Management of chronic constipation in patients with diabetes mellitus

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Abstract
Aim The aim of this review is to provide an overview of the clinical assessment and evidence-based treatment options for managing diabetes-associated chronic constipation.

Methods A literature search of published medical reports in English language was performed using the OVID Portal, from PUBMED and the Cochrane Database of Systematic Reviews, from inception to October 2015. A total of 145 abstracts were identified; duplicate publications were removed and 95 relevant full-text articles were retrieved for potential inclusion.

Results Chronic constipation is one of the most common gastrointestinal symptoms in patients with diabetes, and occurs more frequently than in healthy individuals. Treatment goals include improving symptoms and restoring bowel function by accelerating colonic transit and facilitating defecation. Based on guidelines and data from published literature, food and dietary change with exercise and lifestyle change should be the first step in management. For patients recalcitrant to these changes, laxatives should be the next step of treatment. Treatment should begin with bulking agents such as psyllium, bran or methylcellulose followed by osmotic laxatives if response is poor. Lactulose, polyethylene glycol and lactitol are the most frequently prescribed osmotic agents. Lactulose has a prebiotic effect and a carry-over effect (continued laxative effect for at least 6 to 7 days, post cessation of treatment). Stimulants such as bisacodyl, sodium picosulphate and senna are indicated if osmotic laxatives are not effective. Newer agents such as chloride-channel activators and 5-HT4 agonist can be considered for severe or resistant cases.

Conclusion The primary aim of intervention in diabetic patients with chronic constipation is to better manage the diabetes along with management of constipation. The physician should explain the rationale for prescribing laxatives and educate patients about the potential drawbacks of long-term use of laxatives. They should contact their physician if short-term use of prescribed laxative fails to provide relief.

Keywords Chronic constipation · Diabetes mellitus · Laxatives

Introduction
The prevalence of diabetes mellitus has reached epidemic proportions in both developed and developing countries, affecting more than 366 million people worldwide [1]. This number is likely to increase in the coming years as a result of an ageing global population, urbanization, rising prevalence of obesity and sedentary lifestyles [2]. Diabetes is on the verge of gaining the status of an epidemic in India. As per the 2011 estimate, India is home to 62 million diabetics, with an increase of nearly two million each year. India is expected to cross the 100 million mark by 2030 [3].

Several gastrointestinal (GI) symptoms such as diarrhea, chronic constipation and fecal incontinence are often observed in patients with diabetes mellitus [4–6]; among these, chronic constipation is the most commonly reported [7]. The prevalence of chronic constipation in the general population is reported as around 14% [8]. A recent cross-sectional study with 372 diabetic patients treated at an outpatient clinic reported that about 31% of patients had chronic constipation.
Prevalence studies conducted in the US, Europe and Hong Kong report the rate of chronic constipation in diabetic patients to be 10%, 13% to 22% and 27.5%, respectively, indicating that chronic constipation is a very common GI symptom in diabetics [9–12]. In another cross-sectional study, 13.9% of 224 Indian patients with functional constipation had diabetes [13].

Poor dietary habits, less fluid intake and low physical activity are significant factors leading to chronic constipation. The prevalence of chronic constipation has been reported to be higher in women than in men, in older patients (≥50 years), in those with longer (≥10 years) duration of diabetes mellitus and in those who take concomitant medications such as calcium-channel blockers that promote chronic constipation [14]. The occurrence of chronic constipation is significantly higher in diabetic patients with autonomic neuropathy compared to those without neuropathy (22% vs. 9.2%, p < 0.04) [15].

Measures of general health, social functioning and mental health are significantly impaired in patients suffering from chronic constipation and are comparable with those in other conditions such as osteoarthritis, rheumatoid arthritis and chronic allergies [16]. Given the growing prevalence of diabetes-associated chronic constipation, it is important to focus attention on early identification and appropriate management of these complications for improving both diabetic care and quality of life of the affected patient.

There is no universally accepted definition of constipation. In a real-world clinical setting, constipation tends to be a subjective diagnosis. Frequency of bowel movement is an important factor in the assessment of constipation, yet there is no consensus on how often the ‘normal’ bowel opens. There is wide variation between individuals in ‘normal’ frequency of bowel movements, ranging from three times per day to three times per week, but many patients have expectations of a daily bowel movement. In addition to frequency of stools, consistency of the stool is also important. The Bristol Stool Form Scale is a useful visual aid that was designed to assist in the evaluation of patients with self-reported constipation who do not have infrequent bowel movements, to establish that hard or lumpy stools are indeed present [17].

Based on definition, the prevalence of constipation varies between different populations across the world. The Rome classification is widely recognized as a standardized symptom-based classification of functional GI disorders, including functional constipation (Table 1) [18]. Other definitions of constipation are consistent with the Rome criteria but are less quantitative and more subjective [19]. The Rome criteria are however used principally for research purposes and are not widely applied in clinical practice [20]. The recently developed Rome IV classification defines functional constipation as a functional bowel disorder in which symptoms of difficult, infrequent or incomplete defecation predominate. Patients with functional constipation should not meet the criteria for irritable bowel syndrome, although abdominal pain and/or bloating may be present but are not predominant symptoms. Symptom onset should occur at least 6 months before diagnosis, and symptoms should be present during the last 3 months [21].

Functional constipation is divided into two subtypes: slow-transit constipation or colonic inertia is characterized by a prolonged length of time for stool to pass through the entire colon [22]; obstructive defecation (also called pelvic floor dyssynergia, dyssynergic defecation, anismus, or outlet obstruction) is characterized by difficulty in evacuation or a sense of incomplete evacuation after defecation.

### Table 1: Rome IV diagnostic criteria for functional constipation

Following criteria should be present for at least 3 months with symptom onset at least 6 months prior to diagnosis

1. Presence of ≥2 of the following symptoms:
   - Lumpy or hard stools (Bristol stool form scale 1–2) in ≥25% of defecations
   - Straining during ≥25% of defecations
   - Sensation of incomplete evacuation for ≥25% of defecations
   - Sensation of anorectal obstruction/blockage for ≥25% of defecations
   - Manual maneuvers to facilitate ≥25% of defecations (digital manipulations, pelvic floor support)
   - <3 spontaneous bowel movements per week

2. Loose stools rarely present without the use of laxatives

3. Insufficient criteria for irritable bowel syndrome

*In research studies, the patients with symptoms of opioid-induced constipation should not be diagnosed as FC, since it is difficult to distinguish between opioid side-effects and other causes of constipation. However, clinicians recognize that symptoms of the two conditions might overlap

### Pathophysiology

The exact pathogenesis of chronic constipation in diabetes is not well understood. The autonomic nervous system is intimately involved in the control of GI motility and sensitivity, and a disturbance of this system may be involved in the pathophysiology of constipation [15]. Autonomic dysfunction with a lack of synchronicity between the gut musculature and the sphincters is thought to be the major contributing factor [23]. Battle et al. [24] in their study of colonic myoelectric and motor activity, demonstrated that diabetic patients with chronic constipation had absent gastrocolonic response to feeding, resulting in mild to moderate constipation. High blood sugar levels in both types 1 and 2 diabetes can lead to loss of interstitial cells of Cajal (ICC) and diabetic neuropathy. Damage to the nerves controlling the digestive tract motility can lead to chronic constipation and sometimes alternating bouts of diarrhea [25–28]. For many patients, this condition is chronic, with symptoms persisting 3 months or more [29].
Clinical evaluation

A complete history and physical examination is needed to elicit the cause of constipation. It is imperative to rule out malignancy or other organic causes prior to making the diagnosis of chronic constipation. Evaluation includes recording exhaustive medical and social history including the patient’s psychological status, blood sugar levels, obstetric history (for women) and a complete list of medications that can be associated with constipation. It is important to determine the duration of symptoms to distinguish chronic from transient constipation, the amount of fiber the patient has as part of diet and laxatives or other self-prescribed over-the-counter constipation treatments the patient has indulged in, if any. A complete physical examination with emphasis on the abdomen and perineum is imperative.

The aim of clinical assessment should be to establish a symptom profile, in order to plan individualized bowel care. Evidence-based guidelines suggest that a structured approach is required when assessing a patient with chronic constipation. Routine extensive diagnostic and physiological testing is not recommended for chronic constipation [30, 31]. However, in patients not responding to initial treatment, physiological tests can be used to assess anorectal disorders [32–35].

The objective of this manuscript is to provide an overview of the clinical assessment and evidence-based treatment options for managing diabetes-associated chronic constipation.

Methods

A literature search of published medical reports in English language was performed using the OVID portal, from PUBMED and the Cochrane Database of Systematic Reviews, from inception to October 2015. Abstracts were initially obtained using the following keywords: chronic constipation’, type 1 diabetes’, type 2 diabetes’, treatment’ and ‘trials’. Manual searches of references and review articles supplemented the computerized search, and only full-length articles were considered. The literature search was done by VGM Prasad along with an independent external agency. They then selected studies that satisfied the following inclusion criteria: (1) involving human subjects over the age of 18 years and (2) describing at least one form of treatment for chronic constipation and chronic constipation in diabetes mellitus. Selected studies were evaluated by each reviewer for their quality and evidence according to the Strength of Recommendations Taxonomy (SORT), with levels of evidence from I to III and recommendations from A to C (Tables 2 and 3) [36].

A total of 145 abstracts were identified; duplicate publications were removed and 95 relevant full-text articles were retrieved for potential inclusion. Based on the findings, a practical approach to managing chronic constipation is summarized in Fig. 1.

Evidence-based management

Non-pharmacological treatment

It is imperative to understand the patient’s views and definitions of chronic constipation, which may often differ from medical criteria. Treatment aims to improve symptoms and restore bowel function by accelerating colonic transit and facilitating defecation [37].

Many patients’ symptoms can be relieved with lifestyle and dietary modification, both of which should be implemented before opting for unnecessary tests or prescription medications. The patient should be encouraged to follow a healthy lifestyle, which includes a high-fiber diet, increased water intake and physical activity [38]. A formal evaluation of dietary fiber and fluid intake should be carried out, before recommending further increase in dietary fiber [39].

Food and dietary changes

Dietary fiber can be defined as a plant-derived material that is resistant to digestion by human alimentary enzymes [40, 41]. There are two main types of fiber, insoluble and soluble. Insoluble fiber is not acted on by colonic bacteria and does not create colon gas. It is an important fiber because it retains water within the colon, promoting a large, bulky stool and improved regularity. Soluble fiber is fermented by colonic bacteria. Taken together and in adequate quantities, soluble and insoluble fibers help improve constipation and mineral absorption.

The American Diabetes Association (ADA) guidelines recommend lifestyle changes involving dietary and physical activity as first-line therapy for most individuals with diabetes [42]. These are also first-line therapy for patients who suffer from chronic constipation. Dietary fiber has a role to play in increasing stool weight and improving bowel movement [43]. However, before recommending changes or increase in dietary fiber, a formal evaluation of dietary fiber and fluid intake needs to be conducted as excessive fiber intake can aggravate bloating and flatulence and lead to abdominal cramps. The generally recommended daily dietary fiber intake in adults is 20–30 g [39]. Vegetarianism is associated with high dietary fiber intake. Therefore, thorough evaluation of type of dietary fiber and recommended dose should be conducted [44].

Although there is some evidence from controlled trials confirming the efficacy of high-fiber diets, this treatment fails
to normalize bowel movements in up to 40% of patients, especially in those with slow transit or impaired defecation [45–47]. Voderholzer et al. [48] conducted an observational study among 149 patients with chronic constipation when treated with dietary fiber (plantago ovate seeds); 85% of patients without a pathological finding became symptom-free while 80% of patients with slow transit did not respond.

Health practitioners regularly recommend increased fluid intake to alleviate chronic constipation, although evidence suggesting benefit is limited.

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
<th>Mechanism of action</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Contraindications</th>
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<th>Comments</th>
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<tbody>
<tr>
<td>Bulk-forming laxatives</td>
<td>Wheat bran, psyllium seed husk, methylcellulose</td>
<td>Luminal water binding increases stool bulk and reduces consistency</td>
<td>Useful treatment for small hard stools. Benefit irritable bowel syndrome patients, and colostomy and ileostomy patients</td>
<td>Flatulence and abdominal distension, GI obstruction or impaction</td>
<td>Difficulty in swallowing, intestinal obstruction, colonic atony, and fecal impaction</td>
<td>At least 3 well-designed RCTs showing benefits over placebo</td>
<td>Two controlled trials showed benefits in reducing use of laxatives</td>
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<tr>
<td>Osmotic laxatives</td>
<td>Lactulose [62, 115]</td>
<td>Luminal water binding by creating osmotic gradient</td>
<td>Gentle and effective laxative action, prebiotic effect; does not increase blood sugar</td>
<td>Bloating, flatulence, diarrhea (with large doses) “Too sweet taste” can be masked by diluting in water</td>
<td>Galactosemia, intestinal obstruction</td>
<td>A</td>
<td>Two systematic reviews of RCTs with benefits over placebos</td>
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<tr>
<td>Undigestible disaccharides</td>
<td>Polymethylene glycol (PEG) [62, 116, 117]</td>
<td>Luminal water binding</td>
<td>Does not increase colonic gas</td>
<td>Abdominal distension and pain, nausea, excessive diarrhea (can be controlled with dose adjustment)</td>
<td>Intestinal perforation or obstruction, paralytic ileus, severe inflammatory conditions of the GI tract</td>
<td>A</td>
<td>At least 3 RCTs showing benefits over placebo</td>
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<td>Synthetic macromolecule</td>
<td>Bisacodyl, sodium picosulfate</td>
<td>Act locally to stimulate colonic motility, decrease water absorption from large intestine</td>
<td>Patients unresponsive or intolerant to fiber</td>
<td>Abdominal cramp, hypokalemia</td>
<td>Intestinal obstruction</td>
<td>Senna [118–120] : A</td>
<td>At least 3 controlled trials showing benefits over placebo</td>
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<td>Stimulant laxatives</td>
<td>Senna, aloe, cascar</td>
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Exercise and lifestyle changes

Regular physical exercise helps not only in the digestion process but is also recommended in the ADA guidelines as a key feature in managing diabetes, which in turn can improve GI complications by reducing diabetic neuropathy [49]. The ADA recommends moderate-intensity exercise for \( \geq 150 \) min per week over \( \geq 3 \) times per week with no more than two consecutive days’ gap without exercise, for diabetes patients. The guidelines also recommend reducing sedentary time (break up >90 min spent sitting). A number of studies across different populations have shown that lifestyle changes can reduce the incidence of type 2 diabetes by 28 to 59%, with the effects seen many years after the intervention [50–56].

As chronic constipation can be caused by a host of lifestyle factors, such as change in routine, lack of regular exercise, or ignoring the urge to defecate, lifestyle modification incorporating appropriate amount of exercise is generally recommended as an initial management tool for treating mild to moderate symptoms of chronic constipation in diabetes mellitus patients [42].

Medical management

If adequate relief is not obtained with dietary and lifestyle changes, a range of pharmacological agents can be considered. The most recognized and acceptable treatment is the use of laxatives (Tables 2 and 3). There are no studies assessing a stepwise approach to laxative therapy. The Asian Neurogastroenterology and Motility Association and Rome IV recommend that therapy should begin with a bulk-forming agent, followed by treatment with an osmotic laxative and stimulant laxative in patients with inadequate response to bulk-forming agents [39].

Laxatives aid defecation by decreasing stool consistency (softening) and/or artificially or indirectly stimulating colon motility via one or more mechanism (Table 2) [20]. These formulations can be taken by mouth (liquids, tablets, capsules), or can be given via the rectum (e.g. suppositories, enemas) [20]. Well-designed, placebo-controlled, blinded, clinical trials of older laxatives are sparse; similarly, there is a lack of head-to-head comparisons.

While developing treatment strategies, it is important to recognize that patients with diabetes have compositional changes in the intestinal microbiota compared to non-diabetic patients. Gut microbiota are essential for the digestion and production of organic acids to maintain an appropriate pH environment in the gut [57]. In diabetes patients, there is a loss of gut microbial diversity with an increase in opportunistic pathogens. In a study of 36 men, the relative abundance of Firmicutes (specifically Bacteroides vulgatus, Faecalibacterium prauznitzii) and the Bifidobacterium and Roseburia genera were observed to be significantly lower, while the proportion of Bacteroidetes and Proteobacteria was found to be somewhat higher in diabetic persons compared to their non-diabetic counterparts [58].
Probiotics and prebiotics can eradicate gut dysbiosis and ameliorate inflammatory, metabolic and molecular imbalances, thus preventing or treating diabetes and development of neurodegenerative disease. Probiotic therapies increase insulin sensitivity, inflammation, oxidative stress and GI distress. Prebiotics were shown to increase the level of species in the Bifidobacterium genus, an effect that positively correlates with improved glucose tolerance and glucose-induced insulin secretion and reduced inflammatory markers [59, 60].

Bulk-forming laxatives

Bulk-forming laxatives, also known as fiber laxatives, add soluble fiber to the stool. This helps in retaining fluid in the stool, thus making stool soft and easier to pass. Commonly prescribed bulk-forming laxatives include ispaghula/psyllium husk, bran and methylcellulose [61]. A systematic review by Tramonte et al. (1997) listed six trials on treatment with fiber laxatives, which resulted in increase of 1.4 bowel movement per week [62]. A double-blind trial reported that fiber laxatives gave significant symptom improvement, improved stool consistency and resulted in fewer complaints of abdominal pain [63–65].

Psyllium husk is reported from well-designed, randomized, placebo-controlled studies to improve symptoms and provide natural constipation relief by improving colonic transit time and stool consistency [66–68]. This is an edible soluble fiber and a prebiotic. Psyllium husk swells when combined with water or another liquid, and produces more bulk, which stimulates the intestines to contract. It is also known to have positive effects on heart health, blood pressure and cholesterol levels. It is safe, well-tolerated and improves glycemic control in people with diabetes. In adults with chronic idiopathic constipation, psyllium increased the mean number of stools per
week by 0.9, compared to no change in the placebo group ($p < 0.05$), in one 8-week trial [68]. Another trial found that adults with chronic constipation who received 2 weeks of psyllium were more likely to report normalization of bowel function than those who received placebo (87% vs. 30%, $p < 0.001$) [64]. A third, 2-week study found that 87% of patients allocated to psyllium reported improvement in symptoms compared to 47% of those who received placebo [63]. One study found that psyllium not only improved blood sugar in type 2 diabetic patients but also reduced the risk of coronary heart disease, suggesting that it can be considered as an efficacious option for diabetes patients with chronic constipation [69].

### Osmotic laxatives

Osmotic laxatives work by creating an osmotic gradient that increases the retention of water in the stool, making them soft and enhancing their passage. Osmotic laxatives include both inorganic salts (magnesium compounds) and organic sugars or alcohols such as lactulose, lactitol and polyethylene glycol (PEG). Their dose can be titrated according to the stool output, and they are used for both chronic and occasional constipation [70]. Lactulose and PEG have been shown to be effective and safe treatments for chronic constipation and are commonly used in both pediatric and adult populations. The alternative osmotic laxatives of magnesium hydroxide or magnesium salts are satisfactory for occasional use or where rapid evacuation is required but tend not to be used in the long-term [71]. Osmotic agents are useful when first-line bulk-forming agents do not provide satisfactory outcomes. Abdominal bloating, nausea and flatulence are side effects with some osmotic laxatives [70].

**Lactulose** is a synthetic disaccharide that does not get absorbed in the small intestine nor is it broken down by human enzymes. It stays as a bolus and causes retention of water through osmosis, leading to soft stool. It has a secondary laxative effect in the colon, where it is completely fermented by gut flora, producing metabolites that have osmotic abilities and peristalsis-stimulating effect [72]. Fermentation also leads to production of lactic acid and volatile fatty acids especially acetic acids, which may interfere with glucose metabolism by decreasing glucose hepatic production [73]. A small study evaluated the effect of purified lactulose (27–33 g/day) on glucose tolerance in seven non-insulin dependent diabetic patients during two randomized 10-day periods. At the end of the two periods, blood glucose levels during oral glucose tolerance test were significantly lower when patients received lactulose [72].

In healthy humans, the ingestion of lactulose has been shown to increase bifidobacterial degradation of primary to secondary bile acids. Lactulose can therefore be considered as a prebiotic as it positively affects host health by selectively stimulating the growth or activity of one or a limited number of colonic bacteria (bifidogenic effect). This is supported by data from a prospective, randomized, controlled trial comparing the effect of lactulose and PEG-4000 on colonic flora in 65 patients with chronic idiopathic constipation; fecal bifidobacterial counts were higher in the lactulose group than in the PEG group ($p = 0.04$). The study showed that lactulose induced significant changes in the composition of fecal flora, whereas PEG inhibited most of the metabolic activities of the flora [74]. Bifidobacteria result in acidification of the colonic content, which is important for the energy metabolism and normal development of colonic epithelial cells and acts as a protective factor against colonic disease. In another randomized controlled study, comprising 12 healthy volunteers per group, the effect of lactulose, lactitol and placebo on colonic microflora and enzymatic activity was evaluated. Lactulose provided a better effect on colonic microflora and thus better prebiotic effect than lactitol. Lactulose was a better carbon source for the probiotic intestinal bacteria Bifidobacterium and Lactobacillus than lactitol, resulting in a reduction in detrimental species [75].

The clinical efficacy and safety of lactulose in treating chronic constipation have been established in randomized controlled studies. In a double-blind trial comparing lactulose (60 mL/day) with placebo, lactulose produced significant increase in stools per week (4.5 vs. 1.6 stools/week; $p < 0.05$) as well as stools of a softer consistency. Similarly, in another randomized, double-blind, placebo-controlled trial, lactulose (30 mL of 50% solution) was superior to placebo in improving mean bowel movement frequency per week and reducing severity of symptoms such as cramping, bloating and flatulence [76, 77]. Lactulose has demonstrated superiority to ispaghula in terms of mean bowel movement frequency per week, and a trend of causing less abdominal pain was observed [78]. Connolly et al. [79] reported that, after 1-week treatment with lactulose (15 mL twice daily), consistently more patients continued to produce normal stools than when they had received stimulant laxatives. Thus, lactulose can be considered as an effective osmotic laxative in treating constipation, with a possible positive effect on glycemic control in diabetes patients. It has a superior prebiotic effect as compared to PEG and lactitol in the context of the growing recognition of gut dysbiosis in the pathogenesis of diabetes and constipation, along with the added benefit of carry-over effect, thus making it a suitable laxative for managing constipation in diabetics.

Another group of osmotic laxatives that is commonly used is formulations containing polyethylene glycol. High doses of PEG-based formulations were originally used primarily for colon cleansing prior to colonoscopy. They have also been shown to be useful for fecal disimpaction in both children and the elderly [67, 80, 81]. These formulations are now used to treat chronic constipation. Daily doses of 17 g have been
given for up to 6 months in adults [82, 83]. These are also safe for use in children, pregnant women and the elderly. The most common side effect is diarrhea with liquid stools, which appears to be a function of the dose, occurring in up to 17% with single dose and up to 36% with double dose; thus patients have to be taught to titrate the dose according to their response [71]. Some formulations contain sodium and potassium; it is not known whether the small quantities present give rise to hypernatremia and hyperkalemia in the elderly and those with impaired renal functions [84].

PEG provides well-tolerated and effective relief in constipated patients [85, 86]. In a 6-month placebo-controlled study, 304 patients with chronic constipation received either 17 g per day PEG or placebo. Fifty-two percent of PEG-treated patients compared with 11% of placebo-treated patients (p < 0.001) were successfully relieved for more than 50% of their treatment weeks. No treatment-related safety differences were observed, with the exception of abdominal distension, diarrhea, loose stools, flatulence and nausea (39.7% of PEG-treated patients vs. 25% of placebo-treated patients; p=0.015), which are considered usual effects of laxative use [87]. A retrospective study of institutionalized patients with chronic constipation reported good long-term results for up to 12 months [82], and for up to 5 months in randomized prospective studies in adult [88] and pediatric patients [89].

Most comparative data suggest that lactulose and PEG have similar efficacy in treating patients with chronic constipation [85, 90]. A randomized, triple-crossover study of 57 patients comparing PEG with lactulose showed that the agents have equal effect and were better than having nothing or placebo, in improving stool frequency and ease of defecation [91]. A multicenter, randomized, controlled study conducted among 65 patients reported the same results [74]. There are no data on the efficacy and safety of PEG in diabetes patients.

Milk of magnesia (magnesium hydroxide) is an osmotic laxative where the poorly absorbable magnesium ions cause water to be retained in the intestinal lumen; stimulation of cholecystokinin in release and activation of constitutive nitric oxide synthase might contribute to its laxative actions [92, 93]. Evidence for its efficacy from randomized controlled trials is limited. One crossover study in 64 chronic constipated patients aged 65 years or older revealed that magnesium hydroxide at mean dose of 25 mL daily for 8 weeks produced significantly more normal stool consistency, more frequent bowel movements and reduced requirement for bisacodyl treatment compared with bulk laxative [94]. Reporting of adverse events is limited. In view of the risk of hypermagnesemia, it should not be used in patients with renal impairment.

Stimulant laxatives

If the stool is soft but there is still difficulty in passing it, stimulant laxatives can be prescribed. These laxatives stimulate the muscles in the digestive tract through their direct stimulant/irritant properties. They are usually used on a short-term basis and start working between 6 and 12 h [95]. The most commonly prescribed stimulant laxatives are senna, bisacodyl and sodium picosulphate. They are hydrolyzed in the gut by enterocyte enzymes or colonic flora, stimulate peristalsis and sensory nerve endings, and possibly interfere with electrolyte flux to inhibit water absorption [66].

Newer agents

Prucalopride is a highly selective 5-HT4 agonist stimulating prokinetic activity of the colon with minimal activity on 5-HT3 and hERG receptors. It is reported to accelerate transit and stool output in volunteers and patients [96, 97]. Three large studies in the USA and Europe [19, 98, 99], having identical inclusion criteria (laxative-refractory patients, with 80% having less than one spontaneous complete bowel movement per week), reported that prucalopride was associated with increase in bowel frequency to more than 3 per week in 24% of patients compared with 11% in the placebo group. Prucalopride is approved in Europe for the treatment of chronic constipation [20].

Lubiprostone, a derivative of prostaglandin E1, is a chloride-channel activator that stimulates intestinal fluid secretion. It acts on the enterocytes from the luminal side and is not systemically absorbed, accelerating colonic transit and softening stool consistency [100]. Three double-blind, randomized, placebo-controlled trials have shown the efficacy of lubiprostone in increasing spontaneous bowel movements and improving self-reported symptoms of chronic constipation [101–103]. The long-term use of lubiprostone is reported to be safe [12]. Lubiprostone has been approved by the US FDA for treatment of chronic idiopathic constipation, constipation caused by irritable bowel syndrome and opioid-induced constipation in adults with chronic, non-cancer pain [104].

Linaclotide

Linaclotide is a guanylate cyclase-C agonist that stimulates intestinal fluid secretion and transit. It has been approved by the US FDA for treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation, though it is currently not licensed in the EU. Results from two phase III studies conducted among 1272 patients with chronic constipation reported linaclotide to improve bowel function in 20% of the patients. Abdominal symptoms, global measures of constipation and quality of life were also seen to be significantly improved with no evidence of rebound constipation [105, 106]. Common adverse events were GI-related with diarrhea being the most common [107].
Conclusion

Chronic constipation is one of the most common GI symptoms in patients with diabetes, and occurs more frequently than in healthy individuals [7, 8]. For some, this condition can be chronic, where symptoms can be severe and can significantly affect a patient’s quality of life. As clinical management of diabetes improves and enables better glycemic control to be achieved, prevention and clinical improvement of associated GI complications may be realized. This improvement in glycemic control could be particularly relevant to diabetes-associated changes in the ICC, which are considered to be a major underlying cause of many GI complications. The prevalence of chronic constipation is higher in older adults, women than men and among patients with diabetes who are taking medications that can promote chronic constipation (e.g. calcium-channel blockers) [9, 14]. Although it is not well understood, chronic constipation in this patient population most likely results from slow transit caused by loss of ICC function and smooth muscle myopathy. Moreover, autonomic neuropathy and neuroendocrine imbalances may also play a role [15]. Anorectal dysfunction, either because of anorectal sensory or motor abnormalities, should be considered, because these patients can benefit from biofeedback training.

As there is no specific treatment for diabetes-associated chronic constipation, these patients are generally treated in the same way as those with chronic constipation. A stepwise approach is recommended while handling these patients, given the multiple risk factors, coexisting morbidity and medication-induced causes. Management of medication-induced causes, lifestyle modification and non-pharmacologic therapies should be the first step, in order to avoid unnecessary drug therapy.

There is limited evidence to guide the order in which therapeutic agents should be used, but detailed patient history along with an understanding of the patient’s glycemic control, an understanding of slow or normal transit and absence of defecatory dysfunction, can assist in developing patient-specific treatment pathways. These usually comprise initiating therapy with a bulk-forming agent, except in those who are bedridden, are cognitively impaired, or have other contraindications. For patients with a contraindication or lack of response to a bulking agent, an osmotic agent, such as lactulose or PEG 3500 is indicated, followed by stimulants (bisacodyl, picosulfate, or senna), and finally the newer agents (chloride-channel activators or 5-HT4 agonist) for severe or resistant cases.

Educational interventions and self-management programs directed at medication management and counseling have the potential to improve clinical, humanistic, adherence and cost outcomes. The underlying objective of these interventions should be to assist patients better manage their diabetes along with existing comorbid conditions such as chronic constipation and associated complex medication regimens, reduce complications and improve adherence and related costs. Patient preferences such as cost, convenience and tolerance should be considered while selecting treatment regimens.

Lastly, patients who report frequent use of laxatives need to be educated about the potential complications that can result from their long-term use. When prescribing laxatives to treat chronic constipation, especially in the diabetic patient, the primary healthcare provider should explain the rationale for the prescription to the patient. As a means of increasing compliance to prescribed medications, physicians should address and alleviate probable concerns of diabetic patients by highlighting the benefits of taking the prescribed agent, for example, describing the prebiotic effect and safety of lactulose in patients of diabetes with constipation. The patient should also be instructed to contact the provider if short-term use of the prescribed laxative fails to restore the patient’s regular bowel routine. This will discourage the patient from attempting self-treatment with one or more of the many laxatives that are available over the counter.

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Compliance with ethical standards

Conflicts of interest VGMP, and PA declare that they have no conflicts of interest.

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