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Gastrointestinal disease in SSc: the neglected organ system?

McMahan ZH[1], Pandolfino J[2], Perlman H[3], Del Galdo F[4], Hinchcliff M[5]

1. Department of Internal Medicine, Division of Rheumatology, UTHealth Houston, Houston, TX, USA
2. Department of Internal Medicine, Division of Gastroenterology and Hepatology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
3. Department of Internal Medicine, Division of Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
4. Leeds Institute of Rheumatic and Musculoskeletal Medicine, Faculty of Medicine and Health, University of Leeds, Leeds, United Kingdom
5. Department of Internal Medicine, Section of Rheumatology, Allergy & Immunology, Yale School of Medicine, New Haven, CT, USA

Corresponding author:

Monique Hinchcliff, MD MS

Yale School of Medicine

Department of Internal Medicine

Section of Rheumatology, Allergy & Immunology

The Anlyan Center

PO BOX 208031

New Haven, CT, 06519 USA

Monique.hinchcliff@yale.edu

Mobile: 773.677.3289

ORCID: 0000-0002-8652-9890

Twitter handles:

@YaleScleroderma

@YaleRheumAller1

Abstract:

Purpose of the Review: Identifying outcomes and clinical trial endpoints enabled the discovery of new inflammatory bowel disease (IBD) treatments. Herein, we describe efforts to advance the study of gastrointestinal (GI) manifestations in systemic sclerosis (SSc).

Recent Findings: Insights into the scope of the problem, as well as advancements in the measurement and treatment of SSc-GI, are underway. Proposed SSc esophageal endophenotypes are now defined, risk stratification methods are growing, and new imaging and functional studies are now employed to guide therapeutic interventions. Additional progress is being made in characterizing the gut microbiome in patients with SSc. Research into the role of the immune response in the pathogenesis of SSc-GI disease is also ongoing, evolving simultaneously with the development of methods to facilitate data collection with real-time capture of diet, exercise, and medication data.

Summary: Multidisciplinary teams are working to deepen our understanding of SSc-GI disease pathogenesis, to identify biomarkers for risk stratification and the assessment of disease activity, and to develop and validate outcomes and clinical trial endpoints to pave the way toward effective therapy for SSc-GI disease.

Keywords:

Esophageal gene expression, microbiome, gastrointestinal disease, endoFLIP, neurogastroenterology

Key points:

1. Gastrointestinal complications of systemic sclerosis cause considerable morbidity and can contribute to increased mortality.
2. Less funding and attention have been paid to understanding and developing treatments for the gastrointestinal complications of systemic sclerosis, relative to other affected organs.
3. Factors impeding advancement in systemic sclerosis-gastrointestinal study and treatment include disease heterogeneity, a dearth of validated quantitative outcomes, and many potential confounders (*e.g.,* diet, exercise, environment).
4. Recent advancements permit the study of esophageal gene expression, physiology, and function to inform esophageal disease endophenotyping while work to understand the role of the immune response and gut microbiome in systemic sclerosis continues.
5. The systemic sclerosis research community can imitate the inflammatory bowel disease research community whose development of outcomes and study endpoints ushered in newly approved treatments.

Introduction:

Systemic sclerosis is an autoimmune connective tissue disease that can result in the dysfunction and damage of multiple organ systems, including the skin, heart, vasculature, lungs, musculoskeletal system, kidneys, and gastrointestinal (GI) tract. Due to the significant impact on function and mortality and the easily accessible measures of disease progression, cutaneous and cardiopulmonary complications are the most widely studied and remain the primary focus of most clinical visits and clinical trials (1-3). This collective focus of resources and brainpower has led to the approval of two FDA-approved drugs, nintedanib in 2019 and tocilizumab in 2021, specifically indicated for SSc-associated interstitial lung disease (ILD) (2). While there is widespread agreement across the SSc community that continued research to reverse progression and ultimately prevent SSc-ILD should remain a priority, we must not let this overshadow the critical need to address the GI complications of SSc in our patients (4).

The idea of living with symptoms from a chronic digestive disorder associated with limited ability to eat, absorb nutrients, and have normal bowel movements is nearly unimaginable for most; however, this is a reality that many of our patients endure. Gastrointestinal complications affect over 90% of patients with SSc and can negatively impact function, quality of life, and mortality in severe cases (5). As most of the GI tract may be negatively impacted by SSc, patients can struggle with symptoms that include microstomia and impaired mastication, dysphagia, regurgitation of undigested food, weight loss, bloating, nausea and vomiting, GI bleeding, bloating, chronic diarrhea, severe constipation/pseudo-obstruction, and fecal incontinence. These complications lead to poor quality of daily life, depression, humiliation, social isolation, negative

impacts on personal relationships, and high costs related to medical expenses and hospitalizations (6).

Despite its prevalence, potential severity, and impact on quality of life, little attention has been paid to SSc-GI disease. This has resulted in relatively slow progress in understanding the pathophysiology of SSc GI disease and what drives disease progression. As a result, physicians and patients alike struggle with managing the SSc GI symptoms as there are no known disease-modifying therapies.

Various reasons may explain the relative lack of significant academic advancement in our understanding of this neglected organ manifestation. **First**, heterogeneity in GI involvement in SSc patients is substantial, adding complexity to assessing patients with multi-organ involvement. This renders clinical evaluation and study of SSc GI complications more complex, time-consuming, and costly. Furthermore, high-quality translational studies are more challenging without large groups of well-characterized homogenous patient subgroups. **Second,** objective and quantitative outcomes for SSc GI disease activity, severity/damage, and gut progression measures still need improvement. Excluding select functional studies [e.g., upper endoscopy with pH impedance, high-resolution esophageal manometry, and endoscopic functional luminal impedance plethysmography (endoFLIP)], barium swallow, gastric emptying studies, capsule endoscopy, colonoscopy, and anal defecography are likely insufficiently sensitive to detect subtle changes over time and thus are inadequate outcomes (7). Unlike skin, limitations for acquiring comprehensive GI tissue samples include expense, the need for invasive studies, the patchy nature of the disease, and the inability to obtain full-thickness GI biopsies. **Third**, it can be challenging to determine whether

symptoms stem from SSc or are due to lifestyle and environmental factors because mood, diet, exercise, dysbiosis, medications, and other environmental factors all impact GI function (Figure) (8-11). Diarrhea is a frequent side effect of immunomodulatory medications (*e.g.*, mycophenolate mofetil, azathioprine, methotrexate), antifibrotics (*e.g.,* nintedanib), and vasodilators (*e.g.,* selexipag and epoprostenol) that can lead to treatment discontinuation. Similarly, constipation and increased gastroesophageal reflux symptoms are associated with calcium channel blockade for the treatment of Raynaud phenomenon. Furthermore, GI symptoms may be non-specific and variably associated with specific regions of gut dysfunction (12) and treatment response (5). Historically, these challenges have dissuaded research aimed at understanding SSc-GI disease pathogenesis to identify targeted treatments.

Fortunately, interest and momentum in SSc-GI-related research are increasing, and combined with advanced technologies, there is reason for optimism. Risk stratification based on patients' clinical, demographic, and serologic features, the characterization of more homogenous SSc GI patient subgroups, and the differentiation between SSc-GI progressors and non-progressors are slowly becoming a reality (9, 13-20). Clinical risk factors that predict the development of GI disease severity, such as older age, male sex, diffuse cutaneous disease, and baseline myopathy, are now more clearly defined (PMID: 31202479; PMID: 29193842). The delineation of distinct GI clinical phenotypes may also lend insight into patient risk stratification and understanding of disease pathogenesis. For example, a high burden of autonomic symptoms is reported among patients with more severe upper GI disease, significant Sicca symptoms, limited cutaneous disease, and abnormal gastric transit, suggesting that dysautonomia may

contribute to GI dysfunction in a subset of SSc patients (PMID: 39138019; PMID: 29907667). In contrast, slow colonic transit in patients with SSc is associated with risk factors for progressive vascular disease, including telangiectasia, anti-centromere antibodies, and a history of smoking, suggesting that slow colonic transit may be a consequence of progressive vascular disease in this patient subset (PMID: 34369086).

Associations between autoantibodies and specific GI phenotypes open the doors for more focused translational investigation. For example, in SSc, antibodies to gephyrin, a protein that anchors GABA and glycine receptors at the neural synapse, are associated with moderate to severe constipation, suggesting that abnormal function of this protein may contribute to abnormal enteric neural communications. In contrast, antibodies to vinculin, a protein in the Interstitial Cells of Cajal (e.g., pacemaker cells of the stomach), are associated with slower gastric transit (PMID: 36951252), which is interesting as an inverse correlation is reported between higher levels of circulating anti-vinculin antibody levels and the number of interstitial cells of Cajal (ICC) in the stomach in a non-SSc population (PMID: 32140042). Such hypothesis-generating work can inspire translational studies and ultimately enable the development of more targeted (and likely more impactful) therapeutic trials.

Distinguishing between patients with SSc whose GI disease will progress over time vs those who will not progress and determining the approximate time frame over which such changes will occur has also been a significant obstacle in SSc GI research. To this end, a recent study examined a large, well-characterized cohort of >2,500 patients with SSc. It utilized growth mixture models to estimate the phenotype for each patient and the trajectory of their GI disease over time. The investigators successfully differentiated

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between patients likely to progress on short- and longer-term timelines from those likely to remain stable throughout their disease course. They also identified clinical characteristics that defined the four patient subsets, laying the foundation to enrich GI-focused clinical trials with optimal patient populations.

The application of 'omic' tissue analyses has revolutionized our understanding of many diseases, SSc-GI disease notwithstanding. Gene expression analyses of esophageal biopsies from patients with SSc are feasible, safe, and informative. Three SSc esophageal endophenotypes, including inflammatory, non-inflammatory, and proliferative, are defined, and work is underway to determine which subset(s) develop progressive esophageal dysfunction (13). Additional studies are testing whether symptoms of esophageal dysfunction improve during treatment with tocilizumab because of its anti-inflammatory effects. 'Omics' of the gut microbiome in SSc are also increasing, and we anticipate that results of future studies that include data on local pollutants, diet, exercise, and medications will lead to a more comprehensive understanding of SSc GI dysfunction (21-23). Partnerships with computer scientists are underway to enable the development of smartphone applications to facilitate data capture of diet and exercise information to better account for potential confounders and facilitate more comprehensive analyses.

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Novel approaches to understanding and objectively characterizing GI disease and modifying symptoms are also under development. Our understanding of autonomic and enteric neurobiology is rapidly expanding, with the identification of new ENS cell types and understanding of neuronal stem cells and regeneration. Such advances will provide further insight into the role of specific biological pathways in the development and

progression of SSc-GI disease (5, 25-32). Novel therapeutics in SSc, such as the use of external and internal nerve stimulators for patients with intestinal and anal dysmotility are currently under study in randomized controlled trials (24). The variety of GI interventions are now available to manage and treat patients with gut dysfunction is also rapidly expanding, with several new classes of medications and interventions now available, including potassium competitive acid blockers, sodium/hydrogen exchanger (NHE3) inhibitors, and secretagogues, only some of which have been tested in SSc (PMID: 35386943). The benefits of modern implantable stimulators and vibrating capsules to enhance GI motility in SSc are also available and need to be studied in SSc (PMCID: PMC7685128). Advanced imaging technologies, such as functional magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET CT), are non-invasive measures of disease activity in other organ systems that may ultimately be applied in SSc GI disease. High-resolution manometry, endoFLIP, and advanced ultrasound techniques are also being studied to characterize the physiology of the gut in more detail (33-38). To this end, the success of the regulatory framework for inflammatory bowel disease (IBD) should be considered. In the past decade, the IBD community has made significant strides in identifying outcome measures and endpoints that have supported the approval of new interventions. Similar advancements in quantifying SSc-GI manifestations will undoubtedly advance treatment discovery in SSc GI disease (39-41).

While we are far from where we need to be with this often-neglected manifestation of SSc, the path forward is clearer. With continued multi-disciplinary academic focus and

research support, we are optimistic that this understudied SSc complication will be more treatable in the coming years.

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