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Gastrointestinal involvement in systemic sclerosis: Pathogenesis, assessment, and treatment

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Abstract

Purpose: The majority of patients with systemic sclerosis (SSc) will experience involvement of their gastrointestinal (GI) over the course of their disease. Despite the high prevalence of GI involvement in SSc, the strategies pertaining to the assessment and treatment for this clinical dimension of SSc have historically been limited. However, the present review highlights recent research contributions that enhance our understanding of SSc-GI patient subsets and provides updates on pathogenic mechanisms of disease, assessment and symptom-directed management.

Recent findings: In the past few years, several studies have identified risk factors for more severe GI disease in SSc and have provided insight to optimize diagnosis and management of SSc-GI symptoms. This article also provides a review of currently available investigations and therapies for individual SSc-GI disease manifestations and reflects on actively evolving areas of research, including our understanding the role of the gut microbiome in SSc.

Summary: Here we provide important updates pertaining to the risk stratification, assessment, diagnosis and management of SSc patients with GI symptoms. These findings provide opportunities to enhance patient care and highlight exciting opportunities for future research.

Keywords

Systemic sclerosis; Scleroderma; Gastrointestinal tract; Motility; Microbiome

Introduction

Gastrointestinal tract (GI) involvement occurs in nearly all patients with systemic sclerosis (SSc) [1–3]. GI manifestations of SSc often arise early in the disease course, may be progressive in nature and represent a leading cause of morbidity and mortality [2]. Any region of the GI tract may be involved, and it is not uncommon for patients to experience simultaneous involvement of different regions at one time. Numerous studies

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have demonstrated that SSc-GI involvement adversely affects psychosocial functioning, contributing to diminished quality of life, disability, depression and anxiety, and in severe cases, death [4,5,6].

While the burden of GI disease in SSc is high, treatment options are limited. No approved therapies for SSc-GI manifestations exist. Current treatments largely target symptoms, and there is no evidence that therapies approved for other manifestations of SSc (e.g., interstitial lung disease [ILD]) prevent progression of SSc-GI involvement [7**]. The lack of objective disease activity measures and trial endpoints for GI manifestations of SSc, combined with the heterogenous nature of the natural history of SSc-GI involvement, has hindered our ability to study potential disease modifying therapies in this clinical area of SSc.

The purpose of the present scoping review is to summarize the clinical features and management of SSc-GI involvement. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for scoping reviews [8], we searched PubMed (January, 1990, to May, 2022) using the search terms “systemic sclerosis” or “scleroderma” in combination with the terms “gastrointestinal” and “gut.” We largely selected publications from the past 18 months; however, high quality older publications were included. No PubMed filters or limits were applied to maintain a broad search strategy. We also conducted a manual search of references cited in original research studies and review articles on GI involvement in SSc to identify additional relevant articles. While primary research publications were prioritized, review articles are also cited to provide opportunities for further reading on specific topics.

Pathophysiology

As significant clinical heterogeneity exists in SSc-GI disease [6,9*–11], the underlying pathophysiology is complex and may vary across patient subsets. The classic hypothesis proposed by Sjogren nearly 3 decades ago suggested that SSc-GI disease arises from a 3-step sequential process which includes neural dysfunction, smooth muscle atrophy, and fibrosis [12]. However, autopsy studies have revealed that smooth muscle atrophy, rather than significant fibrosis, is prominent in the SSc GI tract and that areas of atrophy are not associated with significant inflammation or vasculopathy [13,14]. As such, some have proposed that a primary neural or smooth muscle insult drives GI dysfunction and that atrophy, not fibrosis, is the primary outcome of this process [13].

A reduction in neuromuscular communication may contribute to smooth muscle atrophy. Growing evidence suggests that enteric neurons and smooth muscle are targeted by the autoimmune response in SSc[15], and that functional autoantibodies to muscarinic 3 receptors (M3R) play an important role in SSc-GI dysmotility in a small subset of patients with rapidly progressive lower bowel disease [16–19]. These antibodies bind to and block the M3R, preventing acetylcholine from binding to and stimulating GI smooth muscle. Antibodies to vinculin, RNPC3, and nicotinic acetylcholine receptors in autonomic ganglia (AChR) are also associated with GI symptoms in SSc, though these antibodies have not been shown to be pathogenic [20**–22]. However, in patients without SSc, anti-AChR antibodies targeting

ganglia are known to interfere with cholinergic synaptic transmission and are associated with slow GI transit [23].

Dysfunction of the autonomic nervous system likely also contributes to SSc-GI disease [16,24]. The vagus nerve, a key mediator of autonomic function, plays a dominant role in regulating esophageal motility and lower esophageal sphincter function, both of which may be disrupted in SSc [25,26]. Autonomic dysfunction is reported among patients with SSc-GI disease, and a higher overall burden of autonomic symptoms correlates with increased overall GI severity [24,26], and specifically with anorectal motility disorders[27,28], gastric compliance [29,30], and esophageal dysmotility and dysfunction [26,30,31]. Furthermore, the frequent overlap between abnormal gastric emptying and esophageal dysmotility in SSc suggest that common pathogenic mechanisms may exist in difference regions of the GI tract [32]. Interestingly, a loss of the Interstitial Cells of Cajal (ICC) is also reported on SSc esophageal pathology. The ICC's are part of the sensory units of vagal afferents, which provide pacemaker activity to the smooth muscles and can generate peristalsis in the absence of innervation. These cells are key mediators of communication between the enteric nerves and smooth muscles, suggesting again that disrupted communications between the GI nerves and muscles likely contribute to SSc GI dysfunction [13]. In summary, many distinct abnormalities in the neuromuscular communications exist in the gut in patients with SSc. Each of these mechanisms may play a role in driving the clinical GI manifestations, although it remains unclear which patients are affected by each type of dysfunction and how much upstream vascular dysfunction disrupts neural control and contributes to disease pathogenesis.

Upper GI Tract Involvement

Up to 90% of patients with SSc have symptoms of upper GI disease [33,34] Patients may present with symptoms of laryngo-esophageal [35–38] or gastroesophageal reflux disease (GERD) (e.g., hoarseness. oropharyngeal dysphagia, reflux, heartburn), lower esophageal sphincter (LES) dysfunction[39], esophageal dysmotility (distal dysphagia), and gastroparesis (e.g., early satiety, bloating, nausea, vomiting and unintentional weight loss) [1,40,41]. Symptoms may occur in isolation, or in combination, which can complicate both diagnosis and management. GI bleeding may also complicate SSc, and arise from esophagitis, esophageal ulcers, gastritis, gastric ulcers, or gastric antral vascular ectasia (GAVE).

Diagnostic testing for upper GI tract involvement

As GI symptoms in SSc may be attributable to dysfunction in different regions of the gut, diagnostic testing may be helpful in identifying affected areas, particularly because certain GI therapies preferentially target specific GI regions.

In patients who have mild upper GI symptoms, lifestyle management with or without over-the counter GI medications are the recommended first-line interventions prior to testing. If oropharyngeal dysphagia is present, blood work to screen for elevations in muscle enzymes and/or relevant antibodies may be appropriate [36]. If symptoms persist despite negative testing, a modified barium swallow study can be helpful in evaluating the swallow function

(Table 1). If non-diagnostic, further evaluation with laryngoscopy through ENT may be warranted [38].

The diagnostic testing for GERD refractory to first- and second-line therapies usually begins with an upper endoscopy (EGD) to screen for abnormalities in the esophageal and gastric mucosa (Table 1). Such abnormalities may include findings such as esophageal strictures, esophagitis or gastritis, opportunistic infections (e.g., *Candida* esophagitis), Barrett's esophagus (reported in up to 12% of women with SSc), or even a malignancy [42]. Importantly, several distinct mechanisms may contribute to symptoms of GERD in SSc. In patients with symptoms of distal dysphagia and/or persistent symptoms of GERD despite high-dose acid blocking agents, a high-resolution esophageal manometry study (HREM) with pH testing and impedance may be warranted. HREM may be useful in differentiating between patients with normal vs. abnormal esophageal motility (i.e., ineffective esophageal motility or absent peristalsis). HREM can also identify abnormal lower esophageal sphincter pressures and hiatal hernia, which may impact therapeutic decisions. Furthermore, these findings can be helpful for patient risk stratification. For example, absent contractility and a hypotensive lower esophageal sphincter on HREM are risk factors for Barrett's [42]. In addition, a multiple rapid swallow study, which may be performed during manometry [44] can identify patients with peristaltic reserve, which is a good prognostic indicator of long-term esophageal function [45].

Gastric emptying and/or whole gut transit testing (i.e., scintigraphy or smart pill) also play an important role in the assessment of refractory upper GI symptoms in SSc (Table 1). A recent study found that SSc patients with gastroparesis by scintigraphy were likely to have other areas of abnormal transit in the gut. Combined liquid and solid gastric emptying studies were found to be more sensitive in detecting delayed gastric transit compared with solid gastric emptying studies (74% vs 55%, respectively). Moreover, percent liquid emptying correlated best with Reflux ($\rho = -0.33$, P=0.01) and Distension ($\rho = -0.30$, P=0.03) scores on the UCLA GIT 2.0 survey [10].

Treatment of upper GI tract involvement

The treatment of oropharyngeal dysphagia involves diagnosing and treating the underlying cause of symptoms and reducing the risk of aspiration [41] (Table 2). While H2 blockers and proton pump inhibitors remain the standard of care for GERD, a new class of acid blocking agents is emerging. These potassium-competitive acid blockers inhibit proton pump potassium–exchange and do not depending on gastric acid for activation. One of these medications, known as vonoprazan, is available in Japan and can facilitate the healing of erosive esophagitis and improve reflux symptoms in patients with refractory GERD [46*–48]. If the diagnostic work-up suggests that esophageal dysmotility and/or a hypotensive LES is driving the symptoms of refractory reflux, prokinetics may be considered for symptom control [49,50]. The addition of prokinetics to PPI therapy in a large cohort of non-SSc patients with refractory GERD recently demonstrated that combination therapy resulted in improved QoL and fewer reflux episodes [51]. Buspirone was also found to alleviate upper GI symptoms in SSc. In an open label trial, buspirone significantly increased LES pressures and decreased symptoms of heartburn and regurgitation in patients with SSc patients who were already

taking PPI [39]. Although data in favor of prokinetic use for the management of esophageal dysmotility in SSc is limited, a trial of prokinetics may be considered if dysmotility is present.

Surgery in SSc is usually reserved for refractory cases; however, a recent systematic review was conducted to determine whether surgical treatment is feasible and safe in SSc patients with refractory GERD. A total of 7 studies, including 101 patients were included, and 63 patients (62.4%) underwent open fundoplication, 17 (16.8%) laparoscopic fundoplication, 15 (14.9%) Roux en-Y gastric bypass (RYGB), and 6 (5.9%) esophagectomy. Recurrent symptoms were identified in up to 70% undergoing fundoplication and 30% of patients undergoing RYGB, although minimally invasive RYGB was thought to be feasible and safe based on short-term results [52].

Lower GI Tract Involvement

Dysmotility is the defining feature of lower GI tract involvement in SSc and may be present in the small intestine, large intestine, and/or the anorectum [53]. In contrast to the upper GI tract, lower GI tract involvement typically arises in patients with established SSc and less commonly presents in patients with very early or early SSc [54]. However, the symptoms of lower GI tract involvement are among the most troubling symptoms SSc patients experience as they can profoundly affect a patient's social functioning and emotional well-being. For instance, many patients will avoid eating outside of the home or traveling if it involves a long journey. This can lead to social isolation and may contribute to feelings of helplessness and anxiety.

Small intestine involvement

Dysmotility of the small intestine occurs in 40–88% of patients with SSc based on manometry studies [55]. Symptoms often include distension and bloating; prolonged episodes of either constipation or diarrhea are also common. Weight loss can occur, and while the differential diagnosis for weight loss in SSc is broad (Table 3), malabsorption should be considered in any patients with unintentional weight loss. Diagnostic tests include abdominal x-rays, small intestinal manometry, scintigraphy, wireless motility capsules and CT/MRI enterography [40](Table 4).

Small intestinal bacterial overgrowth (SIBO) [56] is estimated to occur in 30–62.5% of patients with SSc [57]. The cause of SIBO in SSc is likely multi-factorial and may be due to use of agents that suppress gastric acids, dysmotility of the small and/or large intestine, as well as a weakened ileocecal valve. Regardless of etiology, symptoms of SIBO are highly disruptive and may include nausea, vomiting, early satiety, bloating, diarrhea, excessive flatulence and weight loss [58]. Hydrogen and methane breath tests after an oral glucose or lactulose bolus are the most commonly used diagnostic tests for SIBO [59], although the sensitivity for these tests is suboptimal, with some studies reporting a sensitivity of only 62% [60]. Interestingly, prospective studies have demonstrated that a sizable percentage of patients with SSc have evidence of SIBO based on breath testing, even in the absence of GI symptoms [57]. These findings are consistent with recent research demonstrating that alterations in the lower GI tract microbiota are a feature of patients with early SSc [61*].

Therefore, it is plausible that dysbiosis is not necessarily a consequence of dysmotility in SSc; instead, dysbiosis may be a driver of dysmotility, similar to irritable bowel syndrome [62].

Large intestine involvement

Constipation is the most common clinical feature of large intestine involvement in SSc [54]. Dysfunction of neuropathic and myopathic processes contributes to delayed colonic transit leading to symptoms such as distension or fullness after meals, abdominal pain and straining during bowel movements [63]. Risk factors for delayed colonic transit include female sex, presence of telangiectasia, presence of anti-centromere antibodies, past history of smoking and a Medsger GI severity score of ≥3 [9]. After constipation, diarrhea is the second most common clinical feature of large intestine involvement in SSc. The diarrhea may be due to various causes, including paradoxical (i.e., overflow) diarrhea and/or overzealous treatment of constipation with stimulant laxatives.

Intestinal pseudo-obstruction affects approximately 10% of patients [64]. Associated with delayed colonic transit [65], pseudo-obstruction results from the inability to move intestinal luminal contents forward in the absence of a mechanical obstructive process. Patients complain initially of nausea and abdominal pain and eventually the inability to pass flatus and increasing abdominal girth [66]. Although intestinal pseudo-obstruction does not represent a true obstructive process, this condition is often recurrent, necessitates hospitalization in many cases, and can be fatal [67].

Anorectum involvement

Involvement of the anorectal dysfunction occurs 50–70% of patients with SSc [68]. Fecal incontinence is the most common symptom and is largely due to neuronal dysfunction [69]. Rectal prolapse can also occur. In this scenario, patients will perceive a bulging sensation in their anus and complain of chronic stool leakage [70]. One small study reported a high recurrence rate of rectal prolapse occurs after restorative surgery [71], rendering the treatment of this complication challenging. Other anorectal clinical manifestations include hemorrhoids, which can develop secondary to chronic constipation in SSc.

Treatment of lower GI tract involvement

Since symptoms of lower GI tract involvement may arise due to dysfunction in different regions of the lower GI tract (e.g., diarrhea may be due to fecal incontinence [anorectum], malabsorption [small intestine], and/or colonic dysmotility [large intestine]), the first step in the management is to identify the underlying cause of symptoms [1,3,41]. Careful history taking, combined with diagnostic testing (Table 4), can often reveal the driving factor for symptoms [41]. Treatment is then tailored according to the suspected underlying etiology. It can take time to establish an effective treatment regimen for lower GI tract symptoms. The optimal approach combines pharmacological interventions with lifestyle modifications, including dietary adaptations (Table 5).

Conclusions

Of all the organ systems affected in SSc, the GI tract has the most diverse clinical manifestations related to SSc and the least number of evidence-based treatment options available. This paradox represents a significant challenge for patients and their health care providers. Emerging research on novel motility measurement modalities, and the roles of the autoimmune response and gut microbiome in SSc has the potential to propel this field forward and improve how we care for patients who suffer from GI complications of SSc.

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Key points

- Diverse clinical manifestations of SSc-GI involvement exist, and careful history taking and diagnostic testing can identify the underlying cause of symptoms.
- Treatment of GI manifestations involves a holistic approach combining pharmacotherapy with lifestyle modification, including dietary adaptations.
- Disease modifying therapies are greatly needed to prevent SSc-GI progression and promising therapeutic targets include the autonomic nervous system, immune system and gut microbiome.

Table 1.

Common diagnostic tests for upper GI tract involvement in SSc

Test	Purpose
Modified barium swallow study (i.e., Video fluoroscopic swallowing study)	Impaired swallowing and/or clearance of food and liquids
Laryngoscopy	Abnormal laryngeal structure or function (e.g., impacts swallowing, breathing, cough)
Barium swallow	Evaluate for stricture, obstruction, GERD
Upper endoscopy	Evaluate esophageal and gastric mucosa
High resolution esophageal manometry	Evaluate for upper or lower esophageal sphincter dysfunction, esophageal dysmotility, and hiatal hernia
pH impedance testing	Determine the amount of reflux that occurs in a typical 24-hour period, whether symptoms are attributable to reflux episodes, and whether acid suppressive therapy is adequate
H. pylori breath test	Diagnose active H. pylori infection, and determine whether treatment cured an H. pylori infection
Gastric emptying study	Screen for gastroparesis

Table 2.

Treatment for the most common upper GI tract symptoms in SSc

Symptoms and causes	Intervention and effect on the GI tract
Oropharyngeal dysphagia	
From laryngeal esophageal reflux: Treat GERD (see below)	Reduces laryngeal irritation
From myositis: immunosuppression	Improves laryngeal muscle function
Distal dysphagia	
From stricture:	EGD with dilation will allow bolus to pass more easily
From dysmotility:	Promotility agent (e.g. metoclopramide, bethanechol, pyridostigmine) to enhance smooth muscle contraction
From infection or esophagitis:	Treat infection or inflammation to alleviate tissue irritation
GERD	
Aggravated by suboptimal habits: Lifestyle modification	Avoid large meals and eating within 3–4 hours of laying down. Minimize intake of aggravating foods. Sleep with head of the bed elevation.
Suspicion of too much acid exposure of unclear etiology	Anti-acid therapy to reduce acidity of reflux and/or reduces reflux episodes
From esophageal dysmotility and food not passing efficiently	Promotility agent (as above) to enhance esophageal transit
From a weak lower esophageal sphincter	Tighten LES to reduce reflux (e.g., buspirone, metoclopramide)
From gastroparesis:	Treat gastroparesis with dietary modification and promotility agents if needed (see below) to improve transit and accommodation
Early satiety and nausea	
From gastroparesis:	Consider gastroparesis diet (smaller more frequent meals, reduce fiber and fat, eat solids first); Consider supplemental medication if needed (e.g., promotility agent, appetite stimulant, medications that help with gastric accommodation) to improve transit, accommodation and nausea

Table 3.

Differential diagnosis for weight loss in SSc

Increased caloric output	Decrease caloric intake
Increased work of breathing	Decreased appetite
Increased effort to move due to physical challenges (e.g., arthropathy, myopathy, joint contractures, diffuse skin disease)	Difficulty with mechanical digestion (e.g., decreased oral aperture, poor dentition, dry mouth)
Increased inflammation due to underlying SSc	Difficulty swallowing
Increased inflammation due to infection *	SIBO, Malabsorption
Increase psychosocial stress related to SSc or external life stressors	Medication side effect (e.g., diarrhea, nausea, vomiting)

* Patients with SSc are at increased risk for infection due to various factors, including malnutrition, immunosuppressant medications, abnormal organ architecture (i.e., parenchymal lung disease causing interstitial abnormalities) aberrant immune function due to underlying SSc

Table 4.

Diagnostic tests for lower GI tract involvement in SSc

Test	Pathologic findings
Abdominal x-ray	Dilated bowel loops; Tightly packed valvulae conniventes
Intestinal manometry	Low-amplitude contractions; Absent or prolonged migrator motor complexes
Scintigraphy	Slow colonic transit
Wireless motility capsules *	Slow colonic transit
CT/MRI enterography	Small intestine involvement; Extraluminal pathology
Hydrogen or methane breath tests	SIBO
Colonoscopy	Obstructing lesions; Mucosal inflammation; Telangiectasias
Barium swallow	Obstruction; Pseudo-obstruction
Defecography	Rectal outlet obstruction
Video capsule endoscopy	Intra-luminal small intestine pathology
Fecal fat, pH tests; Measurement of fat soluable vitamin levels	Malabsorption
Endoanal ultrasound or MR pelvis	Soft tissue masses; Atrophy of internal anal sphincter
Surface electromyography	Sphincter fecal incontinence

* Please note, wireless motility capsules are contraindicated in patients with known, severe gastroparesis or GI strictures.

Table 5.

Treatment for the most common lower GI tract symptoms in SSc

Symptoms and Intervention(s)	Predominant effect of intervention on GI tract
Constipation	
Docusate sodium	Softens stool through increasing osmotic pressure
Senna	Stimulates peristalsis and increases fecal water content
Bisacodyl	Stimulates peristalsis in the colon; increases fluid and salt secretion
Milk of Magnesia	Softens stool through increasing osmotic pressure
Lactulose	Softens stool through increasing osmotic pressure
Linaclotide, Plecanatide, Lubiprostone	Actively stimulate secretion of electrolytes and water into the intestinal lumen and accelerate colonic transit
Prucalopride	Accelerates GI motility, FDA approved for chronic constipation
Pyridostigmine	Accelerates GI motility
Small frequent meals	Stimulate natural peristalsis
Diarrhea	
Loperamide	Inhibit peristalsis; use with caution
Limit foods high in FODMAPs, especially raw fruits and vegetables	May lessen symptoms
Fluid resuscitation	Treat dehydration
Increased foods naturally high in probiotics and prebiotics	Potentially improve bacterial balance in GI tract
SIBO	
Antibiotics	Potentially improve bacterial balance in GI tract
Limit consumption of simple carbs (white flour, white sugar	May lessen symptoms
Anorectal dysfunction	
Physiotherapy	Improve pelvic floor strength
Biofeedback	Re-enforce connection between central nervous system and
Sacral nerve stimulation	Improve incontinence
Percutaneous tibial nerve stimulation	