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MINIREVIEWS

# Gastrointestinal complications of systemic sclerosis

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## Abstract

Systemic sclerosis is an autoimmune disease characterized by progressive skin thickening and tightness. Pulmonary interstitial fibrosis and kidney damage are the most important indicators for mortality; however, the gastrointestinal tract is the most commonly damaged system. Virtually all parts of the gastrointestinal (GI) tract can be involved, although the esophagus is the most frequently reported. The mechanisms that cause such extensive damage are generally unclear, but vascular changes, immunological abnormalities, excessive accumulation of collagen in the submucosa, smooth muscle atrophy and neuropathy may participate because these are the most common histological findings in biopsies and autopsies. Most patients with GI tract involvement complain about dyspepsia, nausea, vomiting, abdominal bloating/distension, and fecal incontinence. These symptoms are generally mild during the early stage of the disease and are likely ignored by physicians. As the disease becomes more advanced, however, patient quality of life is markedly influenced, whereby malnutrition and shortened survival are the usual consequences. The diagnosis for systemic sclerosis is based on manometry measurements and an endoscopy examination. Supportive and symptomatic treatment is the main therapeutic strategy; however, an early diagnosis is critical for successful management.



**Key words:** Systemic sclerosis; Gastrointestinal tract; Manometry; Endoscopy; Diagnosis; Treatment

**Core tip:** Although often overlooked by clinicians, the gastrointestinal tract is the most commonly damaged system in patients with progressive systemic sclerosis. Virtually all parts of the gastrointestinal tract can be involved, although the esophagus is the most frequently reported. The mechanisms of gastrointestinal tract involvement have not been clarified; however, vascular damage, excessive accumulation of collagen, and immunological abnormalities may play a role because they are the most frequent histological findings in biopsies and autopsies. Non-specific symptoms, including dyspepsia, nausea, vomiting, and abdominal distension are common complaints. Although supportive and symptomatic treatment is the main therapeutic strategy for systemic sclerosis, early diagnosis is critical for improving patient prognosis.

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## INTRODUCTION

Systemic sclerosis (SSc) is a chronic autoimmune disease with an unknown etiology. The most common clinical presentations include: Raynaud's phenomenon, skin thickening and tightness caused by widespread vasculopathy and excessive fibrosis. The gastrointestinal (GI) tract is the most commonly involved internal organ in SSc. It is estimated that GI involvement occurs in approximately 70%-90% of SSc patients[1-3]; however, a recent study by Schmeiser *et al*[4] has shown that 98.9% of SSc patients

suffered from GI symptoms. Additionally, the symptoms of GI manifestation can be mild to severe, including pain, dysphagia, vomiting, diarrhea, constipation and fecal incontinence[5]. Anatomically, GI involvement can affect the whole length of the GI, starting from the mouth to the anus. In this review, we have highlighted the clinical features of each anatomical GI region believed to be involved in SSc, as well as the possible treatment approaches.

## PATHOLOGY AND PATHOGENESIS OF THE GI INVOLVEMENT IN SSc

Although the entire GI tract can be affected, the underlying pathological changes and symptoms are similar in all parts of the GI, from the esophagus to the rectum. Additionally, vascular changes, immunological abnormalities, excessive accumulation of collagen in the submucosa and smooth muscle atrophy are histological hallmarks of SSc found in the digestive tract walls from patient biopsies and autopsies[1]. The progression of the GI involvement in SSc patients ranges from a grade of 0-2. These scores were based on the following parameters: (1) Vascular damage to the vasa nervorum (grade 0), which is a part of the characteristic SSc vasculopathy that can lead to ischemia; (2) Neurogenic impairment (grade 1), which is secondary to ischemia but causes damage to neurons of the intestinal wall; and (3) Myogenic dysfunction (grade 2), whereby normal smooth muscle is replaced by collagenous fibrosis and may cause atrophy[2,4]. This progression may explain the characteristic pathological changes observed in SSc patients.

The pathogenesis of the GI complications that occur during SSc is generally unknown. Vascular and auto-immune hypotheses have been proposed to explain the GI histopathological changes observed in SSc[5]. The vascular change hypothesis suggests that the initial GI lesions occur because of a neural dysfunction caused by arteriolar changes in the vasa nervorum or by increased collagen deposition. Moreover, studies have shown that mucosal blood flow to the stomach and duodenum are reduced and that vascular insufficiency occurs before smooth muscle atrophy develops. Additionally, increased proliferation and fibrosis of the adventitia may also occur. All these vascular changes can lead to ischemia, which in turn may cause neuron damage and collagen tissue compression of nerves. Vascular ectasia with focal intra-vascular thrombi and antrum fibromuscular hyperplasia also can occur with SSc, providing additional evidence for the vascular change hypothesis.

It is generally accepted that the immune system participates in SSc pathogenesis. One study has shown that damaged stomach endothelial cells express high levels of the cell adhesion molecules including vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 and can attract activated lymphocytes that move into the damaged sites. The increased $CD4^+/CD8^+$ ratio in the gastric mucosa T cell infiltrate suggests that the acquired immune response is a trigger of GI damage during the early stage of SSc[1]. Additionally, weak expression of vascular endothelial growth factor in the gastric submucosa suggests angiogenesis impairment, which then causes nerve plexuses dysfunction and smooth muscle atrophy. Antibodies to the M3 muscarinic receptor, which can block binding of the enteric cholinergic neurotransmission, have also been detected in SSc patients[6]. As GI damage advances during SSc, severe fibrosis, with abundant type I and Ⅲ collagen deposition in the lamina propria and muscularis mucosa, can be observed, and these changes are associated with smooth muscle atrophy and fibrosis. Furthermore, a prominent T-cell infiltration, with a significantly elevated $CD4^+/CD8^+$ ratio, has been detected in SSc patients with GI involvement. Moreover, over-expression of fibrogenic cytokines, such as transformation growth factor β, connective tissue growth factor, endothelin-1 and α-smooth muscle actin have been observed around intestinal glands and blood vessels[7,8].

The association between autoantibodies and SSc GI damage has also attracted great interest. Howe *et al*[9] reported the presence of anti-myenteric neuron antibodies in some SSc patients, suggesting that this autoantibody may be associated with the GI symptoms that occur in some SSc patients. Nishimagi et al had found that the presence of anti-centromere antibodies (ACA) or Scl-70 antibodies were less frequent in patients with severe GI damage; however, there was an increased frequency of anti-U3RNP (ribose nuclear protein) and anti-U1RNP antibodies as well as an increased ratio of Th/To cells[10,11]. Additionally, there was a higher incidence of severe diarrhea in patients with anti-U3RNP antibodies but not in patients with anti-U1RNP antibodies. Thoua et al found that there was a negative association between diarrhea and pulmonary fibrosis, although this association was not statistically significant. In general, however, there is no reported SSc GI involvement between localized and diffuse SSc subtypes[12].

## CLINICAL FEATURES

The symptoms of GI damage in SSc patients, including pain, dysphagia, vomiting, diarrhea, constipation, fecal incontinence, and weight loss vary in severity. Even in patients without GI symptoms, up to 77% of them had reflux-esophagitis, 85% had distal esophagus dysmotility, and 92% had gastritis when evaluated by oesophago-gastro-duodenoscopy[13]. In fact, the whole GI tract may be involved and contribute to the symptoms listed above; however, different GI regions also have their own specific symptom presentations.

### *Oral cavity*

Facial skin tightness and thickening limits the opening of the mouth and interferes with oral intake and mastication. Approximately 20% of patients develop secondary Sjögren's syndrome, which may cause dysphagia, difficultly in swallowing, and periodontal disease and may further impair a patient's ability to maintain a good quality of life

and nutritional status[9].

### Esophagus

The esophagus is the most commonly involved and most intensively studied GI complication in SSc patients. Up to 96% of SSc patients have esophageal complications, including esophageal motility abnormalities, lower esophageal sphincter (LES) abnormalities, gastroesophageal reflux disease (GERD) and Barrett's esophagus. A recent study has shown that esophageal involvement is more pronounced in SSc patients with positive anti-centromere antibodies compared with patients with increased levels of anti-topoisomerase I (Scl-70) or anti-nuclear antibodies[14].

**Esophageal dysmotility and GERD:** Esophageal dysmotility is the most common GI manifestation in SSc patients. Damage to the distal two-thirds of the esophagus smooth muscle during SSc causes decreased or even complete loss of peristalsis in the smooth muscle and distal portion of the esophagus, delaying food bolus transportation and clearance of refluxed materials from the stomach[15]. Dysphagia and difficulty in swallowing are common complaints.

**GERD:** The damage to the lower two-thirds of the esophagus caused by SSc often leads to a weakened LES. LES abnormalities, which presents as a low baseline pressure, results in the sphincter neither opening normally when swallowing nor closing completely afterwards. Such abnormalities allow for a pathological gastric acid reflux to the esophagus, which causes further damage to the LES. This condition is known as GERD. Initially esophageal damage caused by GERD manifests as simple peptic esophagitis, but it can progress to erosive esophagitis, bleeding and frank ulceration. If left untreated, esophageal stricture, fistulas and achalasia-like syndrome may occur[2]. Patients with GERD usually have heartburn, dysphagia, substernal chest pain, nausea and vomiting after eating; however, the intensity of the symptoms is not related to the severity of GERD. It is reported that GERD severity is associated with pulmonary interstitial fibrosis[1].

**Barrett's esophagus:** Chronic GERD can lead to Barrett's esophagus. The estimated prevalence of Barrett's esophagus in SSc patients is 6.8%-12.7%[16]. Additionally, Barrett's esophagus in SSc patients is associated with an increased risk of esophageal carcinoma[1,2,5].

### Stomach

It is reported that stomach involvement occurs in 10%-75% of SSc patients[17]. The gastric manifestations of SSc include gastric antral vascular ectasia (GAVE), which is typically presented as "watermelon stomach" during gastro-endoscopy examinations. Additionally, GAVE can cause gastric dysmotility, which leads to delayed gastric emptying or gastroparesis. Moreover, these SSc patients may have GI bleeding, early satiety, bloating, dyspepsia, nausea and vomiting.

**GAVE:** The appearance of GAVE under gastroendoscopy observation is unique and is characterized by multiple, parallel longitudinal columns of red vessels within the gastric antrum radiating to the pylorus, resembling the stripes on a watermelon. This condition, therefore, is also known as "watermelon stomach". GAVE can precede an SSc diagnosis[18]. It is estimated that the prevalence of GAVE ranges from 5.7% to 14% of SSc patients[1,5]. GAVE can sometimes manifest itself as severe GI bleeding, although achlorhydria, with or without pernicious anemia, is more common. Furthermore, the pernicious anemia is usually microcytic.

**Gastroparesis:** This condition is the result of chronic gastric motility alternations. These patients may experience delayed gastric emptying or complete gastric paralysis. Delayed emptying can result in early satiety, bloating, dyspepsia, nausea and vomiting. Succussion splashing during examinations often suggests gastroparesis. Delayed emptying occurs equally with solid and liquid meals and can make GERD even worse.

### Small bowel

The small intestine is the second most commonly involved portion of GI tract during SSc, following the esophagus. It is suspected that the small intestine function is compromised in 40% of SSc patients[19]. Although most mild cases have no symptoms, bloating, vomiting, abdominal pain, diarrhea, pseudo-obstruction, malabsorption and weight loss may occur in severely affected patients. Small intestine hypomotility is the primary abnormality and may lead to pseudo-obstruction and bacterial overgrowth, which is the major cause of malnutrition in SSc patients. Additionally, pneumatosis cystoides intestinalis (PCI) may occur but is a rare condition.

**Intestinal hypomotility and secondary bacterial overgrowth:** Intestinal dysmotility has been reported in 40%-88% of SSc patients[5]. Manometric and electrophysiological studies have revealed neuropathy of the enteric nervous system in SSc patients with intestinal dysmotility. Additionally, the autoantibody that inhibits M3-muscarinic receptor-mediated enteric cholinergic neurotransmission was also detected in these patients[20,21]. Intestinal hypomotility can result in nausea, vomiting, bloating, distension, anorexia and abdominal pain. Because decreased motility of the small intestine can result in intestine contents stasis, it is believed that stasis of intestinal contents can cause small intestinal bacterial overgrowth (SIBO). SIBO is defined as the presence of more than $1 \times 10^5$ organisms per millimeter of duodenal aspirate fluid. It is not a rare disorder and has been detected in up to 55.5% of SSc patients[22,23]. Additionally, it has been observed that SIBO is more prevalent in patients with limited SSc. Bacteria overgrowth competes with the host for nutrition and causes malabsorption of fat, proteins, carbohy-

drates and vitamins[5]. SSc patients with SIBO, therefore, have lower levels of serum albumin and total protein, as well as vitamin $B_{12}$ and ferritin. The symptoms caused by SIBO are similar to those caused by small intestinal hypomotility; however, steatorrhea, multiple nutritional deficiencies and weight loss can occur when the flora overgrowth is severe enough to cause prominent malabsorption.

**Small intestine pseudo-obstruction:** This complication is secondary to small intestinal hypomotility because decreased peristalsis, or even aperistalsis, may provoke luminal dilatation and overt pseudo-obstructions. There is no difference in the clinical and radiographic features of the pseudo-obstructions caused by SSc or by other reasons. Abnormal collagen deposition in the small intestinal wall, which can occur during SSc, is irreversible, resulting in recurrence of pseudo-obstructions.

**PCI:** PCI is characterized by the presence of intramural gas in the gastrointestinal tract[24]. It is a rare SSc GI complication. Like small intestinal pseudo-obstructions, it is secondary to small intestine dysmotility. It is basically a radiological diagnosis and usually has no consequences. Rarely, however, intestinal ischemia can occur and surgical intervention is needed. Occasionally, the air-filled cysts in the bowel may rupture, leading to benign pneumoperitoneums[5,25]. Generally, the prognosis of PCI is good.

### *Colon*

Colon involvement is observed in 10%-50% of SSc patients[1,5]. Colon hypomotility is the most common colonic complication during SSc and can cause delayed colon transit. As a result, constipation and evacuation difficulty may occur. Constipation, however, does not often persist for long because of intestinal bacterial overgrowth-induced diarrhea. Therefore, constipation and diarrhea are the most common clinical symptoms of SSc patients. Although wide-mouth diverticula in the colon may occur in SSc patients, it is rarely symptomatic. Colonic telangiectasias are common during SSc and may cause overt bleeding, which can result in anemia.

### *Anorectal SSc*

The reported anorectal involvement in SSc is 50%-70%[5]. Patients may present with chronic diarrhea, fecal incontinence and rectal prolapses. Fecal incontinence is the most frustrating symptom and seriously impairs patient's quality of life. It is reported that 37.1% to 70% of SSc patients develop incontinence[2,5]; however, the prevalence of fecal incontinence is likely under-estimated because most patients are reluctant to report the symptoms. Neuropathy plays a key role in the development of SSc fecal incontinence.

Defecation requires the collaboration of the internal and external sphincter as well as intact rectoanal inhibitory reflex (RAIR). RAIR consists of relaxation of the smooth muscle internal anal sphincter (IAS) and contraction of the striated muscle external anal sphincter (EAS), which makes it possible to maintain anal continence. The IAS is primarily responsible for the anal resting tone and the EAS is primarily responsible for the voluntary contraction of the anal sphincter. IAS weakness leads to passive fecal incontinence, while EAS weakness leads to urge fecal incontinence. As smooth muscle is more likely to be damaged because of SSc, the IAS is more likely to be affected in the anorectum. IAS atrophy may be secondary to vascular or neurological dysfunction. Heyt *et al*[26] demonstrated that SSc patients had a thinned IAS. Additionally, the circular and longitudinal IAS smooth muscle layers were replaced with fibrous tissue. A lower IAS resting pressure is also common in SSc patients with anorectal involvement; however, the squeeze pressure is usually normal, as the EAS is generally not affected. Because there is a decrease in the rectal resting tone in these patients (due to smooth muscle cell atrophy that results from ischemia); rarefaction of innervations and neurogenic dysfunction often occur as well, consequently impairing the RAIR. Thoua *et al*[27] demonstrated that the RAIR was compromised in 46% of SSc patients with incontinence and provided evidence that neuropathy played a key role in the development of fecal incontinence in these observed patients. Furthermore, Malandrini *et al*[28] observed nerve degeneration in the rectal mucosa of SSc patients with fecal incontinence. Most studies have shown that the resting anal pressure is also reduced in fecal-incontinent SSc patients, resulting in an absent or impaired RAIR; however, their maximal squeeze pressures are normal. Additionally, inappropriate collagen and connective tissue deposition often occurs in SSc patients, which disrupts neural fiber connections and insults neural tissue, usually resulting in neuropathy. Interestingly, however, although the IAS response is diminished or absent and the EAS response is normal or increased in rectal-incontinent SSc patients, no correlation between disease duration, ACA status or SSc subtype has been observed[25].

### *Liver and biliary tract*

Liver and biliary involvement in SSc is relatively rare; however, primary biliary cirrhosis (PBC) is the most common hepatobiliary manifestation in SSc patients, with an estimated prevalence of 2.5%[29]. Eight percent of SSc patients have positive anti-mitochondrial antibodies, while anti-glycoprotein and anti-sp100 antibodies have been detected in up to 15% of SSc patients[29-31]. The onset of PBC may precede, occur concomitantly with, or more commonly, follow SSc onset. Patients with a concomitant SSc and PBC disease occurrence have a higher prevalence of calcinosis and telangiectasia than patient with only SSc[32].

## DIAGNOSIS

The diagnosis of SSc related GI disorders generally depends on the location of the involvement. Oral cavity

problems can be diagnosed by routine oral examination. Esophageal motility disorders, such as GERD, can be diagnosed by the combination of upper GI endoscopy and esophageal manometry procedures, together with ambulatory PH studies. Esophageal biopsies can confirm the diagnosis of Barret's esophagus. Electrogastrographic recordings and scintigraphic evaluations following a radiolabeled meal are both useful for the diagnosis of delayed stomach emptying. A typical endoscopic procedure, whereby "watermelon stomach" is obvious, is diagnostic for GAVE. Small bowel manometry is helpful not only in the screening for SSc patients who have small intestine involvement but also in identifying symptomatic patients with intestinal pseudo-obstructions who may benefit from octreotide. Additionally, low resting anal canal pressure and impaired or absent RAIP observations are helpful in diagnosing anorectal disorders.

## TREATMENT

Treatments for SSc-induced GI impairment are generally symptomatic and supportive. Nutrition status assessment should be a routine component of clinical care for SSc patients[33]. Moreover, a multi-disciplinary approach is important for the optimal care of SSc patients with GI involvement.

### *Oral cavity*

For patients with decreased oral aperture, techniques such as facial grimacing exercises, mouth stretching exercises and oral opening augmentations with tongue depressors are recommended. Bilateral commissurotomy may also be performed to increase mouth opening. For patients with dry mouth, attention should be paid to oral hygiene to prevent caries.

### *Esophagus*

For patients with esophageal dysmotility, modified lifestyle measures should be initiated and have proven to be helpful. These measures include frequent small meals, sitting up during and after meals, elevating the heads of patients' beds, and avoiding known irritants and bedtime meals or snacks. Patients with endoscopically documented GERD require chronic treatment with proton-pump inhibitors. Use of prokinetic drugs that increase gastric emptying, such as metoclopramide, may help reduce reflux. Additionally, esophageal strictures can also be dilated under endoscopic guidance. Patients not responding to medication therapy can be treated with anti-reflux surgery. The outcomes of anti-reflux surgeries, however, are variable, and careful pre-operative evaluations are warranted. Partial fundoplications (Toupet procedure) may also be helpful in some patients[32].

### *Stomach*

Bipolar cautery, heat probe, sclerotherapy and laser ablation are available for the treatment of GAVE. Prokinetc drugs, such as metoclopramide, domperidone, prucalopride and tegaserod, are helpful in patients with early stage stomach disease, but become less effective as the disease progresses. Macrolide antibiotics are believed to have motilin agonist properties and have been evaluated in delayed stomach emptying patients. Erythromycin, however, is the most widely studied drug. It has been shown to stimulate intestinal motility even with low dosages; however, its effectiveness may decrease with time[34].

### *Small intestine*

Bacterial overgrowth is the major cause of symptoms in patients with small intestinal involvement. Antibiotics, such as metronidazole (500 mg BID) and ciprofloxacin (500 mg BID), administered for 14 to 28 d can be helpful for these patients. An alterative antibiotic regimen includes oral intake of chloramphenicol and the third generation cephalosporins. Rotating antibiotics monthly is suggested to circumvent bacterial resistance. Probiotics have been proven to be effective and safe for patients with bloating caused by bacterial overgrowth[35]. Lactobacillus can be used to treat this condition because it can competitively inhibit the attachment and growth of pathogenic organisms and restore the microbial balance in the GI tract. Additionally, lactobacillus may also enhance the immune-modulating effects in patients by increasing the IgA response or by modifying mucosal IL-10 and Th1/Th2 lymphocyte levels. Studies have shown that lactobacillus can also produce proteinaceous factors that alter epithelial permeability, inhibit bacterial translocation, and influence the level of gut mucin glycoprotein[5].

Small intestine pseudo-obstructions are common in SSc patients. The initial treatment for this condition should include bowel rest, intravenous fluid infusion and electrolyte correction. Octreotide has also been shown to be effective[36]. The starting dosage is usually 50 μg *bid* (given subcutaneously) during acute onsets; however, the dosage can be increased up to 200 μg if a satisfactory response is not observed. For patients with recurrent pseudo-obstruction episodes, 50 μg of octreotide at bedtime is usually effective and depot octreotide can be prescribed on a monthly basis. Neostigmine can lead to prompt colon decompression; therefore, it can be used for this condition. If octreotide and neostigmine treatments are not effective, however, colonoscopic decompression is normally the treatment of choice. Surgery procedures are reserved for cases of peritonitis and perforation.

### *Colon and anorectal disorders*

Constipation, diarrhea and fecal incontinence are the major symptoms in patients with colon and anorectal involvement. High-fiber diets and bulk-forming laxatives should be avoided in constipated patients because these can worsen constipation. Fluid ingestion and osmotic laxatives, such as senna, lactulose, bisacodyl and polyethylene glycol, are recommended because these medications can alter intestinal mucosa electrolyte transportation and also increase intestinal motor activity. Antibiotics can be given to patients with diarrhea caused by bacteria

overgrowth syndrome. For patients with incontinence, sacral nerve stimulation has been shown to be successful in most patients and may also abolish incontinence in some patients[5]. Posterior anal repair may be considered when sacral nerve stimulation fails. Rectal and vaginal prolapses should be detected and surgically repaired, as these two conditions can contribute to incontinence. Additionally, biofeedback may be helpful in improving rectal continence. Surgical procedures such as dynamic graciloplasties or the installation of artificial bowel sphincters should be considered in patients with resistant and severe incontinence.

### *Liver and biliary disorders*

PBC in SSc patients can be treated with ursodeoxycholic acid, which delays the histological progression rate. Patients with severe liver disorders, however, may need liver transplantation.

In summary, GI involvement in SSc patients is common and sometimes troublesome. An early diagnosis is crucial for improving patient prognosis due to the insidious progressive nature of the disease. Symptomatic and supportive treatments, as well as modified life style measures are the management mainstays for this disease.

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