kidney and dialysis

Review

Constipation in Chronic Kidney Disease: It Is Time to Bridge the Gap

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Abstract: In this narrative review, we briefly describe the general features of constipation, our understanding of its physiopathology, and its diagnosis and treatment, focusing on chronic kidney disease (CKD). Considering that constipation is poorly characterized in CKD, we referred to studies that used the Rome criteria to diagnose constipation in patients to describe a more realistic prevalence based on a standardized tool. A highly variable prevalence of the condition was reported, ranging from 4.5% to 71.7%. The main risk factors associated with constipation reported in these studies were advanced age, low fruit intake, presence of diabetes, and medication use, and the main consequence of constipation in CKD was a worse quality of life. We found a paucity of interventional studies for constipation treatment in CKD; however, in the general population, meta-analyses published in the last decade have reported the beneficial effects of non-pharmacological strategies, which may guide the management of constipated patients with CKD. These strategies include the consumption of fiber, prebiotics, and probiotics, as well as physical exercise and acupuncture. In conclusion, although constipation is a frequent complaint among patients with CKD, there remains a considerable knowledge gap regarding its epidemiology, prognosis, and treatment.

Keywords: constipation; chronic kidney disease; dialysis; gut; bowel habit

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1. Introduction

Constipation is a highly prevalent disorder in all stages of chronic kidney disease (CKD) [1]. Although this condition has a negative impact on a patient's quality of life, [2,3] it is considered a non-life-threatening complaint, and individuals and healthcare providers often do not treat it as a serious clinical condition in patients with CKD. A lack of interest in this area is also manifested in the scientific literature. Studies investigating the characteristics, prevalence using validated tools, and outcomes related to constipation in CKD are scarce [2–7]. Moreover, few studies have investigated non-pharmacological strategies [8–11], including the diet, to treat this disorder in patients with reduced renal function or in those on dialysis therapy. Non-pharmacological strategies are considered the first-line treatment for constipation due to their low cost and fewer side effects compared to laxative drugs [12]: however, there are some concerns regarding their application in CKD [13]. Clinical trials in this context are urgently required.

Understanding the pathophysiological mechanisms of constipation and identifying strategies that have been employed for its treatment in the general population can help health professionals in the field of CKD to define safer and more effective strategies for the management of this problem. In this narrative review, we briefly describe the general features of constipation, including the physiology of defecation, the physiopathology of constipation, and its diagnosis. In addition, the prevalence and associated factors of constipation in patients with CKD are reviewed, along with non-pharmacological interventions to treat this condition.

2. Physiology of Defecation

The large intestine is the distal part of the gastrointestinal tract in humans. It comprises the cecum, colon (ascending, transverse, descending, and sigmoid), rectum, and anus. Cross-sectionally, the large intestinal wall consists of four main layers. The innermost layer is the mucosa, which is composed of a monolayer of epithelial tissue, lamina propria, and a thin portion of smooth muscle. This is followed by the submucosa, which accommodates nerves (including the Meissner's plexus that regulates secretory functions) and blood vessels. The muscular layer surrounds the submucosa and is composed of smooth muscle cells arranged in two regions: an inner circular and an outer longitudinal region. This layer is responsible for mixing and propelling the luminal contents throughout the bowel. Between these muscle layers, the myenteric plexus (also called the Auerbach's plexus) regulates intestinal muscle function. The outermost part, composed of connective tissue, is called the serosa [14].

The large intestine has several functions. It harbors the largest number and diversity of intestinal tract microbes, protects the body against pathogenic infections and toxins, and interacts with the microbiome to promote health. By absorbing water and electrolytes from digestion, the vitamins and metabolites produced by microbial metabolism contribute to nutrition. During the course of these processes, the composition of the chyme is modified along the large intestine, producing feces that are stored in the rectum until they are eliminated [15].

The passage of luminal contents along the large intestine occurs mainly due to two movements resulting from contractions in the muscle layer containing the myenteric plexus (Auerbach's plexus) of the enteric nervous system. The first movement is the haustral contraction, a segmental, weak, and random movement that mixes the chyme to facilitate absorption in the ascending colon. When sequential and unison haustral movements occur, the luminal contents are propelled into distal areas. Propagative waves are found with low or high amplitude; the latter is less frequent and characterizes mass movement, which is stronger and promotes the movement of the chyme to the rectum [15]. The characteristics of the propagative waves are determined by the pressure of intraluminal content against the intestinal wall (mechanical) and the luminal content (chemical) composition, among other stimuli [16]. A circadian rhythm of propagative waves is observed, which occurs mainly upon awakening and after meals; at night, the colon is relaxed [17].

Defecation is an integrative process that involves peristaltic activity and the anorectal region. Approximately one hour before evacuation, an increase in propulsive waves, starting at the proximal colon and propagating distally, is observed [16]. At the time of defecation, a later propagative movement with a greater amplitude occurs. When the stool reaches the rectum, its distention relaxes the internal anal sphincter while stimulating the rectal-vault wall stretch receptor, resulting in the urge to defecate. If the moment is convenient, voluntary relaxation of the external anal sphincter can be permitted to complete evacuation. The defecation reflex triggers highly propulsive contractions in the descending and sigmoid colon. Rectal contraction increases intra-abdominal pressure, which is intensified by voluntary contraction of the abdominal muscles and the diaphragm. The pelvic floor descends, and the puborectalis muscle and external anal sphincter relax, decreasing the resistance to the passage of the fecal mass. During defecation, the squatting position aligns the rectum, where the feces are stored, with the anal canal, creating the appropriate angle for the elimination of stools. These orchestrated actions culminate in the elimination of stools. However, if evacuation is suppressed, retrograde passage of stools back to the rectum occurs, with a subsequent decrease in proximally propagating peristaltic waves. The rectum temporarily accommodates the stool, the sphincter stimulus is dissipated, and spreading contractions are released [18].

3. Constipation: Physiopathology and Diagnose

Constipation is a common gastrointestinal disorder that affects many people worldwide [19]. In the clinical setting, this disturbance is usually associated with infrequent bowel movements. However, affected individuals have reported diverse symptoms, indicating the importance of expanding the assessment to other constipation-related symptoms. Some of these symptoms were incorporated into the Rome criteria (currently in the fourth version): straining during defecation, presence of hard stools, sensation of incomplete evacuation and/or anorectal obstruction, use of manual maneuvers to facilitate defecation, and lower frequency of evacuation (<3 per week) [20]. The Rome criteria have been recommended as a standard diagnostic tool, although many other questionnaires exist [12]. Understanding the plethora of symptoms can guide strategies for preventing and treating constipation.

Constipation can be either primary (or functional) or secondary to some diseases or medications. However, these two types may overlap, which makes it difficult to distinguish between them. Furthermore, three main manifestations have been reported: normal transit constipation, slow transit constipation, and defecatory disorders; different defecatory disorders may also coexist [19].

Normal transit constipation is characterized by abdominal or defecatory discomfort despite an adequate colonic transit time [19]. The basis for slow transit constipation is abnormal colonic motility due to a decreased frequency of high amplitude propagative waves (colonic inertia) and/or uncoordinated motor activity in the distal colon, which promotes resistance (barrier or blockage) to colonic flow. A reduction in intrinsic colonic nerves and/or interstitial Cajal cells, the pacemakers of colonic motility, has been found in slow-transit constipation [19]. The longer the intestinal transit time, the greater is the absorption of water in the colon, making stools harder. Therefore, stool consistency is associated with intestinal transit time, which can be evaluated using the Bristol Stool Scale (BSS) in clinical practice. The BSS graphically describes stools, categorizing them into seven types according to their consistency and form: 1, nut-like; 2, lumpy sausage; 3, sausage with cracks; 4, smooth snake (adequate form); 5, soft blobs; 6, fluffy pieces; and 7, watery [21].

Finally, defecatory disorders include pelvic floor dysfunction and discoordination between the abdominal wall, rectum, anal sphincters, and pelvic floor muscles. It can result from muscular hypertonicity (incomplete relaxation or paradoxical contraction of the pelvic floor and external anal sphincters) or muscular hypotonicity (excessive pelvic floor descent). Although poorly characterized, this manifestation seems to be related to the sensation of incomplete evacuation or obstruction, excessive straining, and manual maneuvers to complete evacuation. It is usually refractory to conventional treatments even after pharmacological treatment [19]. Differential diagnosis is based on clinical features (e.g., digital rectal examination) and anorectal tests such as balloon expulsion, manometry, and defecography.

Given the complexity of etiologic factors, a detailed anamnesis, including clinical history, metabolic disorders, and laxative use, is essential for tailoring constipation treatment [12].

4. Constipation and CKD

Constipation has been reported to affect more patients with CKD than the general population [1]. In a recent review of 19 studies, the prevalence of constipation in patients with CKD/ESKD ranged from 1.6 to 90.3%. The wide variability is likely due to differences in the tools and criteria used to diagnose the problem; only four of these studies used the Rome criteria [1]. In order to overcome, at least in part, such variability and to have a more accurate determination of the prevalence of constipation in the CKD population, in the present review, we reported only studies that assessed functional constipation prevalence using the Rome criteria (Table 1). Even with the standardization of the diagnostic tool, the prevalence of constipation in the ten included studies was still highly variable: 4.5 to 38% in non-dialysis-dependent chronic kidney disease (NDD-CKD) [3–5,7,22], 13.5 to 71.7% in hemodialysis (HD) [2,4,6,10,11,23], and 14.2% to 52% in peritoneal dialysis (PD) [2,4,6,24] (Table 1). Notably, the most frequent symptoms according to the Rome criteria reported by patients with CKD were sensation of incomplete evacuation, sensation of anorectal obstruction, and lumpy or hard stools [7,11,24]. This finding reinforces the importance of a more detailed investigation of constipation symptoms and is not limited to the presence of a low frequency of evacuation.

Table 1. Reported prevalence of constipation according to Rome criteria and risk factors in patients with CKD/ESKD across studies.

Reference	Characteristics	Functional Constipation Prevalence (%)	Factors Associated with Functional Constipation
NDD-CKD			
Lee, et al., 2016 [4]	*n* = 21 Male: 48% Age: 62.2 ± 13.5 eGFR: NR	4.5	NA
Ramos et al., 2019 [22]	*n* = 50 Male: 54% Age: 57.6 ± 12.3 eGFR: 21.4 ± 7.6	38	NA
Ruszkowski et al., 2020 [3]	*n* = 111 Male: 62% Age: 68 (55–74) eGFR: 38 (30–48)	19	Lower glomerular filtration rate Use of paracetamol Use of NSAIDs Lower body pain score Lower vitality score
Ramos et al., 2020 [7]	*n* = 43 Male: 58% Age: 59.0 ± 13.5 eGFR: 21.3 ± 7.9	35	Tendency for a higher total p-cresyl sulfate and a significantly higher urinary p-cresyl sulfate.
Ruszkowski et al., 2021 [5]	*n* = 100 Male: 56% Age: 68 (55.8–74) eGFR: 38 (30–47)	19	Worse sleep quality Lower glomerular filtration rate
HD			
Cano et al., 2007 [6]	*n* = 100 Male: 52% Age: 21 to 86	33	NA
Zhang et al., 2013 [2]	*n* = 478 Male: 54% Age: 53.0 ± 14.2	71.7	Higher age Diabetes Lower quality of life
Ramos et al., 2015 [11]	*n* = 290	32.8	NA
Lee, et al., 2016 [4]	*n* = 98 Male: 60% Age: 66.6 ± 13.6	13.5	NA
dos Santos, et al., 2021 [23]	*n* = 305 Male: 51% Age: 52.2 ± 14.7	30.5	Lower frequency of fruit intake Diabetes
Schincaglia et al., 2021 [10]	*n* = 35 Male: 57% Age: 49.9 ± 12.4	37.1	NA
PD			
Cano et al., 2007 [6]	*n* = 48Male: 65%Age: 19 to 87	27.1	NA
Zhang et al., 2013 [2]	*n* = 127 Male: 54% Age: 45.2 ± 13.1	14.2	Higher age Diabetes Lower quality of life
Lee, et al., 2016 [4]	*n* = 21 Male: 62% Age: 69.1 ± 15.6	14.3	NA
Pereira et al., 2020 [24]	*n* = 58 Male: 50% Age: 52.5 ± 15.1	52	A trend for higher and total and free p-cresyl sulfate

NDD-CKD: non-dialysis-dependent chronic kidney disease; eGFR: estimated glomerular filtration rate; HD: hemodialysis; PD: peritoneal dialysis. NA: not applicable.

The high prevalence of constipation in CKD has been associated with exposure to multiple risk factors, such as dietary fiber and fluid restriction, sedentary lifestyle, comorbidities (e.g., diabetes mellitus), medications (e.g., phosphate binders and iron supplements), and metabolic disorders (e.g., hypercalcemia). As seen in Table 1, the risk factors for constipation found in the studies were older age [2], lower frequency of fruit intake [23], diabetes [2,23], and medications [3].

The main adverse effects of constipation in CKD found in the present review were similar to those observed in the general population, particularly with respect to several aspects of the quality of life [2,3,5]. In CKD patients not on dialysis, the disturbance was further associated with lower renal function [5] and with a tendency for increased gut-derived uremic toxin p-cresyl sulfate (PCS) [7], a finding also seen among patients on peritoneal dialysis [24]. This and other gut-derived toxins have been associated with inflammation and renal fibrosis, indicating a relationship with CKD progression [1].

Therefore, the management of constipation can minimize the additional effects that this condition exerts in patients with CKD and on their quality of life.

5. General Management of Constipation

Because constipation is common and not considered a serious complaint, it is often neglected by individuals and healthcare providers. As a result, people with constipation usually do not seek careful clinical evaluation of the problem and are self-treated with random laxatives. This reality highlights the importance of education in the management of constipation.

There is a consensus that lifestyle and non-pharmacological interventions are first-line therapies for constipation [12]. The most traditional strategies include increasing physical exercise, dietary approaches (especially fiber sources or bulking agents, herbal medicines, and fluids), and toilet habits. Interestingly, some of these strategies have been employed across generations without scientific tests, while researchers have explored only a few of them and much rarely in the context of CKD. Importantly, the underlying potential causes or factors that may contribute to constipation, such as hypothyroidism and hypercalcemia, should be considered.

Laxatives are reserved for patients who do not respond to first-line approaches [12]. There are many classes of laxatives that can be used alone or in combination, and all of them can potentially cause adverse events, particularly with reduced kidney function [12]. It has been suggested that laxatives with a more potent physiological action should be prioritized. Saline (e.g., magnesium hydroxide, sodium phosphate) and osmotic agents (e.g., lactulose and polyethylene glycol) exert a hydrophilic effect, whereas stool softeners (e.g., sodium docusate) decrease fecal surface tension, facilitating the incorporation of water and fats into the stool; all of these laxatives smooth the consistency of stools and can exert a mechanical stimulus for propulsive movements. Adverse events include bloating, cramping, and electrolyte disturbances from magnesium, potassium, sodium, and phosphate, which may be common in CKD. Lubricants (e.g., mineral oil and glycerin), in addition to facilitating the passage of stools, also impair the absorption of water in the colon and improve stool consistency. These agents are not recommended for the elderly because of the risk of aspiration and lipid pneumonitis. The last class includes stimulate/irritative laxatives (e.g., senna, cascara, and bisacodyl). As the name suggests, these laxatives stimulate the myenteric plexus or irritate the intestinal smooth muscle, thereby increasing water and electrolyte secretion into the lumen. There are concerns regarding the long-term use of these agents, particularly anthraquinone derivatives (senna and cascara), due to the risk of neuronal or muscular injury and pseudomelanosis coli, which has been associated with colorectal cancer in experimental models. Novel classes of laxatives as well as the use of prokinetics have been studied in the treatment of constipation [25].

Recently, the gut microbiota has gained interest in the context of gastrointestinal disorders including constipation. Although findings are still inconsistent and no general consensus exists, it seems that the main characteristics of gut microbiota in individuals with constipation are a relative decrease in beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, a relative increase in potential pathogens, and a reduced species richness [26], indicating gut dysbiosis. Consequently, structural changes in the gut microbiota may contribute to dysfunction. Therefore, targeted treatment for dysbiosis of constipation by prebiotics, probiotics, and synbiotics may constitute an additional option.

In addition to the most traditional approaches, some Asian cultures have used acupuncture and other practices to treat gastrointestinal disorders for decades; studies on this topic are currently available in the scientific literature. Table 2 shows the characteristics and main results of systematic reviews with meta-analysis published in the last ten years (2012–2021) that aimed to evaluate general functional constipation treatment with non-pharmacological strategies. The results indicated that such interventions had advantages over placebo or conventional treatment. However, these results were based on a small number of studies and participants. Therefore, these results should be cautiously interpreted.

Table 2. Characteristics and findings of meta-analysis that evaluated the effect of some non-pharmacological strategies in functional constipation treatment in the last decade (2012–2021).

Reference	Objective	Study Selection Criteria	N Studies; N Participants	Main Findings
Dietary interventions				
Yang, et al., 2012 [27]	Effect of dietary fiber intake on constipation by a meta-analysis of RCTs	(1) Investigations intake of dietary fiber and constipation; (2) RCTs with a trial quality ≥3 points by Jadad score; (3) Constipation defined by symptoms according to the Roma criteria or clinical diagnosis; (4) At least one of the following data: stool frequency, stool consistency, treatment success, laxative use, gastrointestinal symptom; (5) Dietary fiber as the only active intervention in treatment group.	5; 195	Dietary fiber showed significant advantage over placebo in number of stools per week (mean difference = 1.19; 95% CI: 0.58–1.80, $p < 0.05$). There was no significant difference in stool consistency, treatment success, laxative use, and painful defecation.
Dimidi et al., 2014 [28]	Effect of probiotics on gut transit time, stool output, and constipation symptoms in adults with functional constipation via RCTs	(1) Adult populations with functional chronic constipation defined by clinical symptoms, a 'physician's opinion', or the Rome I, II, or III criteria; (2) Any species/strains/dose/treatment regimen of live probiotics with placebo control; (3) Reports of the clinical outcomes of stool frequency, stool consistency, stool weight, gut transit time, other gastrointestinal symptoms.	14; 1182	Probiotics may improve whole gut transit time, stool frequency, and stool consistency, with subgroup analysis indicating beneficial effects of *B. lactis* in particular.
Yu et al., 2017 [29]	Effects of prebiotics and synbiotics on adults with functional constipation	(1) RCTs; (2) Adults; (3) FC defined by symptoms according to Rome I, II or III criteria; (4) Compared prebiotics or synbiotics with placebo; (5) Reported one or more of the following: stool frequency, stool consistency, transit time, other constipation-related symptoms, global assessments of constipation severity or satisfactory relief of constipation	5; 199	Galacto-oligosaccharides improves stool frequency, consistency, ease of defecation, and abdominal pain. Synbiotics combinations of fructo-oligosaccharide with probiotics improve stool frequency, consistency, straining defecation, global constipation severity scores, and satisfactory relief of constipation.
Miller et al., 2017 [30]	Effects of probiotic-containing products on stool frequency and intestinal transit time (ITT) in constipated adults	(1) RCTs of probiotic-containing supplements; (2) Primary diagnosis of functional constipation (by self-report, physician opinion, or symptom-based diagnostic criteria) and/or mean stool frequency less than 3 times per week in the absence of organic disease; (3) Non-institutionalized adults with no obvious secondary cause of symptoms; (4) Measures of stool frequency and/or ITT over a minimum 7-day supplementation period.	21; 2656	Supplementation with products containing *Lactobacillus* or *Bifidobacterium* species increases stool frequency and reduces intestinal transit time in constipated adults.

Table 2. *Cont.*

Reference	Objective	Study Selection Criteria	N Studies; N Participants	Main Findings
Zhang et al., 2020 [31]	Effectiveness of probiotics on constipation symptoms in adults with functional constipation via RCTs	(1) RCTs with parallel or cross-over design; (2) Adults; (3) Random allocation of the study participants to probiotic or control; (4) Sufficient information regarding of constipation indicators (transit time, stool frequency, stool consistency, and bloating) in both groups; (5) Probiotics administered in the form of any formulation or dairy product.	15; 1373	Consumption of probiotics, in particular, multispecies probiotics, may substantially reduce the transit time, increase the stool frequency, and improve the stool consistency.
Tan et al., 2020 [32]	Efficacy and safety of herbal medicines (HMs) in the treatment for functional gastrointestinal disorders.	(1) Double- blind RCTs (2) Diagnosis of functional gastrointestinal disorders according to the Rome I-IV criteria or clear description. (3) One of the following comparisons: herbal medicine (HM) alone vs. placebo, HM alone vs. routine western medicine (WM), or HM with WM vs. placebo with WM, which was applied in both groups. (4) For outcome measures, criteria for successful treatment-effective rate (symptom improvement or symptom-free rate; when both of them were reported, symptom-free rate was chosen in the analyses) were clearly stated.	Total: 49; 7396 (constipation: 6; 792)	HMs were better than placebo in alleviating symptoms for constipation (RR = 3.83, 95% CI 2.26–6.50).
Other interventions				
Zhou et al., 2017 [33]	Effectiveness of electroacupuncture (EA) relative to conventional medication in functional constipation (FC)	(1) RCTs; (2) Adult patients diagnosed with FC according to the Rome II/III criteria or the American Gastroenterological Association guideline for chronic FC; (3) Have randomized patients to be treated with EA or anti-constipation medication.	9; not informed	EA was more effective than medication at improving spontaneous bowel movements and total response rate and reducing the symptoms of FC.
Gao et al., 2019 [34]	Effects of exercise on constipation	(1) RCTs; (2) Adults, diagnosed with non-drug or other disease-induced constipation; (3) Participants were able to exercise without assistance; (4) Time and type of exercise interventions were described in detail.	9; 680	Results suggest that exercise, especially aerobic exercise, may be a viable and effective treatment for patients with constipation.
Yaki et al., 2020 [35]	Effect of foot reflexology on functional constipation.	(1) RCTs and quasi-randomized trials. (2) Participants diagnosed with FC. (3) Patients allocated to the experimental group received foot reflexology; the control group did not receive it. (4) The procedure of reflexology was clearly described. (5) Control group received the same regular or routine care as the experimental group. (6) Outcomes: stool number, intensity, bowel movement, symptoms of constipation, and curative rate.	5; 375	Reflexology significantly increased the curative ratio, with a pooled risk ratio of 1.27 (95% CI: 1.16, 1.40, $p < 0.00001$)

RCT: randomized controlled trial; CI: confidence interval; FC, functional constipation.

When evaluating the impact of interventions, it is important to mention that the increase in the frequency of bowel movements does not necessarily reflect an improvement in bowel habits; it should be accompanied by an increase in stool output and softer stools [36]. Attention should also be given to patients with paroxysmal diarrhea. In cases of constipation with fecal impaction, the high intestinal content stimulates the production of mucus, which, combined with prolonged distension of the rectum and relaxation of the internal anal sphincter, may generate pseudo-diarrheas [37].

If constipation is refractory to this sequence of strategies, differential diagnosis of defecatory disorders should be considered [12].

6. Constipation in CKD: Focusing on Non-Pharmacological Strategies

Non-pharmacological strategies to treat constipation in the CKD population have been poorly explored. Our literature search found four food-based interventions for constipation treatment in people with ESKD and none in those with NDD-CKD (Table 3). The first study was published in 2014 and included 41 PD patients with regular laxative use [9]. In this 4-week open randomized trial, patients were assigned to three intervention arms: high-fiber supplement (HFS), high-fiber diet (HFD), or placebo. Subjects in the HFS group were asked to increase their dietary fiber supplement in 2 g increments per day up to the recommended dose of 12 g. Similarly, the HDF group was advised to gradually increase their fiber intake by 2–4 g per day until it reached an additional 12 g of fiber per day. The authors reported that the group advised to increase dietary fiber via food was not able to change it during the study. A laxative dose decrease was observed in both groups, the HFS (38%) and HFD (16%) groups. However, these changes were not significant when compared to the placebo group.

Table 3. Food-based interventions for constipation treatment in CKD/ESKD populations.

Reference	Population	Study Design	Intervention	Findings
Sutton et al., 2014 [9]	41 PD with regular laxative	4-week, open, randomized	Three intervention arms: high fiber supplement (HFS); high fiber diet (HFD) or placebo.	Laxative dose decrease in the HFS group (38%) and the HFD group (16%), but these changes were not significant when compared to the placebo.
Ramos et al., 2015 [11]	50 HD with constipation	4-week, double-blind, randomized	4 mL/day: mineral oil or olive oil or flaxseed oil (dose could be increased).	At the end of follow-up, 59%, 63% and 55% of the patients of the mineral oil, olive oil, and flaxseed oil groups, respectively, were no longer classified as constipated.
Lambert et al., 2020 [8]	20 HD	Non-randomized 10-week repeated-measures, within-subject, pragmatic clinical trial	40 g of raw almonds daily for 4 weeks, followed by a 2-week washout and 4-week control period.	Significant reduction of: reported constipation; Palliative Care Outcome Scale renal score for constipation; Laxative use.
Schincaglia et al., 2021 [10]	35 HD	12-week single-blind clinical trial	10 capsules per day of 500 mg each of mineral oil or Baru almond oil.	Baru almond oil group reduced Rome IV score and the straining on the evacuation score.

CKD: chronic kidney disease; ESKD: end-stage kidney disease; PD: peritoneal dialysis; HD: hemodialysis.

In 2015, Ramos et al. [11] conducted the only double-blind, randomized trial that included HD patients solely with a constipation diagnosis by the Rome III criteria. They compared the effect of mineral oil, olive oil, and flaxseed oil on constipation. After a 4-week intervention, 59%, 63%, and 55% of the patients in the mineral oil, olive oil, and flaxseed oil groups, respectively, were no longer classified as constipated.

Later, in 2020, Lambert et al. [8] tested the effect of the consumption of 40 g of raw almonds daily for four weeks, followed by a 2-week washout and 4-week control period in 20 HD patients. In this non-randomized trial, the authors observed a significant reduction in laxative use and constipation after ten weeks. Although almonds are considered to have high potassium and phosphorus contents (40 g of almonds contain 274 mg potassium and 182 mg phosphorus) [38], no significant changes in laboratory parameters were observed after the intervention.

Finally, in 2021, Schincaglia et al. [10] compared in a 12-week single-blind clinical trial the effect of mineral oil or Baru almond oil in 35 HD participants. Baru almond oil group reduced the Rome IV score and straining on the evacuation score while the mineral group did not show any change in these parameters.

The present review reveals that the classical strategies in the treatment of constipation, such as increasing the level of physical activity and fiber and fluid intake, are poorly explored in CKD. There are some concerns about applying these strategies in this specific population; however, studies that did not focus on constipation have shown the circumstances in which they might be considered.

Patients with CKD, particularly those undergoing dialysis, usually exhibit lower levels of physical activity and functionality [39]. Incorporating aerobic exercise into these patients improves many health-related outcomes, including quality of life [40]. Although there is a lack of studies on exercise and constipation in CKD, the improvement in constipation symptoms by aerobic exercises in the general population was reinforced in a recent systematic review that included a meta-analysis of randomized controlled trials [34]. The underlying mechanisms are not entirely understood, but biomechanical bouncing and compression of the gutby abdominal muscles during exercise appear to stimulate colonic motility.

In general, patients with CKD have a low fiber intake, primarily because of the high content of potassium and phosphate in natural fiber sources [41]. However, recent studies have shown that healthier dietary patterns, including plant-based patterns, are associated with better CKD outcomes [42]. This raises questions regarding the generalization and excess of dietary restriction for the metabolic control of kidney diseases. The relationship between dietary potassium intake, hyperkalemia, and adverse outcomes in CKD remains unclear [43,44]. In addition, the absorption of potassium and phosphate from plant-based and natural foods seems to be lower than that from animal sources or processed foods [45,46]. Thus, the promotion of a diet based on natural foods can help control both hyperkalemia and hyperphosphatemia. From a practical point of view, fruits with lower potassium content offer similar amounts of fiber to those with moderate or high potassium content. In addition, adjustments in the servings of raw vegetables or the use of boiling procedures to remove potassium from vegetables also contribute to promoting more adequate fiber intake in the face of potassium restriction. Although whole grains and beans contain significant amounts of phosphorus; the absorption rate of vegetable-derived phosphorus is low (approximately 40%). When the diet provides an insufficient amount of fiber, supplemental fiber sources should be considered. Table 4 shows the nutritional composition of a typical portion of 10 g of supplemental fiber sources.

Table 4. Dietary fiber, potassium, and phosphate content in 10 g of supplemental fibers' sources.

Food	Fiber (g)	Potassium (mg)	Phosphate (mg)
Wheat bran	4.3	118	101
Oat	1.1	43	52
Oat bran	1.5	57	73
Psyllium husks	7.7	80	NA
Flaxseed	2.8	84	66
Sesame roasted	1.4	47	64
Chia dried	3.3	41	86

United States Department of Agriculture food composition tables [38] NA: not available.

In the context of constipation treatment, a combination of soluble but slowly fermented fibers (e.g., psyllium) and insoluble fibers (e.g., wheat bran) has been suggested for the general population [41]. Since it is not completely fermented by gut microbiota, psyllium maintains its gel-like capacity throughout the colon, softening stools. Insoluble fibers irritate the gut mucosa, which increases the secretion of water into the colon and stimulates peristalsis.

Altogether, it is possible to increase the intake of fibers from fruits, vegetables, whole grains, and supplemental fibers in CKD patients, including HD patients [41]. Nevertheless, these changes should be made gradually, with laboratory tests and bowel habits monitored, and by considering the management of other clinical factors associated with hyperkalemia and hyperphosphatemia. Whenever fluid intake is low and there are no contraindications to increasing it (e.g., overhydration), it should be encouraged.

The gut microbiota is another potential target for the treatment of constipation in CKD. It has been shown that CKD induces some alterations in the intestinal tract, which has been suggested to cause gut dysbiosis [47]. Many interventional studies have been performed to investigate the effects of pre-, pro-, and synbiotics on the gut microbiota of CKD patients and on various clinical outcomes, but few studies have investigated constipation. The beneficial effects of prebiotics and synbiotics on bowel habits have been demonstrated in previous studies of CKD. However, the studies included only a small number of participants [48–50]. Therefore, there is no consensus about the type and dose for biotics supplementation to treat constipation in CKD.

Considering the obstacles in the management of constipation in patients with CKD, special attention should be given to toilet habits because they are easy to implement and free of contraindications. As previously mentioned, squatting during evacuation allows relaxation of the puborectalis muscle and alignment of the rectum, facilitating the passage of stools. This position is adopted in some Asian cultures in which the toilet is attached to the floor. In Western societies, this can be achieved by using a toilet device to elevate the legs as much as possible to simulate leg squatting. This strategy may help with bowel movements, the sensation of bowel emptiness, and lowering the strength and time to defecate [51]. Patients should also be educated about the circadian rhythm of bowel function, not postponing or avoiding defecation, and allowing enough time to complete the evacuation. Poor toilet habits have been shown to decrease the frequency of evacuation, stool weight, and to contribute to worsening constipation [52]. Responding to the call for defecation may be difficult to implement in hemodialysis patients, who need to be connected to the dialysis machine until the procedure is completed. Training on bowel habits, according to the circadian rhythm, may help patients avoid defecation during dialysis.

7. Conclusions and Future Research

Constipation is a highly prevalent problem that negatively affects the quality of life of patients with CKD. However, few studies have explored the various aspects related to constipation in CKD patients. Owing to the lack of evidence in this field, it is not yet possible to establish a clinical protocol to treat constipation in CKD. Based on findings in the general population, whenever possible, non-pharmacological interventions, such as aerobic exercise and adequate fiber and fluid intake, should be employed as first-line treatment. In addition, educating health care professionals and patients about good toilet habits can contribute to positive results. Future studies on constipation epidemiology, prognosis, and treatment are necessary to improve constipation management in CKD patients.

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