

# Evaluation and management of esophageal manifestations in systemic sclerosis

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## Abstract

Systemic sclerosis (SSc) is a multisystemic autoimmune connective tissue disorder; in the gastrointestinal tract, the esophagus is the most commonly affected organ. Symptoms of esophageal disease are due to gastroesophageal reflux disease (GERD) and esophageal motor dysfunction. Since the development of high-resolution manometry (HRM), this method has been preferred for the study of SSc patients with esophageal involvement. Using HRM, classic scleroderma esophagus, defined as absent or ineffective peristalsis of the distal esophagus in combination with a hypotensive lower esophageal sphincter, was found in as many as 55% of SSc patients. Endoscopy is the appropriate test for evaluating dysphagia and identifying evidence and possible complications of GERD. In the therapeutic area, treatment ranges from general supportive measures to the administration of drugs such as proton pump inhibitors and/or prokinetics. However, as many SSc patients do not respond to existing therapies, there is an urgent need for new therapeutic modalities. Buspirone, a 5-hydroxytryptamine 1A receptor agonist, could be a putative therapeutic option, as it was found to exert a significant beneficial effect in SSc patients with esophageal involvement. This review summarizes our knowledge concerning the evaluation and management of esophageal manifestations in SSc patients, including emerging therapeutic modalities.

**Keywords** Systemic sclerosis, scleroderma esophagus, high-resolution manometry, 5-HT1A receptor agonist, buspirone

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## Introduction

Systemic sclerosis (SSc), a connective tissue disease of unknown origin, occurs most frequently in females aged 40-65 years (female:male ratio 8:2). Gastrointestinal tract involvement is very common and the esophagus is the most frequently affected part (up to 90% of patients) [1-4]. The pathogenesis of esophageal involvement in SSc is multifactorial. On the basis of clinical, immunological, and histopathological observations, three pathways have been proposed as being involved in scleroderma: vascular alterations, an abnormal immune response, and disturbances in the regulation of connective tissue metabolism. The pathogenesis of SSc is initiated

with vascular endothelial activation (vasculopathy), reflected in recurrent episodes of reperfusion and vasoconstriction, and this progresses to episodic and sustained tissue ischemia with inappropriate immunological and reparative changes. Excessive deposition of collagen and collagen matrix from activated profibrogenic fibroblasts ensues, resulting in fibrosis and replacement of tissue in the skin and multiple internal organs, including the esophagus [5-11].

## Symptoms and complications of esophageal dysfunction in SSc

Patients with SSc and esophageal involvement usually report two types of symptoms: due to gastroesophageal reflux disease (GERD), such as heartburn and regurgitation, and/or due to esophageal dysmotility, such as dysphagia and chest pain [5,12]. Dysphagia may not only represent a symptom of dysmotility, but could also be the result of *Candida* esophagitis or of peptic stricture formation due to complicated GERD [13]. Overall, the incidence of esophageal symptoms in SSc has been estimated at between 40% and 80%, even though a percentage of patients are totally asymptomatic despite their documented esophageal disease [5,12-16].

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Complications of GERD, such as peptic strictures occur in up to 30% of patients [3,13,17-19], whereas Barrett's esophagus has been found in up to 37% [13,18-20]. Moreover, GERD may contribute to interstitial lung disease via recurrent micro-aspiration of acid causing bronchoconstriction [21]. Although SSc patients have a risk of developing esophageal carcinoma, the use of proton pump inhibitors (PPIs) has decreased its incidence [22].

## Diagnosis

Esophageal involvement can be assessed by the following methods:

### Manometry

Classic manometry was, until recently, the gold standard method for the detection and assessment of esophageal dysmotility, especially in the early stages of esophageal involvement in SSc patients. The typical manometric findings include decreased lower esophageal sphincter (LES) pressure and absent or ineffective peristalsis of the distal esophagus [12,19]. The combination of distal aperistalsis and a hypotensive LES is called classic scleroderma esophagus. Since the development of high-resolution manometry (HRM), this method has been preferred for the study of SSc patients [23]. HRM, using multiple closely spaced pressure sensors, allows a better assessment of the whole esophagus and especially of the LES.

With HRM, the overall frequency of manometric abnormalities reported in SSc patients has been very high, affecting up to 75-80% of them. Hypotensive LES was encountered in more than 50% of patients, whereas esophageal body dysmotility was present in more than 60% of patients. Classic scleroderma esophagus was found in as many as 55% of patients [24-30]. In a well-characterized cohort of patients with SSc, we observed, using recent criteria for esophageal motility diagnosis [31], that classic scleroderma esophagus was the most prevalent contractility pattern in SSc patients [32]. Table 1 summarizes studies demonstrating the importance of HRM.

### pH monitoring

Esophageal pH monitoring, with or without impedance, is considered the gold standard for gastroesophageal reflux detection. However, its role in the management of SSc patients is limited and in clinical practice it is only used in patients with resistant reflux symptoms. Thus, only few studies assess pH parameters in patients with SSc. Abnormal pH monitoring has been seen in up to 85% of patients [33-35]. Although the number of reflux events is similar between SSc patients and non-scleroderma patients, a small but well-designed study [36]

found that SSc patients showed a greater number of events with longer duration. A recent retrospective study suggested a role of pH monitoring as a prognostic factor in patients with SSc and interstitial lung disease [37]. Esophageal pH monitoring was performed in 10 SSc patients referred for lung transplantation and severe reflux, calculated via a self-administered score of pH monitoring. The authors found that the presence of abnormal pH was a better predictor of survival than abnormal pulmonary function tests. Thus, esophageal pH monitoring should be considered early in SSc patients with early-stage lung disease, as this test could identify those in whom intense anti-reflux therapy should be introduced to prevent GERD and its detrimental effects in patients awaiting lung transplantation.

### Endoscopy

Upper endoscopy is the appropriate test for evaluating dysphagia, identifying evidence of GERD, such as esophagitis, and identifying possible reflux complications, such as esophageal stenosis, Barrett's esophagus and esophageal adenocarcinoma. Esophageal manifestations are more common in SSc patients than in the general population; thus, endoscopy should be performed in patients with SSc, even if they do not report reflux symptoms, as it is well known that symptoms are not predictive for the presence of esophagitis [18]. Prevalence of endoscopic esophagitis has been reported in up to 65% [13,14,18,33], whereas Barrett's esophagus was found in up to 7% of SSc patients [38]. A recent, prospective study that included fifty SSc patients with Barrett's esophagus (40 without and 10 with dysplasia) showed an overall 0.7% year rate of progression to adenocarcinoma, not greater than that seen in the general population [39].

### Treatment

In general, the treatment is supportive and patients are advised to chew food well, avoid big bites, and use water as complimentary to solid foods. Moreover, in symptomatic SSc patients with esophageal involvement drug administration targeting either GERD symptoms or dysmotility symptoms could be offered.

### GERD therapies

PPIs are considered as the standard of care for the treatment of GERD in SSc patients. However, the effective dose of PPIs for alleviating reflux symptoms in SSc patients is still under investigation. Few studies using standard doses of PPIs reported symptomatic improvement and healing of esophagitis [40-42]. Even though PPIs demonstrated a clear short-term benefit, the long-term efficacy of these drugs was not sustained and there was no evidence that progression of esophageal dysfunction was prevented [41]. We have to keep in mind that an estimated 40% of SSc patients

**Table 1** Studies that evaluated the important role of high-resolution manometry (HRM) in systemic sclerosis (SSc) disease

Author	Aim of the study – methods – main conclusions
Crowell <i>et al</i> [29]	<ul style="list-style-type: none"> <li>To assess associations between SSc severity, health-related quality of life (HRQOL) and HRM findings in a prospective study of 200 SSc patients and 102 non-SSc (controls)</li> <li>HRM findings, symptoms, and HRQOL data were compared among diffuse SSc, limited SSc, and control subjects</li> <li>Main results of this study: i) severe dysmotility is more common in SSc patients than in controls; ii) SSc esophagus is found in only one-third of SSc patients; and iii) esophageal dysmotility reduces HRQOL in patients with SSc</li> </ul>
Kimmel <i>et al</i> [28]	<ul style="list-style-type: none"> <li>To evaluate the associations between SSc-related systemic manifestations and esophageal dysmotility diagnoses (diagnosis?) using HRM in 79 SSc patients</li> <li>Main conclusion: more severe skin disease and worse pulmonary function were associated with absent esophageal contractility</li> </ul>
Raja <i>et al</i> [35]	<ul style="list-style-type: none"> <li>To evaluate the associations between objectively measured gastroesophageal involvement using HRM, 24-h impedance-pH study, and clinical presentations in 31 SSc patients</li> <li>Main conclusions: i) presence and severity of gastroesophageal symptoms may not accurately reflect the seriousness of esophageal involvement; ii) GERD severity is associated with presence of restrictive lung pattern and pulmonary fibrosis; and iii) HRM and 24-h pH-study should be considered more frequently in the assessment of SSc patients</li> </ul>
Karamanolis <i>et al</i> [32]	<ul style="list-style-type: none"> <li>To assess associations between scleroderma and non-scleroderma esophagus, diagnosed by HRM, and other manifestations of disease (demographic characteristics, patient-reported symptoms, SSc subtypes, pulmonary fibrosis, cutaneous ulcers, and anti-Scl-70 positivity) in 54 SSc patients</li> <li>To make comparisons between scleroderma and non-scleroderma esophagus with computed tomography (CT) findings of esophageal lumen in 26 SSc patients with available data</li> <li>Main conclusions: i) scleroderma esophagus diagnosed by HRM was present in less than 2/3 of symptomatic patients with SSc and associated only with esophageal dilation in CT; and ii) esophageal dilation on chest CT may be a noninvasive alternative for evaluation of SSc patients with esophageal symptoms</li> </ul>
Tang <i>et al</i> [30]	<ul style="list-style-type: none"> <li>To evaluate the impact of cutaneous findings, Raynaud's phenomenon (RP) and pulmonary fibrosis (PF) on demographics, symptoms, and esophageal motility in 28 SSc patients who underwent HRM in a 6-year study</li> <li>Main results: i) heartburn and dysphagia are important symptoms that may be associated with disease progression based on skin changes in SSc; ii) RP was associated with greater esophageal dysmotility; and iii) coughing and wheezing were more severe in patients with PF</li> </ul>
Roman <i>et al</i> [24]	<ul style="list-style-type: none"> <li>To more fully characterize esophageal motility disorders in 51 SSc patients using HRM and to determine predictive factors of esophageal involvement by making associations with other manifestations of the disease (dermatographic data, esophageal symptoms, presence of other organ involvement and autoantibody profile, such as anti-Scl-70 antibodies, anticentromere antibodies [ACA])</li> <li>Main conclusion: diffuse skin involvement, positive Scl-70 and negative ACA may predict esophageal body dysmotility</li> </ul>

showed no response to a standard PPI dose. Thus, a two- to fourfold increase in the daily dose of PPIs, in order to gain better symptom control in patients with a partial response, is common practice [43]. A recent study, involving 148 SSc GERD patients, some of whom showed partial response to PPIs, compared the efficacy of a combination of omeprazole with domperidone, or with alginic acid, in alleviating reflux symptoms. The authors concluded that the addition of domperidone or alginic acid to omeprazole therapy was effective in the majority of non-responsive patients [44]. However, even with this approach, approximately 20% of patients did not respond. This study highlights the necessity for more potent anti-reflux drugs in order to reduce the severity and frequency of reflux symptoms in SSc patients. Endoscopic procedures, such as dilation with balloon dilators, have been proposed for use in patients with peptic strictures related to GERD [43].

### Motility therapies

According to the pathophysiology of SSc, motility abnormalities could be among the mechanisms underlying GERD pathogenesis. Thus, various prokinetic drugs have been used in the treatment of SSc patients with esophageal involvement, such as metoclopramide, erythromycin, and cisapride [45-47]. It has been reported that metoclopramide and erythromycin may increase LES pressure in SSc patients [48-50], while cisapride has been shown to increase LES pressure and the amplitude of distal esophageal body peristalsis [45,51]. Based on these results, prokinetics are used in clinical practice. However, experience with the use of prokinetic drugs in SSc patients is bibliographically limited and has had controversial results. Moreover, their use is restricted because of safety profile issues (central nervous system, cardiovascular side effects).

Domperidone, a peripheral dopamine antagonist, is currently the most common prokinetic agent used in clinical practice in patients with SSc, although data regarding its effect on esophageal motility are conflicting [46,47]. A recent study, involving 10 SSc patients who underwent HRM before and after administration of 10 mg domperidone, challenged the drug's effect on motility. Acute administration of domperidone had no effect upon any manometric parameters compared to the baseline values [52]. Moreover, there is some concern over safety issues, as domperidone has been associated with cases of sudden death due to its cardiac side effects [53,54].

### Emerging therapies

Buspiron, an orally available 5-hydroxytryptamine 1A (5-HT<sub>1A</sub>) receptor agonist, has shown a beneficial effect on esophageal motor function in healthy subjects. Thus, we studied the differences in HRM parameters in 20 SSc patients with esophageal involvement before and after acute administration of 10 mg buspiron. We observed a significant increase in the LES resting pressure in up to 80% of SSc patients, from  $9.4 \pm 2.6$  to  $11.5 \pm 3.3$  mmHg ( $P=0.0002$ ). Moreover, a non-significant trend ( $P=0.09$ ) toward an increased amplitude of esophageal body motility was also observed [52].

Based on this result, buspiron was administered in a 4-week open-label study that included SSc patients with symptomatic esophageal involvement despite PPI administration [55]. Twenty-two consecutive SSc patients underwent HRM before and after a 4-week administration of 20 mg of buspiron, so that the efficacy of long-term buspiron administration on esophageal motor dysfunction and on esophageal symptoms could be evaluated. Following buspiron administration for 4 weeks, an increase in the LES resting pressure was observed in 15 (68%) patients, with an enhancement from  $7.7 \pm 3.9$  to  $12.2 \pm 4.6$  mmHg ( $P<0.00005$ ). In an attempt to identify prognostic factors for the beneficial effect of buspiron, a moderate, but significant, inverse correlation between the increase in LES resting pressure and supra-aortic diameter,

measured by chest computed tomography ( $r=-0.589$ ,  $P=0.017$ ) was found. Moreover, the severity of heartburn and regurgitation significantly decreased at 4 weeks compared with baseline ( $P=0.001$ , and  $P=0.022$ , respectively), whereas no significant improvement was found in the severity scores of chest pain and dysphagia. Concerning the safety issues, buspiron was well tolerated by all patients who completed the study and only self-limited adverse effects that did not affect their daily activities were observed.

### Surgical management

Anti-reflux procedures, such as Nissen fundoplication, are generally considered suboptimal in SSc patients with reflux symptoms, because of the profound esophageal dysmotility seen in this disease. Indeed, 38-71% of patients who underwent fundoplication developed postoperative dysphagia, even though an improvement in the severity of reflux symptoms and in esophageal acid exposure has been reported after surgical intervention [56-58]. In an attempt to identify a better surgical option for the management of SSc-associated gastroesophageal reflux, a recent review of different surgical series proposed Roux-en-Y gastric bypass as an alternative. The authors showed that patients undergoing Roux-en-Y gastric bypass reported better postoperative GERD-related quality of life and less dysphagia compared with those undergoing fundoplication [59]. However, we have to keep in mind that Roux-en-Y should also be pursued with caution, because of the small intestinal dysmotility in SSc patients and the possibility of bacterial overgrowth.

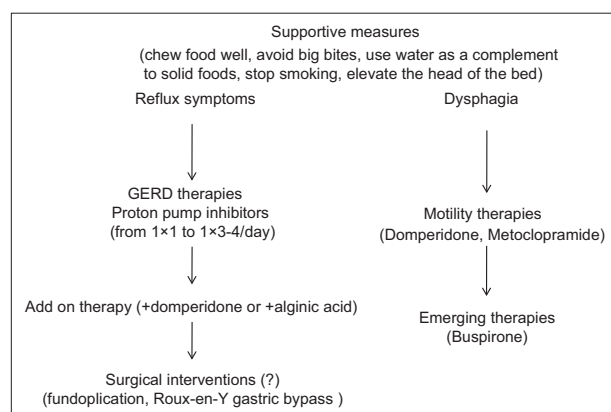
Fig. 1 demonstrates an algorithm for the therapeutic management of SSc.

### Concluding remarks

Esophageal involvement in SSc is common, occurring in up to 90% of patients. It carries significant morbidity and mortality, which can be improved by its early diagnosis and treatment. Nowadays, HRM is the gold standard method used to identify SSc patients with esophageal motility disorders. Treatment for SSc-induced esophageal impairment, which includes PPIs, prokinetics and endoscopic interventions, is still a challenging process. Buspiron, a 5-HT<sub>1A</sub> receptor agonist, was found to exert a significant beneficial effect on both manometric and clinical parameters in the treatment of SSc patients with esophageal involvement, creating new data relating to future therapeutic modalities in that category of patients.

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**Figure 1** Algorithm for therapeutic approach to SSc patients with esophageal manifestations  
SSc, systemic sclerosis; GERD, gastroesophageal reflux disease

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