]. It is notable that this agent increased gastric and intestinal mucin secretion [88, 89], potentially leading to lubrication of the alimentary tract [69, 89]. In an experimental study using adenine-induced CKD mice, lubiprostone improved the composition of the gut microbiota and decreased plasma IS levels [90]. Additionally, lubiprostone exerted favorable effects on the gut epithelial barrier [91, 92]. Thus, lubiprostone may ameliorate not only constipation but also gut dysbiosis and epithelial barrier disruption in CKD patients. Elobixibat is an ileal bile acid transporter inhibitor that blocks bile acid absorption in the ileum and increases the delivery of bile acids into the colon. As described above, bile acids cause fluid secretion and enhance colonic motor activity [56]. Gen et al. reported a decrease in serum phosphate after lubiprostone therapy [87]. Accelerated intestinal transit may reduce phosphate absorption in the small intestine. Tenapanor, an inhibitor of sodium/hydrogen exchanger 3, reduces the absorption of sodium and phosphate in the intestine. This agent may be preferred due to its phosphate-lowering effects.

Mineral oil acts as a lubricant and stool-softening laxative. Ramos et al. examined the effects of olive oil and flaxseed oil in HD patients with constipation and reported increased stool frequency and better consistency [36]. The effects and tolerability of oil administration warrant further study.

Serotonin type 4 receptor agonists

Serotonin type 4 (5-HT_4) receptor agonists stimulate peristalsis and accelerate gastrointestinal transit. Shin et al. reviewed 13 randomized controlled trials on highly selective 5-HT_4 receptor agonists in adults with chronic constipation and concluded that these drugs improved stool frequency and other symptoms of constipation, generally with minor neurological/psychiatric adverse events [93]. However, the efficacy of these drugs has not yet been reported in CKD/ESKD patients. Since CKD-related constipation is often refractory, 5-HT_4 receptor agonists may be used not as a sole therapy but as an additive therapy to other drugs.

Lifestyle-based therapy

In a recent meta-analysis, Gao et al. suggested that exercise, such as walking, may be a feasible and effective strategy to ameliorate constipation-related symptoms and quality of life in the non-CKD population [94]. To the best of our knowledge, it currently remains unknown whether exercise interventions have a similar effect in CKD/ESKD patients. However, exercise therapy was recently suggested to improve physical function [95, 96] and other symptoms, including restless legs syndrome [97], in dialysis patients. Even if the effects of exercise on constipation are not sufficient, habitual exercise is associated with other beneficial effects.

Modulation of the defecation posture may be another option for constipation. During defecation, the squatting position facilitates rectal emptying by anorectal angle straightening, resulting in higher rectal pressure and lower anal pressure with relaxation of the levator ani [98]. Sikirov reported that the squatting position led to quicker evacuation and a more complete sense of bowel emptying than the sitting position [99]. However, most populations in developed countries have become accustomed to sitting on toilet seat. This custom may induce suboptimal bowel habits, particularly in older individuals with reduced straining and pelvic floor weakness. Modi et al. reported that the use of a footstool (defecation posture modification device) provided similar benefits to squatting [98].

These options may be adjunctive approaches at best for CKD patients with constipation, but may be performed safely and inexpensively.

Conclusions

Constipation is often intractable because its pathogenesis is multifactorial, particularly in CKD patients. Accumulating evidence has underlined the potential involvement of CKD-related gut dysbiosis in this complication. Pharmacological, dietary, and lifestyle-based approaches are applicable for its treatment, but their effects have not been fully investigated to date. In addition, appropriate management of constipation may be different according to CKD stage or modality of renal replacement therapy. As described above, CKD-related gut dysbiosis, uremic toxin accumulation, and intestinal dysmotility

worsen in a vicious cycle manner. Treatment of gut dysbiosis in early stages of CKD may be desirable to inhibit their intractable aggravation. Further studies are required on this issue.

Elucidation of the relationship between CKD-related gut dysbiosis and constipation may contribute to the development of novel treatment options for constipation, which may also exert favorable effects on CKD and CVD.

Abbreviations

BSFS: Bristol Stool Form Scale; CKD: Chronic kidney disease; CVD: Cardiovascular disease; DM: Diabetes mellitus; ESKD: End-stage kidney disease; HD: Hemodialysis; IBS-C: Irritable bowel syndrome with predominant constipation; IS: Indoxyl sulfate; PCS: p-Cresyl sulfate; PD: Peritoneal dialysis; SCFA: Short-chain fatty acid; TMAO: Trimethylamine-N-oxide; 5-HT: 5-Hydroxytryptamine

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RI, KY, and TT contributed to the research idea and study design. RI wrote the whole manuscript, and KY and TT read and advised about the content of the manuscript of the final version. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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