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Gastrointestinal manifestations of systemic sclerosis: An updated review

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Abstract

Systemic sclerosis is an autoimmune disease characterized by vascular disease, fibrosis of the skin, and internal organ dysfunction. Gastrointestinal involvement is the most frequent complication of internal organs, impacting up to 90% of patients. Gastrointestinal involvement can affect any region of the gastrointestinal tract from the mouth to the anus, with a predominance of disorders being observed at the level of the upper digestive tract. The gastrointestinal involvement primarily involves the esophagus, small bowel, and rectum. The severity of gastrointestinal involvement affects quality of life and is a marker of worse prognosis and mortality in these patients. In this review, we describe the current findings regarding gastrointestinal involvement by this entity.

Key Words: Systemic sclerosis; Gastrointestinal; Diagnosis; Treatment

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Core Tip: Systemic sclerosis is an autoimmune disease characterized by vasculopathy, fibrosis of the skin, and internal organ dysfunction. Gastrointestinal involvement is the most common complication of internal organs, impacting up to 90% of patients. This involvement can affect any region of the gastrointestinal tract from the mouth to the anus, with a predominance of alterations being observed in the upper digestive tract.

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INTRODUCTION

The term scleroderma comes from the Greek "scleros" (thickened) and "derma" skin (hardened skin). The first report of scleroderma was made in 1753 from Carlo Curzio, but only in the middle of the 19th century was it established as a disease[1,2]. Systemic sclerosis (SSc) is an autoimmune disease, the etiology and pathophysiology of which have not been clearly defined. SSc is characterized by alterations in both humoral and cellular immunity followed by fibroproliferative alterations in the microvasculature with subsequent deposition of collagen fibers[1,2]. In 1892, Sir William Osler described SSc as a "terrible disease"; according to his observations, he found that it affected not only the skin but also multiple organs, such as the heart, lung, kidney, and gastrointestinal tract (GIT)[3]. Only until 1947 did Cristian include for the first time the GI involvement of the disease, which was made possible by advances in imaging techniques, thereby providing an idea of the complexity of the disease[4].

Although Raynaud's phenomenon and skin sclerosis are the most visible clinical features, GI involvement in SSc is the most frequent complication of internal organs, affecting approximately 90% of patients[5,6]. GI involvement can fundamentally impact any region from the mouth to the anus with a linear relationship between the modified Rodnan score and the frequency of GI symptoms of the upper tract[7]. However, in up to 10% of cases, initial disease involvement affects the GIT in the absence of skin disease[4].

In a study in which the risk factors and clinical manifestations related to severe GI dysmotility in patients with SSc were determined, it was associated with male gender [odds ratio (OR) = 2.47, 95% confidence interval (CI): 1.34-4.56, $P = 0.004$], myopathy (OR = 5.53 95%CI: 2.82-10.82, $P < 0.001$), and sicca symptoms (OR = 2.40, 95%CI: 1.30-4.42, $P = 0.005$)[8]. In a cohort of patients with SSc with fewer than 2 years of disease evolution, the probability of developing severe GI compromise was estimated at 9.1% in 2 years and 16.0% in 4 years. Additionally, severe GI disease was associated with an increase in the risk of death greater than 2 times and a decrease of the quality of life related to health and mental health[9]. In SSc patients with GI dysfunction, worse results have been found in the domains that assess quality of life compared to SSc patients without GI dysfunction[10]. A recent study showed that an increased burden of symptoms related to GI dysautonomia was associated with emotional distress[11]. In two meta-analyses, it was found that the mortality attributed to GI alterations was between 4%-7.6%[12,13], and in the subgroup of patients who developed severe GI symptoms, the survival rate was only 15% in 9 years[14]. GI compromise is the third leading cause of mortality in SSc after cardiopulmonary and kidney damage[3,15]. The main organ involved is the esophagus followed by the small bowel (SB) and rectum and anus[14,16]. GI pathology in SSc can present with very mild symptoms in 39% of cases, mild symptoms in 21%, moderate symptoms in 31%, and severe symptoms in 9%[17]. Table 1 summarizes the main clinical manifestation of each part of the GI system[14,16].

Based on the extent of cutaneous involvement, SSc is classified as limited (lcSSc) (80%) and diffuse (dcSSc) (20%). The latter occurs when the involvement is proximal to the elbows and knees; the facial region can be affected in both subtypes. This classification is important in terms of the natural history of the disease, organ involvement, antibody profile, and prognosis[18]. In the EUSTAR cohort, older patients with diffuse involvement acquired earlier and more frequent GI symptoms ($P < 0.05$). Patients with anti-RNA polymerase III antibodies presented lower GI compromise than those with anti-topoisomerase I or anti-centromere antibodies [hazard ratio (HR) = 0.55, 95%CI:

Table 1 Distribution of the main gastrointestinal manifestations in systemic sclerosis (modified from references 14 and 16)

Compromised organ(s)	Percentage of compromise	Clinical manifestations
Oral cavity and oropharynx	30%-70%	Microstomia, xerostomia, odontogenic pathology, squamous cell carcinoma of the tongue, dysfunction of the temporomandibular joint, oropharyngeal dysphagia
Esophagus	80%-90%	Esophageal dysphagia, chest pain, heartburn, regurgitation
Stomach	25%-50%	Gastroparesis, antral gastric vascular ectasia
Small intestine	60%-80%	Dysmotility, small intestinal bacterial overgrowth, chronic intestinal pseudo-obstruction, cystic intestinal pneumatosis, diverticula
Colon	20%-50%	Dysmotility, decreased gastro-colic reflex, constipation, perforation, diverticula
Rectum and anus	50%-70%	Fecal incontinence, defecatory disorder, rectal prolapse

0.34-0.90; HR = 0.59, 95%CI: 0.39 - 0.91, respectively)[19].

Esophageal and gastric symptoms were more frequent in dcSSc than in lcSSc, whereas intestinal symptoms were similar in both forms[20]. dcSSc presents with cough (80%), heartburn (80%), epigastric pain (80%), bloating (80%), diarrhea (73%), nausea (60%), constipation (47%), vomiting (33%), weight loss (27%), and fecal incontinence (13%); in the limited form, less nocturnal epigastric pain, abdominal pain, and diarrhea have been found with a greater frequency of fecal incontinence and meteorism. There are no differences regarding cough, nausea, vomiting, and constipation[1].

There are several challenges in management, for which patients at high risk of progression to severe GI disease must be identified: Determining if existing damage or disease activity is the cause of symptoms, determining if early initiation of pro-motility agents or other GI medications can prevent complications, and defining whether there is a role for immunosuppressants[7]. The objective of this article is to update the pathophysiology and GI manifestations of this entity.

METHODS

For this review, articles were identified through a search in PubMed, Google Scholar, and Semantic Scholar, with the following terms: "Systemic sclerosis", "gastrointestinal", "orofacial", "oropharyngeal", "esophagus", "esophageal manometry", "gastroesophageal reflux disease", "gastric", "gastroparesis", "gastric antral vascular ectasia", "bowel", "SIBO", "pseudo-obstruction", "colon", "rectum", and "anus". Manuscripts published in English were reviewed. Articles published from January 1980 to July 2020 were included. The titles and abstracts of the articles were identified according to the search strategy, and relevant papers were chosen for the review. The articles in this search were screened for additional references.

EPIDEMIOLOGY OF SSC

It is estimated that the incidence of SSC in the United States and Europe is approximately 1-2/100000 inhabitants/year, and the prevalence is 8-30 cases per 100000 people; however, this statistic may vary between different population groups[15]. In Colombia, according to the COPCORD - Colombian Association of Rheumatology registry, the prevalence is 0.02%. The peak of presentation is approximately 30 to 50 years[21]. This entity is more frequent in women with respect to men with a 5:1 ratio, and it affects Afro-descendants, highlighting the earlier presentation in life and the dcSSc subtype, with the latter having a worse prognosis in the evolution of the disease [15,21].

PATHOPHYSIOLOGY

The pathophysiology is characterized by the sum of involvement at the vascular level (vasculopathy), immunological alteration together with an inflammatory state

(autoimmune component), and an increase in fibrogenesis (connective tissue component)[16]. The different physiopathological components can occur simultaneously; however, in earlier forms of the disease, there is a predominance of the inflammatory component and in late-phase fibrosis[22].

Mechanisms of GI engagement in SSs

In the natural history of the disease, progressive fibrotic changes secondary to dysfunction in the deposition of collagen and other components of the extracellular matrix associated with a significant degree of neuromuscular dysfunction, as well as vascular and autoimmune phenomena, will be reflected in the different manifestations, such as dysmotility, malabsorption, malnutrition, and dilation of the intestine [15]. In more severe cases, this disease can lead to serious complications, such as intestinal pseudo-obstruction, perforation, and neoplasia[1,23].

To arrive at the initial alterations of the disease, the multifactorial etiological approach is accepted[14]. It is suggested that a genetic component is part of the initial event for the following pathophysiological phenomena. The presence of human leukocyte antigen DRB1*0802 and DQA1*0501 alleles and epigenetic alterations, such as DNA methylation, particularly hypomethylation, is the most important. Modifications in microRNAs, such as miR-29, have been identified, facilitating the expression of genes that favor collagen deposition. Other external physical and chemical stimuli, such as gadolinium, L-tryptophan and cigarettes, and biologics, such as *Helicobacter pylori*, as well as some viruses and fungi, have the ability to integrate to produce the damage found[16].

To arrive at the pathophysiological development of the disease, two main theories have been proposed[1]. In the first instance, vascular compromise is considered the trigger for autonomic axonal damage, reflected in later sympathetic overactivity and the initial effect on dysmotility through degeneration of cholinergic nerves, rather than muscle[4]. When evaluating GI motor involvement, it is possible to classify it as myogenic (hypomotility) or neurogenic (development of contractions and feedback from the defective system)[14]. However, it should be noted that motor involvement is not the only mechanism of the disease. As a concomitant mechanism, possibly a consequence of the vascular disease, an alternate event, or a predecessor to it, the alterations of the immune system are accepted[16]. An early autoimmune course has been described, where this immunological instability may be responsible for the autonomic nervous alteration[23]. In any case, the most accepted pathophysiological theory is that the disease requires not only one phenomenon but also a series of related or sequential events to reach fibrosis or late outcome.

An attempt has been made to sequentially classify GI compromise according to Sjögren into 4 phases: Grade 0 when there is vascular compromise, grade 1 in the case of neurological damage, grade 2 when there is myogenic dysfunction, and grade 3 in the presence of fibrosis[14]. Notably, studies have not been able to demonstrate a clear correlation between clinical GI involvement and the physiological and histological findings[23]. The final outcome of the different pathophysiological mechanisms will be atrophy of smooth muscle, both in the intestine and in the wall of the blood vessels; over time, the smooth muscle is replaced by fibrotic tissue around the muscle cells with subsequent neuronal degeneration and loss of histological architecture[14].

Vascular dysfunction in SSs

Endothelial vascular hyperresponsiveness, observed by vasoconstriction events with subsequent reperfusion clinically manifested as Raynaud's phenomenon, appears to be the early and initial pathophysiological event[1]. The endothelium is a tissue that continuously performs homeostatic functions through the transport of nutrients, facilitates cell migration, and plays a fundamental role in coagulation. The loss of this balance generates a state of metabolic alteration, a decrease in vasodilator molecules, such as nitric oxide and prostacyclin, and an increase in vasoconstrictors, such as endothelin-1. Similarly, different adhesion molecules, such as selectins and integrins, have been identified[3]. There is also a vascular pro-coagulant state demonstrated by an increase in fibrinogen and irregular release of plasminogen activator; there is an increase in platelet aggregation, fibrin deposition, and formation of intravascular thrombi[16]. Finally, in more advanced stages of the disease, the vascular architecture is lost, with alterations in neoangiogenesis being observed. These phenomena of tissue hypoperfusion lead to a state of hypoxia and ischemia, generating free oxygen radicals and the subsequent stimulation of fibroblast proliferation and increased production of extracellular matrix. In the vascular wall, there is proliferation of the intima and deposition of products, such as proteoglycans, generating fibrosis at this level[16,24].

GI involvement in SSc and fibrosis

At the GIT level, fibroblasts and later myofibroblasts are activated, with overproduction of the extracellular matrix occurring not only through a greater amount of collagen but also through other proteins, such as fibrillin, together with a decrease in collagenase activity[23]. Similarly, there is a transformation to myofibroblasts favored by the action of interleukin (IL)-1, which is capable of generating a larger extracellular matrix, mainly types 1 and 3 collagen, and inhibiting degradation[14]. Fibrosis is due to the exposure of fibroblasts to cytokines, such as transforming growth factor β , together with its receptor (favored by the action of IL-13), platelet-derived growth factor, and growth factor similar to insulin, both for its profibrotic stimulation and its ability to be antiapoptotic by inhibiting Fas-mediated signaling pathways[15,16].

The pathophysiological mechanisms described previously will be reflected in the different GI manifestations of SSc, such as gastric dysrhythmias, elevated levels of vasoactive intestinal peptide, and decreased motilin in serum, by enterochromaffin cells and M cells in the stomach, SB, and colon, leading to a slow wave phenomenon with the consequent effect of intestinal transit[1]. In turn, this hypomotility phenomenon will lead to other phenomena, such as gastroesophageal reflux disease (GERD), gastroparesis, small intestinal bacterial overgrowth (SIBO), intestinal malabsorption, fecal incontinence and, in severe cases, chronic intestinal pseudo-obstruction (CIPO)[14,25-27].

CLINICAL MANIFESTATIONS

Oral cavity and oropharynx

The orofacial region is involved in more than 2/3 of patients; however, orofacial involvement is underdiagnosed, and the corresponding symptoms are frequently overshadowed by severe systemic manifestations[28]. The main oral and maxillofacial compromise includes limited opening of the mouth (microstomy), reduction of the size of the lips (microcheilia), reduction of the interincisal distance, xerostomia, periodontal disease, widening of the periodontal ligament space, squamous cell carcinoma of the tongue, resorption of the zygomatic arch, and reabsorption of the mandibular angle, coronoid process, and condyle, which leads to pathological fractures, and disorders of the temporomandibular joint[29]. Sicca syndrome occurs in approximately 70% of patients, secondary to fibrosis of the salivary glands, and 7%-14% of patients may present with Sjögren's syndrome[29].

Limited oral opening interferes with chewing and oral hygiene[18]. A study that included 163 patients and 231 controls found that SSc patients had more carious teeth and periodontal disease. Additionally, the interincisal distance was smaller (SSc 37.68 mm *vs* controls 44.30 mm, $P < 0.0001$), and they produced less saliva (SSc 147.52 mg/min *vs* controls 163.19 mg/min, $P = 0.0259$)[30]. In an observational study, it was found that SSc patients had more oral symptoms (xerostomia, dysgeusia, dysphagia, and stomatodynia) than healthy controls (78.8% *vs* 28.7%, respectively, $P = 0.001$). Additionally, these patients had more symptoms of temporomandibular disorders (muscle pain when chewing, difficulty opening the mouth, and headache)[31]. In patients with severe limitations in oral opening (< 30 mm), a specific rehabilitation program for oral opening, flexible sectional prostheses, and splint therapy is recommended. Prevention of infections in the mouth and cavities requires education in dental and oral hygiene, periodontal maintenance, and treatment of sicca syndrome [32]. Patients should be evaluated radiologically for early detection of dental caries and mandibular resorption to prevent the occurrence of iatrogenic fractures[29,32].

Pharyngeal abnormalities compromise up to 50% of patients[33]. In a study in which 51 patients with SSc were included, 26% had swallowing abnormalities (oral leakage, retention, penetration, mild or moderate aspiration, and incoordination of the upper esophageal sphincter). The severity of oropharyngeal involvement was correlated with the duration of skin involvement and Raynaud's phenomenon. These alterations were more severe in patients with esophageal dysmotility and were associated with a higher incidence of lung disease[34]. Speech therapy is recommended in patients with oropharyngeal dysfunction to optimize swallowing mechanisms and reduce the risk of aspiration[18].

Esophagus

The esophagus is the most frequently involved internal organ, reaching a prevalence greater than 90% [6]. The symptoms are mainly due to esophageal motility compromised with symptoms, such as dysphagia and chest pain, and GERD with

symptoms, such as heartburn and regurgitation[35]; however, in asymptomatic patients, a high prevalence of alterations in the esophageal mucosa can be found[36].

High-resolution esophageal manometry (HRM) is a tool used to assess esophageal motility. Based on the findings of the HRM, motor disorders of the esophagus are currently classified according to Chicago version 3.0[37]. In a systematic review of patients with SSc, an association was found between absent contractility and high GI symptoms, although asymptomatic patients frequently presented dysmotility of the esophageal body[38]. Patients who are asymptomatic for esophageal involvement may have abnormalities in the HRM in up to 84% of cases[39]. The typical manometric findings are weak or absent peristalsis of the esophageal body and hypotension of the lower esophageal sphincter (LES). The combination of aperistalsis and hypotension of the LES has been called classic SSc esophagus (ESSc)[35]. In a prospective study in which 200 patients were included, 56% had absent contractility, 26% had normal motility, 10% had ineffective esophageal motility, and 33% had ESSc[40]. Meanwhile, in another study, the loss of peristaltic reserve evaluated with multiple rapid swallows was the most common manometric finding in these patients[41].

The presence of anti-Scl 70 antibodies and the absence of anti-centromere antibodies have been associated with dysmotility of the esophageal body[42]. Similarly, in a cohort, it was found that patients with positive anti-RNPC-3 antibodies had more esophageal dysmotility than those with negative antibodies (93% *vs* 62%, respectively, $P < 0.01$)[43].

The absence of contractility in HRM is associated with greater severity of skin involvement and poorer lung function[44,45]. In a recent systematic review, esophageal dysmotility was correlated with decreased carbon monoxide diffusing capacity (< 0.8 predicted value) and interstitial lung disease (ILD) on high-resolution computed tomography (HRCT)[38]. Additionally, the increase in esophageal diameter on HRCT is correlated with greater severity of ILD associated with SSc[46,47].

The treatment of esophageal dysmotility is supportive, and it is recommended that patients take small bites, chew food well, avoid dry or fibrous foods, and drink plenty of water with solid foods[48]. In patients with SSc and esophageal motility disorder, there are no controlled clinical trials evaluating the long-term efficacy of prokinetics, and experts recommend them with a C-level strength of recommendation[18]. The use of prokinetics has been restricted primarily by the cardiovascular safety profile[49].

GERD develops when backflow of gastric contents into the esophagus causes bothersome symptoms or complications[50]. It frequently occurs early in the course of SSc, unlike motility disorders[6]. Patients are at higher risk due to several factors: (1) weak or absent peristalsis; (2) decreased LES pressure; (3) associated hiatal hernia (due to shortening of the esophagus); (4) gastroparesis; (5) autonomic neurological dysfunction; and (6) associated sicca syndrome (due to loss of bicarbonate in saliva)[51].

The nocturnal symptoms can be presented by multiple factors, such as reclining, decreased swallowing and secretion of saliva, and decreased esophageal peristalsis and perception of GERD, with prolonged clearance of acid from the esophagus, and it has been associated with sleep disturbances[52]. In a study including 287 patients with SSc, patients who reported GERD symptoms additionally reported poor sleep quality[53].

The diagnosis is complex and has recently been described in a consensus of experts in which it has been considered that the clinical history, the results of questionnaires, and empirical response to anti-secretory therapy are insufficient to make a conclusive diagnosis in isolation. It has been proposed to evaluate endoscopic findings, pH or pH impedance, and HRM. In this consensus, the conclusive evidence of GERD in esophageal examinations includes advanced erosive esophagitis (Grade C and D according to the Los Angeles classification), long segment Barrett's esophagus (BE) and peptic stricture in endoscopic findings, and acid exposure time (AET) $> 6\%$ in pH or pH-impedance[54].

Treatment in these patients should be applied in a staggered manner, initially with changes in lifestyle, pharmacological therapy, and endoscopic and surgical procedures in selected patients[55]. Acid-suppressing medications, primarily proton pump inhibitors (PPIs), are the cornerstone of treatment[55]. Although specific large-scale controlled clinical trials in patients with SSc-related GERD are lacking, experts recommend that PPIs should be used to treat symptoms and prevent ulcers and esophageal stricture, a strength of recommendation B[18]. A PPI daily dose is started 30-60 min before the first meal of the day, and the dose is increased to twice daily if the response is partial or there are nocturnal symptoms[55]. A matched retrospective case-control study in which 38 patients with SSc and 38 controls who underwent esophageal pH-impedance with double-dose PPI were included found a higher AET $\geq$

4.5% (61% cases *vs* 18% controls $P < 0.001$), higher median bolus clearance, and lower mean nocturnal baseline impedance, which would support ineffective esophageal clearance as the potential mechanism, for which additional therapies with PPIs to control acid reflux should be considered in these patients[56]. A clinical trial that included SSc patients with GERD who had a partial response to PPIs randomized to domperidone and alginic acid found that after treatment with both drugs, the severity and frequency of symptoms and quality of life improved; however, 17% of the patients did not respond to the combination treatment[57]. Acotiamide is a cholinesterase inhibitor, and a patient with SSc and severe GERD without response to PPIs, mosapride, and Rikkunshito, had symptomatic improvement with this prokinetic[58]. Buspirone is a 5-HT_{1A} receptor agonist that increases the resting pressure of the LES in patients with SSc[59]. In a study that included 30 patients with esophageal symptoms who did not respond to PPIs, oral buspirone 20 mg daily improved GERD symptoms at 4 wk of treatment[60]. In patients who do not respond after a standard 8-wk course with PPI in whom upper gastrointestinal endoscopy rules out esophageal injury, GERD should be confirmed with pH-impedance without PPI or a diagnosis of functional esophageal disorders should be made, such as reflux hypersensitivity and functional heartburn, which could be managed with neuromodulators[61].

Patients who do not respond to medical management will require surgical management. Experts have recently generated key recommendations to properly select patients who benefit from anti-reflux surgery, considering patients with heartburn with adequate response to PPIs, hiatal hernia, erosive esophagitis grade B or greater according to the Los Angeles classification and BE patients[62]. However, the results of anti-reflux surgery in SSc have been suboptimal due to the esophageal dysmotility present in these patients[63]. The most widely used methods are fundoplication and Roux-en-Y gastric bypass (RYGB). Most of the literature demonstrates that fundoplication can be safe in patients with weak peristalsis and that postoperative dysphagia cannot be reliably predicted by the preoperative parameters of HRM. Partial fundoplication could be performed in patients with aperistalsis (ESSc) after a multidisciplinary evaluation, and RYGB would be an alternative to partial fundoplication in patients with ESSc after carefully evaluating nutritional status[64]. In a retrospective study that included 23 patients who underwent surgical treatment for GERD (fundoplication, RYGB, and esophagectomy), better control of reflux symptoms and less dysphagia were found in the RYGB group compared with fundoplication, and the post-discharge complications after esophagectomy were also reduced[65]. A more recent retrospective study found that RYGB is a safe anti-reflux procedure and is an alternative to fundoplication in patients with esophageal dysmotility[66].

Patients in whom GERD has not been diagnosed or controlled may have serious complications, such as esophageal stricture, BE, esophageal adenocarcinoma, ILD, and pulmonary fibrosis[67]. Combined with the pulmonary manifestations typical of SSc, these latter complications predispose patients to end-stage lung disease and, ultimately, lung transplantation in refractory cases[68]. There are few studies on this subject, and most of them retrospective, with a small number of patients with end-stage lung disease who are candidates for lung transplantation. The recommendation by experts is to evaluate GERD and, if it is detected, to perform fundoplication as soon as the diagnosis is made to prevent the development of obliterative bronchiolitis syndrome[69].

Stomach

Gastric dysfunction has been reported in up to 50% of patients[27]. The two main changes in the stomach are gastroparesis and gastric antral vascular ectasia (GAVE) [14].

Gastroparesis is a syndrome that is defined by objectively delayed gastric emptying (GE) in the absence of mechanical obstruction and cardinal symptoms, including early satiety, postprandial fullness, nausea, vomiting, bloating, and upper abdominal pain [70]. In a report of patients with SSc, the prevalence of delayed GE using a ¹³C-labeled octanoic acid respiratory test was 47.4%[71]. In a study in which GE was studied by abdominal ultrasound, a delay was observed in 65%-70% of patients with a duration of disease greater than 10 years[72]. Another study in which 20 patients and 20 controls were included, evaluated gastric filling and emptying by trans-abdominal ultrasound in patients with SSc found reduced gastric filling and delayed GE in the fundus and antrum[73].

The gold standard for the diagnosis of gastroparesis is 4-h solid phase GE scintigraphy. The study was carried out with a low-fat meal with an egg white (approximately 240 kcal, 2% fat), and images were taken at 0 h, 1 h, 2 h, and 4 h[74]. According to GE scintigraphy, the severity is classified based on the percentage of gastric

retention at 4 h: Mild (10%-15%), moderate (15%-35%), and severe (> 35%)[75]. Alternative studies recommended by experts are breath tests labelled with the stable nonradioactive isotope ^{13}C using octanoic acid or *Spirulina platensis* incorporated in a solid meal, the wireless motility capsule, and antral or antropyloroduodenal manometry[74].

Treatment strategies in these patients will depend on the classification according to GE scintigraphy based on general measures, changes in diet, nutritional support, prokinetics, antiemetics, symptom modulators, and endoscopic or surgical management[75]. Medications that delay GE should be reviewed and eliminated. The diet is based on small and frequent meals that are low in fat and fiber or, in severe cases, a liquefied diet with the use of nutritional supplements[75]. There are several prokinetics and antiemetics that could be used in gastroparesis and SSc, including metoclopramide, erythromycin, and ghrelin; however, there are very few reports of management specifically in these patients[76-80]. Cisapride showed good initial results [81]; nevertheless, it was withdrawn from the market in many countries due to adverse cardiovascular effects[49,82]. Invasive procedures, including Botox injections and gastric stimulator implantation, appear to have a limited role[6]. After a multidisciplinary discussion, gastric per oral endoscopic myotomy could be a therapeutic option in patients with severe gastroparesis in whom classic treatment fails[83].

Recently, it was observed that SSc can be an independent risk factor for GI bleeding events with an HR of 2.98 (95% CI: 2.21-4.02)[84]. GAVE is part of the spectrum of vascular disease in these patients[16,24]. The prevalence is variable, with reports between 1%-76%[85]. A study that evaluated abnormalities of the GI mucosa by video capsule endoscopy found "watermelon stomach" (34.6%), gastric and/or SB telangiectasia (26.9%), and gastric and/or SB angiodysplasia (38.5%).

Mucosal vascular lesions in the GIT were related to digital ulcers ($P = 0.05$), a high score in the videocapillaroscopy of the nail fold ($P = 0.0009$), anemia ($P = 0.02$), and low levels of ferritin ($P < 0.0001$)[86]. In a study in which 28 patients with SSc and GAVE were included, 61% were found to have cutaneous telangiectasias. Patients with dcSSc developed GAVE earlier in the course of the disease than patients with lcSSc (21.5 mo *vs* 84.3 mo, respectively, $P = 0.025$)[87]. However, in 10.9% of cases, the finding of GAVE preceded the onset of SSc symptoms[88]. Clinical findings (early diffuse disease and rapid progression of skin thickening) and laboratory findings (anti-RNA polymerase III positive and anti-Scl 70 negative) are risk factors for the development of it [89].

GAVE can present with asymptomatic or symptomatic iron deficiency anemia (weakness, fatigue, or dyspnea), occult blood in the stool, and overt bleeding due to melena or hematemesis[14,85]. Endoscopically, the typical "watermelon stomach" is found with prominent, flat, or raised erythematous stripes that radiate from the antrum with a tendency to converge towards the pylorus, the finding of which is the most frequent, and the "honeycomb stomach", where vascular ectasia appears as a coalescence of multiple round angiodysplasias in the antrum[88]. Additionally, patients with GAVE had more erythema or vascular ectasias in other parts of the stomach than patients with SSc without GAVE [26.1% *vs* 5%, $P = 0.003$][90]. Likewise, vascular ectasias have been reported in the esophagus, duodenum, ileum, colon, and rectum, supporting the theory of diffuse vasculopathy[88].

Treatment is symptomatic and includes pharmacological, endoscopic, and surgical management[85]. There are no controlled clinical trials comparing the different types of treatment. Medical management includes iron supplementation and transfusion support in cases of acute GI bleeding and symptomatic anemia. Additionally, there are case reports of management with steroids and hormonal therapy (ethinylestradiol and norethisterone)[88]. Endoscopic treatment is indicated when there is overt or occult GI bleeding with anemia refractory to conservative therapy[88]. It can be performed with sclerotherapy, hot probe, bipolar electrocoagulation, photocoagulation with a Nd-YAG laser (neodymium-doped yttrium aluminum garnet), and argon plasma coagulation (APC). However, APC is the current standard treatment because it has several theoretical advantages, such as limited depth of penetration into the tissue, which decreases the risk of perforation, and symmetrical spread of the coagulation effect in the surrounding target area[91]. APC is effective in most cases, but some patients develop severe, refractory bleeding. In these cases, cyclophosphamide can be used with a reported dose between 750 mg/m² and 1000 mg/m²[89]. In a recent meta-analysis, radiofrequency ablation was found to have efficacy and tolerability comparable to APC and appears to be effective in patients with APC-refractory GAVE [92]. Surgical treatment, mainly antrectomy, is reserved for patients who do not respond to medical or endoscopic therapy[85].

Small bowel

The SB is the second most compromised GIT organ[14]. The dysmotility occurs in up to 60%-80% of cases, depending on the duration of the disease[6]. In a manometric study, more severe phase III abnormalities of the migrant motor complex were found during fasting, a decrease in the median duodenal and duodenal-jejunal index during the postprandial period, and more frequent alterations of the motor activity in response to octreotide infusion[93]. Slow transit is associated with SIBO and CIPO[6].

SIBO affects approximately 40% of patients with SSc[6]. In a study in which 89 patients were included, it was associated with > 5 years of disease duration (OR = 9.38, 95%CI: 1.09-80.47)[94]. It is a cause of malabsorption, and it presents with diarrhea, bloating, weight loss, steatorrhea, and nutritional deterioration with deficiency of iron, vitamin B12, and fat-soluble vitamins (A, D, and E)[95,96]. The gold standard for the diagnosis is traditionally the quantitative culture of jejunal aspirate[95]. It has been defined by the presence of $\geq 10^5$ colony forming units (CFU)/mL aerobic Gram-negative or strict anaerobic bacteria in jejunal aspirate cultures [95]. However, there is recent consensus that a different cutoff point $\geq 10^3$ CFU/mL in aspirate culture of SB should be used[97]. It has false positives due to contamination with the oral and esophageal microbiota and false negatives due to the lack of ability to reach the middle and distal part of the SB[97]. This is an invasive, uncomfortable, and expensive technique for which noninvasive tests have been developed that are relatively simple and less expensive[95,96]. Glucose and lactulose breath tests are the least invasive alternatives for diagnosing. An increase in hydrogen of ≥ 20 p.p.m. above the reference value at 90 min, during the glucose or lactulose breath test, is considered positive[97]. For the study specifically in SSc, it is recommended to perform these breath tests in which expired hydrogen and methane are evaluated[98].

Diagnostic tests have limited performance; therefore, in clinical practice, it is common that when suspected, given classic risk factors and symptoms, empirical treatments with broad-spectrum antibiotics are used that cover aerobic and anaerobic bacteria[95]. In the only systematic review in which treatment was specifically evaluated in SSc, five nonrandomized studies were found that included 78 patients treated with octreotide, ciprofloxacin, rifaximin, norfloxacin, and metronidazole and the combination of amoxicillin, ciprofloxacin, and metronidazole. Due to the heterogeneity of treatments and relatively small sample sizes, it was not possible to perform a meta-analysis[99]. Despite the lack of controlled clinical trials, experts recommend the use of intermittent or rotating antibiotics[18]. Rifaximin is the most studied antibiotic in patients without SSc, and it is the preferred antibiotic due to its effectiveness, limited absorption, and systemic effects[100]. Other antibiotics, such as amoxicillin-clavulanate, ciprofloxacin, doxycycline, metronidazole, neomycin, norfloxacin, tetracycline, and trimethoprim-sulfamethoxazole, have been used[95]. Treatment is generally administered for 7 d to 14 d[95]. Probiotics have been proposed for the prevention and treatment. In a meta-analysis in which 22 studies were included, none involving patients with SSc, supplementation with probiotics had a higher rate of decontamination [risk ratio (RR) = 1.61, 95%CI: 1.19-2.17, $P < 0.05$], reduction in H₂ concentration (WMD = -36.35 ppm, 95%CI: -44.23 to -28.47 ppm, $P < 0.05$), and improvement in abdominal pain score (WMD = -1.17; 95%CI: -2.30 to -0.04, $P < 0.05$) compared to the group without probiotics, but they were not effective in preventing SIBO[101]. Specifically, in patients with SSc, they have been used for the treatment of associated symptoms, such as bloating[102]. In a recent pilot clinical trial conducted in 40 patients with SIBO, after 2 mo of treatment, *Saccharomyces boulardii* alone and in combination with metronidazole eradicated it (33% and 55%, respectively) compared with metronidazole alone (25%). Additionally, it improved GI symptoms and had fewer adverse effects[103]. In general, after the administration of multistrain probiotics in patients with GI and SSc symptoms, adverse events are mild [104].

CIPO affects 3.9% of patients and is more frequent in dcSSc with a disease duration of more than 3 years[105]. In an analysis that included 175 patients with a history of pseudo-obstruction, CIPO was associated with male gender (HR = 1.75, 95%CI: 1.42-2.43), dcSSc (HR = 2.52, 95%CI: 1.59-3.99), myopathy (HR = 1.83, CI 95% 1.09-3.08), and the use of opioids (HR = 2.38, 95%CI: 1.50-3.78). The presence of anti-RNA polymerase III was negatively associated (HR = 0.34, 95%CI: 0.17-0.66) with CIPO[106]. In a study, 5.4% of hospitalizations were associated with intestinal pseudo-obstruction and higher in-hospital mortality in these patients[107]. It is a rare motility disorder with chronic and recurrent symptoms suggestive of intestinal obstruction in the absence of mechanical causes[108]. The main symptoms are nausea, vomiting, constipation, pain, and bloating. This disorder can be associated with SIBO, weight loss, and malnutrition [108]. X-ray examination reveals dilated intestinal loops and hydro-air levels in the

absence of a lesion occupying the lumen[108]. Abdominal radiography and computed tomography are used to rule out anatomic obstruction[23]. Often, it is not a clear diagnosis, and therapeutic options are limited. Treatment in patients with SSc is similar to that in patients with CIPO due to other causes, including prokinetics, such as erythromycin and metoclopramide, laxatives, and occasionally, enemas[109]. In severe cases that require hospitalization, most patients have spontaneous resolution with conservative management with measures, such as intestinal rest, compression with a nasogastric tube, intravenous hydration, and correction of hydroelectrolyte disorders[23]. Octreotide, an analog of somatostatin, can be used[23]. The surgical approach is generally not recommended due to the high risk of prolonged ileus or anastomotic failure[23]. Avoiding the use of opioids in high-risk patients can reduce CIPO events[5].

Additionally, a high prevalence of celiac disease has been reported in patients with SSc, mainly in dcSSc[110,111]; however, there are conflicting results[112].

Colon and rectum

Colonic involvement has been observed in 20% to 50% of patients and can manifest with different patterns of bowel habits, ranging from constipation to diarrhea, through other frequent manifestations, such as bloating, malabsorption, malnutrition, and gastrointestinal bleeding[113,114].

Constipation has been associated with multiple factors, such as the absence or decrease in contractions in the colon, as well as alteration of gastrocolic reflux, generating a decrease in colonic transit. This phenomenon arises from the combination of neuropathy with hypertrophy of the myenteric plexus and atrophy of the smooth muscle, resulting in a decrease in peristalsis, evidenced by the decrease in intestinal transit with abdominal distention and pain as well as colonic pseudo-obstruction, megacolon, fecal impaction, stercoraceous ulcer, and even volvulus[114,115].

Another anatomical phenomenon that arises from muscle atrophy is the presence of diverticula that are generally wide-mouthed and located on the antimesenteric border [114]. Images of patients with colonic involvement due to SSc show diverticula in 42% of patients and dilation of the colon with loss of haustra in 50% of patients[116]. The approach to treating these patients involves identifying possible drugs that cause intestinal transit alteration, as well as rectal examination and the performance of colonoscopy, especially in patients with alarming symptoms, such as weight loss or rectal bleeding[115].

Other studies that may be useful have examined colonic transit by radiopaque markers, scintigraphy, or wireless motility capsules, although they are not regulatory for the approach of these patients, showing times of longer colonic transit than healthy patients[115]. The management of this entity involves the use of prucalopride[117], lubiprostone, linaclotide, and plecanatide, and agents such as fiber generate greater abdominal distension and flatulence. The use of pyridostigmine has even been described for patients with more severe compromise and poor response to the other agents[118]. Another useful therapy is biofeedback, which is useful in patients with evacuation dysfunction documented by anorectal manometry, although it has not been specifically studied in patients with SSc[119]. In the case of identifying pseudo-obstruction or volvulus, the treatment is colonic decompression[120]. A retrospective study that evaluated more than 900 patients over a period of approximately 45 years observed that nonsurgical management based on detorsion was successful in 77.1% of patients, with success being greater in the group of patients who underwent rigid sigmoidoscopy, although 26.4% of patients with endoscopic signs of intestinal gangrene or early recurrence had to undergo emergency surgical management[120].

Fecal incontinence has been found in 20%-39% of patients[121,122]. However, the prevalence of fecal incontinence was determined from small cohorts. The diagnosis of this entity is established with the clinical history, as well as the use of diagnostic tools, such as high-resolution anorectal manometry, endo-anal ultrasound, and less commonly, electromyography[115].

Among the most important findings, an abnormal internal anal resting pressure with a decrease in the resting pressure of the anus rectum has been described[123], as well as an alteration in the maximum voluntary contractions of the external anal sphincter and a reduction or absence in the rectoanal inhibitory reflex[124]. Generally, the treatment of this complication is medical with medications that decrease peristalsis, as well as behavioral therapy with biofeedback[125]. However, the results have been disappointing; therefore, alternatives, such as surgical repair of the anal canal, stoma with defunctionalization, and stimulation therapy for the sacral nerve, have been explored[126].

CONCLUSION

GI involvement is common in patients with SSc. Symptoms can occur before skin involvement. GI compromise can affect any organ of the GIT from the mouth to the anus, mostly affects the esophagus, SB, and rectum. Early diagnosis is key in management to achieve symptomatic control and improve prognosis.

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