

Nutritional Implications of GI-Related Scleroderma



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Scleroderma (SSc) is an autoimmune disease characterized by progressive fibrosis of skin and various internal organs, including the lungs, heart, kidneys, and the gastrointestinal (GI) tract. Second only to skin disease, GI tract involvement is the next most common manifestation of SSc. Any part of the GI tract may be affected, leading to considerable impairment of quality of life. When GI involvement is extensive, severe malnutrition can occur and it can even result in death in about 20% of patients. Early recognition and management may alter the long-term outcome. Effective collaboration with gastroenterologists in the evaluation and management of SSc in a multispecialty partnership model has the potential to produce better outcomes and improve survival in these patients. This article discusses the nutritional implications and current evidence-based management recommendations for the wide range of GI manifestations in SSc.

INTRODUCTION

Scleroderma, or systemic sclerosis (SSc), is an autoimmune disease of unclear etiology, characterized by progressive fibrosis of skin and various internal organs, an ongoing occlusive microvasculopathy, and abnormalities of the immune system. There is wide variability in the prevalence of SSc worldwide. In the United States, about 250 cases per million Americans are afflicted with this disease. Progressive skin thickening is an integral part of the disease, explaining how the term ‘scleroderma’ was

originally coined (Gr., ‘skleros’ = thickening, ‘dermos’ = skin). There are two main subtypes of SSc, based on the extent of skin hardening:

- *limited* SSc (lcSSc, formerly CREST syndrome) only involving the distal extremities (beyond elbows and knees) and face.
- *diffuse* SSc (dcSSc), where skin tightening is widespread, including the trunk and proximal extremities.

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Table 1. Gastrointestinal Manifestations of Scleroderma

Section Affected	Manifestations
Oral/Pharyngeal	<ul style="list-style-type: none"> • Difficulty opening mouth • Difficulty chewing • Dry mouth (Sicca syndrome) • Dental problems • Oropharyngeal dysphagia
Esophagus	<ul style="list-style-type: none"> • Gastroesophageal reflux disease (GERD) • Dysmotility • Stricture • Barrett's esophagus • Adenocarcinoma
Stomach	<ul style="list-style-type: none"> • Gastroparesis • Watermelon stomach (GAVE) • Gastric ulcer
Small Intestine	<ul style="list-style-type: none"> • Chronic intestinal pseudo-obstruction (CIPO) • Small intestinal bacterial overgrowth (SIBO) • Vascular ectasias • Pneumatosis cystoides intestinales
Colon	<ul style="list-style-type: none"> • Wide mouth diverticuli • Megacolon
Rectum and Anal Canal	<ul style="list-style-type: none"> • Fecal incontinence • Rectal prolapse
Other	<ul style="list-style-type: none"> • Primary biliary cirrhosis • Exocrine pancreatic insufficiency

SSc, both limited and diffuse, can also affect multiple internal organ systems, including the lungs, heart, kidneys, and the gastrointestinal tract. Next only to skin involvement, the gastrointestinal (GI) tract is the second most commonly involved organ system, with over 90% of patients experiencing symptoms pertaining to the GI tract.

The management of SSc remains one of medicine's most formidable challenges. So far, no effective disease modifying therapy has been developed that effectively reverses, halts, or even slows down the natural progression of the disease process.

SSc can involve any part of the GI tract – i.e. oral aperture, mouth and oral cavity, oropharynx, esophagus, stomach, small intestine, large intestine, and even rectum and anal canal (Table 1). GI manifestations of scleroderma are very common, and can be a source of significant morbidity and even mortality, especially when the entire GI tract is involved.¹ Patients are also at risk of malnutrition (15%-58%),^{1,2} that can even lead to death in about 20% patients.² Fat malabsorption has been found to occur in 43% of SSc patients, along with reduced serum levels of copper, selenium, carotene, and ascorbic acid.³ Whether these specific nutrient deficiencies are solely a result of reduced oral intake is unclear at this time.

The main pathological findings of GI involvement in SSc are smooth muscle atrophy and enteral wall fibrosis. Involvement can generally involve either the entire GI tract or any part of it. The muscle atrophy in the gut wall is thought to be either a result of involvement of the vasa nervorum (one of the manifestations of widespread scleroderma microvasculopathy), or due to perineural wrapping of collagen (which is formed in excess in scleroderma), leading to impaired denervation of the smooth muscle cell layer of the GI tract.

This article will discuss the nutritional implications of GI involvement in SSc and will emphasize specific management recommendations. Due to space constraints, detailed discussion of the investigations is beyond the scope of this article. Therefore, for investigations, please refer to the article by Kirby⁴ and the other annotated references.

GI MANIFESTATIONS OF SCLERODERMA

Oral

Thickening of perioral skin and fibrosis of perioral tissue leads to a narrow oral aperture (microstomia).

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This results in significant problems during brushing and flossing of teeth and professional dental cleaning. For the same reason, fitting an adult mouthpiece during the recommended annual spirometry becomes difficult, leading to unreliable readings due to air leak around the mouthpiece. Hence, SSc patients often have to resort to a pediatric mouthpiece during spirometry. Patients are also prone to develop considerable dryness of the mouth, due to secondary Sjögren syndrome, seen in about 14%-20% patients.^{5,6} Sjogren syndrome is associated with dental problems, periodontal disease, and oral candida infections.

Oropharynx

Oropharyngeal dysphagia has been found to occur in up to 25% patients.^{7,8} This is particularly true in patients with concomitant polymyositis (known as scleromyositis), seen in about 3% of patients with SSc,⁹ where the striated muscle of the oropharynx and upper esophagus may be affected by an inflammatory process. In patients with advanced and long-standing SSc, the entire esophagus may be involved, as well as the oropharynx. Laryngopharyngeal reflux has been associated with nocturnal cough, distressing sour eructations (oral regurgitation of gastric acid), bronchospastic disease, and intermittent hoarseness of voice.

Esophagus

Esophageal dysmotility much more commonly affects the lower two-thirds of the esophagus leading to dysphagia (predominantly to solids), but also to liquids in advanced cases. Over time, the entire esophagus becomes patulous and aperistaltic. In addition, the lower esophageal sphincter becomes incompetent, encouraging gastro-esophageal reflux disease (GERD) - often seen as an early manifestation of SSc. The problem seems to be more troublesome at night when the patient lies down and the benefit of gravity, which normally keeps food down in the stomach, is lost. There is impaired clearance of the refluxed acidic gastric contents due to esophageal dysmotility, aggravating esophageal irritation, especially at the gastro-esophageal junction and the lower esophagus. This chronic irritation predisposes to ulcerative esophagitis. If not recognized and managed in a timely manner, chronic esophagitis predisposes to esophageal stricture and even metaplastic and dysplastic changes close to the gastro-esophageal junction (where

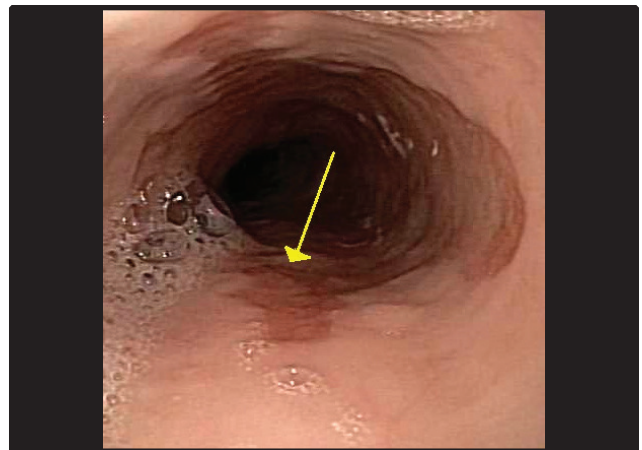


Figure 1. Endoscopy Findings of the Middle Third of the Esophagus in an SSc Patient: Barrett's Esophagus (arrow)

Table 2. Medications Associated with “Pill Esophagitis” and Medications that Can Decrease Esophageal Motility⁴

Pill Esophagitis	<ul style="list-style-type: none"> • Any large pill • Ampicillin • Antivirals (Zalcitabine, Zidovudine) • Aspirin • Ascorbic acid • Bisphosphonates (Alendronate, Risedronate, Ibandronate) • Iron supplements (ferrous sulfate, ferrous succinate) • NSAIDs • Potassium chloride • Quinidine • Rifampicin • Tetracyclines (especially Doxycycline)
Decrease Esophageal Motility	<ul style="list-style-type: none"> • Anticholinergic agents • Beta-blockers • Calcium channel blockers

normal stratified squamous epithelium is replaced by columnar epithelium), leading to Barrett's esophagus (Figure 1). Barrett's esophagus in turn predisposes to esophageal adenocarcinoma. Hence, surveillance endoscopies need to be performed routinely. Studies have shown that about 25% of patients presenting with adenocarcinoma have no prior history of GERD or Barrett's esophagus, indicating that GERD can be subclinical and asymptomatic in a substantial number of patients. Patients with esophageal dysmotility and aperistalsis are also more prone to develop "pill esophagitis"; therefore, certain medications (Table 2) should be swallowed with extreme caution with at least 8 ounces of water, to ensure that their esophageal transit is complete.

Stomach

Gastric dysmotility can lead to gastroparesis in 27%-38% of SSc patients.^{10,11} Symptoms include bloating, flatulence, early satiety, nausea and vomiting. It can aggravate malnutrition and weight loss. Moreover, gastroparesis can also worsen GERD, as the stagnant food is not propelled through the antrum, causing further gastric distension and enhancing reflux through the incompetent lower esophageal sphincter.

Another curious complication of SSc is gastric antral vascular ectasias (GAVE, also known as watermelon stomach). Dilated blood vessels (vascular ectasias) appear in the gastric antrum. The appearance of GAVE resembles the stripes of a watermelon (Figure 2). In addition, isolated mucosal telangiectasias can appear in the stomach, as well as the remaining GI tract. These lesions (GAVE and telangiectasias) can rupture inside the lumen causing acute blood loss or chronic iron deficiency anemia. Bleeding from these lesions cannot be controlled with proton pump inhibitors or other acid reducing agents.

Small Intestine

Symptomatic involvement of the small intestine is not common, occurring in about 15% of patients.¹² However, when it occurs, it is a cause of major morbidity. This problem, known as chronic intestinal pseudo-obstruction (CIPO), leads to severe constipation. There is smooth muscle atrophy, predominantly of the longitudinal muscle layer, leading to a slowing or absence of peristalsis. Malabsorption can occur due to fibrosis of the gut lymphatics. Moreover, slow intestinal transit sets the stage for significant small intestinal bacterial



Figure 2. Endoscopy findings of the pre-pyloric stomach in an SSc patient: gastric antral vascular ectasia (GAVE, watermelon stomach)

overgrowth (SIBO). This can lead to severe diarrhea, abdominal pain and distension, sometimes episodic and sometimes more continuous. Malabsorption and malnutrition from significant intestinal involvement portends an extremely poor prognosis in SSc and is often a challenging problem to manage.

Large Intestine

Collagen deposition and neuronal damage causes hypomotility of the large intestine in about 50% of scleroderma patients.¹³ This results in severe constipation and patients have to resort to laxatives and stool softeners, often with suboptimal response.

Anal Canal

Fecal incontinence, resulting from an incompetent anal sphincter, is not uncommon in SSc. This becomes a social nuisance, especially when patients are also having diarrhea, and can lead to fecal soilage. Patients may become homebound. Fecal incontinence has a major psychological impact and significantly impairs quality of life.

CLINICAL IMPLICATIONS AND MANAGEMENT

Diet and Nutrition

The North American Expert Panel convened by the Canadian Scleroderma Research Group (comprised of gastroenterologists, dietitians, speech pathologists, and rheumatologists) advocates screening all SSc patients for malnutrition and involving a multidisciplinary team (including gastroenterologists and dietitians) in those

diagnosed with malnutrition.¹⁴ SSc patients should be encouraged to record monthly weights and report significant changes in their weight to their provider.²

Oral Diet

Dietary modification is helpful in mild cases of intestinal involvement in SSc. A balanced healthy diet should be continued as long as possible. Intake of fats or sugars should not be restricted.³ Malabsorption and occult GI blood loss leads to vitamin B complex deficiency and iron deficiency. As a result, glossitis, cheilosis, angular stomatitis, and oral ulcers can develop. These nutritional deficiencies should be recognized and corrected as well. If gastroparesis develops, frequent, small, low-fiber, and lower fat meals with higher liquid content should be encouraged.²

Theoretically, restricting simple carbohydrates, fruit juices, sugar alcohols, and fiber (especially fiber bulking agents in those with constipation), may decrease fermentation and thus alleviate symptoms of bacterial overgrowth. Secondary lactose intolerance often develops, which may require additional dietary adjustments. If SIBO becomes a major problem, where possible, patients should be advised to reduce acid lowering agents to allow gastric acid to help keep SIBO at bay. However, this may be problematic in SSc patients, as GERD also needs to be effectively controlled to reduce its complications.

Enteral Nutrition

When severe esophageal dysmotility and aperistalsis makes oral feeding difficult, gastric or jejunal feeding through a percutaneous or surgically placed tube needs to be considered. In one small study of SSc patients, PEG tube feeding was reported to cause successful weight gain and improvement in quality of life.¹⁵

In patients with severe gastroparesis or GERD, nasojejunal tube feedings may be tried temporarily.¹⁶ If the procedure provides symptomatic relief along with improvement in nutritional status, a percutaneous or surgically placed jejunal tube may be an effective and durable solution in carefully selected patients.¹⁷ In refractory gastroparesis, a feeding jejunostomy sometimes needs to be combined with a decompression gastrostomy.¹⁸

Parenteral Nutrition

When malabsorption from CIPO and subsequent SIBO becomes severe and intractable, symptoms may prevent

enteral feeding in maintaining adequate nutrition. This is uncommon, but may occur in a small number of SSc patients. In this situation, parenteral nutrition (PN) may need to be considered. It has become an evolving route of alimentation for SSc patients with severe protein calorie malnutrition.³ Home PN has recently gained considerable attention as an effective means of maintaining adequate nutrition in patients with chronic intestinal failure from intractable scleroderma enteropathy. Its acceptance is based on the cumulative success observed in several retrospective case series each involving a relatively small number of SSc patients.¹⁹⁻²³

Pharmacological Agents

Prokinetic agents such as erythromycin (which stimulates motilin receptors in the intestine), domperidone, and even daily subcutaneous injections of octreotide (Sandostatin®)¹⁷ have been used with some success.

Prokinetic Agents

Prokinetic agents such as cisapride (Propulsid®) and tegaserod maleate (Zelnorm®) are no longer available in the US, but linaclotide (Linzess®),²⁴ has been tried with variable degrees of success in improving lower GI tract motility and regulating bowel movements. Prucalopride.^{25,26} (sold as Resolor® in Europe and as Resotran® in Canada) is in the same class as tegaserod, but does not share the same arrhythmogenic risk of Zelnorm® that led to its withdrawal from the US market. However, it is not available in the US.

Somatostatin Analogue

The somatostatin analogue, octreotide (Sandostatin®),¹⁷ increases the mean frequency of intestinal migratory motor complexes and thus stimulates intestinal motility. Octreotide can also reduce SIBO.¹⁷ It was shown to improve nausea, vomiting, flatulence and abdominal pain in SSc patients with CIPO.¹⁷

Antibiotics

SIBO, leading to episodic diarrhea, gas, bloating, and abdominal distension, can either be controlled with cyclical antibiotics, 7-10 day courses as necessary, or continuously in more severe cases (i.e. those with chronic diarrhea from SIBO) (Table 3). For the latter, rotating three or four antibiotics (Table 3) may be

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Table 3. Antibiotic Therapy for Small Intestinal Bacterial Overgrowth

No duration of therapy has been established but treatment should be short (e.g. 7-14 days) and limited to symptomatic resolution.

Medication	Adult Dose	Daily Frequency
Rifaximin	550mg	2-3x
Amoxicillin	500mg	2x
Vancomycin (oral)	125-500mg	1-4x
Metronidazole	500mg	3x
Ciprofloxacin	500mg	2x
Neomycin*	500mg	2x
Trimethoprim-Sulfamethoxazole*	1 double strength tablet	2x

**Note that these antibiotics have also been reported to provoke D-lactic acidosis*

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effective and help to reduce development of antibiotic resistance. Furthermore, there is some evidence on the benefit of long-term use of oral probiotics such as *Bifidobacterium infantis* (Align®) or *Lactobacillus GG* (Culturelle®).⁴

MOUTH CARE

If there is problem chewing or swallowing, dietary modifications are helpful, e.g. resorting to a soft moist diet, and avoiding dry items such as bread and those that require a lot of chewing such as meat. In addition, it is important to maintain good oral hygiene. If screening reveals poor oral health, a dentistry evaluation is appropriate.²⁷ Secretagogues (Table 4) are helpful in increasing saliva flow. Artificial saliva preparations that have earned ADA (American Dental Association) seal of acceptance can be used as necessary and can be helpful in lubricating the mouth. Oral candida (due to lack of protective saliva) is very common and should not be overlooked, treated when found (Table 4).

OROPHARYNGEAL DYSPHAGIA

When oropharyngeal dysphagia develops, referral to a speech pathologist is prudent.³ Aspiration precautions are particularly important in this subgroup of patients, as aspiration pneumonia not only worsens hypoxia in a SSc patient with pre-existing interstitial lung disease

(ILD), but repeated micro-aspirations have also been implicated in accelerating the rate of progression of ILD in SSc. When oropharyngeal and upper esophageal striated muscles are involved in scleromyositis (discussed above), since this is an inflammatory process, there may be a role for immunosuppressive therapy. Thus, in our practice, selected patients with this problem have benefitted from glucocorticoids and other immunomodulatory agents such as methotrexate, azathioprine or intravenous immunoglobulin.

ESOPHAGEAL PROBLEMS

Although the mainstay of therapy for GERD in SSc is the use of pharmacologic agents, some of the common and simple non-pharmacologic measures that will help manage acid reflux are listed below⁴:

- Frequent small meals
- Avoiding lying down for 1-2 hours after the last meal at night
- Avoiding certain food items (items that are known to relax the lower esophageal sphincter further) such as chocolate, caffeine, mint, fruit juices, fatty foods, etc.

Table 4. Mouth Care**Dry Mouth**

- Secretagogues to increase saliva flow
 - Cevimeline (Evxac®)
 - Pilocarpine (Salagen®)
- Biotene Dry Mouth® toothpaste
- Artificial saliva preparations:
 - NeutraSal® rinse
 - Saliva Orthana® spray

Oral Candida

- Nystatin oral suspension
- Clotrimazole lozenges
- Oral fluconazole

- Avoiding smoking and alcohol, especially before going to bed at night
- Avoiding tight undergarments
- Avoiding weight gain
- Use of liquid medications when pills cannot be taken safely
- Elevating the head end of the bed by 6-8 inches (using wooden blocks) or a wedge pillow
- Assuming a left lateral decubitus position at night. This recommendation is being made based on studies that have demonstrated that a sleep device that maintains recumbent horizontal position with left lateral decubitus position considerably reduces recumbent esophageal acid exposure²⁸ and symptoms of nocturnal acid reflux.²⁹

Acid Reducing Agents

Among pharmacologic agents, proton pump inhibitors (PPI) are by far the most effective acid-reducing agents

that should be used on a long-term basis (Table 5). Sometimes the patient might need a higher than usual dose, and even twice daily in recalcitrant cases. The concerns about bone loss, increased risk of serious GI infections (including *C. difficile* colitis), enhanced proliferation of SIBO, and nutritional deficiencies (iron, calcium, magnesium, vitamin C, and vitamin B12), are real, but if the physician is cognizant of these potential complications of long-term PPI use, and deals with them appropriately, as they occur, the benefits of long-term PPI use in an SSc patient can far outweigh the risks. For breakthrough heartburn even with continuous PPI use, antacids (preferably in a liquid form such as Gaviscon®, Maalox® or Mylanta®) can be used for immediate symptomatic relief. If PPIs are not tolerated or ineffective for any reason, the next option is to use an H₂ receptor antagonist (Table 5).

Prokinetic Agents

Prokinetic agents such as metoclopramide (Reglan®) or domperidone (Motilium®) may be helpful in the early stages of esophageal dysmotility in SSc. Many gastroenterologists prefer the latter, as unlike metoclopramide, it does not significantly cross the blood brain barrier and thus cannot cause the extra-pyramidal side effects that can occur with metoclopramide. However, it is not readily available in the United States, and may need to be obtained from other parts of the world (e.g. buying it online at: www.medisave.ca). Moreover, there is no published evidence about its efficacy in patients with SSc.

Cisapride (Propulsid®), proven to be a very effective prokinetic agent, was withdrawn from the US market in July 2000, due to its risk of inducing QT-prolongation, torsades-de-pointes and sudden cardiac death. However, in cases of severe and intractable SSc associated GERD, it may still be available from the manufacturer through a limited-access compassionate use program under an 'investigational new drug' mechanism (Protocol CIS-USA-154: Cisapride access to adult patients with GERD, gastroparesis, pseudo-obstruction or severe chronic constipation disorders who have failed standard therapy). However, as interactions with CYP3A4 inhibitors (azole antifungals, macrolide antibiotics and grapefruit juice) increase arrhythmogenic risk, these agents should not be co-administered. As the disease progresses, in patients with extensive smooth muscle atrophy and fibrosis, prokinetic agents may eventually become ineffective.

Procedural and Surgical Interventions

For peptic stricture of the esophagus (seen in 20% of patients with GERD), periodic esophageal dilation (using a dilator or bougie) is necessary.

If Barrett’s esophagus is present, periodic (at least annual) endoscopic surveillance is necessary. Some newer forms of therapy have led to a breakthrough in the management of this once incurable condition.⁴ These procedures can be successfully used to eradicate, and thus cure Barrett’s esophagus, e.g. radiofrequency ablation or photodynamic therapy.

In appropriate patients, small foci of in-situ adenocarcinoma arising from Barrett’s mucosa can be removed with radiofrequency ablation or endoscopic mucosal resection. Preferably, these patients should be referred to centers that have expertise in such therapy.⁴ Once invasive adenocarcinoma develops, the prognosis is poor and treatment may require extensive surgery, radiation and/or chemotherapy, especially for metastatic disease.

Sometimes permanent surgical procedures such as 270° Nissen fundoplication or even roux-en-Y gastric bypass are performed for intractable GERD and recurrent bouts of aspiration pneumonia. These procedures may also be performed in some selected patients in order to qualify for a lung transplant for severe lung disease associated with SSc, or sometimes after the lung transplant, to prevent aspiration induced lung injury.³⁰ However, fundoplication should preferably be avoided in SSc-associated GERD, as it is likely to worsen severe dysphagia (by inducing further mechanical obstruction in an already dysmotile esophagus), and thus aggravate the risk of malnutrition that these patients are already prone to develop.

GASTROPARESIS

Similar to esophageal dysmotility, prokinetic agents such as metoclopramide (Reglan®) or domperidone (Motilium®) may be helpful in the early stages of gastroparesis in SSc. As mentioned earlier, the latter is preferred by many gastroenterologists, but is not available in the US. Patients who may benefit from nutrition support should undergo a nasogastric or nasojejunal feeding trial before considering permanent enteral access. In those who do not tolerate it, it saves them from undergoing a procedure they do not need; for those ultimately needing parenteral support, it may be required for insurance coverage purposes, before approval. However, it has to be kept in mind that when

Table 5. Proton pump inhibitors (PPI) and H2 receptor antagonists (H2RA)

Proton pump inhibitors (PPI)	<ul style="list-style-type: none"> • Omeprazole (Prilosec®) • Lansoprazole (Prevacid®) • Rabeprazole (Aciphex®) • Esomeprazole (Nexium®) • Pantoprazole (Protonix®) • Omeprazole + Sodium bicarbonate (Zegerid®) • Dexlansoprazole (Dexilant®)
H2 Receptor Antagonists (H2RA)	<ul style="list-style-type: none"> • Cimetidine (Tagamet®) • Ranitidine (Zantac®) • Famotidine (Pepcid®) • Nizatidine (Axid®)

gastroparesis develops in SSc, bypassing the stomach is often not a solution, because the rest of the GI tract is also likely to be similarly affected by dysmotility. Nevertheless, sometimes a PEG tube needs to be inserted for intermittent gastric decompression when gastric distension from severe gastroparesis causes considerable discomfort, and substantially increases the risk of reflux and aspiration.

GAVE

For GAVE (Figure 2) and isolated gastro-intestinal telangiectasias, several ablative procedures have been used with success.⁴ The preferred endoscopic method is argon plasma coagulation (APC), as the lesions induced by cauterizing the bleeding vessels by APC are more superficial (compared to the other methods) and therefore they lead to minimal scarring of the antrum – a complication that can worsen gastric dysmotility, particularly when the patient has concomitant gastroparesis.

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CONCLUSION

GI tract involvement is the most common extra-cutaneous manifestation of SSc. Any part of the GI tract from the mouth to the anal canal may be affected, potentially causing significant malnutrition, impairment of quality of life and in severe cases, even death. Early recognition and management of GI complications of SSc may favorably alter the long-term outcome. The durable benefits of parenteral nutrition in SSc enteropathy are beginning to emerge. A multidisciplinary approach including rheumatologists, gastroenterologists with expertise in gastrointestinal dysmotility and early involvement of a dietitian familiar with the disease is paramount in producing better outcomes and improving survival in these patients. ■

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