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Gastrointestinal Involvement in Systemic Sclerosis: Overview, Neglected Aspects, Malnutrition, Body Composition and Management

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Abstract

Gastrointestinal tract (GIT) involvement is the most common internal organ manifestation and is present in up to 90% of patients with systemic sclerosis (SSc). Clinical manifestations can differ according to the part of the GIT affected, disease course and symptoms. A majority of the symptoms are caused by GIT dysmotility. Up to 8% of SSc patients develop several GIT symptoms, which increase the mortality. Although GIT involvement is rarely the direct cause of death, it can lead to several comorbidities including malnutrition and negative alterations of body composition. These factors have a negative impact on quality of life and increase the mortality. To date, the treatment is rather symptomatic. The pathogenesis of GIT involvement in SSc still remains to be clarified to improve the treatment approaches including intravenous immunoglobulins and microRNA interventions.

Keywords: gastrointestinal tract, systemic sclerosis, malnutrition, body composition, diagnosis, management

1. Introduction

Systemic sclerosis (SSc), characterised by autoimmune inflammation, vasculopathy and fibrotic tissue deposition as the main pathophysiological features, can affect any organ system. In fact, the aetiology and pathophysiology of SSc are still not completely elucidated [1]. Gastrointestinal tract (GIT) is one of the most commonly involved organ systems in SSc.

Up to 90% of SSc patients are affected by some degree of GIT fibrosis, with no difference in frequency in limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc) subsets. However, more severe involvement and increased mortality occur rather in dcSSc than lcSSc [2, 3]. Dysmotility is the cardinal pathological abnormality, which can affect any part of GIT and contributes to the majority of symptoms [4], which are mostly non-specific and overlapping for a particular anatomical site. GIT involvement varies in extent, severity and course and can manifest even in the absence of cutaneous disease [5].

The pathophysiology of GIT involvement in general corresponds to the skin and other organ involvement in SSc, with the main characteristic pathologic features: vascular abnormalities, immune cell infiltration in tissue, autoantibodies and typical extensive deposition of collagen fibres. This process leads to specific early myenteric neural dysfunction caused by autoantibodies and collagen deposition, vasculopathy in myointimal layer mainly in capillaries preceding the muscle changes, smooth muscle cell infiltration with mononuclear cells with consequent atrophy and fibrosis of enteric connective tissue [1, 6]. Regarding the aetiology, genetic component is supposed to play a significant role in GIT involvement. In the Canadian population study, in which SSc patients were classified according to the ethnicity, population of white patients had less severe GIT involvement compared to North American native population (including American Indians and others), suggesting a predisposition for severity and progression of the disease [7]. Another study identified some haplotypes in an American native population (Choctaw Indians) strongly associated with SSc and more severe progression of this disease (HLA-DRB1*1602, DQB1*0301 and DQA1*0501) [8]. Some studies have also reported high prevalence of *Helicobacter* infection in SSc patients, supporting the hypothesis of infectious aetiology [9]. Smoking has been identified as the only environmental factor associated with increased severity of GIT symptoms in SSc [10].

GIT involvement significantly impacts quality of life and contributes to depression, sleep disturbance and pain [11–13]. It also negatively influences the prognosis with up to 12% of mortality due to fibrosis of GIT and accompanying malnutrition [1]. Up to 8% of SSc patients can develop severe GIT symptoms, which lead to increased mortality with only 15% survival at 9 years [5].

2. Pathophysiology

The pathophysiology of GIT involvement in SSc is a complex process. Unfortunately, it is still poorly understood due to many reasons: heterogeneity of clinical manifestations, the lack of appropriate animal models and the paucity of studies examining the pathophysiology. The key pathogenic mechanisms of GIT involvement, similarly to SSc in general, include fibro-proliferative vasculopathy, immune dysfunction with the participation of various components of immune system and fibrosis [14].

Endothelial injury as the crucial event in SSc results in increased production of reactive oxygen species (ROS) and release of chemokines and growth factors. Recruited immune cells (B- and T-cells and pro-fibrotic macrophages) contribute to further release of ROS, cytokines and pro-fibrotic mediators [15]. These mechanisms lead to reduced blood flow in mucosa, endothelial cell apoptosis, perivascular infiltrates and thickening of the basement membrane [16–18].

The initial step in pathophysiology of GIT dysmotility is neuropathy, followed by myopathy and later by progress to fibrosis [19]. Specific autoantibodies isolated from serum of SSc patients (SSc-IgGs) were described to cause significant smooth muscle dysfunction [20]. The mechanism lies in inhibition of acetylcholine binding on the M3 receptors (M3-Rs) [21, 22]. The action of SSc-IgGs seems to be dependent on the disease stage: in early SSc there is higher affinity of SSc-IgGs to the M3-Rs of myenteric neurons, which represents the neuropathic damage. During the course of the disease, the affinity increases to both smooth muscle cells and myenteric neurons, representing the myopathic phase. This temporal increase of SSc-IgGs affinity could elucidate the progressive character of GIT involvement [14, 19, 23].

Presence and action of M3-R autoantibodies can explain the impaired GIT function explored by manometry before the occurrence of histological changes [14].

Neutralisation of M3-R antibodies by human intravenous immunoglobulins (IVIg) and its antigen-binding fragment F(ab)₂ might reverse the intestinal dysfunction and is considered as a potential therapy [19]. The ultimate smooth muscle cell atrophy and tissue fibrosis lead to the loss of GIT contractile function and disability to respond to any external stimuli; thus any treatment of dysmotility is futile [14].

Alterations in cell-mediated immunity have a significant role in SSc GIT involvement [24, 25]. Interleukin (IL)-4 stimulates type 2 helper (Th₂) polarisation of CD4⁺ T-cells, which is predominant in SSc. Th₂ cells further upregulate humoral immunity [15, 26]. CD4⁺ T-cells in immune cell infiltrates in gastric biopsy specimens with typically increased CD4⁺/CD8⁺ T-cell ratio can be responsible for pathogenic autoantibody production and fibrosis of GIT [14, 27]. Generalised fibrosis with increased deposition of collagens I and III in most layers (muscularis mucosae, submucosa and muscularis propria) was described in gastric wall biopsies, together with strong expression of fibrogenic cytokines (transforming growth factor- β and connective tissue growth factor) and α -smooth muscle actin [28]. Other factors contributing to fibrosis are reduction of matrix metalloproteinase-1 expression and damage and reduction of telocytes—specific stromal cells essential for extracellular matrix scaffolding [29, 30]. Moreover, consequent increased stiffness of GIT wall is an additional potential stimulus for further fibrosis [31].

In addition, differentially expressed microRNAs (miRNAs) targeting both inflammation and fibrotic pathways have a probable role in SSc pathogenesis [32, 33]. Depletion of the miR-29 family, which targets collagen gene expression and regulates fibrosis, probably leads to increased collagen deposition in tissues [34].

3. Clinical manifestations

As mentioned, any part of GIT can be affected, so the clinical manifestations vary according to the involved organ. Large proportion of patients are asymptomatic, or symptoms may be unspecific and overlapping [1]. Fibrosis and dysfunction of GIT lead to many complications, such as gastro-oesophageal reflux disease (GERD) with complications (oesophageal strictures, Barrett's oesophagus), dilation and non-compliance of the stomach (gastroparesis), small intestinal bacterial overgrowth (SIBO), colonic dilation and dysfunction of internal anal sphincter. The vasculopathic manifestations are gastric antral vascular ectasia (GAVE), small intestine vascular ectasia and diverticula in the oesophagus, small intestine and colon, resulting in malabsorption and faecal incontinence [14]. Clinical features are divided according to individual organ involvement.

3.1 Oral cavity and pharynx

There are numerous SSc-related alterations of the oral cavity [35]. Pathognomic fibrosis results in characteristically reduced oral aperture (microstomia), thickening of the sublingual fraenum and widening of periodontal ligaments [36]. In addition, secondary Sjögren's syndrome, reported in about one fifth of SSc patients, can lead to tooth loss along with above-mentioned pathologies. All these factors complicate dental hygiene and food intake and contribute to malnutrition [37]. Up to 20% of SSc patients can develop mandibular resorption predisposing to pathological fractures, osteomyelitis and trigeminal neuralgia [38]. Oropharyngeal

dysphagia manifests in 25% of SSc patients and is caused both by dysmotility and GER as a reflex mechanism [39]. Apart from malnutrition, dysphagia is also a risk factor for aspiration pneumonia [40]. With regard to malignancy, risk of tongue cancer (squamous cell carcinoma) has been reported in dcSSc 25-fold higher compared to general population [41].

3.2 Oesophagus

Oesophageal dysfunction appears to be the most common GIT manifestation in SSc affecting up to 90% SSc patients with higher prevalence and tendency to deteriorate over time in dcSSc compared to lcSSc [42, 43]. Up to 30% of SSc patients may suffer from asymptomatic oesophageal involvement [44]. The main feature of oesophageal involvement is dysphagia due to smooth muscle cell atrophy and destruction of neuronal complexes. Drug-induced dysphagia and *Candida* oesophagitis caused by immunosuppressive treatment should be also taken into account. Reduced lower oesophageal sphincter (LES) tone along with dilation of the lumen, peristalsis disorder and gastroparesis is the main predisposing factor for GERD and consequent complications. Among typical symptoms asthma should not be omitted when taking patient's history [14, 42].

Long-standing GERD results in development of distal reflux oesophagitis and eventually progresses to peptic strictures and Barrett's oesophagus (BE) formation. The prevalence of BE is reported to be 12.7% in SSc patients treated with proton-pump inhibitors (PPIs) [45]. Approximately 20% of these patients develop dysplasia and are at higher risk of adenocarcinoma compared to SSc patients with BE and without dysplasia. However, this risk seems not to be increased in SSc compared to general population with GERD [45, 46].

The recent high-resolution manometry study reported positive correlation of severe oesophageal dysmotility with the duration of SSc and presence of interstitial lung disease (ILD) [47]. GERD can contribute to the emergence of ILD and worsen the ILD in SSc by microaspiration of gastric content; therefore, early diagnosis and administration of high-dose PPI therapy are needed [48, 49].

3.3 Stomach

Gastric involvement leads mainly to gastroparesis and GAVE [50]. Gastroparesis manifests clinically by early satiety, nausea and vomiting, epigastric discomfort and bloating and may progress to complete food intolerance [51, 52]. GAVE, also called "watermelon stomach", is considered a macroscopic manifestation of SSc vasculopathy, corresponds with skin telangiectasias and is associated with Raynaud's phenomenon [53, 54]. The prevalence of GAVE in SSc ranges from 6 to 22% [53–56]. It usually occurs within the first few years from the onset of the disease. Nevertheless, it can also be the first SSc manifestation in the absence of cutaneous involvement, clinically expressed as anaemia of combined aetiology: iron deficiency (sideropenia) and chronic bleeding (occult bleeding, melena or haematemesis) [56]. The presence of GAVE correlated negatively with the positivity of anti-topoisomerase I antibodies, but, in one study, was not associated with anti-RNA polymerase III autoantibodies (anti-RNAP3) [54]. However, on contrary, an association was confirmed in the recent study of EUSTAR population, where 48% of patients with GAVE had anti-RNAP3 positivity compared to 16% of SSc patients without GAVE. Of note, the autoantibody profile was not available for the whole cohort of SSc patients included [57]. A more recent study of EUSTAR population including almost 5000 SSc patients assessing the association of anti-RNAP3 autoantibodies with clinical features and risk of malignancies reported,

among other results, a negative association of anti-RNAP3 with GERD and a positive association of anti-RNAP3 with GAVE (more than eight times increased risk of GAVE in anti-RNAP3-positive patients than in anti-RNAP3-negative SSc patients) [58]. The association with specific antibodies and its potential clinical use is a quest for further studies.

3.4 Small intestine

The small intestine belongs to the most commonly affected organ of GIT involvement in SSc, after the oesophagus and anorectum. Decreased motility results in typical complications, which participate in malabsorption and malnutrition: local small bowel dilation, intestinal pseudo-obstruction and SIBO, development of pneumatosis cystoides intestinalis (PCI) and jejunal diverticula [59]. The range of symptoms is wide, from dyspeptic symptoms to systemic symptoms resulting from malabsorption [14].

Predisposing factors for pseudo-obstruction, either acute or chronic, are both SSc related—dilation, atony and delayed transit—and treatment related, especially the use of opiates [51, 60]. The stasis due to dysmotility of intestinal content predisposes to SIBO that was detected in up to 40–50% of SSc patients [51, 61]. This can, along with the failure of recurrent antibiotics therapy, cause the vulnerability to severe malabsorption [62].

PCI is a rare complication of SSc characterised by multiple gas-filled cysts in submucosa or subserosa [63] as an incidental radiographic (RDG) finding. Contributing factors involve dysmotility with consequent SIBO, ischemic damage and muscular atrophy [64]. Rarely, the rupture can cause benign spontaneous pneumoperitoneum or more severe complications as bowel ischaemia, perforation and peritonitis [63]. The treatment of benign pneumoperitoneum consists of conservative approach (oxygen, antibiotics and bowel rest) or surgery intervention in more severe cases [14].

3.5 Large intestine

Colonic involvement, including hypomotility, telangiectasia and diverticula, affects up to 50% of SSc patients and is often asymptomatic or can typically manifest by chronic constipation and abdominal distension [1]. Dysmotility and the resulting constipation can in extreme cases lead to faecal impaction or perforation requiring surgery. The colon can be dilated with the loss of haustration [14]. SSc patients can also suffer from diarrhoea and severe malabsorption caused by SIBO [65].

Colon and anorectal involvement can manifest by rectal prolapse and diverticula typically described as “wide mouth”, which are mostly asymptomatic and not complicated by diverticulitis. Anorectal involvement is regarded as the second most common with a prevalence of 50–70% [14]. Symptoms include incontinence, tenesmus and painful defaecation. Faecal incontinence, present in 40% SSc patients, is generally attributable to several factors: diarrhoea, internal and external anal sphincter dysfunction, reduced rectal compliance and capacity with impaired recto-anal inhibitory reflex, rectal prolapse and also constipation with overflow [66, 67]. Dysfunction of smooth muscles in internal anal sphincter (neuropathic or myopathic) is supposed to be the initial cause of faecal incontinence [68]. The main cause of sphincter involvement seems to be the vasculopathy and resulting tissue atrophy described in endo-anal ultrasound imaging as a hyperechoic thinned sphincter. On the other hand, thick hypoechoic sphincter due to tissue fibrosis is found in some cases [69].

3.6 Liver and pancreas

Involvement of the liver is less frequent compared to GIT organs mentioned above. Nodular regenerative hyperplasia (NRH), benign liver involvement in SSc, can precede primary biliary cirrhosis (PBC) and can progress to non-cirrhotic portal hypertension [70, 71]. The pathogenesis lies in obliterative changes in portal veins and corresponds with the microvascular damage in SSc. Although NRH is mostly asymptomatic, it can develop into portal hypertension [72].

Primary biliary cirrhosis is the most common liver disorder associated with SSc with a prevalence of about 2%, higher in lcSSc [73]. It can precede the diagnosis of SSc, for example, as a Reynolds syndrome comprising PBC with Raynaud's phenomenon [74]. PBC is associated with anti-centromere antibody positivity [73]. Nevertheless, PBC screening antibodies (anti-mitochondrial, anti-gp21, anti-sp100) are detectable also in 20% of SSc patients with no liver disease [75]. The rate of progression of SSc-related PBC to end-stage liver disease and transplantation is lower compared to non-SSc PBC, but the reason is still unknown [76]. PBC contributes via cholestasis and decreased bile acid secretion to malabsorption and malnutrition [1].

Other rare liver infections in SSc include autoimmune hepatitis, idiopathic portal hypertension and primary sclerosing cholangitis [77, 78]. Specific anti-liver kidney microsomal (anti-LKM) or anti-smooth muscle (anti-SMA) antibodies detected in SSc without liver involvement are attributable to the autoimmune character of SSc [79].

The involvement of the pancreas seems to be rare and the symptoms can overlap with SIBO. The exocrine pancreatic insufficiency can take part in malabsorption [80]. Case reports describe occlusion of medium-sized pancreatic arteries in SSc resulting in haemorrhagic pancreatitis and fatal pancreatic infarction [81].

4. Malnutrition

Prevalence of malnutrition in SSc patients is estimated to be 15–58% [51, 82, 83]. Mortality is significantly increased in underfed SSc patients compared to patients with adequate nutritional intakes, whereas about 4% deaths are attributable to consequences of malnutrition [14, 83]. Both GIT involvement and cachexia from chronic inflammation play a key role in malnutrition [51]. However, there are other additional risk factors for malnutrition worth mentioning, e.g. depression and anxiety, although their significance is uncertain [1, 84].

According to the data from the Canadian Scleroderma Research Group database on almost 600 SSc patients, malnutrition correlates with disease duration and severity, severity of anaemia, abdominal distension and the rate of subjective complains [51]. The American Society of Parenteral and Enteral Nutrition (ASPEN) recommends early screening for malnutrition in every patient with newly diagnosed SSc and then annually [85]. Screening is performed by examination of blood samples for chosen parameters: haemoglobin, iron and vitamin B12, serum levels of fat-soluble vitamins, prealbumin, albumin and additional test for micro- and macronutrient deficiency, particularly in suspected SIBO [86].

Patients at risk are indicated to rigorous monitoring and prompt treatment optimally in cooperation with dietitian and gastroenterologist [85]. At the advanced stage, nasoenteral feeding should be tried, eventually a percutaneous endoscopic gastrostomy or jejunostomy in case of severe gastroparesis. The last-mentioned approach carries the advantage of reduction of pulmonary aspiration risk. The most severe refractory intestinal involvement is indicated to parenteral nutrition (PN) [14].

5. Alterations of body composition

Negative changes of bone mineral density (BMD), weight loss and muscle atrophy are associated with the nutrition insufficiency, but can also be related to reduced ability of physical activities, and severity of the disease. There are only few studies investigating alterations of body composition (BC) in SSc. Up to date, no large study or meta-analysis is available. Studies mostly used dual-energy X-ray absorptiometry, which is a suitable method for measuring BMD, lean body mass (LBM) and fat mass (FM) [87].

Studies have reported reduced BMD, which is determined by many factors: malnutrition and vitamin D deficiency, decreased physical activity, corticosteroid and immunosuppressive treatment and the disease-specific features [88, 89]. Low circulating levels of vitamin D may be related to the extent of skin involvement [90].

Studies on BC including body mass index (BMI) and other methods are scarce and their results differ. One study describes no alterations of FM or LBM in SSc patients compared to control population [90]. On the contrary, another study reported significantly lower BMI, LBM and FM as well as lower BMD in SSc women compared to healthy women, whereas more significant alterations of BC were expressed in dcSSc [91]. BMI significantly negatively correlated with duration of the disease in SSc patients, which was also the only risk factor associated with low LBM (sarcopenia). Of interest, reported negative changes of BC were not associated with current dietary customs [91].

One study reported decreased left ventricular mass (LVM) evaluated by echocardiography as a potential marker of malnutrition, whereas LVM correlated positively with BMI and severity of vascular involvement but negatively with skin thickening [92]. Another study reported the correlation of visceral abdominal fat with the main cardiovascular risk factors [93]. Both these studies are lacking a control group.

There is a strong need for large, well-designed studies including complex methods for evaluation of BC and disease-specific features and an adequate control group, so that the consequences of BC alterations could be properly elucidated and managed.

6. Diagnostic tools

Every patient diagnosed with SSc should be referred to a gastroenterologist, even if asymptomatic regarding GIT involvement [14]. Problematic swallowing and oral pathology should be examined by other specialists (dentists, speech pathologists and eventually an oral surgeon) [1]. Social and psychosocial factors have certain impacts on some GIT symptoms and hence should be taken into consideration too.

A wide spectrum of investigation methods is available for detection of GIT involvement, including laboratory and imaging methods [14]. Endoscopy has a key role in evaluation of oesophageal and gastric involvement and is used for therapeutic interventions as well. Except for video endoscopy, manometry and pH test are also useful in testing dysmotility and reflux (especially refractory GERD) [86, 94]. Barium oesophagogram is indicated for detection of suspect strictures [95]. Barrett's oesophagus requires regular screening by endoscopic biopsies with frequency depending on the baseline finding: no initial dysplasia should be screened every 3–5 years, and low-grade or high-grade dysplasia is recommended for control screening every 3–6 months. Endoscopy is also indicated in anaemia due to suspected GAVE [86]. Gastroparesis should be confirmed by RDG (delayed gastric emptying),

before administration of prokinetics [96]. Endoscopy in small intestinal involvement (e.g. capsule endoscopy) is restricted and difficult, particularly if dysmotility is the main symptom.

Diagnosis of SIBO is based on subjective complaints and objective signs of malabsorption—weight loss and nutrient deficiency—confirmed by results of blood test showing low serum carotene level (marker of vitamin A absorption), low vitamin B12, 25-hydroxyvitamin D, iron, pathologic prothrombin time, etc. [86]. Though breath test has good specificity, the sensitivity is poor (65–70%) and is not able to detect bacterial overgrowth in more distal parts of the small intestine [97, 98]. Invention of appropriate diagnostic tools for evaluation of SIBO is still an unmet need.

7. Patient-reported outcomes

Validation and measurement of the consequences and outcomes related to certain disease and involvement can be challenging. Construction of appropriate questionnaires for evaluating SSc patients' symptoms and correlating them to objective disease features was the task in the last decade [14]. The first questionnaire assessing the overall severity and quality of life in the context of GIT involvement was the Scleroderma Gastrointestinal Tract 1.0 (SSC-GIT 1.0), validated in 2009 [99]. Later it was revised, shortened and adapted into final version called University of California, Los Angeles Scleroderma Clinical Trial Consortium GIT 2.0 (UCLA SCTC GIT 2.0) [100]. This revised questionnaire consists of 33 items taken from SSC-GIT 1.0 and 1 new item evaluating rectal incontinence (faecal soilage). Total GIT score correlates with the overall burden of GIT disease in SSc patients [100].

Another instrument developed by the National Institutes of Health is called Patient-Reported Outcome Measurement Information System (PROMIS) GI symptom item [101]. Compared to UCLA SCTC GIT 2.0, PROMIS contains more items and has additional scales for disrupted swallowing, nausea and vomiting. There is large correlation and satisfactory reliability between this two instruments, but PROMIS seems to be more easily comprehensible for general and low-literacy population, usable across diverse populations and less demanding for respondents to fulfil [102]. The only validated tool for evaluating the malnutrition in SSc patients is Malnutrition Universal Screening Tool (MUST) [103]. MUST is one of screening tools recommended by North American expert panel for initial screening of malnutrition in SSc patients, as it is easy to administer [85]. MUST reflects the weight change and acute dietary intake and can be less sensitive to nutritional status and GIT involvement than another tool Subject's Global Assessment (SGA) [104]. Although MUST can identify the severity of malnutrition in SScs, it does not reflect the symptomatology contributing to this problem [105]. MUST is generally recommended as the screening tool for nutritional status by several groups (*European Society for Clinical Nutrition and Metabolism, ESPEN*; *National Institute for Health and Care Excellence, NICE*; and *North American expert panel* [106]).

8. Therapy

8.1 Current therapeutic options

To date, no specific disease-modifying drugs exist to stop the progress of the disease. Early diagnosis of SSc organ involvement is essential for symptomatic organ-specific treatment, until the irreversible fibrotic and hardly treatable damage

develops [14]. Currently, treatment of SSc-related gastrointestinal involvement is based on symptomatic therapy and includes acid-reducing therapy and administration of antibiotics and prokinetics. Octreotide is prescribed in refractory small intestinal pseudo-obstruction and bacterial overgrowth [40, 107] (**Table 1**).

Manifestation of GIT involvement	Initial therapy/examination	Other therapeutic approaches and lifestyle modifications
GERD	Modification of diet and lifestyle PPI (daily administration)	<ol style="list-style-type: none"> 1) Take PPI at least 30 minutes prior to eating; control the right intake 2) Consider increasing the dose of PPI—twice a day—or change the PPI drug 3) Add an H2 blocker at night 4) If symptoms are still present, perform pH-metry or endoscopy Lifestyle and diet modification: Small meals more frequently during the day, more food in the first half of the day; take a walk after eating; restrict from aggravating foods; sleep with the upper half of the body elevated or lay on the left side
Barrett's oesophagus	Optimal therapy of GERD, monitoring by a gastroenterologist, regular upper endoscopy	Radiofrequency ablation (RFA)—consider in low- or moderate-grade dysplasia, always indicated in high-grade dysplasia
Stricture	Optimal therapy of GERD	Consider endoscopic dilation, in case of persistent dysplasia
Gastroparesis	Prokinetics (after gastric emptying study to confirm delayed gastric emptying)	<ol style="list-style-type: none"> 1) Modification of diet (small meals, walking after meal), adequate liquid intake 2) Metoclopramide (ECG monitoring due to risk of prolonged QT interval) 3) Domperidone or erythromycin (if QT interval is normal) 4) Treatment of nausea
GAVE	Firstly, upper endoscopy to verify the diagnosis; argon plasma therapy in case of active bleeding; support therapy in case of bleeding (red blood cell transfusion, etc.)	<ol style="list-style-type: none"> 1) Repeated sessions of argon plasma therapy 2) Laser therapy as an alternative approach 3) Immunosuppressive therapy in indicated cases
SIBO	Breath test (poor sensitivity) Examination of malabsorption (laboratory tests, body composition) Therapeutic trial with antibiotics (metronidazole, ciprofloxacin, neomycin, rifaximin, amoxicillin, doxycycline)	<ol style="list-style-type: none"> 1) Administration of antibiotics for 2 weeks—in recurrent cases repeat cyclic antibiotics therapy 2) Probiotics 3) Enteral or parenteral nutritional support 4) FODMAP diet*
Intestinal pseudo-obstruction	Clinical assessment Imaging examination to exclude the mechanical cause of obstruction (X-ray, CT) Initial therapy and nutritional support during the hospitalisation	<ol style="list-style-type: none"> 1) Nutritional support 2) Prokinetics (subcutaneous octreotide) 3) Broad-spectrum antibiotics 4) Surgery (in resistant cases, to provide decompression)
Malnutrition	Regular screening, BMI examination, recommended screening tools (MUST) Laboratory markers of malnutrition	<ol style="list-style-type: none"> 1) Nutritional support 2) (Total) parenteral nutrition 3) Percutaneous feeding tubes (endoscopy gastrostomy)

Manifestation of GIT involvement	Initial therapy/examination	Other therapeutic approaches and lifestyle modifications
Constipation	“Bowel hygiene” (adequate liquid and fibre intake), defaecation in timely manner, taking regular exercise or other physical activity	Osmotic laxatives, stool softeners
Diarrhoea	Firstly, identify the cause of diarrhoea (other than SSc or multifactorial)	Management of the cause of diarrhoea (dysmotility, SIBO, fat malabsorption, etc.)
Faecal incontinence	Management of diarrhoea and SIBO, biofeedback, pelvic-floor exercises	Sacral nerve stimulation in resistant cases

**FODMAP foods: inappropriate and irritating ingredients in patients with irritable bowel syndrome or chronic bowel disease (idiopathic bowel inflammation, celiac disease, etc.); FODMAP diet consists of eliminating the intake of these foods: fermentable oligosaccharides (gluten, onion, garlic, etc.), disaccharides (lactose), monosaccharides (fructose) and polyols (alcohol sugars)—these are poorly absorbable carbohydrates in the small intestine. Adapted from Ref. [86]; Abbreviations: GIT, gastrointestinal tract; GERD, gastro-oesophageal reflux disease; PPIs, proton-pump inhibitors; ECG, electrocardiogram; GAVE, gastric antral vascular ectasia, SIBO, small intestinal bacterial overgrowth; CT, computed tomography; BMI, body mass index; MUST, Malnutrition Universal Screening Tool*

Table 1.
Therapeutic intervention and follow-up of SSc patients with GIT involvement

Firstly, non-pharmacological treatment—lifestyle modification—should be applied to improve symptoms: elevation of the head or upper half of the body in the bed, sleeping on the left side, modification of eating regimen (indigestion of multiple small meals during the day, avoidance of eating meal less than 3 or 4 hours before bedtime), loss of weight if obesity, cessation of smoking and minimalizing alcohol intake, avoidance of drinking beverages and taking food or drugs decreasing the LES pressure (caffeine drinks, chocolate, calcium channel blockers, nitrates) and appropriate education about using risk drugs (bisphosphonates, tetracycline, iron, NSAIDs) [86].

The last update of EULAR recommendations published in 2017 has summarised the up-to-date treatment management into three points: (1) PPI for treatment of SSc-related GERD and prevention of oesophageal ulcers, strictures and other adverse consequences, (2) prokinetics for control of the GIT dysmotility and (3) intermittent or rotating cycles of antibiotics for treatment of symptomatic SIBO. However, large randomised control trial (RCT) studies evaluating the above-mentioned medication in SSc are lacking [108].

A small RCT reported favourable effect of PPI on improvement of upper GIT symptoms in SSc [109]. Moreover, omeprazole potentially reduces or regresses the oesophageal fibrosis [110, 111]. On the other hand, long-term therapy with PPI potentially decreases the intestinal absorption and thus causes nutritional deficiency. It is associated with the risk of bacterial overgrowth and infections (*C. difficile*) and more adverse effects (cardiovascular disease, malignancy, dementia, etc.) [112]. H2 receptor antagonists (H2RA) are prescribed as the next step in GERD treatment, either in monotherapy or in combination with PPI [113]. H2RA control mainly the nocturnal histamine-dependent acid secretion, which is refractory to PPI [86].

Treatment by prokinetics is based on individual symptoms of GIT dysmotility and potential benefit to risk [108]. Several non-randomised or uncontrolled studies reported improvement of GI symptoms in SSc [107, 114–116]. Prokinetics improve refractory GERD symptoms via supporting the gastric emptying in cases of gastroparesis in patients treated adequately for GERD. Combination with antiemetics is favourable [86]. Inclusion of prokinetics in combination therapy may have benefits

in the early disease stage. Nevertheless, there is only a little or no profit from using prokinetics in later stages with dominant smooth muscle atrophy [96]. Choice of a certain drug from this group depends on individual benefit for each patient [86]. Small studies in patients with SSc and other connective tissue diseases reported a beneficial effect of cisapride [117–121]. However, cisapride can cause long QT syndrome predisposing to severe arrhythmias; thus it is not commonly available in some countries [122]. Metoclopramide is the first-line therapy in gastroparesis, followed by domperidone, erythromycin, or eventually pyridostigmine. Using these medicaments also requires monitoring for adverse effects [86].

In patients suspected for SIBO, intermittent or rotating administration of antibiotics is indicated. The current approach is based on empirical courses of one or more broad-spectrum antibiotics [123]. A therapeutic trial is performed for 2 weeks, without any testing. After these courses of antibiotics, gastrointestinal symptoms are assessed and if there is no improvement, cyclical courses of antibiotics continue every 2 weeks altered by 2 weeks off [86]. Therapy duration and regimen depend on the severity and recurrence of symptoms and clinical response [86]. Two small studies reported favourable effect of antibiotics in SSc-related SIBO [61, 124]. Nutritional status should not be omitted, and the supplementation should be eventually started at the same time as antibiotics [86]. Probiotics have favourable effect on symptoms and are suitable also in combination with antibiotics [125, 126].

There are more aspects of GIT involvement treatment. Regarding GERD, some studies reported favourable effect of GABA-B (gamma-aminobutyric acid receptor type B) agonists or metabotropic glutamate receptor antagonists (mGluR), which slow the decrease of basal LES pressure [127]. However, the beneficial effect has yet to be studied in SSc [86]. New pharmacological targets are still investigated, e.g. nitrous oxide synthase, cannabinoid, muscarinic or opioid receptors, etc., which reduce the transient LES relaxation. Surgical intervention is not generally recommended in SSc, because of association with increased risk of complications compared to general population, especially worsening of dysphagia [86].

Interventional endoscopy is the method of choice in indicated patients, e.g. endoscopic dilation of confirmed strictures should not be performed empirically due to the risk of perforation [128–130]. Laser or argon plasma coagulation is performed in GAVE, after adequate supplementation therapy of anaemia. Surgery should be the last solution after all strategies fail [86, 131].

Intestinal pseudo-obstruction requires exclusion of mechanical obstruction (RDG or computer tomography). Basal therapeutic approach lies in bowel rest, nutritional support, correcting electrolyte imbalance and use of prokinetics and antibiotics for coexisting SIBO [86]. In most cases (70%), this conservative treatment leads to spontaneous resolution. Some patients are indicated for surgery (9%) [132]. Subcutaneous octreotide at doses 50–200 micrograms per day is also recommended [86].

Treatment of large bowel symptoms is mainly symptomatic, including dietary measure and administration of laxatives or antidiarrhoeal drugs according to the dominant symptomatology [86]. Before the treatment of constipation, obstruction has to be excluded and current medication should be revised to avoid constipating drugs [133]. Aetiology of diarrhoea should be evaluated to exclude other aetiology, e.g. infections or other autoimmune disorders (celiac disease, microscopic colitis, amyloidosis). Antidiarrhoeal drugs (loperamide) have to be used with caution, because of the risk of pseudo-obstruction [86]. Bile acid sequestrants can be used to improve fat malabsorption in case of SIBO [133]. Incontinence is difficult to treat and requires complex approach consisting of management of diarrhoea, behavioural therapy (anorectal biofeedback), pelvic-floor exercise and eventually neuronal stimulation of sacral nerve—a microsurgery intervention [86].

8.2 Therapy of malnutrition

Enteral and sometimes long-term parenteral nutrition is often needed in progressive and advanced disease [1]. There are no studies available on enteral nutrition in SSc patients [83]. The North American expert panel recommends dietary supplementation in similar manner to treatment in patients with chronic diseases. In case of gastroparesis, dietary measures are recommended (low-fibre, low-fat, frequent small meals and higher content of liquid) along with regular monthly monitoring of body weight [83]. Alternative ways of enteral nutrition in case of insufficient oral alimentation are gastric or jejunal feeding [1]; percutaneous endoscopic gastrostomy (PEG) tube feeding, nasojejunal tube, or percutaneous or surgically placed enteral tube feeding in case of refractory gastroparesis and preserved normal small bowel function, or by PN [134, 135].

PN is an emerging option of treatment for patients with refractory malnutrition, where the EN is not sufficient (e.g. SIBO) or where surgical enteral nutrition may be difficult to provide (severe cutaneous fibrosis and thickening) [1]. The main disadvantages of PN are in general the cost and PN-related complications: catheter-related bloodstream infections; liver function abnormalities (e.g. cholestasis); metabolic bone disease; fluid overload, especially in patients with ILD and pulmonary arterial hypertension; electrolyte imbalances; and risk of central vein thrombosis in predisposed patients [136–140]. Moreover, specific problems with PN in SSc are caused by skin involvement, poor quality of veins due to vasculopathy and hand deformities requiring assistance with PN infusion [1].

Data on long-term PN in SSc patients are lacking. However, based on studies on PN in patients with chronic intestinal pathology and the data from retrospective studies on PN nutrition in SSc patients, which reported the improvement of quality of life and patients' profit from this therapy, this therapeutic approach is considered as effective in SSc patients [136, 141–144]. Regular monitoring for complications, control of body weight and adequate altering of nutrient supplements are recommended, along with the establishment of a team for patients' education, prevention of the catheter-related complications and optimising the nutrition intake. The optimal duration of PN needs to be determined [1].

8.3 Future therapeutic prospects

Novel therapeutic options of SSc GIT involvement are investigated, particularly immunosuppressive drugs targeting pro-fibrotic cytokines and IVIGs. Effect of IVIG therapy is multiple: anti-idiotypic-mediated neutralisation of muscarinic, anti-fibroblast or anti-endothelial cell circulating autoantibodies and reduction of pro-fibrotic cytokines. IVIG has a better safety profile compared to immunosuppressive drugs [14]. Observational studies confirmed its potential to improve GIT symptoms and reverse cholinergic dysfunction induced by M3-R autoantibodies in vivo [145–147]. Another therapeutic approach is targeting miRNA-29 by anti-miRNA chemically modified oligonucleotides [148]. However, future large-scale controlled studies are needed to confirm the beneficial effects of these promising approaches in SSc patients.

9. Conclusion

Gastrointestinal involvement is highly prevalent in systemic sclerosis, affects the majority of patients and can be hidden or can precede the obvious skin manifestation. Therefore, overall screening is recommended for early management of the

Field of research		To do
Aetiology	Genetic predisposition Infectious aetiology Environmental factors	Identify special haplotypes Identify pathoorganisms triggering the disease (e.g. <i>Helicobacter pylori</i> [9]) Identify the insult/toxin triggering the disease (smoking, exposition to toxic substances, etc.)
Pathogenesis Pathology	Autoantibodies Cytokines/chemokines	Association of well-known autoantibodies with the disease features and their role in pathogenesis (anti-topoisomerase I, anti-polymerase III, etc.) Identify new autoantibodies and their role in pathogenesis (e.g. IgG antibodies binding the M3 receptor for acetylcholine) Elucidate the role of cytokines/chemokines and cell immunity
Clinical features/ manifestation/phenotype	Onset of the disease Extent and severity of involvement Progression	Factors determining the course of the disease and clinical manifestation
Comorbidities	Malignancy Cardiovascular risk	Identify the factors/disease characteristics increasing the risk of malignancy Determine the risk compared to general population; identify the aetiology and type of specific manifestation
Nutrition Body composition	Markers of malnutrition Prevalence and character of negative changes of body composition	Composition of a sensitive and specific tool for evaluation of nutrition and complications leading to malnutrition (e.g. SIBO) Recommendation of an appropriate tool for examination of body composition and frequency of such testing
Therapy	Future specific therapy, targeted at specific mechanisms (molecules, antibodies, etc.) implicated in pathogenesis of the disease	IVIg (evidence of anti-idiotypic-mediated neutralisation of muscarinic, anti-fibroblast or anti-endothelial cell circulating autoantibodies and reduction of pro-fibrotic cytokines) Targeting RNA with small molecules; anti-miRNA chemically modified oligonucleotides Conventional synthetic/targeted synthetic/biologic/biosimilar DMARDs Stem-cell transplantation

Table 2.
Brief list of unmet needs and tasks for future research

gastrointestinal involvement until the ultimate damage develops. The pathophysiology and specific therapy are still the focus of research, with some promising prospects. To date, the cornerstone of the treatment is mainly symptomatic therapy and adequate nutritional support, best managed in cooperation with other specialists. The general impact of this involvement on patients' health status and quality of life should not be omitted. Large studies are required to examine aetiopathology and treatment options, including new therapeutic agents, and also complex impact of gastrointestinal involvement on patients' status (**Table 2**).

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