International Journal of Research in Medical Sciences
Bagepally RS. Int J Res Med Sci. 2022 Jun;10(6):1382-1389
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20221500

Review Article

Management of chronic constipation in comorbid conditions

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Received: 06 March 2022
Accepted: 29 March 2022

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ABSTRACT

Constipation is a common clinical problem in India. It is also a secondary condition in many disorders. This article focused on clinical assessment and evidence-based treatment options for managing chronic constipation in various disorders. A literature search of published medical reports in the English language was performed using PubMed from inception to 2021. The selected articles satisfied the following inclusion criteria: involved human subjects over the age of 18 years and reported at least one of the comorbidities among hypothyroidism, diabetes and hypertension along with chronic constipation. Chronic constipation is one of the most common gastrointestinal symptoms observed in patients with diabetes, hypertension or hyperthyroidism. Constipation in diabetic patients can occur due to several factors such as autonomic dysfunction, dietary habits and medications. The change in the intestinal microbiota because of chronic constipation can also induce cardiovascular events. The association between these changes and increased blood pressure resulting in hypertension had been discussed in this review. Additionally, the link between disturbed gastrointestinal motility and chronic constipation leading to hypothyroidism had also been explored. Furthermore, the pharmacological and non-pharmacological management of chronic constipation in patients with diabetes, hypertension, and hypothyroidism have been discussed. Emphasis has been placed on the changes required in the existing treatment options for diabetes, hypertension and hypothyroidism along with the use of laxatives, dietary fibers, bulking agents, lifestyle changes and other interventions to manage chronic comorbid constipation.

Keywords: Constipation, Diabetes, Hypertension, Hypothyroidism, Management

INTRODUCTION

Chronic constipation can be defined as unsatisfactory defecation characterized by infrequent stools, difficult stool passage or both for at least 3 months according to the American college of gastroenterology chronic constipation task force. Difficult stool passage includes strain, a sense of difficulty in passing stools, incomplete evacuation, hard/lumpy stools, prolonged time to defecate or need for manual maneuvers to pass stools.[1] It must be noted that chronic constipation has no ideal definition as it changes with patient and physician perspectives, ethnicity and time. Chronic constipation affects about 22% of the adult Indian population, out of which 13% has severe constipation and 6% suffer from constipation associated with certain comorbidities.[2] Chronic constipation increases with age, particularly after 65 years of age and has been reported to be as high as 69% in the elderly and persons suffering from comorbid conditions.[3] A US-based survey reported that the prevalence of constipation in women and men was 20.8% and 8.0%, respectively, while an Indian survey reported it to be 20% and 13%, respectively, both indicating a higher prevalence in women than in men.[3,4] In recent times, the prevalence of chronic constipation with comorbid conditions has raised a concern on the overall health of patients already suffering from chronic conditions.

Chronic constipation frequently occurs as a secondary symptom in many conditions such as neurological,

metabolic and anorectal disorders, intestinal or non-intestinal surgery or because of use of medications for the treatment of various chronic medical conditions.[5-7] A study from West Bengal, India, reported that 61.5% of patients with chronic constipation had associated systemic comorbidities such as diabetes (17.6%), hypothyroidism (10.5%), organic brain disease (19.8%) or a combination of these diseases (13.6%). Moreover, 37.7% of patients in this study were found to be regularly taking drugs known to cause constipation.[8] Medications such as calcium channel blockers (CCBs) for high blood pressure, opioids for chronic pain and tricyclic antidepressants for major depression are known to cause chronic constipation.[9,10] Battle et al in their study of colonic myoelectric and motor activity demonstrated that diabetic patients with chronic constipation had absent gastrocolic responses to feeding, resulting in mild to moderate constipation.[11] Reduction in motor activity of the stomach, small intestine, and colon have also been reported in patients suffering from hypothyroidism.[12] It is also observed that chronic constipation may significantly impact quality of life (QoL) as it restricts social activities and often increases the level of anxiety and depression.[13,14] This review evaluated the prevalence, impact and management of chronic constipation in presence of comorbid conditions such as diabetes, hypertension and hypothyroidism.

A literature search of published medical reports in English from inception to 2021 was performed using PubMed and Google Scholar search engines. Abstracts were identified using the search terms chronic constipation, comorbid conditions, metabolic disorders, type 2 diabetes, hypertension and hypothyroidism. Manual search of references and review articles supplemented the computerized search. Only full text articles were considered for the study. The selected articles satisfied the following inclusion criteria: involved human subjects over the age of 18 years and described at least one form of the comorbidity amongst hypothyroidism, diabetes and hypertension along with chronic constipation.

Chronic constipation in patients with diabetes

Chronic constipation is one of the most commonly reported gastrointestinal symptoms in patients with diabetes. In 2020, the International Diabetes Federation estimated that out of the 463 million people suffering from diabetes in the world, 88 million were Southeast Asians and 77 million belonged to India.[15] From a total of 26 million cases reported in 1990 to 65 million in the year 2016, diabetes had proven to be a pressing concern for Indians.[16] India is expected to cross the 100 million mark by 2030.[17] Evidence suggested that 75% of patients with diabetes had associated gastrointestinal symptoms like heartburn, acid regurgitation, non-cardiac chest pain, dysphagia, postprandial fullness with nausea, bloating, abdominal pain, diarrhea, constipation and fecal incontinence.[18] Piper et al reported that out of 136 diabetic adults, nearly 60% had symptoms of constipation.[18] In an Indian cross-sectional study of 224 patients, 13.9% of patients with functional constipation were found to be diabetics.[17,19] Manoel et al reported that out of 372 patients with diabetes, 31.9% reported constipation. It was also reported that constipation was more prevalent in women (80.2%) as compared to men, in patients older than 50 years and in patients who were suffering from diabetes for longer than 10 years.[20]

Although the underlying cause of chronic constipation in diabetes is likely to be multifactorial, the probable pathophysiology of chronic constipation in diabetic individuals is the disturbance of the autonomic nervous system, which interferes with the control of gastrointestinal motility and sensitivity. The major contributing factor was the autonomic dysfunction with a lack of synchronicity between the gut musculature and the sphincters.[17] Furthermore, poor dietary habits, low fluid intake and physical inactivity are general predisposing factors for chronic constipation.[17] When evaluating constipation in a patient with diabetes, attention should be taken to review the choice of medications as these may be contributors to the etiology. Various correlations between gastrointestinal symptoms and diabetes medications have been observed. Among anti-hyperglycemic medications, dipeptidyl peptidase-4 (DPP4) inhibitors have been found to cause chronic constipation. Physicians often discontinue or do not start DPP4 inhibitors in patients with diabetes because of precipitation of chronic constipation as a side effect.[21]

Management of chronic constipation in diabetes

Despite being one of the most commonly reported gastrointestinal symptoms in patients with diabetes, there was very limited evidence-based treatment for diabetes-related chronic constipation. As such, general treatment measures for diabetes with chronic constipation are extrapolated from the general population. The primary aim of the management of chronic constipation in patients with diabetes is to optimize glycemic control along with the management of chronic constipation. The most suitable approach could be decided by the physician based on the condition of the patient.

Non-pharmacological approach

In patients with mild symptoms of chronic constipation, lifestyle modification may be enough to treat constipation. An increase in physical activity and an increase in consumption of dietary fiber facilitate better management of blood sugar levels.[17,18]

Medical management

A stepwise approach can be adopted if laxatives were considered as a treatment option. Bulk-forming agents can be used as a primary treatment option and in case of inadequate response, the treatment can be continued with

osmotic laxatives and then by stimulant laxatives. It was observed that for patients with a contraindication or lack of response to a bulking agent, an osmotic agent, such as lactulose or polyethylene glycol (PEG) 3500 is used, followed by stimulants (bisacodyl, picosulfate or senna), and finally the newer agents [chloride channel activators or serotonin type 4 (5-HT4) agonists].[17] However, in the tertiary care environment of the open healthcare system in India, a top-down approach was usually preferred in selected patients with chronic constipation. It involves treatment of the primary pathophysiology first like biofeedback for dyssynergic defecation and colokinetic for slow transit constipation.[8]

Table 1: Pharmacological management of chronic constipation.

Agents	Mechanism of action	Dose	Clinical considerations
Bulk-forming laxatives: Ispaghula/psyllium husk, bran and methylcellulose	Stool water retention ability is improved leading to formation of bulk stool; colonic transit time and stool consistency are improved	Initial dose 5 g/day Maximum total fiber including dietary fiber should be 25 g/day	Adequate water intake along with fiber Limited side effects
Osmotic laxatives: Inorganic salts (magnesium compounds) and organic sugars or alcohols such as lactulose, lactitol and PEG	Osmotic gradient created by these agents facilitates the passage of stools by increasing the retention of water in the stool, consequently making them soft	Initial dose 10 g/day Maximum dose 40 g/day (lactulose) Initial dose 17 g/day Maximum dose 34 g/day (single or split dosing (PEG)	For rapid evacuation, magnesium hydroxide or magnesium salts are used Useful in treating children and adults Can lower the blood sugar level Limited side effect – bloating Adequate water intake
Milk of magnesia: Magnesium hydroxide	Osmotic laxative effect is due to the poorly absorbable magnesium ions that cause the water to be retained in the intestinal lumen; additionally, stimulation of cholecystokin causes the release and activation of constitutive nitric oxide synthase	15-30 ml once or twice daily	Produces significantly more normal stool consistency More frequent bowel movements Reduces the requirement for bisacodyl treatment compared with bulk laxative
Stimulant laxatives: Senna, bisacodyl and sodium picosulphate	Enterocyte enzymes or colonic flora of the gut hydrolyze these laxatives. Stimulant laxatives are responsible for stimulation of peristalsis and sensory nerve endings and inhibit water absorption by possibly interfering with the electrolyte flux	Initial dose 8.6 mg once daily in evening Maximum dose 34.4 g split dosed (Senna) Initial dose 5 mg once daily in the evening Maximum dose 15 mg at one time (Bisacodyl)	Short duration of action Preferred therapy in slow colonic transit Sole therapy or as a combination with osmotic agent
Newer agents: Prucalopride (5-HT4 agonist); lubiprostone; pro-secretory agents like peripheral acting guanylate cyclase-C agonists, linaclotide and plecanatide; pyridostigmine	Prucalopride (5-HT4 agonist) Selective 5-HT4 receptor agonist which stimulates the colonic motility	2 mg once daily 1 mg day with severe renal impairment (GFR < 30 ml/min)	Available in Europe and Canada markets; not in USA market
	Lubiprostone Activation of CIC-2 chloride channels on enterocytes leading to passive influx of sodium and water in intestine	24 mcg twice daily Lower dosage available (8 mcg) which is indicated for IBS-C	Increases spontaneous bowel movements Accelerates colon transit time

Continued.

Agents	Mechanism of action	Dose	Clinical considerations
	Pro-secretory agents Activate the guanylate cyclase-C receptor on enterocytes, which further activate CFTR chloride channel leading to passive influx of sodium and water in intestine	145 µg once daily (linaclotide) 3 mg once daily (plecanatide)	Improvements in bowel habit Improves symptoms of constipation
	Pyridostigmine; cholinesterase inhibitor; accelerates colon transit	Initial dose 60 mg three time daily Maximum/therapeutic dose 120 mg thrice daily	Increases colonic transit time, stool frequency, and consistency, and eases the passage of stools

Note: CFTR- cystic fibrosis transmembrane conductance regulator; eGFR- estimated glomerular filtration rate; 5-HT4- serotonin type 4 agonists; IBS-C- irritable bowel syndrome - type C; PEG- polyethylene glycol.

Combination therapy with osmotic and stimulant laxatives or a combination of laxatives with bulking agents can also be considered for treatment.[22] One such combination is of sodium picosulfate/magnesium oxide/ anhydrous citric acid, which caused a purgative effect when ingested with additional fluids and produced watery stools.[23]

Probiotics increase the level of species of the *Bifidobacterium* genus, which in turn improved glucose tolerance and glucose-induced insulin secretion and reduced inflammatory markers.[17] Table 1 explains how various pharmacological agents help in management of constipation.

Chronic constipation in patients with hypertension

Chronic constipation had been linked to the occurrence of cardiovascular events. As hypertension is an indicator for other cardiovascular diseases, it is highly important to monitor and control it. Straining to pass stools can cause blood pressure rise, which can trigger cardiovascular events such as congestive heart failure, arrhythmia, acute coronary disease and aortic dissection. However, most medical interventions focus on treating the cardiovascular event, thereby overlooking the role of chronic constipation in these cardiovascular events.[24] It was often noted that changes to the intestinal microbiota due to chronic constipation can induce atherosclerosis, hypertension, and cardiovascular events. This was further supported by data from previously published studies that reported the association between changes in the intestinal microbiota and increased blood pressure, progression of atherosclerosis and cardiovascular disease.[25-27] Some studies had also indicated that oxidative stress may be another link between chronic constipation and cardiovascular disease.[28]

Therefore, physicians caring for patients with cardiovascular diseases should also acknowledge chronic constipation and associated straining as important cardiovascular risks and appropriately intervene to prevent them.[24]

Pathophysiology of hypertension and chronic constipation

Salt played a major role in the regulation of hypertension and chronic constipation, wherein sodium-proton-exchanger subtype 3 (NHE3) acts as a mediator of sodium absorption in the gut and causes an increase in blood pressure (hypertension) and constipation.[29] As salt intake is increased, it leads to enhanced absorption of sodium, thereby causing hypertension in the elderly.[29] On the other hand, an increase in absorption of sodium in the gut leads to loss of water from the fecal matter, making the stools harder and difficult to defecate, thus causing constipation.[29] A study conducted on the Indian population reported that 16% of patients with functional constipation had a history of hypertension and that antihypertensive medications were the contributor to constipation.[30] Anti-hypertensive medications like CCBs and clonidine were known to cause chronic constipation.[31]

In addition to salt intake, it had been reported that straining during defecation in a constipated person modulates blood pleasure, breathing and heart rate similar to the Valsalva maneuver, wherein blood pressure rises at first with a transient fall in heart rate and then the effect on heart rate and blood pressure are reversed.[24] This is followed by an instant fall in blood pressure, and then an active rise.[24] A case was reported wherein a woman was admitted for congestive heart failure when she strained to defecate (due to chronic constipation) and developed hypertension) (204/88 mm Hg) followed by flash pulmonary edema.[24]

Management of chronic constipation in hypertension

The primary aim in the management of hypertension-associated chronic constipation was relieving the symptoms associated with constipation, reinstating normal bowel movements and improving health-related QoL without any other side effects.[32] To reduce the risks of developing cardiovascular events, it was primarily important to manage and treat chronic constipation

initially, via non-pharmacological therapy by focusing on diet, lifestyle, physical activity, bowel training and fluid therapy. If the non-pharmacologic interventions are unsuccessful, then a switch to pharmacological therapy tailored according to the severity of the condition may become necessary.[32] Physicians recommended that 1.5-2.0 l/day of water and 20-35 g/day of dietary fiber are important for ideal defecation.[24]

Biofeedback and retraining of muscles might be effective in treating chronic constipation.[24] Some of the pharmacological interventions that can be used are stool softeners, stimulant laxatives, osmotic laxatives, bulking agents and combination therapy. Bulking agents like methylcellulose, polycarbophil and psyllium are commonly used. Osmotic laxatives such as magnesium agents, lactulose, sorbitol and polyethylene glycol, can be added as pharmacological therapy.[24,30] Combination therapy of polyethylene glycol/electrolytes and bisacodyl, sodium picosulfate/magnesium oxide/anhydrous citric acid, senna/docusate, senna/psyllium and magnesium citrate/polyethylene glycol is also recommended.[33]

Findings from past studies had suggested a common pathway for the treatment of chronic constipation in hypertensive patients as management of hypertension and chronic constipation are interlinked. Antihypertensive drugs can initiate constipation in hypertensive patients by suppressing the movement of the smooth muscles.[24] In order to manage chronic constipation, the main objective is to better manage hypertension in these patients. Studies have reported two mechanisms by which both hypertension and chronic constipation can be targeted: (a) salt intake has the potential to raise blood pressure and to reduce the sodium absorption in the gut; selective inhibition of NHE3 exchanger reduces systolic blood pressure and increases water content in the stools, displaying a laxative effect and thereby treating chronic constipation effectively;[29] (b) chronic constipation is a side effect of antihypertensives like CCBs. It can be alleviated by either reducing the dose or altering therapy by switching to beta-blockers or angiotensin-converting enzyme inhibitors.[31]

Chronic constipation in patients with hypothyroidism

In India, 42 million people are suffering from thyroid disorders, and the prevalence of constipation in hypothyroidism patients is found to be 11-79%.[34] A survey from Korea observed that among patients suffering from constipation, overt and subclinical hypothyroidism were prevalent in 0.41% (men: 0.36%; women: 0.53%) and 1.76% (men: 1.28%; women: 2.03%) patients, respectively.[35]

The average age of patients with constipation, who had hypothyroidism was observed to be ≥60 years.[19,36,37] In a study by Bennett et al, the patients evaluated were all children with an average age of 7.4 years.[38] Hypothyroidism is usually associated with gastrointestinal motility disorders that range from chronic constipation to more severe conditions like megacolon and pseudo-obstruction.[39] It has been reported that gastric and esophageal motor activities are reduced in hypothyroidism, which leads to chronic constipation.[12] Previous studies have also reported a reduction in motor activity of the stomach, small intestine and colon in hypothyroidism.[12] The mechanism by which the thyroid hormones can influence gastrointestinal motility can be found in synergism between a direct effect of the thyronine and an indirect effect mediated by catecholamines on the muscle cell receptors.[40]

Chronic constipation in hypothyroidism affects QoL, causes stress, and diminishes the overall sense of well-being. These things tend to self-perpetuate and lead profoundly impact on the cardiovascular, endocrine and immune systems.[41] Risk factors of hypothyroidism that contribute to chronic constipation are chronic stress and inflammation of the thyroid gland, estrogen dominance, and low metabolism, which are accompanied by high bacterial endotoxins in patients with a longer duration of hypothyroidism.[42]

Management of chronic constipation in hypothyroidism

As there is no specific treatment for hypothyroidism associated chronic constipation, hypothyroidism is first managed using levothyroxine. Improper thyroid treatment can contribute to chronic constipation.[43] To manage chronic constipation, dietary recommendations such as the need for appropriate fiber and fluid intake are generally the primary intervention in the treatment of chronic constipation.[44]

Osmotic laxatives, effective for both children and adults, are the first line of maintenance therapy for chronic constipation.[44] Mineral oil and milk of magnesia (magnesium hydroxide) are some other laxatives that are also frequently used.[44]

Other commonly used pharmacological treatments are bulking agents (psyllium or ispaghula), stool softeners (docusate sodium or calcium) and stimulant purgatives.[45] Secretagogues such as lubiprostone, linaclotide and plecanatide that enhance the stool volume and consistency, acetylcholinesterase inhibitors such as pyridostigmine and serotonergic agents like prucalopride can enhance gastrointestinal transit.[44]

Transanal irrigation, a treatment typically preferred in children, is generally prescribed for patients not responsive to pharmacological treatment.[44] Vidanga, is a herbal medicine that acts as an effective drug for managing chronic constipation caused by slow intestinal motility in patients with deficiency of thyroid hormones.[34] Synbiotic consumption for a period of 8 weeks is found to significantly reduce chronic constipation in patients with hypothyroidism by

improving the frequency and consistency of stools without negatively affecting appetite.[46]

CONCLUSION

Chronic constipation is frequently reported as a secondary symptom in diseases such as diabetes and hypothyroidism. Lower physical activity, dehydration and constipation-inducing medications are the general risk factors associated with the disease that lead to chronic constipation apart from the pathological origin of constipation caused by the disease. Opioids, diuretics, antidepressants, antispasmodics, anticonvulsants and aluminum antacids are all associated with higher risk of chronic constipation. Chronic constipation is found to be more prevalent in older patients, generally between 45 and 65 years old. A female predominance of chronic constipation is found in patients with diabetes and hypothyroidism. Comparative studies have reported that patients who have chronic constipation along with presumed disease have lower health and social status as compared to patients without chronic constipation. This makes recognition of these risk factors in clinical practice important as they may guide patient management with respect to the underlying medical disorder and help in better management symptoms of chronic constipation. Furthermore, there should be a routine practice of asking patients with these comorbid conditions about the presence of symptoms of chronic constipation.

Apart from treating the comorbid condition, an active lifestyle and fiber-rich diet along with adequate water intake are usually the first-line therapy employed to treat chronic constipation. In recalcitrant cases, use of laxatives is suggested for all comorbid conditions. Cost, patient compliance, and tolerance should be the key guiding parameters while prescribing a treatment regimen for chronic constipation, with the ultimate objective of enabling management of chronic constipation along with the associated co-morbid condition.

ACKNOWLEDGEMENTS

The assistance for conducting literature search and writing was provided by Shalaka Marfatia of pharmEDGE and her team.

Funding: Abbott India Ltd funded the medical writing activity
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Bagepally RS. Management of chronic constipation in comorbid conditions. Int J Res Med Sci 2022;10:1382-9.