ISSN 2307-8960 (online)

# World Journal of *Clinical Cases*

*World J Clin Cases* 2021 July 16; 9(20): 5352-5753

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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## RESPONSIBLE EDITORS FOR THIS ISSUE



**NAME OF JOURNAL**
*World Journal of Clinical Cases*

**ISSN**
ISSN 2307-8960 (online)

**LAUNCH DATE**
April 16, 2013

**FREQUENCY**
Thrice Monthly

**EDITORS-IN-CHIEF**
Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

**EDITORIAL BOARD MEMBERS**
https://www.wjgnet.com/2307-8960/editorialboard.htm

**PUBLICATION DATE**
July 16, 2021



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*World J Clin Cases* 2021 July 16; 9(20): 5408-5419

DOI: 10.12998/wjcc.v9.i20.5408

ISSN 2307-8960 (online)

*MINIREVIEWS*

# Esophageal manifestation in patients with scleroderma

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**Author contributions:** Voulgaris TA wrote the article; Karamanolis GP was responsible for conception and design of the article, the drafting of the article, making critical revisions and final approval of the article.

**Conflict-of-interest statement:** There is no conflict of interest.



**Manuscript source:** Invited manuscript

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** Greece

**Peer-review report's scientific quality classification**

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## Abstract

The esophagus is the most commonly affected part of the gastrointestinal system in patients with systemic sclerosis (SSc). Esophageal involvement may lead to a significant reduction in patient quality of life. The exact pathophysiology is complex and not yet fully elucidated. Ultimately, esophageal smooth muscle becomes atrophied and replaced by fibrous tissue leading to severe motility disturbance of the distal esophagus. Symptoms are mainly attributed to gastroesophageal reflux disease and to esophageal dysmotility. Compelling evidence has correlated esophageal involvement to the severity of pulmonary disease. No formed guidelines exist about the diagnostic modalities used to assess esophageal disease in patients with SSc, though upper gastrointestinal endoscopy is the first and most important modality used as it can reveal alterations commonly observed in patients with SSc. Further exploration can be made by high resolution manometry and pH-impedance study. Proton pump inhibitors remain the mainstay of treatment, while prokinetic agents are commonly used as add-on therapy in patients with symptoms attributed to gastroesophageal reflux disease not responding to standard therapy as well as to motility disturbances. Gastroesophageal reflux disease symptoms in patients with SSc are frequently difficult to manage, and new therapeutic modalities are emerging. The role of surgical treatment is restricted and should only be preserved for resistant cases.

**Key Words:** Systemic sclerosis; Esophagus; Gastroesophageal reflux disease; Esophageal dysmotility; Proton pump inhibitors



**Core Tip:** Gastrointestinal manifestations of systemic sclerosis, a rare autoimmune disease, are the most commonly encountered complications of the disease affecting

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** February 28, 2021
**Peer-review started:** February 28, 2021
**First decision:** April 18, 2021
**Revised:** April 22, 2021
**Accepted:** May 10, 2021
**Article in press:** May 10, 2021
**Published online:** July 16, 2021

**P-Reviewer:** Dantas RO
**S-Editor:** Fan JR
**L-Editor:** Filipodia
**P-Editor:** Li JH

nearly 90% of the systemic sclerosis population. Among the gastrointestinal tract, the esophagus is the most commonly affected. In this review, we will present the current understanding of the pathophysiologic mechanisms of systemic sclerosis, the clinical presentation and diagnosis of esophageal involvement. Finally, we highlight the latest developments in the management of this disease.

**Citation:** Voulgaris TA, Karamanolis GP. Esophageal manifestation in patients with scleroderma. *World J Clin Cases* 2021; 9(20): 5408-5419
**URL:** https://www.wjgnet.com/2307-8960/full/v9/i20/5408.htm
**DOI:** https://dx.doi.org/10.12998/wjcc.v9.i20.5408

## INTRODUCTION

Systemic sclerosis (SSc) is an uncommon immune-mediated multisystemic disease that leads to a significant reduction in patient quality of life and has a high mortality rate [1]. Its global prevalence is estimated to be around 1 in 10000 people, whereas the estimated annual incidence is of less than 10 *per* 100000 individuals, both in Europe and in the United States. SSc is found to be four times higher in women compared to men[2-4].

Five-year survival in SSc largely depends on the subtype of the disease and is reported to be 80% in diffuse and 90% in limited phenotypes. Almost 9 out of 10 patients with SSc will develop at some point during the course of their disease a gastrointestinal (GI) manifestation, though severe involvement leading to increased morbidity and mortality will arise in only 8%. The reported survival of SSc patients with GI involvement is calculated to be 15% at 9 years[5].

SSc can affect any segment of the GI tract from mouth to anus, though the esophagus is the most commonly involved portion of the GI tract followed by the anorectum and the small bowel[6]. Up to 90% of patient will manifest esophageal symptoms and dysfunction[7,8]. Symptoms of esophageal dysfunction may not occur in up to half of the affected patients up until severe tissue damage takes place[9,10].

## PATHOPHYSIOLOGY OF ESOPHAGEAL DISEASE IN SSC

SSc is temporarily considered as an orphan disease, and its origin has not been yet fully elucidated. It is assumed that a combination of environmental factors alongside genetic susceptibility as well as other factors, such as epigenetics, leads to a deregulation of the repairing mechanism of connective tissue in response to injury[11].

Originally a tripartite pathogenesis (vascular injury, autoimmunity and inflammation, fibrosis) has been hypothesized to be the basis of SSc development. However, current data point out that the epithelium, blood-derived cells and disturbances in the wound healing process also possess a critical role in the pathogenesis of SSc[12]. An initial trigger leads to vascular injury due to autoimmunity and/or environmental influences that due to the existence of altered endothelial cells and pericytes/vascular smooth muscle cells steers to impaired vascular remodeling[13,14]. The initially observed disturbed peripheral circulation and activation of endothelial cells, pericytes/vascular smooth muscle cells and fibroblasts induces the production of cytokines, growth factors and chemokines, which in turn promotes in the affected organ the accumulation and activation of different immune cells such as macrophages, mast cells, B and T cells and plasmacytoid dendritic cells.

According to recent data, esophageal inflammation and fibrosis is in a significant manner mediated by Th17 cells. In a recent study focusing on cytokine analysis presenting in the gastric juice from patients with esophageal dysmobility, profibrotic endothelin-1 and the proinflammatory cytokines interleukin (IL)-17, IL-6, IL-1β, IL-9 and IL-2 were significantly increased in patients with esophageal dysmotility, which is known to be associated with atrophy and fibrosis of the smooth muscle layer. These data and especially the increased levels of IL-17 led the researchers to the conclusion that Th17 cells possess a crucial role in the pathogenesis of esophageal fibrosis, a finding compatible with previous studies in SSc patients with skin and lung disease [15]. The end product of this not fully elucidated cascade is the overproduction of

extracellular matrix (ECM) by interstitial fibroblasts of different origin, transited to myofibroblasts due to the abovementioned vascular and inflammatory reactions. ECM accumulation in tissues affected by scleroderma is derived grossly by transforming growth factor (TGF)-β, connective tissue growth factor, plasminogen activator inhibitor-1, fibronectin 1 and other cytokines, though the principal mediator of tissue fibrosis in SSc is thought to be TGF-β[16,17].

A new insight in our understanding of the role of TGF-β in excessive production and collagen deposition in patients with SSc has been recently revealed. TGF-β acts through binding to its receptors and phosphorylation of SMAD2 and SMAD3 proteins. TGF-β action is facilitated by its connection to TGF-β-binding proteins. TGF-β-binding proteins are structural components of the ECM and are involved in the deposition of TGF-β in the ECM and are implicated in TGF-β secretion and regulation of TGF-β activation[18,19].

A recent study has postulated the fact that patients with SSc and esophageal involvement overexpress TGF-β-binding protein-4 in parallel to the observed TGF-β increase[20]. It seems that the above complex mechanism affecting esophageal smooth muscle, nerves and connective tissues contributes to fibrosis and ultimately to esophageal dysfunction[21-23]. Progressively the esophageal smooth muscle becomes atrophied and replaced by fibrous tissue leading to severe motility disturbance of the distal esophagus[24,25].

## CLINICAL PRESENTATION

SSc can manifest with various clinical presentations. Symptoms originate from both structural and functional changes such as a reduced lower esophageal sphincter (LES) pressure, low or absent peristalsis and sicca syndrome. Symptoms such as heartburn, regurgitation, chronic cough and hoarseness are attributed to gastroesophageal reflux disease (GERD) or to esophageal dysmotility when symptoms such as dysphagia, odynophagia and chest pain are present[26,27]. Symptoms related to GERD are the most common in patients with SSc with a prevalence of around 35%, whereas dysphagia occurs rarer in about 4% of patients[21].

The presence of Barrett's esophagus (BE) and adenocarcinoma has also been reported to be increased in patients with SSc, though screening patients with SSc and esophageal disease for esophageal adenocarcinoma (EAC) does not seem to be cost effective[26-29].

Esophageal disease may remain asymptomatic for a long period of time. Even in the absence of symptoms, up to three quarters of patients may show esophageal dilatation on chest tomography and esophageal abnormalities on endoscopy[24,30,31]. This is of special interest due to the fact that recent data point out that esophageal disease in SSc, even among asymptomatic patients, is linked to the development of interstitial lung disease, and patients with more active reflux disease ultimately develop more advanced interstitial lung disease[32]. Even if no causative association between esophageal involvement and pulmonary disease is proven, it is hypothesized that in the setting of unopposed acid reflux in patients with SSc the tracheobronchial aspiration of gastric secretions over time leads to pulmonary fibrosis[24,32-35]. This hypothesis is also based in experimental data coming from a study in a rodent model. According to the researchers, when recurrent gastric fluids were added to rodent lungs, inflammatory cells and cytokines in the lungs were observed, suggesting that GERD and aspiration triggers an inflammatory response, which ultimately may lead to pulmonary fibrosis[36]. Additionally, it has been postulated that the wider the esophagus caliber becomes the greater the diffusing capacity for carbon monoxide and forced vital capacity are[37].

## DIAGNOSIS

There is no gold standard examination for the detection and the assessment of esophageal involvement in patients with SSc. Due to the various esophageal symptoms, usually the first examination undertaken is an upper GI endoscopy. When patient presents with symptoms referring to a motility disorder then additional information can be obtained by high resolution manometry. When the primary complaint of the patient is attributed to GERD, an esophageal pH monitoring with or without impedance may be undertaken.

### Endoscopy

There are no specific guidelines suggesting a mandatory baseline upper GI endoscopy for patients with SSc[38]. Furthermore, there are no specific endoscopic findings for diagnosing SSc, though gastroscopy is a very useful tool in assessing patients' symptoms such as dysphagia or heartburn. The most common endoscopic finding among patients with SSc is erosive esophagitis, which is revealed in one out of two patients[34,39,40]. It must be stated that endoscopic findings of esophagitis may be present in an even larger portion of asymptomatic patients. Thonhofer *et al*[31] revealed findings of erosive esophagitis in 77% of asymptomatic patients with SSc[31]. Moreover, endoscopy can show GERD complications such as benign peptic stenosis, BE and EAC. Patients with SSc tend to have an increased incidence of BE, which can be up to 10.1%[32,34,40]. The increased incidence of BE in patients with SSc is not accompanied with an increase in the incidence of EAC in patients with SSc and BE. A study that followed patients with SSc and BE for up to 3 years reported a yearly rate of EAC in patients with high dysplasia rating up to 4%, which is comparable to the yearly rate of progression to EAC among patients with BE and high grade dysplasia without SSc[41].

### HRM

After its development HRM has substituted conventional manometry as the ideal study for assessing esophageal motility disorders. Although there are no specific recommendations for the role of HRM in clinical practice, it may add substantially significant information about esophageal involvement in SSc[42]. SSc typical manometric presentation consists of a reduced LES resting pressure in combination with diminished amplitude or aperistalsis[27,43,44]. It should be underlined that data regarding the prevalence of the typical manometric presentation, as it is assessed by HRM, are still inconsistent ranging from one out of three patients to one out of two patients[45-47].

An interesting finding in SSc patients with esophageal motility abnormality is the phenomenon of abnormal peristaltic reserve, defined as the absence of contraction and abnormal peristaltic augmentation after multiple rapid swallows[45]. Moreover, Roman *et al*[47] concluded that in the initial phase of esophageal involvement, the middle and not the distal esophagus is first involved, as the mean amplitude of middle esophageal body contractions (but not distal contractions) was significantly decreased in patients with hypotensive peristalsis compared to patients classified with normal peristalsis[47].

However, it should be stressed that there is a discordance regarding the correlation between manometric findings and patient symptoms. Multiple studies have failed to prove such a correlation[48-50], whereas studies using well defined and validated questionnaires, such as the University of California Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0 (UCLA SCTC GIT 2.0) or Gastrointestinal Symptoms Severity Index Scores, support the idea of a correlation between patient symptoms and manometric findings of esophageal involvement[45,51,52].

In any case, we should keep in mind that asymptomatic patients tend to show a great proportion of manometric abnormalities that are compatible with esophageal involvement in HRM. Indeed, Vettori *et al*[53] found that almost 84% of asymptomatic SSc patients had esophageal motility abnormalities in an HRM study. They also concluded that baseline impaired esophageal motility was an independent risk factor of progression to symptomatic upper GI involvement, and therefore HRM may have a role as a predicting tool for early diagnosis of esophageal involvement among patients with SSc[53].

### Esophageal pH monitoring, with or without impedance

As stated above, GERD is the most common clinical presentation of esophageal involvement in SSc patients. The utility of performing an esophageal pH monitoring is graded for patients with typical GERD symptoms that did not respond to proton pump inhibitor (PPI) therapy. Thus, a 24 h pH monitoring combined with impedance is the preferred test in order to confirm the presence of persistent abnormal acid exposure of the esophagus and/or presence of weak acid reflux.

In a large recent study including SSc patients with GERD, PPI partial response was observed in 53.9%[54]. These nonresponders to PPI SSc patients showed on pH-monitoring higher acid exposure times (AETs) than non-SSc patients matched for PPI formulation and dose GERD (61% *vs* 18%, respectively), significantly longer AETs, longer median bolus clearance, lower nocturnal impedance values but lack of increased reflux episodes[55].

Previous studies have shown that abnormal pH monitoring is seen in up to 85% of SSc patients without treatment[48,56,57]. Moreover, a study including GERD patients with or without SSc, revealed that SSc patients tend to have worse GERD symptoms and more severe reflux esophagitis[58].

### Computed tomography scan

Thoracic computed tomography scan can access the existence of pulmonary involvement. It is of special interest that critical information about esophageal involvement could also be drained. It is known that esophageal dilation in computed tomography will be associated to symptomatic esophageal disease in patients with SSc [59]. A study evaluating esophageal abnormalities in SSc patients found that in high-resolution computed tomography with radionuclide transit a ≥ 9 mm threshold for esophageal dilation could accurately predict esophageal dysmotility with a sensitivity of 83.1% and a specificity of 94.1%[60].

## MANAGEMENT

### General principles

Treatment of esophageal involvement in SSc is supportive as no disease specific therapy is available. Treatment focuses on alleviation of each patient's specific symptoms.

### Medical treatment

The management of GERD includes, at the first stage of the disease, dietary and lifestyle interventions such as avoidance of aggravating foods, having meals within three hours before bedtime, head of bed elevation, weight reduction, smoking cessation, alcohol drinking reduction and small and frequent meal consumption. However, the mainstream treatment option includes drug administration, mainly PPIs [61,62]. PPIs should be administered 30–60 min before a meal, beginning initially once daily before breakfast. Even though studies using once daily PPIs dosage in patients with SSc showed symptom alleviation and healing of esophagitis in a percentage of patients, a substantial number of patients were characterized as partial or nonresponders[63-66]. Thus, in such patients, adjustment to twice daily dosing should be considered. According to recent data, the response rate of GERD treatment among SSc patients was less than 50% after taking omeprazole 20 mg twice daily for 4 wk, a percentage significantly lower than that reported for patients without SSc[54,55,67-69]. Authors found that the presence of dysphagia was the only predictor of PPI-partial response GERD in those patients[54].

In another study among patients with SSc and GERD treated with high PPI dose, 60% of those still had a total AET ≥ 4.5%, and 55% had an AET > 6% when evaluated with pH-impedance study[55]. However, the accurate strategy for the treatment of partial or nonresponders to PPIs is not fully elucidated. Vonoprazan is a first-in-class PPI that unlike conventional PPIs functions in the absence of an acidic environment and leads to a more consistent acid suppression compared to other PPIs. Thus, it could be an alternative therapeutic option as it has been proven efficient in the treatment of GERD refractory to traditional PPIs[70,71]. Indeed, a recent study stated that Vonoprazan was efficient in patients with SSc and refractory GERD. Vonoprazan was given to 15 patients among whom 14/15 suffered from PPI-refractory GERD, and the authors found that vonoprazan in the dose of 20 mg offered symptom relief in 83.4% of patients and achieved long term symptom control (≥ 2 years)[72].

PPIs act as an acid suppressor, but it has no effect on esophageal motility and/or LES pressure, which could be a putative GERD mechanism in SSc. So, esophageal dysmotility might explain the fact of the higher prevalence of PPI-partial response GERD in SSc compared to non-SSc patients. Prokinetic agents have a mechanism of action on the esophageal motility by facilitating esophageal motility and increasing LES pressure[73,74]. Therefore, it is rational to hypothesize that they can improve reflux control in patients who have failed PPI treatment. Foocharoen *et al*[67] investigated the role of add-on therapy with either domperidone or algycon in SSc patients. The authors enrolled SSc patients, 59.4% of whom had a partial response after an initial 4 wk trial of omeprazole 20 mg twice a day. Then they were randomly assigned to take omeprazole plus either domperidone or algycon for 4 wk. Only 13% of patients in the domperidone group and 22% of patients in the algycon groups did not respond to the additional therapy. Moreover, quality of life was improved in SSc patients treated with domperidone or aglycone[67]. Therefore, the authors suggested that in

**Table 1 Studies assessing per os pharmacotherapy in patients with systemic sclerosis and esophageal involvement**

| Ref. | Patients (*n*) | Treatment | Treatment duration | Response to treatment |
|---|---|---|---|---|
| Hendel *et al* [63], 1992 | 25 | Omeprazole 20-80 mg (adjustments of the maintenance dose of omeprazole | Mean time of 40 mo | Healing of esophagitis in almost 50% patients |
| Marie *et al*[34], 2006 | 133 | Omeprazole 20-40 mg | Mean duration of 6 yr from treatment initiation | Heartburn (*n* = 103; 77.4%), dysphagia (*n* = 19; 14.3%)<br>Improvement of heartburn: (77.4%)<br>Improvement of dysphagia: (14.3%)<br>Esophagitis healing: 32.3% |
| Pakozdi *et al* [64], 2009 | 21 | Lansoprazole 30 mg | 12 mo | Short-term (6 mo) efficacy in decreasing frequency of symptoms in<br>No long-term benefit |
| Muro *et al*[65], 2009 | 84 | Rabeprazole 10 mg | 8 wk | Effective for the symptom control |
| Foocharoen *et al* [67], 2017 | 148<br>88 | Omeprazole 20 bid<br>Omeprazole + domperidone (*n* = 38)/aglycon (*n* = 37) | 4 wk | 40.1% responded to omeprazole<br>Domperidone and algycon are equally effective treatments when used in combination with omeprazole<br>17% of patients were nonresponsive |
| Stern *et al*[55], 2018 | 38 | Twice daily different PPIs (rabeprazole, dexlansoprazole, esomeprazole, omeprazole, lansoprazole, pantoprazole)-variable dosing schedules | Treatment duration not given | Despite PPIs high-dose:<br>61% of SSc patients had an AET ≥ 4.5%<br>55% of SSc patients had an AET > 6% |
| Foocharoen *et al* [54], 2020 | 243 | Omeprazole 20 mg bid | 4 wk | PPI-partial response: 53.9% |
| Tabuchi *et al* [72], 2021 | 15 (14/15 with PPI-partial response) | Vonoprazan 10-20 mg | > 2 yr | Symptom relief in 83.4%<br>Long-term symptom control in 87% |
| Johnson *et al* [77], 1987 | 12 | Metoclopramide 10 mg X 2 | 1 wk from treatment initiation | Significant reduction of reflux events: in 91.6%<br>All but 2 patients attained LES pressure values that fell in the normal range after metoclopramide treatment |
| Karamanolis *et al*[84], 2016 | 22 | Buspirone 20 mg | 4 wk | Improvement in the severity of heartburn: 70%<br>Improvement in the severity of regurgitation in 58%<br>Improvement in dysphagia in 50% and in chest pain in 25% |

AET: Acid exposure times; bid: Twice a day; LES: Lower esophageal sphincter; PPIs: Proton pump inhibitors; SSc: Systemic sclerosis.

PPI-partial responder patients, a trial of adding domperidone to PPIs can be administered, whereas in patients suffering from side effects due to prokinetic administration, algycon in combination with PPI can be a favorable therapeutic option.

Besides domperidone, other prokinetic drugs, such as metoclopramide, erythromycin and cisapride, have also been evaluated among SSc patients. It is thought that they could contribute to GERD control through increasing LES tone and gastric emptying, and they might also improve symptoms originating from esophageal motility disturbance such as dysphagia[33,75-77]. Unfortunately, there are scarce data about their use in SSc patients even if they are frequently used in clinical practice[78]. Moreover, their chronic use is withheld due to additional toxicities[79] (Table 1).

In patients with SSc, stricture formation, due to GERD, may occur in up to 29% of them[25], and in such cases esophageal balloon dilatation is advised[80]. It is of special note for the clinician to keep in mind that dysphagia in patients with SSc may also be due to candida esophagitis, as fungal cultures from the esophagus of patients with SSc

were positive in 38%[26]. In cases of esophageal candidiasis, systemic antifungal therapy is always required. The recommended treatment in patients who can tolerate oral therapy is oral fluconazole 200–400 mg (3–6 mg/kg) daily or intravenous fluconazole 400 mg (6 mg/kg) daily in patients who cannot tolerate oral treatment for 14–21 d[81].

### Novel therapies

Studies in healthy volunteers evaluating the effect of buspirone, an orally available 5-hydroxytryptamine receptor agonist, in LES have proven its ability to increase LES residual pressure and increase esophageal motility[82]. This beneficial effect has been evaluated in a pioneer study in patients with SSc and esophageal involvement[83]. According to the study findings, a single 10 mg buspirone dose led to a significant increase in the LES resting pressure in up to 80% of SSc patients and showed a trend to increase the amplitude of esophageal body motility. Based on these findings, a 4 wk open-label trial of 20 mg of oral buspirone in 22 SSc patients with esophageal involvement indeed verified the beneficial effect of buspirone in increasing the LES resting pressure. This effect was translated to an improvement in patient symptom severity of heartburn and regurgitation, though no improvement in chest pain or dysphagia was observed[84].

### Surgery

Generally, in patients with well documented long-standing GERD, antireflux surgery is an option[61]. Unfortunately, Nissen fundoplication results were suboptimal in SSc patients, possibly due to concomitant esophageal dysmotility. Even though amelioration in the severity of reflux symptoms was observed, postoperative dysphagia was observed in up to 71% of patients[85-87]. However, a recent study including SSc patients showed improved long-term (mean follow-up of 36 wk) postoperative results after minimally invasive fundoplication, such as Toupet and Dor. The authors reported that 41% of patients had no symptoms, 56% had reduced symptoms, and persistent dysphagia was noted in only 11.7% of patients[88].

Besides fundoplication, Roux-en-Y gastric bypass (RYGBP) has also been evaluated as a viable surgical alternative for GERD patients with complete aperistalsis. It is thought that the small gastric pouch has minimal acid content, as the acid-producing mucosa of the fundus is excluded, and the roux limb prevents biliary reflux into the pouch and the esophagus. In an interesting study comparing RYGBP *vs* fundoplication, the authors found a statistically lower incidence and severity of postoperative dysphagia in the RYGBP group as well as an improved reflux control[89]. Adding to this study, Yan *et al*[90] showed GERD symptom resolution or improvement in all patients with RYGBP, while only 50% of the fundoplication group reported partial improvement[90]. It should be mentioned that RYGBP predisposes to bacterial overgrowth, which especially in patients with SSc and possible impaired intestinal motility may further deteriorate a patient's clinical status. Other surgical alternatives tested in patients with SSc include biliary/duodenal diversion and esophagectomy with either gastric or colon with variable success and increased mortality[91].

## CONCLUSION

Esophageal involvement is very common among patients with SSc, grossly affecting patient quality of life. Upper GI endoscopy is the primary and most often used diagnostic modality evaluating patient symptoms and possible complications, while useful information can be drawn by esophageal HRM and/or pH impedance study, depending on patient symptoms. PPIs remain the cornerstone in esophageal involvement treatment, even if a significant percentage of patients partially or not fully respond to them. In such cases, a trial of prokinetic agents may alleviate patient symptoms, while promising data have arisen using buspirone, an orally available 5-hydroxytryptamine 1A receptor agonist. Surgical treatments should be preserved for well documented, poorly responding to pharmacological modalities cases due to suboptimal results.

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