Current Rheumatology Reports (2019) 21: 42
https://doi.org/10.1007/s11926-019-0841-x

SCLERODERMA (J VARGA, SECTION EDITOR)

GI Manifestations With a Focus on the Esophagus: Recent Progress in Understanding Pathogenesis

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Published online: 3 July 2019

Abstract

Purpose of Review Esophageal dysfunction is common in systemic sclerosis (SSc) patients. Limited treatment options are available for scleroderma esophageal disease. Here, we discuss recent updates on the diagnosis, treatment, and characterization that have been made in patients with scleroderma esophageal disease.

Recent Findings In the past few years, novel diagnostic tools have provided insight into esophageal dysmotility in SSc patients. New drugs are being tested and might improve symptoms and quality of life in SSc patients with esophageal dysfunction. Molecular stratification methods have facilitated the identification of molecular signatures in the esophagus of SSc patients. The Friend leukemia integration 1 (Fli1) conditional knockout mouse is the first animal model to report an esophageal phenotype with SSc features.

Summary The clinical presentation in SSc patients with esophageal dysfunction is heterogeneous, complicating diagnosis and management. The improvement of diagnostic tools for esophageal symptoms and dysfunction and the use of molecular approaches in SSc mouse models and patient biopsies offer an opportunity to improve the characterization of SSc esophageal disease, which should help improve management and treatment decisions.

Keywords Systemic sclerosis · Esophagus · Manometry · Impedance · Esophageal reflux monitoring · Functional luminal imaging probe

Abbreviations

Fli1	Friend leukemia integration 1
K14	Keratin-14
SSc	Systemic sclerosis
ILD	Interstitial lung disease
CT	Computed tomography
PPI	Proton-pump inhibitor
BI	Baseline impedance
NERD	Non-erosive reflux disease
ACPA	Anti-citrullinated peptide antibodies
RA	Rheumatoid arthritis
LES	Lower esophageal sphincter
EGJ	Esophagogastric junction
IQR	Interquartile range
HRM	High-resolution manometry
MRS	Multiple rapid swallows
EPT	Esophageal pressure topography
GISSI	Gastrointestinal Symptoms Severity Index
GIT	University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract
HRIM	High-resolution impedance manometry
FLIP	Functional luminal imaging probe

This article is part of the Topical Collection on *Scleroderma*

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Introduction

Systemic sclerosis (SSc) is a complex autoimmune disease with multisystem manifestation [1]. Disease pathogenesis is attributed to smooth muscle atrophy, fibrosis, vasculopathy, and inflammation [1, 2]. Esophageal symptoms and dysfunction have been reported in 50–90% of SSc patients, which makes the esophagus the second most commonly affected organ in SSc patients [3, 4]. Autopsy studies of patients with

scleroderma esophagus demonstrate smooth muscle atrophy as opposed to fibrosis as the predominate pathology [5]. Despite increasing efforts to better understand the nature of scleroderma esophageal disease, our knowledge of its pathogenesis remains poorly understood. Inconsistent associations have been reported between SSc clinical manifestations (disease subtype, serum autoantibodies, Raynaud's phenomenon, interstitial lung disease) and esophageal dysfunction [6–10]. Consequently, the management of esophageal diseases in SSc patients continues to be challenging, and no disease-modifying treatment exists. However, recent scientific advances from clinical and translational investigations hold promise for future progress toward improving the outcome and the quality of life for these patients. In this review, we describe the latest advances made in the evaluation, management, and pathogenesis of scleroderma esophageal disease.

Autoantibodies

Serum autoantibodies against a variety of self-antigens have been detected in SSc and have been associated with clinical manifestations, but the correlations with esophageal dysfunction have been inconsistent [6–11]. Anti-citrullinated peptide autoantibodies (ACPA) are the most relevant biomarker for the detection of rheumatoid arthritis (RA), with detection levels ranging between 50 and 75% [12]. A recent meta-analysis determined the prevalence of ACPA to be 9.2% in SSc patients [13]. Furthermore, ACPA-positive SSc patients had an increased risk of esophageal involvement, along with erosive arthritis, pulmonary fibrosis, and diffuse skin involvement. This suggests either the existence of an SSc-RA syndrome or that ACPA is associated with a specific clinical phenotype.

Computed Tomography

Several studies have reported the prevalence of esophageal dilatation in SSc using chest computed tomography (CT) scans [14–17]. Furthermore, esophageal dysfunction has been correlated with the presence of esophageal dilatation [16, 17]. It has been suggested that microaspiration caused by esophageal dysfunction might be involved in the development and/or progression of interstitial lung disease (ILD) in SSc, but this hypothesis is unproven [9, 10, 18]. A recent study analyzed the esophageal diameter of 121 SSc patients with ILD and 48 SSc without ILD along with 121 pulmonary clinic patients and 110 normal subjects [19•]. Esophagi from SSc patients with ILD had greater diameters than those from SSc patients without ILD. Interestingly, esophageal dilatation was greater in SSc patients (with or without ILD) than pulmonary clinic patients. This observation suggests that increased esophageal dilatation in SSc patients with ILD cannot be completely attributable to increased disease severity. Another study also investigated the association between esophageal dilatation and SSc ILD using high-resolution computed tomography [20•]. Increased ILD (increased lung fibrosis and ground glass opacity) was associated with greater esophageal diameter. Furthermore, increased esophageal diameter was correlated with lower forced vital capacity and diffusing capacity for carbon monoxide. This study also showed that SSc patients with greater diameter esophagi were more likely to be positive for Scl-70 serum autoantibodies. Given that both of these studies were retrospective cross-sectional investigations, longitudinal studies are still needed to demonstrate whether or not esophageal dilatation predicts progression of ILD in SSc patients.

Esophageal pH-Impedance

Gastroesophageal reflux disease (GERD) is common in SSc patients and can lead to serious complications such as bleeding, stricture, Barrett's esophagus, and esophageal adenocarcinoma [21]. Furthermore, as mentioned above, GERD might be involved in the progression of ILD [9, 10, 18]. GERD in SSc patients is commonly treated with proton pump inhibitors (PPIs) [3]. Recently, the effectiveness of PPI therapy was evaluated in SSc patients [22•]. Analyses of combined pH-impedance testing demonstrated that acid exposure time (AET) of more than 4.5% was seen in 61% of SSc patients, while 55% of SSc patients have an AET of more than 6%. These AET values were observed despite the fact that SSc patients were on high-dose PPIs. Interestingly, these AET values were much greater than those of historical cohorts of patients with GERD also on twice-daily PPIs [23]. Furthermore, SSc patients had longer AET, longer median bolus clearance time, and lower mean nocturnal baseline impedance when compared with matched controls on high-dose PPIs. Hence, the threshold to escalate PPI therapy should be low in SSc patients with persistent reflux symptoms while on PPIs. Moreover, this study suggests a rationale to utilize pH-impedance testing in those SSc patients to guide that management decision. The test should be done with the patients taking their potentially inadequate regimen, and if the study shows a persistently abnormal AET, their therapy should be adjusted to a more potent regimen, be that higher dosage or more potent PPI medication.

Combined esophageal multichannel intraluminal impedance-pH monitoring is often used for the assessment of GERD. Changes in resistance (i.e., impedance) to alternating current passed between pairs of metallic rings mounted along a catheter are measured to detect anterograde or retrograde bolus movement within the esophagus in a pH-independent fashion. Given the negative correlation between

electrical impedance and the ionic concentration of the intraluminal content, the resistance of esophageal boluses with high ionic concentrations is relatively low, compared with relatively high baseline impedance of the esophageal epithelium [24]. It has also been suggested that the measurement of esophageal baseline impedance (BI) using 24-h multichannel intraluminal impedance-pH monitoring might be useful for the evaluation of the esophageal mucosal integrity [25, 26]. A recent study evaluated and compared esophageal baseline impedance in SSc patients, non-erosive reflux disease (NERD) patients, and healthy control subjects [27]. Lower values of esophageal baseline impedance were found in SSc patients compared with NERD and healthy controls. These differences in BI were observed both in the proximal and distal esophagi. These findings suggest a greater and more extensive compromise of mucosal integrity in SSc than in NERD patients.

Functional Luminal Imaging Probe

The functional luminal imaging probe (FLIP) is a novel diagnostic tool devised to measure the distensibility of the esophageal body and esophagogastric junction (EGJ) that is used to assess esophageal function. FLIP consists of a compliant bag mounted on a catheter over a series of ring electrodes that provides data on pressure and regional cross-sectional area during volumetric distension of the esophagus using the principle of impedance planimetry. FLIP studies have proven it to be a valuable tool for the evaluation of conditions with abnormalities in mechanical properties of the esophageal wall and/or EGJ, such as achalasia and eosinophilic esophagitis [28–30]. FLIP has also been used in a small study of 12 SSc patients with reflux or dysphagia (11 women, median age 53, duration of disease 1–20 years) [31]. Lower EGJ yield pressure was reported in SSc subjects (median 40 mmHg (interquartile range (IQR) 2.8–7.7)) compared with healthy control subjects (median 6.2 mmHg (IQR 1.85–2.67)). Furthermore, healthy controls had a higher pressure-strain elastic modulus (median 2.41 kPa (IQR 1.85–2.67)) than patients with SSc (median 1.73 kPa (IQR 1.16–2.15)), demonstrating that SSc patients have reduced resistance to distension. Limitations of this study include the small size of the population studied and their heterogeneous clinical profiles.

Esophageal Manometry

High-resolution manometry (HRM) measures esophageal pressures during a series of swallows and utilizes a catheter with multiple sensors spaced 1 cm apart spanning from the hypopharynx to the stomach. Esophageal pressure topography (EPT) is a space-time pressure plot generated using computer software that interpolates pressure values between the pressure sensors (Fig. 1). HRM and EPT have greatly improved the standardization of esophageal manometry and are at the foundation of a new consensus classification system for esophageal motility disorders [32••]. Additionally, the American College of Rheumatology updated its SSc criteria in 2013 improving the specificity and sensitivity of the diagnosis of SSc. The associations between SSc-related systemic manifestations and esophageal function were evaluated in 79 SSc patients (85% female, ages 25 to 77 years) using HRM/EPT (Table 1) [33]. Heterogeneous esophageal motility diagnoses were observed among SSc patients. More extensive skin disease (assessed using modified Rodnan skin score) and worse lung function were associated with absent contractility on HRM. However, no relationship was observed between disease duration, autoantibodies, reported symptoms of dysphagia or reflux, and esophageal motility diagnosis. Another study which analyzed 122 SSc patients (75% women, mean age 53.3 ± 15.5 years) using HRM/EPT also observed diverse esophageal motility diagnoses (Table 1) [34]. Absent contractility was seen in 60% of SSc patients. These SSc patients were younger and had more severe reflux. Moreover, erosive esophagitis, hiatal hernia, and esophageal strictures were more likely to occur in SSc patients with absent contractility compared with patients with normal or ineffective esophageal motility. Taken together, these studies illustrate the need for more HRM studies to better understand the pathophysiological mechanisms of SSc scleroderma esophageal disease. Also, HRM studies have now shown consistently that only a subset of SSc patients exhibit the classic scleroderma esophagus motor pattern, defined by a hypotensive LES and weak or absent peristalsis. Consequently, it has been widely advised that the term "scleroderma esophagus" be abandoned as it is neither sensitive nor specific for a SSc diagnosis [37]. Interestingly, a recent study investigated functional esophageal alterations by high-resolution impedance manometry (HRIM) in 45 SSc patients without esophageal symptoms and disease duration of less than 3 years (Table 1) [35•]. HRIM abnormalities were found in up to 84% of these SSc patients, and the finding of impaired esophageal motility at baseline was predictive of the development of esophageal symptoms over time. Furthermore, SSc patients negative for the anti-centromere antibody had a higher prevalence of HRIM abnormalities. The findings from this study suggest that including HRIM in the baseline assessment of SSc patients may have prognostic utility even in the absence of esophageal symptoms.

It has also been proposed that incorporating multiple rapid swallows (MRS) into an HRM protocol allows for the assessment of "peristaltic reserve" [38, 39]. The adequacy of peristaltic reserve was assessed in 111 SSc patients during HRM [36•], and an abnormal MRS response was the most common manometric finding compared with controls (Table 1). Contraction augmentation (37%) and peristaltic augmentation

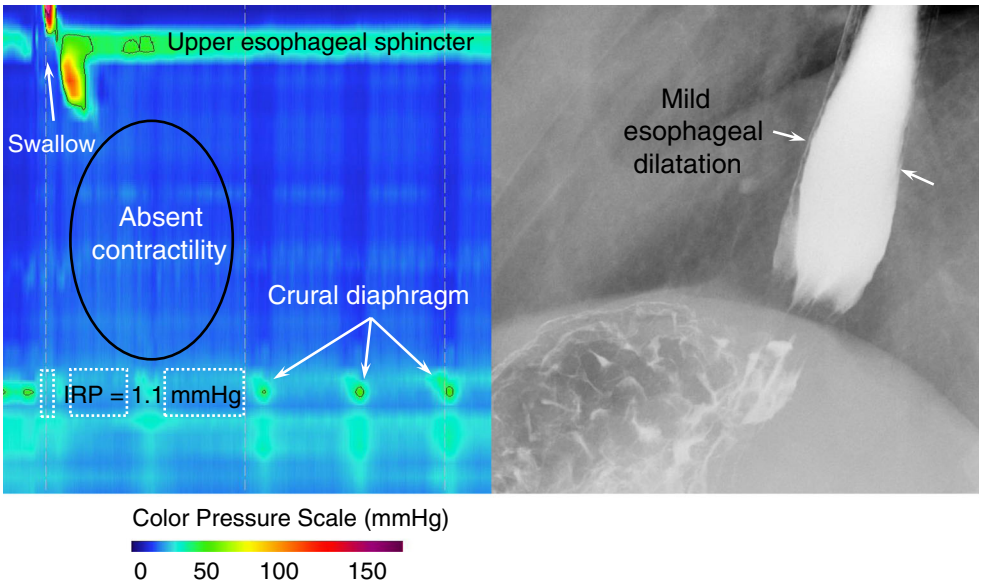

Fig. 1 High-resolution manometry recording (left) and corresponding radiograph of a barium swallow (right) showing the classic findings of scleroderma esophagus, absent peristalsis, hypotensive lower esophageal sphincter, and mild esophageal dilation with stasis of barium. The integrated relaxation pressure (IRP) is a measure of the adequacy of sphincter relaxation after a swallow with 15 mmHg being the upper limit of normal. Note the absence of any contractile response beyond the proximal esophagus (top) and the absence of any lower esophageal sphincter contraction between the crural diaphragm contractions

(18%) were observed significantly less frequently after MRS in SSc patients than in controls (83% and 100%, respectively). Moreover, impaired peristaltic reserve was observed in the majority of patients with SSc and was independent of the baseline motility diagnosis. These findings could be useful for the management of SSc patients as it could help identifying patients requiring more intensive treatment.

Health-Related Quality of Life Studies

A negative impact on health-related quality of life (HRQOL) has been reported in SSc patients with gastrointestinal tract involvement [40, 41]. Recently, findings from HRQOL GIT 2.0 (University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract) questionnaires have been correlated with HRM findings and SSc patient characteristics. A study of 40 Egyptian SSc patients (32 females, mean age 43 ± 10.3 years) found a correlation between HRM findings and patient-reported symptoms [42]. The emotional score was positively correlated with GIT score, reflux symptoms, and esophageal distension was demonstrated. Moreover, a positive correlation was also observed between the social function score and total GIT scores, reflux symptoms, and esophageal distension. This suggests that GI manifestations lead to decreased social interactions and cause psychological distress. Regression analyses have shown a negative correlation between reflux symptoms and GIT scores. Another study performed on 200 SSc patients (85% female) and 102 controls found that SSc patients with

Table 1 Summary of the high-resolution manometry (HRM) studies performed in SSc patients

Authors of the study	Summary of the study
Kimmel et al. [33]	• Associations between SSc-related systemic manifestations and esophageal function were evaluated in 79 SSc patients • More extensive skin disease and worse lung function were associated with absent contractility on HRM
Aggarwal et al. [34]	• 122 SSc patients were analyzed by HRM • Absent contractility was seen in 60% of SSc patients • Erosive esophagitis, hiatal hernia, and esophageal strictures were more likely to occur in SSc patients with absent contractility compared with patients with normal or ineffective esophageal motility
Vettori et al. [35•]	• Functional esophageal alterations were investigated by high-resolution impedance manometry (HRIM) in 45 SSc patients without esophageal symptoms and disease duration of less than 3 years • HRIM abnormalities were found in up to 84% of these SSc patients, and the finding of impaired esophageal motility at baseline was predictive of the development of esophageal symptoms over time • SSc patients negative for the anti-centromere antibody had a higher prevalence of HRIM abnormalities
Carlson et al. [36•]	• The adequacy of peristaltic reserve was assessed in 111 SSc patients during HRM • An abnormal multiple rapid swallow (MRS) response was the most common manometric finding compared with controls • Contraction augmentation (37%) and peristaltic augmentation (18%) were observed significantly less frequently after MRS in SSc patients than in controls • Impaired peristaltic reserve was observed in the majority of SSc patients and was independent of the baseline motility diagnosis

abnormal esophageal motility reported more severe reflux on the GIT and more severe dysphagia, chest pain, and heartburn on the Gastrointestinal Symptoms Severity Index (GISSI) [37]. More frequent and severe dyspeptic and lower GI symptoms were also reported on the GIT and GISSI in SSc patients with absent contractility. Moreover, decreased condition-specific HRQOL correlated with more severe esophageal dysfunction. Finally, the severity of esophageal dysmotility could be predicted by the duration of SSc diagnosis, total GIT scores, and the presence of interstitial lung disease. These studies confirm the negative impact of esophageal motor dysfunction on the quality of life in SSc patients.

New Treatment

As mentioned previously, GERD and esophageal motor dysfunction are the ultimate cause of esophageal symptoms in SSc patients. No treatment exists to effectively reverse these abnormalities. PPIs and prokinetic agents are commonly used to treat symptoms, but the evidence supporting their use is limited. Buspirone, a 5-hydroxy-tryptamine 1A receptor agonist, was shown to strongly stimulate esophageal peristalsis and LES function [43, 44]. In a 4-week prospective open-label trial, the administration of 20 mg buspirone daily was shown to significantly increase LES resting pressure in SSc patients, while other manometric parameters were unchanged [45•]. Furthermore, a better response to buspirone was observed in SSc patients with less esophagus dilatation, suggesting that patients with a less severely affected esophageal function would respond better to treatment. The symptoms of regurgitation and heartburn were also improved significantly from baseline following the 4-week administration of buspirone. Although a more conclusive evaluation is needed with randomized, placebo-controlled investigations, this suggests that buspirone administration could be used in SSc patients with reflux symptoms as an alternative or adjunct to standard treatments.

Molecular Stratification in Patients With Scleroderma Esophageal Disease

The molecular mechanisms that regulate the pathogenesis of SSc esophageal disease are still poorly understood. Consequently, there is no biomarker for disease progression and no disease-modifying treatments for SSc esophageal disease. Recently, a genomic approach was used to demonstrate the heterogeneity of SSc esophageal disease patients at the molecular level [46•]. Gene expression profiling of esophageal biopsies of SSc patients using DNA microarrays identified two molecular intrinsic subsets of SSc esophageal disease patients. An inflammatory gene expression signature was found in one group of patients while a non-inflammatory/proliferative signature was found in another subset. The comparison of clinical, demographic, disease, and histopathological features between the two molecular subsets showed no significant differences in the clinical phenotypes (skin disease subtype, serum autoantibodies, smoking history, lung disease), with the exception of age; patients harboring an inflammatory gene signature were significantly older. Hence, this study suggests that patient subsets identified by gene expression are distinct from clinically defined subsets. Limitations of this study include the absence of healthy control subjects, the low sample size number, the low success rate in obtaining esophageal biopsies deeper than the epithelium, and the absence of esophageal functional studies. Despite these limitations, this was the first study to provide insight into the genetic pathogenesis of SSc esophageal disease and holds promise for the identification of new therapeutic targets.

Mouse Models of Scleroderma Esophageal Disease

Mouse models are powerful tools to model human diseases and to perform preclinical testing of new therapies. Because of the molecular and physiological similarities between mouse and human and because of their shorter life cycle and gestation time, mice are valuable models for studying human diseases, including autoimmune diseases. Numerous studies have used mouse models to recapitulate one or more aspects of SSc and to better understand SSc pathogenesis [47, 48]. However, most of these studies have focused on the pathogenic mechanisms of skin and lung fibrosis [47, 48]. Only one study reported mouse models of SSc having an esophageal phenotype [49•]. The lack of studies investigating scleroderma esophageal diseases may be partially explained by histological differences between the human and mouse esophagi (Fig. 2). In rodents, but not humans, the superficial squamous cells undergo keratinization [50]. Moreover, in human, the muscularis mucosa of the proximal esophagus is composed of skeletal muscle, which gradually transitions to smooth muscle in the distal esophagus. On the other hand, the entire mouse esophagus is composed of striated muscle. Lastly, submucosal glands are absent from mouse esophagus and present in humans. The other explanation for the lack of studies reporting scleroderma esophageal disease might be that investigators are simply not harvesting the esophagus when analyzing new SSc mouse models.

Friend leukemia virus integration 1 (Fli1) belongs to the family of Ets transcription factors that have been shown to regulate fibrogenesis [51]. Constitutive Fli1 suppression has been observed in skin keratinocytes, dermal fibroblasts, and dermal microvascular endothelial cells in SSc patients [52]. Recently, conditional *Fli1* knockout in mouse epithelial cells has been

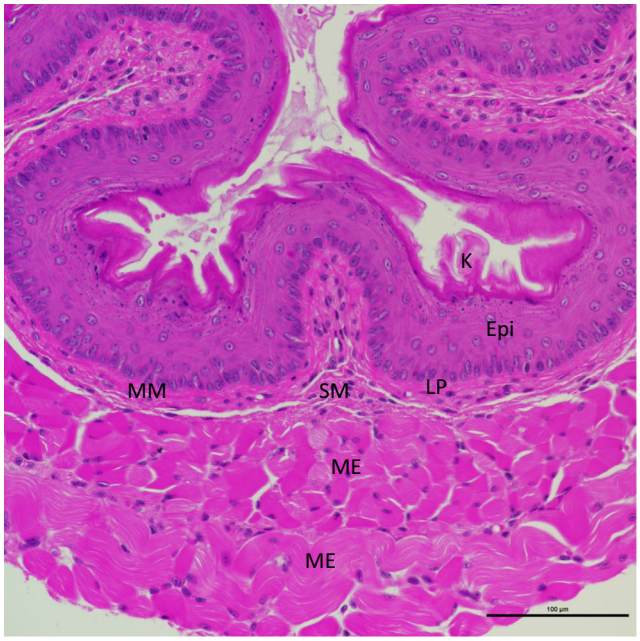

Fig. 2 Mouse esophageal histology. The esophageal mucosa consists of three layers: a stratified epithelium, the lamina propria that contains connective tissue, and the muscularis mucosa that is composed of smooth muscle. The submucosa contains connective tissue, blood and lymphatic vessels, immune cells, nerve cells, and small mucous glands. In rodents but not humans, the superficial squamous cells undergo keratinization. Unlike human, the entire mouse esophagus is composed of striated muscle. K keratin, Epi epithelium, LP lamina propria, MM muscularis mucosa, SM submucosa, ME muscularis externa. Scale bars, 100 μM

generated using the *keratin-14* (K14) promoter [49•]. Mice with *Fli1* loss in K14-positive cells led to spontaneous skin fibrosis, autoimmunity with ILD, and esophageal fibrosis. Increased accumulation of collagen in the esophagus was accompanied by increased expression of fibrosis-related genes such as *Col1a1*, *Col1a2*, *Il1b*, *Il6*, *Il8*, *and Tgfb1*. Studies have suggested that epithelial cells may play a role in early disease manifestation in SSc patients [53, 54]. Interestingly, increased expression of IL-1β was confirmed in the esophageal epithelium by immunohistochemistry. Moreover, *Rag1*-deficient mice (absence of mature B cells and T cells) that received T cell transfer from *Fli1*-deficient mice did not develop esophageal fibrosis. Additionally, mice with both *Fli1* and *Rag1* deficiencies were still able to develop esophageal fibrosis. Therefore, findings from this study support the concept of a central role for esophageal epithelial cells in the development of fibrosis and also indicate that esophageal involvement is not mediated by autoimmunity but rather by the Fli1 deficiency in esophageal epithelial cells.

Conclusions

Increasing efforts have been made in recent years to investigate esophageal dysfunction in SSc patients. The development and/or improvement of diagnostic tools have allowed the characterization of clinical and/or molecular subsets of SSc patients, but further research is needed to improve our understanding of esophageal dysmotility and reflux. New therapies are urgently needed to improve the outcome and quality of life of SSc patients with esophageal dysmotility. Although the number of mouse models that have a scleroderma esophageal disease phenotype is still quite limited, valuable insights have been gained from these models. More mouse models are needed to gain a deeper understanding of scleroderma esophageal disease, hopefully leading to an improvement in patient outcomes.

Author Contributions P.K. and M.-P.T. wrote the manuscript.

Grant Support This work was supported by NIH NIDDK P01 DK117824.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- •• Of major importance

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