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Review

Gastrointestinal Manifestations of Systemic Sclerosis: Screening and Management to Improve Outcomes

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Abstract

Gastrointestinal (GI) involvement is among the most common and clinically important manifestations of systemic sclerosis (SSc), affecting up to 90% of patients and substantially contributing to morbidity and reduced quality of life. SSc-related GI disease results from microvascular injury, enteric nervous system dysfunction, and progressive smooth muscle atrophy with fibrosis, producing widespread dysmotility throughout the gastrointestinal tract. Clinical involvement can extend from the oral cavity to the anorectum, with esophageal dysfunction, gastroesophageal reflux disease (GERD), gastroparesis, small intestinal bacterial overgrowth (SIBO), and intestinal pseudo-obstruction among the major manifestations. Recent diagnostic advances, including high-resolution esophageal manometry (HRM), ambulatory pH-impedance monitoring, and improved imaging, have strengthened early detection and characterization of GI involvement. Treatment remains largely supportive and symptom-directed, including acid suppression, prokinetic therapy, nutritional optimization, and endoscopic or surgical management of complications. Growing evidence on the gut microbiome, immune-mediated mechanisms, and the gut-brain axis is expanding understanding of disease pathophysiology and may guide future targeted therapies. This review synthesizes current evidence on the epidemiology, pathophysiology, clinical manifestations, and management of gastrointestinal involvement in systemic sclerosis, emphasizing early recognition and multidisciplinary care. We conclude by outlining persistent management challenges and future directions to improve diagnostic precision, therapeutic development, and patient-centered outcomes.

Keywords: scleroderma, systemic; gastrointestinal involvement; gastroesophageal reflux disease; small intestinal bacterial overgrowth; screening; management

1. Introduction

Systemic sclerosis (SSc), also known as scleroderma, is a chronic autoimmune connective tissue disease that is characterized by vasculopathy, immune dysregulation, and progressive fibrosis of the skin and visceral organs. The pathophysiology of SSc consists of endothelial cell injury which is followed by dense deposition of extracellular matrix with myofibroblasts and predominantly type I collagen [1]. Collagen can accumulate in organs such as the skin, gastrointestinal tract, blood vessels, and lungs. While the cutaneous manifestations of SSc are the most visible feature of the disease, organ involvement is significantly associated with increased mortality and impacts a patient's quality of life [2].

Among the visceral organs, the gastrointestinal (GI) tract is frequently involved in SSc with manifestations occurring in approximately 75–90 percent of patients over the course of the illness [3]. Vascular dysfunction in the GI tract causes ischemia, leading to neuronal injury, then progressive fibrosis and atrophy of the intestinal wall. Immune-mediated inflammation, including T-cell infiltration, further damages the gastrointestinal mucosa. As a result, any segment within the GI tract from the oral cavity to the anorectum can be affected, leading to a broad spectrum of symptoms including dysphagia, gastroesophageal reflux, pseudo-obstruction, diarrhea, and constipation [3].

GI symptoms in SSc are varied, making diagnosis and treatment challenging. Management depends on disease severity, organ involvement, and progression, and is mainly supportive as no disease-modifying therapies exist. Treatment options include acid suppressants, nutritional support, antibiotics, and prokinetics [3]. Despite its high prevalence and frequent impact, GI involvement in SSc remains poorly understood and underrecognized.

Several reviews published in recent years have examined selected aspects of gastrointestinal involvement in systemic sclerosis, including gastrointestinal dysmotility, nutritional complications, and emerging microbiome-related mechanisms [4,5]. However, many of these reviews focus on individual disease manifestations or pathophysiologic

pathways rather than providing a comprehensive framework for screening and management across the entire gastrointestinal tract. In contrast, the present review synthesizes contemporary evidence spanning the oral cavity to the anorectum, with particular emphasis on practical screening strategies, diagnostic evaluation, nutritional assessment, and multidisciplinary management. Furthermore, we integrate recently published evidence together with recommendations from major gastroenterology and rheumatology societies, including the American College of Gastroenterology [6,7], the European Society for Clinical Nutrition and Metabolism [8], and the European Alliance of Associations for Rheumatology [9], to provide a clinically focused and guideline-informed update for practicing clinicians.

This review aims to summarize the current evidence on epidemiology, pathophysiology, diagnostic challenges, and management of gastrointestinal manifestations in systemic sclerosis. In addition, it also seeks to provide guidance to clinicians to improve the screening, monitoring, and management of patients with GI involvement.

2. Epidemiology

Gastrointestinal involvement is highly prevalent in SSc, affecting nearly 90% of patients and occurring with similar frequency in both diffuse and limited SSc populations. The esophagus is the most affected site with manifestations including dysphagia, heartburn, or regurgitation [10]. GI involvement is associated with increased morbidity and mortality, with complications of the GI tract being the 4th most common cause of mortality in SSc patients. Severe GI disease defined as malabsorption, hyperalimentation, pseudo-obstruction and/or >10% weight loss has been shown to be associated with a >2-fold increase in the risk of death [11]. Overall, gastrointestinal involvement represents a common and clinically important feature of SSc with a substantial impact on patient outcomes and quality of life.

3. Pathophysiology of Gastrointestinal Involvement in Systemic Sclerosis

The pathogenesis of GI involvement in SSc reflects the convergence of three interrelated processes: microvascular dysfunction, enteric nervous system injury, and progressive smooth muscle atrophy with collagen deposition [12]. Early in disease, immune-mediated endothelial injury leads to chronic ischemia of the gut wall, accompanied by neurogenic dysfunction of the myenteric plexus. Over time, this evolves into irreversible myopathy with replacement of smooth muscle by fibrotic tissue within the muscularis propria and submucosa. The result is impaired compliance, diminished peristaltic activity, and progressive hypomotility throughout the GI tract. Although this sequence is presented linearly for clarity, the underlying pathophysiology is better understood as a complex, overlapping network in which vascular injury, autoimmunity, neural damage, and muscle atrophy occur simultaneously and reinforce one another [13] (Fig. 1).

3.1 Motility Dysfunction

The typical progression in SSc starts with neurovascular injury, which leads to myopathic degeneration. This sequence results in the hallmark motility issues seen in SSc: diminished or absent propulsive contractions in the small intestine and colon, weakened sphincter function, stagnation within the lumen, and reduced ability to clear intraluminal contents. In the gastrointestinal tract, motility disruption begins with neural alterations and then myointimal hyperplasia which narrows the internal vessel lumen of small arteries. This targets small arteries, arterioles and the capillaries found in the submucosa, muscularis propria and the vasa vasorum (the tiny blood vessels feeding the enteric nerves). Subsequently, the muscularis propria's smooth muscle deteriorates, accompanied by collagen deposition, muscular fibrosis, and dysfunction of the neural plexus [4]. Additionally, patients with SSc have fewer gap junctions (intercellular channels that connect adjacent intestinal cells enabling direct communication via the exchange of ions and small molecules), making peristalsis in the colon more challenging [14].

Esophageal involvement is particularly significant, with the distal two-thirds, comprised of smooth muscle, being most affected. This results in ineffective or absent peristalsis. Concurrent hypotonia of the lower esophageal sphincter (LES) contributes to the characteristic "scleroderma esophagus" phenotype [15]. The combination of impaired bolus clearance and diminished LES barrier function promotes severe gastroesophageal reflux disease (GERD), prolonged esophageal acid exposure, and mucosal injury, thereby increasing the risk for erosive esophagitis, peptic stricture, and Barrett's esophagus [15].

3.2 Gut-Brain Axis

Disruption of the gut-brain axis and related neuronal dysfunction play a significant role in the gastrointestinal impairment observed in SSc. The intricate communication network connecting the central nervous system, autonomic nervous system, enteric nervous system, immune system, and gut microbiota is substantially compromised due to immune-mediated injury. Reduced activity within the enteric nervous system, together with alterations in endothelial cells and the basement membrane, result in ischemic damage, tissue fibrosis and GI dysmotility. Additionally, vasospasm and the production of autoantibodies adversely affect the autonomic nervous system [16].

Autoantibodies against muscarinic-3 receptors impede cholinergic signaling in both the central and peripheral nervous systems, thereby decreasing smooth muscle contractility and contributing to gastrointestinal dysmotility. Neural dysfunction has been recognized as an early manifestation of SSc related GI dysmotility [14].

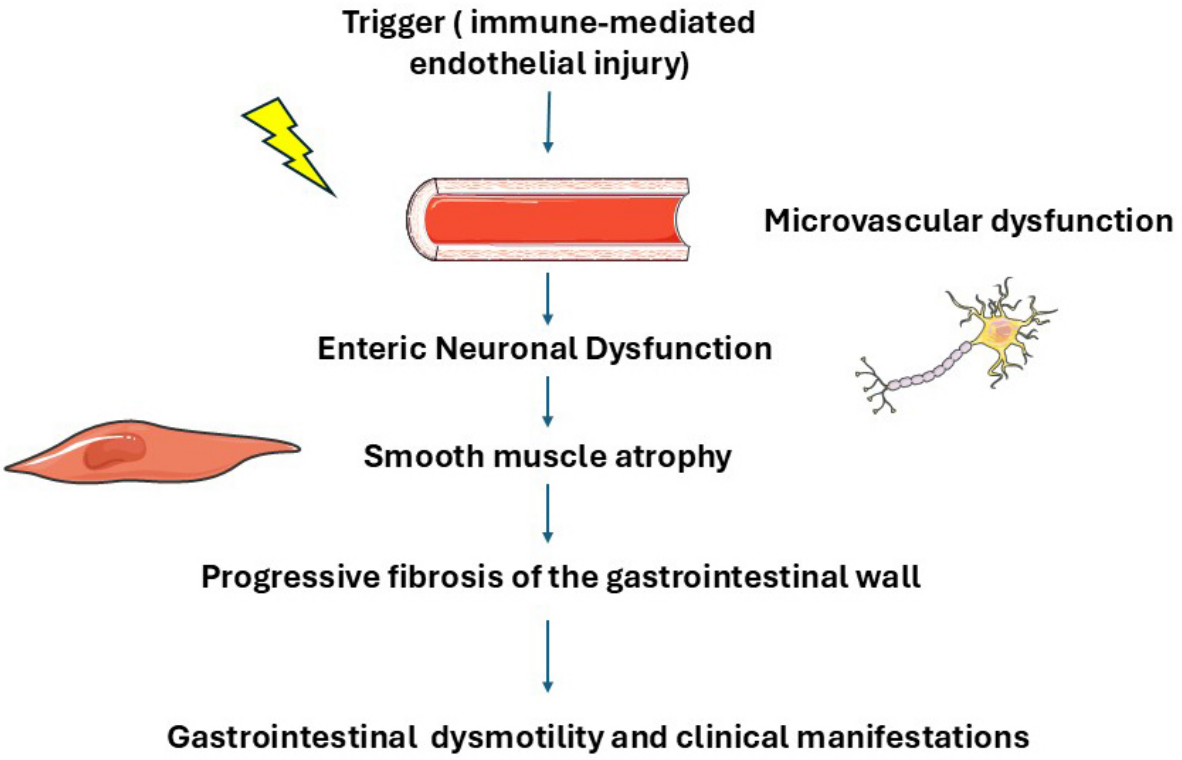

Fig. 1. Proposed pathophysiologic cascade of gastrointestinal involvement in systemic sclerosis. Immune-mediated endothelial injury leads to microvascular dysfunction, chronic ischemia of the gut wall accompanied by neurogenic dysfunction of the myenteric plexus. Progressive smooth muscle atrophy and replacement with fibrotic tissue culminate in impaired gastrointestinal motility and the spectrum of clinical manifestations observed in systemic sclerosis. (Software: Microsoft PowerPoint Version: Microsoft PowerPoint for Microsoft 365; Manufacturer: Microsoft Corporation; City/Country: Redmond, WA, USA).

3.3 Gut Microbiome

Recent research in SSc has focused on gut microbiota, revealing that changes in microbial balance correlate with disease progression, clinical subsets, prognosis, and therapy response. Altered microbiomes have also been found at fibrotic sites like the skin and GI tract.

One study compared gut bacteria levels in SSc patients using the UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument (GIT 2.0). Patients with higher GIT scores (SSc/GIT+) had reduced alpha diversity (a measure of microbial variety and abundance) compared to those without GI involvement, and greater symptom severity was linked to lower diversity. Abdominal distention correlated, but did not reach statistical significance, with beta diversity (a measure of difference in microbial composition between samples) (p = 0.077), indicating a possible relationship between GI symptom severity and microbial composition. Higher GIT scores were associated with decreased *Clostridium*, and *Coprococcus* (commensals), an increase in *Klebsiella* and *Enterococcus* (pathobionts) and an increase in *Lactobacillus* (commensal). Additionally, greater beta diversity aligned with more severe GI symptoms [17].

3.4 Diet/Nutrition

Gastrointestinal involvement in SSc patients can significantly impair nutritional intake. The GI system is among the most affected organs in SSc. Early signs of vascular injury along the GI tract lead to reduced GI motility, mainly due to denervation. Oral and oropharyngeal ulcers can cause mechanical difficulties that hinder both a patient's ability and desire to eat. Malnutrition remains a major concern for those with SSc, as poor nutrition influences prognosis, choice of medication, and how medications are processed by the body. Nevertheless, nutritional assessment is rarely included as part of standard care in SSc [18].

Dietary changes can help relieve symptoms in patients with GI involvement. A low FODMAP diet, which limits certain carbohydrates, is linked to reduced diarrhea, bloating, gas, and luminal distention. About 40% of SSc patients experience lactose and fructose malabsorption, increasing osmotic diarrhea and gas. Fructose also raises small bowel water more than glucose, worsening abdominal distention. Many patients opt for lactose-free diets [14,19].

A low-fat diet can reduce diarrhea and steatorrhea in patients with fat malabsorption. In SSc patients, fat malabsorption leads free fatty acids to bind calcium, increasing calcium-oxalate formation and risk of enteric hyperoxaluria

and oxalate nephropathy. Supplementing with medium-chain triglycerides (MCAT) is beneficial, as they are better absorbed [20,21].

For SSc patients with GI symptoms, recommended diets include frequent small soft meals and supplements like iron, B12, and fat-soluble vitamins. Pancreatic enzymes may also be used, with guidance from dietitians and gastroenterologists [21].

Formal nutritional assessment should be incorporated into routine care for patients with systemic sclerosis and gastrointestinal involvement. Malnutrition is common in systemic sclerosis and has been associated with adverse clinical outcomes and increased mortality [22,23]. Assessment should include serial weight monitoring, body mass index, evaluation of unintentional weight loss, and screening for micronutrient deficiencies including iron, vitamin B12, folate, vitamin D, and fat-soluble vitamins. Recent studies have also demonstrated the utility of standardized malnutrition assessment frameworks, including Global Leadership Initiative on Malnutrition (GLIM) criteria, for identifying patients at increased nutritional risk [24].

3.5 Pelvic Floor Dysfunction

In relation to the pelvic floor, SSc may result in microvascular damage within the connective tissue surrounding pelvic floor muscles, thereby impacting their function. These manifestations can lead to pelvic floor dysfunction (PFD), including urinary incontinence, fecal leakage, tenesmus, sexual dysfunction, and other complications. Data regarding PFD is frequently underreported owing to reluctance and stigma associated with disclosing such symptoms.

Vascular injury, fibrous changes of the internal anal sphincter, and neuron damage contribute to anorectal symptoms in 50–70% of SSc patients. Sphincter dysfunction results from smooth muscle atrophy or increased fibrosis, causing altered anal pressure and impaired rectoanal inhibitory reflex, which leads to fecal incontinence (up to 50%), rectal prolapse, and leakage [21,25,26].

4. Oral Cavity Manifestations, Screening, and Management

4.1 Clinical Manifestations

Oral involvement is common in SSc and is frequently under-recognized despite its substantial impact on nutrition, oral health, and overall quality of life. One of the most characteristic manifestations is microstomia, which results from progressive perioral skin tightening and fibrosis. Reduced oral aperture interferes with mastication, speech, and routine dental care and may contribute to the delayed diagnosis and treatment of dental disease. Patients often report difficulty opening the mouth fully, jaw stiffness, and pain with prolonged chewing [10,27].

Xerostomia and salivary hypofunction are also prevalent and may occur due to salivary gland involvement or overlap with secondary sicca syndromes. Reduced salivary flow impairs bolus formation and lubrication, contributing to dysphagia and taste disturbance. In addition, loss of the protective antimicrobial and buffering properties of saliva predisposes patients to dental caries, oral discomfort, and recurrent oral candidiasis.

Dental and periodontal disease are highly prevalent in SSc [28,29] and result from a combination of xerostomia, impaired oral hygiene (microstomia and poor hand dexterity), and possible reflux-related enamel erosion. Periodontitis, gingival inflammation, and accelerated tooth decay are commonly observed, often progressing silently until advanced disease is present. These complications further impair nutrition and may contribute to the systemic inflammatory burden [29,30,31,32].

Additional oral manifestations include mucosal telangiectasias, mucosal fragility, tongue stiffness, and, in long-standing disease, mandibular resorption. These skeletal changes may contribute to facial pain, malocclusion, and further compromise of oral function [10,27]

4.2 Screening and Assessment

Given the high burden of oral disease in SSc, a structured oral health evaluation should be incorporated into routine care. Patients should undergo baseline dental assessment at the time of diagnosis, with at least semiannual follow-up thereafter depending on individual risk factors. Routine clinical visits should include targeted symptom screening for dry mouth, oral pain or burning, chewing difficulty, dysphagia, recurrent oral candidiasis, bleeding gums, and dental instability [30].

Measurement of interincisal distance provides an objective marker of microstomia progression and can help guide early intervention. Focused examination of gingiva, dentition, and oral mucosa is essential, along with careful medication review for agents that may exacerbate xerostomia or increase infection risk.

4.3 Management

Management of microstomia centers on daily jaw stretching and facial range-of-motion exercises to preserve oral aperture. Warm compresses and massage prior to exercises may improve tolerability. Dental care should be adapted using pediatric-sized instruments, bite blocks, and shorter, staged visits when access is limited [10,27,31]

Xerostomia management includes frequent water intake, sugar-free chewing gum or lozenges, avoidance of acidic beverages, and nighttime humidification. Topical saliva substitutes and moisturizing gels provide symptomatic relief. High-fluoride toothpaste and professional fluoride varnish are recommended for patients at elevated caries risk. Pharmacologic sialagogues such as pilocarpine or cevimeline may be considered in appropriate patients without contraindications [29,33].

Periodontal disease requires meticulous plaque control using adaptive devices such as electric toothbrushes and floss holders, with early referral for periodontal care. Oral candidiasis should be treated promptly with topical or systemic antifungal therapy depending on severity and host factors [34].

5. Esophageal Manifestations, Screening, and Management

5.1 Clinical Manifestations

Esophageal involvement is the most frequent gastrointestinal manifestation of systemic sclerosis and represents a major source of morbidity. The classic clinical features include severe GERD with heartburn and regurgitation, dysphagia due to dysmotility or peptic stricture, chronic cough and hoarseness from laryngopharyngeal reflux, and aspiration-related pulmonary symptoms. Complications include erosive esophagitis, peptic strictures, and Barrett's esophagus [35]. Imaging may demonstrate esophageal dilation, impaired motility and a patulous esophagus on contrast esophagogram and cross-sectional imaging (Figs. 2,3).

5.2 Screening and Assessment

Patients should be screened at every clinical visit for reflux symptoms, dysphagia, odynophagia, weight loss, anemia, and respiratory symptoms suggestive of aspiration. Patients with mild GERD symptoms generally do not require invasive evaluation unless alarm features are present. Upper endoscopy is indicated for refractory symptoms despite optimized medical therapy, or suspected complications such as stricture, erosive esophagitis or Barrett's esophagus [15] (Fig. 4).

High-resolution esophageal manometry (HRM) is useful for characterizing dysmotility patterns and guiding management decisions, while ambulatory pH or pH-impedance monitoring should be considered (this measures the number of reflux episodes in the span of 24 hours) when symptoms persist despite acid suppression or when non-acid reflux is suspected [36].

Although current screening guidelines rely on traditional risk factors, multiple SSc cohort studies demonstrate a markedly increased prevalence of Barrett's esophagus, supporting consideration of earlier endoscopic evaluation in patients with chronic reflux symptoms [37,38].

5.3 Management

Management of esophageal disease in SSc requires a multimodal approach. Lifestyle and behavioral modifications serve as adjunctive therapy and include head-of-bed elevation, avoidance of late evening meals, smaller meal volumes, and identification of patient-specific reflux triggers. Medications that exacerbate LES hypotonia, such as anticholinergics, should be reviewed when clinically feasible.

Proton pump inhibitors (PPIs) are the cornerstone of therapy and should be initiated in all symptomatic patients and considered in asymptomatic patients as many patients have subclinical manifestations. Dosing should be optimized with administration 30–60 minutes prior to meals, and many patients require twice-daily therapy for adequate symptom control. Nocturnal symptoms may benefit from adjunctive bedtime H2 receptor antagonists. Alginate-based therapies can be useful for post-prandial regurgitation and as adjunctive therapy in refractory disease [39].

Prokinetic agents may be considered in selected patients with symptomatic upper gastrointestinal dysmotility, particularly when esophageal symptoms overlap with delayed gastric emptying. However, large randomized trials of prokinetic agents specifically in SSc is lacking and there is a need for evaluation of the safety and long-term effects of these medications in this patient population. Detailed discussion of specific prokinetic agents and treatment considerations is provided in the Gastric Manifestations section.

Esophageal strictures require endoscopic dilation in conjunction with aggressive acid suppression. Barrett's esophagus should be managed according to standard surveillance and endoscopic eradication protocols based on dysplasia status, with periodic surveillance for nondysplastic Barrett's and endoscopic eradication therapy for confirmed dysplasia [15,40].

Anti-reflux surgery and endoscopic interventions require careful multidisciplinary evaluation, as severe aperistalsis increases the risk of postoperative dysphagia. Decisions should be guided by manometric and reflux testing and made in collaboration with experienced esophageal specialists [41].

6. Gastric Manifestations, Screening, and Management

6.1 Clinical Manifestations

Gastric involvement is common in systemic sclerosis and may occur in both diffuse and limited cutaneous subtypes, often reflecting progressive smooth muscle dysfunction and fibrosis [42]. Gastroparesis manifests as persistent nausea, vomiting, abdominal distension, early satiety, and weight loss [43]. Autonomic dysfunction and enteric neuropathy may further contribute to impaired antral contractility and delayed gastric emptying [44].

Complications of gastric involvement include gastritis, gastric ulcers, and gastric antral vascular ectasia (GAVE). GAVE is characterized endoscopically by longitudinal erythematous stripes in the antrum ("watermelon stomach") and may present with chronic iron deficiency anemia or overt gastrointestinal bleeding independent of portal hypertension [45]. Histologically, GAVE is characterized by dilated, ectatic capillaries in the lamina propria with intraluminal fibrin thrombi. Chronic gastric dysmotility may contribute to malnutrition, sarcopenia, and im-

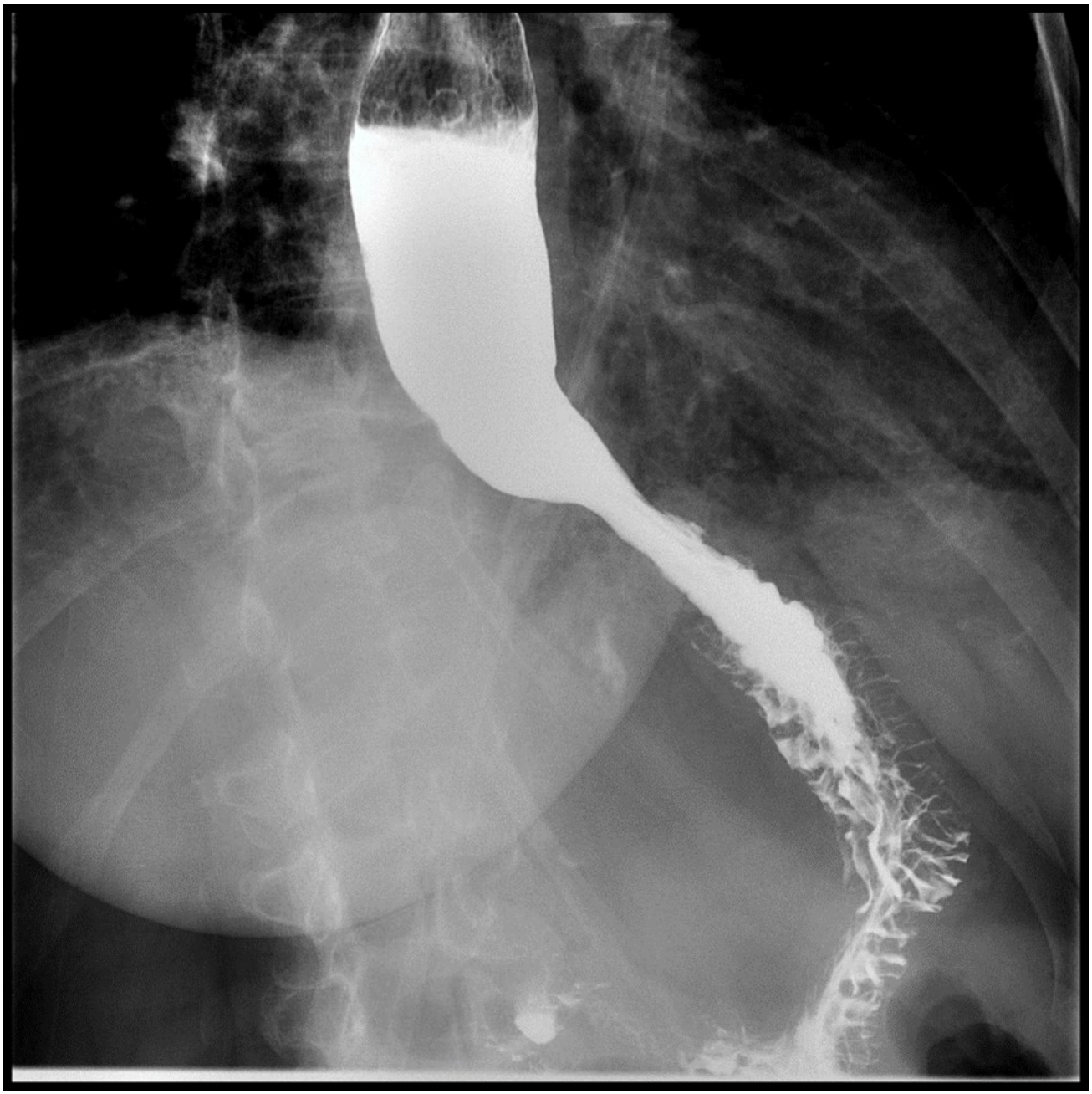

Fig. 2. Esophagram demonstrating esophageal dysmotility in systemic sclerosis. Contrast esophagram demonstrating a dilated esophagus with impaired peristalsis and delayed transit of contrast, consistent with esophageal dysmotility in systemic sclerosis (Patient permission was not required as no HIPAA information is reported).

paired quality of life, particularly when overlapping with small intestinal involvement [46,47].

6.2 Screening and Assessment

Given the high prevalence of gastric involvement in SSc, routine symptom screening is essential to preserve quality of life and prevent complications. Periodic monitoring of hemoglobin and iron studies should be considered in patients with suspected or established GAVE [48].

In patients with suspected gastroparesis, upper endoscopy should first be performed to exclude mechanical obstruction. If no obstruction is identified, gastric emptying scintigraphy should be performed, with delayed emptying defined as greater than 10% retention at 4 hours [49].

6.3 Management

Management should be guided by symptom severity and impact on nutritional status and quality of life. Proton pump inhibitors (PPIs) are the first line treatment of GERD, relieving symptoms and preventing ulceration and stricture formation [50]. It is worth noting that patients should also adjust their lifestyle by eating smaller and more frequent

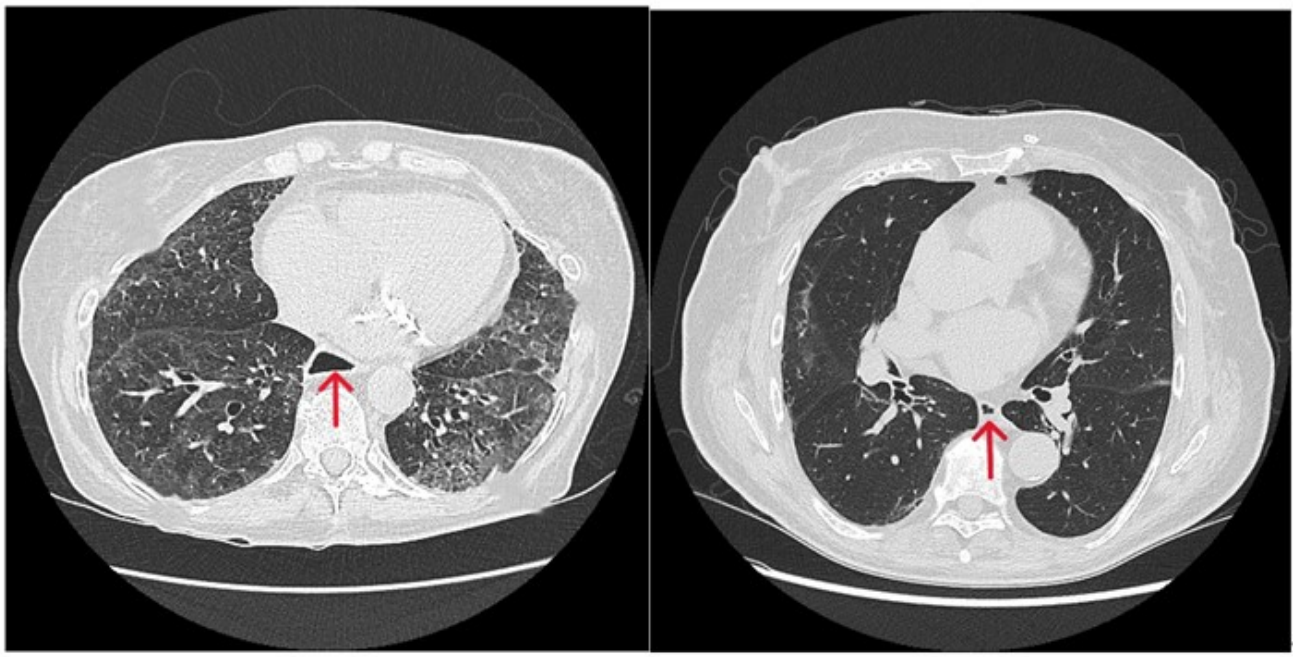

Fig. 3. Chest CT comparison of dilated esophagus in scleroderma vs normal esophagus in non-scleroderma. Axial CT of the chest demonstrates a markedly dilated esophagus (arrow, left CT), consistent with advanced esophageal involvement in systemic sclerosis compared to a normal esophagus (arrow, right CT) (Patient permission was not required as no HIPAA information is reported).

meals, limiting alcohol/caffeine, losing weight and avoiding eating meals 2–3 hours before bedtime. Early involvement of nutrition specialists may be beneficial in patients with significant weight loss or persistent symptoms.

If symptom control is inadequate, proton pump inhibitor dosing may be optimized or therapy adjusted accordingly. If nocturnal symptoms persist, a bedtime H2 receptor antagonist may be added. Dietary modification for gastroparesis includes small, frequent meals, reduced fat and fiber intake, and avoidance of carbonated beverages and tobacco. Patients may receive high-calorie liquids if nutritional status requires it [51]. Pharmacological therapy is mainly provided for symptom relief rather than disease modification. Metoclopramide is a first-line prokinetic agent; however, its use should be limited to the shortest effective duration due to the risk of tardive dyskinesia [51]. Alternative agents such as erythromycin and azithromycin may be used as motilin agonists to increase gastric motility [52].

In refractory cases, advanced interventions such as gastric peroral endoscopic pyloromyotomy (G-POEM), pyloric botox injections, jejunal feeding tube placement, or gastric electrical stimulation may be considered in specialized centers [51]. Management of GAVE primarily involves endoscopic therapy, most commonly argon plasma coagulation (APC), which often requires multiple treatment sessions. Iron supplementation or transfusion support may be necessary in cases of chronic blood loss [48].

7. Small Intestine Manifestations, Screening, and Management

7.1 Clinical Manifestations

Between 40–88% of SSc patients experience small intestine dysmotility leading to a variety of clinical manifestations [4]. Systemic sclerosis leads to smooth muscle atrophy and fibrosis of the small intestine, accompanied by vasculopathy that results in hypomotility. Symptoms such as flatulence, abdominal cramping, chronic bloating and constipation result from impaired peristalsis [4]. Luminal stasis promotes bacterial proliferation, which can lead to small intestinal bacterial overgrowth (SIBO). The clinical features of SIBO overlap with dysmotility-related symptoms, although diarrhea is more prominent due to mucosal inflammation and malabsorption [49].

Severe manifestations such as clinically significant malabsorption and vitamin B12 deficiency are less common but may occur in advanced disease [42]. Patients should be monitored for weight loss, micronutrient deficiencies, and electrolyte disturbances, particularly in advanced disease [4].

Chronic intestinal pseudo-obstruction (CIPO) represents one of the most severe small bowel complications of SSc and reflects advanced neuromuscular dysfunction. Patients present with abdominal distension, pain, nausea, vomiting, and radiographic evidence of bowel dilation in the absence of mechanical obstruction. Recurrent episodes may lead to hospitalization, malnutrition, and sepsis. Early recognition is critical, as management requires bowel rest,

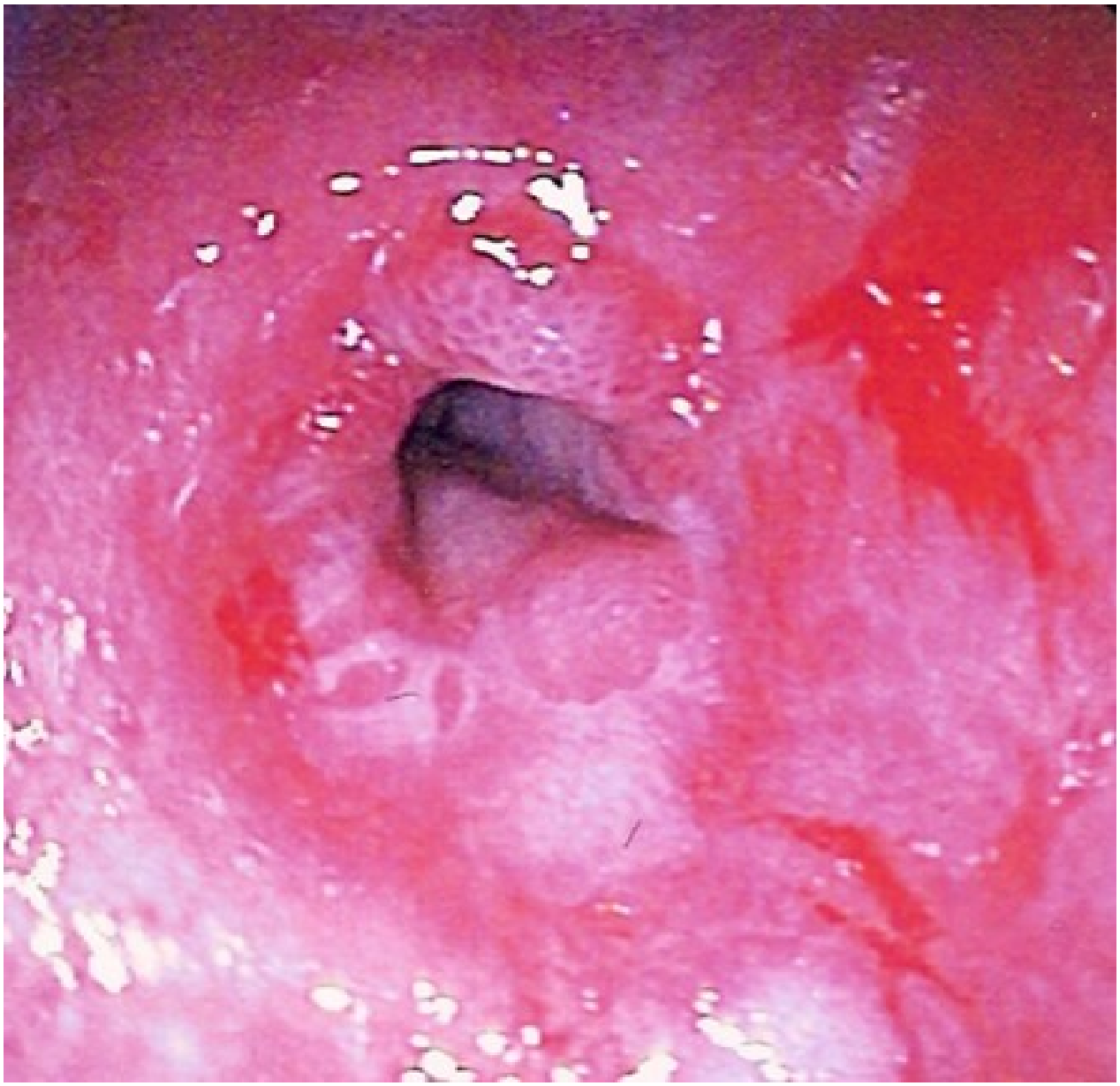

Fig. 4. Endoscopic view of gastroesophageal junction demonstrating stricture and esophagitis. The transition from normal squamous epithelium to columnar-lined mucosa is visible, reflecting chronic gastroesophageal reflux and mucosal injury commonly observed in systemic sclerosis–associated esophageal disease (from the Wikimedia Commons https://commons.wikimedia.org/w/index.php?search=scleroderma+esophagus&title=Special%3AMediaSearch&type=image).

decompression, prokinetic therapy, avoidance of opioids, and in severe cases parenteral nutrition [49]. Radiographic findings may demonstrate dilated bowel with a characteristic 'hide-bound' appearance due to closely packed valvulae conniventes. Cross-sectional imaging may demonstrate dilated bowel loops with air-fluid levels in the absence of a transition point.

7.2 Screening and Assessment

Patients with intestinal manifestations should undergo structured evaluation to prevent progression to serious complications such as malnutrition or intestinal pseudo-obstruction. Patients with dysmotility symptoms should undergo laboratory evaluation to assess nutritional status, including a complete blood count to evaluate for anemia, serum vitamin B12 levels, comprehensive metabolic panel, and micronutrient assessment as indicated [43]. Small bowel dysmotility may be evaluated using upper gastrointestinal contrast studies or dedicated transit studies. Malabsorption may be evaluated using stool studies, including a 72-hour fecal fat collection to assess for steatorrhea.

SIBO may be diagnosed via small bowel aspirate and culture, with $\geq 10^3$ CFU/mL of colonic-type bacteria considered diagnostic. Although small bowel aspirate and cul-

ture remain the diagnostic gold standard, hydrogen and methane breath testing are more commonly used in clinical practice due to their noninvasive nature, despite variable sensitivity and specificity [53].

7.3 Management

SIBO management usually includes the administration of antibiotics to reduce the intestinal bacterial overgrowth. Rifaximin is commonly used off label for 7–14 days, with repeat or cyclic therapy considered in recurrent cases. In patients with recurrent SIBO, rotating antibiotic regimens may be necessary to prevent recurrence and antimicrobial resistance. Nutritional optimization is an essential component of management. Identified nutritional deficiencies, particularly vitamin B12 deficiency, should be corrected.

Prokinetic therapy, such as metoclopramide, may reduce stasis and improve intestinal transit. Opioids and anticholinergic agents should be avoided, as they may further impair intestinal motility [54]. Patients with recurrent or refractory SIBO or significant intestinal dysmotility should be referred to a gastroenterologist for specialized evaluation [49]. In patients with progressive malnutrition or recurrent pseudo-obstruction, escalation to enteral feeding via jejunal tube or, in severe refractory cases, parenteral nutrition may be required. Multidisciplinary management involving gastroenterology and nutritional specialists is recommended. Overall, small intestinal involvement in SSc represents a progressive motility disorder spectrum ranging from mild dysmotility to life-threatening pseudo-obstruction and malabsorption, requiring proactive monitoring and individualized management strategies.

8. Large Intestine Manifestations, Screening, and Management

8.1 Clinical Manifestations

Colonic involvement in Systemic Sclerosis is characterized by hypomotility secondary to smooth muscle atrophy and fibrosis, resulting in chronic constipation, abdominal distention, and bloating [14]. In advanced disease, patients may develop colonic pseudo-obstruction, presenting with obstructive symptoms in the absence of a mechanical cause.

Anorectal dysfunction is common and contributes significantly to morbidity. Internal anal sphincter involvement leads to decreased resting pressure, causing fecal incontinence and urgency [14,55]. Additional abnormalities include impaired rectal compliance and reduced rectoanal inhibitory reflex, resulting in tenesmus and incomplete evacuation [14]. These features reflect combined neuropathic and myopathic injury affecting anorectal function. Mega-diverticula are large “wide-mouthed” pouches primarily forming in the colon in SSc, due to chronic muscle weakness and atrophy. These are typically asymptomatic.

8.2 Screening and Assessment

Early recognition of gastrointestinal involvement is essential. Clinical evaluation should include detailed assessment of bowel habits, stool consistency, and continence.

Anorectal manometry is the primary modality for assessing sphincter function and coordination, while balloon expulsion testing evaluates defecatory disorders [55]. Colonic transit study helps identify delayed transit associated with hypomotility. Radiologic imaging, including contrast studies, may reveal colonic dilation and loss of haustration, while abdominal radiographs or CT scans are useful in suspected pseudo-obstruction [56]. Colonoscopy is reserved for excluding alternative pathology, such as malignancy or inflammatory bowel disease.

8.3 Management

Management is largely supportive and symptom based. Constipation is treated with hydration, cautious use of fiber, and osmotic or stimulant laxatives; prokinetic agents may be considered in selected patients. Acute colonic pseudo-obstruction requires bowel rest, decompression, and correction of electrolyte abnormalities, with antibiotics indicated when bacterial overgrowth is suspected.

Fecal incontinence is managed with antidiarrheal agents such as loperamide, along with pelvic floor therapy and biofeedback [55]. Sacral nerve stimulation may be considered in refractory cases, although evidence remains limited [57]. Surgical intervention is reserved for severe complications and approached cautiously due to increased perioperative risk. A multidisciplinary approach is essential to optimize outcomes and quality of life.

9. Future Directions

• Develop and validate objective biomarkers, including high-resolution manometry metrics, microbiome signatures, and serologic markers, to improve early detection and predict disease progression.

• Conduct prospective studies on the gut microbiome’s role in disease pathogenesis and treatment response, including the effects of dietary and microbiome-targeted interventions.

• Evaluate emerging therapies, including novel prokinetic agents, neuromodulators, and endoscopic techniques, in well-designed clinical trials.

10. Conclusion

Gastrointestinal involvement in systemic sclerosis is common and clinically important, affecting multiple regions of the gastrointestinal tract and substantially reducing quality of life. Its pathophysiology reflects the interaction of microvascular injury, neural dysfunction, and progressive smooth muscle fibrosis, producing a range of motility disorders that evolve over time and often require multi-

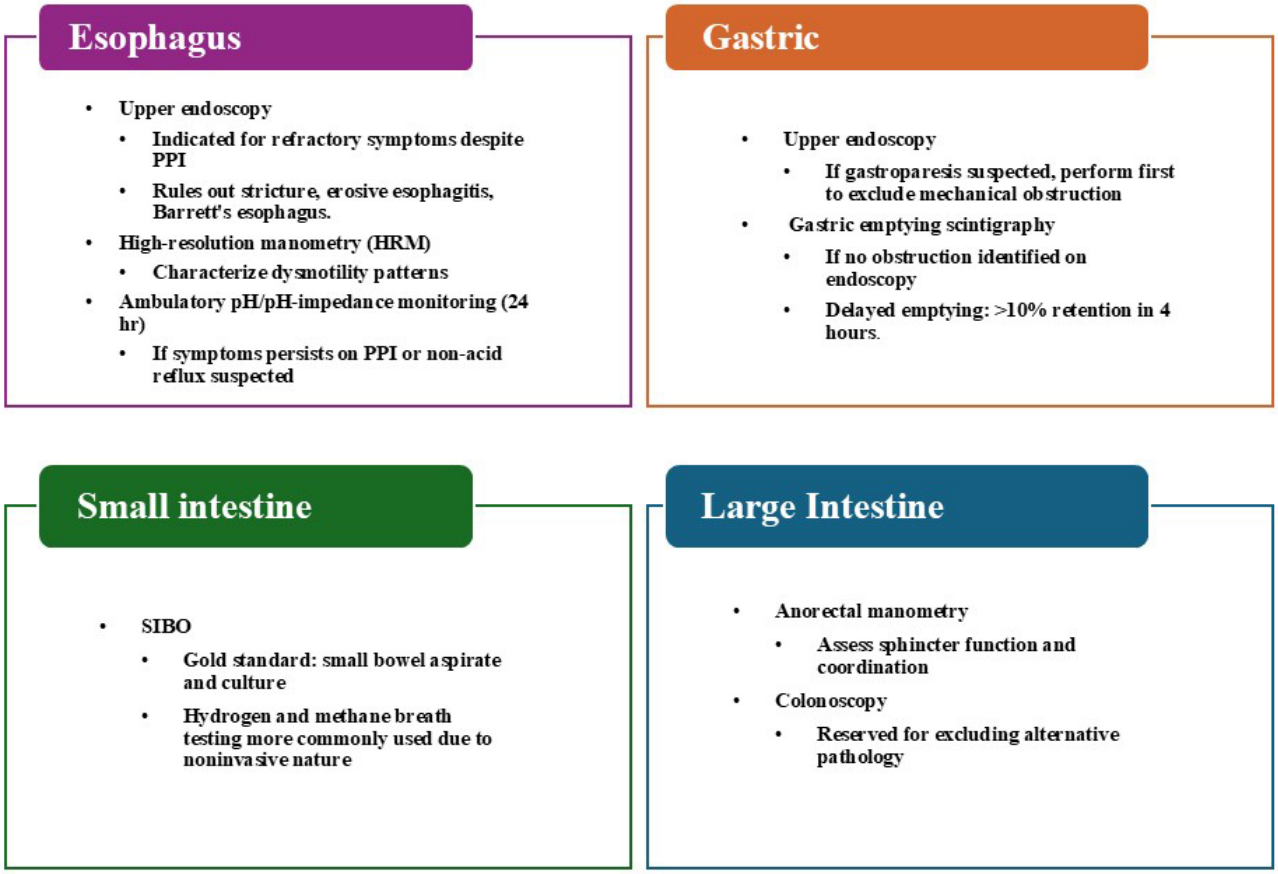

Fig. 5. Diagnostic evaluation of GI involvement in systemic sclerosis. Flowchart of screening assessments. (Software: Microsoft PowerPoint Version: Microsoft PowerPoint for Microsoft 365; Manufacturer: Microsoft Corporation; City/Country: Redmond, WA, USA).

disciplinary care. Although diagnostic tools such as high-resolution manometry, pH-impedance testing, and cross-sectional imaging have advanced, early recognition remains difficult because symptoms are heterogeneous and often insidious (Fig. 5).

Current treatment remains largely supportive, emphasizing symptom control, prevention of complications, and nutritional optimization. Pharmacologic and endoscopic therapies have improved outcomes for specific manifestations, including GERD, gastroparesis, and SIBO; however, no disease-modifying treatments currently target the underlying pathobiology of gastrointestinal involvement in SSc. Management is further limited by the absence of disease-specific guidelines, standardized protocols, and validated SSc-specific screening practices, leaving many patients undiagnosed until complications develop.

Emerging research on the gut microbiome, immune dysregulation, and neurogastroenterology offers promising directions for future study. Improving long-term outcomes will require biomarker development, refined risk stratification, and integrated multidisciplinary care. A major unmet need is a validated measure of gastrointestinal outcomes across the entire tract for use as an endpoint in randomized controlled trials of disease-modifying therapies in SSc. Ultimately, deeper mechanistic insight into gastrointestinal involvement in systemic sclerosis is essential for developing targeted therapies and personalized management strategies.

Key Points

• Gastrointestinal involvement affects up to 90% of patients with systemic sclerosis and represents a major contributor to morbidity and reduced quality of life.

• The pathogenesis of GI disease in SSc is driven by microvascular injury, enteric nervous system dysfunction, and progressive smooth muscle atrophy with fibrosis, resulting in widespread dysmotility.

• Esophageal involvement is the most common manifestation, characterized by impaired peristalsis and lower esophageal sphincter dysfunction, leading to severe gastroesophageal reflux and its complications.

• Small intestinal and colonic involvement can lead to clinically significant complications, including small intestinal bacterial overgrowth (SIBO), malabsorption, and intestinal pseudo-obstruction.

• Diagnosis requires a multimodal approach incorporating symptom assessment, high-resolution manometry,

pH-impedance monitoring, imaging, and targeted laboratory evaluation.

• Management remains largely supportive and symptom-based, including acid suppression, prokinetic therapy, nutritional optimization, and endoscopic or surgical interventions for complications.

Availability of Data and Materials

Not applicable.

Author Contributions

RP, KM, GK, IP and AS: Manuscript design, review, editing. CD: Manuscript initial draft, design, review, editing. All authors contributed to revising the manuscript critically for important intellectual content. All authors read and approved of the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The individual radiographic studies were obtained from original patients. According to University of Pennsylvania policy, informed consent was not required because no patient identifiers were included.

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Conflicts of Interest

Given his role as an Editorial Board Member, <Chris Derk> had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to <Kassem Sharif>. The other authors declare no conflicts of interest.

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