Chapter 17
Management Diarrhea in Systemic Sclerosis

Elizabeth R. Volkmann

Introduction

Gastrointestinal tract (GIT) dysfunction is a leading cause of morbidity and mortality in patients with systemic sclerosis (SSc). The majority of patients with SSc (over 90%) have some involvement of their GIT over the course of their disease [1, 2]. Unlike other features of SSc, such as cutaneous sclerosis, the course of GIT involvement is often progressive over time. The various manifestations of SSc-GIT dysfunction can evolve late into the SSc disease course, even when other aspects of this condition (e.g., interstitial lung disease [ILD]) are quiescent.

Despite the disease burden of GIT dysfunction in SSc, this dimension of SSc remains poorly understood from both a pathological and treatment perspective. Lower GIT dysfunction, in particular, adversely affects quality of life [3], is associated with depressive symptoms [4], can cause profound malnourishment and weight loss [5, 6], and in certain cases, can lead to death [7].

E. R. Volkmann (✉)
Department of Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, USA
e-mail: evolkmann@mednet.ucla.edu

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Diarrhea is a common manifestation of SSc-GIT dysfunction [1]. The present chapter summarizes the clinical presentation and management of diarrhea in SSc. Through highlighting two demonstrative clinical vignettes, this chapter presents strategies for ameliorating diarrhea and improving nutritional status in patients with SSc.

Pathogenesis of Lower GIT Dysfunction in SSc

As described above, our understanding of the pathogenesis of lower GIT dysfunction is limited [8]. Historical studies demonstrated that patients with SSc-GIT involvement had evidence of vasculopathy, smooth muscle atrophy, as well as neural dysfunction and fibrosis [8]. However, these early studies focused primarily on upper GIT pathology [9, 10]. Subsequent reports demonstrated that auto-antibodies may contribute in specific manifestations of SSc-GIT dysfunction, such as dysmotility [11–13]. Smoking has also been associated with increased GIT symptoms as described in one large (N = 606) observational cohort study in Canada [14].

More recent studies have suggested that changes in the lower GIT microbiota may contribute to SSc-GIT dysfunction [15, 16]. Observational studies have demonstrated microbial community differences between patients with SSc and healthy controls [17–22]. These studies have described depletions in beneficial commensal genera (e.g., *Faecalibacterium*, *Clostridium*, and *Bacteroides*), as well as enrichments in potentially pathobiont genera (e.g., *Fusobacterium*, *Prevotella, Ruminococcus Akkermansia*) in the lower GIT in SSc patients [17–19]. In addition, these reports have demonstrated important connections between lower GIT microbial composition and specific SSc disease features (e.g., ILD [17, 18]), as well as SSc-GIT symptoms [17–19]. The aforementioned investigations into the GIT microbiome in SSc have stimulated new research efforts in this area that may ultimately reveal important treatment targets for managing SSc-GIT dysfunction.

However, in clinical practice, the etiology of diarrhea is often multi-factorial. While the SSc disease state itself can contribute to diarrhea, a plethora of other factors may also contribute to these symptoms (Table 17.1). While caring for patients with SSc, health care providers need to explore and address all possible causes of diarrhea.

Table 17.1 Common causes of diarrhea in patients with SSc

Cause	Diagnostic clues
SSc-related dysmotility	Alternating cycles of distention/constipation with periods of diarrhea, or loose stools
Small intestine bacterial overgrowth (SIBO) with malabsorption	Bloating/distension are common, as is increased flatulence. Constipation can also occur. Symptoms are often temporarily alleviated with antibiotics.
Intestinal pseudo-obstruction	Pain and cramping are more prominent than with other causes of diarrhea. Nausea and vomiting can occur. While constipation and distention are the predominant symptoms of pseudo-obstruction, overflow diarrhea can occur.
Antibiotic use	Diarrhea onset/worsening is within 3–4 days of initiation of antibiotics.
Medication side effects (e.g. mycophenolate)	Diarrhea improves upon cessation of the offending medication.
Food intolerances (e.g., dairy, gluten)	Diarrhea improves after eliminating the offending food and recurs once the food is reintroduced.
Overlap syndrome with inflammatory bowel disease (IBD)	SSc-diarrhea symptoms can be indistinguishable from IBD-diarrhea symptoms. Further gastrointestinal testing (e.g., colonoscopy) is often necessary to detect IBD.

(continued)

Table 17.1 (continued)

Cause	Diagnostic clues
Overlap syndrome with irritable bowel syndrome (IBS)	Careful history taking reveals an emotional component to symptoms. Diarrhea alternating with constipation is common. Stress is often a trigger for symptoms. Further gastrointestinal testing (e.g., colonoscopy) is often necessary to rule out IBD.
Excessive consumption of sugar alcohols	Food intake diary reveals consumption of sugar-free foods, including soda, gum and other foods that contain substances, such as sorbitol, maltitol.
Gastrointestinal infection	Suspicion is raised in an immunocompromised host.[a] extra-intestinal signs of infection may be present, such as fevers, chills, and weight loss.
Foodborne illness	Acute onset of symptoms; history of intake of foods commonly associated with foodborne illnesses (e.g. fried rice, raw milk, raw seafood, undercooked meat, lettuce, sprouts); exposure to daycares; or travel history.

[a]An immunocompromised state can be induced by medications (e.g., mycophenolate, cyclophosphamide, etc.), but it can also be caused by malnutrition

Assessment of Lower GIT Dysfunction in SSc

In clinical practice, self-reported symptoms of lower GIT dysfunction are the cornerstone to monitoring disease progression and treatment response. Whereas pulmonary function tests (PFT) are employed to monitor progression of ILD, no valid, objective measures of disease activity exist for SSc-GIT dysfunction. Patients may be reluctant to share intimate details of their bowel habits; therefore, the provider should

solicit this history with sensitivity and compassion. Using a metric, such as the UCLA SCTC GIT 2.0 [23], may help the provider understand the clinical course of symptoms. The GIT 2.0 is a 34-item self-administered questionnaire that contains 7 domains; one of which is diarrhea [23]. The GIT 2.0 provides a total score of GIT severity (summation of all scales except constipation) and has relatively good reliability and validity across different SSc cohorts [24–26].

Additional tools may also be helpful in assessing diarrhea in patients with SSc, such as the Subjective Global Assessment (SGA) [27]. This metric combines clinical history data (e.g., weight changes, gastrointestinal symptoms, dietary intake, functionality) with physical examination findings [27]. The Patient-Reported Outcomes Measurement Information System (PROMIS) GIT symptom item bank assesses GIT-specific symptoms and correlates well with the GIT 2.0 [28]. The Malnutrition Universal Screen Tool (MUST) can help identify patients who are at risk for malnutrition due to diarrhea and has been evaluated in SSc [5, 29].

Assessment of SSc lower GIT symptoms can also include a variety of imaging and diagnostic procedures that are often orchestrated through a consulting gastroenterologist [8]. Table 17.2 summarizes commonly performed studies in SSc patients with diarrhea.

Table 17.2 Diagnostic testing in patients with SSc suffering from diarrhea

Diagnostic test	Purpose
Colonoscopy	Detect obstructing lesions, mucosal inflammation, telangiectasias
CT or MR enterography	Evaluate for small bowel disease and extraluminal pathology
Barium study	Detect obstruction/pseudo-obstruction

(continued)

Table 17.2 (continued)

Diagnostic test	Purpose
Defecography	Evaluate for rectal outlet obstruction
Abdominal X-ray	Assess for pneumatosis intestinalis
Video capsule endoscopy	Assess for intraluminal small-bowel pathology
Breath tests (hydrogen, bile acids, nonradioactive glucose, lactulose)	Diagnose SIBO[a]
Fecal fat, pH tests; measurements for fat soluble vitamin levels	Diagnose malabsorption
Anorectal manometry	Detect anorectal motility problems
Surface electromyography	Evaluate for sphincter fecal incontinence

[a]The gold standard for diagnosing SIBO is aspiration and culture of jejunal fluid, but this is rarely performed in clinical practice due to the invasive nature of the procedure

Clinical Cases: Focus on Diarrhea in SSc

Case 1: JK

Presentation

JK is a 76-year-old Caucasian female with a 30-year history of limited cutaneous systemic sclerosis. Her SSc-related disease manifestations include mild Raynaud's phenomenon, gastroesophageal reflux disease (GERD), and ILD. She is antinuclear antibody (ANA) positive, but negative for SSc-specific serologies, including centromere, anti-topoisomerase I and RNA Polymerase III. The patient has never received immunosuppressive therapy for her SSc.

Upon presentation, she described episodes of constipation alternating with episodes of diarrhea for the past few years. Specifically, over the course of 4–5 days, she developed increased bloating/distension and constipation. Subsequently, she experienced profuse, watery diarrhea for 1–2 days. She also reported decreased appetite and a 10-lb weight loss over the last year. She avoided eating out at restaurants and traveling by plane, as both caused her symptoms to worsen. She had no significant life stressors; however, her GIT symptoms caused her emotional distress.

On physical examination, she was a thin woman with a slightly distended abdomen that was non-tender and without rebound or guarding. Her laboratory testing revealed a mild anemia and hypovitaminosis D, without any signs of systemic inflammation. The patient underwent age-appropriate screening for colon cancer 3 years prior, and the colonoscopy was unremarkable. She refused to undergo another colonoscopy, or any other GIT testing at this time.

Detailed dietary history revealed that the patient consumed an abundance of raw fruits and vegetables for breakfast, lunch and dinner. She seldom ate meat, but did consume seafood on occasion. She consumed some dairy and wheat products. When she became constipated, she would drink an abundance polyethylene glycol. She took no other bowel medications.

Intervention

The initial management approach was to help the patient have a daily bowel movement. The patient's diarrhea was likely due to overflow diarrhea in combination with excessive use of polyethylene glycol during severe distension episodes. She was started on prucalopride, a pro-motility agent that is effective in the treatment of slow-transit constipation [30] and has been studied in patients with SSc [31]. She was instructed to use polyethylene glycol sparingly.

In addition, she was advised to limit her consumption of raw fruits and vegetables, particularly those high in

Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols (FODMAPs). These compounds can often worsen distention and bloating, especially when consumed raw. While some recommend avoiding all foods high in FODMAPs, it is the author's opinion that many patients can tolerate vegetables containing high FODMAPs, as long as they are cooked well. For example, steamed artichokes are generally well tolerated and are an excellent source of inulin, a natural prebiotic. Prebiotics are substances, which help promote the growth of healthy, commensal gut bacteria. Animal studies have demonstrated that consumption of Jerusalem artichoke tubers modified the microbiota ecology in the large intestine to a great extent than the consumption of probiotics [32].

Probiotics were not prescribed for this patient. Probiotics are live microorganisms (typically *Bifidobacterium* and *Lactobacillus*) that are administered as food or supplements [33]. A very small, open-label study (N = 10) of SSc patients with moderate to severe bloating symptoms demonstrated that the administration of *Bifidobacterium* and *Lactobacillus* led to a significant improvement of GIT symptoms as measured by the GIT 2.0 [34]. However, this study lacked a control group. There is no compelling evidence presently that probiotics exhibit meaningful disease-modifying effects on any human diseases [35, 36]. Furthermore, in several unique SSc cohorts, the abundance of *Lactobacillus* was actually increased compared with healthy controls [17–20].

She was also started on a natural fiber supplement after the prucalopride was introduced to increase the bulk of her stools. This was started slowly by adding a few tablespoons of ground flaxseed to her morning oatmeal. Eventually, she increased the amount of ground flaxseed to approximately one half a cup per day (mixed with either oatmeal and yogurt, primarily).

At her follow up visit 3 months later, the patient reported near resolution of her diarrhea. With the addition of prucalopride and the avoidance of raw foods high in FODMAPs, the patient was able to have a daily bowel movement. Instead of

requiring large doses of polyethylene glycol 1–2 times per week, the patient only needed this medication once a month, and typically, this was after a day, during which she deviated from her dietary plan.

Lessons learned from Case 1

- Diarrhea is a not uncommon manifestation of slow transit constipation, especially when laxatives are used in excess or overflow diarrhea occurs.
- Adhering to a low FODMAP diet may help ameliorate GIT dysfunction; however, vegetables with high FODMAPs are often tolerated when cooked well.
- Pro-motility agents can help to regulate bowel movements even in patients with diarrhea, if the underlying cause of symptoms is dysmotility.

Case 2: SC

Presentation

SC is a 66 year old Caucasian female with a 12-year history of diffuse SSc with a history of renal crisis, ILD, Raynaud's phenomenon, digital ulcers and GERD (ANA positive, Scl-70 positive). She had been treated early in the course of her disease with multiple courses of intravenous cyclophosphamide administered approximately monthly over 2 years. She was then transitioned to azathioprine for another 5 years as maintenance therapy.

Upon presentation to the clinic, she had been off of immunosuppressant therapy for 4 years. Her main complaint was diarrhea, and she reported between 15 and 30 episodes of watery diarrhea daily. She also had frequent digital ulcer infections that required multiple courses of broad-spectrum antibiotic therapy.

The patient adhered to a low FODMAP diet, but had experienced profound weight loss (>30 lbs) over the past year. She also reported fatigue and depression due to the fact

that her GIT symptoms prevented her from traveling to visit her grandchildren.

On physical examination, she was cachectic and had a flat, non-tender abdomen. Her laboratory testing revealed a low prealbumin, low hemoglobin, low albumin and multiple other vitamin deficiencies including carotene, vitamin B12, folate, and iron. Lactulose breath testing was positive. Stool examination demonstrated *Clostridium difficile* infection positivity. Colonoscopy showed non-specific inflammation in various parts of the colon.

Intervention

The cause of the patient's diarrhea was likely due to both *C. difficile* infection and small intestine bacterial overgrowth (SIBO) with malabsorption [37]. The patient did not recall having problems with constipation prior to the onset of her diarrhea. Chronic antibiotic use and her extensive history of immunosuppressive therapy may have contributed to SIBO.

The patient was treated with oral vancomycin for her *Clostridium difficile* infection. Her diarrhea improved, but she still had multiple episodes of loose, watery stools even after treatment of her infection. Shortly thereafter, she was given another course of antibiotics for a urinary tract infection and developed worsening diarrhea secondary to *C. difficile* recurrence. She was treated again with oral vancomycin, but her symptoms and the infection persisted upon repeat testing.

At this juncture, the patient was referred for fecal transplant for treatment-refractory *C. difficile* infection. The most common indication for fecal transplantation is recurrent *C. difficile* infection (typically three or more infections). Within a week of the transplant, the patient reported resolution of her diarrhea. For an entire year following the transplant, the patient experienced no diarrhea. With vitamin supplementation and referral to a nutritionist who specializes in SSc, her vitamin levels normalized and she regained weight.

Studies have demonstrated that administration of immunosuppressive agents can alter the GIT microbiome. For

instance, cyclophosphamide (CYC) reduced the diversity and shifted the microbiota composition towards a reduction in *Bacteroidetes* in one animal study [38]. It is plausible that patients who receive immunosuppression may be at heightened risk for the development of SIBO independent of the SSc disease state.

Furthermore, repeated courses of antibiotics have profound effects on the GIT microbiome and can cause dysbiosis [39, 40]. While short courses of antibiotics can ameliorate GIT symptoms in patients with SIBO [41], the long-term use of rotating cycles of antibiotics is likely more harmful than beneficial given the enduring impact of antibiotics on the GIT microbiome. However, more research is needed in this area, particularly to understand the long-term effects of agents such as Rifaximin [42], which is used to treat irritable bowel syndrome (IBS) [43] and has been tested in small group of patients with SSc [44].

Lessons Learned from Case 2

- It is important to rule out infection in patients with SSc, even when SIBO is present.
- Frequent courses of antibiotics can drive dysbiosis in the GIT microbiota.
- Fecal transplantation may be a viable option in the future to treat dysbiosis in patients with SSc and studies assessing this intervention are underway.

Summary and Recommendations

Diarrhea is a common complication of SSc with diverse underlying etiologies. The most common causes of diarrhea directly attributable to SSc are SSc-related dysmotility and SIBO with malabsorption; however, other causes should be considered, as described in Table 17.1.

The treatment approach to managing diarrhea in SSc depends on the underlying cause(s) of symptoms and often involves a multi-disciplinary approach. Gastroenterology

consultation is particularly helpful in complicated cases, when overlap GIT conditions (e.g., inflammatory bowel disease (IBD), IBS) are present, and/or when further diagnostic testing is indicated (Table 17.2). Anti-diarrheal medication should be used sparingly (after *C. difficile* infection has been ruled out), as these agents can cause severe constipation and rectal prolapse [45].

Nutritional consultation is also beneficial, especially since patients may develop highly restrictive diets when they suffer from diarrhea that can compromise their nutritional status. Table 17.3 highlights nutritional strategies that can be helpful to

Table 17.3 Nutritional strategies to explore when managing diarrhea in SSc

- Limit consumption of raw fruits and vegetables
- If raw fruits and vegetables are consumed, eat these foods in isolation, preferably early in the day
- Consider following the low FODMAP diet, or at least using it as a guide to determine what foods you can/cannot tolerate
- Cook vegetables well (steamed, roasted, sautéed). If diarrhea is severe, consume vegetables in soups and purees primarily.
- Trial of the elimination diet to identify dietary intolerances[a]
- Increase consumption of healthy fats (e.g., olive oil, avocado, flax seed [ground or oil])
- Gradually increase consumption of cultured foods (e.g., yogurt, milks- these can be derived from animals [cows, goats, sheep] or from nuts, oats, rice, or hemp for individuals who cannot tolerate dairy)
- Gradually increase consumption of fermented foods (e.g., sauerkraut, pickles, kombucha)
- Limit consumption of processed foods (i.e. food that comes in packages with more than 5–10 ingredients)

[a]The author rarely finds food allergy testing helpful. Instead, she recommends that patients try eliminating certain foods (e.g., gluten, dairy) for 1 month and then re-introducing them one at a time to determine whether symptoms subside during cessation and worsen during re-introduction. Elimination diets should only be performed under the close supervision of a medical professional to ensure that the patient is receiving an adequate source of key vitamins, minerals and calories during the elimination phase of this process.

explore in patients with SSc. Often, patients need to be followed closely to observe how their symptoms change and evolve with specific dietary modifications. While the low FODMAP diet is used frequently in clinical practice, no controlled trials have evaluated its impact on SSc-GIT dysfunction. Furthermore, consuming a low FODMAP diet can alter the gut microbiota and metabolome, and it is unclear how these alterations affect immune function and health [46, 47]. Fiber supplementation should be used judiciously in patients with diarrhea as it can lead to constipation and fecal impaction [48, 49]. I therefore recommend introducing a natural fiber supplement (e.g., ground flaxseed) in small amounts initially.

Since changes in the microbiome likely underlie the symptomatic improvement that patients experience with diet changes [50–52], it is important to recognize that adherence to dietary changes is critical. Studies have demonstrated that the GIT shifts in microbial composition occur rapidly in response to dietary changes [53]. One study found that switching mice from a low-fat, plant polysaccharide-rich diet to a high-fat, high-sugar "Western" diet altered the composition of the microbiome in just 1 day [54]. Therefore, both the patient and the health care provider need to understand that sustainable improvements in GIT function will only occur when the patient is fully committed to adhering to their dietary plan.

If the patient has anxiety, depression, and/or any component of IBS, these issues also require attention. Various modalities can be helpful in these cases including psychotherapy, psychoactive medication, biofeedback, and meditation [55, 56].

In summary, diarrhea is a troubling complication of SSc that adversely affects quality of life and can lead to malnutrition and in severe cases, death. No disease-modifying treatments exist to manage this feature of SSc, but new research on the GIT microbiome will hopefully help uncover novel targets for therapeutic intervention.

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