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Review

2022 Seoul Consensus on Clinical Practice Guidelines for Functional Constipation

Young Sin Cho,[1] Yoo Jin Lee,[2] Jeong Eun Shin,[3]* Hye-Kyung Jung,[4] Seon-Young Park,[5] Seung Joo Kang,[6] Kyung Ho Song,[7] Jung-Wook Kim,[8] Hyun Chul Lim,[9] Hee Sun Park,[10] Seong-Jung Kim,[11] Ra Ri Cha,[12] Ki Bae Bang,[3] Chang Seok Bang,[13] Sung Kyun Yim,[14] Seung-Bum Ryoo,[15] Bong Hyeon Kye,[16] Woong Bae Ji,[17] Miyoung Choi,[18] In-Kyung Sung,[19] and Suck Chei Choi,[20]*; the Korean Society of Neurogastroenterology and Motility

[1]Division of Gastroenterology, Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, Cheonan, Chungcheongnam-do, Korea; [2]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Korea; [3]Division of Gastroenterology, Department of Internal Medicine, Dankook University Hospital, Cheonan, Chungcheongnam-do, Korea; [4]Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, Korea; [5]Division of Gastroenterology, Department of Internal Medicine, Chonnam National University Hospital, Gwangju, Korea; [6]Department of Internal Medicine, Seoul National University Hospital Healthcare System Gangnam Center, Seoul, Korea; [7]Division of Gastroenterology, Department of Internal Medicine, CHA University Ilsan Medical Center, CHA University School of Medicine, Ilsan, Gyeonggi-do, Korea; [8]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, Kyung Hee University, Seoul, Korea; [9]Department of Internal Medicine, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Gyeonggi-do, Korea; [10]Department of Radiology, Konkuk University School of Medicine, Seoul, Korea; [11]Department of Internal Medicine, Chosun University Hospital, Gwangju, Korea; [12]Department of Internal Medicine, Gyeongsang National University Changwon Hospital, Gyeongsang National University College of Medicine, Changwon, Gyeongsangnam-do, Korea; [13]Department of Internal Medicine, College of Medicine, Hallym University, Chuncheon, Gangwon-do, Korea; [14]Division of Gastroenterology, Department of Internal Medicine, Biomedical Research Institute, Jeonbuk National University Hospital, Jeonju, Jeollabuk-do, Korea; [15]Department of Surgery, Seoul National University College of Medicine, Seoul, Korea; [16]Department of Surgery, The Catholic University of Korea, St. Vincent's Hospital, Suwon, Gyeonggi-do, Korea; [17]Division of Colon and Rectal Surgery, Korea University Ansan Hospital, Ansan, Gyeonggi-do, Korea; [18]Division of Healthcare Technology Assessment Research, National Evidence-Based Healthcare Collaborating Agency, Seoul, Korea; [19]Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Korea; and [20]Department of Gastroenterology, Digestive Research Disease Institute, Wonkwang University School of Medicine, Iksan, Jeollabuk-do, Korea

Chronic constipation is one of the most common digestive diseases encountered in clinical practice. Constipation manifests as a variety of symptoms, such as infrequent bowel movements, hard stools, feeling of incomplete evacuation, straining at defecation, a sense of anorectal blockage during defecation, and use of digital maneuvers to assist defecation. During the diagnosis of chronic constipation, the Bristol Stool Form Scale, colonoscopy, and a digital rectal examination are useful for objective symptom evaluation and differential diagnosis of secondary constipation. Physiological tests for functional constipation have complementary roles and are recommended for patients who have failed to respond to treatment with available laxatives and those who are strongly suspected of having a defecatory disorder. As new evidence on the diagnosis and management of functional constipation emerged, the need to revise the previous guideline was suggested. Therefore, these evidence-based guidelines have proposed recommendations developed using a systematic review and meta-analysis of the treatment options available for functional constipation. The benefits and cautions of new pharmacological agents (such as lubiprostone and linaclotide) and conventional laxatives have been described through a meta-analysis. The guidelines consist of 34 recommendations, including 3 concerning the definition and epidemiology of functional constipation, 9 regarding diagnoses, and 22 regarding managements. Clinicians (including primary physicians, general health professionals, medical students, residents, and other healthcare professionals) and patients can refer to these guidelines to make informed decisions regarding the management of functional constipation.
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Constipation; Diagnosis; Guideline; Meta-analysis; Therapeutics

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*Correspondence: Jeong Eun Shin and Suck Chei Choi are equally responsible for this work.
Jeong Eun Shin, MD, PhD
Department of Internal Medicine, Dankook University College of Medicine, 201 Manghyang-ro, Dongnam-gu, Cheonan, Chungcheongnam-do 31116, Korea
Tel: +82-41-556-3052, Fax: +82-41-556-3256, E-mail: dreun@dankook.ac.kr
Suck Chei Choi, MD, PhD
Department of Gastroenterology, Digestive Research Disease Institute, Wonkwang University School of Medicine, 895 Muwang-ro, Iksan, Jeollabuk-do 54538, Korea
Tel: +82-63-859-2563, Fax: +82-63-855-2025, E-mail: medcsc@wku.ac.kr
Young Sin Cho and Yoo Jin Lee equally contributed to this work as the first authors.

Introduction

Constipation is an unsatisfactory symptom that occurs during defecation. The Rome IV criteria have mentioned the following as constipation-related symptoms in adults: infrequent bowel movements, hard or lumpy stools, excessive straining, sensation of incomplete evacuation or blockage, and use of manual maneuvers to facilitate evacuation.[1] A meta-analysis of 45 population-based studies worldwide revealed that chronic constipation has a prevalence of approximately 14%; however, the included studies were considerably varied in terms of the geographic location and definition of constipation.[2] Furthermore, in the recently reported Rome Foundation Global Study, functional constipation had the highest prevalence rate among functional gastrointestinal disorders.[3]

These socioeconomic characteristics of functional constipation have a significantly negative impact on the quality of life (QoL) and generate a socio-economic burden. In one study, constipation had a significant impact on mental as well as physical health, and the magnitude of this impact was similar to that of allergies, musculoskeletal disease, and inflammatory bowel disease.[4] A recent Asian study revealed that the health burden of constipation was high in diabetes, irritable bowel syndrome, and gastroesophageal reflux disease.[5] In the United States (US), it is estimated that 13 000 000 work days have been lost due to constipation.[4] Furthermore, from 2006 to 2011, the number of constipation-related visits to emergency departments in the country increased by 41.5%, while the cost of these visits increased by 121.4%.[6]

The clinical and social impacts of functional constipation necessitate an accurate diagnosis and effective treatment of chronic constipation. However, functional constipation is a chronic condition with frequent suboptimal outcomes; therefore, its diagnosis and treatment are challenging. Furthermore, important differences between Asia (including Korea) and the West in terms of the lifestyle and eating habits, patients' symptoms, prescription medications, and range of over-the-counter medications available warrant the development of management guidelines based on Asian perspectives.

Since the latest Korean guidelines on functional constipation were last revised in 2016,[7] a considerable amount of new evidence on the condition's epidemiology, diagnosis, and management has emerged. However, there was a limitation that it was difficult to reflect new evidence for functional constipation because the previous guidelines used adaptation process. Therefore, the current guidelines (commissioned by the Korean Society of Neurogastroenterology and Motility [KSNM]) have been proposed with the following aims: (1) to update the previous guidelines by considering all of these developments and (2) to develop a new standard for the diagnosis and treatment of functional constipation using de novo method not only in Korea but also in other Asian countries. We intend to develop guidelines for functional constipation grounded on evidence-based diagnostic and treatment modalities through an expert consensus. These guidelines cover several options for the management of functional constipation, summarize the benefits and cautions of each, and provide information on probable outcomes.

Methods

These guidelines describe approaches for the practical management of adult patients with functional constipation based on scientific evidence and expert consensus. We targeted patients with constipation aged over 18 years, while children as well as individuals with special circumstances (such as opioid-induced constipation) were excluded. These guidelines cover the epidemiology of constipation, pros and cons of existing diagnostic tools, and several treatment options available (such as lifestyle modifications, medications, and surgery). We only included the commonly accepted or widely used methods, and briefly introduced new treatment modalities (including medicines) that are supported by some clinical evidence.

The present guidelines provide a practical, evidence-based guide for clinicians (gastroenterologists, surgeons, and general physicians), medical staff (nurses, paramedical teams, medical students, and healthcare providers), patients, and the public.

The working group for this effort consisted of 14 gastroenterologists from the clinical practice guideline committee and the constipation research study group of the KSNM. In addition, one radiologist and three expert surgeons recommended by the Korean Society of Abdominal Radiology and the Korean Society of Coloproctology joined the working group to provide a multidisciplinary perspective to the diagnosis and treatment of functional constipation. These clinical practice guidelines were developed using evidence-based medicine methodology, and one methodological expert joined the working team. Additionally, 11 experts who participated in voting and consistently provided advice during the guideline development process were recommended by the Asian Neurogastroenterology and Motility Association (ANMA) to secure the generality of these guidelines in Asia.

The development of these guidelines began in June 2021. These guidelines were developed using a combination of de novo and adaptation methods, in consideration of the current development of diagnosis and managements for functional constipation. Compared to the development of previous guidelines, in the development of the current guidelines, the adaptation method was used in the absence of differences in the scientific evidence or the presence of systematic reviews and meta-analyses. To establish the methodology of guideline development, a methodology expert (Mi-young Choi) conducted 3 workshops on literature search and quality assessment, meta-analysis practice, guideline grading of recommendations and levels of evidence, and expert consensus. Furthermore, 17 meetings related to guideline development were also held.

The main processes related to the development of recommendations in these guidelines were as follows: (1) derivation of key questions tailored to the "population, intervention, comparator, and outcome" (PICO) format; (2) selection of appropriate search keywords; (3) systematic review (Preferred Reporting Items for Systematic Reviews and Meta-analyses [PRISMA] plot); (4) quality assessment of the selected literature; (5) meta-analysis; (6) summarizing of evidence profiles based on the "grading of recommendations, assessment, development and evaluation" (GRADE) criteria; (7) determination of the quality of evidence (with the GRADEpro software) and the strength of recommendation; and (8) expert consensus using e-mails and open discussion. To derive the key questions, the working team searched for existing guidelines and selected topics regarding functional constipation management during the guideline-development meetings. The key questions were categorized according to three aspects, namely definition and epidemiology, diagnosis, and management. The team conducted a literature search and meta-analysis accordingly. One-to-two experts were assigned to each key question. The key questions were selected using the nominal group technique in accordance with the PICO format.[8] Thus, 35 sentence-type key questions were prepared, and the possibility of guideline development was reviewed and confirmed (Supplementary Table 1).

A literature search was conducted in the Ovid-MEDLINE, EMBASE, Cochrane Library, and KoreaMed databases using keywords for each key question, and the search results were complemented by a manual search. There were no limitations on the search year, and the search was completed in August 2021. The process of selecting the final searched literature was performed by each guideline working team because it required clinical expertise. Two members independently reviewed the first and second selections and exclusions to increase objectivity. During the first selection, the titles and abstracts of the literature were reviewed. In the second selection, the original texts of the first selected literature were reviewed; if any article was excluded, the reason for exclusion was recorded. In both selection processes, differences in opinions among the reviewers were resolved through consensus.

For the retrieved literature, the common inclusion criteria were as follows: (1) studies on adult human participants or patients; (2) articles in English or Korean; (3) systematic reviews and meta-analyses, randomized controlled or nonrandomized trials, and observational studies; (4) published until August 2021; and (5) studies with proper reporting of results. The common exclusion criteria were as follows: (1) studies on children; (2) studies without proper reporting of results; (3) unavailable original articles; and (4) case series and reports, expert opinions, narrative reviews, and guidelines.

Two or more working group members independently conducted a quality assessment of the final selected literature for each key question; in case of a disagreement, a consensus was reached through discussions. The quality assessment tools were selected based on the study design. Accordingly, systematic literature reviews were assessed using "A MeaSurement Tool to Assess Systematic Reviews," while randomized comparative clinical trials were assessed using the Cochrane's Risk of Bias tool. Nonrandomized studies were assessed using the "Risk Of Bias In Non-randomized Studies of Interventions" tool.[9] For the summary of evidence, a meta-analysis was performed when quantitative synthesis was deemed possible; qualitative synthesis was applied when the heterogeneity was large or when meta-analysis was not deemed appropriate. The

level of evidence was categorized into four levels (high, moderate, low, and very low) by assessing the study design and quality of evidence and considering the risk of bias, inconsistency, indirectness, imprecision, and publication bias. Evidence profiles were created based on the GRADE criteria. The recommendations were classified as "strong" or "conditional" according to the level of evidence, clinical usefulness, and benefits and cautions (Table 1).[10]

The modified Delphi method was used for expert consensus on draft recommendations based on the key questions. In the first round, a 65-expert panel (54 from KSNM and 11 from ANMA) agreed to participate and provided their responses via email. Each statement was rated on a scale of 1 to 5 (1 = strongly disagree, 2 = disagree, 3 = undecided, 4 = agree with reservation, and 5 = strongly agree). A score of 4-5 was considered an agreement. If more than 80% of all responses agreed with a recommendation, a consensus was considered to have been reached. In the first consensus, 33 of the total 35 recommendations were agreed upon; the remaining two recommendations on colectomy and sacral nerve stimulation (SNS) did not reach an agreement of more than 80%. After the first email vote, the working group revised their recommendations for colectomy. However, we decided against recommending a statement on SNS following the expert opinion that related evidence was insufficient and inappropriate. The second round of voting by face-to-face agreement was held on September 24, 2022, for the revised recommendation. An additional e-mail survey was conducted with the ANMA experts who participated in the first voting round. The recommendation for colectomy was accepted with an 86.2% agreement, and 34 recommendations were finally adopted (Table 2). Two external experts (Joon Seong Lee and Kyung Sik Park) reviewed the recommendations regarding the necessity, appropriateness, healthcare setting, level of care, and balance between benefits and harms.

Guideline development received all budget support from KSNM; however, no separate financial support was received. Furthermore, the financial support from KSNM did not influence the decisions taken during guideline development. All members of the working team who participated in guideline development declared any competing interests in writing. The competing interests of all members of the guideline development group have been summarized in Supplementary Table 2. These guidelines will be uploaded on the websites of the KSNM. Furthermore, these guidelines will also be published in Korean. Finally, these guidelines will be updated every three-to-five years to consider the new evidence accumulated.

Definition and Epidemiology

Definition

Statement 1. Constipation is defined as the occurrence of symptoms of infrequent bowel movements, hard stools, a feeling of incomplete evacuation, straining at defecation, a sense of anorectal blockage during defecation, and use of digital maneuvers to assist defecation.

- Level of evidence: not applicable
- Strength of recommendation: not applicable
- Experts' opinions: strongly agree, 78.5%; agree with reservation, 18.5%; undecided, 1.5%; disagree, 1.5%; and strongly disagree, 0.0%.

Table 1. Definition of Levels of Evidence and Strength of Recommendation (Adapted From Andrews et al[10])

Level of evidence	
High	At least one RCT or SR/meta-analysis with no concerns regarding study quality
Moderate	At least one RCT or SR/meta-analysis with minor concerns regarding study quality or, at least one cohort/case-control/diagnostic test design study with no concerns regarding study quality
Low	At least one cohort/case-control/diagnostic test study with minor concerns regarding study quality, or at least one single arm before-after study or cross-sectional study with no concerns regarding study quality
Very low	At least one cohort/case-control/diagnostic test design study with serious concerns regarding study quality, or at least one single arm before-after study or cross-sectional study with minor/severe concerns regarding study quality
Grade of recommendation	
Strong for	Strong recommendations are offered when the desirable effects of an intervention clearly outweigh the undesirable effects
Conditional for	Conditional recommendations are offered when trade-offs are less certain, either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

RCT, randomized controlled trial; SR, systematic review.

Table 2. Summary of the Seoul Consensus on Functional Constipation

	Level of evidence	Strength of recommendation
Definition and epidemiology		
1 Constipation is defined as the occurrence of symptoms of infrequent bowel movements, hard stools, a feeling of incomplete evacuation, straining at defecation, a sense of anorectal blockage during defecation, and use of digital maneuvers to assist defecation.	NA	NA
2 The prevalence of constipation is higher in the elderly population.	Moderate	NA
3 The prevalence of constipation is higher in females than in males.	High	NA
Diagnosis		
4 Type 1 and 2 stools (according to the Bristol Stool Form Scale) can be used to predict slow-transit constipation in patients with chronic constipation.	Moderate	Conditional
5 Digital rectal examination is useful for identifying organic anorectal causes of constipation (such as anorectal masses, rectal prolapse, and rectoceles).	Moderate	Strong
6 Abnormal findings on digital rectal examination, suggesting defecatory disorders, can prompt the referral for physiological tests.	Moderate	Strong
7 Colonoscopy should be performed in patients with constipation who have alarm symptoms or have not undergone appropriate colon cancer screening.	Low	Strong
8 Physiological tests are recommended for patients with functional constipation who have failed to respond to treatment with available laxatives (for a minimum of 12 weeks and under a recommended therapeutic regimen) or who are strongly suspected of having a defecatory disorder.	Very low	Strong
9 Although poorly standardized, the balloon expulsion test may be useful for screening for defecatory disorders.	Moderate	Conditional
10 Anorectal manometry is useful for diagnosing defecatory disorders in patients with constipation. However, it should be performed alongside other anorectal physiological tests to confirm the diagnosis.	Moderate	Strong
11 Defecography is useful for assessing structural abnormality of the pelvic floor or pelvic dyssynergia in patients with chronic constipation who are suspected of having an evacuation disorder.	Moderate	Strong
12 Segmental colon transit time is useful for differentiating slow-transit constipation from defecatory disorder in patients with chronic constipation.	Low	Strong
Management		
13 Dietary fiber is effective in improving the symptoms of chronic constipation by reducing the colon transit time and increasing the bowel frequency.	Moderate	Strong
14 Exercises can be recommended since they may improve symptoms in some patients with chronic constipation. Besides, exercises confer health benefits to people of all age groups.	Low	Conditional
15 Bulking agents increase the frequency of defecation and are effective and safe for the management of chronic constipation.	Moderate	Strong
16 The use of bulking agents, especially insoluble fiber, in patients with chronic constipation is limited by adverse events, particularly abdominal pain, bloating, flatulence, and nausea.	Low	Conditional
17 Magnesium salts improve stool frequency and consistency.	High	Strong
18 Magnesium salts can cause hypermagnesemia in patients with an impaired renal function.	Low	Strong
19 Non-absorbable carbohydrates are effective in patients with chronic constipation.	Low	Strong
20 Long-term administration and use in elderly patients of non-absorbable carbohydrates may be considered as serious side effects are rare.	Low	Conditional
21 Polyethylene glycol is effective in the management of chronic constipation.	High	Strong
22 Polyethylene glycol is safe and tolerable for long-term treatment in patients with chronic constipation and can be considered for use in the elderly.	Moderate	Conditional
23 The administration of stimulant laxatives is recommended to relieve symptoms in patients with chronic constipation.	Moderate	Strong
24 The use of stimulant laxatives in patients with chronic constipation should be recommended for a short-term period due to limited evidence on the long-term safety of these laxatives.	Low	Conditional

Table 2. Continued

		Level of evidence	Strength of recommendation
25	Probiotics can be used to relieve constipation symptoms in patients with chronic constipation. However, because the effects of probiotics vary depending on their species/strains and because the results between studies are inconsistent, it is recommended to use probiotics as a supplementary treatment.	Low	Conditional
26	Prucalopride is a highly selective serotonin (5-hydroxytryptamine)-4 agonist that accelerates the whole gut motility. It is effective in the management of chronic constipation, even in patients who exhibit an inadequate response to conventional laxatives.	High	Strong
27	Lubiprostone, the chloride channel activator, is effective and safe for the management of chronic constipation. It does not cause clinically significant adverse effects, such as electrolyte imbalance and renal dysfunction.	High	Strong
28	Linaclotide, an intestinal secretagogue, is effective and safe for the management of chronic constipation.	High	Strong
29	Biofeedback therapy is effective and safe for treating patients with defecatory disorders.	Moderate	Strong
30	Biofeedback therapy has long-term therapeutic effects and improves the quality of life in patients with defecatory disorders.	Moderate	Strong
31	Enemas can be effective in the subset of patients with refractory defecatory disorders.	Low	Conditional
32	Enemas should be used with caution because there are no standardized guidelines on their use and they may cause adverse events, such as electrolyte imbalance and rectal mucosal injury.	Low	Conditional
33	Colectomy can be considered in highly selected patients with medically intractable (non-responsive) slow-transit constipation who do not have defecatory disorders and other gastrointestinal motility disorders.	Moderate	Conditional
34	Surgery for obstructed defecation syndrome can be indicated in patients with reparable structural abnormalities (such as rectocele, rectal intussusception, or rectal prolapse).	Low	Conditional

NA, not applicable.

Constipation is a common, symptom-based, functional gastrointestinal disorder characterized by unsatisfactory defecation due to infrequent stools, difficult stool passage, or both.[11] The term "constipation" can have varying meanings among individuals, given that it mainly depends on how individuals perceive their bowel habits. Nevertheless, the majority of the patients with constipation have one or more of the following symptoms: infrequent defecation (< 3 per week) with hard or lumpy stools that are difficult to expulse, a sensation of incomplete evacuation, a sensation of anal blockage during defecation, and the requirement of manual digital maneuvers to achieve evacuation.[1,7] These symptoms persist chronically, limiting one's social life and lowering their QoL, resulting in social and economic burdens.[12] Constipation may occur secondary to various causative diseases, such as endocrine diseases, metabolic diseases, neurological diseases, mental diseases, and gastrointestinal obstruction; therapeutic drugs may be required to control them. A diagnosis of functional constipation is established in the absence of such causes. The criteria for primary functional constipation were developed by an international group of experts and were revised to the Rome IV diagnostic criteria.[1] Functional constipation is classified as normal transit constipation, slow-transit constipation (STC), and functional defecation disorder according to colon transit time (CTT) and anorectal function; however, these subtypes are considered to overlap rather than being distinguished from each other.[13,14] Patients with hard stools may have STC,[15] but the subtype of functional constipation cannot be distinguished based on the constipation symptoms alone.

Epidemiology

Statement 2. The prevalence of constipation is higher in the elderly population.

- Level of evidence: moderate
- Strength of recommendation: not applicable
- Experts' opinions: strongly agree, 81.6%; agree with reservation, 16.9%; undecided, 1.5%; disagree, 0.0%; and strongly disagree, 0.0%.

A systematic literature review revealed that constipation has a global prevalence of approximately 14.0% (95% confidence interval [CI], 12.0-17.0%). However, the prevalence of constipation varies according to the region, being relatively low in Southeast Asia.[2] In Korea, the prevalence of self-reported constipation was 16.5%.[11] The prevalence of constipation is reported in various ways accord-

ing to the applied constipation diagnostic criteria; recently, the prevalence of constipation using the Rome IV criteria in the US was reported to be approximately 24.0%.[16]

The prevalence of constipation increases as the population ages.[17,18] In a Chinese study using the Rome III criteria, the prevalence of constipation in a population aged 60 years or older was 32.6% (634/1942); it increased with age, being 44.8% in those aged 80 years and older.[19] The prevalence of chronic adult constipation diagnosed using the Rome III and IV criteria was relatively high in the elderly population in five cross-sectional studies.[20-24] In a Finnish study, the prevalence of constipation in nursing homes increased to 79.0% and 81.0% in older women and men, respectively.[25]

Various physiological and colon motility changes occur with aging; these include a reduced number of neurons in the myenteric plexus, increased collagen deposition in the left colon, decreased high-amplitude propagation contractions, and changes in the anorectal function. The incidence of constipation also increases due to multifactorial causes, such as changes in the dietary intake, impaired mobility, presence of comorbidities, increased usage of medications that contribute to constipation, and age-related intrinsic intestinal changes.[17,26]

Statement 3. The prevalence of constipation is higher in females than in males.

- Level of evidence: high
- Strength of recommendation: not applicable
- Experts' opinions: strongly agree, 69.2%; agree with reservation, 27.7%; undecided, 3.1%; disagree, 0.0%; and strongly disagree, 0.0%.

Previous studies have revealed a higher prevalence of chronic constipation in women than in men. A systematic review revealed that functional constipation was significantly associated with sex, with a female predominance (odds ratio [OR], 2.22; 95% CI, 1.87-2.62).[2] We performed a meta-analysis of six cross-sectional studies that investigated the prevalence of adult chronic constipation diagnosed using the Rome III and IV criteria[20-24,27]; the prevalence was approximately 1.98 times higher in females than in males (95% CI, 1.31-2.98). This female predominance has been attributed to female sex hormones; a study on healthy Korean adults revealed that the CTT was longer in the luteal phase than in the follicular phase of the menstrual cycle (40.9 ± 19.0 hours vs 20.6 ±19.2 hours, $P < 0.05$).[28] Furthermore, a Japanese study revealed sex-based differences in the prevalence rate of functional constipation by age[29]: the prevalence increased sharply among males over 60 years of age, while it decreased among females in the same age group. Functional constipation was the most common among females between 30 and 59 years of age, possibly because higher progesterone levels in the luteal phase are associated with a prolonged intestinal transit time.[29]

The difference in the prevalence of constipation between males and females disappears with increasing age, and this phenomenon may be due to changes in the physical and psychological factors (such as female hormones, sociocultural role changes, or underlying diseases that accompany aging).[29]

Diagnosis

Bristol Stool Form Scale

Statement 4. Type 1 and 2 stools (according to the Bristol Stool Form Scale) can be used to predict slow-transit constipation in patients with chronic constipation.

- Level of evidence: moderate
- Strength of recommendation: conditional
- Experts' opinion: strongly agree, 29.2%; agree with reservation, 63.1%; undecided, 7.7%; disagree, 0.0%; and strongly disagree, 0.0%.

The stool form is often used to predict CTT in patients with constipation. The Bristol Stool Form Scale (BSFS) is a useful visual aid that has been proposed as a quick and reliable indicator of constipation (Fig. 1).[7,30] It uses simple visual descriptors of common stool forms and consistency that are rated on a 7-point scale. Its utility was endorsed by the Rome Foundation.[1]

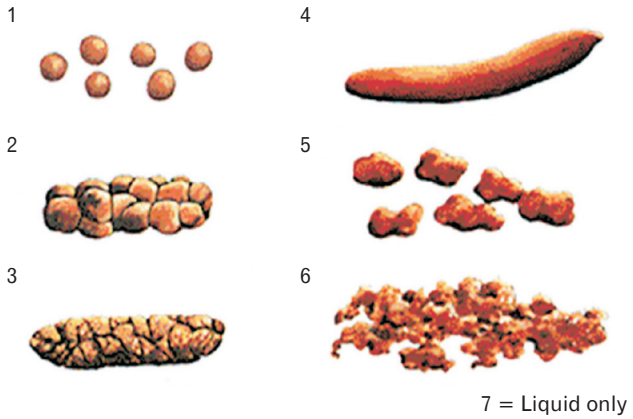

Figure 1. The Bristol Stool Form Scale. Adapted from Shin et al.[7]

Several studies have demonstrated reasonable correlations between BSFS and CTT.[31] BSFS types 1 and 2 are associated with a slower transit, while types 6 and 7 are associated with more rapid transit. A post hoc analysis was performed on 110 participants, including 46 adults with chronic constipation and 64 healthy adults from 9 US sites; it revealed that BSFS type < 3 predicted delayed whole-gut transit (sensitivity, 85.0%; specificity, 82.0%) and delayed colonic transit (sensitivity, 82.0% and specificity, 83.0%) in constipated patients, but not in healthy adults.[15] However, no correlations were observed between the bowel transit time and stool frequency in both constipated and healthy adults.[15] Thus, some patients show discrepancies between stool hardness and the frequency of bowel movements, which are the main symptoms of constipation; BSFS is particularly useful for assessing such patients.[15,30,32]

A recent Asian study found that an optimal mean 5-day BSFS type of ≤ 3 predicted delayed CTT with 68.0% sensitivity, 69.7% specificity, and 69.4% accuracy. Accordingly, the authors suggested that BSFS types 1-3, and not 1 and 2, could be used as surrogates for delayed CTT in Eastern patients with constipation.[33] Although the BSFS has been relatively well validated for CTT prediction, it is necessary to confirm whether the standard types (ie, types 1 and 2) can be commonly applied to all patients.

Abdominal X-ray

An abdominal X-ray is a simple and inexpensive test that can be performed on patients suspected of constipation. This test can quantify the fecal burden and serve as a basis for triage for further workup. A recent study showed that a chief complaint of constipation was an independent predictor of having fecal loading in an abdominal X-ray.[34] However, other studies show a limited value for the role of abdominal X-ray in diagnosing constipation.[35,36] Although the evidence is limited, an abdominal X-ray is helpful in assessing the presence of complications related to constipation. Fecal impaction may be seen as a speckled low-density soft tissue mass within a distended large bowel.[37] Pneumoperitoneum from stercoral perforation can be detected on abdominal X-ray by air external to the bowel wall, air along the peritoneal ligaments, and air in the right upper abdominal quadrant.[38] Abdominal X-ray in patients with colonic pseudo-obstruction often demonstrate air-fluid levels with marked colonic distention. The pathognomonic finding for colonic pseudo-obstruction is a dilated colon from the cecum to the splenic flexure or even the rectum.[39]

Digital Rectal Examination

Statement 5. Digital rectal examination is useful for identifying organic anorectal causes of constipation (such as anorectal masses, rectal prolapse, and rectoceles).

- Level of evidence: moderate
- Strength of recommendation: strong
- Experts' opinion: strongly agree, 56.9%; agree with reservation, 38.5%; undecided, 1.5%; disagree, 3.1%; and strongly disagree, 0.0%.

Statement 6. Abnormal findings on digital rectal examination, suggesting defecatory disorders, can prompt the referral for physiological tests.

- Level of evidence: moderate
- Strength of recommendation: strong
- Experts' opinions: strongly agree, 50.8%; agree with reservation, 40.0%; undecided, 4.6%; disagree, 4.6%; and strongly disagree, 0.0%.

Digital rectal examination (DRE) is a vital physical examination tool for the initial evaluation of patients with constipation. DRE can detect stool in the rectal vault, anorectal masses, hemorrhoids, rectal prolapse, rectocele, and puborectalis tenderness, all of which may cause constipation.[40]

DRE should include palpation of abnormal structures in the anorectal region as well as detection of functional alterations in the puborectalis muscle and anal sphincter during simulated evacuation. DRE performed both at rest and during straining can identify defecatory disorders (DDs), an inappropriate anal descent, and other structural abnormalities. Tantiphlachiva et al[41] proposed that an impaired perineal descent, paradoxical anal contraction, and impaired push effort on DRE are suggestive of DD. If 2 of these findings are present, DRE can help diagnose DDs with a sensitivity and specificity of 75.0% and 87.0%, respectively. A Korean study investigated the accuracy of DRE for DD diagnosis in patients with chronic constipation.[42] DRE could detect DDs with a sensitivity and positive predictive value of 93.2% and 91.0%, respectively, when high-resolution manometry was used as the reference standard. Despite a low specificity of 58.7%, the authors suggested that DRE could be useful as a screening test for DD. A meta-analysis of 4 studies (2329 patients) revealed a negative predictive value of 64.0%, making DRE unsuitable for excluding

the diagnosis of DDs in constipated patients.[43] However, a recent meta-analysis of six studies revealed an acceptable sensitivity and specificity of DRE for detecting DDs when compared with that of other physiological tests.[44]

Several studies have demonstrated that DRE is a useful, low-cost screening tool that can use at bedside. However, normal DRE findings do not exclude DD, and abnormal findings should be confirmed by functional tests for diagnosing DD. Accordingly, findings suggesting DDs in DRE can facilitate referral for physiological tests.

Colonoscopy

Statement 7. Colonoscopy should be performed in patients with constipation who have alarm symptoms or have not undergone appropriate colon cancer screening.

- Level of evidence: low
- Strength of recommendation: strong
- Experts' opinion: strongly agree, 86.2%; agree with reservation, 12.3%; undecided, 1.5%; disagree, 0.0%; and strongly disagree, 0.0%.

Some guidelines recommend a simple blood test to identify the secondary causes of constipation under clinical suspicion.[40,45] However, a systematic review revealed that routine blood testing, radiography, and endoscopy in the work-up of patients with constipation without alarm symptoms do not provide much information.[32] Accordingly, routine or extensive laboratory and radiological evaluations are not recommended in most patients with constipation.

Because the diagnostic yield of colonoscopies in patients with constipation as the sole indication is similar to that of the asymptomatic population, routine colonoscopy is also unwarranted in most patients with constipation.[46-48] However, colonoscopy should be considered for all constipated patients with alarm signs and symptoms, including blood in stool, unexplained anemia, unintentional weight loss, and abdominal or rectal masses.[40] Patients who have not undergone an age-appropriate colon cancer screening after onset of constipation are also indicated for colonoscopy.[40,49] Recently, the US Multi-society Task Force on Colorectal Cancer suggested that average-risk colorectal cancer screening should begin at 45 years of age and is not recommended after 85 years of age.[50] In Korea, colonoscopy is recommended for colorectal cancer screening in adults aged 50 years or older with an average risk of colorectal cancer.[51] The appropriate timing and interval for colonoscopic surveillance are then determined using the results of the index colonoscopy.[52]

Indication of Physiological Testing

Statement 8. Physiological tests are recommended for patients with functional constipation who have failed to respond to treatment with available laxatives (for a minimum of 12 weeks and under a recommended therapeutic regimen) or who are strongly suspected of having a defecatory disorder.

- Level of evidence: very low
- Strength of recommendation: strong
- Experts' opinion: strongly agree, 33.9%; agree with reservation, 52.3%; undecided, 7.7%; disagree, 6.1%; and strongly disagree, 0.0%.

The first step in the treatment of functional constipation is to modify the lifestyle and diet of the affected individuals. Laxatives are then administered as needed; these include bulking laxatives, osmotic laxatives, stimulant laxatives, prokinetics, and secretagogues.[7,13]

Physiological tests for functional constipation are recommended for patients who do not respond to pharmacological treatment.[7,13,53] However, there is no consensus on the choice of drug type, order of usage, dosage of drug, and treatment duration for the assessment of pharmacological non-responders. Gwee et al[53] proposed the following laxative dosages and treatment durations for the assessment of pharmacological non-responders: bisacodyl at 10 mg every night for at least 4 weeks (while considering a total treatment period of up to 12 weeks if access to specialized centers was limited), prucalopride at 2 mg daily for up to 12 weeks, or a combination therapy of

Table 3. Summary of the Various Agents of Chronic Constipation (Adapted From Soh et al[55])

Category	Agent	Range of dosage	Duration of treatment
Osmotic laxatives	Polyethylene glycol	13-39 g/day	Up to 6 mo
	Lactulose	15-60 mL	1-12 wk
Stimulant laxatives	Bisacodyl	5-10 mg/day	4 wk
5-HT_4 agonist	Prucalopride		
	> 65 yr	1 mg/day	12 wk
	18-65 yr	2 mg/day	12 wk
Prosecretory agents	Linaclotide	16-72 μg/day	12 wk
	Lubiprostone	145-290 μg/day	Up to 6 mo

5-HT_4, 5-hydroxytryptamine type 4.

a stimulant or prokinetic agent with an osmotic agent.

Staller et al[54] suggested that refractory constipation did not respond to stimulant and osmotic over-the-counter agents administered at labeled doses and to at least one or more of the novel prosecretory agents (lubiprostone and linaclotide) or 5-hydroxytryptamine type 4 receptor (5-HT_4) agonists where available. In a systematic review for determining the definition of pharmacologically refractory constipation, they suggested that a minimum of 12 weeks of continuous treatment constituted an adequate pharmacological trial (Table 3).[55] The pharmacological agents investigated were conventional laxatives (osmotic and stimulant laxatives) and 5-HT_4 agonists or prosecretory agents (lubiprostone and linaclotide).[55] Accordingly, we propose that pharmacological non-responders be defined as "patients who have failed to respond to treatment with available laxatives (for a minimum of 12 weeks and under a recommended therapeutic regimen)."

Furthermore, because patients with DDs can be managed very effectively with biofeedback therapy, enabling the cessation of laxatives and an improvement in the QoL, physiological tests may be considered earlier in cases of strongly suspected DD.[1]

Balloon Expulsion Test

Statement 9. Although poorly standardized, the balloon expulsion test may be useful for screening for defecatory disorders.

- Level of evidence: moderate
- Strength of recommendation: conditional
- Experts' opinion: strongly agree, 27.7%; agree with reservation, 53.9%; undecided, 16.9%; disagree, 1.5%; and strongly disagree, 0.0%.

The balloon expulsion test (BET) is a simple, office-based test that assesses a patient's ability to expel a water- or air-filled balloon inserted into the rectum and the time taken for expulsion. Although BET is usually performed using anorectal manometry (ARM) in tertiary institutions, it is a useful screening test for the diagnosis of DDs in clinics where ARM is unavailable. However, the methodology of this test is poorly standardized; furthermore, its results are influenced by demographic factors, with men having a shorter expulsion time than women and that increasing with age.[56] A recent systematic review and meta-analysis evaluating the performance of BET for DD diagnosis revealed that neither the participant position (seated or left lateral decubitus) nor the maximum expulsion time (1-5 minutes) significantly affected the test performance relative to that of reference tests.[57] Although given that cut-off values vary, an expulsion time of longer than 1-3 minutes is generally considered abnormal and suggestive of DD.[58,59] An uncontrolled study assessed the usefulness of BET for identifying constipated patients who did not have DD; its findings suggested that BET was able to screen DDs in constipated patients (sensitivity, 87.5%; specificity, 89.0%; positive predictive value, 64.0%; and negative predictive values, 97.0%).[58]

BET findings may be normal in patients with DDs who are able to compensate by excessive straining.[45] However, 25.0% of the healthy participants in one study could not expel the balloon within 2 minutes.[60] Accordingly, some studies have shown disappointing results regarding the usefulness of BET as a screening test for DD, with low negative predictive values of 15-72%.[43,61] In contrast, another systemic review and meta-analysis on 15 studies comprising 2090 participants revealed that BET was associated with an area under the curve of 0.80 in DD diagnosis, supporting its use as a screening tool.[57] Considering its simplicity and easy availability, BET can be a useful screening tool for DD. However, a firm diagnosis requires confirmation with other physiological tests.

Anorectal Manometry

Statement 10. Anorectal manometry is useful for diagnosing defecatory disorders in patients with constipation. However, it should be performed alongside other anorectal physiological tests to confirm the diagnosis.

- Level of evidence: moderate
- Strength of recommendation: strong
- Experts' opinions: agree strongly (61.5%), agree with reservation (33.9%), disagree (3.1%), disagree (1.5%), and disagree strongly (0%).

ARM involves the use of pressure sensors to measure the anorectal pressure during defecation; it is considered the best anorectal physiological test for diagnosis of DD. It helps detect abnormalities in the sphincter function and recto-anal coordination, which may be critical to the pathophysiology of DD.[62] High-resolution ARM has enabled data acquisition of a high spatial resolution and continuous visualization of the anorectal pressure activity.[63,64] High-resolution ARM is currently performed in more than 50% of all gastrointestinal motility laboratories worldwide[65] and is well correlated with traditional ARM.[66]

However, there are significant discrepancies among the methods of data acquisition, analysis, and interpretation using ARM.[65] An international survey of 107 institutes revealed that no center fully complied with the published guidelines.[65] Hence, the International Anorectal Working Group proposed a protocol for anorectal function testing with a standardized sequence of maneuvers.[67] Nevertheless, a recent systematic review and meta-analysis of 15 studies comprising 2140 patients revealed a suboptimal diagnostic accuracy of ARM for DD diagnosis (under the curve, 0.78 [95% CI, 0.72-0.82]; sensitivity [high, 79.0%]; specificity [poor; 64.0%]).[68]

To date, a single gold-standard physiological test for DD diagnosis is unavailable, and there is limited agreement among the existing tests.[69] Based on the Rome IV criteria, two or more abnormal anorectal and imaging tests are needed for diagnosing DD.[69] Traditionally, ARM has been considered a critical tool for DD diagnosis; however, it should be combined with other anorectal physiological tests to confirm the diagnosis.

Defecography

Statement 11. Defecography is useful for assessing structural abnormality of the pelvic floor or pelvic dyssynergia in patients with chronic constipation who are suspected of having an evacuation disorder.

- Level of evidence: moderate
- Strength of recommendation: strong
- Experts' opinions: strongly agree, 56.9%; agree with reservation, 43.1%; undecided, 0.0%; disagree, 0.0%; and strongly disagree, 0.0%.

Defecography allows the real-time fluoroscopic or magnetic resonance imaging of defecation.[7,70] It enables dynamic evaluation of the anatomy and function of the anorectum and the pelvic floor at all stages of simulated defecation.[71] It is particularly useful for identifying structural abnormalities of the pelvic floor (such as rectocele, enterocele, intussusception, rectal prolapse [internal or external], perineal descent, and megarectum) and functional abnormalities encompassing pelvic dyssynergia.[70,72,73] Defecography is considered when ARM or BET yield inconclusive results and therapeutic trials elicit inadequate responses in patients with chronic constipation.[74,75]

Fluoroscopic defecography using barium is a commonly performed technique, although the reproducibility is known to be poor, normal ranges are ambiguous, and the standardized parameters for defecographic analysis (including the radiation exposure required) are still incomplete.[74,76] Comparatively, magnetic resonance defecography is free from radiation, better tolerated, and enables better visualization of anatomic landmarks for measuring the pelvic floor motion.[71,77-80] However, it is performed with the patient in a non-physiological posture, is expensive, and is not commonly available in clinical practice.[7]

Although defecography is considered for evaluating structural abnormalities of the pelvic floor, it is better to consider the results of two or more tests for the diagnosis of an evacuation disorder, because its pathophysiology is usually more complicated than generally accepted.[74,76]

Colon Transit Time

Statement 12. Segmental colon transit time is useful for differentiating slow-transit constipation from defecatory disorder in patients with chronic constipation.

- Level of evidence: low
- Strength of recommendation: strong
- Experts' opinion: strongly agree, 36.9%; agree with reservation, 53.9%; undecided, 9.2%; disagree, 0.0%; and strongly disagree, 0.0%.

The CTT test, a simple method of assessing colonic motility, is widely used for screening of patients with chronic constipation because it is easily measured, reliable, inexpensive, and convenient for the patients.[81] This technique requires the oral administration of one capsule containing multiple (20-24) radio-opaque markers a once day for 3 days, followed by abdominal radiography on days 4 and 7.[82] The total CTT values in a healthy Korean adult men and women are 22.3 ± 16.1 hours and 30.1 ± 21.4 hours, respectively.[28] The normal CTT values vary among age groups, sexes, races, and methodologies.[7]

Segmental CTT facilitates the differentiation of chronic constipation subtypes, such as colonic inertia or STC (delayed right CTT), hindgut dysfunction (delayed left CTT), and pelvic outlet obstruction (delayed rectosigmoid CTT), according to the distribution of colon markers.[83-87] However, the test is less reproducible in evacuation disorders and colon inertia, and more than half of the patients with DDs show STC.[88] Therefore, clinicians should also consider other tests according to the patient's symptoms and test availability.

Management

Lifestyle Modification

Dietary fiber

Statement 13. Dietary fiber is effective in improving the symptoms of chronic constipation by reducing the colon transit time and increasing the bowel frequency.

- Level of evidence: moderate
- Strength of recommendation: strong
- Experts' opinions: strongly agree, 53.8%; agree with reservation, 43.1%; undecided, 3.1%; disagree, 0.0%; and strongly disagree, 0.0%.

Dietary fibers are carbohydrate polymers that are digested in the distal small and large intestines to short-chain fatty acids and gases, such as methane and carbon dioxide; these affect the sensation and movement of the gastrointestinal tract. The fibers are usually classified as soluble (psyllium, inulin, and methylcellulose) and insoluble (bran, rye bread, and lignin). A recent meta-analysis revealed that fiber supplements were relatively safe without serious adverse effects, and accelerated CTT and softening of the stool composition.[89,90]

We selected 15 randomized controlled trials (RCTs) that compared fiber supplementation and placebo in patients with chronic idiopathic constipation (CIC). Four, nine, and three of these RCTs investigated soluble, mixed, and insoluble fibers, respectively, and their characteristics are summarized in Supplementary Figure 1 and Supplementary Table 3.[91-105] In this analysis, the number of spontaneous bowel movements (SBMs) per week was significantly increased at 4 weeks in the fiber group as compared to in the placebo group (Supplementary Fig. 2A). The CTT was significantly decreased in the fiber group as compared to in the placebo group (Supplementary Fig. 2B). The stool consistency did not differ significantly between the fiber and placebo groups. Similarly, a systematic review by Rao and Brenner on 20 primary studies (5 fruit-based, 2 food with prebiotics, and 13 fibers) revealed that fiber intake increased the number of SBMs per week and improved stool consistency with fewer adverse events.[106] Dietary fiber can help manage fiber deficiency-led constipation, and its effect can be enhanced with fluid consumption and physical activity.[107-109] In conclusion, dietary fiber is relatively safe and improves symptoms of functional constipation by reducing the CTT and increasing the number of SBMs. However, dietary fiber may not be effective in cases of severe constipation, STC, and DD.[110] Dietary fiber, especially insoluble fiber, may also aggravate constipation-related symptoms (such as abdominal distention and flatulence).[111]

Water intake

Several studies have shown an association between inadequate water intake and constipation. Thus, many clinicians recommend adequate water intake for the initial treatment of chronic constipation.[20,112-114] A previous RCT revealed that water intake enhanced the effect of fiber intake in patients with chronic constipation.[115] However, there is a lack of strong scientific evidence to recommend water intake alone for chronic constipation management. Although increased water intake may be helpful in patients with inadequate water intake or promote the effects of fiber intake in patients with chronic constipation, more data are needed to support the recommendation of water intake for the management of patients with chronic constipation.

Exercise

Statement 14. Exercises can be recommended since they may improve symptoms in some patients with chronic constipation. Besides, exercises confer health benefits to people of all age groups.

- Level of evidence: low
- Strength of recommendation: conditional
- Experts' opinion: strongly agree, 24.6%; agree with reservation, 55.4%; undecided, 18.5%; disagree, 1.5%; and strongly disagree, 0.0%.

There are inconsistent reports on the association of physical activity with constipation in adults (Supplementary Table 4). Three cross-sectional studies suggested that the prevalence of constipation was higher in patients with physical inactivity, no vigorous activity, or moderate recreational activity.[113,116] However, another study that analyzed a database created after a survey of public events revealed that the constipation severity was associated with higher physical activity levels.[112]

One study revealed that women who engaged in more physical activities had a shorter CTT.[117] A recent study showed that core strengthening exercises decreased the total and left CTT in healthy young women.[118]

Until now, no systematic review has evaluated the effect of

exercise on chronic constipation management, because previous studies employed different interventions for constipation (exercise or physical activity with or without other lifestyle modifications [such as education and adequate fiber or water intake]) and different endpoints for determining the improvement in constipation (Supplementary Table 5). Moreover, these studies included patients with different characteristics (age, sex, and residence [community-based vs institutionalized]). Supplementary Table 5 presents six studies on the effects of physical activity on constipation symptoms and colon transit. There were 4 studies with benefit of intervention of physical activity and 2 studies without benefit of intervention of physical activity. Two studies on elderly institutionalized and physically inactive patients yielded inconsistent results.[119,120] Another study involving inactive patients aged over 45 years revealed that exercise led to a decrease in the CTT.[121] We recommend exercise for constipation management, in spite of a lack of evidence, since it may improve the symptoms in some patients with chronic constipation and confer health benefits to people of all ages.

Medical Treatment

Bulking agent

Statement 15. Bulking agents increase the frequency of defecation and are effective and safe for the management of chronic constipation.

- Level of evidence: moderate
- Strength of recommendation: strong
- Experts' opinion: strongly agree, 63.0%; agree with reservation, 33.9%; undecided, 3.1%; disagree, 0.0%; and strongly disagree, 0.0%.

Commonly used bulk-forming agents include soluble fibers (e.g. psyllium) and insoluble fibers (eg, wheat bran, methylcellulose, and polycarbophil). Bulking agents are often recommended as first-line treatment options for patients with chronic constipation; however, their usage has relatively little support in large RCTs on patients with chronic constipation. This is influenced by their safety, low costs, and efficacy data from the trials, together with long-standing clinical experience with bulking agents.

Supplementation with bulking agents increases stool frequency. One study revealed that compared with the placebo, bulking agents (including soluble fibers) led to greater improvements in global symptoms (47.4% vs 86.5%), pain on defecation, and stool consistency; an increase in the mean number of stools per week (baseline, 2.9 stools per week; after therapy, 3.8 stools per week); and a reduction in the number of days between stools (Supplementary Table 6).

Evidence on the benefits of bulking agents, including insoluble fibers, is conflicting and mainly derived from smaller studies on small patient numbers. Insoluble fiber supplementation reportedly reduced the use of laxatives by 59.0% (placebo group: 8.0% increase). Compared with the placebo, it also led to improvements in straining (28.6% vs 55.6%), pain on defecation, and stool consistency. It also increased the mean number of stools per week (baseline, 5.1 stools per week; after therapy, 6.4 stools per week; Supplementary Table 6). Studies have shown that methylcellulose and polycarbophil can be used for the treatment of constipation; however, only a few double-blind studies on these agents are available.[122,123]

Statement 16. The use of bulking agents, especially insoluble fiber, in patients with chronic constipation is limited by adverse events, particularly abdominal pain, bloating, flatulence, and nausea.

- Level of evidence: low
- Strength of recommendation: conditional
- Experts' opinions: strongly agree, 30.8%; agree with reservation, 50.8%; undecided, 16.9%; disagree, 1.5%; and strongly disagree, 0.0%.

A meta-analysis of three studies on fiber intake-related side effects revealed that abdominal bloating was significantly increased in fiber groups[104,105] (relative risk [RR], 1.98; 95% CI, 1.05-3.73). Furthermore, flatulence (RR, 2.37; 95% CI, 0.74-7.63) and nausea (RR, 2.61; CI, 0.79-8.66) were common in the fiber group (no statistical difference; Supplementary Fig. 3). These adverse events were mainly reported in studies on insoluble fibers, such as bran or rye bread.

If insoluble fibers are used as the bulking agents for constipation treatment, side effects may occur, particularly in patients with hard stools. Furthermore, patients with normal-transit constipation showed a good response, while those with STC and DDs showed a poor response, to bulking agents in one study.[124] Therefore, these concerns should be considered during treatment; they can be addressed by prescribing osmotic laxatives before increasing the dietary fiber intake or by slowly increasing the fiber intake from an initial small dose (depending on the tolerance and efficacy).[111,125,126]

Benefits: Bulking agents can increase the frequency of defecation and relieve global symptoms and pain during defecation at a low cost.
Cautions: Bulking agents, especially insoluble bulking agents, may aggravate constipation-related symptoms (such as abdominal distention and flatulence) in cases of slow-transit constipation and defecatory disorders.

Magnesium salt

Statement 17. Magnesium salts improve stool frequency and consistency.

- Level of evidence: high
- Strength of recommendation: strong
- Experts' opinions: strongly agree, 76.9%; agree with reservation, 23.1%; undecided, 0.0%; disagree, 0.0%; strongly disagree, 0.0%.

Magnesium salts are considered excellent conventional laxatives; they are osmotic laxatives that mainly soften hard stools. They have low costs, allow easy dosage adjustment, and are easily ingested.[127] Although their prescription has been based on empirical evidence for several years, 2 RCTs have recently shown the efficacy of magnesium oxide in the management of chronic constipation in adults.

The first randomized, double-blind, placebo-controlled study revealed that compared with the placebo, magnesium oxide significantly improved the abdominal symptoms, CTT, SBMs, stool form, and QoL.[128] The overall symptom improvement was significantly higher in the magnesium oxide group than in the placebo group (70.6% vs 25.0%). Another RCT compared magnesium oxide with Senna (a stimulant laxative); the overall response rate, SBMs, and QoL were comparable between the two.[129] Furthermore, neither treatment group experienced any serious side effects from the treatment.

Statement 18. Magnesium salts can cause hypermagnesemia in patients with an impaired renal function.

- Level of evidence: low
- Strength of recommendation: strong
- Experts' opinions: strongly agree, 52.3%; agree with reservation, 38.5%; undecided, 9.2%; disagree, 0.0%; strongly disagree, 0.0%.

Magnesium salt-induced hypermagnesemia has resulted in serious outcomes in some cases.[130-133] An impaired renal function and higher magnesium salt dosage are factors associated with hypermagnesemia. Furthermore, magnesium salts should be avoided in pregnant and lactating women, because there is insufficient evidence of their safety in these populations. Several studies have found that magnesium salts can reach fetuses through transplacental transfer and infants through breast milk.[134] Fatal hypermagnesemia has been reported after magnesium administration in cases of megacolon and bowel obstruction.[135,136] It is associated with altered magnesium absorption due to disruption of the intestinal mucosal barrier and decreased gastrointestinal motility.[137] Therefore, caution is needed when prescribing magnesium salts in these cases. Clinical symptoms of hypermagnesemia in mild cases include nausea, headache, lethargy, and flushing; in severe cases, the symptoms include respiratory failure, complete heart block, and cardiac arrest.[138] Generally, adults take 1-2 g of the active ingredient divided into two or three doses per day. However, because 2 g/day can cause hypermagnesemia, we recommend starting with a dose of approximately 1 g divided into 2 doses per day and adjusting the dose according to the symptoms.[138] It is important to monitor the serum magnesium levels in patients receiving magnesium, particularly those with chronic kidney disease and those receiving high doses of magnesium oxide.

Benefits: Magnesium salts are known to be excellent laxatives with low costs, easy dosage adjustment, and easy usage.
Cautions: Magnesium salt-induced hypermagnesemia has been reported to result in serious outcomes. Magnesium salts should be avoided in patients with an impaired kidney function and pregnant and lactating women.

Non-absorbable carbohydrates

Statement 19. Non-absorbable carbohydrates are effective in patients with chronic constipation.

- Level of evidence: low
- Strength of recommendation: strong
- Experts' opinions: strongly agree, 55.4%; agree with reservation, 36.9%; undecided, 6.2%; disagree, 1.5%; strongly disagree, 0.0%.

Non-absorbable carbohydrates include hyperosmolar laxatives; lactulose, lactitol, and sorbitol are used clinically. Lactulose is a

poorly absorbed synthetic disaccharide composed of galactose and fructose. It is not absorbed in the small bowel but is metabolized by bacteria in the large bowel. It promotes bowel movement by increasing the intestinal osmotic pressure and acidity.[139] Its onset of action occurs within 24-48 hours of administration, and a dose of 15-60 mL is recommended for adults. Sorbitol is a poorly absorbed sugar alcohol whose effects may be similar to those of lactulose.[140]

We selected three RCTs that compared non-absorbable carbohydrates and placebos in patients with chronic constipation[141-143]; their characteristics are summarized in Supplementary Table 7. A meta-analysis of these three RCTs (457 patients) revealed that non-absorbable carbohydrates were more efficacious than placebos, with lower rates of treatment failure (RR, 2.61; 95% CI, 1.76-3.85); treatment failure was defined by no changes in the bowel movement, additional laxative use, and scores indicating severe or very severe symptoms (Supplementary Fig. 4). In a similar study that compared osmotic compounds, sorbitol was as effective as lactulose in improving constipation; however, it was cheaper and better tolerated.[144]

Non-absorbable carbohydrates are metabolized by the gut flora in the large intestine to form gas, which can cause bloating and flatulence. The sweet taste of lactulose may affect the tolerability of treatment. A recent RCT revealed that patients treated with lactulose experienced diarrhea, abdominal pain, abdominal distension, and abnormal gastrointestinal sounds. However, there were no significant differences in the adverse drug reactions between the lactulose and placebo groups.[143] A recent meta-analysis concluded that lactitol and lactulose had similar efficacies against the symptoms of constipation and were tolerated similarly in patients.[145]

Statement 20. Long-term administration and use in elderly patients of non-absorbable carbohydrates may be considered as serious side effects are rare.

- Level of evidence: low
- Strength of recommendation: conditional
- Experts' opinions: strongly agree, 30.8%; agree with reservation, 55.4%; undecided, 9.2%; disagree, 4.6%; strongly disagree, 0.0%.

Two RCTs on elderly populations supported the efficacy of lactulose for improving the stool frequency as well as the need for additional laxatives.[141,142] Furthermore, another study on elderly patients with chronic constipation revealed that lactitol increased the frequency of defecation, improved stool consistency, and reduced the use of other laxatives.[146] Non-absorbable carbohydrates cause adverse events, such as flatulence, abdominal pain, nausea, and diarrhea; however, most events are transient. Considering that no previous studies have revealed serious side effects even after administration for more than 4 weeks, a long-term treatment with non-absorbable carbohydrates can be considered safe and well-tolerated.

To confirm the safety of non-absorbable carbohydrates in adult patients with chronic constipation, four RCTs comparing non-absorbable carbohydrates with polyethylene glycol (PEG; known to be relatively safe) were analyzed.[147-150] A meta-analysis found no significant differences in the incidence of abdominal pain, bloating, and flatulence between the non-absorbable carbohydrate and PEG groups (Supplementary Fig. 5). In a study on patients with constipation aged 70 years or older who were administered with lactulose or PEG for more than 6 months, no significant differences in severe adverse events (12.6% vs 19.5%) and drug discontinuation (6.3% vs 2.5%) were found between the two.[149] These findings suggest a similar tolerability between non-absorbable carbohydrates and PEG; thus, non-absorbable carbohydrates can be considered a treatment option for elderly patients with constipation. Alternatively, lactulose is not absorbed into the blood and does not affect nutrient absorption, fetal development, or breastfeeding; thus, it is safe in special cases of special medical conditions.[151,152] Pieber et al[153] confirmed that the administration of the recommended daily dose of lactulose (20-30 g) to patients with chronic constipation did not affect the blood glucose levels of those with type 2 diabetes mellitus. Several studies have also demonstrated the renoprotective effects and tolerability of lactulose in patients with chronic kidney disease.[154-156] In animal models of adenine-induced chronic kidney disease, lactulose-modified gut microbiota have been shown to suppress uremic toxin production and improve the renal function.[157] Therefore, lactulose can be safely administered to patients with constipation in special medical scenarios, such as those involving elderly patients, pregnant and lactating women, patients with diabetes mellitus, and patients with chronic kidney disease.

Benefits: Non-absorbable carbohydrates are effective in relieving symptoms of functional constipation. In addition, there are few drug-related side effects; thus, they can be used safely for the long-term and in special cases (such as those involving elderly patients, pregnant and lactating women, patients with diabetes mellitus, and patients with chronic kidney disease).
Cautions: Bloating and flatulence may occur with non-absorbable carbohydrate usage.

Polyethylene glycol

Statement 21. Polyethylene glycol is effective in the management of chronic constipation.

- Level of evidence: high
- Strength of recommendation: strong
- Experts' opinions: strongly agree, 83.1%; agree with reservation, 16.9%; undecided, 0.0%; disagree, 0.0%; strongly disagree, 0.0%.

PEG is a non-absorbable and non-metabolized agent that produces intraluminal osmotic gradients, which lead to fluid retention in the colon cavity and facilitate stool passage.[158] PEG is a commonly used osmotic laxative and has been known to be effective and safe for the treatment of chronic constipation.[7,159] We performed a meta-analysis to confirm the same. Eight RCTs that compared the efficacy and safety of PEG and placebo for chronic constipation treatment were identified (Supplementary Table 8).[160-166] In a meta-analysis including six RCTs with 829 patients,[160-162,164-166] PEG was more efficacious than the placebo in terms of treatment success (normalization of bowel frequency [≥ 3 SBMs/week] and relief from Rome-based symptoms). Accordingly, 56.4% and 26.1% of the patients with chronic constipation responded to PEG and the placebo, respectively (relative risk [RR], 0.55; 95% CI, 0.42-0.71; Supplementary Fig. 6). Another meta-analysis of five RCTs (649 patients) revealed that compared with patients treated with the placebo, patients treated with PEG experienced a statistically significant improvement in the stool frequency (RR, 2.17; 95% CI, 1.66-2.67; Supplementary Fig. 7).[160,161,163-165] PEG can be used effectively and safely without significant adverse events. In an RCT on 100 patients with chronic constipation, PEG treatment resulted in a greater incidence of diarrhea and flatulence as compared with the placebo; however, this difference was not statistically significant, and most events were mild or moderate.[164] Furthermore, in a pooled analysis of three RCTs including 161 patients, there was no significant difference in the safety between PEG and the placebo (RR, 1.16; 95% CI, 0.80-1.70; Supplementary Fig. 8).[164,166,167]

Statement 22. Polyethylene glycol is safe and tolerable for long-term treatment in patients with chronic constipation and can be considered for use in the elderly.

- Level of evidence: moderate
- Strength of recommendation: conditional
- Experts' opinions: strongly agree, 52.3%; agree with reservation, 41.6%; undecided, 4.6%; disagree, 1.5%; strongly disagree 0.0%.

PEG is thought to be well tolerated in patients with constipation without significant adverse events.[7] It is not metabolized by colonic bacteria and does not increase colonic gas; therefore, the incidence of bloating and flatulence with its usage is lesser.[168] Although PEG usage can be accompanied by gastrointestinal complaints (including diarrhea, abdominal pain, and nausea), no serious adverse events have been reported.[159] A meta-analysis of two RCTs (374 patients)[162,165] revealed that compared with the placebo, PEG remained effective even over a long-term (6 months; RR, 0.43; 95% CI, 0.24-0.79). An RCT on 70 patients treated with either PEG or the placebo for 24 weeks revealed no significant differences in the adverse events between the two. Furthermore, abdominal pain, flatulence, and borborygmi decreased during treatment with PEG.[162] In another RCT on 304 patients who underwent a 6-month treatment with PEG or the placebo, no significant differences in safety were noted between the two; however, the overall gastrointestinal complaints were higher in the PEG group (PEG vs placebo, 39.7% vs 25%; P = 0.015).[165] This RCT also included elderly patients (age ≥ 65 years), who accounted for 25.0% of the study population (n = 75/304); a similar efficacy was observed in these patients (46.0% difference in treatment success) over the 6-month treatment period. Moreover, no significant differences in the adverse events or clinically significant laboratory changes were observed in the elderly subgroup.[165] In an open-label study in which PEG was administered for more than 12 months, there were no clinically significant differences in the hematology or blood chemistry results (especially electrolytes) between the elderly and the remaining patients with constipation included in the study.[169] Considering its favorable efficacy, safety, and tolerability profile, PEG is acceptable for the long-term treatment of patients with chronic constipation (including those among the elderly).[7] Furthermore, PEG is not absorbed into the blood through the intestine; thus, in pregnant women, it does not affect the mother or the fetus significantly.[170,171] Recently, Li et al[151] compared the effects of PEG and lactulose in pregnant women with constipation, and found no fetal abnormalities in both group; they

reported that PEG shortened the treatment period. Therefore, PEG can be considered a therapeutic agent for pregnant women with chronic constipation.

Benefits: Polyethylene glycol is an effective drug even in elderly patients with constipation and is safe for long-term use and in special situations (such as pregnancy).
Cautions: Polyethylene glycol can cause abdominal discomforts, such as diarrhea, abdominal pain, and nausea.

Stimulant laxative

Statement 23. The administration of stimulant laxatives is recommended to relieve symptoms in patients with chronic constipation.

- Level of evidence: moderate
- Strength of recommendation: strong
- Experts' opinions: strongly agree, 46.2%; agree with reservation, 44.6%; undecided, 7.7%; disagree, 1.5%; strongly disagree, 0.0%.

Stimulant laxatives induce propagative contractions of the colon and increase water and electrolyte secretion into the intestinal lumen.[49] These agents include surfactant laxatives (dehydrocholic acid, castor oil, and docusate), anthraquinone (Senna, aloe, and cascara), and polyphenols (bisacodyl, sodium picosulfate, and phenolphthalein). In Korea, stimulant laxatives are available over the counter, and most are present in combination with other laxatives. Although the effects and appropriate doses and usage of each drug are unclear, bisacodyl and anthraquinone take 6-8 hours and 8-12 hours to exert an effect, respectively.[110,172]

Two double-blind, placebo-controlled studies have shown the efficacy of bisacodyl and sodium picosulfate for chronic constipation management in adults.[173,174] Both studies revealed that compared with the placebo, stimulant laxatives led to an increased number of complete SBMs (CSBMs) per week and improved the stool consistency. In a recently published meta-analysis,[175] bisacodyl and sodium picosulfate led to a significant increase in the CSBMs per week (mean difference, 2.46; 95% CI, 0.90-4.03). The positive global assessment rates of the efficacies of bisacodyl and sodium picosulfate were 78.0-99.0%. Another network meta-analysis demonstrated the superiority of bisacodyl to other drugs in terms of the number of SBMs/week.[176] A recent RCT revealed that compared with the placebo, Senna and magnesium salts significantly improved the bowel frequency and QoL scores.[129]

Statement 24. The use of stimulant laxatives in patients with chronic constipation should be recommended for a short-term period due to limited evidence on the long-term safety of these laxatives.

- Level of evidence: low
- Strength of recommendation: conditional
- Experts' opinions: strongly agree, 43.1%; agree with reservation, 43.1%; undecided, 13.8%; disagree, 0.0%; strongly disagree, 0.0%.

A recent meta-analysis revealed that adverse events following stimulant laxative usage were generally mild but common (occurring in up to 72.0% of the patients).[175] Diarrhea, abdominal pain, nausea, and headache were reported as adverse events in patients using stimulant laxatives. There are two safety concerns regarding the long-term use of stimulant laxatives. First, stimulant laxatives can be abused in patients with eating disorders.[177] Second, there is a possibility of a cathartic colon following long-term administration of stimulant laxatives.[178] However, no severe adverse events were identified in cohort studies of constipated patients using sodium picosulfate for more than 12 months.[179,180] A recent systematic review of over-the-counter therapy for chronic constipation recommended Senna as a first-line laxative.[106] Although studies on this have yielded conflicting findings, current evidence for the safety of stimulant laxatives (in comparison with the placebo) is available for up to 4 weeks. Based on the limited evidence on the long-term safety and the fact that other relevant treatment options exist, we support the short-term use of stimulant laxatives.

Benefits: Stimulant laxatives are effective in relieving the symptoms of functional constipation and can be considered as rescue therapy.
Cautions: There are concerns regarding the long-term safety and abuse of stimulant laxatives.

Probiotics

Statement 25. Probiotics can be used to relieve constipation symptoms in patients with chronic constipation. However, because the effects of probiotics vary depending on their species/strains and because the results between studies are inconsistent, it is recommended to use probiotics as a supplementary treatment.

- Level of evidence: low
- Strength of recommendation: conditional
- Experts' opinions: strongly agree, 29.2%; agree with reservation, 50.8%; undecided,16.9%; disagree, 3.1%; strongly disagree, 0.0%.

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host according to the Food and Agricultural Organization (FAO)/WHO (World Health Organization) definition.[181] There is evidence that probiotics are effective for acute infectious diarrhea, antibiotic-associated diarrhea, *Clostridioides difficile*-associated diarrhea, hepatic encephalopathy, ulcerative colitis, functional gastrointestinal disorders, and necrotizing enterocolitis.[182,183] To identify the effect of probiotics on functional constipation, we searched electronic databases and selected 25 RCTs comparing probiotics and placebo in functional constipation.[184-208] The characteristics of the included 25 RCTs are summarized in Supplementary Table 9. Changes in the SBMs per week at 4 weeks increased in the probiotic group (Supplementary Fig. 9). However, the heterogeneity between the studies was very high (I^2 = 97%). This may be due to the different probiotic strains, doses, and administration durations in each study. Changes in the SBMs per week at 2 weeks and 8-12 weeks showed similar results. Changes in stool consistency also showed significant improvement in probiotic group, with high heterogeneity (I^2 = 89%). Adverse events in the probiotic group were not significantly different from those in the placebo group. A meta-analysis analyzing the effect of probiotics on functional constipation in adults showed that probiotics reduced whole gut transit time significantly and improved incomplete evacuation.[209] Summary of findings is presented in Supplementary Figure 10. Considering the above results, probiotics seem to increase the frequency of bowel movements and alleviate symptoms of functional constipation. However, there is a limitation in recommending specific probiotic strains and doses, such as medications, because the studies used different strains and doses of probiotics and showed heterogeneous effects according to the strain and dose. Therefore, although the overall effect of probiotics is acknowledged, their use as an adjunct to other treatments for chronic constipation is recommended.[210] Overall, the adverse effects of probiotics were not significantly different from those of placebo. However, sepsis has been reported to occur when probiotics are administered to patients with severe pancreatitis. Therefore, caution is needed in immunosuppressed patients, patients in intensive care units, and patients with a central line.[211]

Benefits: Some probiotics can increase spontaneous bowel movement and improve stool consistency.
Cautions: Caution should be exercised in immunocompromised patients, patients in intensive care units, and patients with central lines.

Prucalopride

Statement 26. Prucalopride is a highly selective serotonin (5-hydroxytryptamine)-4 agonist that accelerates the whole gut motility. It is effective in the management of chronic constipation, even in patients who exhibit an inadequate response to conventional laxatives.

- Level of evidence: high
- Strength of recommendation: strong
- Experts' opinions: strongly agree, 76.9%; agree with reservation, 20.0%; undecided, 3.1%; disagree, 0.0%; strongly disagree, 0.0%.

Prucalopride is a highly selective 5-HT_4 agonist that accelerates whole gut motility.[212] While its use was authorized in Korea in October 2012, it remains commercially unavailable in some Asian countries. The recommended dose of prucalopride is 2 mg once daily.

Several studies have demonstrated that prucalopride improves the bowel function and constipation-related symptoms in patients with CIC with an inadequate response to conventional laxatives.[213-216] Furthermore, prucalopride has beneficial effects in elderly patients with CIC,[217] and achieves long-term satisfaction with bowel function for up to 18 months.[213]

For a meta-analysis, we selected 9 RCTs comparing prucalopride and placebo in patients with CIC; these RCTs are shortly summarized in Supplementary Table 10.[213-221] The proportion of patients with ≥ 3 CSBMs per week was higher in the 1 mg (OR, 2.90; 95% CI, 1.49-5.68) and 2 mg (OR, 2.51; 95% CI, 1.87-3.37) prucalopride groups than in the placebo group (Supplementary Fig. 11). Adverse events, such as headache,

nausea, abdominal pain, and diarrhea, were more frequent in the 2 mg group than in the placebo group (OR, 1.78; 95% CI, 1.28-2.49); however, their incidence did not differ significantly between the 1 mg and placebo groups (OR, 1.81; 95% CI, 0.77-4.27; Supplementary Fig. 12). These findings are summarized in Supplementary Figure 13. A recent meta-analysis revealed that 1 mg of prucalopride was safer for treating chronic constipation, and 2 mg of prucalopride could be more effective in increasing the SBMs per week.[222]

A large observational, population-based, cohort study found that prucalopride did not increase the risk of major cardiovascular adverse events; this is thought to be due to its high selective affinity for the intestinal 5-HT_4 receptor.[223] However, the use of prucalopride in some constipated patients requires clinical attention. Because prucalopride is primarily excreted in the urine, its clearance is significantly reduced in patients with severe renal impairment.[224] Acute tubular necrosis has been reported in patients treated with prucalopride, although the causal relationship remains unclear.[225] Similarly, caution should be taken when administering this drug to patients with progressive hepatic impairment (Child–Pugh class C) and the elderly (> 65 years). Therefore, it is recommended to reduce the dose of prucalopride to 1 mg once a day in patients with severe renal or advanced hepatic impairment and the elderly population.

Benefits: Prucalopride improves the bowel function and constipation-related symptoms in patients with chronic idiopathic constipation. No major cardiovascular toxicities have been reported.
Cautions: Caution must be exercised in patients with severe renal impairment (impaired glomerular filtration rate < 30 mL/min/m^2), those with progressive hepatic impairment (Child–Pugh class C), and the elderly (> 65 years). Dose reduction (1 mg) is recommended in such patients.

Lubiprostone

Statement 27. Lubiprostone, the chloride channel activator, is effective and safe for the management of chronic constipation. It does not cause clinically significant adverse effects, such as electrolyte imbalance and renal dysfunction.

- Level of evidence: high
- Strength of recommendation: strong
- Experts' opinions: strongly agree, 67.7%; agree with reservation, 29.2%; undecided, 3.1%; disagree, 0%; strongly disagree, 0.0%.

Lubiprostone is a prostone that stimulates chloride secretion through the activation of chloride channels in the gastrointestinal tract.[226] This enhances gastrointestinal fluid secretion and transit and improves the symptoms of constipation.[227] The US Food and Drug Administration (FDA) approved 24 μg and 8 μg of lubiprostone (twice daily) for the treatment of adults with functional constipation and constipated adult women with the irritable bowel syndrome, respectively.[228] Lubiprostone was also approved for use in Korea by the K-FDA in 2019.

For a meta-analysis, we selected six RCTs comparing lubiprostone and the placebo in patients with CIC; the characteristics of these RCTs are summarized in Supplementary Table 11.[229-234] The number of SBMs per week at 4 weeks increased significantly in the lubiprostone group as compared to in the placebo group (mean difference, 1.74; 95% CI, 0.80-2.69; Supplementary Fig. 14). The proportion of patients with > 3 SBMs per week at 4 weeks was higher in the lubiprostone group (Supplementary Fig. 15). Overall, adverse events occurred more frequently in the lubiprostone group than in the placebo group; nausea was the most common adverse event in the lubiprostone group. However, serious adverse events did not differ significantly between the 2 groups. These findings are summarized in Supplementary Figure 16. Similar results were obtained in a meta-analysis by Li et al,[235] who reported that lubiprostone increased bowel movements, stool consistency, degree of straining, and degree of abdominal pain or discomfort.

The safety and effectiveness of long-term lubiprostone usage were reported in a prospective, open-label trial and an extended RCT.[236,237] The prospective, open-label study enrolled 248 patients with CIC aged over 18 years; they were directed to take lubiprostone (24 mg twice a day) as needed for 48 weeks. The mean symptom ratings for abdominal discomfort, constipation severity, and bloating decreased during the 48-week period. The most common treatment-related adverse events were nausea (19.8%), diarrhea (9.7%), and headache (6.9%).[236] Another study analyzed the electrolyte changes following short-term and long-term lubiprostone use; lubiprostone did not cause clinically meaningful electrolyte imbalances or affect the renal function markers.[238] However, patients with liver dysfunction exhibit high levels of active metabolites of lubiprostone, and dose adjustment is recommended in those with Child–Pugh class B or C.[239] Approved in only some Asian countries thus far, lubiprostone has limited availability in several Asian countries.

Benefits: Lubiprostone can increase spontaneous bowel movements, improve stool consistency, and decrease straining- and constipation-related symptoms. It can be safely used in patients with renal impairment.
Caution: Nausea is a common adverse event; the medication can be taken with meals to reduce nausea. Dose reduction is required in patients with moderate-to-severe hepatic dysfunction. This medication is prohibited in pregnant women.

Linaclotide

Statement 28. Linaclotide, an intestinal secretagogue, is effective and safe for the management of chronic constipation.

- Level of evidence: high
- Strength of recommendation: strong
- Experts' opinions: strongly agree, 64.6%; agree with reservation, 29.2%; undecided, 6.2%; disagree, 0.0%; strongly disagree, 0.0%.

Linaclotide is a guanylate cyclase-C agonist that induces fluid secretion in the intestinal lumen and accelerates intestinal transit. Several meta-analyses have evaluated the therapeutic efficacy of linaclotide in patients with CIC.[172,240-244] However, inconsistent article selection criteria in each study resulted in inaccurate pooled estimates.

The clinical efficacy of linaclotide in CIC treatment was systematically reviewed. Phase III RCTs were included to evaluate the therapeutic efficacy of linaclotide in patients with CIC. A meta-analysis (with a sensitivity analysis) was performed. Five RCTs were finally included (Supplementary Fig. 17 and Supplementary Tables 12 and 13).[245-248] The efficacy of linaclotide was higher than that of the placebo (RR, 3.06; 95% CI, 2.19-4.27; I^2: 32%); the primary endpoints were as follows: ≥3 CSBMs and an increase of ≥ 1 CSBM per week or ≥ 3 SBMs and an increase of ≥ 1 SBM per week (Supplementary Fig. 18). Subgroup analysis according to the linaclotide dosage and duration yielded consistent results (Supplementary Fig. 19 and 20). The adverse event rate was higher in the linaclotide group than in the placebo group (RR, 1.21; 95% CI, 1.11-1.31; I^2, 13%). However, diarrhea was the most common adverse event and did not require further management. Serious adverse events have not been specifically reported in the published literature (Supplementary Fig. 21 and 22).[245-248] Linaclotide is currently unavailable in several Asian countries, including Korea. Furthermore, several studies have found that linaclotide improves bloating or abdominal discomfort in patients with chronic constipation.[246,247] Linaclotide is also known to be effective in treating symptoms of irritable bowel syndrome with constipation.[243] Given this evidence, linaclotide is expected to be effective in the treatment of constipation and abdominal symptoms. Overall, linaclotide is an effective treatment for chronic constipation (Supplementary Fig. 23).

Benefits: Linaclotide showed a higher efficacy than the placebo in patients with chronic idiopathic constipation.
Cautions: The rate of adverse events was higher in the linaclotide group than in the placebo group. However, diarrhea was the most common adverse event and did not require any further management. Serious adverse events have not been specifically reported in the published literature.

Behavioral therapy: Biofeedback Therapy

Statement 29. Biofeedback therapy is effective and safe for treating patients with defecatory disorders.

- Level of evidence: moderate
- Strength of recommendation: strong
- Experts' opinions: strongly agree, 61.5%; agree with reservation, 35.5%; undecided, 1.5%; disagree, 1.5%; strongly disagree, 0.0%.

Biofeedback therapy is a behavioral therapy that converts physiological anorectal and pelvic floor muscle activity (determined using electromyography [EMG] or manometry) to simple visual or auditory information that allows patients to learn how to control dyssynergic anorectal and pelvic floor muscle function. Notably, biofeedback therapy effectively improves CSBMs and satisfaction in patients with STC combined with DD, but not in those with isolated STC (70.0% vs 8.0%).[249] Thus, patients must be carefully evaluated to determine their eligibility for biofeedback therapy. RCTs have revealed symptom improvements in 50.0-80.0% of the patients with DDs following biofeedback therapy, irrespective of whether they also have STC.[250-262] Most RCTs revealed that for DD, biofeedback therapy was superior to other modalities (such as counseling, sham-biofeedback, placebo, diazepam, and PEG) in terms of improvements in the symptoms and anorectal physiology on manometry or EMG.[250,252,253,257,259-261] Only two small RCTs from a single research group revealed biofeedback to be inferior to other, more invasive methods (such as botulinum toxin injection and surgery).[256,258] These RCTs revealed that surgery was highly effective, with a clinical improvement rate of 95%. However, a

high complication rate of 10.0-15.0% was also noted, with complications including fecal incontinence, rectal intussusception, and wound infection; these studies were criticized for having a low statistical power and a simpler biofeedback protocol as compared to that of other studies.[263]

Some factors have been suggested as predictors of biofeedback therapy outcomes in DD management. Harder stool consistency, digital maneuvers to facilitate defecation, shorter duration of laxative use, higher resting anal sphincter pressure, integrated pressurized volume, prolonged balloon expulsion time, and baseline satisfaction of the patient have been reported as predictors of a desirable outcome.[264-266] Notably, co-existing STC does not affect the outcome of biofeedback therapy and can improve the transition time.[249,265] The biofeedback modality (manometry or EMG; office-based or home-based) does not affect the therapy outcome.[251,267] A previous study revealed no significant differences in the improvement of dyssynergic contraction and symptoms between manometric and EMG-based biofeedback.[267] A recent study revealed that home-based biofeedback was non-inferior to traditional office-based biofeedback in terms of improvement of the symptoms and anorectal physiology.[251] To date, no adverse events related to biofeedback therapy have been reported.

Statement 30. Biofeedback therapy has long-term therapeutic effects and improves the quality of life in patients with defecatory disorders.

- Level of evidence: moderate
- Strength of recommendation: strong
- Experts' opinions: strongly agree, 52.3%; agree with reservation, 38.5%; undecided, 6.2%; disagree, 3.0%; strongly disagree, 0.0%.

Several RCTs and cohort studies have reported long-lasting therapeutic effects of biofeedback therapy for DD. RCTs with a follow-up period of more than 6 months (maximum, 24 months) revealed that compared to in controls, the therapeutic effects of biofeedback therapy were sustained until the end of the follow-up in most patients.[253,261,268] The study with the longest follow-up period was a retrospective cohort study (median follow-up: 44 months [range, 12-68 months]); it revealed sustained therapeutic effects in 82.5% of the initial responders.[269] The long-term effect of biofeedback also seems to be uninfluenced by the treatment modality (manometry or EMG).[267] No long-term adverse events have been reported. RCTs have also revealed that compared to the controls, patients who underwent biofeedback therapy showed a greater improvement in the QoL scores.[250,253,254,260,262,270] This effect of biofeedback on the QoL might also be a long-lasting one because one RCT comparing biofeedback and PEG revealed that patients who underwent biofeedback had a significantly better QoL at the 6-month follow-up.[253]

Benefits: Biofeedback is an effective treatment modality for defecatory disorders, irrespective of the co-existence of slow-transit constipation. Furthermore, biofeedback therapy has long-lasting therapeutic effects and can improve the quality of life of patients. To date, no adverse events have been reported.
Cautions: Biofeedback therapy cannot be assumed to be effective for all types of constipation. Only those with defecatory disorders are candidates for biofeedback therapy.

Local Treatment: Enema

Statement 31. Enemas can be effective in the subset of patients with refractory defecatory disorders.

- Level of evidence: low
- Strength of recommendation: conditional
- Experts' opinions: strongly agree, 20.0%; agree with reservation, 61.5%; undecided, 15.4%; disagree, 3.1%; strongly disagree, 0.0%.

An enema is a popular treatment option for managing constipation. However, despite its long history, there is insufficient evidence to support its effectiveness. Nevertheless, several clinicians and patients find it empirically effective in real-life clinical settings. Enemas may stimulate the colon to contract and eliminate stool by distending the rectum. In clinical practice, it is usually effective in eliminating stool in the rectum but not in the proximal colon. Because there is insufficient evidence, enemas should not be performed routinely; however, they can be pursued as an effective option for impacted stools in the rectum and for those who do not respond to other medical treatments appropriately. Various substances are used for enemas, including water, soap suds, glycerin, lactulose, sorbitol, and phosphate; ready-made products are also available that can be used immediately.

Rectal suppositories are widely used in real life for the treatment of constipation. As with enemas, there is limited evidence for their use. However, they have been a popular treatment option for decades and have been included in many guidelines for constipation; glycerin and bisacodyl suppositories are commonly used.

Statement 32: Enemas should be used with caution because there are no standardized guidelines on their use and they may cause adverse events, such as electrolyte imbalance and rectal mucosal injury.

- Level of evidence: low
- Strength of recommendation: conditional
- Experts' opinions: strongly agree, 49.2%; agree with reservation, 44.6%; undecided, 3.1%; disagree, 3.1%; strongly disagree, 0.0%.

Because of limited evidence, there are no standardized protocols for enema administration, and the risk of associated adverse events is unclear. Various adverse events have been reported for phosphate enemas, such as hyperphosphatemia, hypocalcemia, hypernatremia, hypokalemia, and metabolic acidosis.[271] Notably, these electrolyte imbalances are highly related to reported deaths by phosphate enemas.[271,272]

Adverse events due to phosphate enemas were related to old age, cardiological diseases, and renal failure. Thus, phosphate enemas must be used carefully, or even avoided, in patients with these risk factors. During enema administration, the device tip can cause mechanical injury to the rectal mucosa and perforation. The risk of perforation may be related to a weak rectal wall, obstruction, or the patient's position; a single-center study revealed the incidence of enema-associated perforation to be 1.4%.[272] Thus, enemas must be

Table 4. Summary of the Efficacy and Cautions of Lifestyle Modification and Medical Treatment

Management	Level of evidence	Strength	Cautions
Dietary fiber	++	▲	Slow-transit constipation and defecatory disorders
Exercise	+	▽	
Bulking agent	++	▲	Insoluble bulking agents (abdominal distention, flatulence)
Magnesium salt	+++	▲	Impaired renal function, pregnancy, lactating women
Non-absorbable carbohydrates	+	▲	Bloating and flatulence
Polyethylene glycol	+++	▲	Diarrhea, abdominal pain, and nausea
Stimulant agent	++	▲	Long-term safety and abuse
Probiotics	+	▽	Immunocompromised patients
Prucalopride	+++	▲	Renal and hepatic impairment, elderly
Lubiprostone	+++	▲	Nausea, hepatic dysfunction, pregnancy
Linaclotide	+++	▲	Diarrhea

+, low; ++, moderate; +++, high; ▲, strong; ▽, conditional.

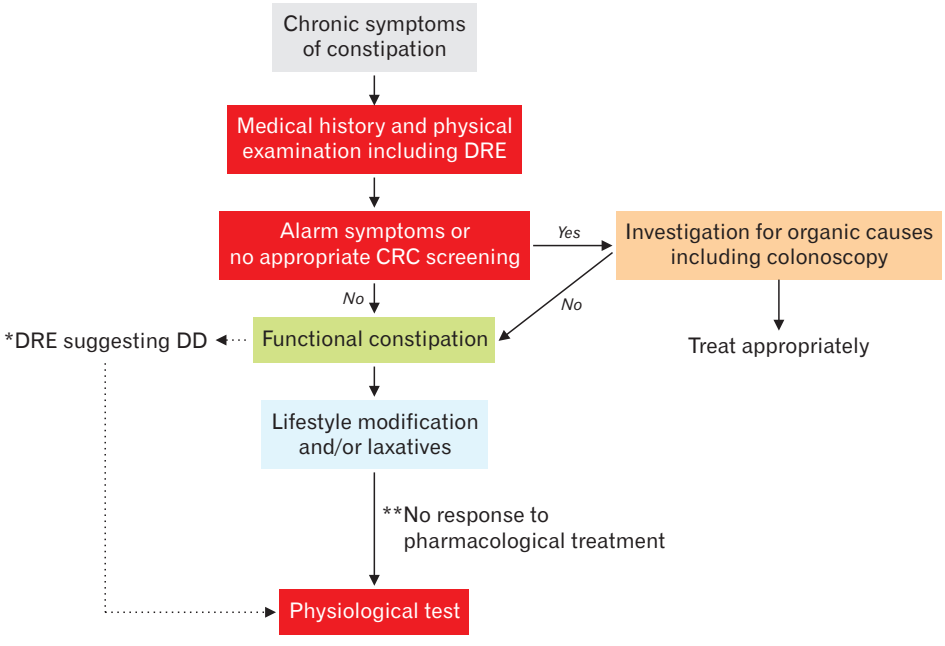

Figure 2. Initial approach of patients with chronic constipation. *Physiological test can be considered earlier in cases of strongly suspected defecatory disorders in digital rectal examination (DRE). DD, dyssynergic defecation. **Patients who have failed to respond to treatment with available laxatives (for a minimum of 12 weeks and under a recommended therapeutic regimen).

performed with caution, and clinicians must be aware of the associated adverse events.

Benefits: Enemas can be effective in patients with defecatory disorders who do not respond to other treatment options.
Cautions: There is insufficient evidence on the use of enemas. In our experience, only stool in the rectum can be effectively removed with an enema. Critical adverse events can occur, such as electrolyte imbalances and bowel perforation.

Surgical Treatment

Surgery

Statement 33. Colectomy can be considered in highly selected patients with medically intractable (non-responsive) slow-transit constipation who do not have defecatory disorders and other gastrointestinal motility disorders.

- Level of evidence: moderate
- Strength of recommendation: conditional
- Experts' opinions: strongly agree, 48.3%; agree with reservation, 37.9%; undecided, 6.9%; disagree, 6.9%; strongly disagree, 0.0%.

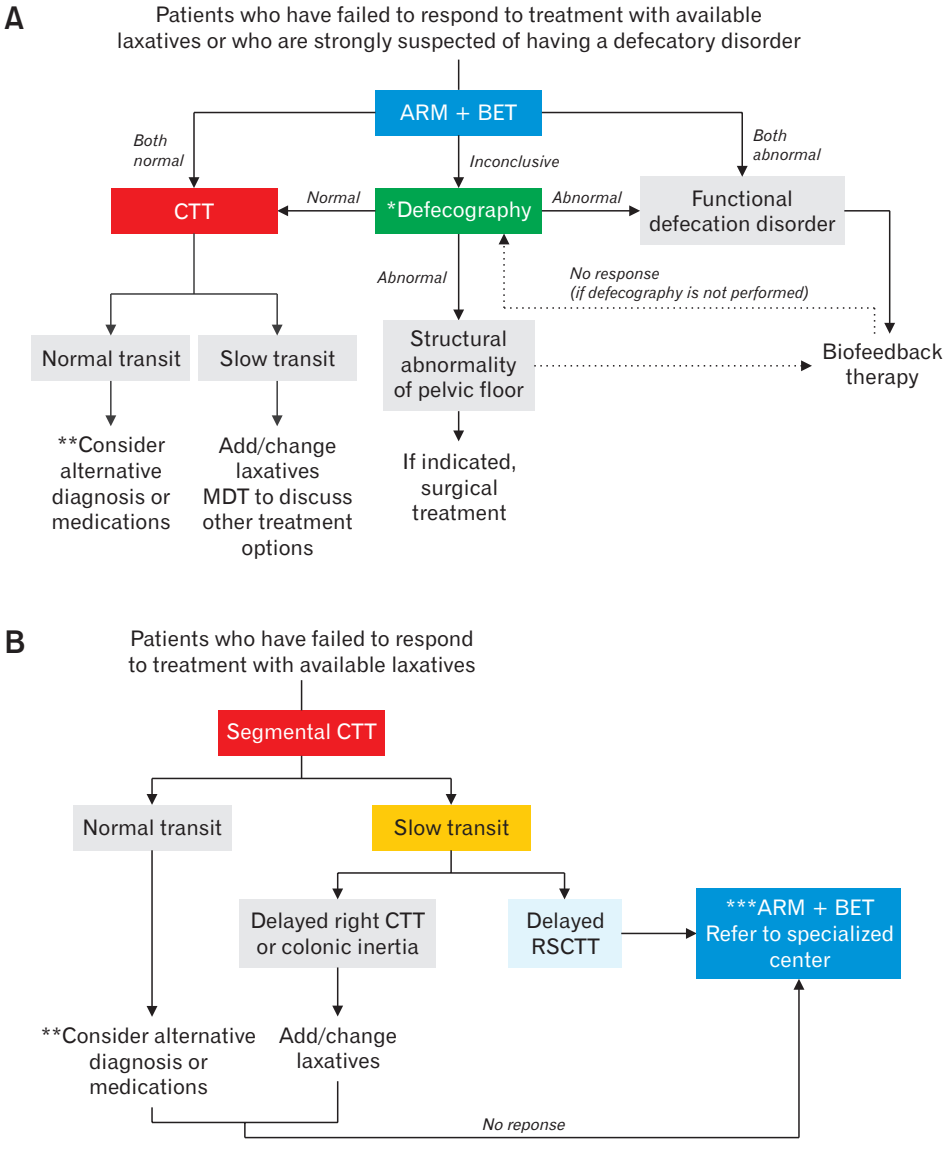

Figure 3. Diagnostic approach of functional constipation. (A) Diagnostic algorithm in specialized centers where anorectal manometry (ARM) can be available. (B) A possible diagnostic algorithm in medical institutions where ARM cannot be available. *Defecography could be performed concurrently with ARM when it is feasible or when structural abnormalities of the pelvic floor are clinically suspected. **Consider chronic constipation due to other causes such as drug, underlying disease, or IBS-C, etc. ***Apply the diagnostic algorithm in Figure 3A. BET, balloon expulsion test; CTT, colon transit time; STC, slow transit constipation; RSCTT, rectosigmoid CTT; FDD, functional defecation disorder; MDT, multidisciplinary team.

After a previous search for the Korean guideline, the 2015 revised edition, there have been 4 prospective and 13 retrospective cohort studies for evaluating outcomes after colectomy, but no RCT until August 2021. All studies revealed an improvement in the defecation frequency or QoL after colectomy.[273-288] A literature review of previous reports revealed average bowel movements of 1-3 (range, 0.5-6) per day after total colectomy with ileorectal anastomosis; the overall success rate was more than 90% (range, 65.0-100.0%).[289] In a recent systematic review and meta-analysis, most patients had a satisfactory or good outcome after colectomy (average follow-up: 4.3 years [range, 1-11 years]). The overall global satisfaction rating was 85.6% (95% CI, 81.4-89.3%; I^2 = 76.9%), based on data from 1616 patients.[290] However, more computed tomography scans and operative interventions were observed to have been undertaken after colectomy, and the healthcare resource utilization did not decrease. This raised questions about the true benefit of surgery for STC.[291] Patient selection is key to achieving successful outcomes following colectomy, because surgical resection is the final option and can cause irreversible changes. Colectomy can be considered a last resort in patients with medically refractory constipation and can finalize all other interventions.[292] The patients should be completely evaluated to exclude any other medical or psychological disorders that may have aggravated the symptoms. Constipation with combined pelvic floor disorders or pan-enteric dysmotility has also been considered a relative contraindication.[293-295]

Statement 34: Surgery for obstructed defecation syndrome can be indicated in patients with reparable structural abnormalities (such as rectocele, rectal intussusception, or rectal prolapse).

- Level of evidence: low
- Strength of recommendation: conditional
- Experts' opinions: strongly agree, 23.1%; agree with reservation, 63.1%; undecided, 10.8%; disagree, 1.5%; strongly disagree, 1.5%.

Obstructed defecation syndrome (ODS) is a distressing condition that can severely affect the QoL despite its benign prognosis.[296] Its typical symptoms are excessive straining, constipation, and incomplete evacuation of the rectum (which can cause fecal incon-

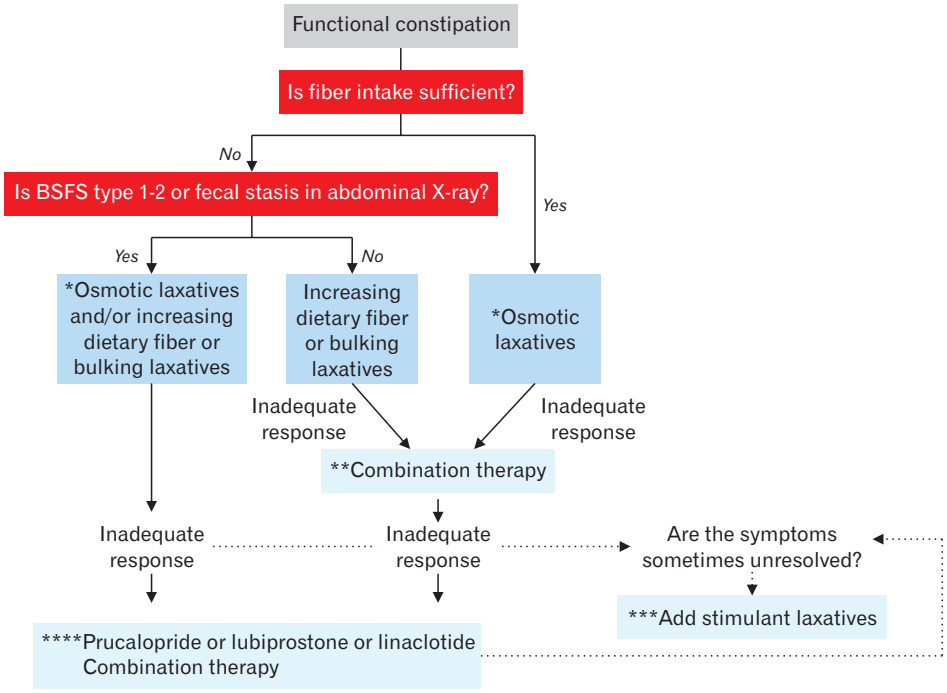

Figure 4. Algorithm for medical treatment of patients with functional constipation. *Magnesium salts should not be used in cases of abnormal renal function, and nonabsorbable carbohydrate is recommended to be prescribed in the absence of gas or ileus to improve patient compliance. **Combination treatment with bulking laxatives and osmotic laxatives can be considered at the start of treatment. If clinically needed, consider combination therapy based on action mechanisms, benefits, and cautions of the laxatives. ***Stimulant laxatives can be considered as rescue therapy due to concerns about long-term safety and abuse. ****Prucalopride, lubiprostone, and linaclotide can be used as monotherapy or in combination with each other or with laxatives already used and may be selected as a first-line agent in some cases.

tinence).[297] Following the release of the 2015 Korean guidelines for chronic functional constipation,[7] three RCTs on surgical treatment for ODS were reported.[298-300] However, these studies compared patient outcomes among different surgical procedures and not between medical and surgical treatments.

Surgical treatments with a transperineal approach have been used to anatomically correct a rectocele by reinforcing the barrier between the rectum and the vagina. In 2017, a systemic review revealed an overall perioperative complication rate of 11.5% (95% CI, 7.2-16.6%; I^2 = 87%), a global improvement of 72.8% (95% CI, 66.8-78.3%; I^2 = 86%), and an anatomical recurrence rate of 17% (95% CI, 11.7-23.3%; I^2 = 89%) at a mean follow-up of 23.4 months.[297] Another possible pathogenesis of ODS may be mucosal obstruction from the redundant rectal wall. Stapled transanal rectal resection (STARR) is used to correct ODS. Current evidence on the safety and efficacy of STARR for ODS is adequate in the context of this condition, which can significantly affect QoL.[297] A meta-analysis summarized the outcomes of STARR for ODS as follows[297]: overall procedural complication rate, 16.9% (95% CI, 12.7-21.5%; I^2 = 93%); patient global satisfaction rating, 76.3% (95% CI, 72.8-79.5%; I^2 =59%); and rate of recurrent prolapse, 4.3% (95% CI, 2.0-7.3%; I^2 = 78%).[297] Another surgical option may be straightening the intussusception and effacing the rectocele through the resuspension of the prolapsed rectum. According to a meta-analysis, morbidity rates ranged between 5.0-15.0%, with mesh complications accounting for 0.5% of the overall morbidity. Good or satisfactory outcomes occurred in 83% of 328 patients (95% CI, 74.0-91.0%; I^2 = 77%); 20.0-97.0% of the patients reported improvements in constipation after laparoscopic ventral mesh rectopexy. Approximately 2.0-7.0% of the patients developed anatomical recurrence.[301]

After summarizing the perioperative and long-term outcomes from several reports related to surgical treatments for ODS, we believe that surgical options can help improve the symptoms of chronic constipation arising from pelvic outlet obstruction. However, there are no established indications for appropriate patient selection and procedural standardization. Therefore, none of the surgical procedures have been proposed as a gold standard for ODS. However, if a surgical procedure can be applied to a particular case, several options are available and can be pursued based on the patient's condition.

Sacral nerve stimulation

SNS was first developed to treat urinary voiding dysfunction.[302] Since then, SNS has been established as a bridge treatment for fecal incontinence and has been recently studied as a new option for the surgical treatment of refractory chronic constipation.

To date, three randomized studies have determined whether SNS improves constipation symptoms in adults.[303-305] In these studies, SNS did not bring about significant improvements in "defecation with strain," "time spent in toilet," and the "Wexner score." However, defecation with a feeling of complete evacuation showed a significant improvement.

In a study by Zerbib et al,[303] serious adverse events were observed in nine out of 36 patients (wound infections [n = 2]); electrode wire displacement, sciatica, sinusitis, and vagal response [n = 1 each]; and abdominal pain [n = 3]); furthermore, 25 cases of device-related events were also noted. In a study by Dinning et al,[304] 73 adverse events occurred in 55 patients; these included implant site pain (44.0%), wound infection (16.0%), and urological adverse events (23.0%).

Taken together, the harm seems to outweigh the benefits. However, considering the effects and drawbacks of conventional surgical treatment and the fact that SNS is less invasive than conventional surgical treatment, SNS should be considered when non-surgical treatment is ineffective in patients with chronic constipation. Sufficient explanation for choosing a surgical treatment should be provided to patients with constipation in whom the previous treatment is ineffective. The patients should be carefully informed that the proven effect of SNS is not larger than its side effects, and that only alleviation of some symptoms can be expected. However, they should be informed that it is less invasive than other surgical treatments.

Conclusion

The 2022 Seoul Consensus on Clinical Practice Guidelines for functional constipation provides evidence-based information derived from systematic reviews and meta-analyses of recent literature. In the development of these guidelines, reliability, and expertise were increased through the participation of ANMA-recommended experts and a multidisciplinary approach. These guidelines describe the use of diagnostic methods that can be performed at primary medical institutions, such as BSFS, DRE, and colonoscopy, and present specific indications for physiological testing. Furthermore, these guidelines have suggested several treatment options, summarized the benefits and cautions of each treatment method, and presented specific guidelines for clinical situations in which each treatment method is preferred (Table 4). These guidelines suggest a new algorithm for the diagnosis and treatment of functional

constipation based on recommendations generated by referring to expert opinions and the domestic and foreign medical environments (Fig. 2-4). The present guidelines will be updated periodically in response to new evidence.

Supplementary Materials

Note: To access the supplementary tables and figures mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm23066.

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