Evaluation of gastrointestinal involvement in scleroderma

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'Involvement of the gastrointestinal tract in SSc is extremely frequent; it is a leading cause of morbidity and the third most common cause of mortality in this disease'

Scleroderma (SSc) is a multisystem disease characterized by functional and structural abnormalities of small blood vessels, fibrosis of the skin and internal organs, immune system activation, and autoimmunity. The cause of SSc is unknown. An integrated hypothesis of the pathogenesis of SSc includes a combination of abnormalities in the vascular and immune systems on a background of genetic susceptibility and in the presence of environmental stimuli. This leads to further augmentation of the immune system's activation and, ultimately, to fibroblast proliferation, collagen deposition and destruction of normal tissue architecture [1]. A growing body of evidence suggests that a complex cascade of primary and secondary mediators, such as growth factors, chemokines and endothelin (ET)-1, play a crucial role in the disease pathophysiology [2–4].

The vascular hypothesis suggests that the primary event in SSc occurs at the level of capillaries and small vessels, and manifests as endothelial cell injury and activation. An increased expression of adhesion molecules (selectins, integrins and members of immunoglobulin superfamily) on endothelial cells, lymphocytes and fibroblasts mediate cell–cell and cell–matrix interactions and leads to increased recruitment of inflammatory cells and their binding to endothelial cells and fibroblasts [5,6]. The activation of the immune system is of paramount importance in the pathogenesis of SSc. B cells from SSc patients exhibit an increased expression of CD19 that induces SSc-specific autoantibody production in transgenic mice. Similarly, B cells from a tight-skin mouse (a model of SSc) show augmented CD19 signaling and chronic B cell activation.

CD19 loss results in inhibition of chronic B cell hyper-reactivity and elimination of autoantibody production, which is associated with improvement in skin fibrosis and a parallel decrease in interleukin (IL)-6 production by B cells [7]. Alternatively, B cells regulate T-cell activation through their antigen-presenting and costimulatory abilities [8]. Following the activation of lymphocytes and monocytes, multiple profibrotic cytokines and chemokines are released. These factors are important mediators in modulating leukocyte–endothelial interactions: they may damage endothelial cells and activate and modulate behavior of fibroblasts. As a consequence of these processes, the activated fibroblasts synthesize excessive extracellular matrix components, which accumulate in diverse organs and lead to the final stage: fibrosis [9–11].

One of the key factors implicated in SSc is ET-1. ET-1 is a potent profibrotic cytokine released from damaged or activated endothelial cells, with multiple biological effects, such as stimulation of extracellular matrix biosynthesis, neutrophil adhesion, platelet aggregation and reduction of matrix-degrading enzymes production [12–14]. ET-1 has also been shown to modulate the interaction between lymphocytes and fibroblasts, to induce expression of intercellular adhesion molecule-1 on fibroblasts and thereby to act as a potent proinflammatory mediator with immunoregulatory functions for immune cells infiltrating and binding to connective tissues [15]. ET-1 induces the production of cytokines and growth factors such as vascular endothelial growth factor and basic fibroblast growth factor-2 [16–19], and has a proliferative effect on vascular smooth muscle cells and fibroblasts [20].

Two other key factors overexpressed in SSc and highly involved in its pathogenesis are transforming growth factor (TGF)-β and connective tissue growth factor (CTGF). TGF-β promotes deposition of extracellular matrix by inducing expression of matrix genes and decreasing the expression of matrix metalloproteinases, while increasing that of tissue inhibitors of metalloproteinases [21–23]. TGF-β may also regulate collagen production indirectly, by its effect on other cytokines and growth factors. TGF-β produces upregulation of platelet-derived growth factor (PDGF)α receptors upon continual stimulation of SSc fibroblasts [24] and induces endothelial cell production of

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ET-1 [25]. CTGF has been directly implicated in the excessive matrix deposition characteristic of SSc lesions. CTGF promotes fibroblast proliferation, matrix production, granulation tissue formation and cell adhesion and migration in a wide variety of cell types [26,27]. In contrast to the situation in normal dermal fibroblasts, CTGF is constitutively overexpressed in dermal fibrotic lesions, such as in SSc [28]. The elevated expression of the CTGF promoter in SSc fibroblasts appears to be independent of the Smad3 signaling pathway and of TGF-β response element [29,30]. Therefore, CTGF in SSc fibroblasts is not subject to the negative regulatory controls that normally suppress the TGF-β: induced wound-healing response. Whereas TGF-β is essential for the initiation of fibrosis, it is the persistent TGF-β-independent CTGF expression that may result in a sustained fibrotic response [31,32].

Emerging data suggest that chemokines may be essential contributors to tissue damage in SSc. Monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α, RANTES protein and IL-8 have been found in increased amounts in blood or involved tissue from SSc patients [33,34].

These chemokines act through several pathways and mechanisms, including attraction of inflammatory cells, direct action on target cells (e.g., as fibroblasts and endothelial cells), stimulation of production and activation of TGF-β, stimulation of extracellular matrix production and stimulation of angiogenesis, a necessary process for the influx of fibroblasts and inflammatory cells that are required for fibrosis to develop [35]. In another profibrotic pathway, MCP-1 inhibits alveolar epithelial cell-derived prostaglandin E2 synthesis, resulting in enhanced proliferation of fibroblasts [36].

Gastrointestinal tract: involvement & assessment

Involvement of the gastrointestinal tract (GIT) in SSc is extremely frequent; it is a leading cause of morbidity and the third most common cause of mortality in this disease. Esophageal abnormalities occur in up to 90% of patients, stomach involvement can be documented in 50% or more of patients, and small bowel, colonic and anorectal involvement occur in 50–70% of SSc patients [37–39].

The pathogenesis of GIT involvement is thought to include early vascular damage to the vasa nervorum of the nerves innervating the GIT. This leads to neurological dysfunction, particularly involving autonomic pathways [40,41]. The activation of the immune system may contribute to neurological dysfunction, by production of antibodies which specifically inhibit M3-muscarinic receptor-mediated enteric cholinergic neurotransmission [42]. With damage to innervation, the smooth muscle atrophies and is eventually replaced by fibrotic tissue. With increasing atrophy and tissue replacement, the GIT becomes progressively less effective and less responsive to therapeutic agents [43].

There are no data regarding the role of gastrointestinal hormones and peptides (e.g., bombesin, ghrelin and leptin) in GIT involvement.

Signs & symptoms

Motility disorders are the main manifestation of GIT involvement in SSc. The clinical spectrum ranges from asymptomatic to severe paresis and may affect any area from the esophagus to the anus [39,41,44].

Esophageal involvement is the most frequent gastrointestinal manifestation of SSc and occurs in up to 90% of patients. Heartburn and dysphagia are the most common complaints. Additional complaints include hoarseness, atypical chest pain, nocturnal cough and regurgitation [38]. Esophageal dysmotility and gastroesophageal reflux disease (GERD) occur in the majority of SSc patients. Late complications include esophageal stenosis, strictures and, ultimately, intestinal metaplasia. The prevalence of Barrett's esophagus in SSc was found to be 12.7%, which is similar to the prevalence in patients with gastroesophageal reflux disease [45]. Whether these patients have an increased risk of developing esophageal carcinoma is not as clear, due to the low prevalence of esophageal carcinoma in SSc patients [46]. Gastric dysfunction has been reported in 50% of SSc patients [47]. Gastric dysmotility may lead to symptoms of nausea, vomiting, regurgitation, early satiety, abdominal bloating, heartburn and GERD. Autonomic dysfunction plays an important role in the pathogenesis of this dysmotility [40].

Small-bowel involvement has been reported in 50–70% of SSc patients [37–39], and may lead to high morbidity and life-threatening complications, such as severe malabsorption and pseudo-obstruction. Small bowel hypomotility induces stasis of intestinal contents and bacterial overgrowth, which contribute to bloating, abdominal pain, nausea, vomiting, malabsorption, diarrhea and weight loss [48]. Bacterial overgrowth has been detected in 62.5% of a

group of SSc patients [49]. Pneumatosis cystoides intestinalis (PCI) is a rare complication of SSc and is considered a poor prognostic sign [50,51]. PCI is characterized by development of multiple intramural air-filled cysts, secondary to anerobic bacterial overgrowth in the intestine and increased intraluminal production of hydrogen. The cysts may rupture and cause pneumoperitoneum and secondary peritonitis. The risk of perforation is already increased in SSc patients due to fibrosis and loss of compliance of intestinal wall [50,51].

The colon is frequently involved in SSc, although it is not always symptomatic. Abnormal motility pattern has been found in 75% of asymptomatic SSc patients [52]. Constipation secondary to prolonged colonic transit time develops in 34% of patients. Alternatively, 79% of patients complain of episodic diarrhea, due to bacterial overgrowth and malabsorption [53]. Fecal incontinence is an under-reported, but a frequent complication of SSc. A total of 15–37% of patients suffer from incontinence [53,54].

Vascular lesions of the mucosa may cause severe anemia in SSc patients. The lesions may be scattered throughout the entire intestine or may involve only the stomach cardia. This was previously named 'watermelon stomach' and is now termed gastric antral venous ectasia (GAVE) [55].

Assessment tools

There is no single measure to assess the extent and severity of GIT involvement in SSc patients (tables 1–4). Although several modalities are available to investigate esophageal motility disorders (e.g., manometry, myoelectric change, biopsy and transit times), manometry is the preferred one. Manometric abnormalities (hypomotility and reduced lower esophageal sphincter pressure) are documented in 80–85% of SSc patients [56–58]. Approximately a third of patients with abnormalities are asymptomatic [56,59], while 20% of patients have esophagus-related symptoms and normal esophageal function [39,60]. Acid esophagitis is a very common symptom/sign in SSc. For assessment of acid esophagitis, esophageal pH studies are potentially the most useful test, providing 24 h assessment of the duration of acid reflux, degree of symptom correlation and allowing the opportunity to track response to therapy. In non-SSc patients with symptoms of esophagitis, pH monitoring had a 26% false-negative rate [61,62].

A combination of manometry and pH monitoring may increase the sensitivity and the positive and negative predictive value in assessing esophageal involvement in SSc. Gastroesophageal endoscopy is a reliable measure to assess the complications of gastroesophageal reflux, such as Barrett's esophagus, stricture and carcinoma, and to rule out other causes of dysphagia.

Stomach and small bowel gamma camera scintigraphy has been used extensively in research and clinical practice, and is regarded as the preferred test in the evaluation of gastric motor function, especially in impaired gastric emptying and antral motor function [62]. However, scintigraphic imaging involves exposure to radiation, is relatively costly and time-consuming, and there is marked within-patient variability (intraindividual coefficient of variation of almost 15% in healthy individuals) [62]. Octanoic acid breath test (^{13}C bound to a medium-chain triglyceride) is a promising test for the assessment of gastric-emptying. It avoids radiation and can be applied at the bedside or in the community. Studies have reported good correlation between the gastric emptying parameters determined by breath test and by scintigraphy, and a high degree of intraindividual reproducibility (mean coefficient of variation 12%) [63], although other studies demonstrate variable results [64,65]. More studies are needed to evaluate the accuracy of the test in patients with accelerated or markedly delayed gastric emptying. Barium studies of the upper GIT are widely available, inexpensive and are best used to define anatomy and to rule-out a mechanical obstruction. This test is not a measure of gastric function or motility, although prolonged retention of barium in the stomach (>6 h) is suggestive of gastroparesis [66].

Small intestinal manometry may be useful in assessing basal small-bowel motility in SSc patients and in documentation of outcome. The prevalence of abnormal motility pattern consistent with neuropathic and myopathic dysfunction was found to be as high as 80–88% in SSc patients, disregarding symptomatic status [67,68]. A small study regarding the outcome of intestinal involvement in SSc patients exhibited deterioration of small-bowel activity on manometry in all eight evaluated patients at 5-year follow-up [69]. Small-bowel series and computed tomography (CT) enterography are useful in the assessment of intestinal pseudo-obstruction. Their main goal is to rule-out mechanical obstruction. The finding of multiple sites of abnormality within the gastrointestinal tract provides strong evidence for chronic intestinal pseudo-obstruction [70].

The gold standard for diagnosis of bacterial overgrowth has been quantitative culture of an aspirate of luminal fluid from the jejunum.

Table 1. Assessment tools, usefulness and validity in SSc for the esophagus.

Test	Reflux	Esophagitis	Motility	Stricture	Barrett esophagus	Validated in SSc
UGI study	+	+/-	+	+++	-	Yes
Scintigraphy (isotope scan)	++	-	++	-	-	Yes
UGI endoscopy	-	+++	+/-	++	+++	Yes
Biopsy plus histology	-	+++	-	+++	+++	Yes
Manometry	-	-	+++	-	-	Yes
pH monitoring	+++	-	-	-	-	Yes
VCE (pill cam)	-	+++	+/-	C/I	+++	No

C/I: Contraindicated; SSc: Scleroderma; UGI: Upper gastrointestinal tract; VCE: Video capsule endoscopy.

Growth of 10 million or more organisms per ml in either aerobic or anaerobic conditions is the criterion for a positive culture. Problems with use of jejunal cultures as a test for bacterial overgrowth include lack of standardization of the collection method, the requirement for intubation of the upper gastrointestinal (GI) tract and their relative high cost. Various breath tests have been proposed as noninvasive tests for small intestinal bacterial overgrowth. Bile acids or hydrogen breath tests have reasonable content validity versus bacterial counts from the jejunum [71]. The sensitivity of bile acid breath test is 0.70 and its specificity ranges from 0.87 to 0.90 [71]. However, this test has never received widespread acceptance in the USA, probably owing to problems with both false positives and false negatives [72,73].

A widely available alternative breath test uses nonradioactive glucose and measures breath hydrogen excretion as the signal. As in other breath tests, sensitivity and specificity vary widely, in this case from 62 to 93% and from 78 to 100%, respectively [72,74,75]. The D-Xylose test correlates with fecal fat and jejunal flora, and was found to be abnormal in 13% of SSc patients [76,77]. It was also able to demonstrate change when antibiotics were used to document response with respect to malabsorption. The lactulose test examines small intestinal permeability, but there are very little data with respect to this test in SSc [77]. The 72-h fecal fat test on a 100-g fat diet revealed a 100% abnormality among SSc patients with x-ray abnormalities, and was sensitive to change when giving pancreatic enzymes. It also appeared to respond to antibiotics in patients with malabsorption [76,78]. Unfortunately, this is not an easy test and its feasibility when performing 72 h fecal fat collections is relatively low.

Serum levels of B12, folic acid, iron, carotene, vitamins A and D, homocysteine and prothrombin time are helpful and sensitive in evaluating malabsorption and nutritional deficits [79].

Endoscopy of the large bowel is an essential part of the examination of every new patient with constipation, anorectal symptoms or lower GI bleeding. It may provide information regarding benign or malignant obstructing lesion and mucosal inflammation (although there is no increased risk of colon cancer in SSc) or the cause of bleeding, such as telangiectasias or watermelon rectum. The value of this procedure in asymptomatic patients is questionable.

Anorectal manometry is a sensitive measure for anorectal motility problems in SSc. This test is as frequently abnormal as esophageal motility [80,81], and includes a number of specific tests that are helpful in the diagnostic assessment of these patients and in delineating the pathophysiological mechanism. Anorectal manometry can measure sphincter pressures with reasonable reproducibility, but normal ranges must be established in each laboratory for each technique used. Controlled clinical trials validating the usefulness of anorectal manometry in the diagnosis and

Table 2. Assessment tools, usefulness and validity in SSc for the stomach.

Test	Gastroparesis	GAVE	Validated in SSc
UGI study	+	-	Yes
UGI endoscopy	+	+++	Yes
Isotope scan	+++	-	Yes
VCE	C/I	+++	No
Octanoic acid breath test	+++	-	No

C/I: Contraindicated; GAVE: Gastric antral vascular ectasia; SSc: Scleroderma; UGI: Upper gastrointestinal tract; VCE: Video capsule endoscopy.

Table 3. Assessment tools, usefulness and validity in SSc for the small bowel.

Test	Motility	Structure	Bacterial overgrowth	Absorption	Validated in SSc
UGI study	+	++	_	+/-	No
Manometry	+++	-	_	_	Yes
VCE	+/-	+++	-	-	No
CT enterography	-	+++	_	-	No
Breath tests	+	-	+++	++	No
Jejunal cultures	-	-	+++	-	No

CT: Computed tomography; SSc: Scleroderma; UGI: Upper gastrointestinal tract; VCE: Video capsule endoscopy.

treatment of constipation are needed. Clinical practice and uncontrolled studies suggest that the indications for anorectal manometry are [82]:

- Fecal incontinence: to define functional weakness of one or both sphincter muscles;
- Prediction of responses to biofeedback training, where, of course, the manometry itself is used to provide the feedback for the training.

Surface electromyography (EMG) appears to have a definite role in the evaluation of sphincter fecal incontinence. EMG has been used in assessment of damage to the innervation of the external anal sphincter in patients with fecal incontinence (damage to the pudendal nerve); however, these EMG findings have not been validated against histological evidence of damage [80,83]. The severity of EMG changes is not correlated with the magnitude of incontinence [84,85]. There are no studies regarding anorectal EMG in SSc. Barium enema is not usually necessary for assessment of the anorectal area in patients with fecal incontinence or constipation, except to help exclude intraluminal mucosal disease or to assess bowel dilation. Endoanal ultrasound and MRI can identify anal sphincter structural pathology, which may be clinically occult, and/or amenable to surgical repair. Only MRI can identify external sphincter atrophy, whereas ultrasound is more sensitive for internal sphincter imaging [86]. There are no studies regarding use of endoanal ultrasonography in SSc. Endoanal MRI in SSc patients with fecal incontinence demonstrates anterior sphincter deformity and slower gadolinium-enhancement pattern on dynamic studies of the internal sphincter: abnormalities that are absent in patients with incontinence from other causes [87].

Colon transit studies are useful for objective confirmation of patients' subjective complaint of constipation and/or decreased bowel frequency, confirmation of slow transit and documentation of regional delays in transit [80].

There is need for accurate data on the frequency of gastric and intestinal vascular malformations in SSc. Video capsule endoscopy (VCE) is a promising test for assessing intraluminal small-bowel pathology [88], its use might be hampered by the dysmotility problems and stenosis; however, its feasibility must be assessed in SSc.

Table 4. Assessment tools, usefulness and validity in SSc for the colon.

Test	Motility	Structure	Continence	Vascular malformations	Validated in SSc
Colonoscopy	-	+++	-	+++	No
Barium enema	-	++	-	-	No
CT colography	-	+++	-	-	No
Manometry	+++	-	+++	-	Yes
EMG	-	-	+++	-	No
MRI	-	+++	+++	-	Yes
Endoscopic US	-	+++	+++	-	No

CT: Computed tomography; EMG: Electromyography; MRI: Magnetic resonance imaging; SSc: Scleroderma; US: Ultrasonography.

Although the GIT is frequently involved in SSc patients, the measures used to assess the degree of involvement suffer from lack of data regarding their content/convergent validity, reproducibility/reliability and their sensitivity to change.

While there is no validated questionnaire specifically designed for gastrointestinal involvement in SSc, the visual analog scale of the Health Assessment Questionnaire (HAQ), modified for SSc, is available [89,90]. It is limited in its specifics and a more comprehensive, symptom based, patient-performed tool is needed.

Symptom-based questionnaires have been proven useful in the assessment of disease activity in diseases involving the gastrointestinal tract, such as inflammatory bowel diseases. Crohn's Disease Activity Index (CDAI) is calculated based mostly on symptoms and a few objective clinical data, and is used successfully to assess disease activity response to therapy and remission in clinical studies. Development of a validated questionnaire that is SSc-GI specific may help predict prognosis and provide information about any relationship of the GI tract lesions to skin and other visceral involvement.

Although the GIT is frequently involved in SSc, the impact on quality of life is underappreciated. Social activities and quality of life were found to be impaired in 20% of SSc patients with intestinal problems [53]. Decreased functional status and abnormal GI functioning are significantly correlated with depression among patients with SSc [91].

We and our colleagues are currently working on a symptom-based questionnaire to assess the activity and severity of gastrointestinal involvement in SSc, and to validate it against a combination of imaging techniques, laboratory measures and patient's well-being and function questionnaires.

Current therapy

To date, the management of GIT involvement in SSc remains empirical and symptom driven. We will describe the principle therapies presently used for SSc-GIT involvement, partly to demonstrate the paucicity of such treatments in SSc (Table 5).

Symptomatic esophageal disease is effectively treated in most cases with proton-pump inhibitors (PPIs). PPIs have become the standard medical therapy for GERD, particularly for severe or complicated disease. PPIs more effectively inhibit gastric acid secretion than histamine-2-receptor antagonists, and are highly efficient in healing reflux esophagitis, even when severe (healing rate of 80% of severe cases) [92]. 50% of the patients may require two- to fourfold of the recommended dose [92]. Modification of lifestyle (ingestion of small meals, avoidance of large meals within 3 h of bedtime, avoidance of fatty meals, alcohol and other antireflux measures) is beneficial [92].

Another set of medications, prokinetic drugs, are more effective in the early stage of disease, prior to replacement of smooth muscle by fibrous tissue [93]. In the gut, serotonin (5-hydroxytryptamine [5-HT]) exerts a variety of effects on intrinsic enteric neurons, extrinsic afferents, enterocytes and smooth muscle cells. 5-HT plays a major part in the complex regulation of gastrointestinal motility through multiple receptor types [94]. Metoclopramide, an antagonist of 5-HT3 and dopamine (D2) receptors, induces release of acetylcholine in the myenteric plexus. The drug may improve symptoms of GERD by increasing the lower esophageal pressure, and it is indicated for treatment of gastroparesis in SSc [95]. Metoclopramide was less effective in late diffuse SSc patients (mean disease duration of 9.5 ± 2.5 years), although it still significantly increased lower esophageal pressure [96]. It has little effect on small-bowel function and colon. The drug exhibits central antiemetic activity, but extrapyramidal side effects related to its dopaminergic antagonist properties limit its usefulness [37].

Cisapride improves motility throughout the GIT in SSc, by its agonist action on the 5-HT4 receptor and by enhancing release of acetylcholine in the myenteric plexus [97,98], but it is now under restricted use due to its potential cardiac toxicity [99]. Tegaserod, a 5-HT4 receptor partial agonist, has been approved by the US FDA for treatment of women with constipation-predominant irritable bowel disease or functional constipation. Tegaserod was found to accelerate transit time in small intestine and colon, and to increase gastric emptying [100]. There are no trials regarding its use in SSc. Due to its motilin agonist properties, Erythromycin stimulates gastric and gall bladder emptying, and enhances intestinal motility when given in small doses, although most patients develop tachyphylaxis after several weeks of therapy [38]. Restarting the medication after a period of 4–6 weeks free of drug restores its effectiveness in most patients [66]. Domperidone is a D2 receptor-blocking agent, which has been demonstrated to increase gastric emptying and to relieve pseudoobstruction, but

Table 5. Therapies in SSc: gastrointestinal problems.

Problem	Treatment	Dose range	Proven in SSc	Proven in other disease	Ref.
GERD	PPI (omeprazole)	20–80 mg/day	Yes	Yes	[91,92]
	Lifestyle changes		Yes	Yes	[91]
Gastroparesis	Prokinetic drugs				
	Metoclopramide	10 mg t.i.d.	Yes	Yes	[94,95]
	Domperidone	10 mg t.i.d.	Yes	Yes	[100]
	Cisapride	10–20 mg b.i.d.–q.i.d.	Yes	Yes	[96,97]
	Erythromycin	50–100 mg q.i.d.	Yes	Yes	[38,58]
	Tegaserod	6 mg b.i.d.	No	No	[99]
	Gastric pacing		No	No	
Intestinal pseudo-obstruction (prokinetic drugs)	Domperidone	10 mg t.i.d.	Yes	Yes	[100]
	Cisapride	10–20 mg b.i.d.-q.i.d.	Yes	Yes	[96,97]
	Tegaserod	6 mg b.i.d.	No	Yes	[99]
	Octreotide	50 mcg	Yes	Yes	[101]
	Octreotide plus erythromycin	50 mcg + 200 mg t.i.d.	Yes	Yes	[102]
	Elemental diet, correct nutritional deficiencies			Yes	[75]
Intestinal pseudo-obstruction (antiobiotics)	Amoxicillin-clavulanic acid	500 mg t.i.d.	No	Yes	[75]
	Ciprofloxacin	250 mg b.i.d.			
	Doxycycline	100 mg b.i.d.			
	Metronidazole	250 mg t.i.d.			
	Neomycin	500 mg q.i.d.			
	Parenteral nutrition (severe cases)		Yes	Yes	[104,105]
Fecal incontinence	Biofeedback plus diet		No	Yes	[106]
	Antidiarrheal agents		No	No	[106]
	Sacral nerve stimulation		Yes	Yes	[107]
	Artificial sphincters		No	Yes	[107]
GAVE	Endoscopic ablation techniques		Yes	Yes	[108–111]

b.i.d.: Twice daily; GAVE: Gastric antral venous ectasia; GERD: Gastroesophageal reflux disease; PPI: Proton pump inhibitor; q.i.d.: Once daily; SSc: Scleroderma; t.i.d.: Three-times daily.

it is only useful in mild cases [38,101]. In a small study of five SSc patients and six healthy controls, the somatostatin analog, octreotide, was found to be effective in pseudo-obstruction secondary to SSc, by inducing intestinal motility in all patients and reducing bacterial overgrowth [102]. Combination therapy with erythromycin and octreotide might demonstrate additive benefits. Administration of erythromycin and octreotide for 20–33 weeks was demonstrated to induce long-term benefit in five of 14 SSc patients with pseudo-obstruction [103].

Gastric electrical stimulation by an implantable neurostimulator is a new and promising treatment option in severe gastroparesis, although it has not been validated in SSc [58].

Bacterial overgrowth is treated with antibiotics given intermittently or in rotation. Effective antibiotic treatment must cover both aerobic and anaerobic enteral bacteria. The most used regimens include metronidazole, quinolones, tetracyclines and amoxicillin-clavulanic acid [38].

A single short course of an antibiotic (7–10 days) may improve symptoms for up to several months in 46–90% and render breath tests negative in 20–75% of patients with bacterial overgrowth. However, patients with intestinal failure may require either repeated or continuous rotating courses of antibiotics [79,104]. There are no trials regarding the efficacy of these regimens in SSc. In patients with malabsorption, supplemental oral nutrition, elemental diet, medium-chain triglycerides and fat-soluble vitamins should be used. In more severe cases, evaluation for tube feeding or total parenteral nutrition (TPN) should be considered. Patients may do well for years with TPN administration: 11 of 15 SSc patients with severe GIT involvement demonstrated improved quality of life following long-term, home central venous hyperalimentation. Two cases of septicemia and two cases of superior vena cava obstruction were reported, but there were no other serious side effects [105,106]. Dietary adjustments, antidiarrheal agents and behavioral therapy with biofeedback may be effective in patients with fecal incontinence, although the available data are inconclusive [107]. Surgery should be avoided, as SSc patients tolerate this poorly and it should be considered only in severe cases. Implantation of sacral nerve stimulators and artificial sphincters might be an effective alternative to surgery [108]. In a small study, fecal continence was regained in four of five SSc incontinent patients following sacral nerve stimulators [108]. There are no data concerning artificial sphincter use in SSc.

Vascular lesions (GAVE) are successfully treated by endoscopic ablation techniques such as multipolar electrocoagulation, argon plasma coagulation, heat probe and laser therapy [109,110]. Multipolar coagulation generates heat when high-frequency current is passed from one or more electrodes through a small volume of tissue to one or more electrodes built into the same accessory. The resulting heat can produce cutting or coagulation. Argon plasma coagulation is a noncontact method that uses ionized argon gas to perform electrocautery. The ablation is more superficial, so the risk of perforation is lowered. In addition, the procedure is less expensive than laser. Yttrium aluminium garnet (YAG) laser can provide deep-tissue penetration and coagulation. It is a highly efficient therapy, but, unfortunately, lasers are expensive and their use is technically demanding. Endoscopic thermal ablation effectively controls acute bleeding and abolishes or reduces transfusion requirements in 85–93% of patients with GAVE (including SSc patients) [111,112]. Most patients require a mean of six treatment sessions [112]. Side effects of all endoscopic ablation techniques may include iatrogenic ulceration at the site of treatment, bleeding and transient abdominal pain. Antral scarring and hyperplastic polyps have also been reported after APC or YAG laser [109].

Future perspective

It is clear that there is no single measure to evaluate GI tract involvement in SSc patients. The development of accurate clinical, biochemical, functional and imaging assessment tools sensitive to the disease stage will facilitate research into new technologies and therapies directed to alter the development and progression of SSc-GIT disease. Potential therapeutic interventions include biologic therapies, bioengineered antibodies or small molecules, resetting the immune system, improvement of the vascular function by growth factors (e.g., implant of endothelial progenitor cells).

Extracellular blockade of the TGF-β signaling axis, involving interference at the level of the ligand or of its receptor, represents a potential molecular strategy to ameliorate the fibrotic process in SSc. Other potential and interesting targets are PDGF, anti-CD20 depletion therapy and chemokines such as macrophage inflammatory protein-1, monocyte chemotactic protein-1 and IL-8.

Technological improvements achieved in general gastroenterology will be increasingly applied in SSc patients (e.g., the ability to visualize the small bowel by VCE and double-balloon endoscopy), thereby increasing therapeutic opportunities to improve access throughout the entire GIT. To date, there are no clinical or laboratory markers to assess fibrosis. Development of such markers may play a future role in the evaluation of the response to fibroblast-targeting therapeutic strategies in SSc patients. New devices and procedures are continuously evolving for motility and incontinence problems. It is hoped that research regarding the role of the endocannabinoid system and neurokinins in SSc-related motility disorder might reveal new promising therapeutic targets.

Acknowledgements

We wish to thank Elaine Furst for her help in editing this article.

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